Review

Recent Advances in Combating Bacterial Infections by Using Hybrid Nano-Systems

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Abstract: In recent years, antimicrobial resistance in many human pathogens has become a serious health concern. Since infections with resistant pathogens cannot be treated with traditional antimicrobial drugs, new strategies are necessary to fight bacterial infections. Hybrid nano-systems may provide a solution to this problem, by combining multiple mechanisms for killing bacteria to synergistically increase the effectiveness of the antimicrobial treatment. In this review, we highlight recent advances in the development of hybrid nano-systems for the treatment of bacterial infections. We discuss the use of hybrid nano-systems for combinational therapy, focusing on various triggering mechanisms for drug release and the development of biomimetic nanomaterials. We also examine inherently antimicrobial nano-systems and their uses in preventing infections due to wounds and medical implants. This review summarizes recent advances and provides insight into the future development of antimicrobial treatments using hybrid nanomaterials.

Keywords: stimuli-triggered nano-systems; hybrid nano-systems; biomimetics; bacterial infections

1. Introduction

While antimicrobial agents have shown great success in combating bacterial infections, bacterial infections are still a major global health concern. A recent study of healthcare burdens estimated that, in 2019, 7.7 million deaths worldwide were caused by bacterial infections [1]. Several challenges remain in combatting bacterial infections, such as bacterial evasion of the host immune system, physiological barriers to drug delivery, and the severe side effects of some antibiotics. One of the most significant challenges in this regard is the development of antimicrobial resistance (AMR) in many different types of bacteria. While AMR occurs naturally in bacteria due to genetic variability, bacterial AMR has become more prevalent due to the strong selective pressure caused by the widespread overuse of antimicrobial treatments in clinical, industrial, and agricultural settings [2]. In a recent study from *The Lancet*, it was estimated that in 2019 there were 4.95 million deaths worldwide associated with AMR [3]. For these reasons, the World Health Organization lists AMR as one of the top ten global public health threats [4].

Traditional antimicrobial treatments rely on a variety of mechanisms to kill or inhibit the growth of pathogenic bacteria. Many of these mechanisms target essential processes in the microbe, such as the synthesis of proteins and nucleic acids, while other mechanisms target key structural components of the bacterial cell, such as the cell wall or cell membrane [5]. Many mutations can confer AMR by changing how the bacterial cell interacts with the antimicrobial agent. The main mechanisms by which a mutation imparts resistance are the inactivation of the antibiotic, the modification of the antibiotic target site, or the alteration of bacterial membrane permeability to the antibiotic [5,6]. Because AMR bacteria can no longer be treated with traditional antibiotic strategies, new treatments must be developed that evade AMR.

Nanoparticles have been suggested as potential therapeutic agents for combatting AMR [7–9]. Undoubtedly part of the attraction of antimicrobial nanomaterials relates to the

difficulty of bacteria developing resistance to their mechanism of action; however, there remain obstacles to the use of antimicrobial nanomaterials for clinical applications. For example, some researchers have indicated that microbes can develop "nanoresistance", allowing them to evade treatment by nanoparticles [10]. Another concern is the potential for inorganic nanomaterials to show toxicity to host cells. To improve the biocompatibility of nanoparticles, hybrid nano-systems have been developed, which combine the desirable properties of inorganic nanoparticles with biocompatible materials, such as liposomes or polymers.

In this review, we will discuss recent advances in the use of hybrid nano-systems as antimicrobial agents, highlighting how these hybrid nano-systems can be used to treat AMR bacteria as shown in Scheme 1. We will first discuss the use of nanomaterials as drug carrier systems, which combine the antimicrobial activity of various drugs with various endogenous or exogenous triggers, allowing for controlled drug release. We will also discuss biomimetic nano-systems, which increase biocompatibility and allow for targeted treatment of infections. Then, we will discuss inherently antimicrobial nano-systems, which combine the antimicrobial properties of metals with various external stimuli to achieve antimicrobial activity.
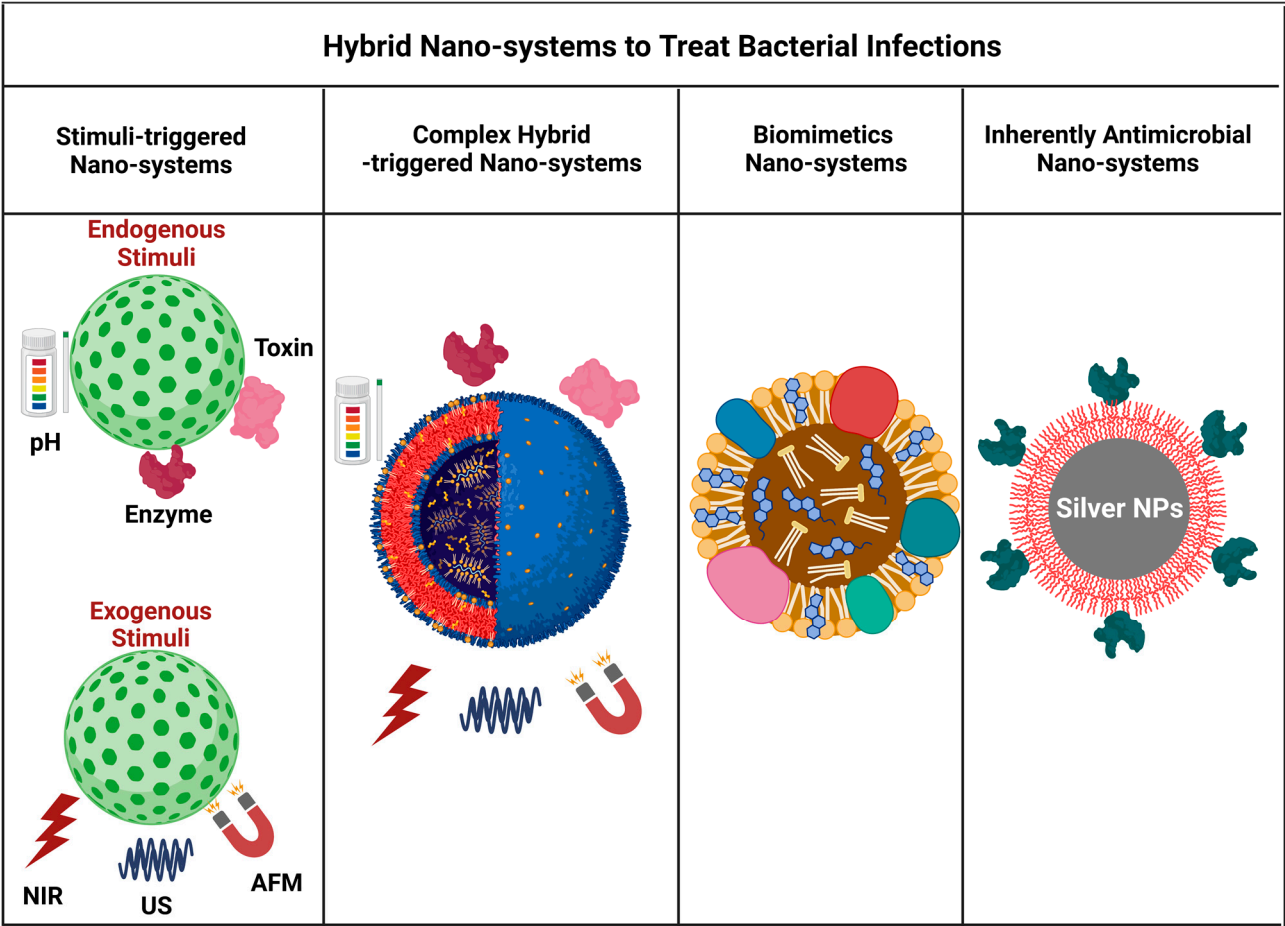
Scheme 1. Schematic of hybrid nano-systems used to combat antimicrobial resistance.

2. Hybrid Nano-Systems for Combinational Therapy

Stimuli-responsive hybrid nano-systems, a combination of metallic inorganic nanoparticles with "soft matter" drug delivery systems such as liposomes, polymers, and hydrogels, have been developed in recent years. This approach shows great potential for providing a targeted release of antibiotics in response to specific environmental cues. Inorganic nanoparticles, including metal, mesoporous silica, and quantum dots, are increasingly being used

as vehicles for delivering antibiotics [11]. By incorporating inorganic nanoparticles into soft matter systems, a range of unique benefits can be achieved. This approach combines the desirable drug delivery features of traditional vehicles, including excellent colloidal stability, ease of fabrication, biocompatibility, and high drug-loading capacities, with innovative stimuli-responsive mechanisms for releasing antibiotics that are imparted by the inorganic nanoparticles [12]. When combined, inorganic nanoparticles and traditional drug delivery systems offer a straightforward and adaptable method to create unique antibiotic release mechanisms that respond to stimuli. This can lead to a boost in the effectiveness of antimicrobial treatments. In this review, we aim to fill the gap in the existing literature by discussing the creation of innovative antibiotic delivery systems that respond to stimuli. This is achieved by co-formulating inorganic nanoparticles with soft matter drug delivery systems (Table 1).

2.1. Stimuli-Triggered Drug Delivery

In order to achieve smart therapeutic responses, drug delivery systems can be influenced by external or internal stimuli to enhance their antibiotic activity. This can result in controlled release of the payload in the specific biological compartment, as well as prompt treatment of the pathological event. The following sections provide a detailed explanation of each individual stimulus. It covers the hybrid nanomaterials for combinational therapy against bacterial infections, which includes delivery systems triggered by endogenous or exogenous stimuli and hybrid nano-systems reported in the literature for the treatment of bacterial infections.

2.1.1. Drug Delivery Triggered by Endogenous Stimuli

Nanomaterials that respond to endogenous stimuli can effectively utilize the unique changes that occur in the microenvironment of certain diseases, such as inflammatory conditions, bacterial infections, and tumors. This principle has been the inspiration for the development of many chemical stimuli-responsive nanomaterials. Microorganisms have a particular microenvironment surrounding them, and many microbial lesions exhibit low pH levels, the secretion of distinctive bacterial enzymes, and bacterial toxins. One can create highly effective and multi-purpose stimuli-triggered nano-systems by utilizing environmental cues.

A highly effective drug delivery nano-system exists that responds to pH levels and can combat harmful microbes including *Helicobacter pylori*, *Listeria*, *Salmonella*, *Campylobacter rectus*, *Escherichia coli*, and *Shigella flexneri* [13]. These microbes are known to thrive in acidic environments within the body, including the stomach (pH 1.0–2.0), vagina (pH 4.0–5.0), skin (pH 4.0–5.5), intestines (pH 5.0–8.0), and bladder (pH 4.5–8.0) [14]. The lining of the stomach, also known as the stomach mucosa, is highly susceptible to the harmful effects of the spiral bacterium *H. pylori*. This bacterium is linked to the development of gastritis, gastric ulcers, and associated forms of cancer. When treating *H. pylori* infection, antibiotics are often paired with proton pump inhibitors (PPIs) to lessen the production of gastric acid. This is necessary as gastric acid can decrease the effectiveness of antibiotics. PPIs are effective due to their binding to proton pumps, which helps in reducing acid secretion. However, prolonged use can lead to several adverse effects like headaches and diarrhea, and in severe cases, anxiety or depression. Therefore, it would be advantageous to develop an alternative treatment with equivalent or better therapeutic efficacy compared to current antibiotic treatments, without the need for PPIs. A new micromotor made of magnesium (Mg) and covered with a pH-sensitive polymer coating has been reported by Li et al. [15]. A micromotor, made of Mg and gold coated with Au, can temporarily neutralize stomach fluid acidity in vitro and in vivo [15]. Its payload is encapsulated within a pH-sensitive polymer layer, and when in an acidic environment, Mg reacts with the acids to produce hydrogen bubbles, propelling the motor and reducing protons [15]. These artificial motors can neutralize gastric pH in under 20 min, modifying the surrounding area without interfering with the proton pumps' function [15]. This method has minimal effect

