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Nanoparticle Approaches against Bacterial Infections

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Abstract

Despite the wide success of antibiotics, the treatment of bacterial infection still faces significant challenges, particularly the emergence of antibiotic resistance. As a result, nanoparticle drug delivery platforms including liposomes, polymeric nanoparticles, dendrimers, and various inorganic nanoparticles have been increasingly exploited to enhance the therapeutic effectiveness of existing antibiotics. This review focuses on areas where nanoparticle approaches hold significant potential to advance the treatment of bacterial infection. These areas include targeted antibiotic delivery, environmentally responsive antibiotic delivery, combinatorial antibiotic delivery, nanoparticle-enabled antibacterial vaccination, and nanoparticle-based bacterial detection. In each area we highlight the innovative antimicrobial nanoparticle platforms and review their progress made against bacterial infections.

Keywords

Nanomedicine; nanoparticles; bacteria; infectious diseases; antimicrobial delivery

1. Introduction

Despite the profound success achieved by the use of antibiotics against infectious diseases, bacterial infections continue to impose significant challenges on global healthcare^{1, 2}. Eradication of certain bacterial infections such as tuberculosis remains difficult due to the complex mechanisms of the pathogen in subverting its host's immune system as well as the delivery barriers that prevent antibiotics from reaching sites of infection^{3, 4}. Highly potent antibiotics, including certain aminoglycosides and fluoroquinolones, generate severe adverse effects and are reserved only for serious infections^{5, 6}. More significantly, the emergence of antibiotic resistance has generated alarming impact, threatening to set back the progress against a range of infectious diseases to the pre-antibiotic era^{7, 8}. The widespread drug resistance is further exacerbated by the retreat of the pharmaceutical sector from new antibiotic development⁹. These challenges, together, highlight the demand for alternative and effective antimicrobial strategies.

Over the last few decades, the application of nanotechnology, particularly the use of nanoparticles for drug delivery, has generated significant impact in medicine^{10, 11}. Various nanoparticle delivery platforms, especially liposomes, polymeric nanoparticles, dendrimers,

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and inorganic nanoparticles, have received significant attention (Figure 1). Drug molecules loaded into nanocarriers through physical encapsulation, adsorption, or chemical conjugation exhibit an improved pharmacokinetic profile and therapeutic index when compared to their free drug counterparts¹². Other advantages of nanoparticle delivery systems, including improved drug solubility, prolonged systemic circulation, sustained and controlled release, precise drug targeting, and concurrent delivery of multiple drugs, have also been validated in various studies¹³. As a result, a number of nanoparticle-based drug delivery systems have been approved for clinical use to treat a variety of infectious diseases, and many other antimicrobial nanoparticle formulations are currently under various stages of pre-clinical and clinical tests¹⁴.

As the ability to engineer multifunctional nanoparticles continually advances, numerous innovative approaches have emerged, further improving on nanoparticle therapeutic efficacy against bacterial infection. In this review article, we select five areas where nanoparticle approaches hold significant potential to improve upon current treatments. These areas include: (1) targeted antibiotic delivery, (2) environmentally responsive antibiotic delivery, (3) combinatorial antibiotic delivery, (4) nanoparticle-enabled antibacterial vaccination, and (5) nanoparticle-based bacterial detection. Progresses made in these areas offer tremendous opportunities for alternative and more effective antimicrobial strategies that alter the pharmacokinetics of existing antibiotics, produce new antibiotics with novel microbial inhibition mechanisms, or allow for more rapid and sensitive microbial detection. Collectively, they address the aforementioned challenges including overcoming antibiotic resistance. Herein, we review each area with highlights of the current and forthcoming nanoparticle platforms against bacterial infections.

