APSB
Acta Pharmaceutica Sinica B

2021

REVIEW

Membrane-disruptive peptides/peptidomimetics-based therapeutics: Promising systems to combat bacteria and cancer in the drug-resistant era

Liming Lin[a,b], Jiaying Chi[b], Yilang Yan[b], Rui Luo[b], Xiaoqian Feng[a,b], Yuwei Zheng[b], Dongyi Xian[b], Xin Li[d], Guilan Quan[b], Daojun Liu[c], Chuanbin Wu[b], Chao Lu[b,*], Xin Pan[a]

[a]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
[b]College of Pharmacy, Jinan University, Guangzhou 511443, China
[c]Shantou University Medical College, Shantou 515041, China
[d]The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou 510630, China

Abstract Membrane-disruptive peptides/peptidomimetics (MDPs) are antimicrobials or anticarcinogens that present a general killing mechanism through the physical disruption of cell membranes, in contrast to conventional chemotherapeutic drugs, which act on precise targets such as DNA or specific enzymes. Owing to their rapid action, broad-spectrum activity, and mechanisms of action that potentially hinder the development of resistance, MDPs have been increasingly considered as future therapeutics in the drug-resistant era. Recently, growing experimental evidence has demonstrated that MDPs can also be utilized as adjuvants to enhance the therapeutic effects of other agents. In this review, we evaluate the literature around the broad-spectrum antimicrobial properties and anticancer activity of MDPs, and summarize the current development and mechanisms of MDPs alone or in combination with other agents. Notably, this review highlights recent advances in the design of various MDP-based drug delivery systems that can improve the therapeutic effect of MDPs, minimize side effects, and promote the co-delivery of multiple chemotherapeutics, for more efficient antimicrobial and anticancer therapy.

*Corresponding author. Tel./fax: +86 20 39943115.
E-mail address: chaolu@jnu.edu.cn (Chao Lu).

1. Introduction

In the last decade, antimicrobial resistance (AMR) has sparked a global health crisis due to the inability of conventional therapeutics to treat bacterial infection[1]. It is estimated that AMR may become the leading cause of death and account for 10 million deaths by 2050 (Fig. 1A)[2,3]. The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* species), so-called because of their ability to "escape" the effects of clinically useful antibiotics (Fig. 1B), are the main causes of hospital-acquired infections, such as invasive infections and sepsis in burn patient, pneumonia, as well as surgical wound infections[4,5].

Cancer is the leading cause of death in many countries according to a recent study conducted in 21 countries from five continents (Fig. 1C)[6]. The top three cancer types for estimated cases and deaths worldwide are female breast cancer (11.7% of total cases), closely followed by lung cancer (11.4%) and colorectal cancer (10.0%), in which female breast cancer and lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death, respectively (Fig. 1D)[7]. Furthermore, while the global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020, insurgence of drug resistance during

chemotherapy is still a major cause of cancer relapse and consequent failure of therapy for cancer patients[7,8].

Under the current global pandemic of chemo-resistance or multi-drug resistance (MDR) situation, membrane-disruptive peptide/peptidomimetics (MDPs), defined as peptides or their mimics that present a killing activity against drug-resistant cells through a membrane disruption mechanism, have received much attention. Among those, one of the most important classes of MDPs are represented by antimicrobial peptides (AMPs), including natural AMPs and synthetic mimics of AMPs (SMAMPs)[9−11]. While these MDPs offer the advantage of targeting and disrupting bacterial cell membranes, increasing experimental researches demonstrate that some of these compounds could also provide anticancer activity, thus termed as anticancer peptides (ACPs). The unique killing mechanisms could endow MDPs with not only rapid killing kinetics, broad-spectrum activity, and low resistance rates in combating microbial infections and cancer, but also potentials in enhancing the therapeutic efficiency by permeabilizing cell membrane, promoting the intracellular drug accumulation, and increasing the sensitivity of cells to drug interference[12−15].

In this contribution, we present a comprehensive review to summarize the common type, structure−activity relationships, and acting mechanisms of MDPs. Subsequently, this review highlights
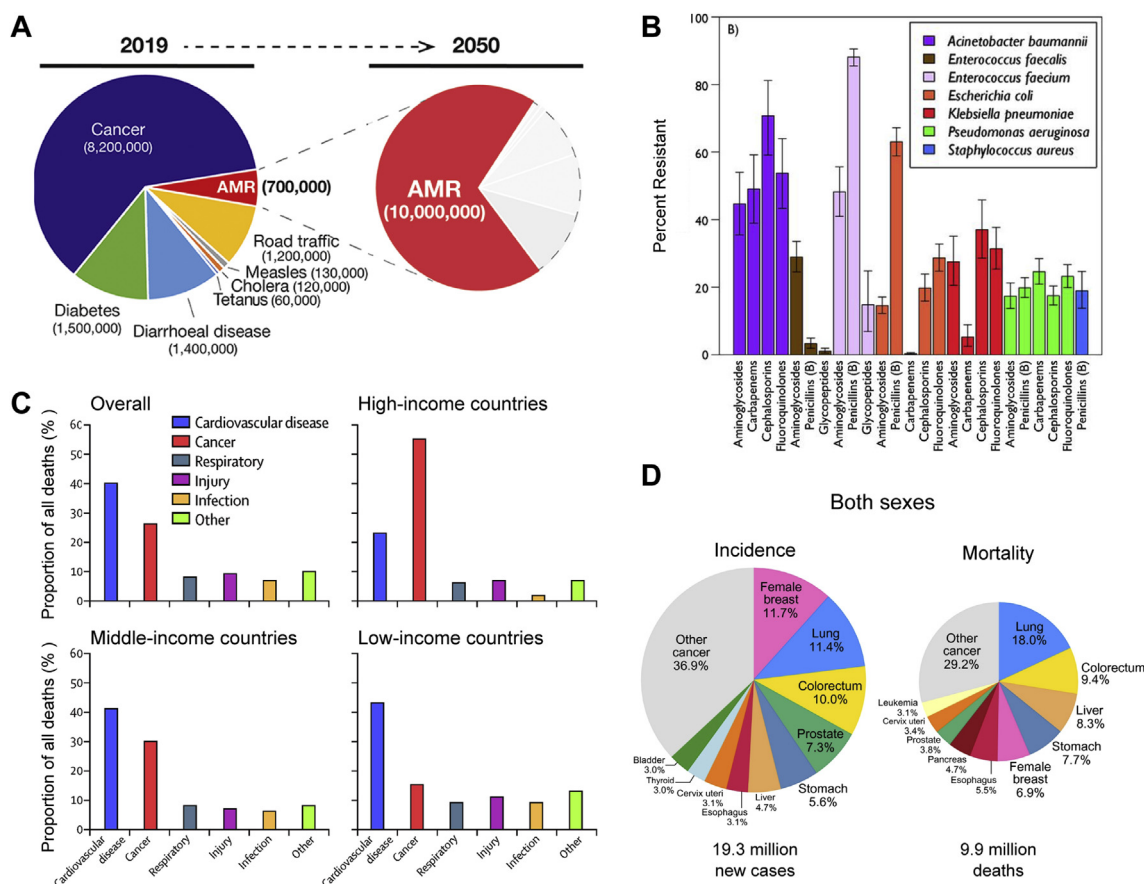
Figure 1   Current situation and global trends of AMR and cancer. (A) AMR is a global epidemic that is projected to result in a higher mortality rate than both cancer and diabetes in future. Reproduced with permission from Ref. 2. Copyright © 2020, Frontiers Media S.A. (B) Global antibiotic resistance rates for WHO priority pathogens. Reproduced with permission from Ref. 4. Copyright © 2019, BMJ. (C) Different proportions of the most common causes of death in high, middle and low income countries. Reproduced with permission from Ref. 6. Copyright © 2020, Elsevier. (D) The incidence and mortality for top 10 cancer types for man and woman. Reproduced with permission from Ref. 7. Copyright © 2019, John Wiley and Sons.

the therapeutic potential of MDPs in combination with other agents, including small-molecule drugs, metal materials, and photoresponsive materials. In particular, this review illustrates the rational design, enhanced therapeutic effect, and potential applications of various MDP-based drug delivery systems for intravenous, transdermal, pulmonary, and oral routes of administration.

2. MDPs and their mechanisms of action

2.1. AMPs for antibacterial application

Natural AMPs represent a wide range of short, cationic, gene-encoded peptides found in the innate immune system of a wide range of organisms ranging from prokaryotes to humans, providing a fast-acting weapon against invading pathogens, including bacteria, fungi, and yeast[16–18]. According to Antimicrobial Peptide Database[37], more than 3000 natural AMPs have been discovered, of which 74.1% are from animals, 11.0% from plants, 11.8% from bacteria and fungi, and a small part of AMPs from archaea and protists. In addition, several AMPs have been approved for clinical application and food storage, including gramicidin D, gramicidin S, bacitracin, polymyxin B (PMB), daptomycin (DAP), nisin, and colistin[15,37]. Peptides, such as

ghrelin[19], D2A21[20], and brilacidin (PMX-30063)[21], have entered phase II or even phase III trials.

2.1.1. Peptide-membrane interactions

AMPs have already been described as molecules presenting killing mechanisms at the membrane level but also acting toward intracellular targets (e.g., DNA, RNA, and enzymes) in some cases, which significantly improve their therapeutic effect compared to one-target-specific drugs (Fig. 2A)[22]. Although factors, such as cationic charge, hydrophobicity, secondary structures, specific sequences, molecular weight, size, and shape, all exert influence on the performance of these agents to varying degrees. An amphiphilic structure and a net positive charge are the most important and common features that affect the mode of action of AMPs[9,14,23]. Natural AMPs generally consist of 12−50 amino acids, containing >2 cationic amino acids (e.g., lysine and arginine) and approximately 50% hydrophobic amino acids (e.g., tryptophan, leucine, and alanine)[9,24]. In addition to the structural parameters of AMPs, the membrane lipid composition of bacteria is also a crucial prerequisite for the interaction between AMPs and bacteria. The bacterial membrane is an amphiphilic structure; therefore, the amphiphilic nature of AMPs affects their interaction with the bacterial cell membrane. In general, the outermost leaflet of the bacterial cytoplasmic membrane contains a high percentage

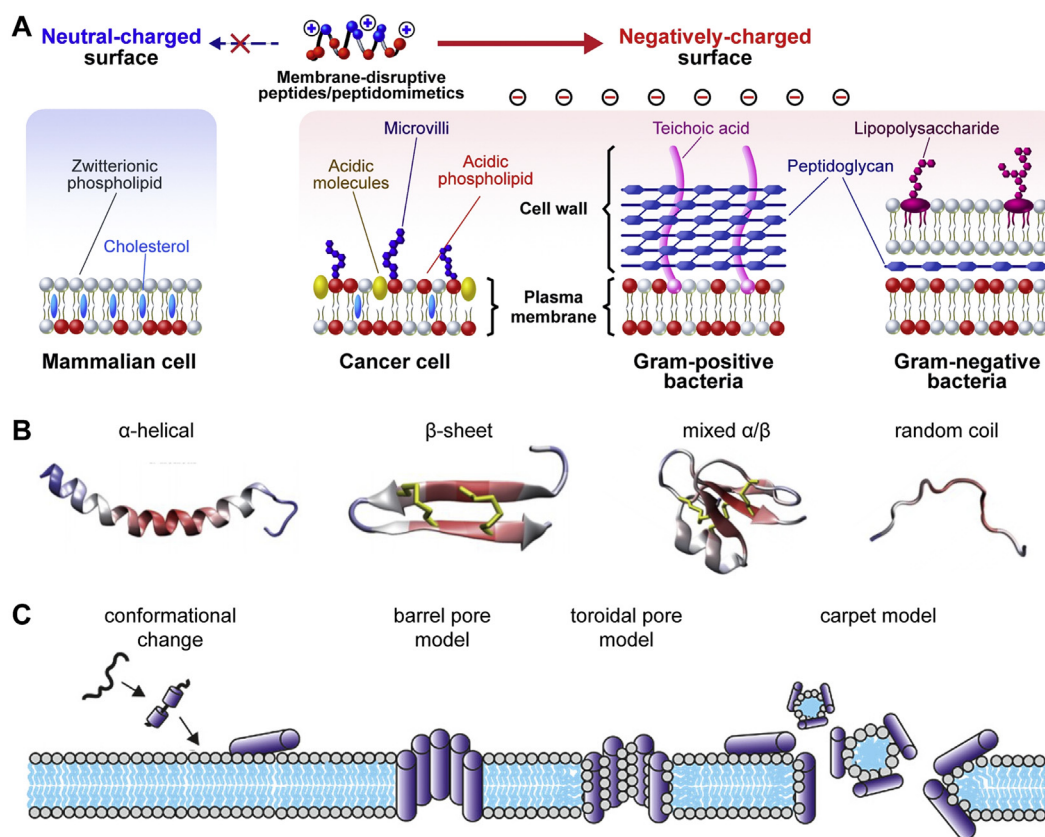**Figure 2** Understanding of killing mechanism of MDPs. (A) Different compositions between mammalian cells, cancer and microbial cells accounting for high selectivity of MDPs. (B) Four representative secondary structures of AMPs. Reproduced with permission from Ref. 28. Copyright © 2014, The Royal Society of Chemistry. (C) Representative acting modes of AMPs. Reproduced with permission from Ref. 29. Copyright © 2019, MDPI AG.

of lipids with negatively charged head groups, such as phosphatidylglycerol, cardiolipin, and phosphatidylserine. Apart from anionic phospholipids, teichoic acid on the surface of Gram-positive bacteria and lipopolysaccharide (LPS) in the cell wall of Gram-negative bacteria also carry a strong negative charge[25]. Therefore, it is widely recognized that the electrostatic interaction between AMPs and negatively charged bacterial surfaces is the driving force of their selectivity for bacteria over mammalian cells, in which the outer leaflet of the mammalian cell membrane is principally composed of lipids with zero net charges, such as phosphatidylcholine and sphingomyelin[15]. In addition, the hydrophobicity of AMPs also plays an essential role in affecting membrane function and integrity[26]. In the transmembrane process, the hydrophobic part of AMPs drives the penetration of the peptide into the hydrophobic lipid bilayer interior, and the penetration process causes depolarization and permeabilization of bacterial membranes[27].