on stomach function, ensuring no undesirable outcomes compared to conventional PPIs. Recently, Song et al. have reported the first design of an active drug combination therapy for treating *H. pylori*, which is based on self-propelled micromotors with a magnesium/gold Janus structure as shown in Figure 1 [16]. These micromotors can penetrate the mucus layer, deliver amoxicillin and clarithromycin simultaneously, and release these antibiotics in a pH-responsive manner [16]. The self-propelled micromotors improve antimicrobial efficiency and offer a promising future for active treatment of bacterial infections due to their self-propulsion, biocompatibility, and biodegradability [16].
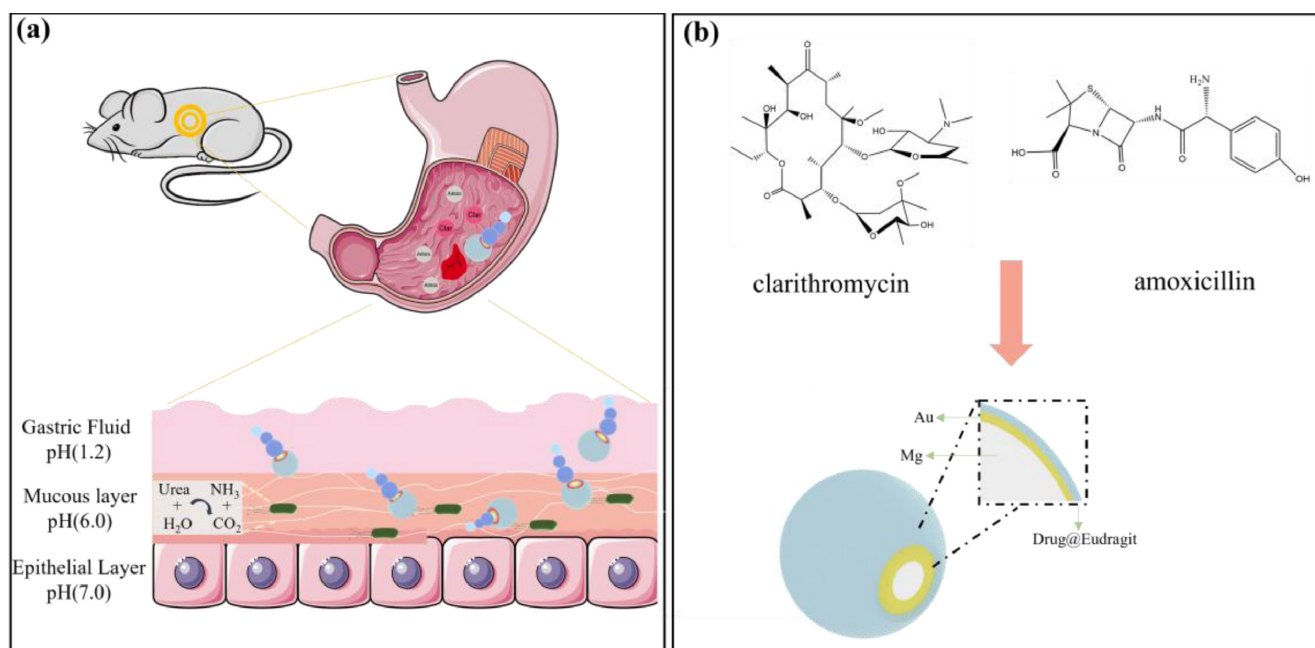

Figure 1. (**a**) Schematic illustration of in vivo propulsion and drug delivery of Mg/Au/Eur micromotors in a mouse stomach. (**b**) Drug-loaded Mg/Au/Eur micromotor. Adapted with permission from Ref. [16]. Copyright 2020, Applied Materials Today.

Bacteria surfaces contain numerous physiological and molecular cues that can be harnessed for effective targeting purposes. *H. pylori* uses urea transport proteins located on its membrane to transport urea into the cytoplasm, ultimately enabling the urease enzyme to generate ammonia. This is crucial for the bacterium, as it serves as a protective mechanism against the highly acidic environment of the stomach. The Zhang group conjugated urea to chitosan through two different linkages, resulting in urea-modified chitosan derivative UCCs-2. This derivative served as a targeting moiety to the urea transport channel protein UreI of *H. pylori* and was used as a targeting ligand on pH-sensitive bilayer PLGA/UCCs-2 nanoparticles. In achieving optimal results for the eradication of *H. pylori*, a variety of chitosan (CS) microparticles and NPs loaded with antibiotics were utilized by Zhang group [17–20]. Another method of targeting the bacterial surface is through electrostatic targeting, which makes use of the negative charge of the bacterial surface. A considerable number of bacteria exhibit a negative surface charge at physiological pH levels, making them susceptible to targeting through the use of commonly available ligands like cationic peptides or lipopeptides [21–23]. These compounds operate by interacting with and damaging the cell membranes of bacteria [24,25].

Pathogenic bacteria have various virulence factors that enable them to colonize, invade, and replicate in immune-competent hosts. Along with negatively charged surfaces and pH gradients, these factors include bacterial toxins, fibronectin proteins, and collagen adhesins, as well as a range of enzymes such as phosphatase, phospholipase, and lipase [26]. A straightforward approach to pinpointing the infection location involves adding a complementary substrate or antibody to the surface of the antibiotic delivery vehicle. As the

enzyme breaks down the substrate, it punctures the carrier and releases the antibiotic close to the site of infection. In the past ten years, several nano-systems have been developed that are sensitive to hyaluronidase [27], phosphatase [28], and lipase [29,30], which have been utilized to deliver antibiotics in synchronization to infection sites. Rathnayake et al. have developed a novel method for delivering antibiotics within cells as shown in Figure 2 [31]. They utilized mesoporous silica nanoparticles that were loaded with colistin (Col) and coated with a bacteria-targeting peptide called LL-37, which was conjugated on the liposomal shell. The liposomal shell was used to prevent premature drug release before the nanoassembly approached the targeted bacteria. Upon encountering lipase in the local environment of *P. aeruginosa*, the liposome bilayer degrades and releases the encapsulated Col. In comparison to free Col, Col@MSN@LL-(LL-37) showed a significant 6.7-fold rise in antimicrobial effectiveness. The researchers found that this approach effectively inhibited the growth of *P. aeruginosa*, in vitro for both planktonic and intracellular infections [31].

Table 1. Hybrid nanomaterials for combinational therapy against bacterial infections.

Nanomaterials	Trigger	Target Pathogen	Drug	Active Targeting	Ref.
		Endogenous Triggered DDS			
PLGA-PLH-PEG nanoparticles	pH	*S. aureus* *E. coli*	Vancomycin	Electrostatic	[21]
Squalenoylated penicillin bioconjugates	pH	*S. aureus*	β-lactam antibiotics	NA	[32]
Chitosan-modified gold nanoparticles, liposome	pH	*H. pylori*	Doxycycline	NA	[17]
Mesoporous silica nanoparticles, pH-sensitive nanovalves	pH	*F. tularemia*	Moxifloxacin	NA	[33]
Ureido-conjugated chitosan/TPP multifunctional nanoparticle	pH	*H. pylori*	Amoxicillin	Ureido targeting groups	[18]
Triblock polymers PEG-b-PCL-b-PAE	pH	*S. aureus*	Vancomycin	Electrostatic	[22]
Mg-based micromotor	pH	*H. pylori*	pH-sensitive polymer coating	NA	[15]
Mg-based micromotor	pH	*H. pylori*	Ciprofloxacin	NA	[34]
Solid lipid Np	pH	MSSA, MRSA	Vancomycin	NA	[35]
AMX-PLGA/UCCs-2 nanoparticles	pH	*H. pylori*	Amoxicillin	UCCs-2 as targeting moiety	[20]
Cysteine conjugated chitosan/PMLA	pH	*H. pylori*	Amoxicillin	NA	[19]
AMP (LL37) and lipid (OA) self-assembly	pH	*E. coli*	LL 37	Electrostatic	[24]
Antimicrobial peptide-reduced gold nanoclusters	pH	*E. coli, P. aeruginosa, S. aureus, S. epidermidis*	Antimicrobial peptide	Electrostatic	[25]
Hyaluronic acid (HA)-based nanocapsules	Enzyme (hyaluronidase)	*S. aureus, E. coli*	Polyhexanide	NA	[36]
Chitosan-modified gold nanoparticles (AuChi-liposome)	Enzyme (phospholipase A2)	*H. pylori*	Doxycycline	NA	[28]

Table 1. *Cont.*

Nanomaterials	Trigger	Target Pathogen	Drug	Active Targeting	Ref.
PGA and Bla-responsive polymeric vesicles	Enzyme (penicillin Gamidase (PGA) and b-lactamase (Bla)	MRSA, *B. longum*, *L. acidophilus, and E. faecalis*	Vancomycin, gentamycin, quin-upristin/dalfopristin (Synercid)	NA	[37]
MSNP/LIPID bilayer	Enzyme (Lipase)	*S. aureus*	Gentamycin	Bacteria-targeting peptide ubiquicidin (UBI29–41)	[29]
Monoolein liquid crystal nanoparticles (MO-LCNPs)	Enzyme (Lipase)	*P. aeruginosa*, *S. aureus*	Rifampicin Ciprofloxacin	NA	[30]
Gold nanoparticle-stabilized phospholipid liposomes.	Alpha-toxin	MRSA	Vancomycin	NA	[38]
Liposome-based nanoreactors	Alpha-toxin	MRSA	Rifampicin	NA	[39]
Exogenous Triggered DDS					
Hollow microspheres (HMs) shell PLGA Core-Van, polypyrrole nanoparticles	PPT (808 nm, 0.5 W/cm^2, 15 min)	*S. aureus* (subcutaneous bacterial abscesses)	Vancomycin	NA	[40]
Reduced graphene oxide (rGO)-embedded polymeric nanofiber mats	PPT (980 nm, 1 W/cm^2, 10 min)	*E. coli* K12 *S. aureus* *S. epidermidis*	Ampicillin cefepime	NA	[41]
PDA-PEG-Van	PPT (808 nm, 0.78 W/cm^2, 10 min)	MRSA	Vancomycin		[42]
Vancomycin (Van)-modified gold nanostars	PPT	MRSA	Vancomycin	Vancomycin	[43]
Bubble liposomes	US (0.15 or 0.44 W/cm^2)	*C. trachomatis*	Doxycycline ceftizoxime	NA	[44]
Microbubble-mediated low-intensity ultrasound	US (100 mW/cm^2; 46.5 KHz; 33% duty cycle; 12 h)	*E. coli*	Gentamycin	NA	[45]
Dextran sulfate-shelled perfluoropentane (PFP)-cored NBs	US (f = 2.5 MHz; P = 5 W; t = 10 min)	MRSA	Vancomycin	NA	[46]
microbubble suspension	US (1.1 MHz, 2.5 Mpa, 5500 cycles at 20 ms pulse duration) for 20 s	UTI (*E. faecalis*)	Gentamycin	NA	[47]
(Pd@Pt-T790)	US	MRSA	T790 as sonosensitizer	NA	[48]
iron oxide nanoparticles (NPs) encapsulated into polymeric microspheres	Magnetic	*S. aureus*	ciprofloxacin	NA	[49]

