

Review

Phototherapy-based combination strategies for bacterial infection treatment

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Abstract

The development of nanomedicine is expected to provide an innovative direction for addressing challenges associated with multidrug-resistant (MDR) bacteria. In the past decades, although nanotechnology-based phototherapy has been developed for antimicrobial treatment since it rarely causes bacterial resistance, the clinical application of single-mode phototherapy has been limited due to poor tissue penetration of light sources. Therefore, combinatorial strategies are being developed. In this review, we first summarized the current phototherapy agents, which were classified into two functional categories: organic phototherapy agents (e.g., small molecule photosensitizers, small molecule photosensitizer-loaded nanoparticles and polymer-based photosensitizers) and inorganic phototherapy agents (e.g., carbo-based nanomaterials, metal-based nanomaterials, composite nanomaterials and quantum dots). Then the development of emerging phototherapy-based combinatorial strategies, including combination with chemotherapy, combination with chemodynamic therapy, combination with gas therapy, and multiple combination therapy, are presented and future directions are further discussed. The purpose of this review is to highlight the potential of phototherapy to deal with bacterial infections and to propose that the combination therapy strategy is an effective way to solve the challenges of single-mode phototherapy.

Key words: Bacterial infection, Multidrug-resistance, Phototherapy, Combinatorial strategies, Nanomedicine

Introduction

Bacterial infections are caused by harmful bacteria invading the host, which may cause severe diseases including pneumonia, tuberculosis, sepsis, cholera, meningitis and osteomyelitis [1-5]. Although the discovery of antibiotics has been saving millions of lives [6], unfortunately, conventional antibiotics treatment has problems such as a low utilization rate and severe side effects [7-9]. More seriously, the overuse and misuse of antibiotics inevitably increase the prevalence of multidrug-resistant (MDR) pathogenic bacteria [10], which has become a global public health problem in the past decades [6]. According to statistics from the World Health Organization (WHO), nearly 80% of MDR micro-

organisms have arisen due to the global overuse or misuse of antibiotics, and infection by these strains is accompanied by severe adverse effects such as thrombophlebitis and epidermal necrolysis [11]. Under this circumstance, massive efforts have been made to develop new strategies for efficient bacterial infections therapy without causing drug resistance.

The use of light in modern medicine was introduced in the 19th century. Based on the advances in our understanding of the physical properties of light and light-matter interactions, medical technology has been developed in parallel [12]. A classic example of the early success of light-induced therapy was the treatment of lupus vulgaris with

ultraviolet (UV) light, which was discovered by physician Niels Finsen, who won the Nobel Prize in Physiology or Medicine in 1903 for this discovery. A notable milestone in the 1960s was the treatment of severe hyperbilirubinemia using blue-light phototherapy, which subsequently cured millions of infants of this condition [13]. Presently, numerous laser-based diagnostic and therapeutic devices have been widely used in clinical practice.

Over recent decades, the developments of phototherapy antibacterial strategies, such as photodynamic treatment and photothermal treatment [14], have attracted striking attention in nanomedicine because of their good controllability. Different from conventional antibiotics, phototherapy rarely causes bacterial resistance [15]. Therefore, phototherapy is a minimally invasive and effective modality that provides a convenient method for ablating bacterial infections using light irradiation in a clinically safe manner [16, 17]. **Figure 1A** shows that the mechanism of photodynamic treatment or photothermal treatment activity by a phototherapy agent. Despite the rapid progress and distinctive advantage of phototherapy, single-mode phototherapy techniques face several challenges, including limitations in targeting the infection site. Fortunately, combination with chemotherapy, chemodynamic therapy, gas therapy and multiple combination therapy, can effectively combat these challenges while maximizing the advantage of each therapeutic mode (**Figure 1B**). In this review, we aim to present a discussion on the significant research progress in combinatorial strategies using phototherapy. Firstly, we introduced phototherapeutic agents systematically, summarized the development of phototherapy and discussed the challenges of single-mode phototherapy. Furthermore, the advantages of combination therapy

for the treatment of bacterial infections were emphasized. Finally, we discussed the major challenges and problems facing therapeutic nanomedicine in bacteria infectious therapy, and propose possible future directions in this field.

Phototherapy agents for bacterial infection therapy

Photosensitizers play an important role in phototherapy. The first generation photosensitizers mainly include hematoporphyrin derivatives and porfimer sodium, and their phototherapy performance was limited by the short wavelength of excitation in deep tissues. To solve the disadvantage of the first generation photosensitizers, researchers further developed second generation photosensitizers with near-infrared activation. However, the low cell/tissue specificity of the second generation photosensitizers still prevented them from being used in clinical therapeutics. Over the past few years, novel nanomaterial-based photosensitizers have been received extensive attention and been studied, and these photosensitizers can be divided into organic and inorganic agents. In this part, we will compare the advantages and disadvantages of these two kinds of agents.

Organic phototherapy agents

Small molecule photosensitizers, small molecule photosensitizers-loaded nanoparticles and polymer-based photosensitizers are the three primary classifications of organic phototherapy agents, all of which have several common advantages, including 1) good biocompatibility; 2) structures and performances that are easy to characterize; 3) easy chemical modification.

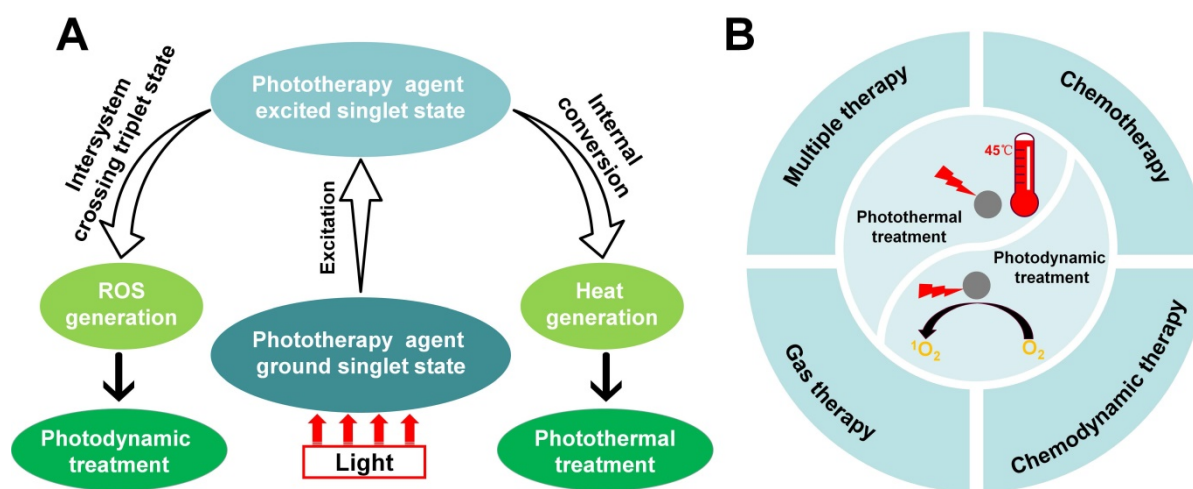


Figure 1. (A) The mechanism of photodynamic treatment or photothermal treatment activity by phototherapy agent. (B) Combination of different therapies with phototherapy (photodynamic treatment and photothermal treatment), including combination with chemotherapy, combination with chemodynamic therapy, combination with gas therapy and multiple combination therapy.

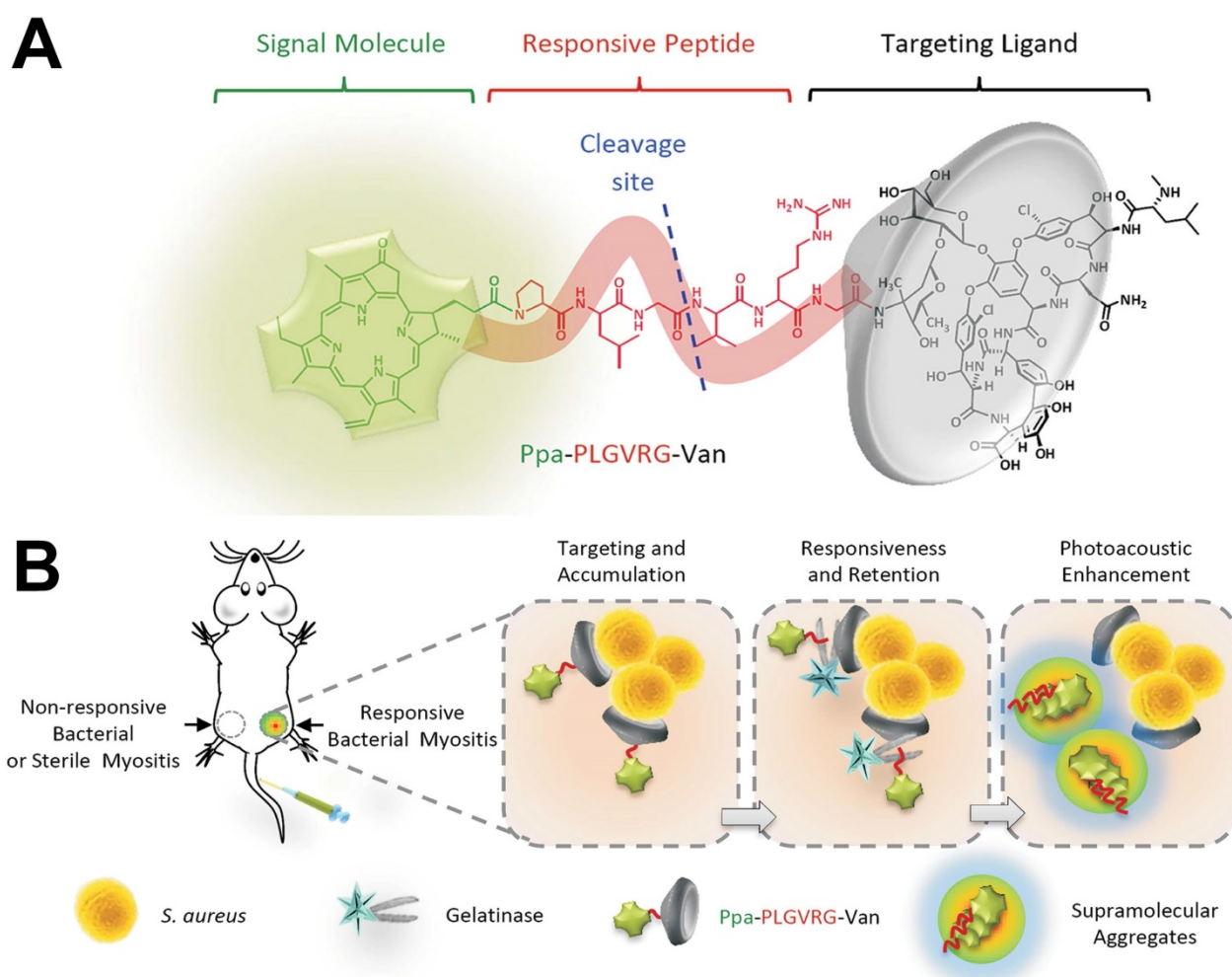


Figure 2. (A) Constituent elements of Ppa-PLGVRG-Van. Ppa: pyropheophorbide- α , signal molecule; PLGVRG: Pro-Leu-Gly-Val-Arg-Gly, an enzyme-responsive peptide linker; Van: vancomycin, a targeting ligand. (B) Illustration of bacterial infection imaging based on an *in vivo* aggregation strategy [18]. Copyright 2016, Wiley-VCH.