2.1.2. Sequence

Recent studies have suggested that some AMPs with specific sequences can target specific receptors or essential components of the bacterial membrane other than electrostatic effects[30]. For example, both microcins and colicins contain specific sequences to recognize outer membrane receptors specifically expressed by enterobacteria, thus exhibiting a narrow spectrum of activity[31]. Additionally, several AMPs, such as PMB[32] and human β-defensins[33], specifically interact with LPS or their lipid component Lipid A composing the outer membrane of Gram-negative bacteria. Another favorite target for AMPs is the peptidoglycan precursor, Lipid II, which is selectively bound by a series of defensins to block bacterial cell wall biosynthesis[34,35]. Overall, regardless of how AMPs interact with the cell membrane, such interactions at the surface of microorganisms are required for the activity of AMPs.

2.1.3. Secondary structures

In addition to various amino acid residue compositions, the secondary structures of AMPs also have a significant influence on their amphiphilic and transmembrane behavior. When in contact with microbial cell membranes, most AMPs fold into secondary structures. AMPs can be categorized into four families based on their secondary structure: α-helical, β-sheet, combined α-helix and β-sheet (αβ), and random coil (Fig. 2B), of which α-helical peptides represent the largest proportion of AMPs that have been found[23,36]. In general, the hydrophobicity increases in the following order: random coil < α-helix < β-sheet, and an α-helix secondary structure appears to be more compact than a random coil[37]. Secondary structures, such as α-helices and β-sheets, promote the interaction of natural AMPs with the bacterial cell membrane[38].

2.1.4. Other common features

Natural AMPs share several common features. One important structural feature is capping interactions observed at the N-terminus of the peptide. Tossi's group[39] reported a statistical analysis of residue distribution in the N-terminal region of α-helical AMPs from different sources, observing that glycine at position 1 is a preponderant. Glycine usually acts as a capping residue α-helix and offers resistance to proteolytic cleavage by aminopeptidases. Additionally, peptide amidation is commonly used to improve the resistance of many peptides, such as cecropins, melittin, dermaseptins, PGLa, prophenin, and polyphemusin. Amidation prevents

cleavage by carboxypeptidases and offers an additional hydrogen bond for the formation of α-helices[25].

2.1.5. Antimicrobial mechanisms

Various models of membrane permeation, such as the "barrel-stave," "toroidal," and "carpet" models, have been proposed to describe the probable action mechanism of AMPs (Fig. 2C). All these models assume that AMPs adopt a facially amphiphilic conformation where the hydrophilic and hydrophobic side chains segregate into distinctly opposing regions or faces upon binding to bacterial membranes. In the barrel-stave model, AMP aggregates and spans the membrane, and the perpendicularly inserted AMPs use their hydrophobic face to interact with the hydrophobic lipid tails, forming a peptide bundle in the membrane with a central lumen (1–2 nm) much like a barrel composed of AMPs as staves[9,40]. In the toroidal pore model, the hydrophilic segment of AMPs interacts with the lipid head, inducing a local membrane curvature so that the pore lumen is lined partly by AMPs and partly by lipid heads. As a result, the pore size is dependent on the state of the lipid bilayer, usually forming transmembrane pores around 3–10 nm in diameter. The carpet model describes that the AMPs first bind parallel to the membrane, cover the surface of the membrane in a carpet-like manner, disintegrate the lipid bilayer by forming micelle-like particles, and then form defects larger than 10 nm. In contrast to other models, the carpet model does not require a specific peptide length or structure; thus, many complicated or badly defined AMP-mimetic polymers exert their activity by a "carpet model" mechanism[9,41]. Furthermore, regardless of the chosen membrane perturbation model, a high local membrane-bound concentration (threshold concentration) is required for membrane disruption. AMPs have a stronger interaction with bacterial membranes than mammalian ones. The local concentration of AMPs in a bacterial membrane is much higher than its concentration in the aqueous phase[14].

Although membrane disruption is thought to be the primary mechanism for the antibacterial activity of most AMPs, some studies have recently suggested that some AMPs can kill bacteria by acting with intracellular targets[42,43]. Some AMPs can also cross the membrane to interact with intracellular proteins, DNAs, and organelles, such as PR-39, which can act as a proteolytic agent and inhibit protein and DNA synthesis[44]; And indolicin, which enters the cytoplasm and kills bacterial cells by binding to DNA and inhibiting its synthesis[45]. A study also reported that AMP, Bac71-35, exerts its bactericidal activity by binding to ribosomes and inhibiting protein synthesis[46]. Moreover, some AMPs can also inhibit proteases of microbes; for example, Histatin 5 prevents periodontal tissue destruction by strongly inhibiting the trypsin-like protease produced by *Bacteroides gingivalis*[47]. The translocation of AMPs into the cytoplasmic membrane is a prerequisite for intracellular activity. Moreover, AMPs with cell-penetrating properties can be applied as drug delivery vectors to transport bioactive substances across the cell membrane and their target site[48].

Recently, an increasing number of AMPs are found to exhibit properties of innate immune response modulation, including epithelial cell proliferation, enhanced wound healing, angiogenesis, and regulation of cytokine and chemokine secretion[25]. Many cationic AMPs such as LL-37 and CP26 are capable of neutralizing bacterial endotoxins (*e.g.*, LPS) and reducing endotoxin-induced inflammatory responses. In addition, some AMPs can modulate host immunity by interacting with different receptors on the cell surface (*e.g.*, Toll-like receptor) or cytosol (NOD-like

receptors)[49]. For example, LL-37 can attenuate the Toll-like receptor responses and modulate mitogen-activated protein kinase pathways and responses of tumor necrosis factor and interleukin, to regulate inflammatory responses of macrophages, epithelial cells, peripheral blood mononuclear cells, and whole blood leukocytes[50]. On the other hand, AMPs play a role in the adaptive immune response in which AMPs act as adjuvants to enhance adaptive immunity by directing immune functions towards helper T-cells (Th1 and Th2)[51]. For example, researchers found that cells overexpressing defensins promoted a strong Th1 response, stimulated proliferation of cytotoxic T-cells and natural killer cells, increased production of IL-12 and IFN-γ in mice[52]. Altogether, AMPs exert direct antibacterial activity *via* membrane disruptive mechanisms and play a vital role in innate and adaptive responses, providing efficient protection to the host.

2.2.   SMAMPs for antibacterial application

SMAMPs, such as synthetic AMPs, peptidomimetics, oligomers, and polymers, have become one of the most significant MDP components. These mimics are usually designed to capture the essential physicochemical features of natural AMPs and mimic their functions and structural characteristics, such as amphiphilicity, cationic charge, secondary structure, and composition[9,10,15]. Furthermore, SMAMPs exhibit significant advantages over natural AMPs, such as enhanced antimicrobial activity, flexible framework for chemical modification, improved physicochemical stability, and better compatibility with drug-delivery methodology[53]. Recently, unnatural antibacterial peptidomimetics of various backbone structure have emerged with promising potential, such as poly(α-amino acid)s[54−57], poly(β-amino acid)s[58,59], polymethacrylate[60−62], polymethacrylamide[63,64], poly(2-oxazoline)[65,66], polycarbonates[67,68], polynorbornene[69,70], peptidopolysaccharides[41,71], poly(isobutylene-*alt-N*-alkyl maleimide)[72−74], β-peptides[75], peptoids, and AApeptides[76−80]. The antibacterial performance of these MDPs is primarily affected by factors, such as amphiphilicity, charge, cationic chemical functionality, molecular weight, sequence, biodegradability, and subunit stereoisomerism.

In the past decades, numerous studies, including scanning electron microscopy (SEM), transmission electron microscopy (TEM) and confocal laser scanning microscopy (CLSM) imaging following SYTO9/PI staining, have been conducted to confirm the membrane-disruption effects of SMAMPs[81]. Using high-resolution imaging techniques, such as cryo-TEM and 3D structured illumination microscopy (3D-SIM), Qiao's group[82] found that some SMAMPs, specifically their designed "structurally nanoengineered antimicrobial peptide polymers", may exhibit not only membrane rupture effects but also intracellular activities. Cai and Wu's group[55,57] conducted computational molecular dynamics (MD) simulations, finding that the enhanced interactions of SMAMPs with a lipid membrane played a significant role in enhancing bacterial membrane perturbation and driving the penetration of the peptidomimetics into the bacterial cytoplasm. Recently, some published studies also demonstrated that these kinds of polymer mimics may not only interact with membrane lipids but also specific targets, such as peptidoglycan matrices, LPSs, and lipoteichoic acids[41,83−86]. Furthermore, membrane-disruptive peptidomimetics may provide less opportunity for acquired drug resistance. Yang's group[87] reported that multiple treatments of bacteria with the SMAMPs pEt_20 do not develop

drug resistance as evidenced by an *in vitro* evolution model and genetic sequencing.

2.2.1.   Amphiphilicity

Pioneer studies suggest that amphiphilicity is one of the most important factors determining antimicrobial activity, cytotoxicity, and selectivity of SMAMPs[15,88]. Similar to AMPs, their amphiphilic nature enables SMAMPs to electrostatically interact with the bacterial membrane, whereas their hydrophobic moiety could intensify the interaction of peptidomimetics into the hydrophobic core of the bacterial lipid bilayer[41,89]. However, because less negatively charged lipids are found in the outer leaflet of the mammalian membrane than in the bacterial membrane, an excessive proportion of hydrophobic segments in SMAMPs will result in undesired hemolysis and deterioration of selectivity owing to a significant decrease in the charging effect[88]. Therefore, balanced amphiphilicity is required to achieve high activity and selectivity simultaneously.

The hydrophilic/hydrophobic balance of SMAMPs is difficult to quantify and varies depending on the type of material. Several strategies, including "segregated monomer," "facially amphiphilic," and "same centered" approach, have been typically used by polymer chemists to adjust the hydrophilic/hydrophobic balance of macromolecular antimicrobials (Fig. 3A)[9]. Among them, the "segregated monomer" approach is referred to randomly polymerize relative non-polar monomers with cationic monomers at varied feed ratios between the two monomers to prepare amphiphilic antibacterial copolymers. For example, Yang's group[67] synthesized random polycarbonate copolymers with varying charge density degrees able to form dynamic micelles that readily exposed charged/hydrophobic sequences and exhibited enhanced antibacterial effects against both Gram-positive and -negative bacteria at optimal cationic charge/hydrophobicity ratios. Similarly, antibacterial polymers prepared through a "facially amphiphilic" approach are composed of amphiphilic repeat units in which each unit has both a non-polar moiety and a separate cationic charged moiety, where the non-polar moiety can be adjusted to change the hydrophilic/hydrophobic balance. Tew's group[69] prepared a class of amphiphilic polynorbornene derivatives bearing primary amines and variable-length alkyl moieties as pendant groups that allowed excellent control over the monomer composition, molecular weight, polydispersity, and amphiphilicity to achieve suitable antibacterial activity and selectivity. The third approach is to use "same centered" repeat units, where the repeat unit used to produce homopolymers consist of a long hydrophobic alkyl chain directly attached to a positively charged moiety. Tew's group[90] synthesized a series of amphiphilic polynorbornenes with different quaternary alkyl pyridinium side chains; the alkyl substituents (ethyl, butyl, hexyl, octyl, decyl, and phenylethyl) had a distinct impact on activity and selectivity by balancing the hydrophobic/hydrophilic interactions.

