Antibacterial polymeric nanostructures for biomedical applications

Jing Chen, Fangyingkai Wang, Qiuming Liu and Jianzhong Du*

The high incidence of bacterial infection and the growing resistance of bacteria to conventional antibiotics have resulted in the strong need for the development of new generation of antibiotics. Nano-sized particles have been considered as novel antibacterial agents with high surface area and high reactivity. The overall antibacterial properties of antimicrobial nanostructures can be significantly enhanced compared with conventional antibacterial agents not in a regular nanostructure, showing a better effect in inhibiting the growth and reproduction of microbials such as bacteria and fungi, etc. In this review, recent advances in the research and applications of antimicrobial polymeric nanostructures have been highlighted, including silver-decorated polymer micelles and vesicles, antimicrobial polymer micelles and vesicles, and antimicrobial peptide-based vesicles, etc. Furthermore, we proposed the current challenges and future research directions in the field of antibacterial polymeric nanostructures for the real-world biomedical applications.

Introduction

Antibiotics are naturally occurring or synthetic organic compounds which inhibit or destroy selective bacteria or other microorganisms, generally at low concentrations.1 Compared with a wide range of active chemical agents (biocides) which have a broad spectrum of activity, antibiotics tend to have specific intracellular targets.1

Although many generations of antibiotics have been developed, antibiotic-resistant bacteria are becoming a more and more important threat to public health due to the overuse and the improper use of antibiotics. Therefore, new antimicrobial agents are needed and much work has been devoted to developing highly efficient compounds that are also less susceptible to development of resistance by bacteria.1,2

Among the new antimicrobial agents, silver,3 quaternary ammonium moieties,4,5 silica-based6–9 and carbon-based materials,10–12 reactive-oxygen-species-generating conjugated polymers,13–17 antimicrobial peptides,18 etc. have been widely

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studied. The antibacterial mechanisms of these agents are varied from cell wall/membrane-damaging abrasiveness, release of metal ions to inhibit certain oxidative enzymes, denaturation of protein or interference with DNA/RNA replication, etc.19

The antibacterial activity is related to many factors such as formulation effects, presence of an organic load, synergy, temperature, and dilution.1,20–23 To enhance the antibacterial activities, a great number of work in designing the ideal antibacterial nanoparticles have been investigated. Overall, synthetic chemistry, morphology, size and surface charge of particles are among the most relevant variables affecting antibacterial activity.24–28

In the last few decades, growing attention has been paid to antimicrobial polymers and their nanostructures due to their broad applications in human and animal health care.13,14,29–34 Usually, these polymers can form secondary structures to enrich the antibacterial groups that have the extra ability for drug delivery. Therefore, they are able to kill bacteria upon contact with durable and sustainable antimicrobial activities when covalently attached to the surfaces of a variety of materials.35,36

In this review, we aim to focus on the antibacterial mechanisms and the recent advances of polymeric nanostructures, including silver-decorated polymeric micelles and vesicles, natural or synthetic cationic antimicrobial agent conjugated polymeric nanostructures, etc. We also aim to highlight the approaches to stabilize the silver, to control the shape, to normalize the size, and to reduce the cytotoxicity of silver decorated polymeric nanoparticles. We will discuss the self-assemblies based on cationic antimicrobial polymers and antimicrobial peptides, with the purpose of increasing the antibacterial efficacy and possessing the potential drug delivery capabilities. Finally, we aim to highlight current challenges in the field of antibacterial polymeric nanostructures for real-world biomedical applications.