Table 1. *Cont.*

Nanomaterials	Trigger	Target Pathogen	Drug	Active Targeting	Ref.
$MnFe_2O_4$ superparamagnetic nanoparticles, pegylated chitosan as shell	Magnetic	*S. aureus* *S. epidermitis,* *B. subtilis, E. coli,* *P. aeruginosa,* and MRSA	Vancomycin	NA	[50]
Iron oxide nanoparticles	Magnetic	*S. aureus, B. subtilis,* *E. coli*, and *P. aeruginosa*	Gentamicin	NA	[51]
Fe_3O_4 nanoparticles, chitosan microbeads cross-linked with varying lengths of polyethylene glycol dimethacrylate	Magnetic	*S. aureus*	Vancomycin	NA	[52]
MNPs@Ag@HA	Magnetic	*S. aureus, E. coli* *S. aureus* biofilm	Gentamicin	NA	[53]
Hybrid Nano-systems					
MNP Eudragit®S100	pH Magnetic	*H. pylori*	Amoxicillin	NA	[54]
SiO_2-Cy-Van	Bacteria-activated polyelectrolyte dissociation	MRSA	Vancomycin conjugate poly(acrylic acid)	Vancomycin	[55]
Amphiphilic block copolymer consisting of biotinylated poly(ethylene glycol)-b-poly(β-amino ester)-b-poly(ethylene glycol) grafted with PEGylated lipid (Biotin-PEG-b-PAE(-g-PEGb-DSPE)-b-PEG-Biotin)	pH, enzyme	*P. aeruginosa,* (Sepsis)	Ciprofloxacin, and an anti-inflammatory agent (2-[(aminoc-arbonyl)amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide, TPCA-1)	Intercellular adhesion molecule-1 antibodies	[56]
Amphiphilic poly (ethylene glycol)–poly(ε-caprolactone) (PECL) copolymers,	pH, enzyme (Lipase)	*P. aeruginosa*	Ciprofloxacin	Vancomycin as targeting ligand	[57]
Amp-MSN@FA@CaP@FA	pH	*E. coli, S. aureus*	AMP	Folic acid	[58]
Multimetallic microparticles (MMPs), PLGA, AgNP, ZnO NP	NA	*M. tuberculosis*	Rifampicin	NA	[59]
MSN, PGEDA, CB [7], TPE-(COOH)$_4$	NA	*S. aureus, E. coli*	Amoxicillin	Electrostatic	[60]
Mesoporous silica nanoparticles decorated with polycationic dendrimers	NA	*E. coli*	Levofloxacin	Electrostatic	[61]
DAP-GCS-PDA@GNRs	pH, PPT 808 nm laser (0.5 W/cm^2) for 0–8 min	MRSA	Daptomycin (DAP)	Electrostatic	[62]
Porous silicon np, CARG peptide identified by phage library	NA	*S. aureus,* *P. aeruginosa*	Vancomycin	CARG Peptide	[63]

Table 1. *Cont.*

Nanomaterials	Trigger	Target Pathogen	Drug	Active Targeting	Ref.
Fusogenic pSi nanoparticle system (F-pSi)	NA	*S. aureus*	siRNA	Macrophage-targeting peptide (F-siIRF5-CRV)	[64]
Au@AgNP@SiO$_2$@Nc-Van	PTT, (780 nm, 30 mW/cm^2 for 30 min)	Van-sensitive *B. subtilis*, Van-resistant *E. faecium*, *E. faecalis*, *E. coli*	Vancomycin	NA	[65]
TRIDENT, natural fatty acid, lecithin, DSPEPEG2000, IR780	PTT (808 nm, 0.5 W/cm^2)	MDR *S. aureus* *E. coli* (Sepsis)	Imipenem	NA	[66]
Black phosphorus quantum dots (BPQDs) and thermal-sensitive liposome	PTT (1 W, 808 nm, 15 min)	MRSA	Vancomycin	NA	[67]
AA@Ru@HA-MoS	Enzyme, PTT (808 nm, 0.5 W/cm^2 for 7 min)	*S. aureus* and MDR *P. aeruginosa*	Pro drug ascorbic acid	Ciprofloxacin as a catalyst with targeting effect	[68]
Lipid–dendrimer hybrid nanoparticles (LDH-NPs)	pH	MRSA	Vancomycin	Electrostatic	[69]
Maltohexaose-decorated cholesterol and bacteria-responsive lipid compositions, a smart nanoliposomes platform (MLP18)	Enzyme, US	MRSA	Purpurin 18 as sonosensitizer	Bacteria-targeting maltohexaose	[70]
Metal–organic frameworks (MOFs)/antibiotics	pH	*S. aureus*	Tetracycline	Hyaluronic acid (HA) targeting	[71]
P(HEMA-co-DMA) as templet, Van-OA@PPy	PTT (808 nm, 1.0 W/cm^2 for 5 min)	MRSA	Vancomycin	Vancomycin conjugated oleic acid	[72]
AIE fluorophore TTD, Micelle	White light irradiation (250 mW/cm^2)	*M. tuberculosis*	Rifampicin	TTD targeting	[73]
D-TiO$_2$/Au@UCN nanocomposites.	PTT (980 nm laser 0.68 W/cm^2)	*E. coli* and MRSA	Ampicillin	NA	[74]
Ison@Man-Se NPs		*M. tuberculosis*	Isoniazid	Mannose targeting	[75]

Pathogenic bacteria secrete virulence factors known as bacterial toxins, which are highly sophisticated proteins that can disrupt cellular membranes or act intracellularly with a high level of specificity for their target cells. One such toxin is α-toxin, a pore-forming toxin secreted by *S. aureus* [76]. α-toxin disrupts the cellular membrane by forming pores, which alters the permeability of the membrane [77]. The small pores, measuring approximately 2.5 nm in size, enable water, ions, and small molecules to pass through without control. This can lead to the rapid release of vital molecules like ATP, loss of membrane potential and ionic gradients, and irreversible swelling due to osmosis, ultimately resulting in cell lysis [78,79]. These pore-forming toxins can be exploited in the targeted treatment of bacterial infections to avoid ligand off-target problems and any damage to normal cells. Wu et al. have developed a new method using phase-changing materials (PCMs) for treating bacterial infections using toxin pore-formation activity as an endoge-

nous stimulus to deliver drugs and control their release. This system utilizes lipids as a gate material to coat a eutectic mixture of two fatty acids. Encapsulating calcium peroxide (CaO_2) and rifampicin into the eutectic mixture forms liposome-based nanoreactors that can release drugs in response to toxins. When these nanoreactors encounter pathogenic bacteria in vivo, they are penetrated by bacterial toxins, creating pores. Water molecules then enter the nanoreactors through the pores and react with CaO_2 to produce hydrogen peroxide (H_2O_2). At the same time, some of the H_2O_2 breaks down into oxygen which powers the release of antibiotics. Additionally, the nanoreactors stimulate the body's immune response by capturing bacterial toxins and reducing their toxicity. This process significantly improves the therapeutic effect on bacterial-infected mice [39]. In another interesting approach, bacterial toxins were utilized to trigger antibiotic release from liposomes stabilized with gold nanoparticles, which subsequently inhibited the growth of toxin-secreting *S. aureus* bacteria [38]. Chitosan-modified gold nanoparticles attached to liposome surfaces improve their stability and prevent drug leakage. However, bacterial toxins can still penetrate the liposome membrane and form pores, through which the drug is released to combat the toxin-secreting methicillin-resistant *S. aureus* (MRSA) and other bacterial infections. This method shows promise in treating various bacterial infections caused by pore-forming toxins.

2.1.2. Drug Delivery Triggered by Exogenous Stimuli

Nanomaterials with the ability to react to external physical stimuli such as light, ultrasound, and magnetic fields have demonstrated significant potential in precisely delivering therapeutic agents. This is achieved by utilizing the unique optical, magnetic, and physiochemical properties of metallic inorganic NPs. These smart materials, which respond to exogenous stimuli, can control drug release. Numerous strategies have been explored to formulate these nano-systems with multiple functionalities, a lower degree of variability, and high precision in order to address the pressing need for on-demand and targeted drug delivery for bacterial infections.

Light is often used as a trigger for the development of responsive drug delivery systems that utilize frequencies in the ultraviolet, visible, or near-infrared (NIR) [80]. NIR-triggered systems have received attention for applications in treating in bacterial infections as well as in cancer research [80–87]. NIR-responsive materials are usually called photothermal agents. Photothermal heating occurs due to the absorption of light by an ensemble of electrons on the surface of certain conductive materials and the subsequent dissipation of that energy as heat. Plasmonically active metal NPs such as Au NPs, Ag NPs, and Cu NPs, black phosphorus, carbon tubes, and polydopamine nanoparticles are particularly powerful photothermal agents because of their large absorption cross sections, tunable optical properties, and highly efficient light-to-heat conversion [88]. In such metallic NPs, most of the energy gained by the electrons during photo-excitation at this resonance is dissipated as heat, through electron–photon collisions, leading to the heating of the NPs and the surrounding environment. Photothermal heating can either be used to deliver thermal energy to a localized area or, alternatively to the entire drug carrier, causing the destruction of the capsule material and triggering the release of the drug from the charged therapeutics [89,90]. Some early demonstrations of the use of photothermal effects to release antibacterial agents from drug carriers have been reported in a number of research studies [40–42]. Wang et al. developed a new strategy for effective control and killing of Gram-positive bacteria based on vancomycin (Van)-modified gold nanostars (AuNSs). The Van-modified AuNSs (AuNSs@Van) can not only selectively detect MRSA, but also kill MRSA in vitro under near-infrared laser irradiation (808 nm for 10 min, 2.5 W/cm^2) [43]. In addition, AuNSs@Van shows satisfactory biocompatibility and antibacterial activity in treating bacterial infections in vivo. The attractive feature of AuNSs@Van is that it can actively attack the Gram-positive bacteria by binding to the D-Ala D-Ala moiety of the cell wall of the Gram-positive bacteria and anchoring to the surface of the bacteria [91,92].

Subsequently, irradiation with an NIR laser produces hyperthermia in situ, which leads to the death of bacteria.
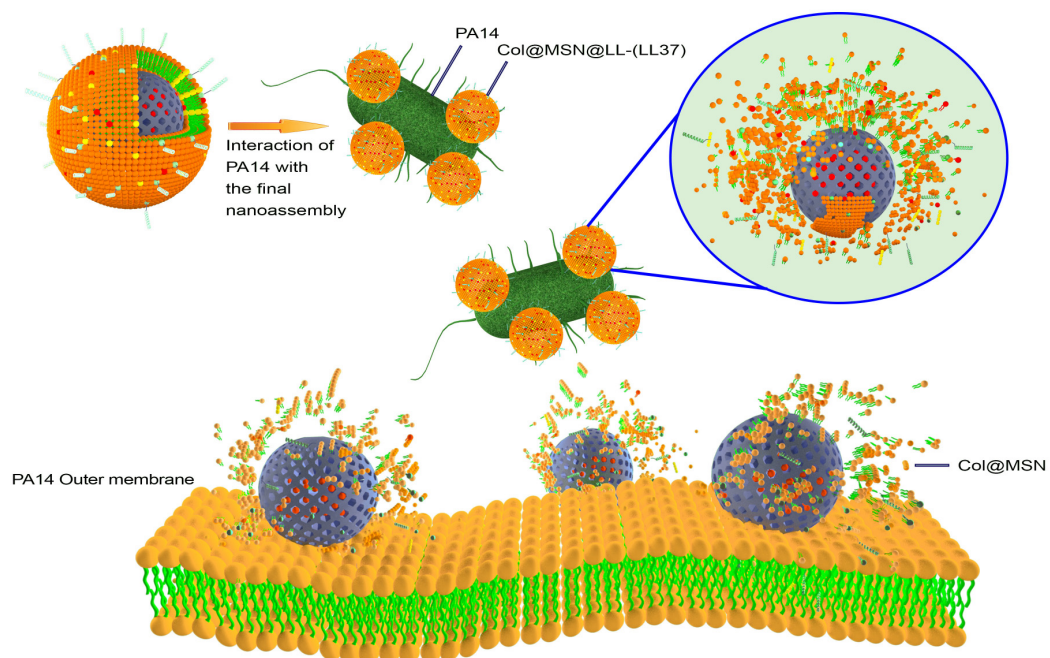
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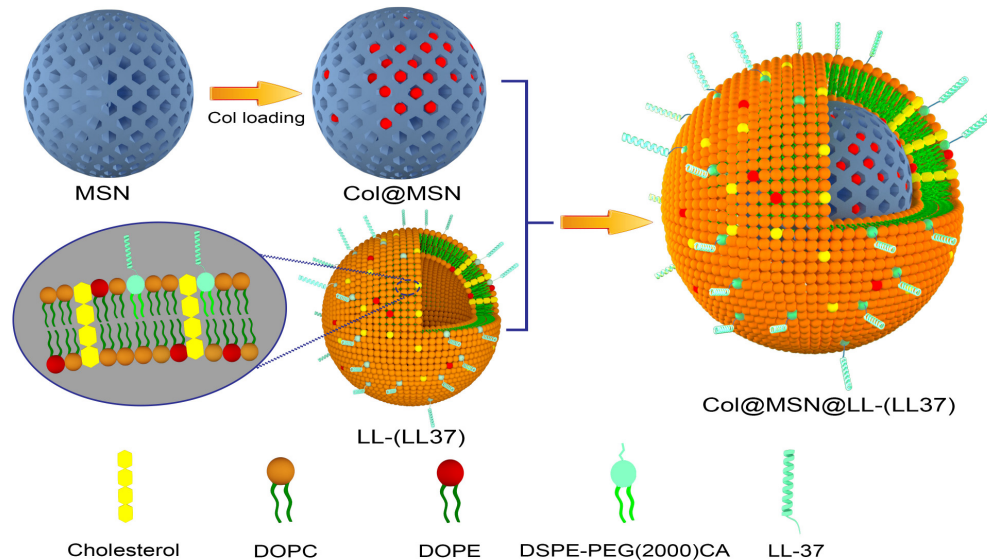
b.