One of the key structural parameters related to helically folded AMPs is the presentation of their facial amphiphilicity upon folding. The clustering of various residues forming hydrophobic and cationic faces on the helical periphery in either a dispersed or perfectly segregated manner (Fig. 3B), which eventually affects the membrane activity of SMAMPs[93]. Therefore, helical SMAMPs may display enhanced membrane activity and permeation by AMP-mimicking models of membrane disruption. For instance, Cai's group[80] reported a class of antimicrobial helical sulfono-γ-AApeptide foldamers that can form stable helical structures in solution and display broad-spectrum and significant
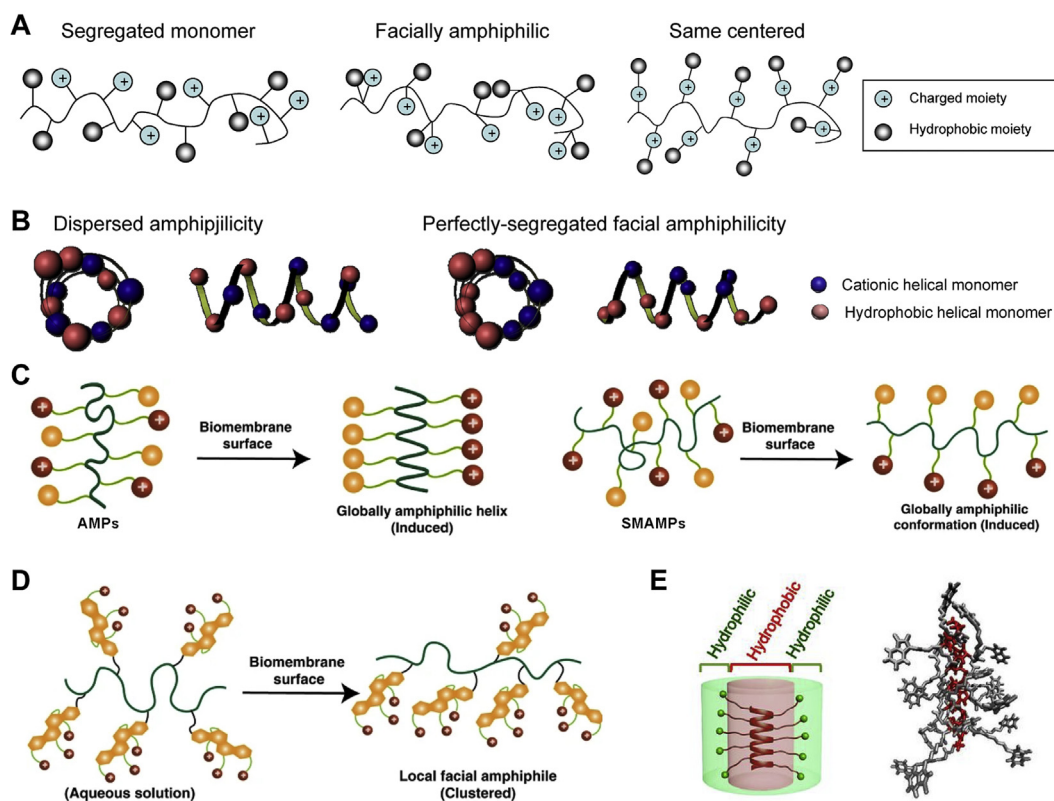
Figure 3 Understanding of the amphiphilicity of SMAMPs. (A) Schematic illustration of strategies for balancing hydrophobicity and hydrophilicity of SMAMPs. (B) Schematic illustration of facial amphiphilicity in helical AMPs. Reproduced with permission from Ref. 9. Copyright © 2018, Elsevier. (C) Globally amphiphilic conformation adopted by SMAMPs upon binding to the biomembrane surface. (D) A flexible macromolecular chain clustering intrinsic local facial amphiphiles. (C) and (D) are reproduced with permission from Ref. 91. Copyright © 2018, Springer Nature. (E) Radially amphiphilic conformation of SMAMPs. Reproduced with permission from Ref. 92. Copyright © 2015, National Academy of Sciences.

antimicrobial activity, taking a mode of action analogous to that of AMPs. However, most antimicrobial polymers with AMP-mimicking designs naturally adopt globally amphiphilic but conformationally irregular helical structures upon binding to negatively charged bacterial membranes (Fig. 3C)[94]. Tang's group[91] argued that most of these approaches rely on uncontrolled polymeric self-aggregation to achieve irregular facial amphiphilicity without helical structures. This conformation would be difficult to manipulate, suffers from a very high entropic penalty from a whole macromolecule, and is unfavorable for adequate interactions with the biomembrane surface. Thus, these polymers suffer from poor selectivity, high cytotoxicity, and low activity against bacteria. Tang's group[89] recently reported a class of cationic bile acid-based polymers as promising amphiphilic antimicrobials, where each repeating unit possesses cluster local facial amphiphilicity to enhance interactions with bacterial cell membranes without requiring a global conformational arrangement associated with highly unfavorable entropic loss (Fig. 3D). In addition, Cheng's group[92] reported a class of unique amphiphilic polypeptides with a hydrophobic internal helical core and a charged exterior shell possessing radial amphiphilicity (Fig. 3E). The radially amphiphilic structure enables SMAMPs to effectively interact with the negatively charged bacterial membrane and protect the polypeptide backbone from proteolytic degradation.

2.2.2. Charge and molecular architecture

The cationic charge indicates that polymers interact with negatively charged bacterial membranes. Several cationic groups have been widely used to endow the cationic characteristics of antibacterial polymers, such as amine groups[95,96], guanidinium groups[57,87], and phosphonium salts[97,98]. Kuroda's group[95] found that amphiphilic poly(methacrylate) systems containing primary or tertiary amine groups exhibit potent antibacterial activity with less or even no hemolytic behavior, whereas copolymers containing quaternary ammonium groups required additional hydrophobic groups to express antibacterial and hemolytic activities. Yan's group[99−101] developed several antibacterial poly(ionic liquid)s (PILs) based on imidazolium-type ionic liquid (IL) monomers with enhanced efficacy, aggregation-induced emission (AIE), and redox−responsive properties, showing promise for antibacterial applications.

Generally, increasing the charging effects (*i.e.*, charge density and number) of MDPs can promote their binding to the anionic biomembrane surface and thus improve membrane-disruptive activities. To date, many linear peptides/peptidomimetics, such as chitosan (CS)[102], linear polyethyleneimine (PEI)[103], α-poly(L-lysine) (PLL)[37], and ε-poly(L-lysine) (EPL)[104,105] have been shown to provide abundant positively charged residues for attaching bacteria. However, increasing studies have demonstrated that

that diverse molecular architecture, including cyclic, dendritic, brush, and star-shaped structures, may impart a more significant difference in regulating the charging effects, membrane-disruptive activities, and selectivity of MDPs (Fig. 4A).

In addition to linear AMPs, cyclic peptides/peptidomimetics have also been demonstrated to have excellent protease stability, high specificity towards bacteria, and enhanced bioavailability[106−109]. For example, Dathe's group[106] reported that the cyclization of peptides can enhance their cationic charge density to favorably accumulate on negatively charged bilayers and change the environment of the chromophores associated with the formation of a hydrophobic cluster for a pronounced amphipathicity, enhancing the antimicrobial activity and selectivity of these peptides. Furthermore, some designed cyclic peptides can self-assemble to induce nanotube formation on the surface of

phospholipid bilayers, the properties and orientation of which depend on the structure of the cyclic peptide structure[107], as shown in Fig. 4B.

Owing to their regularly branched structure, very low polydispersity, and high local concentration of positive charge on the molecule periphery[110], dendrimers were also regarded as antimicrobial macromolecules, such as poly(amidoamine) (PAMAM)[111], poly(propyleneimine)[112,113], dendritic peptides from L-lysine[114], and branched peptides[115−118]. Reymond's group developed a series of antimicrobial peptide dendrimers, including G3KL[115], TNS18[116], and T7[117], verifying their high potency in killing bacteria and reducing toxicity against mammalian cells Fig. 4C.

Comparatively, brush-like SMAMPs have attracted tremendous interest in recent years owing to their advantages of easy synthesis and modification. Chan-Park's group[41] fabricated a
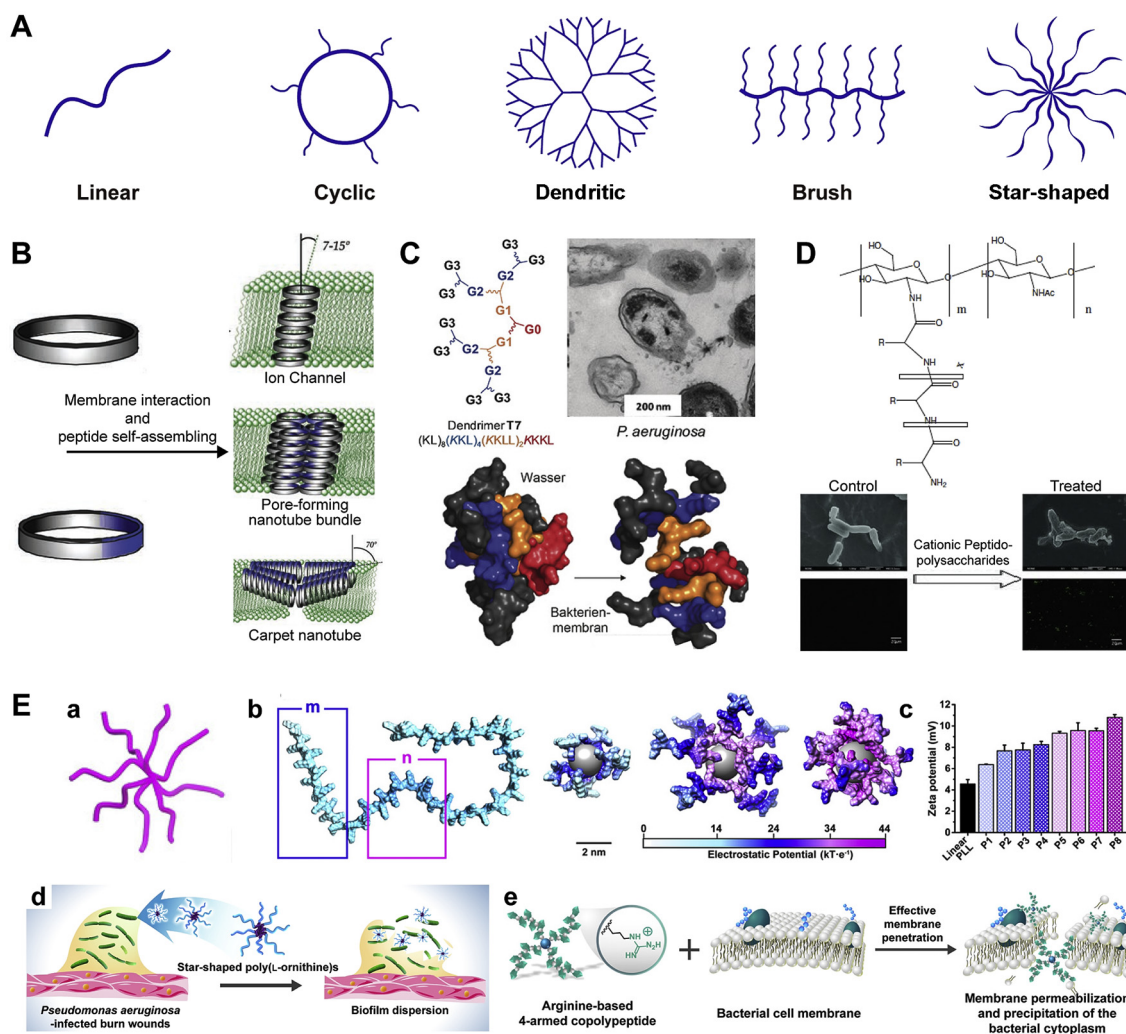

Figure 4 Charging-state optimization of SMAMPs for high antibacterial activity and selectivity. (A) Schematic illustration of representative shapes of SMAMPs. (B) Representative example of cyclic peptide. Reproduced with permission from Ref. 107. Copyright © 2014, Bentham Science Publishers. (C) Structure of representative dendrimer and the antimicrobial action. Reproduced with permission from Ref. 117. Copyright © 2018, John Wiley and Sons. (D) Representative brush SMAMPs and their antimicrobial action. Reproduced with permission from Ref. 41. Copyright © 2012, John Wiley and Sons. (E) Representative star-shaped SMAMPs. Schematic structure (a), surface electrostatic potentials (b) and zeta potentials (c) of star-shaped PLL. Reproduced with permission from Ref. 55. Copyright © 2019, John Wiley and Sons. (d) Unnatural star-shaped PLOs with efficient biofilm-disruptive capacity against *P. aeruginosa*. Reproduced with permission from Ref. 56. Copyright © 2020, John Wiley and Sons. (e) Four-armed poly(arginine-*alt*-glycine) with excellent membrane perturbation capability. Reproduced with permission from Ref. 57. Copyright © 2020, American Chemical Society.

series of cationic brush-like CS-*g*-polylysine with a CS backbone and PLL side chain, finding that the antimicrobial activities of copolymers improved significantly as the grafted PLL length increased (Fig. 4D). In this study, pure PLL grafted in the peptidopolysaccharide copolymer resulted in enhanced antimicrobial activity and selectivity compared to the lysine/phenylalanine copeptide graft, indicating that constructing multi-armed antimicrobials may be more promising than changing the hydrophilic/hydrophobic balance of the structure.