Small molecule photosensitizers

Recently, the small molecules commonly used as organic phototherapy agents mainly including protoporphyrin IX (PpIX), chlorine e6 (Ce6), indocyanine green (ICG) and other photosensitizers. However, several disadvantages still remain in the use of small molecule phototherapy agents. For example, due to the lack of the ability to target bacteria or infection sites, the enrichment of small molecule phototherapy agents at the infected site was not enough, which would further affect their therapeutic performance. To solve this problem, Wang *et al.* [18] developed a new molecular probe (Ppa-PLGVRG-Van), including a signal molecule (pyropheophorbide- α , Ppa), an enzyme-responsive peptide linker (Pro-Leu-Gly-Val-Arg-Gly, PLGVRG), and a targeting ligand (vancomycin, Van) (Figure 2A). Figure 2B shows that Ppa-PLGVRG-Van could accumulate at the site of responsive bacterial myositis *via* the targeting molecule (Van). Then, the peptide linker is cleaved by gelatinase to make the supramolecular form of

hydrophobic building blocks, which readily self-aggregates *in situ* and significantly enhances the photoacoustic signal for detecting the bacterial infection by imaging. Thus, the specific accumulation of Ppa-PLGVRG-Van at the bacterial infection sites leads to a significant function of Ppa *in situ*. We believe that this strategy of chemically functionalizing phototherapy agents can be expanded to enhance the therapeutic effect of other phototherapy agents in bacterial infections.

Small molecule photosensitizer-loaded nanoparticles

To enhance the therapeutic effect of small molecule photosensitizers, in addition to the above strategies, another approach is to extend the circulation time of photosensitizers, and enhance the stability at the same time. To achieve this goal, the small molecule photosensitizers can be conjugated with a variety of synthetic biomaterials, or encapsulated into nanoparticles to form small molecule photosensitizer-loaded nanoparticles, such as polymer nanoparticles, liposome, upconversion

nanoparticles and other inorganic nanoparticles. All the small molecule photosensitizers -loaded nanoparticles and the corresponding information can be found in **Table 1**. The payload of conjugated or encapsulated drugs can be enriched in the bacterial infection zone *via* the enhanced penetration and retention (EPR) effect [38-40], and kill bacteria under light irradiation. Moreover, to reduce the side effects, the components of nanoparticles are also required to be degradable *in vivo* to guarantee rapid clearance after eradicating bacterial infections [41]. Therefore, biodegradability is one of the important considerations in developing small molecule photosensitizer-loaded nanoparticles. When bacteria infects and invades the host, the expression of enzymes (*e.g.*, phosphatase, phospholipase and protease) at the site of infection will significantly increase, the pH value will decrease to an acidic pH, and the local temperature will increase, thus forming a special microenvironment of bacterial infection [40, 42, 43]. Therefore, the prepared small molecule photosensitizer-loaded nanoparticles, which can respond to the microenvironment of bacterial infected tissues, are the best choices to improve the phototherapy efficacy and helpful to slow down the emergence of side effects. For example, Yan *et al.* [24] synthesized silica nanoparticles doped with Ce6. This hybrid structure exhibits enhanced photostability and a high antibacterial efficiency towards *Staphylococcus aureus* (*S. aureus*) and methicillin-resistant *S. aureus* (MRSA). Therefore, this work demonstrates an

effective platform to improve the efficiency of small molecule photosensitizers for better treatment of wound infections.

In addition, nanosized metal organic frameworks (NMOFs) exhibit an advantage of encapsulating many small molecules due to their highly porous structure. In addition, they can reduce the self-quenching of small molecule photosensitizers and show great photodynamic treatment efficacy. For example, Bagchi *et al.* [30] prepared a squaraine (SQ)-encapsulated zeolitic imidazolate framework-8 (ZIF-8) NMOF (ZIF8-SQ) by a postsynthetic strategy. The insertion of SQ within the ZIF-8 cavity could lower the free diffusion of SQ molecules in biological media and limit the SQ aggregation possibilities. *In vitro* antibacterial tests confirmed that ZIF8-SQ could provide unparalleled photodynamic treatment action against MRSA.

In recent years, bioresponsive nanoparticles have achieved remarkable results in the treatment of bacterial infections *via* phototherapy [44, 45]. Sun *et al.* developed pH sensitive nanoparticles combined with ammonium methylbenzene blue for the photodynamic treatment of bacterial infections, showing an efficient biofilm eradication capability [31]. Wang *et al.* [44] designed an antibacterial hydrogel in an acidic environment. The hydrogel loading photothermal agent could cure wounds infected with a MRSA biofilm in a short period of time.

Table 1. Small molecule photosensitizers-loaded nanoparticles for antibacterial activities

Type	Photosensitizer	Loading method	Phototherapy type	Target microbe	Ref.
Vesicle	Ce6	Conjugate	Photodynamic treatment	<i>S. aureus</i>	[19]
	IR-780	Encapsulation	Photodynamic treatment and photothermal treatment	MRSA	[20]
Polymer nanoparticles	Ce6	Encapsulation	Photodynamic treatment	MRSA	[21]
	ICG	Encapsulation	Photodynamic treatment	<i>P. aeruginosa</i>	[22]
	PpIX	Encapsulation	Photodynamic treatment	<i>S. aureus</i>	[23]
Silica nanoparticles	Ce6	Conjugate	Photodynamic treatment	MRSA	[24-26]
MnO ₂ nanoparticles	Ce6	Encapsulation	Photodynamic treatment	<i>S. aureus</i>	[27]
Mesoporous Polydopamine nanoparticles	ICG	Encapsulation	Photodynamic treatment and photothermal treatment	<i>S. aureus</i>	[28]
F ₂ O ₄ nanoparticles	Ce6	Conjugate	Photodynamic treatment	<i>S. aureus</i> <i>E. coli</i>	[29]
Nanoscale metal-organic frameworks	Squaraine	Encapsulation	Photodynamic treatment	<i>S. aureus</i>	[30]
Carboxymethyl chitosan nanoparticles	MB	Encapsulation	Photodynamic treatment	<i>E. coli</i> , <i>S. aureus</i> , MRSA	[31]
Nanofiber	Cypate	Encapsulation	Photothermal treatment	MRSA	[44]
UCNPs	SiPc	Encapsulation	Photodynamic treatment	<i>E. coli</i> , <i>S. aureus</i>	[32]
	MB	Encapsulation	Photodynamic treatment	<i>S. aureus</i> , <i>E. coli</i>	[33]
	MB	Encapsulation	Photodynamic treatment	<i>S. aureus</i> , <i>E. coli</i>	[34]
	ZnPc	Encapsulation	Photodynamic treatment	<i>S. aureus</i>	[35]
	CPZ	Conjugate	Photodynamic treatment	MRSA	[15]
	PSeV	Encapsulation	Photodynamic treatment and photothermal treatment	MRSA	[36]
	Curcumin	Conjugate	Photodynamic treatment	MRSA	[37]

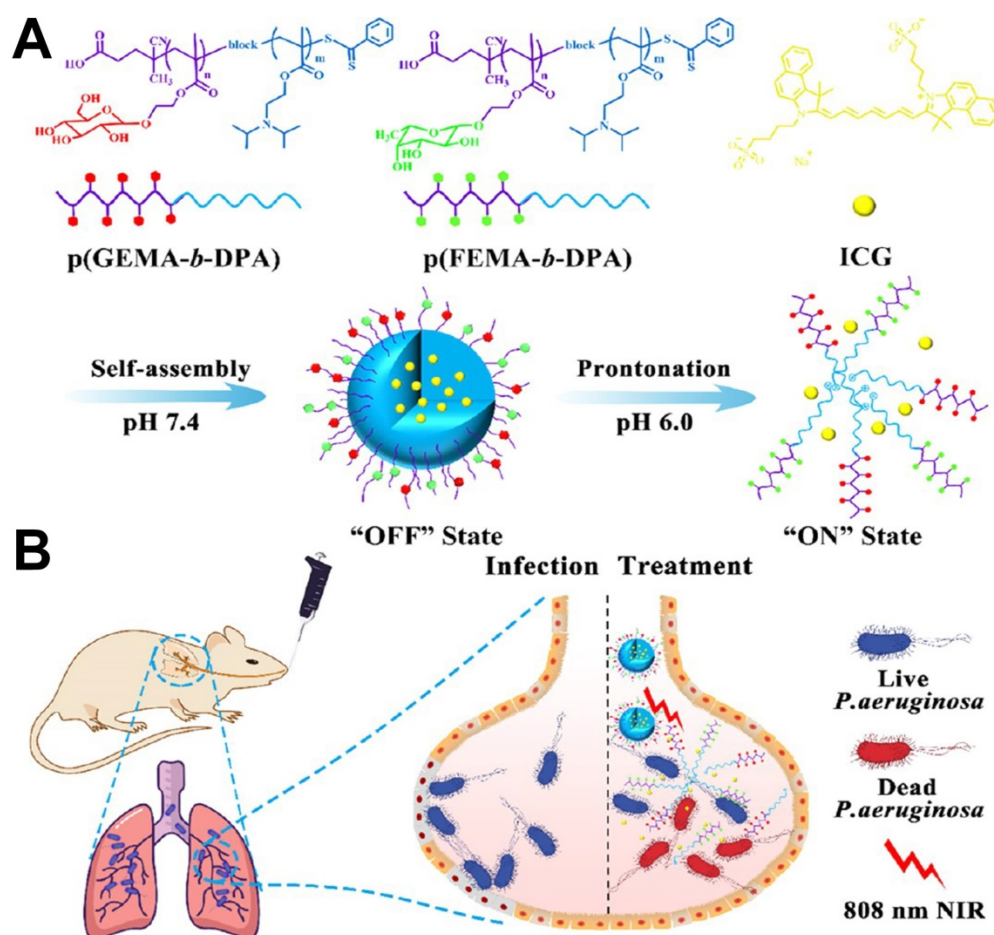


Figure 3. (A) Schematic illustration of preparation of the nanovehicle (gadofullerene nanoparticles, GFNPs) and (B) killing *P. aeruginosa* at infected alveoli by photothermal treatment [22]. Copyright 2019, ACS Publications.

To realize the targeted delivery of photosensitizers, target ligands can be modified on nanoparticles. For example, Zhang *et al.* [22] prepared a pH-tunable ON/OFF nanovehicle with a heteromultivalent and glycomimetic shell for targeting bacterial lectins and an acid-responsive core for the controlled release of phototherapeutic agent at infectious sites. As shown in **Figure 3**, the shell of the nanovehicle was composed of heteromultivalent glycomimetics, which could bind tightly to bacteria and subsequently inhibit biofilm formation. The core was composed of acid-sensitive polymers that changed from hydrophobic to hydrophilic through protonated effects under an acidic microenvironment. Under physiological conditions, the hydrophobic core of nanotherapeutics was in the “OFF” state and locks the phototherapeutic agent in the cage. Upon arriving at the infection site, the nanotherapeutics were in the “ON” state under an acid microenvironment, promoting the release of phototherapeutic agent which induced oxygen species (ROS) and heat under NIR laser illumination. Therefore, this heteromultivalent ligand-decorated nanovehicle could effectively avoid side effects on normal tissue and the

occurrence of bacterial resistance.