2. Targeted antibiotic delivery

Bacterial infection increases vascular permeability, which makes passive targeting possible. At the infection sites, the release and accumulation of bacterial components such as bacterial protease and lipopolysaccharide from gram-negative bacteria or lipoteichoic acid from gram-positive bacteria are known to trigger various inflammatory mediators that directly stimulate vascular permeability^{15, 16}. These bacterial components also activate immune cells, which in turn interact with vascular endothelium through multiple inflammatory and vascular mediators, leading to gap widening, barrier dysfunction, and eventually increased permeability¹⁷. Moreover, dysfunctional lymphatic drainage has also been reported in bacterial infection, which potentially promotes nanoparticle accumulation at the sites of infection¹⁸. These features of bacterial infection suggest that the enhanced permeation and retention (EPR) effect can be harnessed by nanoparticles for targeted antibiotic delivery¹⁹. In fact, both uncoated liposomes and PEGylated liposomes have been shown to accumulate selectively at soft tissue infected by *Staphylococcus aureus* (*S. aureus*), and their retention times correlated closely with size^{20–23}. Similar results were observed for superparamagnetic iron oxide nanoparticles (SPIONs) at the soft tissue of rats and in the lungs of mice infected by *S. aureus*²⁴.

Pathogenic bacteria maintain a negative surface charge under physiological conditions. Therefore, cationic nanoparticles capable of binding with bacteria via electrostatic

interactions have been explored for effective bacterial targeting^{25, 26}. This strategy is attractive for its multivalent effect and the ability to target polymicrobial infections. As a result, a diverse range of bactericidal polymers and peptides has been incorporated into various nanoparticle designs for antibacterial applications²⁷. More importantly, nanoparticle formulation can increase the local charge and mass densities of the bactericidal components, resulting in enhanced therapeutic index. For example, a self-assembled cationic peptide nanoparticle has shown strong antimicrobial properties while inducing minimal systemic toxicity²⁸. Furthermore, improving the biodegradability of the nanoparticles can further reduce cationic charge related toxicity. In this perspective, cationic nanoparticles self-assembled from polycarbonate-based block co-polymers with high biodegradability have been shown to kill bacteria without inducing obvious hemolytic activity and systemic toxicity²⁹.

Active targeting with pathogen-binding ligands directly conjugated to the surface of nanoparticles is another strategy to target bacteria. For example, small molecules such as vancomycin have been conjugated to the surfaces of dendrimers³⁰, iron oxide nanoparticles³¹, gold nanoparticles³², and porous silica nanoparticles³³, resulting in preferential binding of nanoparticles to gram-positive bacteria. The targeting efficiency of small molecules was also found to be strongly dependent on molecular orientation, surface density, and length of the spacer used in conjugation³⁴. In addition to small molecules, lectins, particularly those with selective agglutination activities, have also been used as ligands to target bacteria³⁵. Polymeric nanoparticles conjugated with mannose-specific or fucose-specific lectins showed enhanced binding affinity to the carbohydrate receptors on *Helicobacter pylori* (*H. pylori*) surfaces, suggesting a promising approach for site-specific and gastroretentive drug delivery to treat *H. pylori* infection³⁶. Besides lectins, other protein ligands such as single-domain antibodies³⁷ and bacteriophage tailspike proteins³⁸ are highly specific targeting ligands and their conjugation to nanoparticles has resulted in targeted delivery platforms effective against a variety of bacterial infections. Furthermore, aptamers have also become a class of attractive targeting moieties owing largely to the advancement in bacterium-based aptamer selection techniques, which continually improve aptamer binding affinity and specificity. These targeting molecules have been extensively explored to target nanoparticles to pathogenic bacteria such as *Salmonella typhimurium* (*S. typhimurium*) and *Mycobacterium tuberculosis* (*M. tuberculosis*)^{39, 40}.

Moreover, bacteria can survive ingestion by phagocytic cells such as macrophages, hence evading the immune system and the bactericidal action of antibiotics³. However macrophages are able to transport drugs to the site of infection by a chemotactic mechanism^{41, 42}. Therefore, targeting antimicrobial nanoparticles to macrophages as opposed to bacteria has become an attractive strategy for improving antibiotic therapy, particularly to treat intracellular bacterial infection⁴³. It has been observed that following passive targeting to the infection sites, nanoparticles could preferentially be taken up by macrophages due to the spontaneous scavenging feature of macrophages^{23, 24}. Such macrophage uptake could be further enhanced by attaching targeting ligands onto the nanoparticles^{44, 45}. In this regard, various ligands, including mannose, maleylated bovine

serum albumin and O-steroyl amylopectin, have been applied to successfully enhance macrophage uptake of nanoparticles for the treatment of intracellular infection^{46, 47}.