More recently, cationic star-shaped antimicrobials have been developed as unique molecular scaffolds that provide a high charge density for binding anionic bacterial bilayers[82,119−123]. Cai's group[55−57] highlighted that enhancing the cationic charge density of SMAMPs by transforming their backbone from linear to star-shaped could facilitate their electrostatic binding affinity toward bacterial cell membranes and give them a unique membrane perturbation capability (Fig. 4E). To reduce hemolysis and improve the selectivity for pathogens over mammalian cells, they first synthesized a series of star-shaped PLLs with no hydrophobic amino acid residue involvement and demonstrated that high antimicrobial activity and high selectivity could be simultaneously achieved by modulating the number and length of the arms of star-shaped polycations. Moreover, they further modulated the amphiphilicity of antimicrobials by fabricating star-shaped polypeptides from PLL homologs (*i.e.*, poly(L-ornithine)s (PLOs), PLLs, and poly(L-α,ζ-diaminoheptylic acid)) with varying numbers of methylene groups in their side chains. They found that unnatural amino acid-based star-shaped PLOs demonstrated enhanced charge density, broad-spectrum microbicidal activity, remarkable proteolytic stability, and an efficient biofilm-disruptive capacity against *P. aeruginosa*[56]. To overcome the poor membrane perturbation capability of these nonamphiphilic star-shaped polycations, they further introduced guanidinium into the system, finding that four-armed poly(arginine-*alt*-glycine) can interact with both the headgroups and unsaturated tails of phospholipids in bacterial membranes through multiple peptide–membrane interactions, allowing it to penetrate deeper inside the biologically inaccessible high-energy barrier of the hydrophobic lipid bilayer interior to cause membrane permeabilization and intracellular-damaging action[57].

2.2.3. Chemical functionality and microenvironment-responsive design

Tumor microenvironments featuring angiogenesis, maladjusted biosynthesis intermediates, acidosis, and hypoxia, are different from normal tissues[124]. Similarly, infection sites also present many distinct characteristics, including a local acidic environment, higher expression of specific enzymes (*i.e.*, phosphatase, phospholipase, and protease), abundant H_2O_2, and the existence of bacterial toxins[125]. Biofilms are well-organized bacterial communities with self-produced extracellular polymeric substances (EPS) consisting of polysaccharides, proteins, glycoproteins, and nucleic acids[126]. The self-produced EPS can serve as a natural barrier to protect these embedded bacteria from extracellular damage, leading to high antibiotic resistance. In addition, the EPS and heterogeneity of biofilm lead to the establishment of stable gradients that comprise the biofilm microenvironment, including low pH, overexpressed enzymes (such as esterase, lipase, and gelatinase), and hypoxia[126,127]. Quorum-sensing is a population density-based cell−cell communication process that can orchestrate bacterial behaviors within a microenvironment to promote community establishment by regulating specific genes[128]. The

social interactions of bacterial cells are another typical characteristic of biofilms in which quorum-sensing molecules are involved and play an important role during the process[129]. Numerous signaling molecules, such as acyl homoserine lactones, peptides, autoinducer-2, diffusion signaling factors, and α-hydroxyketones, have been studied in bacteria and have become interesting targets for developing antibiofilm strategies[130].

As SMAMPs offer greater structural flexibility than natural AMPs, the microenvironment-responsive design provided a unique significance for enhancing the therapeutic efficacy and reducing undesired side effects of MDPs. Cheng's group[131] developed pH-responsive helix-coil conformation transitionable antimicrobial polypeptides (HCT-AMPs) to selectively kill *Helicobacter pylori* (Fig. 5A). The polypeptides containing both glutamic acid residues and cationic residues functionalized with hydrophobic moieties displayed a distorted helix pH due to intramolecular electrostatic interactions and exhibited minimal toxicity to commensal bacteria at physiological neutral pH. However, when the polypeptides enter the stomach at pH 1−3, the protonation of glutamic acid quenches the intramolecular electrostatic interactions, and HCT-AMPs resume helical conformation with enhanced peptide-bacteria interactions to induce enhanced antibacterial activity against *H. pylori*. In another study, Cheng's group[132] designed another HCT-AMP to minimize toxicity against mammalian cells while maintaining high antimicrobial activity (Fig. 5B). By introducing anionic phosphorylated tyrosine into the cationic polypeptide, the high membrane activity of the polypeptide can be activated by bacterial phosphatase. In addition, Yang's group[133] prepared a stealth lipase-sensitive antibacterial nanopolymer G2-*g*-(PCL-*b*-PEG) consisting of a dendritic polycation (G2) as the inner core and poly(-caprolactone-*b*-ethylene glycol) (PCL-*b*-PEG) as the outer shell, which can expose the bactericidal G2 core under the PCL's responsive degradation by bacterial lipase (Fig. 5C). Wang's group[134] designed a transformable CS-peptide conjugate (CPC) in response to bacterial gelatinase (Fig. 5D). The CPC contains a CS backbone, an enzyme-cleavable peptide (GPLGVRGC) with a PEG terminal, and an antibacterial peptide CGGGKLAKLAKKLA-KLAK (KLAK), which initially self-assembles into nanoparticles and then transforms into nanofibers in the presence of gelatinase, exposing KLAK and leading to its interaction with the bacterial membrane as well as the subsequent cell membrane disruption.

2.3. MDPs for antitumor application

2.3.1. Antitumor mechanisms

While AMPs and their mimetics have promising potential in antibacterial applications, recent studies have indicated that some of these compounds could display antitumor functions as ACPs[135,136]. The primary cause of this is the negatively charged cancer cell surface, as in bacterial cells, which may promote the specific activity of AMPs and SMAMPs toward cancer cells (Fig. 2A). In healthy mammalian cells, negatively charged phospholipid is primarily located in the inner membrane leaflets. However, the asymmetry between the inner and outer cytoplasmic membrane leaflets is lost in cancer cells, leading to the overexpression of negatively charged PS on the surface of the cell membrane. Moreover, the increased content of other anionic molecules, such as *O*-glycosylated mucins, sialylated gangliosides, heparin sulfates, and sialic acid residues, also provoke elevated negative charges on cancer cells[11,136]. As a high cholesterol content in normal cell membranes is necessary to modulate cell fluidity and block the entry/passage of cationic peptides, the increased membrane fluidity
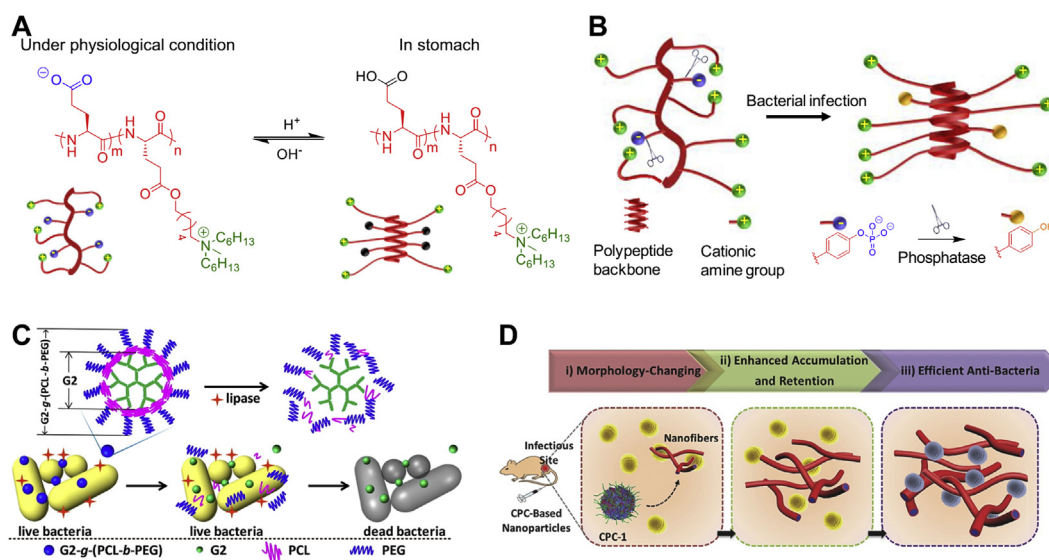
Figure 5 Design of microenvironment-responsive MDPs. (A) Schematic illustration of the pH-responsive conformation transition of HCT-AMP. Reproduced with permission from Ref. 131. Copyright © 2017, National Academy of Sciences. (B) Schematic illustration of enzyme-responsive conformation transition of HCT-AMP. Reproduced with permission from Ref. 132. Copyright © 2017 John Wiley and Sons. (C) Design of a stealth lipase-sensitive antibacterial nanopolymer G2-*g*-(PCL-*b*-PEG). Reproduced with permission from Ref. 133. Copyright © 2015, American Chemical Society. (D) Schematic illustration of *in situ* morphology transformation and antibacterial activity of CS-peptide conjugate triggered by bacterial gelatinase. Reproduced with permission from Ref. 134. Copyright © 2017, John Wiley and Sons.

of most cancer cells will further induce their increased susceptibility towards the lytic action of ACPs due to their lower levels of cholesterol in their membranes[137,138]. In addition, the elevated number and distorted features of microvilli on cancer cells also increase the surface area and contact with ACPs[139]. These cancer cell properties favor the binding and membrane disruption of ACPs. Hence, action modes, such as "barrel-stave" and "carpet" models, used for describing AMP-mediated pore-forming mechanisms, are also applied in this case.

As the membrane disruption action of ACPs and their mimics is largely dependent on their selective interaction with cancer compared to normal cell membranes. Therefore, it can advance the exertion of other modes of action (Fig. 6A): (1) Upon binding to cancer cells, AMPs can induce the destabilization and disruption of cancer cell membranes, eventually leading to cancer cell death *via* necrosis[11]. (2) Some peptides, such as magainin 2, can exhibit anticancer effects by forming ion-permeable channels on cancer cell membranes, leading to the leakage of Na$^+$, K$^+$, and Cl$^-$ ions[140] (3) Owing to its high negative charge (*i.e.*, cardiolipin) during apoptosis, the mitochondrial membrane can also become a major target of MDPs, thus inducing mitochondrial damage and ultimately apoptosis of cancer cells[141,142]. (4) Furthermore, other non-membranolytic mechanisms, including mediated immunity[143], hormonal receptors[144], inhibition of DNA synthesis[145], and anti-angiogenic effects[146], are also possible modes of action involved in the anticancer process of ACPs.

2.3.2. Structure−activity relationship
Recently, several natural AMPs have been reported to have anticancer activity, such as cecropins, magainin 2, defensins, melittin, lactoferricin, and LL-37[150]. Previous research has indicated that the structure−activity relationship of ACPs and their mimics is similar to that of AMP and SMAMPs[150,151]. Blancafort's group[152]

demonstrated that melittin could act as ACPs, disrupt cancer cell membrane, and induce cell death with IC$_{50}$ values from 0.94 to 1.49 µmol/L in human TNBC and HER2-enriched breast cancer cells. To illustrate the necessity of positively charged residues on the anticancer activity of melittin, they designed a negatively charged melittin peptide (DEDE-melittin) by replacing the positively charged sequence in the C-terminus of melittin, finding that melittin lost its anticancer activity in the tested cell lines. Furthermore, by grafting a positively charged sequence in the C-terminus of DEDE-melittin, the anticancer activity of DEDE-melittin was restored. Similarly, truncating amino acid residues in the cationic N-terminal fraction of bovine cathelicidin-derived peptide BMAP-28 or substituting its hydrophobic C-terminal region with more hydrophilic amino acids would drastically impair their ability to permeabilize the cell membrane, reducing the anticancer activity[153]. Additionally, natural AMPs with anticancer activity are usually observed to be amphipathic molecules (*e.g.*, human LL-37) that adopt an α-helical conformation in the presence of a cell membrane or β-sheet peptides (*e.g.*, lactoferricin) generally stabilized by disulfide bonds[150,154,155].