Silver-decorated polymeric nanostructures

Silver nanoparticles are some of the most widely commercialized nanomaterials used in clinical care and consumer products,37–43 which have shown great toxicity to a broad range of microorganisms (Fig. 1) and can effectively kill both Gram-negative and Gram-positive bacteria, such as *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*).39–41,44,45 As a naturally antibacterial metal, a silver nanoparticle likely has multiple mechanisms of antibacterial activity (Fig. 1).46

First, the membrane permeability of bacteria was thought to be affected by nanoparticles because of the presence of a large number of nanoparticles inside the bacteria. Interaction of silver particles with bacteria membrane and intracellular proteins, particularly sulfur-containing membrane proteins and phosphorus-containing DNA, interferes with cell division and

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causes cell death. Following, some research studies also confirmed the presence of biocidal ionic silver released from nanoparticle surfaces. Upon exposure to ionic silver, bacteria DNA conglomeration defense mechanisms protect it from the toxic surrounding environment but this compromises the bacteria replication ability. Thus, the responses to ionic silver and nanoparticles are different, but both are essential to a complete understanding of the antibacterial activity of silver nanoparticles.

However, the agglomeration problem of silver nanoparticles has significantly restricted their applications. Once silver nanoparticles agglomerate to form micro particles or aggregates, their antibacterial activities decrease sharply. Therefore, templates such as polymer micelles, polymer vesicles, microgels and dendrimers have been used to prevent particle agglomeration. However, for many decades the agglomeration problem has not been solved thoroughly. Therefore, exploring a facile, efficient and controlled template for preparing silver nanoparticles with long-term stability is still of interest for many scientists.

For example, our group reported the design and preparation of water dispersible silver-decorated polymer vesicles and micelles based on an amphiphilic block-statistical copolymer, PEO-b-P(DMA-stat-tBA) (polymer 1 in Fig. 2) and its partially hydrolysed derivative, PEO-b-P(DMA-stat-tBA-stat-AA) (polymer 2 in Fig. 2). In both block copolymers, PDMA chains displayed variable pKₐ values due to the interaction of each block in the copolymer chains. Therefore, it is possible to prepare different nanostructures by simply changing the pH of the copolymer solution. Then silver nanoparticles were in situ generated in the membrane of the polymer vesicles or the core of the micelles (Fig. 2).

Those water dispersible silver-decorated polymer micelles and vesicles showed excellent antibacterial efficacy against E. coli with quite low minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC).

To further prepare ultrafine water-dispersible silver nanoparticles with long-term stability, a role-switching method was developed based on a soft deformable block copolymer vesicle. As illustrated in Fig. 3, by vesicle templating, the Ag⁺ ions can be easily absorbed by the PAA segments within the loose vesicle membrane, leading to an even distribution of Ag⁺ ions. During the process of reduction, the pH jump leads to the break-up of the Ag⁺-adsorbed polymer vesicles to afford ultrafine silver nanoparticles without the loss of the uniformity of the distribution of Ag⁺ ions.

Those ultrafine silver nanoparticles showed excellent antibacterial efficacy against both Gram-negative and Gram-positive bacteria with quite low MICs of 16.9 μg mL⁻¹ and 8.45 μg mL⁻¹, respectively. The key point of this role-switching method is using polymer vesicle as the template and its subsequent deformation into micelles during the reduction process of Ag⁺ to Ag(0) to stabilize the final silver nanoparticles.

Besides the agglomeration problem, the metabolization of silver nanoparticles is another major challenge to their applications, especially for in vivo antibacterial treatment. Our group recently reported an enzymatically degradable polymer vesicle decorated with silver nanoparticles, which showed low cytotoxicity against human normal liver L02 cells near the minimum inhibitory concentrations (MICs) but excellent antibacterial efficacy against both Gram-negative and Gram-positive bacteria with quite low MICs of 3.56 μg mL⁻¹ and 7.12 μg mL⁻¹, respectively, exhibiting promising potential applications in nanomedicine.

Alternatively, to decrease the cytotoxicity of silver nanoparticles and increase the tensile strength of materials, nanocomposites from a waterborne polyetherurethane (PEU) ionomer and silver nanoparticles were prepared without the use of any cross-linker.
The PEU showed high tensile strength and the addition of silver nanoparticles further increased its thermal stability, and the PEU–Ag nanocomposites exhibited a strong bacteriostatic effect on the growth of *E. coli* and *S. aureus*.