3. Environmentally responsive antibiotic delivery

To further improve upon the therapeutic efficacy of antimicrobial nanoparticles, researchers have explored environmentally responsive nanoparticles that remain inactive until they are triggered by cues found in the microenvironment of infection sites. These external stimuli can be physical signals such as temperature, electric field, magnetic field, and ultrasound; they can also be chemical signals such as pH, ionic strength, redox potential, and enzymatic activities⁴⁸.

Among these environmental stimuli, pH gradients have been widely used to design novel, responsive nanoparticles for antibiotic delivery. At the organ level, nanoparticles have been designed to respond to the pH gradient along the gastrointestinal (GI) tract⁴⁹ and the acidic environment of human skin⁵⁰ for site-specific antibiotic delivery. At the intracellular level, nanoparticles have been formulated to respond to the acidic pH inside the endolysosomal compartments for triggered drug release^{51–53}. In addition to pH gradient, bacterial enzymatic activities, including those of secreted toxins, have also been used to trigger the release of antimicrobial agents to inhibit the growth of the target bacteria.

Charged polymers have been adsorbed onto liposome surfaces with opposite charge to stabilize the liposomes^{54, 55}. Such stabilization is pH sensitive and has been extensively used to treat various intracellular bacterial infections including *Salmonella enterica* (*S. enterica*)^{56, 57} as well as cases of septic shock^{58, 59}. Based on a similar mechanism, ionic liposomes can be employed to carry oppositely charged drug molecules for pH-sensitive drug release. In addition, loading liposomes with membrane disrupting toxins such as hemolysin⁶⁰ and listeriolysin that are responsive to endosomal acidification has also shown potential for the treatment of intracellular infections⁶¹.

Recently, a new environment-responsive delivery strategy has emerged that involves the attachment of small charged nanoparticles onto liposome surfaces for liposome stabilization and triggered antimicrobial delivery (Figure 2). The nonspecific adsorption of charged nanoparticles onto phospholipid bilayers provided steric repulsion that inhibited liposome fusion. It also reduced liposome surface tension and thus further enhanced liposome stability^{62, 63}. Intriguingly, the charge and charge density of both the nanoparticle stabilizers and the liposomes could be precisely tailored to enable stimulus-responsive binding and detachment of the nanoparticles, thereby allowing for an on-demand control over liposome fusion activity for smart drug delivery. For instance, cationic liposomes bound with negatively charged gold nanoparticles only fused with bacteria at acidic pH, which made them suitable for treating various skin pathogens that thrive in acidic infection sites such as the case with *Propionibacterium acnes* (*P. acnes*)⁶⁴. Conversely, anionic liposomes stabilized by positively charged gold nanoparticles were highly stable in gastric acid, but capable of fusing with bacteria at physiological pH, making them suitable to treat gastric pathogens such as *H. pylori*⁶⁵. Even in the absence of such stimulus-induced detachment of the nanoparticle stabilizers, these liposomes still had a substantial fraction of

their surface areas exposed and highly accessible to bacterial toxins. This feature allowed the liposomes to respond to various bacteria such as *S. aureus* that secrete pore-forming toxins to trigger drug release from the liposomes⁶⁶. Aimed at improving the topical applications of nanoparticle-stabilized liposomes, a hydrogel form of the delivery system was recently developed, which not only preserved the structural integrity of the nanoparticle-stabilized liposomes, but also allowed for controllable viscoelasticity and tunable liposome release rate⁶⁷.