Synthetic cationic peptidomimetics and polymers have also shown significant anticancer activity by capturing the essential physicochemical features of these natural ACPs. Kuroda's group[135] reported a series of methacrylate random copolymers consisting of cationic and hydrophobic side chains to mimic the action mode of ACPs. These copolymers showed significant *in vitro* cytotoxicity to proliferating three metastatic prostate cancer cells, and polymers with higher hydrophobicity and longer cationic side chains resulted in deeper penetration of cancer cell membranes and increased membrane disruption. The copolymer was also effective in killing dormant cancer cells resistant to docetaxel in the *in vitro* tumor spheroid model, inducing more than 90% cell death in DU145 and PC-3 spheroids. In another
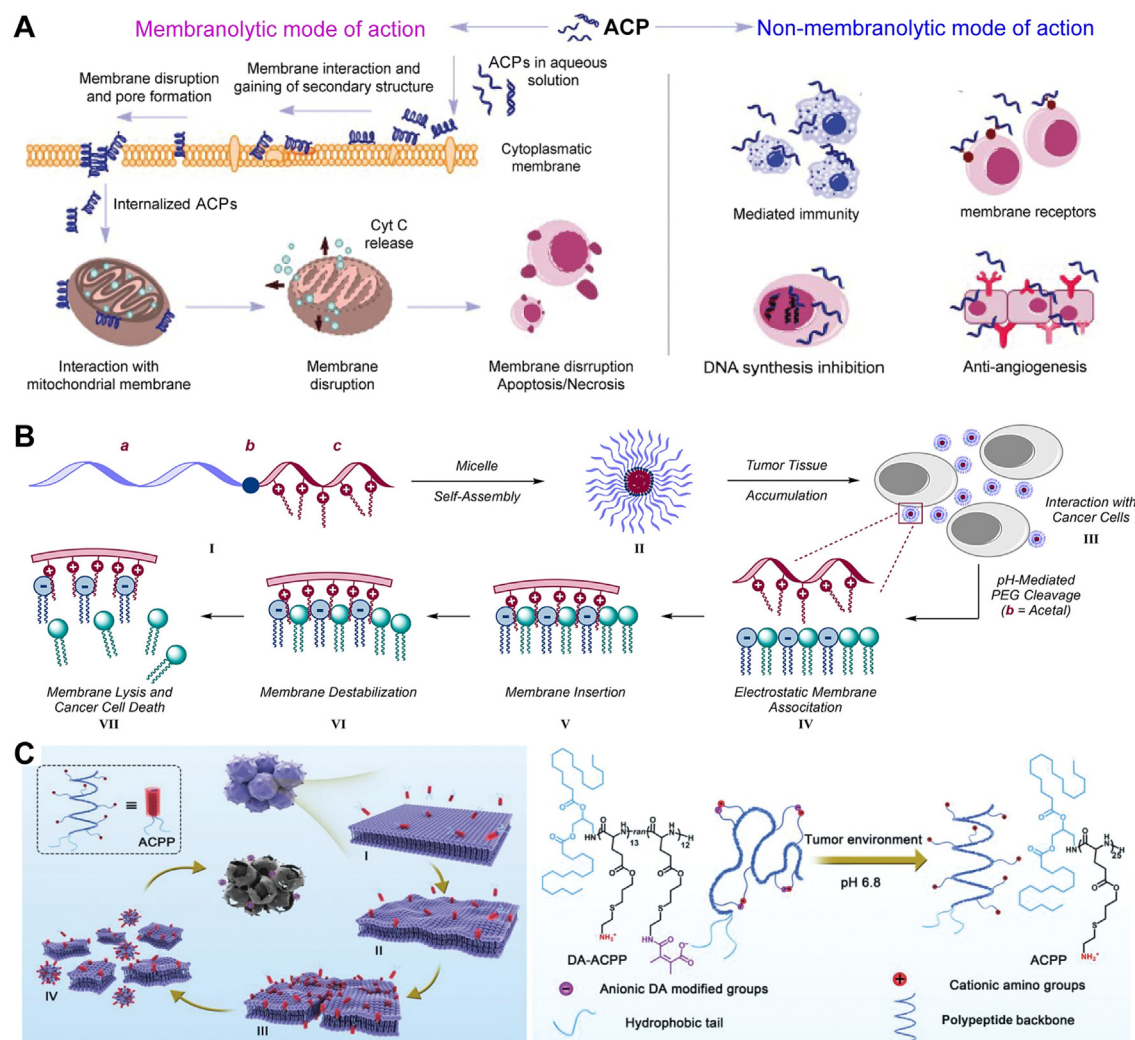
Figure 6 Acting modes and representative examples of ACPs. (A) Different acting modes of ACPs. Reproduced with permission from Ref. 147. Copyright © 2017, ClinMed International Library. (B) Mechanism of action for pH-sensitive macromolecular chemotherapeutic agents. Reproduced with permission from Ref. 148. Copyright © 2018, American Chemical Society. (C) Schematic illustration of the design and anticancer mechanism of ACPP and DA-ACPP. Reproduced with permission from Ref. 149. Copyright © 2020, John Wiley and Sons.

study, Yang's group[148] reported self-assembled cationic polymers that exhibit enhanced permeability and retention (EPR) effect in tumor tissue and selectively release the containing cationic polycarbonate in the acidic environment of tumor tissue to disrupt cancer cells (Fig. 6B). Chen's group[149] reported an α-helical cationic anticancer polypeptide (ACPP) consisting of abundant cationic long side chains and membrane phospholipid-mimicking hydrophobic tails to increase the interaction between the polymer and cancer cells. The cationic polypeptide exhibits a broad spectrum of anticancer activity against 12 cancer cell lines with IC_{50} values ranging from 14 to 30 μg/mL, inducing rapid necrosis of cancer cells through a membrane-distraction mechanism. Furthermore, to improve the biocompatibility of ACPP, Chen's group[149] developed a pH-sensitive zwitter ionic derivative of ACPP (DA-ACPP) by modifying the primary amino groups in the side chains of ACPP with 2,3-dimethylmaleicanhydride (DA, Fig. 6C), which could convert back to cationic ACPP in acidic tumor microenvironments and selectively kill cancer cells. Furthermore, tumor growth in both 4T1 orthotopic breast tumors

and B16-F10 melanoma pulmonary metastatic models could be effectively inhibited by DA-ACPP without inducing side effects.

3. Multi-drug combination therapy

Combination therapy is a unique strategy, used to achieve effective disease treatment through the application of multiple mechanisms in conjunction. It is beneficial for improving therapeutic effects, reducing dosage and undesirable side effects, and reducing the occurrence of drug resistance. In this manuscript, examples of MDPs cooperating with other agents are discussed, in order to illustrate the therapeutic potential of these strategies.

3.1. Combination therapy of MDPs and small-molecule drugs

MDPs can increase the permeability of anionic cell membranes through their unique membrane-disruption mechanisms, which is useful for promoting the ability of drugs to cross membranes,

increasing the sensitivity of cells to drug interference[156]. Therefore, MDPs hold great potential for enhancing the therapeutic efficacy of small-molecule drugs, such as antibiotics and anticancer drugs.

Conventional antibiotic therapy experienced a glorious period in antibacterial treatment, before an increasing number of bacteria acquired resistance to them. Antibiotics kill bacteria through several mechanisms, including: 1) inhibiting cell wall synthesis (*e.g.*, by targeting penicillin-binding proteins); 2) inhibiting protein synthesis (*e.g.*, by targeting 30S and 50S subunits of the bacterial ribosome); 3) disrupting DNA or RNA synthesis (*e.g.*, by interfering with either nucleotide or nucleic acid biosynthetic processes in the cell); 4) inhibiting folic acid metabolism (*e.g.*, by inhibiting dihydropteroate synthase or dihydrofolate reductase); or 5) changing cell permeability (*e.g.*, by interacting with LPSs or by

causing the formation of pores)[157,158]. The major targets of antibiotics are located inside the bacterial cell (as shown in Fig. 7A), yet MDR bacteria have developed multiple mechanisms to decrease the concentrations of antibiotics within bacterial cells, leading to the failure of these antibiotic therapies (Fig. 7A). Therefore, MDPs, exhibiting membrane permeability, are being considered as a class of potential antibiotics to reverse AMR[159].

Several studies have reported synergistic effects of MDPs and antibiotics. In terms of AMP application, Typas's group[160] recently reported that the natural AMPs colistin and macrolide could provide a strong synergistic effect against MDR Gram-negative bacteria. In that study, synergy occurred at low colistin concentrations (less than 0.3 μg/mL) and was active even against the intrinsically colistin-resistant *K. pneumoniae* strain. Yang's group[161] reported the synergistic effect between the AMP DP7

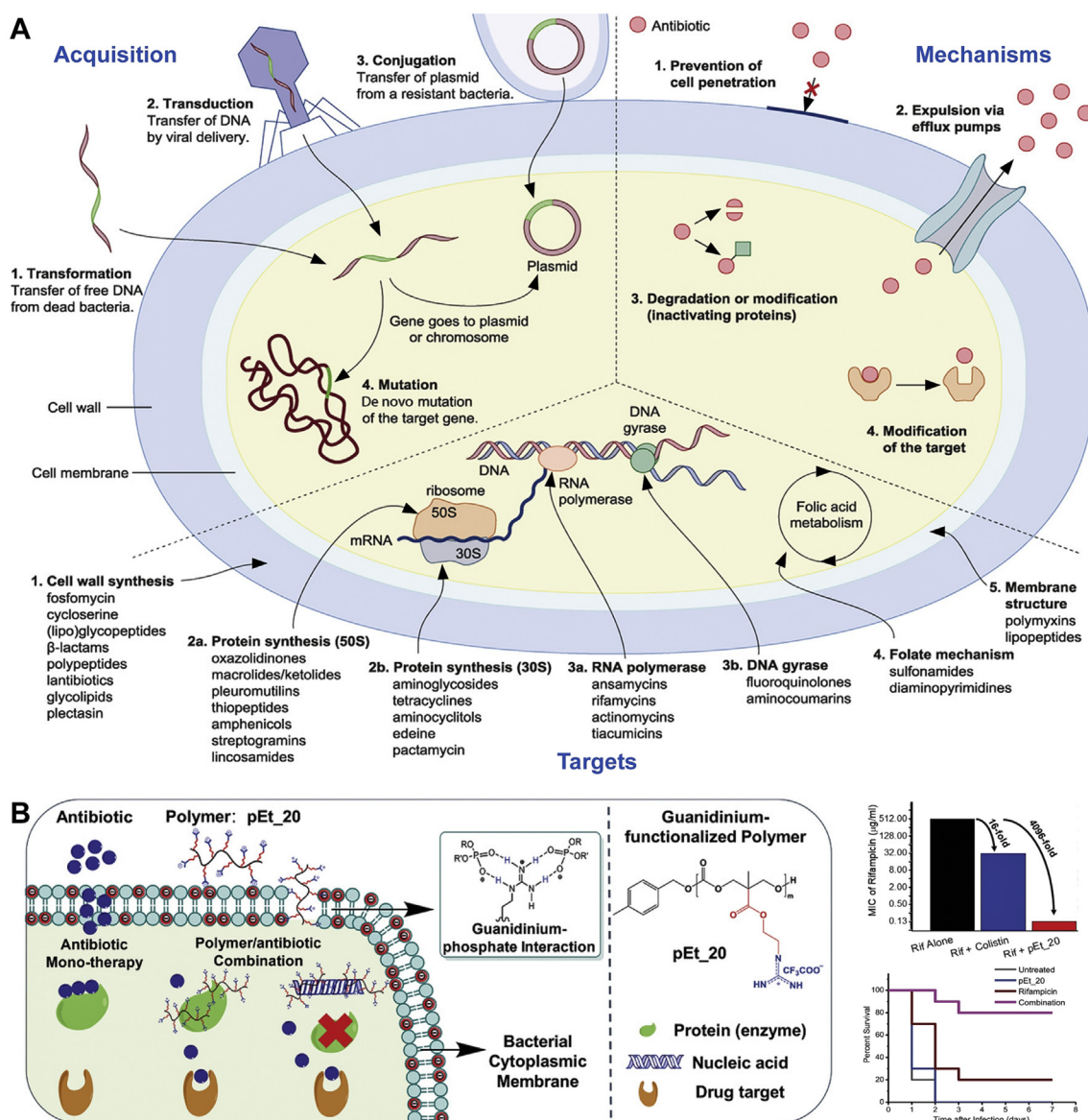**Figure 7** Combination therapy of MDPs and antibiotics. (A) The resistance acquisition pathways, the main mechanisms of resistance, and the main targets for antibiotics. Reproduced with permission from Ref. 158. Copyright © 2016, John Wiley and Sons. (B) Structure of guanidinium-functionalized polycarbonates and their combination therapy with antibiotics. Reproduced with permission from Ref. 159. Copyright © 2020, John Wiley and Sons.

and several different antibiotics on more than a few clinical bacterial strains. The study showed that the combination of DP7 with vancomycin or azithromycin (AZM) achieved the most potent synergistic effect against antibiotic-resistant bacteria, which was attributed to the reduced cell wall proteins and cell wall disruption caused by antibiotics and DP7, respectively.