On the other hand, the targeting of nanoparticles to bacterial cells can be promoted *via* electrostatic interaction. For example, Shi *et al.* [23] designed and synthesized pH-sensitive mixed-shell-polymeric-micelles (MSPMs) composed of poly(ethylene glycol)-*b*-poly(ϵ -caprolactone) (PEG-*b*-PCL) and poly(ϵ -caprolactone)-*b*-poly(β -amino ester) (PCL-*b*-PAE). The potential of MSPMs could change from a negative charge to a positive charge due to charge-switching of the PAE blocks at a low pH, which would promote the targeting of MSPMs to bacterial cells *via* electrostatic interactions. In a murine model, **Figure 4** shows that the experimental group administered PpIX-loaded MSPMs exhibited a faster recovery rate after infection with vancomycin-resistant *staphylococcal*, while the differences in the bacterial eradication efficacies of the groups treated with saline, vancomycin, and PpIX-loaded single shell-polymeric-micelles (SSPMs) composed of PEG-*b*-PCL were minimal. Taken together, these studies provided promising approaches for the treatment of MDR bacterial infection.

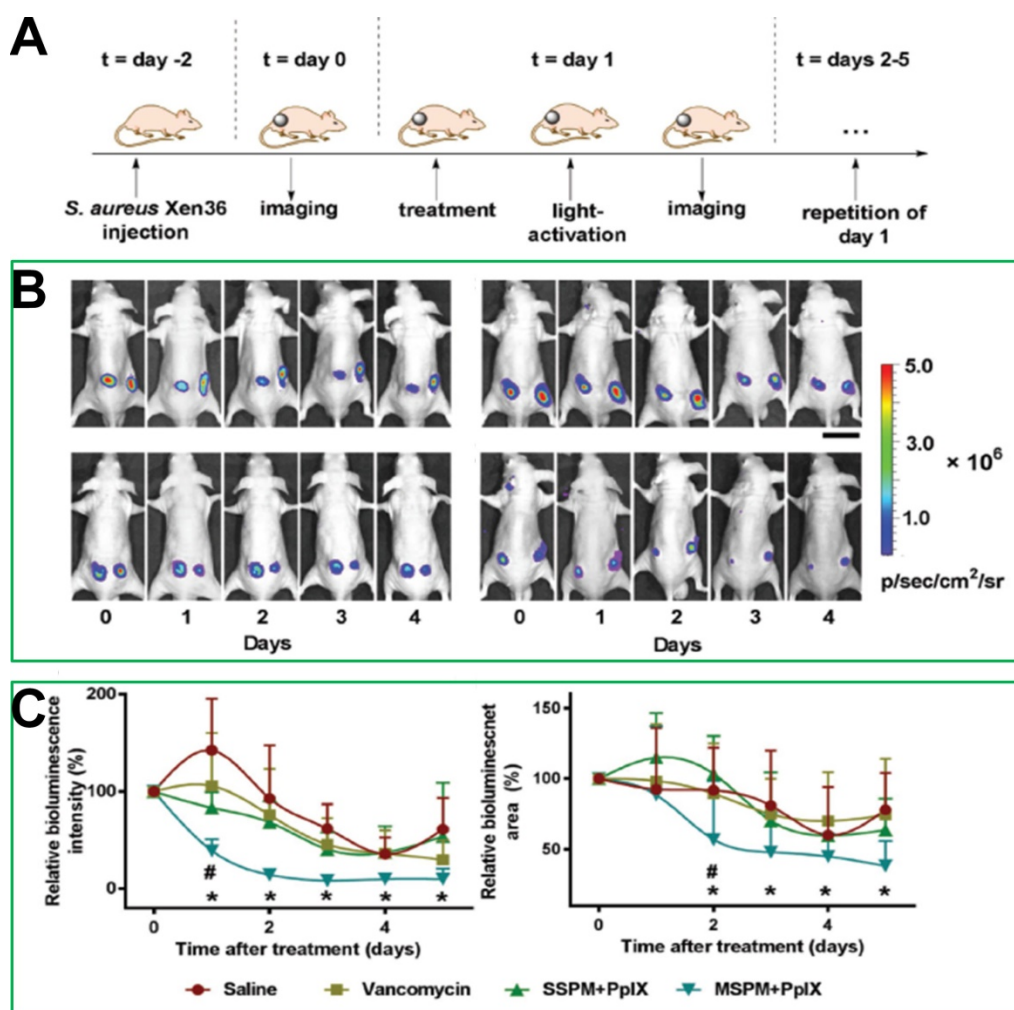


Figure 4. (A) The building process of the vancomycin-resistant staphylococcal infection in a murine model and the photodynamic treatment procedure. (B) Bioluminescence images after the treatments with different strategies. (C) Relative bioluminescence intensities and relative bioluminescence areas after each treatment [23]. Copyright 2017, Wiley-VCH.

Because upconversion nanoparticles (UCNPs) have the unique ability of upconverting NIR light to UV and visible emissions [46], they are also commonly used in phototherapy. Sun *et al.* [33] designed and synthesized antibacterial a core-shell UCNPs@SiO₂(MB), in which the core was NaYF₄:Yb,Er,Gd and the shell was methylene blue (MB)-loaded silica, which could convert NIR light into visible photons to activate MB through fluorescence resonance energy transfer (FRET) and generate ROS to rapidly kill both Gram-positive *S. aureus* (94.5%) and Gram-negative *E. coli* (93.2%). To develop highly effective antibacterial UCNPs, Zhou *et al.* [36] reported a photosensitizer (PS) prepared through the self-assembly of poly(selenoviologen) on the surface of core-shell NaYF₄:Yb/Tm@NaYF₄ UCNPs. **Figure 5** shows a schematic illustration of the main synthetic procedure and synergistic photodynamic treatment and photothermal treatment strategies. The hybrid UCNP/PSeV PS showed a strong ROS generation ability and high photothermal conversion efficiency

(~52.5%) under the mildest reported-to-date irradiation conditions ($\lambda=980$ nm, 150 mW/cm², 4 min) and led to a high efficiency in killing MRSA both *in vitro* and *in vivo*.

Polymer-based photosensitizers

Polymer-based photosensitizers are in-between small molecules and nanoparticles. Many conjugated polymers and conjugated polymer nanoparticles (CPNs) have been utilized as photodynamic and photothermal treatment agents for bacterial infection therapy [47-51].

For example, Feng *et al.* [51] reported photothermal-responsive CPNs for the rapid and effective killing of bacteria. These CPNs are composed of poly[2,6'-4,8-di(5-ethylhexylthienyl)benzo[1,2-b;3,4-b]dithiophenealt-5-dibutylloctyl-3,6-bis(5-bromothiophen-2-yl)pyrrolo[3,4-c]pyrrole-1,4-dione] (PDPP-DBT) and matrix polymer DSPE-PEG2000-MAL. To enhance the interaction of CPNs with bacteria cells, the resulting CPNs were further modified with the

positively charged Tat peptide (RKKRRQRRRC) by chemical conjugation between the maleimide groups and thiol groups. *In vivo* and *in vitro* experimental results confirmed that CPNs-Tat could enhance the interaction with bacteria cells with the formation of CPN-Tat/bacteria aggregates, and these photothermal-responsive CPNs converts light into heat and produces local hyperthermia to kill bacteria within a few minutes under NIR irradiation. Therefore, this photothermal-responsive strategy offers another rapid and effective modality for combating bacterial infections.

Inorganic phototherapy agents

Compared with organic phototherapy agents, many inorganic phototherapy agents exhibit strong optical absorption and efficient photothermal conversion, and therefore, they are commonly used as photothermal treatment agents (PTTs) to fight bacterial infections. There are many factors influencing the phototherapy performance of inorganic PTTs, including their size, shape, concentration and surface modification. According to the morphology of inorganic PTTs, they can be classified into nanorods, nanocages, nanodots, nanocubes, nanosheets, nanostars, nanoflowers, nanoeggs, nanopopcorn, and numerous other 2D materials [52]. In this part, we classify most PTTs into 4 categories: carbon-based nanomaterials (*e.g.*, graphene derivatives and carbon nanotubes), metal-based nanomaterials (*e.g.*, Au and CuS) [53],

composite nanomaterials and other nanomaterials (*e.g.*, quantum dots). In fact, overlaps cannot be avoided in some cases for our classification.

Carbon-based nanomaterials

Carbon-based nanomaterials have been widely as phototherapy agents studied in antibacterial therapy because of their relatively high bacterial toxicity, negligible mammalian cytotoxicity and other favourable properties. In recent years, graphene-based nanomaterials (GBNs), such as graphene, reduced graphene oxide (rGO), grapheneoxide (GO) and other chemically modified-graphene, have been widely used in antibacterial therapy research. **Table 2** shows the carbon-based nanomaterials commonly used in antibacterial therapy.

To achieve the more specific and effective photothermal sterilization of GBNs, they were usually modified with some functional molecules or nanostructures. For example, Qian *et al.* [54] developed surface-adaptive and biocompatible glycol chitosan-conjugated carboxyl graphene (GCS-CG), which could target to the acidic environments of infected abscesses without damage to healthy tissue (**Figure 6**). The *in vitro* experimental results demonstrated that the aqueous solution of GCS-CG showed the rapid production of heat energy with NIR irradiation. This kind of GO-based nanomaterial could be applied as a new potential photothermal treatment agent in treating bacterial infection and even MDR bacteria.

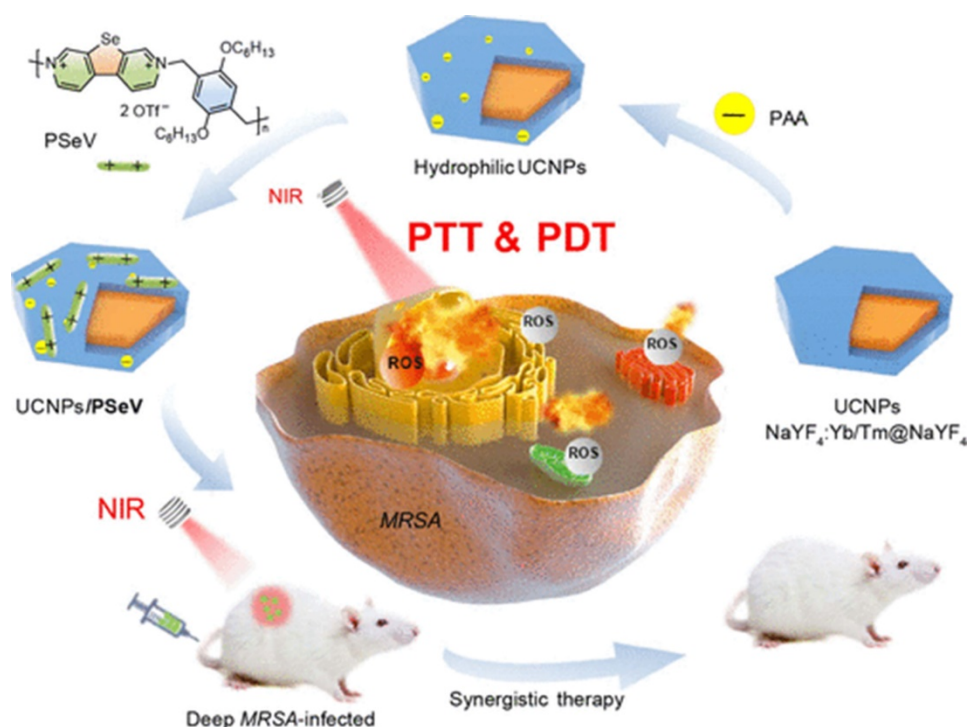


Figure 5. Schematic illustration of the main synthetic procedure and coordinated antimicrobial strategy of photodynamic treatment and photothermal treatment [36]. Copyright 2020, ACS Publications.