Overall, the silver-decorated polymeric nanoparticles have a strong antimicrobial activity against both Gram-positive and Gram-negative bacteria. However, further studies are needed to solve the agglomeration and the cytotoxicity problems to meet various requirements such as higher concentration. In addition, synthetic nanocomposites may have limited biocompatibility, leading to inflammation phenomena and even hazardous immunogenic responses. Such problems have been partially solved by using natural or bio-inspired polymers. Further studies on the silver-decorated polymeric nanoparticles for *in vivo* applications may greatly contribute to this area.

### Cationic antimicrobial agent conjugated polymeric nanostructures

Cationic compounds have emerged as promising candidates as antimicrobial agents with decreased potential for resistance development. Among them, cationic surfactants, lipids, peptides, and natural or synthetic cationic polymers have been intensively studied as antimicrobial agents by themselves or in sophisticated formulations.

Usually, the following sequence of events occurs with microorganisms exposed to cationic agents: (i) adsorption and penetration of the agent into the cell wall; (ii) reaction with the cytoplasmic membrane (lipid or protein) followed by membrane disorganization; (iii) leakage of intracellular low-molecular-weight materials; (iv) degradation of proteins and nucleic acids; and (v) wall lysis caused by autolytic enzymes. These would be a loss of structural organization and integrity of the cytoplasmic membrane in bacteria, together with other damaging effects to the bacterial cells.

In this section, polymeric cationic antibacterial agents, and synthetic and natural antimicrobial peptides have been highlighted.

### Polymeric cationic antibacterial agents

Fig. 5 shows a possible mechanism of polymeric cationic antibacterial activity. Normal bacterial membranes (panel a) are stabilized by Ca$^{2+}$ ions binding anionic charged phospholipids. Cationic polymers rapidly displace Ca$^{2+}$ (panel b), leading to loss of fluidity (panel c) and eventual phase separation of different lipids. Domains in the membrane then undergo a transition to more smaller micelles.

Furthermore, antimicrobial cationic polymers can effectively inhibit the growth of bacteria and other microbes without releasing low molecular weight toxic chemicals into the environment. It is noteworthy that the common bacterial strains, such as *E. coli* and *S. aureus*, do not develop resistance against polymeric biocides. Antimicrobial polymers usually contain polycationic structures, such as substituted quaternary ammonium compounds, phosphonium salts, *N*-alkyl pyridinium salts, and rhodamine derivatives.
Unlike common antimicrobial polymer films, self-assembled cationic polymeric nanoparticles can form a secondary structure before interacting with the microbial membrane, and are expected to have better antimicrobial properties. In the natural cationic antimicrobial polymers, chitosan is one of the most widely applied polymers due to its great biological activities, low toxicity toward mammalian cells, antibacterial activity in controlling growth of bacteria and inhibiting viral multiplication.

Wang’s group investigated the use of chitosan nanoparticles as bactericidal agents in poly(methyl methacrylate) (PMMA) bone cement. To increase the antibacterial activity and solubility of chitosan, quaternary ammonium chitosan derivative nanoparticles have also been prepared. The results showed that chitosan and quaternary ammonium chitosan nanoparticles provided a significant additional bactericidal effect to the bone cement with no cytotoxicity, indicating a new promising strategy for combating joint implant infection.

Polymers with quaternary ammonium moieties have good antibacterial property, which can be further enhanced when forming nanoparticles because of the increase in the local concentration of cationic charge.

For example, Hedrick et al. reported a quaternary ammonium compound containing biodegradable and in vivo applicable antimicrobial polymer nanoparticles synthesized by metal-free organocatalytic ring-opening polymerization of functional cyclic carbonate (Fig. 6A–C). The cationic polymer micelles have a strong effect against growth drug-resistant Gram-positive bacteria, as well as fungi. As shown in the transmission electron microscopy (TEM) results (Fig. 6D), the cell walls and membranes of the microorganisms were damaged, and cell lysis was observed after treatment with the micelles. Their MIC values vary from 4.3–10.8 μM as they are cell-type-dependent.