Pioneering studies have demonstrated a new strategy of increasing antibiotic potency and reverse drug resistance through the use of synthesized, polymer-based MDPs[92,159,162]. Cheng's group[92] reported that the radially amphiphilic polypeptide PHLG-Blm$_{40}$ could be applied as an effective adjuvant, to improve the permeation of commercial antibiotics in bacteria and enhance their antimicrobial activity. The minimum inhibitory concentration (MIC) values of streptomycin, when co-delivered with PHLG-Blm$_{40}$, were 400 times lower than those of streptomycin used alone. In another study by Yang's group[162], a vitamin E-containing, biodegradable, antimicrobial, cationic polycarbonate VE/BnCl(1:30) was developed, and a strong synergistic effect was demonstrated when VE/BnCl(1:30) was used in combination with antibiotics. Checkerboard analyses showed that the use of doxycycline in conjunction with polymer VE/BnCl(1:30) showed the

most pronounced synergistic effect (ΣFBC index < 0.2) against *P. aeruginosa*. The polymer increased the bacterial membrane permeability, facilitating the penetration of small molecule antibiotics and leading to the killing of the bacteria at concentrations significantly below the minimum bactericidal concentrations (MBCs) of both the polymer and antibiotics.

In a more recent study from the same group[87], pEt_20, a guanidinium-functionalized polycarbonate containing 20 repeating units with an ethyl group as the hydrophobic spacer, was demonstrated to have excellent potential as an antimicrobial against MDR infections. It was shown to kill bacteria by a unique mechanism of membrane translocation followed by precipitation of cytosolic materials. Through the interactions between the polymer and proteins and genes in the cytoplasm, translating to an overwhelming cytosolic stress, pEt_20 successfully mitigated and even reversed resistance against different antibiotics. Evidence of this was provided by the reversing of the rifampicin resistance phenotype in *A. baumannii*, with a 2.5×10^5-fold reduction in MIC and a 4096-fold reduction in MBC (Fig. 7B). This synergistic effect was further demonstrated in a mouse model of bacteremia caused by MDR *A. baumannii*,
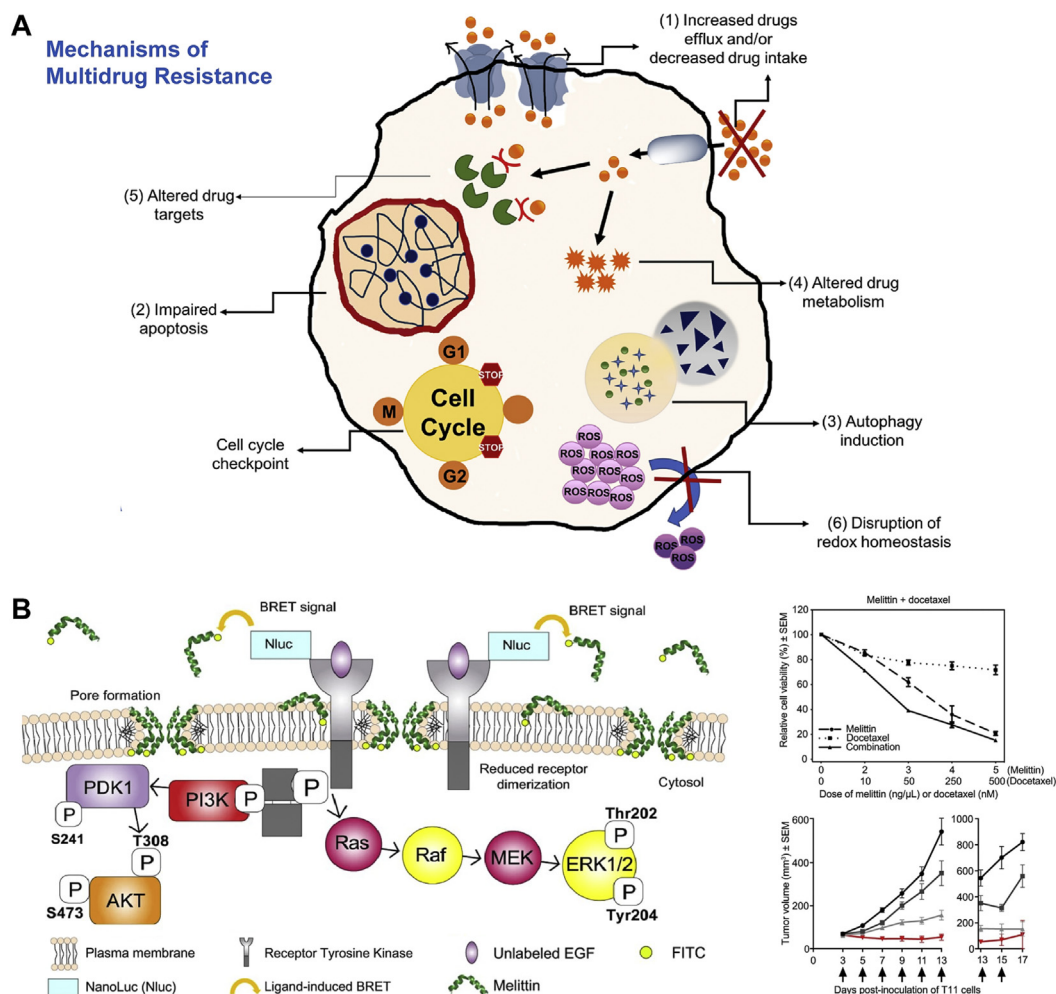
Figure 8 Combination therapy of MDPs and chemotherapeutic agents to overcome MDR in cancer. (A) Mechanisms of multi-drug resistance in cancer cells. Reproduced with permission from Ref. 11. Copyright © 2020, Elsevier. (B) Melittin interacts with plasma membrane (left), and the combination therapy of melittin and docetaxel induces breast cancer cell death (right). Reproduced with permission from Ref. 152. Copyright © 2020, Springer Nature.

in which combination therapy provided a significantly higher survival rate and a greater reduction of the blood bacterial load than monotherapy.

Multiple recent reviews have summarized that cancer cells can develop MDR through multiple mechanisms, including but not limited to (1) increased drug efflux and/or decreased drug uptake, (2) impaired apoptotic pathway, (3) induction of autophagy, alteration of (4) drug metabolism, (5) drug target, or (6) the disruption of redox homeostasis (Fig. 8A)[11,163]. Most of these mechanisms are similar to those of MDR bacteria. Therefore, MDPs with membrane-permeability effects also show promise as adjuvants, to enhance the effectiveness of chemotherapy and to reverse multidrug resistance in cancer. Recently, Blancafort's group[152] investigated and discussed the potential synergies between the MDP melittin and chemotherapeutic agents toincrease breast cancer cell death (Fig. 8B). They showed that docetaxel and cisplatin exhibited strong synergistic interactions with melittin. To further investigate the efficacy of the combination of melittin and docetaxel in reducing the growth of triple-negative breast cancers, they performed *in vivo* experiments by transplanting T11 cells in BALB/c mice, then exposed these cells to the combination therapeutics. The results demonstrated that melittin could sensitize cancer cells to docetaxel treatment, has a great potential to

increase the efficacy and/or reduce the dose of chemotherapeutic drugs, and it enables more cost-effective treatments with potentially fewer side effects. Moreover, melittin was observed to upregulate immune checkpoint PD-L1 expression, thus decreasing the immune-suppressive effects of the tumor microenvironment.

MDPs can also be developed as delivery vehicles for chemotherapeutic drugs, providing opportunities for efficient selective killing, improved biocompatibility, and additive anticancer activity. For example, Kostarelos's group[164] reported the complexation of the chemotherapeutic drug doxorubicin (DOX) with the cationic poly-L-lysine dendrimer (DOX-DM), exhibiting enhanced penetration and retention in prostate multicellular tumor spheroids, as well as improved therapeutic effects in B16F10 tumor-bearing mice.

3.2. Combination therapy of MDPs and metal materials

Over the past few years, the long-term antibacterial and biofilm prevention effects of metal-based nanoparticles have been extensively reported. Metal-based nanoparticles are considered an effective antibiotic alternative with low resistance rates, because they are able to differentiate bacterial cells from mammalian cells through the metal transport system of bacteria and
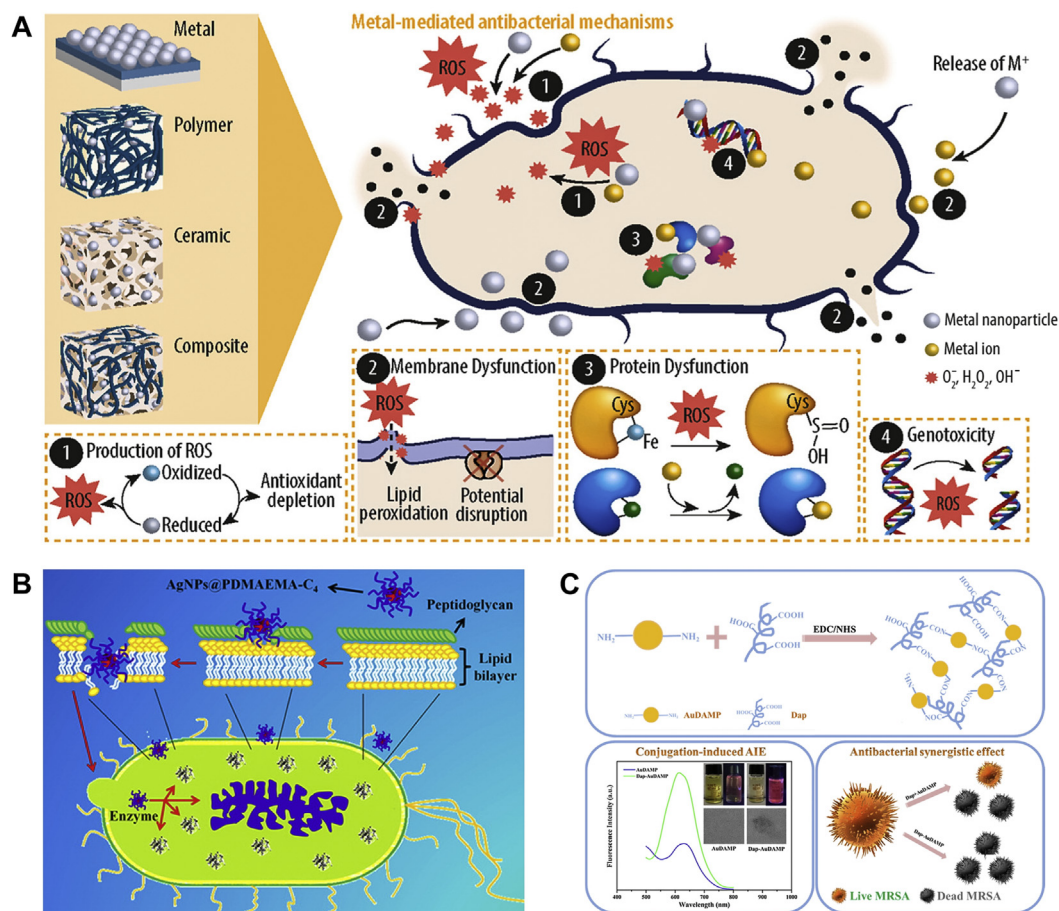
Figure 9 Combination therapy of MDPs and metal materials. (A) Antibacterial mechanisms of metal materials. Reproduced with permission from Ref. 169. Copyright © 2021, Elsevier. (B) Polymer-Ag nanocomposites with enhanced antimicrobial activity. Reproduced with permission from Ref. 170. Copyright © 2014, American Chemical Society. (C) The design of conjugation-induced AIE enhancement and synergistic antibacterial effect of Dap-Au NCs. Reproduced with permission from Ref. 171. Copyright © 2019, Elsevier.

metalloproteins, and prompt bactericidal efficiency *via* multiple mechanisms[3,165]. Metal-based nanoparticles, ranging from 1 to 100 nm, usually provide strong, targeted, and extended antimicrobial activity *via* several major pathways (Fig. 9A): (1) metal nanomaterials produce extracellular and intracellular reactive oxygen species (ROS), leading to increased oxidative stress and cell instability; (2) metal nanoparticles and/or released metal ions physically interact with bacterial cell membrane or wall, then high ROS levels can cause damage to the plasma membrane, leading to impaired membrane function, impaired nutrient assimilation, and leakage of the cell content; and (3) upon metal uptake, metal nanoparticles and released metal ions can directly interfere with both proteins and DNA/RNA, impairing their function and disturbing cellular metabolism. These modes of action occur simultaneously or successively and eventually induce bacterial cell death[3,166–169]. Metal ions, such as Ag^+, Cu^{2+}, and Zn^{2+}, usually exert antibacterial properties by interacting with bacterial cell membranes and intracellular targets, while compounds such as TiO_2, ZnO, and Au are associated with the formation of ROS.

In recent years, silver nanoparticles (AgNPs) and gold nanoparticles (AuNPs) have been extensively investigated and found to have enhanced effects against pathogens in combination with MDPs[172–175]. For example, Ulrich's group[172] showed that PMB exerted synergistic antibacterial activity with AgNPs against all tested Gram-negative bacteria. Jia's group[170] reported a nanocomposite of cationic polymers and AgNPs, in which these two compounds display synergistic antibacterial effects, endowing the whole system with superior antibacterial performance against both Gram-negative and -positive bacteria (Fig. 9B). The possible mechanism of the synergistic effect between MDP and AgNPs is highly dependent on the disruption of bacterial membrane integrity, effective cellular internalization of the nanoparticles, and the subsequent inhibition of intracellular enzymatic activity caused by the interaction between AgNPs and thiol groups of active sites in enzymes.