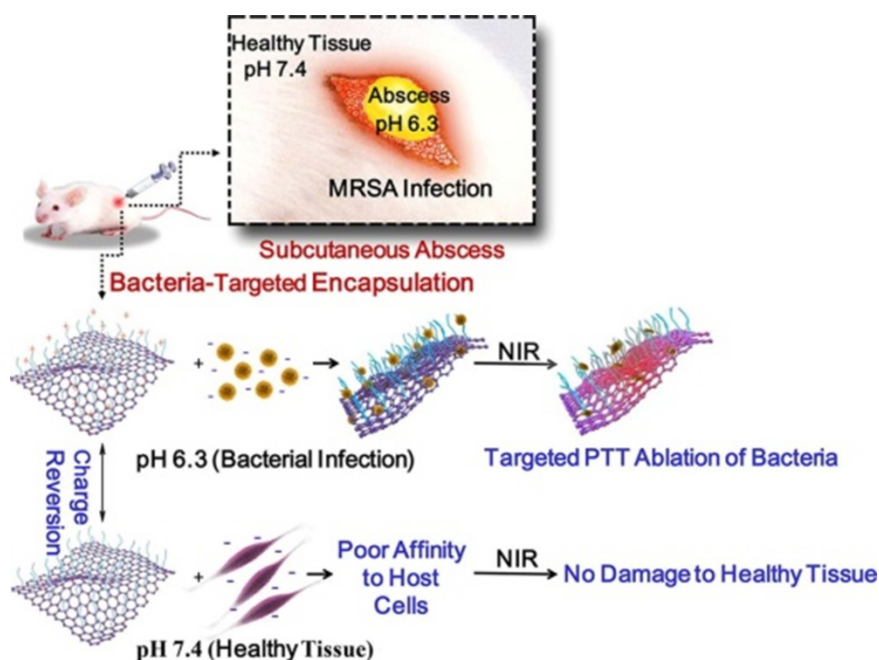


Figure 6. Schematic illustration of the antibacterial mechanism of glycol chitosan conjugated carboxyl graphene (GCS-CG) [54]. Copyright 2018, Elsevier.

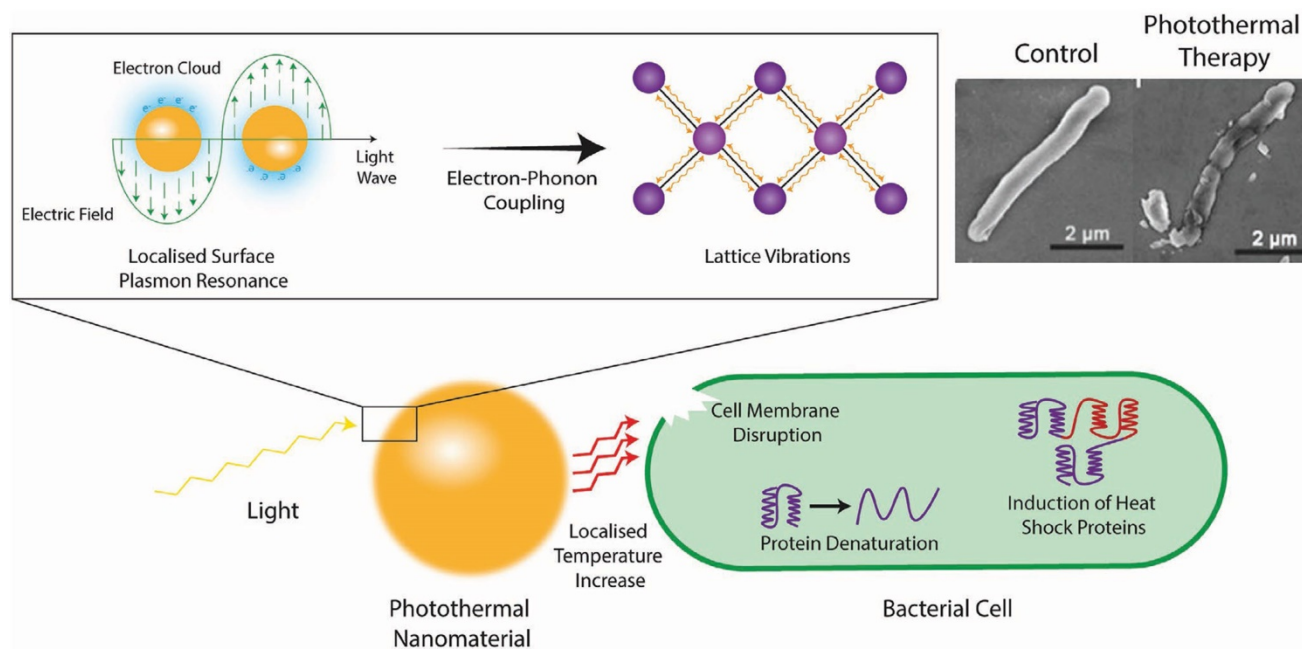


Figure 7. Schematic representation of the photothermal conversion of light to heat and the subsequent antimicrobial mechanism taking place. Top right are scanning electron micrographs of *E. coli* cells before (left) and after (right) treatment with photothermal nanomaterials [69]. Copyright 2018, Wiley-VCH.

Table 2. Comparison of photothermal carbon nanomaterials for antibacterial activities

Material	Shape	Irradiation (λ)	Target microbe	Ref.
GCS-CG	Sheet	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[54]
Ag@G-SAS	Sheet	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[56]
FGO-FA	Sheet	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[57]
AA@GS@HA-MNPs	Sheet	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[58]
GO-IO-CS	Sheet	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[59]
Van-rGO	Sheet	808 nm	<i>E. coli</i>	[60]
MRGOGA	Sheet	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[61]
GAS-Ab-MWNT	Tube	800 nm	Planktonic and GAS	[62]
IgG-MWCNT	Tube	808 nm	MRSA	[63]

Metal-based nanomaterials

Metal nanomaterials are the material most commonly used for photothermal treatment due to their broad spectral absorption range and light stability [53, 55]. **Figure 7** shows the antibacterial mechanism of the photothermal conversion of metal nanomaterials. In short, the electromagnetic field causes electrons in the conduction band at the surface of the metal nanomaterials to rapidly oscillate [64]. This absorbed energy induces vibrations in the

metallic lattice *via* electron–photon coupling, which is subsequently transferred into thermal energy causing a local temperature increase [65]. In order to kill pathogens specifically, these nanomaterials could target the pathogen by conjugating targeting ligands (such as antibodies) on their surface, which would increase the local temperature around the pathogen and cause cell death through a suite of actions including the denaturation of essential proteins/enzymes, induction of heat shock proteins, disruption of metabolic signaling and rupture of the cell membrane [54, 66–68]. The commonly investigated inorganic PTTs and their images with corresponding shape are shown in **Table 3**.

For example, Norman *et al.* [71] prepared gold nanorods with covalently conjugating primary resistance antibodies, which could selectively target

the Gram-negative pathogen, *Pseudomonas aeruginosa*. The subsequent attachment of these gold nanorods to the pathogenic bacterial cell surface could significantly reduce the bacteria cell viability under near-infrared radiation ($\lambda=785$ nm). Similarly, Wang *et al.* [109] prepared oval-shaped gold nanoparticles, with anti-salmonella antibodies bound on their surface (**Figure 8**). When oval-shaped gold nanoparticles are attached to bacterial cells, the heat locally generated during NIR irradiation ($\lambda=785$ nm) could cause irreparable cellular damage of *Salmonella typhimurium* bacteria. The successful bioconjugation of photothermal nanomaterials with targeting ligands shows promise in improving the selectivity to enhance the photothermal treatment effect of metal nanomaterial-based PTTs.

Table 3. Comparison of photothermal metal nanomaterials for antibacterial activities

Material	Shape	Irradiation (λ)	Target microbe	Ref.
Au	Sphere	525 nm	<i>S. aureus</i>	[70]
	Popcorn	670 nm	<i>S. typhimurium</i>	[71]
	Oval	670 nm	<i>S. typhimurium</i>	[72]
	Star	808 nm	<i>S. aureus</i>	[73]
	Cluster	808 nm	<i>E. coli</i>	[74]
	Rod	810 nm	<i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i> , <i>S. mutans</i> , <i>S. oralis</i> , <i>S. salivarius</i> , <i>S. sobrinus</i> .	[75]
AuPd	Sheet	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[76]
Au@SiO ₂	----	810 nm	<i>E. faecalis</i>	[77]
AuNSs	Star	808 nm	MRSA	[78]
AuNRs–PVCL gel	Rod	785 nm	AMR <i>E. coli</i> , AMR <i>A. baumannii</i> , AMR <i>E. faecalis</i>	[79]
Au@Ag NPs	Sphere	800 nm	<i>S. aureus</i>	[80]
Au–Ag–Au NRs	Rod	785 nm	<i>E. coli</i>	[81]
Au@PtAg NRs	Rod	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[82]
PEG–Au@Ag NPs	Triangle	808 nm	<i>E. coli</i>	[83]
AuNP–N–C	Sphere	808 nm	MRSA	[84]
Apt@AuNRs	Sphere and rod	808 nm	MRSA	[85]
AuNR@HSK	Sphere	785 nm	<i>E. coli</i>	[86]
AuNR@PAA–Van	Rod	808 nm	<i>E. coli</i>	[87]
Tetra@AuNR@TiO ₂	Tubes	830 nm	<i>S. mutans</i>	[88]
Fe ₃ O ₄ –Au	Eggs	808 nm	<i>A. baumannii</i> , <i>E. coli</i> , <i>S. pyogenes</i> , <i>S. saprophyticus</i> , <i>E. faecalis</i> and <i>E. faecium</i>	[89]
	Necklace	785 nm	<i>E. coli</i> and <i>S. typhimurium</i>	[90]
Fe ₃ O ₄ –alumina	Sphere	808 nm	<i>A. baumannii</i> , <i>E. coli</i> , <i>E. faecalis</i> and <i>S. pyogenes</i>	[91]
Fe ₃ C ₂	Spheroid	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[92]
In ₂ Se ₃	Sheets	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[93]
CuS	Plate-like	980 nm	<i>S. aureus</i> and <i>E. coli</i>	[94]
CuS–PVP	hexagonal nanoplates	808 nm	<i>S. aureus</i>	[95]
BSA–CuS	Platelike or sphere	980 nm;	<i>S. aureus</i> , <i>E. coli</i> , <i>A. baumannii</i> , <i>S. haemolyticus</i> , MRSA	[96–98]
		808 nm		
Ce6-labeled BSA–CuS	Sphere	1064 nm	<i>S. aureus</i> and <i>E. coli</i>	[99]
LuVO ₄ :Nd ³⁺ /Yb ³⁺ /Er ³⁺ @SiO ₂ @Cu ₂ S	Olivelike	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[100]
PEG–MoS ₂	Flower-like	808 nm	Ampr <i>E. coli</i> and <i>B. subtilis</i>	[101]
CS–Fe ₃ O ₄ –MoS ₂	Sheet	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[102]
MoS ₂ –BNN6	Sheet	808 nm	<i>S. aureus</i> , Ampr <i>E. coli</i> , <i>E. faecalis</i>	[103]
MoS ₂ –penicillin	Sheet	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[104]
MoO ₃ –x/Ag	Sheet	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[105]
Cs _{0.33} WO ₃ on CA–PVP decorated microchannels	Sphere	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[106]
GTA–PEG–W ₁₈ O ₃₉	Sheet	808 nm	<i>E. coli</i>	[107]
Van–LaB ₆ @SiO ₂ /Fe ₃ O ₄	Sphere	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[108]
Ag	Triangular	808 nm	<i>S. aureus</i> and <i>E. coli</i>	[69]