Meanwhile, polymeric nanoparticles have been extensively studied for responsive antibiotic delivery. For example, tri-block copolymer nanoparticles composed of poly(lactic-co-glycolic acid) (PLGA), poly(L-histidine) and poly(ethylene glycol) (PEG) have been reported for acid-responsive antibiotic delivery⁶⁸. These nanoparticles maintained a negative charge at neutral pH; however, when exposed to an acidic pH, the protonation of the imidazole groups switched the surface charge to a positive one, resulting in enhanced bacterial binding and improved antibacterial efficacy. As another example, heparin and chitosan have been applied to form base-sensitive nanoparticles for treating gastric pathogens such as *H. pylori*. The polymers self-assembled to form nanoparticles at pH 1.2–2.5; however, upon contact with *H. pylori* at the gastric epithelium with physiological pH, the chitosan deprotonated, causing nanoparticle disassembly and release of drugs for bacteria killing⁶⁹. Moreover, by tailoring the pKa of amphiphilic copolymers, a wide range of polymeric nanoparticles has been engineered, which precisely respond to the subtle changes of pH along the GI tract for site-specific antibiotic delivery. Enzyme-sensitive polymeric nanoparticles have also been developed for intracellular delivery in macrophages. For example, a triple-layered nanogel formulation has been reported, which contained a bacterial lipase-sensitive poly(ϵ -caprolactone) interlayer between the cross-linked polyphosphoester core and the PEG shell⁷⁰. Following macrophage uptake, the presence of bacterial phosphatase or phospholipase triggered rapid drug release, which subsequently inhibited the growth of *S. aureus*⁴⁷.

4. Combinatorial antibiotic delivery

Combining two or more distinct antibiotics represents a common strategy in treating bacterial infections with the aim to broaden the antimicrobial spectrum, generate synergistic effects, and counteract antibiotic resistance. However, varying pharmacokinetics, biodistributions, toxicity profiles, and membrane transport properties among different drug compounds complicate dosing and scheduling optimization, which in turn compromise drug synergy *in vivo*⁷¹. In this regard, nanoparticles offer unique properties to enhance combinatorial antibiotic delivery and numerous applications have been investigated to address a variety of bacterial infections (Table 1).

Liposomes are a highly versatile platform for combinatorial delivery. Hydrophilic drugs can be directly encapsulated in the aqueous compartments of liposomes, while hydrophobic drugs can be incorporated into the lipid bilayer membranes⁷². For example, isoniazid and rifampicin, first line antitubercular drugs, have been loaded in the aqueous compartment and the lipid bilayer, respectively. The resulting liposomal formulation has shown increased efficacy compared to free drug counterparts at the same dosages^{73–75}. Liposomal

formulation can also reduce drug toxicity to the host cells, thereby allowing for co-delivery of combinatorial antibiotics that are otherwise too toxic in their free forms. For example, drug compounds such as gallium (Ga) and bismuth derivatives are antibiotics that inhibit bacterial growth by interrupting their iron uptake. Although they have shown synergetic effects in combination with other antibiotics, their usage has been limited by severe toxicity⁷⁶. To address this challenge, Ga³⁺ was combined with gentamicin and loaded into liposomes. The formulation reduced Ga toxicity and improved efficacy against highly resistant *Pseudomonas aeruginosa* (*P. aeruginosa*)⁷⁷. Similarly, bismuth-ethanedithiol (BiEDT) was encapsulated together with tobramycin into liposomes, resulting in the elimination of BiEDT's toxic effect on human lung cells while increasing its antibacterial efficacy against *P. aeruginosa* and *Burkholderia cepacia* (*B. cepacia*)^{78–80}. A recent *in vivo* study showed that the same drug combination in a liposome formulation enhanced efficacy in reducing bacterial burden in rats chronically infected with *P. aeruginosa*⁸¹.

Moreover, liposomal formulation of combinatorial antibiotics enables ratiometric control over the drugs and thus unifies the pharmacokinetics of different drug molecules and ensures parallel tissue distribution. These advantages serve to enhance the antimicrobial efficacy of the drugs. For example, using the dosage and dosing schedule derived from *in vitro* studies, the co-administration of gentamicin and ceftazidime only resulted in an additive effect in a rat model of an acute unilateral *Klebsiella pneumoniae* (*K. pneumoniae*) infection⁸². In contrast, the corresponding liposomal formulation encapsulating both gentamicin and ceftazidime showed a synergistic effect that led to a shorter course of treatment at lower cumulative doses⁸³. The benefit of ratiometric delivery using liposomes was also reported in other combination therapies in treating *S. aureus*^{84, 85}, *M. tuberculosis*^{73, 74}, *Mycobacterium avium* (*M. avium*)^{86, 87}, and *H. pylori*^{88, 89}.