Previous studies by Zheng's group[176] conducted MD simulation studies to describe AuNP-mediated membrane penetration, disruption, and nanoscale hole formation, indicating that AuNPs are a promising platform for achieving designated goals in their delivery, diagnostic, and therapeutic applications. According to the simulation results, it is possible to promote internalization and minimize the toxicity of AuNPs by carefully regulating their surface charge densities. In antibacterial applications, AuNPs can interact with LPS) and proteins in the outer membrane of bacteria, leading to deposition on the membrane[177]. The deposited metal nanoparticles can penetrate the bacterial membrane, allowing better intercalation of the conjugated MDPs within the inner membrane, thus making the MDP-AuNP conjugates more active than the nonconjugated MDP itself. Taking advantage of individual components, several bioconjugates composed of metal nanoparticles and membrane-disruptive peptides/polymers have been developed, and show promising therapeutic efficacy against bacterial infection[177–179].

Wang's group[171] demonstrated the enhanced antimicrobial activity of a hybrid formed by conjugating natural AMP DAP and gold nanoclusters (DAP–Au NCs) (Fig. 9C). The conjugate effectively destroyed the bacterial membrane *via* the action of DAP and promoted internalization of the nanoparticles. The conjugated Au NCs continuously generated ROS within the bacteria to induce severe DNA breakage, while continuous ROS bombings limited the capacity of bacteria to develop resistance. In addition, a significant fluorescence enhancement of DAP–Au NCs was observed due to a

novel AIE pattern, indicating that the conjugates could act as a theragnostic nanoplatform during bacterial treatment. Tang's group[179] developed metallopolymer–antibiotic bioconjugates on gold nanoparticles Au@PCo NPs as an antibacterial agent. The Au@PCo NPs taken advantages and synergistic effect of multiple components, including interaction with negatively charged bacterial membranes mediated by cationic metallopolymers, larger bacterial contact area, and enhanced penetration into bacterial cells provided by the small-sized AuNPs, as well as the improved vitality of penicillin-G to kill bacteria; thus showing excellent broad-spectrum antibacterial effects.

3.3.   Combination therapy of MDPs and photoresponsive materials

Recently, external-stimuli-activated therapies, such as photothermal therapy (PTT) and photodynamic therapy (PDT), have emerged as efficient alternative strategies for combating tumor and bacterial infections[180,181]. Compared to internal stimuli, external stimuli techniques possess more advantages in the temporal and spatial control of nanomedicine with minimal invasiveness, which is beneficial for achieving more precise, rapid, and efficient therapeutic efficacy in local treatment[156].

As an emerging physical therapeutic approach, PTT utilizes photothermal agents (PTAs) to convert near-infrared (NIR) light energy into heat, causing irreversible damage to bacterial or cancer cells with minimal damage to normal tissues[182]. Comparatively, PDT employs photosensitizers (PSs) and specific light irradiation to generate ROS in the presence of oxygen[182]. ROS, such as superoxide anion ($\cdot O_2^-$), singlet oxygen ($^1O_2$), hydroxyl radicals ($\cdot OH$), and hydrogen peroxide (H_2O_2), subsequently exhibit antibacterial or anticancer effects by initiating oxidative damage to the cytoplasmic membrane, proteins, and DNA of cells[183].

Over the past decade, many kinds of PTAs have been developed for PTT, including noble metal nanomaterials (*e.g.*, AuNPs and AgNPs), metallic sulfides (*e.g.*, CuS and MoS_2), inorganic materials (*e.g.*, graphene oxide (GO) nanosheets, black phosphorus nanosheets, and prussian blue nanoparticles), natural materials (*e.g.*, melanin), and other organic compounds (*e.g.*, indocyanine green (ICG))[183]. Meanwhile, PSs for PDT have also been developed, mainly including organic compounds [*e.g.*, porphyrines, phthalocyanines, phenothiazines, methylene blue (MB), chlorin-e6 (Ce6), AIE luminogens (AIEgens)-based PSs], and inorganic photocatalysts (*e.g.*, TiO_2 and ZnO, Fig. 10A)[183–185]. As seen in the photoresponsive mechanisms shown in Fig. 10B, the primary photothermal conversion mechanisms of PTAs are divided into localized surface plasmon resonance (LSPR) effects, electron-hole generation and relaxation, and conjugation or hyperconjugation effects. PDT can be achieved *via* several pathways under light irradiation, including photocatalysts, PSs, surface plasmon resonance (SPR), and heterojunction and up-conversion luminescence[183,186].

Despite these advances, the applications of PTT and PDT have several limitations when these therapies are performed alone. First, the applications of PTAs and PSs are limited by their poor photostability, thermal stability, rapid aggregation, and degradation in polar solvents[156,182]. Moreover, when the increased temperature produced by PTT is too high for complete elimination of bacterial or cancer cells, non-localized heat and hyperthermia may also lead to increased damage to healthy tissues[189]. In addition, PDT may be less efficient in treating Gram-negative bacteria as it
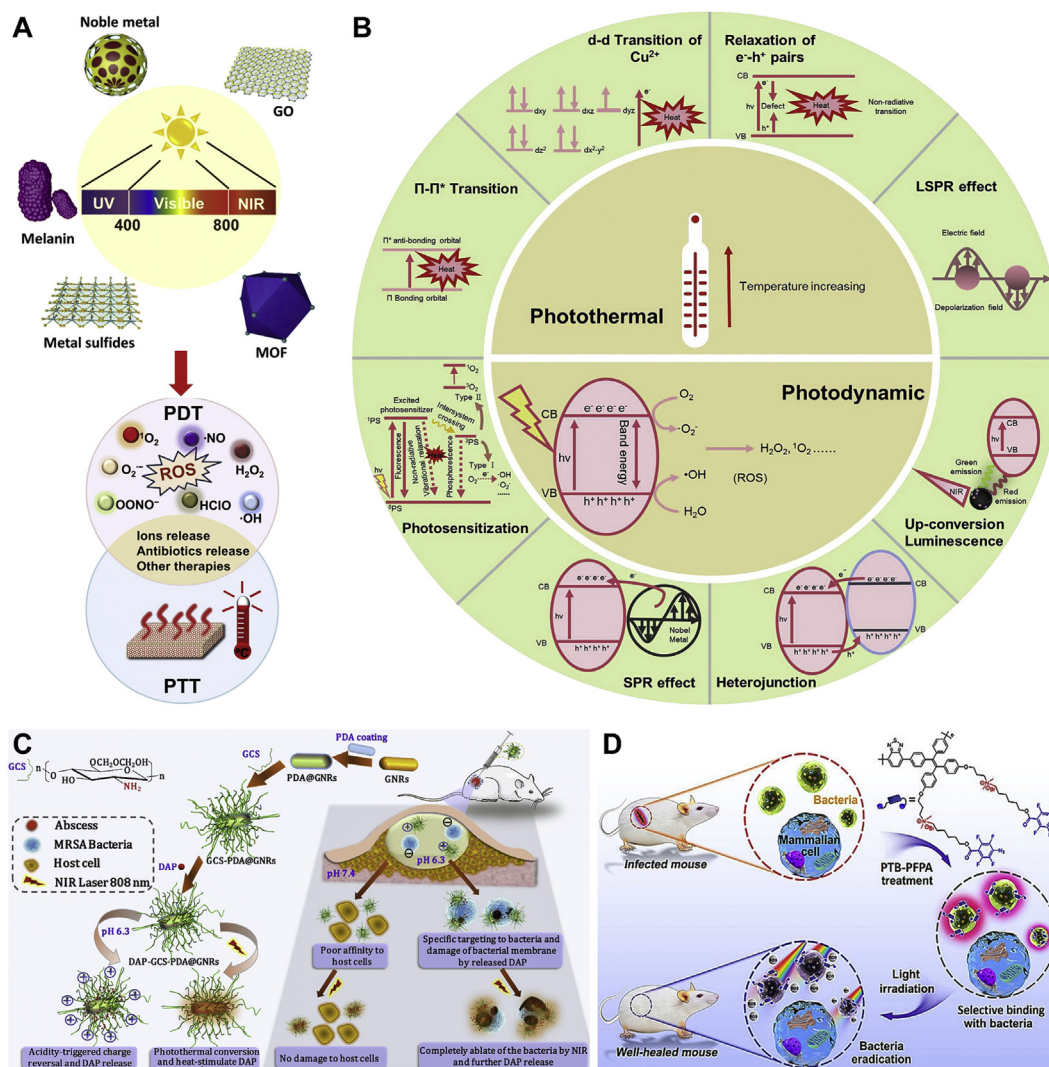
Figure 10 Combination therapy of MDPs and photoresponsive materials. Schematic illustration of photoresponsive materials (A) and their mechanisms of action (B). Reproduced with permission from Ref. 185. Copyright © 2020, Elsevier. (C) Schematic illustration of an efficient chemo-photothermal therapeutic platform based on polydopamine-coated gold nanorods. Reproduced with permission from Ref. 187. Copyright © 2018, Elsevier. (D) Schematic illustration of an AIE-active conjugated polymer with high ROS-generation ability. Reproduced with permission from Ref. 188. Copyright © 2020, John Wiley and Sons.

is more difficult for the produced ROS to penetrate through the complex cell walls of such bacterial strains. Therefore, cationic MDPs demonstrate great potential for improving the properties of photoresponsive materials, increasing the permeability of bacterial and cancer cell membranes, and further strengthening PTT and PDT efficacy by reducing the heat and ROS resistance of these cells.

Recently, many studies have provided evidence for the synergistic effect of MDPs and photoresponsive materials[182]. For example, Deng's group[187] reported an MDP and photothermal hybrid platform, GCS-PDA@GNRs, applying two types of MDPs, glycol chitosan (GCS) and DAP (Fig. 10C). When located in the low pH environment of bacterial infection sites, the pH-responsive GCS grafted on the nanoparticle surface would become positively charged, allowing it to electrostatically interact with, accumulate, and remain at local infection sites. Meanwhile, the acidity-activated release of DAP could effectively damage the bacterial membrane, inducing an

increase in permeability and heat resistance reduction of bacterial cells, thus resulting in a large enhancement of the antimicrobial efficiency of PTT.

In PDT applications, Xu's group[190] have developed eosin Y (EY)-based antibacterial polycations, which exhibit remarkable synergistic antibacterial activity due to the combination of the photodynamic effect of EY and membrane-disruption effect of quaternary ammonium polycations. Similarly, Tang's group[188] recently designed a unique aggregation-induced emitter (AIE)-conjugated amphipathic polymer called PTB-APFB by incorporating tetraphenylthene (TPE) bearing ammonium units and 4-azidoperfluorobenzoate (APFB) moieties on its side chains (Fig. 10D). The polymer effectively produced ROS and radicals in its aggregated state, under light. Meanwhile, because of its AIE features, the binding behavior of PTB-APFB can be easily studied by confocal laser scanning microscopy. Results showed that the amphipathic structure endows the polymer with superb

selectivity towards microorganisms over mammalian cells, and may also play an important role in making bacteria more sensitive to ROS.

To enhance the antitumor effect of photoresponsive materials, Ghandehari's group[191] reported a strategy for conjugating PS meso-tetra (4-carboxyphenyl) porphyrin with a hyperbranched PAMAM dendrimer or linear N-(2-hydroxypropyl) methacrylamide copolymer. The study showed that these polymeric conjugates displayed increased phototoxicity activity by ~100- and 4000-fold in mouth epidermal carcinoma (KB) and human adenocarcinoma alveolar basal epithelial (A549) cells.

4. MDPs-based formulations and their applications

4.1. Overview of MDPs-based formulations design

4.1.1. Challenges and advantages

Despite the promising activities of MDPs, the clinical applications of some natural AMPs and SMAMPs are still limited by their own nature, through susceptibility to degradation by proteases, toxicity toward normal human cell membranes, rapid clearance via the reticuloendothelial system (RES), and limited permeability across different physiological barriers[55,192]. Therefore, the development of appropriate delivery systems is necessary for the clinical application of MDPs.

Strategies have been developed to construct favorable formulations, in order to achieve ideal therapeutic effects. For example, surface modification by poly(ethylene glycol) (PEG) is a common strategy used by nano-formulations to increase the blood circulation half-life, because PEG can endow nanoparticles with stealth properties, meant to bypass recognition and elimination by the RES[193,194]. Furthermore, by constructing stimuli-responsive nanocarriers, on-demand release of therapeutics can be triggered by changes in pH, temperature, redox potential, or enzyme levels found in the complex microenvironment of cells and tissues. Recent studies have implicated that some materials can not only be used as drug carriers but also display therapeutic activity, such as cationic polymers[37,118], metal/metal oxides[156,195], and inorganic materials[196], on their own. Using a co-delivery system for therapeutic delivery offers a unique opportunity to improve the precision of spatial targeting and temporal release, which is conducive to better synergistic effects among drugs[178,197].