Figure 2. (**a**) Synthetic route of Col@MSN@LL-(LL-37), final nanoassembly. (**b**) Hypothetical mechanism of the action of Col@MSN@LL-(LL-37) upon interaction with PA14. Adapted with permission from Ref. [31]. Copyright 2020, American Chemical Society.

Recently, Patel et al. have reported the gold nanorod-based hybrid liposomal nanosystem to combat intracellular bacterial infections as shown in Figure 3 [93]. Gold nanorods act as a photothermic agent, which is then coated with mesoporous silica that provides a surface for drug loading. This entire nanoassembly is then wrapped in a thermosensitive liposome that was functionalized with a mycobacteria-targeting peptide. The bacteria-

targeting nano-system specifically targets the mycobacteria and then, upon exposure to NIR light, converts the NIR light to heat, causing the heat-sensitive liposome to melt and release the drug in a controlled manner [93].
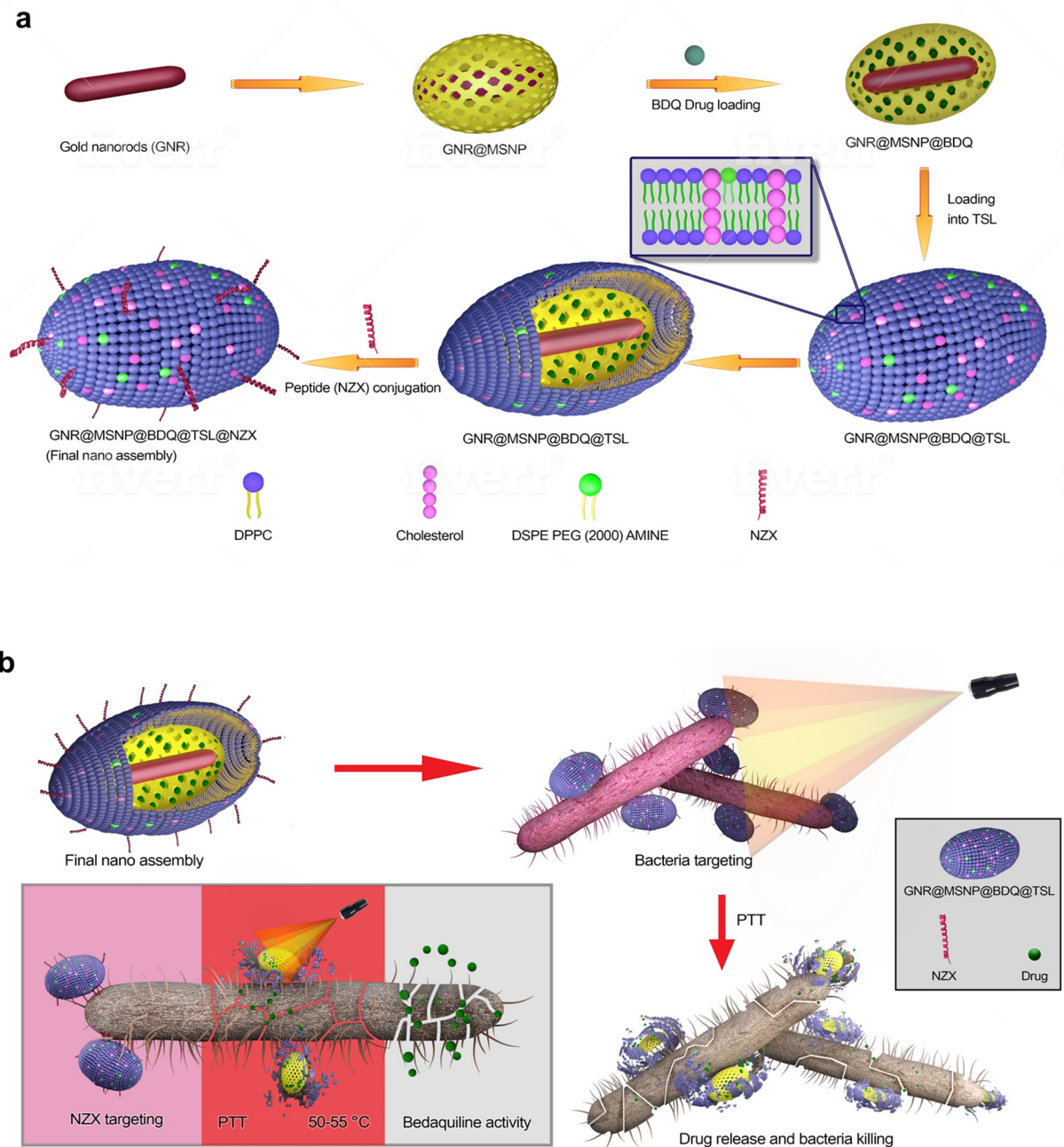

Figure 3. (**a**) Schematic illustration of stepwise synthesis of the final nano-assembly: (**b**) Application of final nano-assembly: GNR@MSNP@BDQ@TSL@NZX for targeting and killing Msmeg using 808 nm NIR laser light. Adapted with permission from Ref. [93]. Copyright 2020 Nano select Wiley.

In addition to photothermal therapy, ultrasound (US)-based drug delivery systems have gained importance in treating bacterial infections. Sonodynamic therapy (SDT) is a novel US-based modality that responds to ultrasonic stimulation and activates sonosensitizers to produce reactive oxygen species (ROS), cavitation, gas bubbles, hyperthermia, etc. [94]. The precise mechanism by which SDT works remains unresolved due to the complexity of the SDT process but possible theories include the generation of ROS [95], ultrasonic cavitation effect [96], and thermal destruction [97,98]. The most acceptable mechanism at present is ROS production induced by cavitation or sonosensitizers, which causes

apoptosis. US at a frequency of 0.8–3 MHz is an external stimulus that is used for diagnostic and therapeutic purposes [99]. US can be used at low frequency to diagnose a disease or at high frequency to treat a disease by responsive drug delivery. When designing a US-mediated delivery system, three main criteria must be considered. These are: (1) high drug loading capacity, (2) effective drug release after exposure to a specific US frequency, and (3) the ability to monitor drug release for imaging and therapeutic applications [100]. US can be used for drug delivery and to increase drug permeability through biological barriers by increasing the temperature and creating a cavitation bubble [101]. Ultrasound-activated microbubbles/nanobubbles are one attractive intracellular delivery modality solution for various bacterial infections such as *Chlamydia trachomatis* [44], *E. coli* [45], MRSA wound infections [46], and *Enterococcus faecalis* intracellular urinary tract infections (UTI) [47]. Gas bubbles stabilized by a polymer or surfactant coating have been in clinical use as ultrasound imaging contrast agents for over two decades [102]. Once introduced into the body, the passage of the microbubbles/nanobubbles can be easily monitored by diagnostic imaging, while drug delivery is achieved through the application of a higher intensity ultrasound pulse to the target site, thereby limiting side effects elsewhere. The movement of the microbubbles in response to ultrasound not only releases the drug but also helps promote its convection into surrounding tissue and the permeabilization of cell membranes, through a process known as sonoporation. The combination of these phenomena enhances both the distribution of the drug throughout the target site and its intracellular uptake [47,103]. Xin Pang et al. used purpurin 18 as a potent sonosensitizer and loaded it into a bacteria-responsive nanoliposome platform for precise diagnosis and SDT of multidrug-resistant (MDR) bacteria, as shown in Figure 4 [70]. The nanoliposomes (MLP18) consist of purpurin 18, maltohexaose-modified cholesterol, and dioctadecanoyl-sn-glycero-3-phospho-(1-racglycerol) (DSPG). Maltohexaose-modified cholesterol shows bacterial specificity through the maltodextrin transporter pathway; in addition, DSPG is susceptible to bacterial overexpression of phospholipase A2 (PLA2). As a result, the as-synthesized MLP18 enables bacterial targeting and the release of PLA2-activated sonosensitizers. Importantly, this also allows bacterial infections to be distinguished from aseptic inflammation caused by lipopolysaccharide (LPS). Subsequently, due to considerable bacteria-specific drug accumulation, MLP18 showed an excellent sonodynamic effect on MDR bacteria in vitro and completely inhibited bacterial infections in vivo by US irradiation [70]. Another interesting study on nanoparticle-mediated SDT for acne was published by Xiang et al. They reported the development of a sodium hyaluronate microneedle patch that facilitates the transdermal delivery of ultrasound-responsive nanoparticles for the effective treatment of acne [104]. The patch contains nanoparticles made of a zinc porphyrin-based metal–organic framework and zinc oxide (ZnTCPP@ZnO). They demonstrated activated oxygen-mediated killing of *Propionibacterium acnes* with an antibacterial efficiency of 99.73% after 15 min of ultrasound irradiation, resulting in a decrease in levels of acne-related factors such as tumor necrosis factor, interleukins, and matrix metalloproteinases [104]. Furthermore, zinc ions increased the expression of DNA replication-related genes, promoting fibroblast proliferation and, as a result, skin repair. Through the interface engineering of ultrasound response, this research leads to a highly effective acne treatment strategy.

Finally, magnetic stimuli-responsive drug delivery systems were first developed by Freeman in 1960 [105]. The use of magnetic force is safer than light irradiation, ultrasound, or electrical fields because it does not physically interact with the body. Magnetically guided systems have been widely explored for cancer diagnosis/therapy [106], as a drug delivery vehicle for bacterial infections/biofilms, and as diagnosis tools [107,108]. Magnetic nanoparticles (MNPs) have been encapsulated in shells made of functionalized polymeric microspheres [49], PEGylated chitosan [50], or chitosan microbeads [51,52]. These MNP-based nano-systems have been extensively used to load various antibiotics such as ciprofloxacin, vancomycin, and gentamycin have been widely investigated for their potential to penetrate into bacteria cells, which may inactivate bacteria and antibiotic-resistant bacteria [49–52,109]. MNPs show great potential as magnetic drug delivery