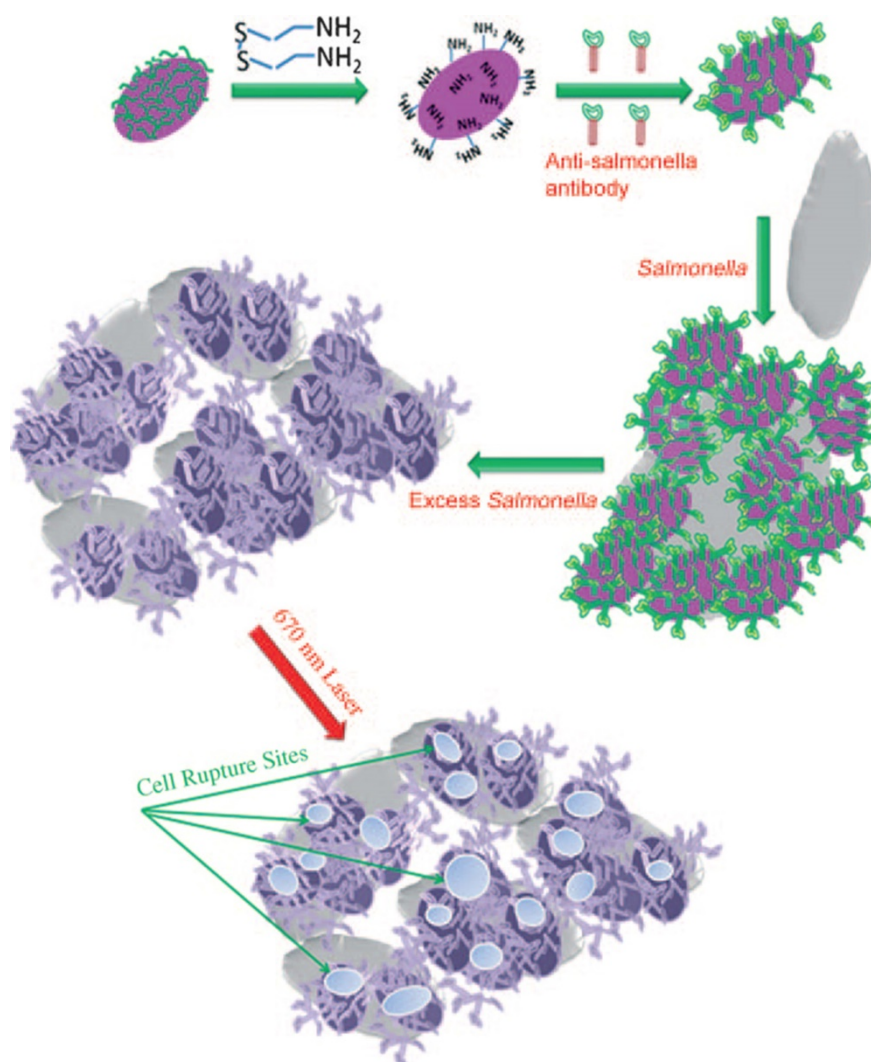


Figure 8. Schematic illustration of antibody-conjugated oval-shaped gold nanoparticles to selectively target and destroy pathogenic bacteria [109]. Copyright 2010, Wiley-VCH.

Composite nanomaterials

To fully exploit the effect of different types of photothermal agents, increasing numbers of composite-based nanomaterials photothermal agents have been designed and prepared [110]. For example, Feng *et al.* [111] prepared a rGO and AuNS nanocomposite (rGO/AuNS) *via* a seed-mediated growth method (**Figure 9**). The results of *in vitro* experiments confirmed that MRSA could be killed completely when incubated with rGO/AuNS (50 µg/mL) under NIR irradiation (808 nm, 3 W/cm²) for 6 min. Therefore, this indicates that rGO/AuNS can be used as a dual functional photothermal agent for synergistically killing MDR bacteria. Similarly, Luo *et al.* [112] developed a facile assembly of Au NPs decorated GO/nanocellulose paper, which has an intense antimicrobial activity against both Gram-positive and Gram-negative bacteria due to its excellent photothermal conversion performance. Besides, the satisfactory *in vitro* antibacterial

performance demonstrated that these functionalized papers could be applied for skin disinfection or medical device sterilization.

In addition, black phosphorus (BP) nanosheets, a rising star among 2D materials, have recently attracted widespread attention in antibacterial applications owing to their high photothermal conversion efficiency, large surface area-to-volume ratio, excellent biocompatibility, and good biodegradation [126]. In particular, a variety of composite materials based on black phosphorus and metal nanoparticles have been developed and proved to exhibit an excellent antibacterial efficiency [127, 128]. For instance, Aksoy *et al.* [129] designed and prepared new a BP/Au nanocomposite as a photothermal antibacterial agent to kill an important nosocomial pathogen *E. faecalis*. *In vitro* studies have shown that because the BP/Au nanocomposite has higher photothermal conversion efficiency, it more efficiently destroyed the bacterial cell membrane than bare BP, with a biofilm inhibition rate of 58% achieved

under NIR light irradiation. The photothermal composite nanomaterials can be found in **Table 4**.

Table 4. Comparison of photothermal composite nanomaterials for antibacterial activities

Material	Irradiation (λ)	Target microbe	Ref.
Ag+-GCS-PDA@AuNRs	808 nm	<i>E. coli</i> and MRSA	[113]
Dap-GCS-PDA@AuNRs	808 nm	MRSA	[114]
AuNC@Dap/PDA-aSpa	808 nm	<i>S. aureus</i>	[115]
PDA@Au-Hap NPs	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[116]
PATA-C ₄ @CuS	980 nm	<i>S. aureus</i> , <i>B. amyloliquefaciens</i> , <i>P. aeruginosa</i> and <i>E. coli</i>	[117]
Au@Rubby/GO	785 nm	<i>E. coli</i> and <i>S. aureus</i>	[110]
GO-IONP-Ag	808 nm	<i>S. aureus</i>	[118]
Au-QCMC-GO/nanocellulose paper	808 nm	<i>E. coli</i> , <i>P. aeruginosa</i> and <i>B. subtilis</i>	[112]
GO-Tob@CuS	980 nm	<i>E. coli</i> and <i>P. aeruginosa</i>	[119]
Fe ₃ O ₄ @GO-QCS	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[120]
rGO/AuNS	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[111]
rGO/MSN/Ag	808 nm	<i>E. coli</i> , <i>P. putida</i> and <i>Rhodococcus</i>	[121]
Ag@rGO-Fe ₃ O ₄ -PEI	785 nm	<i>E. coli</i>	[122]
rGO-Fe ₃ O ₄ -Au-Ag-Au	785 nm	<i>E. coli</i>	[123]
Ag/ZnO/rGO	808 nm	<i>E. coli</i>	[124]
Fe ₃ O ₄ -CNT-PNIPAM	808 nm	<i>E. coli</i> and <i>S. aureus</i>	[125]
BP/Au	808 nm	<i>E. faecalis</i>	[129]

Quantum dots

Quantum dots (QDs) have garnered increasing

attention as another kind of promising photosensitizers due to their ease-of-synthesis, favourable dispersibility in water, and widely controllable optical properties. Currently, QDs mainly include metal-based (Cd, Pb, and In) semiconductor QDs, carbon QDs and graphene QDs. However, compared with metal-based semiconductor QDs, carbon QDs and graphene QDs are safer, more sustainable, and more biocompatible for potential biomedical applications [130-132]. Most GQDs exhibit photothermal performance [133]. Recently, it has been reported that GQDs have photodynamic characteristics rather than photothermal effects [134]. Carbon QDs (CQDs) can reportedly generate ROS for PDT applications *via* light absorption [136]. For example, Wei *et al.* [137] synthesized CQDs from citric acid and 1,5-diaminonaphthalene in ethanol using a one-pot solvothermal method (**Figure 10A**), and the *in vitro* antibacterial photodynamic inactivation of both Gram-positive and Gram-negative bacteria are shown in **Figure 10B**.

Single-mode phototherapy

Photodynamic treatment

Photodynamic treatment is a photochemistry-based technology that relies on the generation of singlet oxygen (¹O₂) and ROS under light irradiation

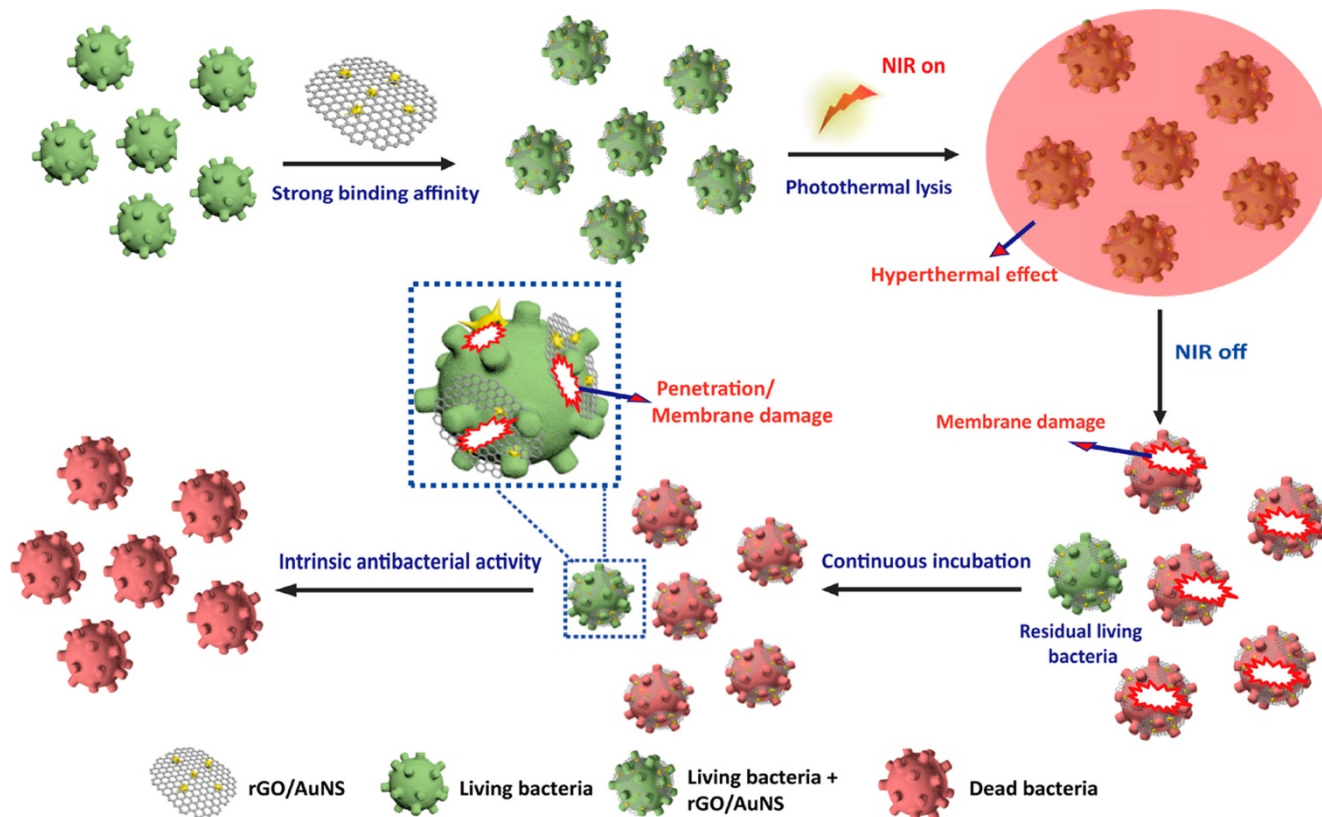


Figure 9. Schematic illustration of 2D reduced graphene oxide supported Au nanostar nanocomposite (rGO/AuNS) triggered antibacterial photothermal lysis [111]. Copyright 2019, ACS publication.