Polymeric nanoparticles represent another emerging platform for combinatorial antibiotic delivery to treat bacterial infection. In general, drug molecules can be directly encapsulated into the polymeric cores. For precise ratiometric loading and controlled drug release, multiple drugs can be covalently conjugated to the polymer backbone followed by nanoparticle preparation^{90–92}. In addition, using emulsion techniques, both hydrophobic and hydrophilic drug molecules can be co-encapsulated into the polymeric cores^{93, 94}. As a result, several polymeric nanoparticle systems have been reported for delivering antibiotic combinations. For example, the combination of rifampin and azithromycin was delivered with PLGA nanoparticles and showed better efficacy *in vitro* compared to free drugs in treating persistent chlamydial infection⁹⁵. Nanoparticles made of gliadin, a vegetal protein commonly derived as a fraction of wheat gluten, were used to co-encapsulate clarithromycin and omeprazole, which achieved better efficacy against *H. pylori* bacteria in rats^{96, 97}. The gliadin nanoparticles were further conjugated with lectin and used in triple therapy with amoxicillin, clarithromycin, and omeprazole⁹⁸, resulting in superior *in vivo* clearance of *H. pylori* compared to the non-conjugated formulation and free drugs. Moreover, PLGA nanoparticles were also used for oral delivery of anti-tuberculosis drugs (ATDs)^{99, 100}. In 8) these studies, three or four frontline ATDs, including rifampicin, isoniazid, pyrazinamide and ethambutol, were co-encapsulated inside PLGA nanoparticles through an emulsion

technique, and the resulting nanoparticle formulation improved bacterial clearance in *M. tuberculosis* infected mice and guinea pigs via oral administration.

5. Nanoparticle-enabled antibacterial vaccination

Vaccines can protect against or treat infections by manipulating the host's immune responses, and their success in controlling former epidemics worldwide has been considered as the most effective public health intervention ever achieved^{101, 102}. The vaccine strategy also holds the promise to halt antibiotic resistance by reducing the exposure of bacteria to widely used antimicrobial agents^{103, 104}. However, the majority of existing vaccines predominantly drive the generation of neutralizing or opsonizing antibodies against pathogens, a mechanism that is ineffective against a number of infections¹⁰⁵. Vaccine development against these diseases is further hampered by incomplete understanding of the enormously complex human immune system and the underlying mechanisms of protection¹⁰⁶. To address these challenges, nanoparticles offer unique advantages for immune modulation against bacterial infections^{107, 108}.

Nanoparticles have been extensively explored to overcome the instability, undesirable systemic biodistribution, and toxicity frequently associated with the administration of soluble molecules^{109, 110}. It has been reported that conjugation of antigens to nanoparticle surfaces facilitated B-cell activation¹¹¹, due to a higher quantity of antigens that were delivered to antigen presenting cells (APCs)¹¹². With the advancement in nanoparticle engineering, fabrication techniques long established for manufacturing nanoparticle-based drug delivery systems including layer-by-layer assembly^{113, 114}, facile spray-drying process¹¹⁵, and soft lithography-based PRINT technology¹¹⁶ have also been increasingly applied to improve on antigen loading. Recently, natural cellular membrane-coated nanoparticles have also been shown to detain membrane-damaging toxins and divert them away from their cellular targets^{117, 118}. Such a toxin-detainment strategy was applied to safely deliver intact staphylococcal α -hemolysin to APCs and induced superior protective immunity against toxin-mediated adverse effects in mice when compared to vaccination with heat-denatured toxins (Figure 3)¹¹⁹. This approach maintained a faithful antigenic presentation while removing toxin virulence, therefore avoiding the trade-off between efficacy and safety that remains a major challenge of current toxoid development.