However, quaternary ammonium compounds may lead to haemolysis, which is a major harmful side effect of many cationic polymers. Therefore, polymers without quaternary ammonium have been selected for the preparation of antibacterial polymeric nanoparticles.

Among these polycationic substances, poly[2-(tert-butylamino-ethyl) methacrylate] (PTA) has a high antibacterial activity and a low toxicity to human cells. It is partially hydrophilic and partially hydrophobic in neutral water as its pKₐ is 9.12 and can exchange with the Ca²⁺ or/and Mg²⁺ cation in the outer membrane of bacteria. Once they are displaced by an external agent, the outer membrane is disorganized and the lysis of cell occurs, which results in the death of the bacteria. Therefore, PTA exhibits antibacterial activity without quaternization, which is not the case with other amine-containing polycationic substances.

For example, Jang et al. coated PTA chains on the surface of silica nanoparticles, which showed size-dependent antimicrobial efficacy.

In 2012, we synthesized PTA-based ABC triblock copolymers (PEO₄₃-b-PCL₂₀-b-PTA₂₀ and PEO₅₁-b-PCL₂₀-b-PTA₁₀), which were then self-assembled into water-dispersible and biodegradable polymer micelles with good antibacterial activity in the absence of quaternary ammonium moieties or loaded biocides. Upon degradation of PCL, the PEO and PTA blocks were cut off (Fig. 7A).
The self-assembled nanostructure leads to strong interactions between the polymer and the cell wall/membrane due to higher local concentrations of positive charges, which eventually translate to effective antimicrobial activities. Micelles from PEO43-b-PCL20-b-PTA20 (polymer 1) have MBC values of 0.30 and 0.15 mM against *E. coli* and *S. aureus*, respectively (Fig. 7B). The MBCs of micelles from PEO43-b-PCL20-b-PTA30 (polymer 2) are 0.20 and 0.08 mM, respectively (Fig. 7B).87

Furthermore, we developed a novel thermo- and pH-responsive antimicrobial diblock copolymer, PMEO2MA20-b-PTA20, where PMEO2MA is thermo-responsive poly[2-(2-methoxyethoxy)ethyl methacrylate] and PTA is pH-responsive and antibacterial,88 which can be directly dissolved in water to form conventional simple polymer vesicles by simply raising the temperature.

Compared to the individual polymer chains, polymer vesicles exhibit much better antimicrobial efficacy against both Gram-negative and Gram-positive bacteria under physiological conditions with neither quaternary ammonium moieties nor the loading of any external antibiotics as a result of their increased local concentrations of cationic charges.88

Moreover, this copolymer can self-assemble into an “armed” high-genus block copolymer vesicle by a solvent switch method, which is different from the above direct dissolution method (Fig. 8a and b).89 Interestingly, branched cylinders were formed at 20 °C when DMF was replaced by pure neutral water, which could be eventually transformed into perforated high-genus vesicles when heated to a higher temperature at 37 °C (Fig. 8a and b).89

The high-genus vesicles have more internal barriers than the simple polymer vesicles, showing better antibacterial activity against both Gram-positive and Gram-negative bacteria without quaternary ammonium moieties or the loading of any external antibiotics compared to the non-self-assembled individual polymer chains, or the above-mentioned conventional simple vesicle.89

In addition, the haemolysis experiment confirmed that the *H*50 value of this high-genus vesicle was 4.7 mg mL⁻¹, suggesting its excellent blood compatibility.89

Moreover, the high-genus vesicle could also be used as an efficient drug delivery carrier with more internal barriers for drug molecules than conventional simple vesicles, which can efficiently kill liver cancer cells (HCCLM3) in a dose-dependent fashion (Fig. 8c). Therefore, this “armed” drug delivery vehicle makes antibacterial and anticancer therapeutic processes proceed.
spontaneously, representing a safer and more efficient drug delivery system in nanomedicine.99

Recently, dendrimers have received considerable attention for antibacterial applications because of their unique properties such as controlled size, low dispersivity and flexibility of modifying the terminal functional groups.90–93 Those dendrimers could also be self-assembled into nanoparticles for improving the antibacterial activity.