in the presence of photosensitizers and oxygen [138], and has been reported to be effective in killing both Gram-negative and Gram-positive bacteria [139-141]. It is generally believed that photosensitizers can undergo type I (electron transfer) and/or type II (energy transfer) processes to produce highly reactive ROS under light irradiation [142]. Type I processes produce radical and radical anion species (*e.g.*, $O_2^{\cdot-}$, and $\cdot HO$), while type II processes generate 1O_2 [143]. However, antioxidant molecules, for example, glutathione, are present in the complex abscesses site, which could protect bacteria from the toxicity of photodynamic treatment. In addition, the hypoxic microenvironment of an infection site limits the efficacy of oxygen-dependent photodynamic treatment to kill bacteria [144]. Moreover, most existing photosensitizers (*e.g.*, PpIX) often aggregate in aqueous solution because of their large conjugated molecular structures. This aggregation usually results in a lack or low levels of ROS generation due to aggregation-caused quenching, which severely hampers the application of photosensitizers in photodynamic treatment [25]. Herein, Yoon *et al.* found that boronic acid-functionalized phthalocyanine (PcN4-BA) displays an uncommon phenomenon, an aggregation-enhanced photodynamic effect. The combination of the ability to form uniform nanostructured self-assemblies in water, highly efficient ROS generation and boronic acid-induced targeting cause PcN4-BA to exhibit excellent

performances in antimicrobial photodynamic treatment [145].

Photothermal treatment

The mechanism of photothermal antibacterial treatment occurs by producing local high heat through the phototherapy agent, which can cause the irreversible ablation of bacteria by the denaturation of their proteins/enzymes, inhibiting their essential intracellular reactions [146, 147]. Therefore, photothermal nanomaterials have been proposed as a promising solution for the targeted treatment of pathogenic micro-organisms as they are controllable and can be localized to the immediate area surrounding the nanomaterial [148, 149]. Currently, NIR laser-triggered photothermal treatment based on various nanoagents has become one of the most effective antibacterial strategies due to the high spatial resolution and tissue penetration depth of NIR lasers [104, 150]. Additionally, NIR lasers can be focused on a target area to promote blood circulation and relieve inflammation of tissues. However, there are still some limitations to photothermal treatment alone, whose antibacterial effect is restricted by the following issues: 1) high power density and long-term exposure of NIR lasers can damage healthy tissues [151]; 2) it is difficult to kill the heat-resistant bacteria [152]; 3) the phototherapy agent cannot rapidly and effectively eradicate bacteria due to its poor diffusivity [153]. Photothermal treatment-based synergistic therapy

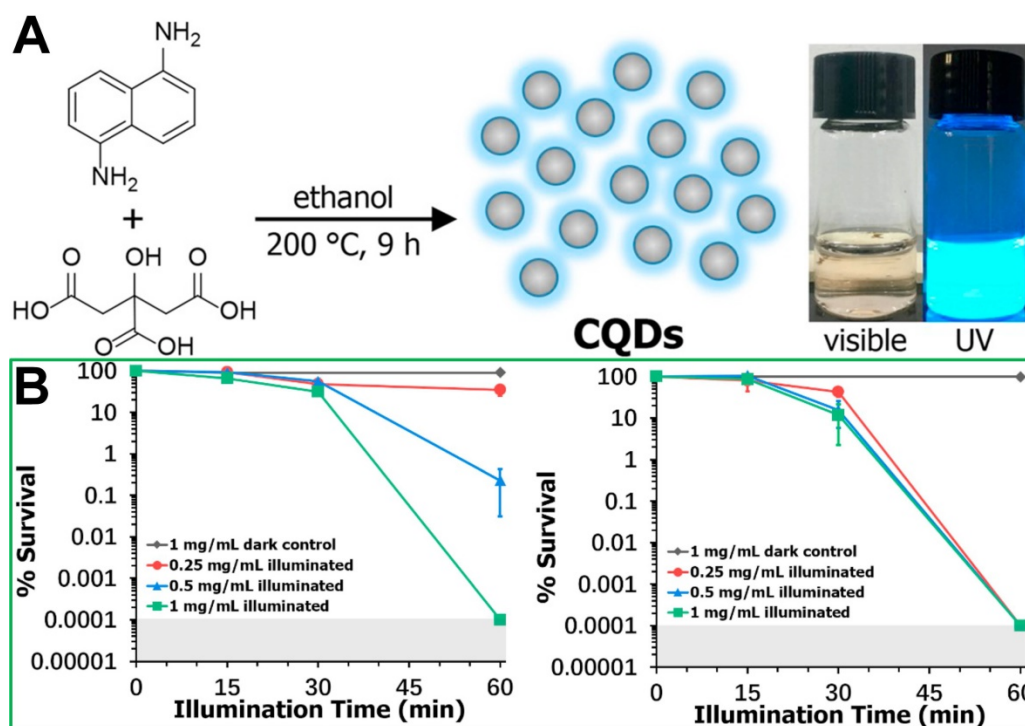


Figure 10. (A) Synthesis roadmap of carbon quantum dots (CQDs) and their appearance as an aqueous suspension under visible and UV light illumination. (B) Concentration and illumination time dependent photodynamic inactivation studies employing CQDs against *S. aureus* ATCC-6538 and *E. coli* 8099 [137]. Copyright 2020, Elsevier.

(e.g., a combination with chemotherapy or gas therapy) is a promising strategy for addressing these limitations and integrates the advantages of single modality approaches to shorten antibacterial time and improve antibacterial efficiency [35].

Advantages and disadvantages of phototherapy

Compared to traditional antibiotic therapy, both photodynamic treatment and photothermal treatment have several advantages in bacterial infections therapy. For example, treatment strategy can be adjusted in a timely manner according to the actual situation since the irradiation site and time can be precisely controlled. Notably, the limited irradiation area can reduce side effects and ensure more locally concentrated energy, which would significantly improve the therapeutic effect. However, despite these advantages, there are still disadvantages. For photodynamic treatment, the high concentrations of glutathione and hypoxic microenvironment at the infection site can limit the efficacy of ROS-dependent photodynamic treatment to kill bacteria. For photothermal treatment, it is difficult to kill the heat-resistant bacteria even when treated at high temperatures such as 45 °C. Moreover, so far, a wide range of the clinical application of single-mode phototherapy is limited due to the poor tissue penetration of light source. Fortunately, the second NIR window (NIR-II, 1000–1700 nm) provides a solution for deep-tissue therapy and diagnosis. Therefore, the development of photosensitizers based on the second NIR window may be the focus of future research.

Combined phototherapy

To address the intractability of bacteria, single-mode therapy is insufficient for clinical use. Phototherapy combined with other therapeutic methods provides a better alternative for infectious therapy through their respective therapeutic advantages.

Combination with chemotherapy

At present, antibiotics used as the main chemotherapy drugs are used in the treatment of bacterial infection [154]. It is well known that oral and intravenous administrations are the two main forms of antibiotic treatment, which may lead to only a small proportion of the drug being concentrated at the site of the lesion, resulting in less effective treatment [44]. In order to maintain the effective treatment concentration of antibiotics at the infected site and ensure the treatment effect, it is often necessary to increase the dosage of drugs or prolong the treatment

cycle. However, large dose or long time of drug use would enhance the harmful effects of drugs in the human body and produce severe side effects. The common toxicity and side effects of antibiotics are shown in **Table 5**, mainly involving the gastrointestinal tract, liver, kidney and other organs. To overcome these difficulties, chemotherapy in combination with phototherapy has been significantly emphasized in many recent studies. Nanosystems offer a clue to solving the drawbacks of chemotherapy while introducing a more advanced therapeutic effect [155–157].

Table 5. The common toxic and side effects of each type of antibiotics

Type	Adverse events
Penicillins	Pain and allergic reactions
Cephalosporins	Allergic reactions
Macrolides	Gastrointestinal side effects, temporary auditory impairment and cardiotoxicity
Tetracyclines	Gastrointestinal side effects and nephrotoxicity
Polymyxins	Nephrotoxicity, allergic reactions and neurotoxicity

Nanoparticles such as AuNPs, graphene, and other polymer nanoparticles capable of photothermal conversion have been designed to deliver antibiotics to the infected sites for achieving chem-photothermal therapy under NIR irradiation [118, 158,159]. These synergetic strategies can not only fully exploit the advantages of enhancing the antibacterial effect, but also reduce the side effects of antibiotics. For example, Liang *et al.* [20] developed a smart biocompatible thermo-responsive-inspired drug-delivery nano-transporter (TRIDENT) for the synergistic eradication of MDR bacteria through combined chemo-photothermal therapy. As shown in **Figure 11A**, under NIR irradiation, the prepared imipenem (IMP)-loaded IR780 TRIDENT (IMP/IR780@TRN) could increase the local temperature to kill the bacteria under NIR irradiation. IMP/IR780@TRN can melted at temperatures above 43 °C, which causes IMP to be released from the NPs and damage the MDR bacteria. Even low doses of IMP-encapsulated TRIDENT could eradicate clinical MRSA according to *in vitro* and *in vivo* evidence. Therefore, this combination therapy strategy can reduce the use of antibiotics to prevent MDR while ensuring efficacy.

In another report, Wu *et al.* [160] designed a chemo-photothermal combination therapy system (PDA NP-Cip/GC hydrogel, abbreviated as Gel-Cip). As **Figure 11B** shows, the phototherapy agent polydopamine (PDA) NPs were firstly used to load the antibiotic ciprofloxacin (Cip) *via* π - π stacking and/or hydrogen bonding interactions, and then the Cip-loaded PDA NPs was mixed with glycol chitosan

(GC) to form an injectable hydrogel through Schiff base reaction and/or Michael addition. Both *in vitro* and *in vivo* evidence confirmed that this combination treatment of Gel-Cip and NIR light irradiation could eradicate both Gram-positive and Gram-negative bacteria.