systems, which can control the movement and location of antibiotics, resulting in a rapid, and efficient treatment specifically for biofilms [110]. In one study by Alwarze et al., magnetic hyperthermia together with controlled antibiotic delivery was used to create a unique magnetic-responsive nanocarrier for combination therapy against biofilms [111]. The antibiotic-loaded mesoporous silica nanoparticles (MSNs) were functionalized with a thermo-responsive polymer layer and decorated with super-paramagnetic iron oxide nanoparticles (SPIONs) on the outermost surface. When an alternating magnetic field (AMF) is applied, the SPIONs generate heat, reaching the temperature required to induce a change in polymer conformation from linear to globular, resulting in pore uncapping and antibiotic cargo release. According to the findings of their study, combining hyperthermia and antibiotic treatment is a promising approach for the effective management of biofilm-associated infections [111].
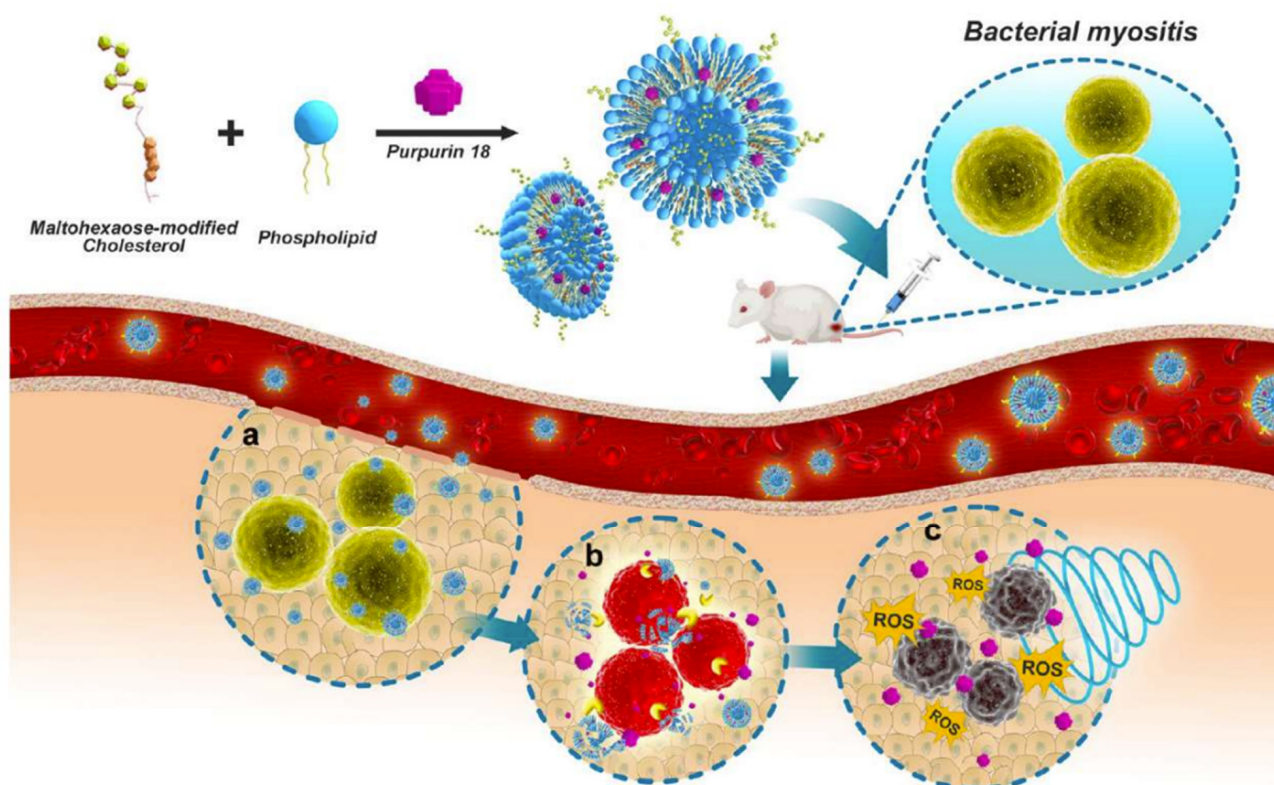

Figure 4. Scheme illustration of MLP18 nanoliposomes for diagnosis and eradiation of MDR bacterial infection. Taking advantage of the bacteria-specific maltodextrin transporter pathway, MLP18 after intravenous injection selectively navigates to the bacterial infection site (**a**). Afterward, the oversecreted PLA2 enzyme in bacterial infection microenvironment effectively degrades the lipid skeleton of MLP18, activating an efficient release and internalization of sonoensitizer into bacteria. Due to the excellent optical properties of P18, the bacteria show an obvious NIR FL/PA signal, changing from yellow to red (**b**). Upon ultrasound irradiation, cytotoxic ROS are generated and then mediate bacterial death (**c**). Adapted with permission from Ref. [70]. Copyright 2020, American Chemical Society.

2.2. Complex Hybrid Triggered Nano-Systems

In order to combine the unique properties of organic and inorganic NPs in one nanoplatform, a number of hybrid nanocomposites have been developed in recent years. The advantage of designing complex hybrid nano-systems is that multiple different stimuli can be accommodated in a single package [112]. This requires the use of different stimuli-responsive linkers with two or more nano-systems. These hybrid nano-systems offer numerous opportunities to selectively target and kill intracellular MDR bacterial

infections. Intracellular MDR bacterial infections are very difficult to treat because they evade the host's immune system [113]. Researchers have developed strategies to treat intracellular MDR bacterial infections using hybrid nano-systems, specifically focusing on (1) targeting bacteria directly, (2) targeting the infectious microenvironment (IME), and (3) targeting host cells (macrophages).
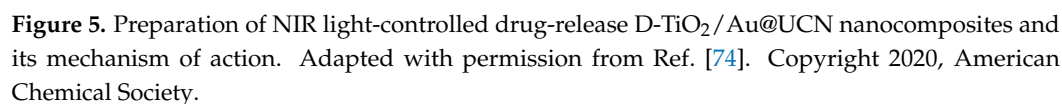
Targeted delivery of antibiotics to bacteria would be a novel strategy to reduce antimicrobial resistance since the drug dosage is low. However, most antibiotics lack the ability to act in a targeted manner. Recent advances in nanotechnology allow investigators to load drugs inside nanoparticles, and simultaneously, nanoparticles can be conjugated with a cationic polymer/ligand [61,62] or with a targeting peptide [63,64] to recognize specific bacterial infections. Hussain et al. proposed in vivo screening of *S. aureus* in a lung infection model to identify a targeting ligand that specifically recognizes *S. aureus* and could thus improve antibiotic delivery at sites of infection [63]. In their studies, they found that the nine-amino acid long cyclic peptide CARGGLKSC (CARG) was able to increase vancomycin release after the peptide was conjugated to vancomycin-loaded porous silicon nanoparticles, thereby significantly enhancing mouse survival during bacterial lung infection and decreasing the systemic toxicity of vancomycin. It is interesting to note that the CARG peptides bound specifically to *S. aureus* and not to *P. aeruginosa* in vitro. This result is consistent with in vivo studies in the lungs and skin of *S. aureus*-infected mice compared to results in healthy mice and *P. aeruginosa*-infected mouse models. These studies demonstrate the potential of targeting pathogens directly at the site of the infection using nanoparticles to improve antibiotic bioavailability at infectious sites, potentially preventing antimicrobial resistance caused by antibiotic overdose administration.

Hybrid strategies for targeting the IME include dual endogenous stimuli-responsive nano-systems (e.g., pH/enzyme) [56,57] and endo/exogenous stimuli-responsive nano-systems, which utilize pH/magnetic [54], pH/PTT [62], enzyme/PTT [68], and enzyme/US [70] triggers. The codelivery of an antibiotic and an anti-inflammatory agent to the site of infection was proposed as a novel strategy for sepsis therapy, to diminish the bacteria and the inflammation response simultaneously [56]. Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection, particularly bacterial infection. Two major factors are involved in the pathogenesis of sepsis: (1) invading pathogens and (2) activation of the host's immune system. When bacteria enter the body, the host's immune system is activated to eradicate invading bacteria by recruiting macrophages that recognize lipopolysaccharides on a Gram-negative bacterium via toll-like receptors. Macrophages also release pro-inflammatory cytokines (such as TNF-, IL-1, etc.), that activate endothelial cells lining the blood vessels to increase the expression of intracellular adhesion molecules (ICAM-1) for the recruitment of leukocytes to eliminate bacteria [114–116]. Based on this observation, Zhang et al. designed a novel polymer nanoparticle coated with ICAM-1 antibody to target the affected vasculature [56]. The nanoparticles were designed to be broken down by the IME in response to the low pH and bacterial enzymes, triggering drug release. An antibiotic and an anti-inflammatory agent were loaded into the polymeric micelle core through hydrophobic interactions. Finally, the anti-ICAM-1 antibody was applied to the surface of the polymeric micelles. It is expected that the multifunctional polymeric micelles can simultaneously eliminate the bacteria and attenuate the inflammatory responses caused by the bacterial invasion. In an infectious lesion, the activated endothelium strongly expresses ICAM-1 molecules and vascular permeability is increased. After intravenous injection, antibody-coated nanoparticles can recognize and bind to the infected vasculature to facilitate the deposition of NPs at the site of infection. The nanoparticles then release the charged drugs in response to the acidity and bacterial enzymes present in the IME. Zhao et al. have reported a nano-system responsive to pathogen infection that targets the endoplasmic reticulum of macrophages [117]. The nanoplatform consists of large-pore mesoporous silica nanoparticles (MSNs) grafted with an endoplasmic reticulum-targeting peptide and a pathogen infection-responsive cap containing the ROS-cleavable borobenzylic acid linker and bovine serum albumin [117]. The capped MSNs

demonstrated the ability to efficiently load the antimicrobial peptide melittin and rapidly release the load when triggered by H_2O_2 or the pathogen–macrophage interaction system, but had no apparent toxicity to macrophages. In a murine model of systemic infection, the nanoplatform efficiently prevented renal dysfunction, alleviated inflammatory symptoms, and protected the mice from death. This study developed a nanoplatform that targeted macrophage organelles to treat life-threatening systemic infections [117].

Antimicrobial resistance is associated with bacterial survival inside host cells [113], because the cells have low permeability to antibiotic entry that leads to chronic and re-current infections [118,119], including pulmonary infections [120], endocarditis [121], and osteomyelitis [122]. Thus, targeting intracellular bacteria may be a key to clinical success. In addition, targeting phagocytes is a smart route for the targeted delivery of antibiotics to infectious lesions. Macrophages are important scavenger cells that remove bacteria. However, sometimes the elimination of the bacteria is not complete, which can lead to chronic infections. One of the main features of tuberculosis (TB) pathogenesis is the escape of *Mycobacterium tuberculosis* (Mtb) from phagolysosomal destruction. Pi et al. studied a macrophage-targeted mannosyl–selenium nanoparticle hybrid nano-system (Man-Se NPs) to deliver isoniazid to the intracellular Mtb [75]. The authors synthesized Man-Se NPs for macrophage targeting and encapsulated isoniazid in the nanoparticles. The hybrid system Ison@Man-Se NPs could be used for the synergistic treatment of TB. Mtb can survive in host cells because the intracellular drug concentration is limited, and Mtb escapes destruction by phagolysosomes. Ison@Man-Se NPs promote the fusion of Mtb in lysosomes to initiate innate immunity against lysosomal destruction of Mtb, and isoniazid release is accelerated to allow more effective direct Mtb killing in lysosomes. Ison@Man-Se NPs also promote autophagosome formation to initiate innate immunity for Mtb sequestration by autophago-some lysosomes. Finally, Ison@Man-Se NPs regulate macrophage polarization and cytokine production of host cells to trigger innate immunity for Mtb antibacterial M1 inhibition. This macrophage-targeted nanomaterial-assisted synergistic bactericidal strategy with broad innate immunity functions and remarkably low cytotoxicity could potentially serve as a more effective therapeutic against tuberculosis and multidrug-resistant tuberculosis [75].

Hybrid nano-systems consisting of a combination of photothermal therapy [66,67,72], photodynamic therapy [65], and antibacterial properties are widely used to combat MDR bacterial infections [65–67,72]. Xu et al. developed an effective hybrid nano-platform to treat ampicillin-resistant MRSA [74]. The NIR-active (980 nm laser (0.68 W cm^2)) photocatalytic platform was composed of a shell structure of upconversion nanocrystals (UCN) decorated on an Au/dark TiO$_2$ core as shown in Figure 5. The heart of this system is the strong photocatalytic activity in the visible region enabled by gold surface plasmon resonance on dark TiO$_2$ (DTiO$_2$). Simulation and experiment show a greatly increased light absorption in the visible range for an optimized Au/D-TiO$_2$ combination. Using ampicillin sodium (AMP) as a model drug, the authors illustrated the effective use of this principle by demonstrating NIR light-triggered photocatalytic payload release. Importantly, the photocatalytically generated ROS can effectively inactivate AMP-resistant bacterial strains, thus maintaining an antibacterial effect even after full drug release. A major advantage of this strategy is the long-lasting secondary antibacterial effect arising directly from photogenerated ROS, which was sufficient to significantly destroy drug-resistant bacteria. Importantly, this NIR light-triggered system is effective in the biologically transparent window for mammalian tissue and is therefore able to inactivate bacteria even through 2 mm of skin tissue. Overall, the authors believed that this NIR light-active photocatalytic cascade can greatly expand TiO$_2$-based photocatalysis and its applications in destroying microorganisms resistant to antibiotics and heat [74].