For example, Yao had modified the poly(amidoamine) (PAMAM) dendrimers with quaternized carboxymethyl chitosan (CM-HTCC). The CM-HTCC–PAMAM nanoparticles exhibited better antibacterial activity against Gram-negative bacteria E. coli, but slightly affected the growth of Gram-positive bacteria S. aureus compared with quaternized chitosan.94

**Antimicrobial peptides**

Antimicrobial peptides (AMPs) are natural, amphiphilic sequences of 5–50 amino acid residues with net positive charges.63,95 They are produced by bacteria, plants and animals (both vertebrates and invertebrates).63,64,96,97 Recently, AMPs have been termed “natural antibiotics” because they show a broad-spectrum of antimicrobial activities against various microorganisms, including Gram-positive and Gram-negative bacteria, fungi and viruses.63 A list of well-studied antibacterial peptides is summarized in Table 1.

AMPs are generally accepted as positively charged peptides interacting directly with the negatively charged cellular membranes of bacterial cells, resulting in an increase of membrane permeability, which leads to rapid cell death.98,99 The mechanism of the antimicrobial activities of AMPs has been studied for some selected peptides. Functions of these peptides vary from membrane permeabilization to actions on an array of intracellular target molecules including immune-modulatory activities. The peptides can be membrane-disruptive, resulting in cell lysis. Alternatively, the membrane interaction can lead to the formation of transient pores and the transport of peptides inside the cell, bringing them into contact with intracellular targets.

As shown in Fig. 9, the listed models explaining the mechanisms of membrane permeabilization include: (A) carpet, peptide chains cover the surface of membranes in a carpet-like manner and dissolve it like a detergent beyond a threshold concentration for which a high peptide-to-lipid ratio is required; (B) barrel stave, the peptides bind to the cell membrane, then the peptides themselves insert into the hydrophobic core of the membrane forming a pore, causing leakage of the cytoplasmic material and death of the cell; (C) wormhole or toroidal, the peptides aggregate and tempt the lipid monolayers to bend continuously through the pore so that both the inserted peptides and the lipid head groups line the water core; (D) aggregate channel, the peptides insert into the membrane and then cluster into unstructured aggregates that span the membrane. These aggregates are proposed to have water molecules associated with them providing channels for leakage of ions and possibly larger molecules through the membrane (Fig. 9).100–102

However, these natural peptides as well as their peptide analogues are expensive to prepare and difficult to produce on a large scale, limiting their potential use to certain pharmaceutical applications.

Recently, a number of nonnatural peptides with designed sequences have been elaborated to provide biologically active structures.116–118 In particular, facially amphiphilic peptides built from amino acids can mimic both the structures and biological function of natural antimicrobial peptides such as magainins and cecropins.

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**Table 1** Representative antibacterial peptides

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<tr>
<th>Antimicrobial peptide name</th>
<th>Structure</th>
<th>Sequence</th>
<th>Antibacterial activities</th>
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<tbody>
<tr>
<td>Magainin</td>
<td>z-Helix</td>
<td>GIGKFLHSACKFGKAFVGEIMNS</td>
<td>+</td>
</tr>
<tr>
<td>β-Defensin3</td>
<td>β-Sheet</td>
<td>GIINLQKYCCVRVGGRCVAVLSC(LPKEEQIGKC2</td>
<td>+</td>
</tr>
<tr>
<td>Lactoferrin B</td>
<td>β-Hairpin</td>
<td>FKCR,RRWQWRMKKLGAPSCYVRRFA</td>
<td>+</td>
</tr>
<tr>
<td>Polymyxin E (colistin)</td>
<td>Cyclic polypeptides</td>
<td>Fatty acid-Dab1-T-Dab-Dab2-Dab-Dlb1-Dab-Dab-Dab1</td>
<td>–</td>
</tr>
</tbody>
</table>