Besides delivering antigens, nanoparticles can concurrently carry adjuvants to mimic natural microbes for enhanced vaccination efficacy^{120, 121}. Particularly, various toll-like receptor (TLR) ligands including small molecules, carbohydrates, DNAs, and RNAs, together with antigens have been delivered using nanoparticles, resulting in equivalent immune responses compared to soluble antigen formulations but at significantly reduced dosages^{122–125}. More importantly, nanoparticles allow for programmable presentation of adjuvants and antigens to immune cells for desirable responses. For example, combinations of TLR agonists, as opposed to a single adjuvant, have been concurrently loaded into nanoparticles to mimic the combinatorial TLR activation that occurs in natural infections, therefore resulting in more vigorous immune responses^{126–128}. In addition, nanoparticles allow for the sequential presentation of antigens and adjuvants to be programmed for optimal immune responses. For example, encapsulation of antigens and TLR agonists into the same nanoparticles has shown

advantages for the induction of effector T-cell responses^{124, 129} due to the manner in which antigen processing occurs in dendritic cells^{130, 131}. In contrast, delivery of antigens and TLR agonists in separate nanoparticles seemed to benefit antibody responses¹³². Recent advancement in controlling the intra-nanoparticle architecture and adjuvant distribution has provided additional capability for programming nanoparticle-based immune modulation¹³³. For example, when an interbilayer-crosslinked multilamellar vesicles were used as synthetic vaccines, the TLR-4 agonist monophosphoryl lipid A (MPLA) was incorporated throughout the vesicle layers and elicited stronger serum IgG titres as compared to the vesicles carrying the same amount of MPLA but attached only on the vesicle surfaces (Figure 4)¹³⁴.

Targeting vaccines to desired sites for safe and effective immune responses is another advantage of using nanoparticles for vaccine delivery. For example, a cationic nanogel loaded with a subunit fragment of *Clostridium botulinum* (*C. botulinum*) type-A neurotoxin has been shown to facilitate persistent antigen adherence to the nasal epithelium and effective uptake by mucosal dendritic cells¹³⁵. This platform not only elicited strong systemic and mucosal immune responses, but also prevented exposure of the upper respiratory tract and the central nervous system to toxic antigens. As another example, nanoparticles responsive to the pH gradient of the GI tract have been able to protect antigens while in the stomach but release them in the lower GI tract for subsequent translocation across the intestinal epithelium¹³⁶. A similar strategy has also shown promise for targeting antigen-transcytosing M cells overlying Peyer's patches for further enhanced immunity¹³⁷. In addition, nanoparticle-based vaccine platforms can effectively target lymph node-residing immune cells. It has been shown that smaller nanoparticles transport faster to the lymph node¹³⁸, but larger particles are retained longer within the lymph node¹³⁹. Such distinct correlations indicate the importance of size optimization in lymphatic targeting for desired immune responses. At the single-cell level, numerous nanoparticle formulations have been designed to escape endosomes following their uptake by APCs^{140–142}. These nanoparticles specifically deposited vaccine payloads into the cytosol and showed promise to enhance CD8+ T-cell priming.

6. Nanoparticle-based bacterial detection

Rapid and sensitive bacterial detection is crucial for identification of the infection source, allowing for treatment with the appropriate antibiotics and thus preventing the spread of the disease^{143, 144}. Bacterial culture and biochemical staining remain the current gold standard in the clinic despite laborious processing, long procedural times and limitations in identifying certain pathogenic species. Among the various existing diagnostic approaches, those based on polymerase chain reaction (PCR) and sequencing have shown particular promise as highly sensitive tools for microbial identification^{145, 146}. However, quantitative real-time PCR-based systems are often too expensive in resource-limited settings, and the current sequencing techniques still lack practical applicability for patient care^{147, 148}. In this regard, nanoparticles offer unique opportunities for generic, accurate and point-of-care detection of pathogens^{149, 150}.

Using conventional organic fluorophores for bacterial detection is limited by the molecules' short lifetime and low sensitivity. To overcome these challenges, silica nanoparticles have

been used to encapsulate thousands of fluorescent molecules in a single particle, resulting in significantly stronger fluorescence signals¹⁵¹. This strategy has resulted in ultra sensitive bacterial detection at a single cell level. Meanwhile, semiconductor quantum dots (QDs) have also emerged as a promising class of fluorophores for bacterial detection. Compared to organic fluorophores, QDs are brighter and more stable; they also exhibit broad absorption and narrow emission spectra, a property useful for simultaneous excitation and detection¹⁵². Ligand-conjugated QDs have been extensively explored for the detection of various bacteria, including *Escherichia coli* (*E. coli*), *S. typhimurium*, *Mycobacterium bovis* (*M. bovis*), and oral bacteria^{153–155}. Additional strategies have been explored to further improve the sensitivity of QD-based bacterial detection systems. For example, the binding affinity of QDs coated with zinc(II)-dipicolylamine coordination complexes, a bacterial ligand, has been shown to correlate to the size of the QDs¹⁵⁶. Based on this observation, QDs with tailored sizes have been developed to distinguish different mutants of the same bacterial species. As another example, streptavidin-coated QDs have been used to label engineered bacteriophages following an *in vivo* amplification and biotinylation process¹⁵⁷. This method enabled specific detection of as few as 10 bacteria per milliliter in testing samples.