Figure 5. Preparation of NIR light-controlled drug-release D-TiO$_2$/Au@UCN nanocomposites and its mechanism of action. Adapted with permission from Ref. [74]. Copyright 2020, American Chemical Society.

Considering exogenous stimuli-reactive drug delivery, sonodynamic therapy using ultrasound waves is now proving to be a promising approach to eradicate bacterial infections [123]. Antimicrobial sonodynamic therapy (aSDT) relies on the interaction of low-frequency ultrasound (US) and a nontoxic sonosensitizer to generate ROS that are highly cytotoxic in virtually all bacteria without concern for resistance [123]. Compared to photo/hyperthermia-induced antibacterial therapies that are limited to skin lesions [124–127], aSDT takes advantage of superior tissue penetrability and non-

invasiveness of ultrasound, showing great potential in deeply seated diseases [128,129]. Sun et al. developed a Pd@Pt-T790 nanoplatform to combat MRSA-induced myositis by using Pd@Pt nanoplatelets to act as sonosensitizer carriers, effectively delivering not only a sonosensitizer (T790) to the lesions but also providing the sonosensitizer with rich oxygen through the nanozyme activity of the nanoplatelets [48]. Noble metal nanoparticles (NPs) such as Au, Pd, and Pt act as nanozymes to produce ROS, resulting in remarkable antibacterial activity against both Gram-negative and Gram-positive bacteria [130–134].

Even more remarkable, the modification of Pd@Pt with a sonosensitizer significantly blocked the catalase-like activity of Pd@Pt, whereas, upon US irradiation, nanozyme activity was effectively restored to enhance oxygen generation for catalysis. Such blocking and activating enzyme activity has been particularly important for reducing the potential toxicity and side effects of nanozymes on normal tissues and has the potential to realize active, controllable, and disease-site-specific catalytic behavior of nanozymes. The Pd@Pt-T790-based SDT hybrid nano-system took advantage of this US-switchable enzyme activity, excellent accumulation at infection sites, as well as excellent biocompatibility, and could be successfully applied to eradicate MRSA-induced myositis. Furthermore, SDT could be used simultaneously for non-invasive monitoring by photoacoustic imaging and magnetic resonance imaging. The developed US-switchable nanozyme system offers a promising strategy to actively, controllably, and precisely enhance the sonodynamic eradication of deep-seated bacterial infections [48].

2.3. Biomimetic Nano-Systems

Due to the biocompatibility, toxicity, and stability issues of existing nanoparticles, new nanotherapeutics approaches are still needed. Effective drug delivery systems must allow for long-term in vivo retention, controlled and targeted cargo release, immune escape, the shielding of cargo from rapid degradation, and the ability to cross specific barriers in vivo [133–135]. Hence, various bioengineering and biomimetic strategies have been applied, whereby cell membranes are isolated and used to coat NP cores for drug delivery and vaccine development [136]. In an effort to replicate mammalian physiology, there have been many recent efforts to produce biomimetic systems better suited to in vivo drug delivery. One of the most prominent approaches to NP functionalization relies upon the use of cell membrane coating [137]. Cell membrane coating technology is a simple top-down approach that utilizes the cell membrane as a carrier, facilitating the undetected targeted delivery of core NPs without specific regard to the properties of the inner core nanomaterial. As the membrane coatings are structurally and functionally similar to those of host cells, they can express specific markers useful for appropriate NP delivery [135].

Such cell biomimetic approaches include efforts to replicate the surface composition, shape, and movement of normal cellular physiology [138]. NPs coated with cell membranes could offer dual solutions, as translocated cell membranes could easily perform the function of the natural cell membrane, due to the successful transfer of membrane proteins along with the surface chemistry of lipid bilayer, effectively camouflaging the NPs. For example, CD47, an integral membrane protein expressed on red blood cells (RBCs) and platelets, functions as a "do not eat me" signal that prevents macrophage-mediated clearance from circulation [135]. When NPs are encompassed in a natural cell membrane, additional external modifications are no longer required. To date, cell membrane coating approaches have sought to mimic the surfaces of bacteria, cancer cells, platelets, RBCs, stem cells, and leukocytes. This coating strategy has been explored in fields including drug delivery, vascular injury repair, tumor imaging, optical therapy, detoxification, and immunotherapy [135].

These biomimetic nanoparticles possess multiple advantages, such as the diversity, tunability, and reproducibility of synthetic nanomaterials, as well as the functionality, complexity, and biocompatibility of biological materials. Due to their intrinsic activity, nature-inspired nanoparticles themselves can function as effective nanotherapies or nanovaccines against infectious diseases. Alternatively, they may serve as advanced nanocarriers for

site-specific delivery of therapeutics or vaccines [136]. Additionally, a localized drug delivery within target cells may be obtained by biomimetic surface functionalization of these nanocarriers with specific biological ligands or moieties similar to the combination and functionality of external cell membranes. There are two main types of biomimetic drug carriers: (1) existing biological entities, like inactivated viral vectors and bacteria vectors, and (2) synthetic drug carriers, which are engineered biomimetic nanoparticles with properties similar to biological materials. It should be noted that the second type is safer for in vivo therapeutic applications [139].

In this review, we summarize recent advances in membrane-cloaked nanoplatforms to mimic the natural entities in biological fluids ranging from inherent host cells (e.g., erythrocytes, leukocytes, platelets, and exosomes) to invasive pathogens (e.g., bacteria and viruses) based on cell membrane-mimicking and pathogen-mimicking strategies for the management of infectious diseases through of drug delivery, vaccination, detoxification, and immune modulation strategies (Table 2). These approaches provide excellent means for an in-depth exploration of how nanomedicine interacts with the surrounding environment and how to optimize the structures of nanomaterials for improved theranostics in vivo [137].

Zhang et al. have reported the coating of plasma membranes of gastric epithelial cells onto clarithromycin-loaded polymeric cores, which showed superior therapeutic efficacy towards *H. pylori* in an infected mouse model when compared with the free drug counterpart as well as a non-targeted nanoparticle control group [140]. Yang et al. demonstrated antibiotic-loaded polymeric nanoparticles coated with the membrane of an extracellular vesicle secreted by *S. aureus* as an active-targeting antibiotic carrier to alleviate metastatic infection in an *S. aureus* bacteremia-bearing mouse model. They also confirmed that these biomimetic nanoparticles were internalized at higher efficiency by *S. aureus*-infected macrophages than by the naive counterpart and confer their cargoes with strikingly improved efficacy in kidney and lung, which bear the highest metastatic bacterial burden and represent the most common sites for *S. aureus* infection [141]. Another biomimetic approach described by Zhang et al. was the use of polymeric nanoparticles coated with the membrane of intact red blood cells. These biomimetic nano-systems act as nanosponges that absorb and neutralize toxins, such as bacterial virulence factors associated with numerous bacterial infections. These biomimetic nanosponges were used to treat severe MRSA infections, such as MRSA bacteremia and MRSA-induced sepsis. This study shows that, more significantly, inhibition of toxins prevents infection through nonbactericidal pathways and therefore is expected to pose less selective pressure for resistance development. Using a mouse model, in vivo studies further demonstrate that, by neutralizing the hemolytic activity, RBC-NS confer significant survival benefits against whole-secreted protein-induced lethality [142]. Green et al. have reported the use of biodegradable polymeric nanoparticles coated with red blood cells to circulate through the blood for extended periods of time while also acting as a detoxification device, specifically to detoxify the bacterial pore-forming toxin, α-toxin, from the blood in a mouse model of sepsis. They have shown that the anisotropic shape and membrane coating synergize to resist cellular uptake and reduce clearance from the blood while enhancing drug delivery efficacy [143].

Table 2. List of Biomimetic nano-systems for treatment of bacterial infections.

Drug Delivery NP	Biomimetic Membrane	Pathogen	Drug	Ref.
Polymeric cores	Plasma membranes of gastric epithelial cells	*H. pylori*	Clarithromycin	[140]
Polymeric nanoparticles, poly(lactic-co-glycolic acid) (PLGA) nanoparticle	Membrane of extracellular vesicle secreted by *S. aureus*	*S. aureus*	Vancomycin (Van) and rifampicin (Rif)	[141]

Table 2. *Cont.*

Drug Delivery NP	Biomimetic Membrane	Pathogen	Drug	Ref.
Polymeric nanoparticles	Red blood cells	MRSA	N/A	[142]
Polymeric nanoparticles	Red blood cells	Bacterial pore-forming toxin	N/A	[143]
	Neutrophil membrane-coated nanoparticles	MRSA	Sparfloxacin (SPX)	[144]
Gold nanoparticle	Bacteria outer membrane	*E. coli*	N/A	[145]
BSA nanoparticles	Hollow outer membrane vesicles of bacteria	Carbapenem-resistant *K. pneumoniae*	N/A	[146]

Zhang et al. have reported the use of neutrophil membrane-coated nanoparticles loaded with sparfloxacin (SPX) in the treatment of inflammation because neutrophils can participate in various inflammatory responses and accumulate at inflammatory sites to eliminate pathogens. These neutrophil membrane-coated nanoparticles (NM-NP-SPX) possessed precise targeting ability and, just like naturally occurring neutrophils, could accumulate at inflammatory sites when the inflammation bursts. Through in vivo experiments, they have found that the concentration of three representative inflammatory cytokines in blood, bacteria, and inflammatory cells in the lungs of the mice with pneumonia was reduced significantly in the initial 24 h after the injection of NM-NP-SPX, which meant that NM-NP-SPX could greatly reduce the risk of death for patients with inflammation [144]. Another interesting approach is biomimetic nanoparticle-based vaccine systems that have been developed to better manipulate immune responses and potentially enhance antimicrobial immunity. Zhang et al. have published an article about biomimetic NPs in which a bacterial outer membrane-coated gold nanoparticle system is used as a new and exciting antibacterial vaccine. They have reported that this nano-system is capable of generating antibody responses that are durable and of higher avidity than those elicited by outer membrane vesicles only [145]. Bin et al. have developed a nano-system with hollow outer membrane vesicles of carbapenem-resistant *Klebsiella pneumoniae*, reinforced internally by size-controlled BSA nanoparticles to obtain uniform and stable vaccines through hydrophobic interaction to treat carbapenem-resistant *K. pneumoniae*. They have found subcutaneous BN-OMVs vaccination mediated significantly higher CRKP-specific antibody titers and was able to increase the survival rate of the mice infected with a lethal dose of CRKP after BN-OMV immunization [146].

2.4. Inherently Antimicrobial Nano-Systems

Inherently antimicrobial properties have been established for a number of materials, including silver, copper, and certain polymers, such as chitosan [146]. Nanomaterials made of these inherently antimicrobial materials have attracted attention for combatting AMR because bacterial resistance to these materials is rare. However, many inherently antimicrobial nanomaterials can be cytotoxic, so they are often combined with other materials in hybrid nano-systems to increase their biocompatibility. These inherently antimicrobial nano-systems have many practical applications. In this review, we will discuss the use of inherently antimicrobial nano-systems for wound healing applications, focusing on the hybridization of inherently antimicrobial nanomaterials with photothermal therapies. We will also discuss the modification of implant surfaces with inherently antimicrobial nanomaterials to combat implant-associated infections and biofilms.

2.4.1. Wound Healing

Wounds can be a serious health problem, especially when they become infected. If not properly treated, wounds with chronic infections can progress to sepsis, multi-

organ dysfunction, and in severe cases, death. Difficulties in treating infected wounds are exacerbated by multidrug-resistant (MDR) bacteria, which can make traditional treatment options ineffective. Thus, it has been suggested that inherently antimicrobial nano-systems could be useful for treating MDR infections due to the rarity of antimicrobial resistance to these materials. While many of these inherently antimicrobial nanomaterials are cytotoxic at high concentrations, they are ideal for topical treatments, such as antimicrobial creams and adhesive patches. Due to these characteristics, inherently antimicrobial nanomaterials are a promising treatment for combatting wound infections.