a Cysteines forming disulfide bonds are numbered with subscripts to indicate their pairings. b Aminobutyric acid (Abu), 2,3-didehydroalanine (Dha), 2,3-didehydrobutyryline (Dhb). c The fatty acid molecule is 6-methyloctanoic acid for colistin A and 6-methylheptanoic acid for colistin B, diaminobutyric acid (Dab).
For example, Tew and co-workers\textsuperscript{116} have designed a series of facially amphiphilic arylamide polymers that capture the physical and biological properties of this class of antimicrobial peptides synthesized from inexpensive monomers. The design process was aided by molecular calculations with density functional theory-computed torsional potentials. These amphiphilic polymers may be applied in situations where inexpensive antimicrobial agents are required.

In another example, one kind of poly(oxanorbornene)-based synthetic mimics of antimicrobial peptides (SMAMPs) was reported.\textsuperscript{119} This was achieved by carefully designing the distribution of the chemical functional groups on the polymer backbone, so that the polymers were also facially amphiphilic. It was further demonstrated that such polymer-based SMAMPs also target the bacterial membrane, most likely by a mechanism similar to that of AMPs. The combined properties of excellent antimicrobial activity, cell selectivity, low resistance formation potential and easy availability make SMAMPs ideal candidates for biomedical applications (Fig. 10).

The antibacterial efficacy can be enhanced significantly when an individual antibacterial polymer chain self-assembled into polymer micelles or vesicles due to the concentration of local positive charges.\textsuperscript{87–89}

For example, Yang and coworkers designed a short amphiphilic peptide (CG\textsubscript{3}R\textsubscript{6}TAT), which contains a hydrophilic block of cell penetrating peptide TAT and six arginine residues (R\textsubscript{6} or Arg\textsubscript{6}) for adding more cationic charges to improve membrane translocation.\textsuperscript{72} Under the driving force of the hydrophobic block of cholesterol the core–shell nanoparticles formed by self-assembly. The nanoparticles showed strong antimicrobial properties against a range of bacteria, yeasts and fungi. What’s more, the nanoparticles can also cross the blood-brain barrier and suppress bacterial growth in infected brains (Fig. 11).

Compared with solid nanoparticles, polymer vesicles are excellent carriers, which can be used to deliver drugs,\textsuperscript{120–123} antioxidant agents,\textsuperscript{124} magnetic resonance imaging (MRI) contrast agents,\textsuperscript{125–127} proteins, DNA and RNA, etc.\textsuperscript{128,129}

To combine the advantages of the antibacterial capability of AMPs and the drug delivery capability of polymer vesicles, our group recently reported a novel kind of “armed” carrier: an antibacterial polypeptide-grafted chitosan-based vesicle with an excellent antibacterial efficacy against both Gram-positive and Gram-negative bacteria (Fig. 12).\textsuperscript{130}

One sixth of –COOH groups in the acid-functionalized chitosan were grafted by an antibacterial peptide [poly(Lys\textsubscript{11-stat}Phe\textsubscript{10})-g-Cs\textsubscript{10-stat-Cs\textsubscript{10-stat}-ECs\textsubscript{12}r-polymers 8 in Fig. 13) vesicles

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The membrane of such kind of vesicle is composed of both hydrophobic and entrapped hydrophilic moieties, which has a “fuzzy” boundary between hydrophilic and hydrophobic moieties, providing new opportunities for making a range of functional materials. Drugs are released faster in the presence of protease due to biodegradation of polypeptides in the vesicle membrane.