Besides fluorescence-based detection techniques, iron oxide nanoparticles have received much attention, owing largely to their intrinsic magnetic properties^{158, 159}. Iron oxide nanoparticles coated with pathogen-specific antibodies have been widely used to isolate living bacteria from human blood samples under a magnetic field^{160, 161}. More recently, this technique has been coupled with microfluidic technology and has resulted in high-throughput bacterial detection under various clinical settings^{162–164}. Meanwhile, paramagnetic iron oxide nanoparticles that allow for signal readout with magnetic resonance imaging (MRI) systems have become an attractive new option for ultrasensitive bacterial detection. For *in vitro* diagnosis, iron oxide nanoparticles with a diameter of 21 nm have been coupled with a DNA hybridization technique to enhance the capturing of bacterial 16S rRNAs with a miniaturized micro-NMR system, resulting in rapid and specific pathogen profiling in clinical samples (Figure 5)¹⁶⁵. For *in vivo* diagnosis, iron oxide nanoparticles have also been explored to detect a variety of pathogenic bacteria in animal models, where the high spatial resolution and excellent soft tissue contrast of MRI provided information on both bacterial localization and corresponding host responses¹⁶⁶.

Gold nanoparticles are another emerging nanoparticle platform for bacterial detection. These nanoparticles possess strong light scattering properties and change their plasmon resonance spectrum upon aggregation. This phenomenon has been widely explored for the detection of bacteria-specific DNAs, proteins, and live bacteria¹⁶⁷. For example, individual gold nanoparticles have been precisely cross-linked with switchable linkers, which were designed to break in the presence of target subjects¹⁶⁸. As a result, this design amplified the pathogen-induced nanoparticle aggregation-dispersion process and allowed for visible detection of *E. coli* at a concentration of 100 CFU/mL. In addition, gold nanoparticles can non-specifically quench fluorescent molecules. Based on this phenomenon, a fluorophore displacement strategy has been developed for bacterial detection¹⁶⁹. In this strategy, gold nanoparticles adsorbed with fluorescent polymers such as poly(paraphenyleneethynylene) and polylysine selectively interacted with bacteria and released the bound fluorescent polymers which were

initially quenched by the gold nanoparticles. The recovered polymer fluorescence allowed for the effective identification of bacteria within minutes.

Recently, rapid progress has been made by integrating nanoparticle-based microbial detection into miniaturized devices such as microfluidic systems and lab-on-a-chip for broader applications¹⁷⁰. These devices potentially perform assays with adequate sensitivity, specificity and reproducibility, yet demand little user input^{163, 171}. The combination of nanoparticle-based detection principles with such devices provide unprecedented opportunities in under-developed regions to perform routine tests, detect the presence of an infectious agent with epidemic potential, and provide guidance for the regional disease control.

7. Conclusions

The advent of nanotechnology, particularly nanoparticle engineering, together with the accumulation of knowledge on infectious diseases, has allowed for significant advancement in the field of antibacterial drug delivery. Major efforts have been devoted to developing various nanoparticle-based delivery platforms including liposomes, polymeric nanoparticles, dendrimers, and inorganic nanoparticles. These nanoparticle approaches have shown excellent outcomes in treating and detecting bacterial pathogens by enabling targeted, responsive, and combinatorial delivery of antibiotics, effective antibacterial vaccination, and rapid detection of bacteria. It is expected that nanotechnology will continue bringing improvements to antimicrobial delivery systems for efficacious, patient-compliant, and cost effective therapeutics as well as the specific and sensitive detection of various infectious diseases.

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Figure 1.