Table 3 summarizes recent advances in the use of inherently antimicrobial nano-systems for wound healing applications. Wound healing via inherently antimicrobial nanomaterials has long focused on silver nanoparticles due to their well-established antimicrobial properties. Recent works have improved the known antibacterial properties of silver nanoparticles (AgNPs) by incorporation into a hydrogel [147,148]. Another approach to improve the properties of AgNPs is by hybridization with other nanomaterials to synergistically increase the antimicrobial efficacy. For example, both black phosphorous nanosheets doped with AgNP and AgNP-carrying mesoporous silica-coated single-walled carbon nanotubes have shown increased antibacterial properties when compared to AgNPs alone and have promoted wound healing in mice and animal skin models [149,150]. Other studies have combined the inherent antimicrobial properties of AgNPs with phototherapy to develop hybrid nanotherapies, using a wide variety of photothermal and photosensitizing agents [148,151–153]. Furthermore, both photothermal therapy (PTT), which uses near-infrared (NIR) light to induce localized hyperthermia, and photodynamic therapy (PDT), which uses photochemical reactions to generate ROS, have been combined with many different inherently antimicrobial nanomaterials to increase their efficacy.

The photothermal and photodynamic properties of copper sulfide nanomaterials have made them attractive options for inherently antimicrobial hybrid nano-systems since phototherapy can be combined with the release of Cu^{2+} ions [126,154]. Qiao et al. developed dual-functional copper sulfide nanodots (CuS NDs) to address chronic nonhealing wounds associated with diabetes mellitus [154]. The CuS NDs were shown to kill MDR bacteria through synergistic mechanisms: hyperthermia due to the photothermal properties of CuS NDs, the release of antibacterial Cu^{2+} ions, and ROS generation due to the photodynamic properties of CuS NDs [154]. Furthermore, the CuS NDs were found to accelerate wound healing in diabetic mice, due to their hypoxia-mimicking capabilities [154]. Cu^{2+} ions have been shown to increase the expression of hypoxia-induced factors, which promote angiogenesis. Angiogenesis, or the formation of new blood vessels, is a crucial part of wound healing and may be impaired in chronic diabetic wounds [155]. Thus, due to their combined antimicrobial, photothermal, photodynamic, and angiogenesis-promoting properties, CuS NDs were an effective hybrid nano-system for the treatment of chronic wound infections and the promotion of wound healing.

Table 3. Antimicrobial wound healing nano-systems.

Material	Infection	Ref.
Silver-based Nanomaterials		
AgNP in hyaluronic acid hydrogel	*E. coli*, *S. aureus*, *P. aeruginosa*	[147]
GA-AgNP hydrogel + NIR laser	*E. coli*, *S. aureus*	[148]
SWCNTs@mSiO$_2$-TSD@Ag	MDR *E. coli*, MDR *S. aureus*	[149]
BPN-AgNP	*E. coli*	[150]
Ag$_2$S QD/mSiO$_2$ NP hydrogel + NIR laser	*E. coli*, MRSA	[151]
CG/PDA@Ag + NIR laser	*E. coli*, *S. aureus*	[152]
Au/AgNPs	*E. coli*, MRSA	[153]

Table 3. *Cont.*

Material	Infection	Ref.
IM-POP-AgNPs	*E. coli*, *S. aureus*	[156]
S-nitroso-MSA/AgNP in alginate hydrogel	*E. coli*, *S. aureus*, *S. mutans*	[157]
Biogenic AgNPs/PLA/PEG nanofilm	*S. aureus*, *P. aeruginosa*	[158]
OCOS-AgNPs-pADMs	*E. coli*, *S. aureus*	[159]
Electrospun CA/SSD nanofibers	*E. coli*, *B. subtilis*	[160]
Copper-based Nanomaterials		
PATA-C4@CuS nanoclusters	Levoflaxin-resistant *S. aureus*, *E. coli*, *P. aeruginosa*, *B. amyloloquefaciens*	[126]
CuS NDs + NIR laser	MRSA, ESBL-producing *E. coli*	[154]
BSA-CuS + NIR laser	*S. aureus*, *A. baumannii*, *S. haemolyticus*	[161]
Polyphenol-crosslinked CMCS-CuNPs	*E. coli*, *S. aureus*	[162]
Molybdenum-based Nanomaterial		
CF-MoS$_2$ + NIR laser	*E. coli*, *S. aureus*	[163]
PEG-MoS$_2$ NFs + NIR laser	*B. subtilis*, AmpR *E. coli*	[164]
MoS$_2$-BNN6 + NIR laser	AmpR *E. coli*, *E. faecalis*, & *S. aureus*	[165]
Gold-based Nanomaterials		
UsAuNPs/MOFs	*E. coli*, *S. aureus*	[166]
CSAu@ MMT/gelatin	*E. coli*, *S. aureus*, MRSA	[167]
PDA@Au-HAp NPs + NIR laser	*E. coli*, *S. aureus*	[168]
Polymer-based Nanomaterials		
Guanidine nanogel	*E. coli*, *S. aureus*	[169]
PDMAPS-co-PMA-Ade/chitosan hydrogel	*E. coli*, *S. aureus*	[170]
PHCI hydrogel	*E. coli*, *S. aureus*	[171]
rGB/QCS/PDA-PAM	MRSA	[172]
Other Nanomaterials		
Y$_2$O$_3$ in lauric acid–peptide conjugate gel	*E. coli*, *S. aureus*	[173]

The photothermal properties of molybdenum sulfate nanoparticles have also generated interest in their use as hybrid nano-systems with inherently antimicrobial properties [163–165]. In one prominent study, MoS$_2$ nanoflowers functionalized with polyethylene glycol (PEG-MoS$_2$ NFs) were used to catalyze the decomposition of H$_2$O$_2$ to the hydroxyl radical to kill bacteria [164]. This peroxidase (POD)-like activity was combined with PTT to increase the antibacterial efficiency of the nano-system against ampicillin-resistant *E. coli* and *B. subtilis* [164]. Additionally, the hyperthermia caused by PTT increased the rate of glutathione oxidation, which contributed to the antibacterial activity, due to the role that glutathione has in preventing cellular damage due to oxidative stress [164]. The combined effects of hyperthermia and the catalytic activity of PEG-MoS$_2$ NFs made them a potent hybrid nano-system for wound healing applications. The ability to behave as a POD-like catalyst has been observed in other nanomaterials, making them appealing candidates for wound healing applications. The POD-like activity of ultra-small gold nanoparticles (UsAuNPs) was investigated by Hu and colleagues for the treatment of infected wounds (Figure 6) [166]. The POD-like activity of these nanoparticles not only gave them inherently antimicrobial properties but also enabled the UsAuNPs to act as nanozymes, that is nanoparticles that mimic the reaction mechanisms of naturally occurring enzymes. Due to their ultra-small size, UsAuNPs have high enzymatic activity; however, UsAuNPs are

unstable and tend to for aggregates due to their large surface energy. Hybridization with a molecular organic framework (MOF) stabilized the UsAuNPs and improved their catalytic performance [166]. Compared with pure MOFs, the UsAuNPs/MOFs showed increased catalytic efficiency in the presence of H_2O_2, which was maintained under a wide range of pH, salinity, and temperature, indicating increased stability of the hybrid nanozyme [166]. The POD-like activity of this hybrid nano-system was confirmed via the oxidation of 3,3′,5,5′-tetramethylbenzidine (TMB), with the TMB oxidation peak used as an indicator of the conversion of H_2O_2 to the hydroxyl radical [166]. In vitro assays showed that the UsAuNP/MOF hybrids were effective against *S. aureus* and *E. coli* [166]. Furthermore, the POD-like activity of the UsAuNPs/MOFs was shown to shorten wound healing time in BALB/c mice, with a smaller amount of H_2O_2 required than the 100×10^{-3} to 1 M normally used for wound disinfection [166]. The POD-like activity of the UsAuNP/MOF nanozyme, which was effective in killing bacteria, and its biocompatibility made it excellent for wound healing applications.
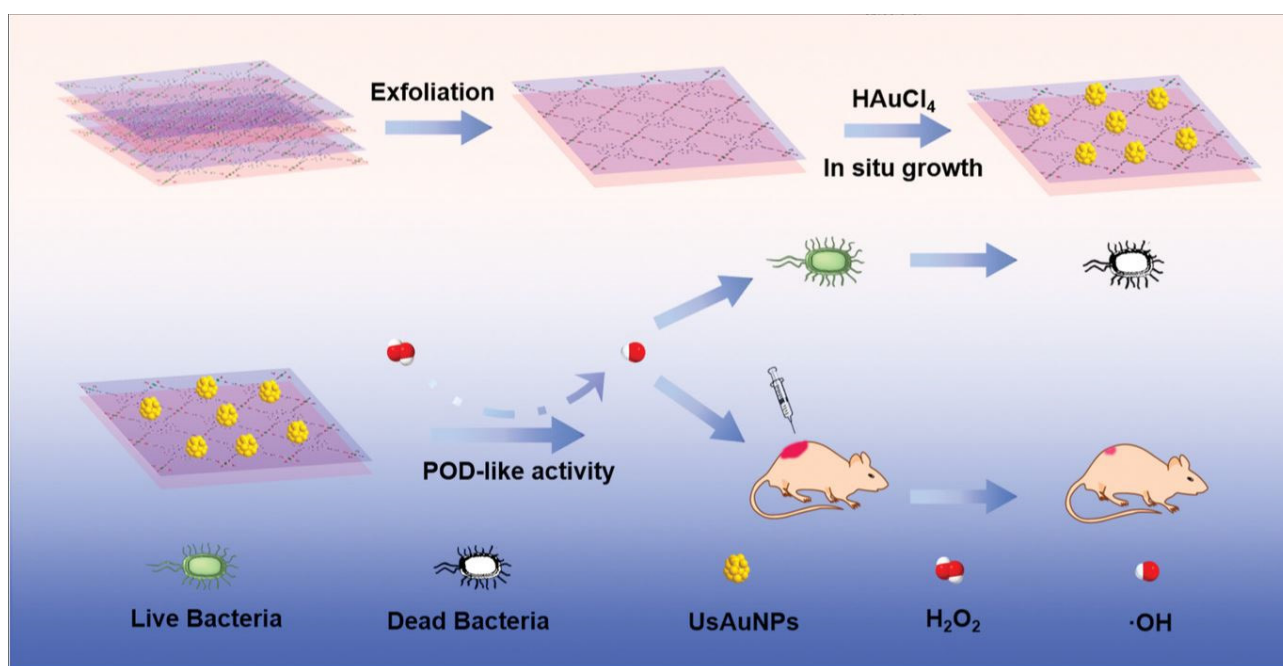

Figure 6. Schematic illustration of the preparation and the POD-like activity of UsAuNPs/MOFs hybrid for antibacterial therapy. Adapted with permission from Ref. [166]. Copyright 2020 Small, Wiley.

While the treatment of infected wounds has been an area of major importance for inherently antimicrobial nano-systems, another application of these systems has been in monitoring wound healing through imaging. Different imaging techniques have emerged as a method to monitor infections and their treatment with nano-systems in real time. Previously photoacoustic imaging has been used with Au/Ag hybrid nanoparticles to monitor silver ion release and improve wound healing in methicillin-resistant *S. aureus* (MRSA)-infected rat models [153]. More recently, He and colleagues have used gold-silver nanoshells (AuAgNSs) for PTT-assisted antibacterial treatment of wounds and real-time imaging of infected wounds [174]. The conjugation of 3,3′-diethylthiatricarbocyanine iodide (DTTC), a Raman reporter, to the AuAgNSs allows real-time monitoring of residual bacteria via surface-enhanced Raman scattering (SERS) imaging. SERS imaging using the AuAgNSs-DTTC showed suitable sensitivity, with the ability to detect 600 CFU/mL extended-spectrum β-lactamase (ESBL) *E. coli* and 300 CFU/mL MRSA [174]. Furthermore, the SERS imaging of AuAgNSs-DTTC allowed for in vivo tracking of bacteria for up to 8 days [174]. In addition to their effectiveness in SERS imaging of bacteria both in vitro and in vivo, the AuAgNSs-DTTC also showed effective antibacterial properties in vitro and

wound healing applications in vivo. The antibacterial effect of the AuAgNSs-DTTC is due to the synergistic effect of PTT and silver ions release [174]. However, recent research has focused on treating chronic wounds, photothermal ablation and imaging, and the use of novel materials to generate reactive oxygen species through enzyme-like nanoparticles.