This vesicle has excellent antibacterial activity (Fig. 13), excellent blood compatibility and low cytotoxicity. To confirm the enhancement of the antibacterial efficacy of [poly(Lys\textsubscript{11-stat}Phe\textsubscript{10})-g-Cs\textsubscript{10-stat-Cs\textsubscript{10-stat}-ECs\textsubscript{12}] vesicles (polymer 8 in Fig. 13) vesicles
Compared with the individual polymer chain, the self-assembled nanostructure can significantly improve the antibacterial efficacy resulting from the 2nd or 3rd structure-dependent highly concentrated antibacterial agents. Meanwhile, based on this antibacterial enhancement property it is possible to restore the antibacterial activity of some currently less effective or ineffective antibiotics, and to decrease the risk of antibiotic-resistance of a new generation of antibiotics in the future.

Nowadays, infection has the trend to happen together with multiple complications, such as cancer, over-reaction of the immune system and so on. Also, the complications will seriously threaten patients’ lives. Thus, compounded functional or “smart” nanostructures with both excellent antibacterial activities and controlled drug delivery capabilities are desired to solve this problem. For example, our group has recently reported several antibacterial polymeric vesicles with promising capability of delivering anticancer and other drugs simultaneously.89,130 Wang et al. revealed that conjugated polymers can provide efficient antimicrobial and anticancer activities by generating reactive oxygen species upon light radiation.15–17

In general, biocompatibility and biodegradability of nanoparticles are important issues for in vivo biomedical applications. Therefore, well-designed biocompatible and biodegradable polymers are needed for further decreasing the cytotoxicity of silver nanoparticles and other conjugated antibacterial agents.

Furthermore, more and more “smart” antibacterial nano-carriers with specific targeting, stable structure, high drug loading efficiency, and sensitivity to conditions are needed to be designed to meet various biomedical requirements. Moreover, the overall evaluation based on in vitro and in vivo studies on the antibacterial activity, drug delivery efficacy, biocompatibility and biodegradability of functional antimicrobial polymeric nanostructures is also required to meet the clinical requirements.

Moreover, deeper insight into the observation of more physiologically and biologically relevant modes of bacterial interaction with nano-materials is strongly needed in the future to develop new approaches and materials with broad and persistent microbe killing capability and low toxicity to mammalian cells. Hopefully, antibacterial polymeric nanostructures by the self-assembly technique may provide an alternative way to design more effective, more clinically promising, and less antibiotic-resistant multifunctional biomedical nanomaterials.

**Abbreviations**

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>Abu</td>
<td>Aminobutyric acid</td>
</tr>
<tr>
<td>AMP</td>
<td>Antimicrobial peptide</td>
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<tr>
<td>Arg</td>
<td>Arginine</td>
</tr>
<tr>
<td>CM-HTCC</td>
<td>Quaternized carboxymethyl chitosan–COOH</td>
</tr>
<tr>
<td>Dab</td>
<td>Diaminobutyric acid</td>
</tr>
<tr>
<td>Dha</td>
<td>2,3-Didehydroalanine</td>
</tr>
<tr>
<td>Dhb</td>
<td>2,3-Didehydrobutyryne</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>E. coli</td>
<td>Escherichia coli</td>
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Compared to the poly(Lys11-stat-Phe10) chain (polymer 4 in Fig. 13, which is the effective antibacterial component in polymer 8), their MICs against both Gram-negative E. coli and Gram-positive S. aureus were evaluated (Fig. 13): 16 µg mL⁻¹ (polymer 8 vesicles) and 31 µg mL⁻¹ (polymer 4 chain which is not in any assembled state). This is due to a higher local positive charge density in vesicles as mentioned before.

Overall, patients after tumor surgery may benefit from this “armed” carrier because it is highly anti-inflammatory and is able to deliver anticancer and antiepileptic drugs simultaneously. This concept can also be extended to design a variety of new delivery vehicles with antibacterial, antitumor, and many other functions.

**Conclusions and future outlooks**

Polymeric nanoparticles have been identified to inhibit a variety of bacterial species in vitro, including some multi-drug-resistant microbes. In this review, the recent advances in the antibacterial polymeric nanostructures such as micelles and vesicles have been highlighted.
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Notes and references

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