Schematic illustration of major nanoparticle-based delivery platforms for treating bacterial infections: (A) liposome, (B) polymeric nanoparticle, (C) dendrimer, and (D) inorganic nanoparticle.

Figure 2. Schematic illustration of a phospholipid liposome stabilized by charged gold nanoparticles and its drug release in response to pH change or the presence of bacterial toxin.

Figure 3. Schematic preparation of nanoparticle-detained toxins, denoted 'nanotoxoid', consisting of substrate-supported RBC membranes into which pore-forming toxins can spontaneously incorporate. Reproduced with permission from reference 119.

Figure 4.

Schematic illustration of interbilayer-crosslinked multilamellar vesicles (ICMV) for vaccine delivery: (A) OVA-loaded ICMVs with MPLA only on the external surface, and (B) OVA-loaded ICMVs with MPLA throughout the lipid multilayers. Reproduced with permission from reference 134.

Figure 5.

Magneto-DNA assay for the detection of bacterial 16S rRNA. Total RNA is extracted from the specimen, and the 16S rRNA is amplified by asymmetric RT-PCR. Single-strand DNA of the amplified product is then captured by beads conjugated with capture probes, followed by hybridizing with MNPs to form a magnetic sandwich complex. Samples are subsequently analyzed using a miniaturized micro-NMR (μ NMR) system. Reproduced with permission from reference 165.

Table 1

Combinatorial nanoparticles for antibacterial drug delivery

Platform	Formulation	Drug Combination	Targeted bacteria	References
Liposomes	DPPC, DMPG and cholesterol	Gallium and gentamicin	<i>P. aeruginosa</i>	[77]
	DSPC and cholesterol	Bismuth-ethanedithiol (BiEDT) and tobramycin	<i>P. aeruginosa</i> and <i>B. cenocepacia</i>	[78]
	PEGylated liposome	Daptomycin and clarithromycin	MRSA	[85]
	PG, PC and cholesterol	Clarithromycin and ofloxacin	<i>M. avium</i>	[86]
	PC, SA, and cholesterol	Ciprofloxacin and vancomycin	MRSA	[84]
	PC, PEG-DSPE, and cholesterol	Gentamicin and ceftazidime	<i>K. pneumoniae</i>	[83]
	DPPC and cholesterol	Isoniazid and rifampicin	<i>M. tuberculosis</i>	[75]
	PG, PC and cholesterol	Streptomycin and ciprofloxacin	<i>M. avium</i>	[87]
	PC, PE, SA and cholesterol	Amoxicillin trihydrate and ranitidine bismuth citrate	<i>H. pylori</i>	[88]
	PAA, PAH, PC, and cholesterol	Amoxicillin and metronidazole	<i>H. pylori</i>	[89]
Polymeric nanoparticles	PLGA	Rifampin and azithromycin	<i>C. trachomatis</i> and <i>C. pneumoniae</i>	[95]
	PLGA	Rifampicin, isoniazid, pyrazinamide, and ethambutol.	<i>M. tuberculosis</i>	[99]
	Sodium alginate and chitosan	Rifampicin, isoniazid, pyrazinamide, and ethambutol.	<i>M. tuberculosis</i>	[100]
	Chitosan and glutamic acid	Amoxicillin, clarithromycin, and omeprazole	<i>H. pylori</i>	[97]
	Gliadin and Pluronic F-68	Clarithromycin and omeprazole	<i>H. pylori</i>	[98]
	Gliadin, lectin and Pluronic F-68	Amoxicillin, clarithromycin and omeprazole	<i>H. pylori</i>	[96]

Acronyms:

DPPC: 1,2-dipalmitoyl-sn-glycero-3-phosphocholine,
DMPG: 1,2-dimyristoyl-sn-glycero-3-phosphoglycerol
DSPC: 1,2-distearoyl-sn-glycero-3-phosphocholine
DSPE 1,2-distearoyl-sn-glycero-3-phosphoethanolamine
DPPC: dipalmitoylphosphatidylcholine
PG: egg yolk phosphatidylglycerol
PE: phosphatidylethanolamine
PC: phosphatidylcholine
SA: stearylamine
PLGA: poly(lactic acid-co-glycolic acid)
PAA: poly(acrylic acid)
PAH: poly(allylamine hydrochloride)