Combination with chemodynamic therapy

Although chemo-photothermic combined therapy strategies can significantly improve the effect of photothermal treatment and reduce the dosage of

antibiotics, the use of antibiotics has the risk of producing drug-resistant bacteria. To avoid the occurrence of drug-resistant bacteria, and improve the effect of photothermal treatment at the same time, non-antibiotic combined photothermal treatment strategies have been developed. To our best knowledge, the less reactive H_2O_2 can be converted into a highly reactive hydroxyl radical ($\cdot OH$) through the iron-mediated Fenton chemistry, which will cause the oxidative stress and alteration of biomolecules (*e.g.*, proteins and DNA) [161, 162]. It has been

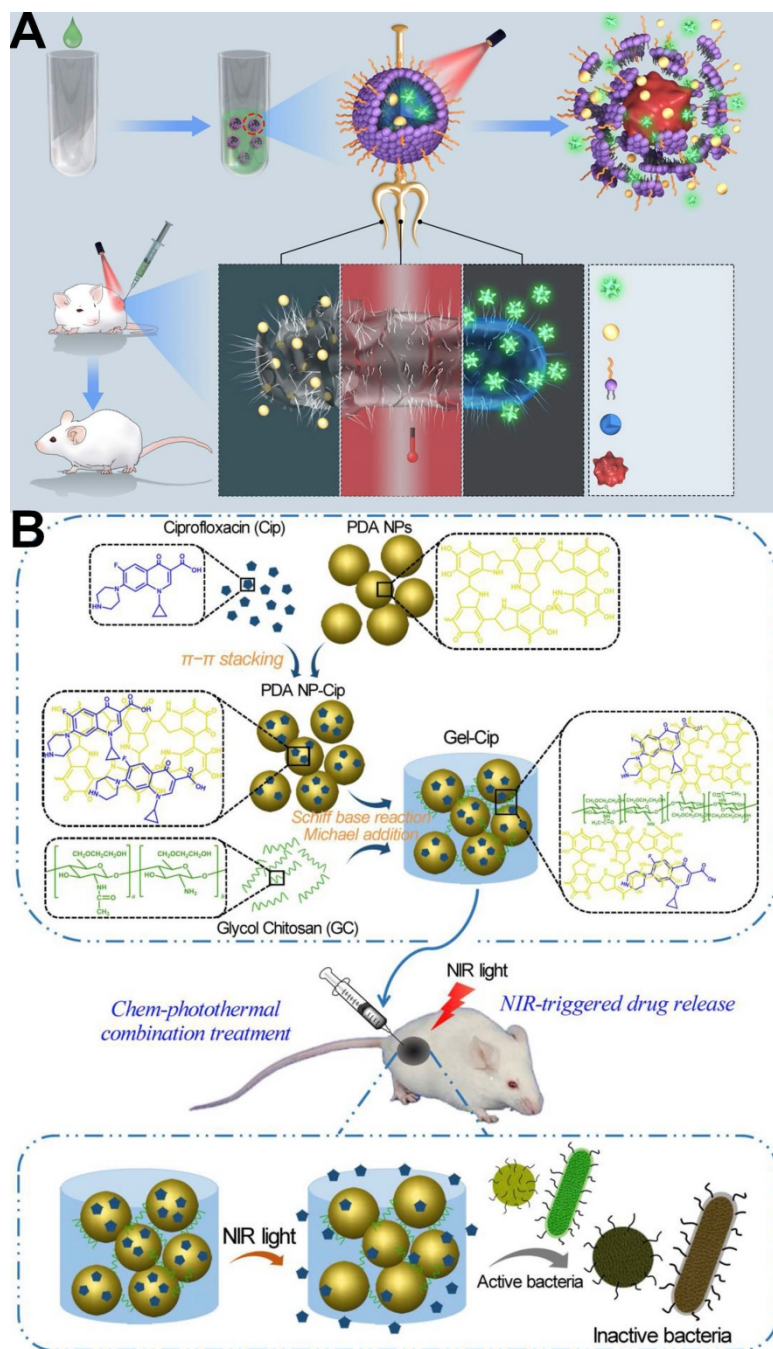


Figure 11. (A) Schematics of NIR-activated thermo-responsive-inspired drug-delivery nanotransporter (TRIDENT) for killing antibiotic-resistant bacteria [20]. Copyright 2019, Nature Publishing Group. (B) Synthetic route of PDA NP-Cip/GC hydrogel and NIR light irradiation-triggered Cip release from PDA NP-Cip/GC hydrogel for bacterial inactivation, Cip: Ciprofloxacin; PDA: Polydopamine; GC: glycol chitosan [160]. Copyright 2019, Elsevier.

discovered that there is a significant overproduction of H_2O_2 in the microenvironment of bacterial infection site [163]. Therefore, the biofilm formation of bacteria could be prevented by applying ferromagnetic NPs to produce $\cdot OH$ [164]. In addition, nanoenzymes are nanomaterials with peroxidase- and oxidase-like properties, and also have been explored as powerful tools to kill bacteria due to their capability to catalyze the formation of ROS [164-167]. For instance, noble metal NPs, such as Au, Pd, and Pt, have attracted extensive attention in the antibacterial field [168-171]. Though this is an inspiring protocol with promising antibacterial outcomes, the existing metal-carrying nanomaterials often have low reaction rates due to the insufficient catalyst ion amount, which results in slow $\cdot OH$ generation and unsatisfactory chemodynamic therapy outcome [172-175]. Therefore, it is necessary to design multimode antibacterial nanomaterials with chemodynamic therapeutic effects. For example, Zhao *et al.* [101] combined catalysis with the NIR photothermal effect and developed a biocompatible antibacterial system based on polyethylene glycol functionalized molybdenum disulfide nanoflowers (PEG-MoS₂ NFs). *In vitro* experiments confirmed that this combination therapy system could provide a faster and more effective kill outcome for Gram-negative ampicillin resistant *Escherichia coli* and Gram-positive endospore-forming *Bacillus subtilis* than chemodynamic treatment or photothermal treatment alone (Figure 12).

In addition, to address the impact of low oxygen content in the infection microenvironment during antimicrobial photodynamic treatment, Liu *et al.* [21]

utilized manganese dioxide (MnO₂), since it could effectively catalyze H_2O_2 conversion into H_2O and O_2 [176, 177] to prepare a photosensitizer (Ce6)-carrying MnO₂ nanometre system (Ce6@MnO₂-PEG NPs). Owing to the ability of MnO₂ to convert H_2O_2 into O_2 , Ce6@MnO₂-PEG NPs could greatly enhance the photodynamic treatment-induced antibacterial efficacy within the oxygen-deficient/ H_2O_2 -enriched environment compared to free Ce6.

Combination with gas therapy

Recently, due to the therapeutic efficiency, mild side effect, and rare chance to induce bacterial MDR, gas therapy has attracted enormous attention in antibacterial applications [178]. Among the gases used, NO is the one that has been most extensively explored due to its multi-antibacterial mechanisms [179, 180], including inhibiting bacterial growth by reacting with bacterial DNA and blocking the repair of damaged DNA, and reacting with ROS to generate reactive peroxynitrite (ONOO⁻) molecules with enhanced bactericidal activity. However, a high concentration of gas can inevitably damage *in vivo* normal tissues [181, 182]. Therefore, photothermal treatment combined with gas therapy formed another kind of strategy for antimicrobial therapy. For example, Gao *et al.* [183] reported a new near-infrared 808 nm laser-mediated NO-releasing nanovehicle (MoS₂-BNN6), that could not only exhibit photothermal treatment efficacy but also precisely control NO release to generate oxidative/nitrosative stress under NIR irradiation ($\lambda=808$ nm). *In vivo* results showed that MoS₂-BNN6 with enhanced photo-

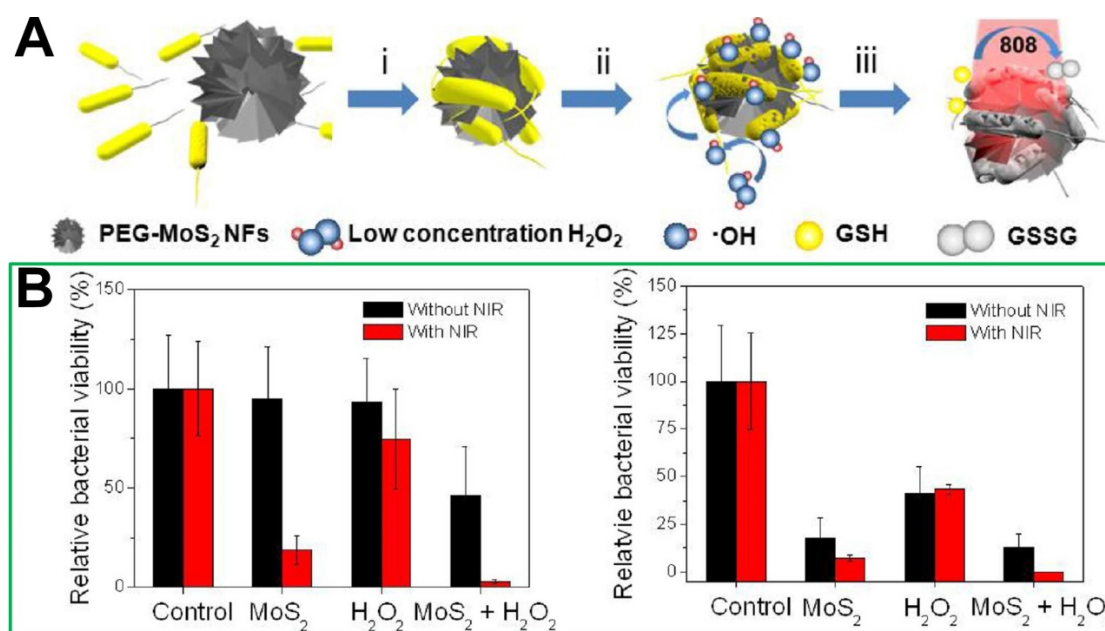


Figure 12. (A) Synthetic route of polyethylene glycol functionalized molybdenum disulfide nanoflowers (PEG-MoS₂ NFs). (B) Relative bacteria viabilities of *E. coli* and *B. subtilis* after incubation with different conditions without or with NIR irradiation [101]. Copyright 2016, ACS Publications.

thermal treatment/NO synergetic antibacterial function achieves >97.2% inactivation of bacteria within 10 min of NIR irradiation, and could also effectively repair wounds through the formation of collagen fibres and elimination of inflammation during tissue reconstruction. Similarly, Cai *et al.* [28] presented an all-in-one phototherapeutic nano-platform AI-MPDA, which includes L-arginine (L-Arg), ICG and mesoporous polydopamine (MPDA) (**Figure 13A**). AI-MPDA not only generated heat but also produced ROS and catalyzed L-Arg to release NO under NIR irradiation, furthermore, the released NO significantly enhanced the therapeutic effects of photodynamic treatment and low-temperature photothermal treatment (≤ 45 °C), contributing to the elimination of bacterial biofilm. Different from NO gas, hydrogen (H_2) can selectively scavenge intracellular ROS without inducing any toxic effect on normal cells even at high concentrations [184, 185], which has been recognized as a green, safe and excellent antioxidant combined photothermal treatment in antibacterial and wound-healing therapies. For example, Xue *et al.* [186] reported a NIR-mediated hydrogen release photothermal agent, PdH nanohydride, which combined both merits of bioactive hydrogen and the photothermal effect of Pd, exhibiting excellent antibacterial activities *in vitro* and *in vivo* due to its synergistic hydrogen-photothermal antibacterial process occurring through oxidative stress and membrane damage pathway.

Additionally, carbon monoxide (CO) has been

considered a potent antibacterial agent against diverse microorganisms [187] *via* the p38-mediated surface expression of toll-like receptor 4 (TLR-4), activation of host immune responses [188], and inhibition of cellular respiration [189]. Furthermore, it even exhibits a high eradication effect on bacterial biofilms [190]. Therefore, CO therapy has been also combined with phototherapy for antibacterial treatment. Cai *et al.* developed a photodynamic treatment-driven CO-controlled delivery system (Ce6&CO@FADP) by the chemical conjugation of Ce6 and physical encapsulation of CORM-401 into peptide dendrimer nanogels [191]. The schematic illustration of the preparation of Ce6&CO@FADP can be found in **Figure 13B**. The *In vitro* antibacterial effect shows that the survival rate of the Ce6&CO@FADP-treated *E. coli* was only 0.5%, which is significantly lower than that achieved by other treatment groups. Therefore, the combination of CO and photodynamic treatment has a good prospect in bacterial infection treatment.