2.4.2. Surface Modification of Implants

Implant-associated infections can contribute to medical complications, extend hospitalizations, and increase treatment costs. Current antibiotic treatments for implant-associated infections are often ineffective because many of the bacteria that infect the cells around the implant can form biofilms. Biofilms, which contain bacteria adhered to a surface and surrounded by an extracellular matrix, are difficult to combat with traditional antimicrobial drugs because they impede the penetration of the drugs and block host defenses. This action of biofilms can lead to antibiotic resistance and chronic infections. While some work has been done on the antimicrobial targeting of biofilms, other research has found success in creating inherently antimicrobial coatings for implants to prevent bacterial adhesion to the surface (Table 4).

The modification of implant surfaces with metallic nanoparticles, such as gold, silver, or copper, is a useful strategy for combatting biofilms due to the inherently antimicrobial properties of these nanomaterials. These nanomaterials have broad-spectrum antibacterial activity, long-term stability, and low risk of causing antibiotic resistance, as well as other properties to support the function of the implant in vivo. For example, electrophoretic deposition of ZnO coatings on stainless steel implants has been shown to be effective in preventing the corrosion of the implant material and the preventing growth of *S. aureus* and *S. enteric* [175]. Titanium joint implants coated with AgNPs have been shown to support similar bone formation in uninfected rat tibias over the course of 12 weeks compared to uncoated implants [176]. In addition, the silver ions released by these AgNPs formed less toxic Ag_2S, which was accumulated mostly in the osseous tissue directly surrounding the implant surface [176]. Tissue engineering has also been accomplished with nonmetal materials, such as silk fibroin scaffolds containing AgNPs, which have been shown to support the differentiation of human mesenchymal stem cells and to be effective against Gram-negative bacteria and antibiotic-resistant bacteria [177]. Recently, inherently antimicrobial nano-systems have been used to modify bone implants, stents, and catheters in order to prevent implant-associated infections.

Table 4. Inherently antimicrobial nano-systems used for implants.

Material	Infection	Ref.
Nanomaterial-Modified Implants		
Ag-coated Ti joint implants	N/A	[176]
nZnO-coated implants	S. enteric	[175]
TNTs-AgNPs-(CHI/ADA)10	*E. coli, S. aureus*	[178]
TNT/AgNP composite coated Ti6Al4V surface	*E. coli, S. aureus*	[179]
PDA-AgNP-coated titanium surface	*S. aureus*	[180]
Nanomaterial-Modified Stents		
TiO$_2$ NT@AgNP stents	*S. aureus*	[181]
AgNP biliary stents	*E. coli, S. aureus*, Quail chicken enterococcus D, *E. cloacae, K. pneumoniae, E. faecalis*	[182]
PU/PU-PTX-PCL/PU-AgNP tri-layer membrane stents	*E. coli* and *S. aureus*	[183]
JQ alloy stents	N/A	[184]

Table 4. *Cont.*

Material	Infection	Ref.
hCOLIII-based ECM-mimetic-coated stents	N/A	[185]
EVA/BS@SN ureteral J-shaped stents	*E. coli*	[186]
SF/CS/Cu coating for cardiovascular stents	N/A	[187]
PVP-AgNPs coated on silicone hydrogel	*E. coli*	[188]
Nanomaterial-Modified Catheters		
Ag/Cu-coated catheters	MRSA	[189]
ACPs@AgNP-coated catheter	Drug resistant *S. aureus*	[190]
AgPEI NP-coated catheter	*Candida* species	[191]
PDA-CMC-AgNP-coated urinary catheter	*E. coli, S. aureus*	[192]
ZnO coated central venous catheter	*P. aeruginosa, E. coli, S. aureus*	[193]
ZnO NP-grafted silicone catheter	*P. aeruginosa*	[194]
AgNP-coated mini catheters	*P. aeruginosa*	[195]
GO/CU coating	*C. parapsilosis*	[196]
Ag/TiOx-PDMS nanofilm	*P. aeruginosa, E. coli, S. aureus*	[197]
Nanomaterial Modified Tissue Scaffolds		
AgNP-silk fibroin scaffold	*E. coli, S. aureus*	[177]
PCL/AgNP-coated tissue scaffold	*E. coli*	[198]
Chitosan-CMC-FZO@Hap scaffold	*E. coli, S. paratyphi, S. aureus, & L. monocytogenes*	[199]
Hap/AgNP-loaded cellulose scaffold	*E. coli, S. aureus*	[200]
CuFe$_2$O$_4$-MXene/PLLA tracheal scaffold	*S. aureus, P. aeruginosa*	[201]
Ag/MBG scaffold	*E. coli, S. aureus*	[202]
LgNP/PCL nanofiber scaffold	*S. aureus*	[203]

Antimicrobial properties and biocompatibility are crucial factors in the long-term success of titanium bone implants. Yuan et al. [178] developed a nano-system for bone implants with inherently antimicrobial activity and high biocompatibility by using titanium dioxide nanotubes (TNTs or TiO$_2$-NTs) loaded with AgNPs and coated with chitosan (CHI) and dialdehyde alginate (ADA) using a layer by layer (LBL) technique. They designed this hybrid nanomaterial with the (CHI/ADA)$_{10}$ multilayer film that would degrade in physiological conditions and slowly release the silver ions from the loaded AgNPs. The results showed that the TNTs-AgNPs-(CHI/ADA)$_{10}$ slowed silver ion release when compared to TNTs-AgNPs without the LBL addition [178]. Furthermore, osteoblast adhesion in vitro was shown to be increased in the TNTs-AgNPs-(CHI/ADA)$_{10}$ when compared to TNTs or TNTs-AgNPs, and lactate dehydrogenase, a marker of cytotoxicity, was lower in the TNTs-AgNPs-(CHI/ADA)$_{10}$ than in TNT-AgNPs [178]. These results indicated that the TNTs-AgNPs-(CHI/ADA)$_{10}$ had greater biocompatibility and less cytotoxicity than similar nano-systems without the (CHI/ADA)$_{10}$ multilayer film. TNTs-AgNPs-(CHI/ADA)$_{10}$ were also shown to prevent the bacterial adhesion of *S. aureus* and *E. coli*, and the TNTs-AgNPs-(CHI/ADA)$_{10}$ nano-system was shown to have an antibacterial efficiency only slightly less than TNTs-AgNPs without the LBL addition of (CHI/ADA)$_{10}$ [178]. The biocompatibility and antimicrobial activity of TNTs-AgNPs-(CHI/ADA)$_{10}$ due to their gradual release of ions were demonstrated by Yuan and colleagues, but similar approaches to inherently antimicrobial nano-systems have been applied to stents.

The most common treatment for patients with cardiovascular atherosclerosis is stent implantation, which can lead to numerous complications such as blood clotting or delayed endothelialization. Dai et al. [181] developed an inherently antimicrobial nano-system

for use in vascular stents using TiO$_2$-NTs loaded with AgNPs and pre-treated with UV radiation. While TiO$_2$-NTs are excellent drug carriers, they have been reported to induce thrombosis, which reduces their biocompatibility. However, it has previously been shown that UV irradiation can improve the anticoagulant activity of TiO$_2$ films by inhibiting fibrinogen adsorption and platelet adhesion through the generation of ROS [204,205]. Furthermore, TiO$_2$-NTs can also carry inorganic materials, such as AgNPs, which are more stable during UV irradiation than organic drugs. For these reasons, Dai et al. tested UV-treated TiO$_2$-NTs loaded with AgNPs (UV-NTs@AgNPs) as a potential material for stents [181]. UV-NTs@AgNPs exhibited anticoagulant properties and selective inhibition of smooth muscle cells and macrophages in vitro [181]. When implanted in the abdominal aorta of Sprague Dawley rats, UV-NTs@AgNPs had decreased thickness of tissue formed on the surface of the nano-system when compared to the untreated TiO$_2$-NTs@AgNPs, showing greater histocompatibility. Additionally, tissue around the implants showed more inflammation in the non-irradiated TiO$_2$-NTs@AgNPs, and the UV-NTs@AgNPs had lower intimal hyperplasia thickness than the non-irradiated nano-systems [181]. Furthermore, the UV-NTs@AgNPs showed greater biocompatibility than the non-irradiated TiO$_2$-NTs@AgNPs. These results indicated that the UV-NTs@AgNPs were a good candidate for vascular stents. The antibacterial properties of AgNPs made them not only useful for stents but also for other implants, such as catheters.

The use of intravenous catheters (IVCs) in patients can often lead to the development of infections. IVC-related infections are most commonly caused by *Staphylococcus* bacteria, including MRSA. While using aseptic techniques for inserting the catheter can reduce IVC-related infections, it does not completely prevent IVC-associated infections and is insufficient to prevent infections caused by antimicrobial-resistant organisms, such as MRSA. Due to their effectiveness against a broad spectrum of microorganisms, silver and copper nanoparticles are a natural choice for the coating of polyurethane catheters. Ballo and colleagues used direct current magnetron sputtering to coat polyurethane catheters with a 67% AgNPs 33% copper NPs mixture and tested their effectiveness against MRSA both in vitro and in vivo [189]. While the Ag/Cu coating was effective in vitro, preventing 80% of catheter colonization by MRSA, the catheter coating was less effective in vivo [189]. When inserted into the jugular vein of female Wistar rats, the Ag/Cu-coated catheters only prevented 22% of infections [189]. However, the Ag/Cu-coated catheters did show a decrease in bacteremia compared to uncoated catheters. The adhesion of plasma proteins and the formation of a fibrin sheath on the surface of the catheter likely inhibited the antimicrobial activity of the Ag/Cu-coated catheters in vivo, which probably contributed to their poorer performance [189]. While the Ag/Cu-coated catheters did not perform as well in vivo as they did in vitro, further studies could improve the nano-system by preventing the formation of the fibrin sheath or the deposition of plasma proteins.

3. Future Work

While significant advances have already been made in recent years to develop hybrid nano-systems for combating bacterial infections, several challenges remain to the implementation of these nano-systems that will provide a focus for future studies. Much of current research is focused on developing proof-of-concept nanomaterials, but future work must focus on testing these materials in vivo for extended periods of time. These future studies will be useful in determining the efficacy and safety of these hybrid nano-systems and establishing any potential side effects.

Additional research may also be necessary to address other problems with current antimicrobial agents, such as barriers to drug delivery or bacterial defense mechanisms. For example, hybrid nano-systems are being developed to target bacterial biofilms, but more work is necessary to improve the efficacy of these nano-systems, particularly in vivo. Overall, hybrid nano-systems offer many promising advantages for the treatment of bacterial infections due to their improved biocompatibility and ability to target the sites of

infection for the controlled release of antimicrobial agents, but challenges still remain to establish the safety and efficacy of these nano-systems in vitro.

4. Conclusions

The continued incidence of AMR bacteria is a major health concern that has highlighted the need for new and innovative treatments for bacterial infections. Hybrid nano-systems offer promising treatments for AMR infections due to their ability to specifically target and kill bacterial cells through a variety of different mechanisms. In this review, we have summarized recent advances in the use of hybrid nano-systems for the treatment of bacterial infections, focusing on stimuli-responsive nano-systems and inherently antimicrobial nano-systems. These hybrid nano-systems can overcome some of the limitations of traditional antimicrobial treatments due to their unique properties, such as their photothermal properties or their antimicrobial properties. Furthermore, these nano-systems can be modified with various ligands to allow for the specific binding to biomolecules. While there are still some challenges to the clinical implementation of hybrid nano-systems for the treatment of bacterial infections, based on the literature review presented here, these nanomaterials-based treatments show great potential for the treatment of bacterial infections and may be essential in fighting antimicrobial-resistant pathogens.

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