Multiple combination therapy

Because multi-channel antibacterial therapy has good antibacterial effects with the continuous development of nanomedicine, multiple combination therapy strategies have been developed and used in bacterial infection treatment in recent years. The heat induced by photothermal treatment can not only increase the ambient temperature of tissue to achieve antimicrobial efficacy but also increase blood flow and oxygen supply to enhance the 1O_2 generation of photodynamic treatment, and so the multiple

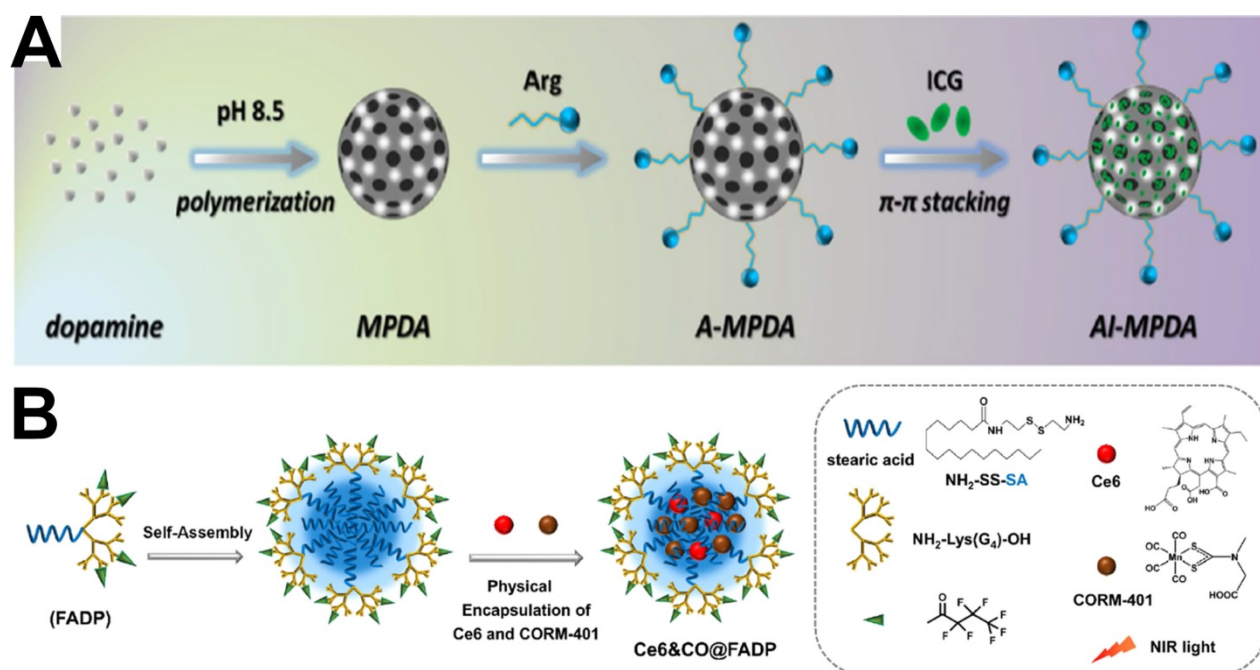


Figure 13. (A) Synthetic route of ICG-loaded L-arginine conjugate mesoporous polydopamine nanoparticles (AI-MPDA) [28]. Copyright 2018, Wiley-VCH. (B) The schematic illustration for the preparation of Ce6&CO@FADP, FADP: fluorinated amphiphilic dendritic peptide [191]. Copyright 2020, ACS publication.

treatment strategy combined with photodynamic and photothermal therapy achieves a better antibacterial effect than that achieved by the individual therapies alone. For example, Zhang *et al.* [135] utilized the intrinsic antibacterial action of chitosan oligosaccharide (COS) and the photodynamic and photothermal properties of graphene quantum dots (GQDs) to prepare COS functionalized GQDs (GQDs-COS) that exhibit multiple synergetic antibacterial activities, and could interact with negatively charged bacterial surfaces *via* electrostatic attraction. Additionally, under 450 nm light irradiation, GQDs-COS could simultaneously kill Gram-positive and Gram-negative bacteria *via* three types of antibacterial activity (photodynamic, photothermal and chemical therapy). In addition, as wound repair is very important in local bacterial

infection treatment, Zhou *et al.* [192] reported hybrid hollow core-shell heterostructured AuAgCu₂O NSs, including a hollow gold-silver (AuAg) core and Cu₂O shell. The AuAgCu₂O NSs have been used as a photothermal therapeutic agent for cutaneous chronic wound and nonhealing keratitis with drug resistant bacterial infection. As shown in **Figure 14**, under NIR irradiation, the silver ion could be released from the hollow AuAg core and cooperate with the photothermal treatment of Au to eradicate MDR bacteria, including extended-spectrum β -lactamase *Escherichia coli* and MRSA. In addition, wound-healing effects could be boosted because of the rapid endothelial cell angiogenesis and fibroblast cell migration achieved by the copper ion released from the Cu₂O shell.

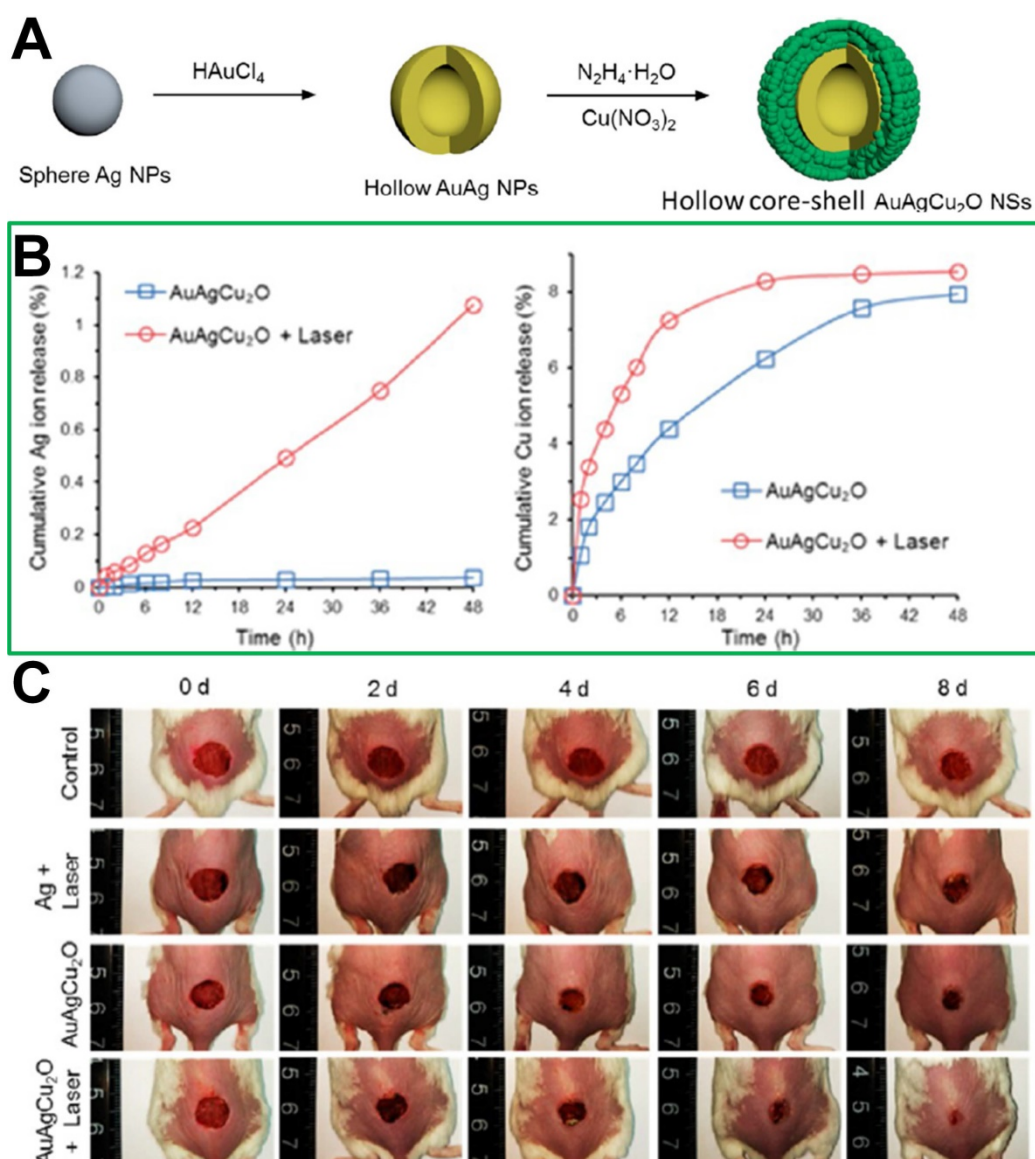


Figure 14. (A) Synthetic route of AuAgCu₂O NSs (a hollow gold-silver (AuAg) core and Cu₂O shell). (B) Cumulative release amounts of Ag and Cu ions from AuAgCu₂O NS hydrogel suspension. (C) Representative macroscopic appearance of MRSA-infected full-thickness dorsal cutaneous incisions on BALB/c mice disposed by diverse treatments [192]. Copyright 2020, ACS publications.

Conclusions and perspectives

Intensive efforts have been devoted to the development of phototherapy-based antibacterial nanomaterials to deal with bacterial infections. In this review, we first summarized recent commonly used phototherapy agents, including organic phototherapy agents (*e.g.*, small molecule photosensitizers and loaded-photosensitizer nanoparticles) and inorganic phototherapy agents (metal nanomaterial, upconversion nanoparticles and quantum dots). Then the advantages and disadvantages of single mode photothermal treatment were analyzed by introducing their specific situations. Moreover, to address the limitations of photothermal therapy in bacterial infection treatment, many combination therapy strategies have emerged, such as combination with chemotherapy, combination with chemodynamic therapy, combination with gas therapy and multiple combination therapy. In particular, combination with chemodynamic therapy and gas therapy can solve the problem of MDR resistance very well due to the lack of antibiotics used in the combination therapy system.

In the future, only very biocompatible antibacterial nanomaterials are promising for potential clinical application. Therefore, although these combined strategies have shown promising results in the treatment of infectious diseases, many important fundamental issues of nanomaterials must be studied in depth and fully elaborated, including the synergistic action mechanisms, accumulation of lesions, metabolic pathways and toxicities toward vital organs. More importantly, before designing nanomedicine, it is necessary to consider how to use them in patients (*e.g.*, intravenous injection, oral, subcutaneous injection or spray). Additionally, for deep tissue infection, phototherapy cannot be used unless the site of infection has been identified, which severely limits its clinical use in antibacterial infections treatment. Moreover, a consensus has been reached among researchers worldwide that the patient survival rate can be greatly increased if the disease is effectively diagnosed and treated at the early stage [193, 194]. Based on this investigation, Wang *et al.* reported a magnetic nanosystem combined with photodynamic treatment, which could identify bacterial species for early sepsis diagnosis and extracorporeal photodynamic blood disinfection [29]. Therefore, designing a phototherapy-based nanoplatform with integrated diagnosis and treatment abilities is a very promising strategy to address bacterial infections and should have good imaging capabilities (*e.g.*, magnetic resonance imaging, fluorescence imaging, ultrasound, etc.) at the

infected site to accurately guide light to the site, to prevent toxicity to normal tissues during the phototherapy process.

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Competing Interests

The authors have declared that no competing interest exists.

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