4.1.2. Application

Nanoscale drug delivery systems such as liposomes, micelles, and solid lipid nanoparticles (SLNs) have shown potential for the delivery of MDPs, as they can improve drug bioavailability by both protecting drugs from elimination and reducing their burst release[198,199]. For example, Liu's group[200] prepared nanoparticles that were cyclosporin A (CsA)-loaded, PEGylated, CS-modified, and lipid-based. Their study showed that the conformational clouds of PEG hindered the interaction between plasma protein and nanoparticles, which significantly prolonged the circulation time and improved the bioavailability of CsA.

To reduce drug elimination, polyionic complex (PIC) micelles, self-assembled from cationic AMP MSI-78 and a number of the anionic copolymer methoxy poly(ethylene glycol)-b-poly(α-glutamic acid), were prepared by Wang's group[201] MSI-78 showed a sustained release from the PIC micelles without burst release, which is beneficial for improving the bioavailability of AMP.

Due to their amphiphilic nature, the selectivity of MDPs for bacterial or cancer cells over mammalian cells is usually unsatisfactory. Hence, it is necessary to develop an appropriate drug delivery system to improve the selectivity of MDPs. To improve the selectivity of PMB and reduce its nephro- and neurotoxicity, several polymyxin formulations have been reported, such as SLNs[202], polyion complexes[203], liposomes[204], and polysaccharide materials[205]. Recently, Arpanaei's group[206] reported that anionic, functionally mesoporous silica nanoparticles could act as potential carriers for PMB delivery, because they could encapsulate a high load of PMB and retain antibacterial activity with enhanced biocompatibility.

In another application, Wu's group[207] presented a biomimetic strategy to construct virus-inspired, surface-nanoengineered antimicrobial liposomes, simultaneously achieving enhanced antimicrobial activity and selectivity of lipopeptides (Fig. 11A). When amphipathic lipopeptides were loaded onto the liposome by anchoring their hydrocarbon tails into the lipid bilayer interior via hydrophobic interactions, the nonspecific binding between lipopeptides and mammalian cells could be blocked to induce lower hemolysis and cytotoxicity. Furthermore, the drug loading strategy successfully enriched the targeting moieties of lipopeptides on the surface of the liposome, which played a crucial role in facilitating high-efficiency and high-selectivity bacteria binding, rapidly invading bacterial cells via the plasma membrane fusion pathway, and inducing a local "burst" release of lipopeptide to cause irreversible damage of bacterial cell membrane.

In antitumor application, Li's group[208] developed a melittin-loaded zeolitic imidazolate framework-8 (MLT@ZIF-8) nanoparticles (NPs) for anticancer therapy. The ZIF-8 metal−organic framework (MOF) was observed to be an efficient nanoplatform for improving the stability and inhibiting the hemolytic activity of MLT. When compared with melittin alone, MLT@ZIF-8 NPs displayed enhanced cellular uptake and antitumor effects on cancer cells.

In addition to MDP enhancing the effectiveness of drugs or drug vectors, it has recently been found that some drug vectors, such as 2D graphene, can in turn enhance the effects of antimicrobial peptides. Yang's group[209] developed a melittin-graphene/GO complex, which displayed an up-to-20-fold enhancement in antibacterial activity against both Gram-negative and -positive bacteria. They found that the sharp edges or corners of the graphene/GO sheets behaved like "nanoknives", exerting a strong effect on sensitizing lipid membranes. Furthermore, with such similar mechanical disturbance to cell membranes as that caused by melittin at high concentrations, this combination decreased the threshold working concentration of the melittin peptide, resulting in remarkably enhanced antibacterial activity[210]. Similarly, Shao's group[211] fabricated a novel nisin-g-MGO nanohybrid by loading Fe_3O_4 NPs onto GO nanosheets, to endow the whole system with magnetic properties, followed by grafting nisin onto it. The nisin-g-MGO nanohybrids were capable of destroying the integrity of the bacterial cell membrane, owing to the altered membrane permeability induced by the presence of nisin and the sharp edge cutting effect of the GO sheets. In addition to their superior antibacterial effect, long-term stability, and good compatibility, the loaded Fe_3O_4 NPs endow the nanohybrids with a sufficiently strong magnetic separation capacity to separate them, useful for many potential therapeutic applications.

Compared with monotherapy, the combination of MDPs and other therapeutic drugs has been proposed as a promising strategy for the enhancement of bacterial or cancer therapy, via multiple mechanisms of action in the hopes of both achieving enhanced therapeutic efficacy and preventing bacteria from developing
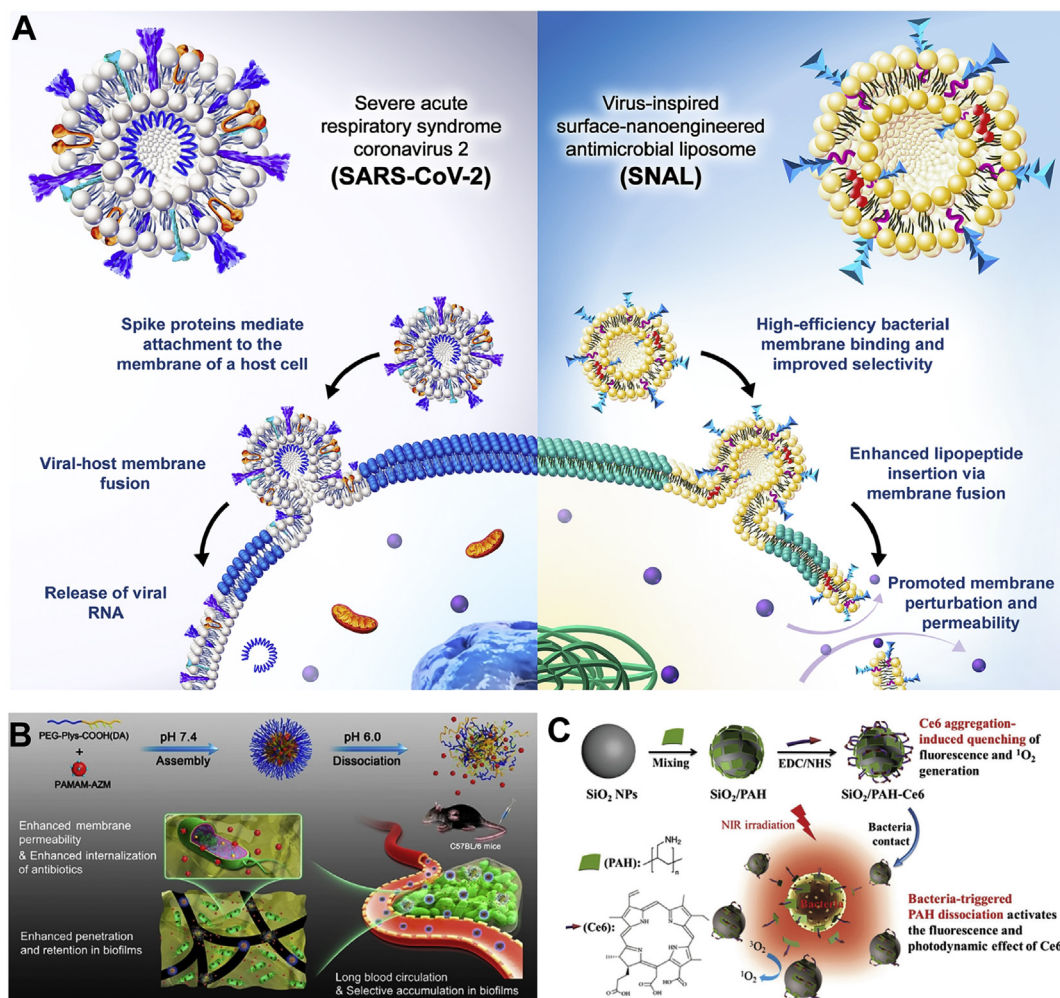
Figure 11 MDPs-based delivery systems for high selectivity and microenvironment−responsive properties. (A) Schematic illustrations of the structure and antibacterial mechanism of virus-inspired surface-nanoengineered antimicrobial liposome with enhanced antibacterial effect and improved selectivity. Reproduced with permission from Ref. 207. Copyright © 2020, Elsevier. (B) Schematic illustration of a pH-sensitive AZM-conjugated cluster nanoparticles. Reproduced with permission from Ref. 212. Copyright © 2020, American Chemical Society. (C) Schematic illustration of a bacteria-activated photodynamic nanosystem based on polyelectrolyte-coated silica nanoparticles. Reproduced with permission from Ref. 213. Copyright © 2017, The Royal Society of Chemistry.

resistance[162,214−217]. Therefore, many different MDP-based co-delivery systems have been developed. Liu's group[215] developed novel AMP-modified AZM-loaded liposomes for the treatment of MRSA infections. The cationic AMP DP7-C not only endowed the liposomes with a positively charged surface to improve stability and mediate sustained release of AZM, but could also activate host immune responses and synergize with AZM against bacterial infections.

In considering the bacterial microenvironment, Ji's group[212] fabricated size and charge adaptive AZM-conjugated clustered nanoparticles (AZM-DA NPs), which can disassemble and release secondary AZM-conjugated PAMAM nanoparticles (PAMAM-AZM NPs) under an acidic biofilm microenvironment (Fig. 11B). The small and positively charged PAMAM-AZM NPs improved the penetration and retention inside biofilms, enhanced permeabilization of the bacterial membrane, and increased internalization of AZM. This combination exhibited remarkable antibiofilm activity and achieved excellent *in vivo* therapeutic effects in a chronic lung infection model *via* intravenous administration. Li's group[213] developed a bacteria-activated, photodynamic nanosystem based on polyelectrolyte-coated silica nanoparticles modified with a Ce6 to enhance antibacterial activity (Fig. 11C). Studies have shown that cationic PAH polyelectrolyte layers modified with chlorin e6 can be effectively extracted by bacteria from silica nanoparticles and bound to the anionic bacterial surface, changing the aggregation state of Ce6 and leading to bacteria-activated fluorescence and photodynamic effects upon NIR laser irradiation. This has been shown to completely eliminate MRSA bacteria and has the potential to reduce bacterial resistance.

In terms of antitumor applications, some AMPs or SAMPs have unique cell-penetrating properties that enhance anticancer effects by facilitating the intracellular and intranuclear uptake of chemotherapeutic drugs. For example, to increase the intracellular concentration of anticancer agents, Liang's group[218] developed pH-sensitive polymeric micelles for synergistic cancer therapy by conjugating the synthetic poly(β-amino ester)-poly(ethylene glycol) copolymer to the therapeutic peptide CGKRK$_D$(KLAKLAK)$_2$.

Interestingly, the CGKRK sequence in the therapeutic peptide acted as a tumor-targeting ligand while the $_D$(KLAKLAK)$_2$ sequence disrupted mitochondrial membranes and killed cancer cells *via* an apoptosis pathway. Under acidic conditions, the micelles disassembled and released the loaded docetaxel and therapeutic peptide for killing cancer cells, as confirmed by the 5 times reduction in IC$_{50}$ of DTX-loaded micelles. Similarly, Lim's group[219] developed a liposomal complex system [Lipo (Pep, Ce6)], consisting of a Ce6-conjugated di-block copolymer [PEG-PLL(-*g*-Ce6)] and a $_D$(KLAKLAK)$_2$ peptide, for synergistic cancer therapy. Because of the membrane-lytic ability of $_D$(KLAKLAK)$_2$ and singlet oxygen species generated by Ce6 under light illumination, the KB cells treated with Lipo(Pep, Ce6) exhibited accelerated lysis of the endosomal membrane, efficiently protecting drugs from endosomal degradation and inducing mitochondria-dependent apoptosis. The Lipo(Pep, Ce6) efficiently reduced cell viability of KB cells and displayed CI (combination index-affected factors) values lower than 1, indicating the strong synergistic effects of the peptide and Ce6.

To potentiate intranuclear delivery, Huang's group[220] developed an *N*-(2-hydroxypropyl) methacrylamide (HPMA) polymer-based drug delivery system for DOX delivery. In this system, an AMP-derived biomimetic peptide SVS-1 with efficient cell membrane penetration and nuclear translocation effects was conjugated to the HPMA copolymer backbone. The results showed that SVS-1 promoted the cellular uptake and nuclear accumulation of HPMA copolymer and DOX for antitumor activity.

4.2. MDP-based intravenous delivery systems

4.2.1. Challenges and advantages

Intravenous delivery is one of the most commonly used administration routes in clinical therapy, and is the fastest invasive administration route, offering the advantages of good drug delivery control, high bioavailability at low doses, and rapid onset effect. Nanomedicines administered *via* intravenous delivery can rapidly reach the targeted tissue and organs in the body through blood circulation and achieve a rapid onset effect, which is suitable for the delivery of some MDPs that are susceptible to enzymatic degradation in the gastrointestinal tract[221]. In addition,
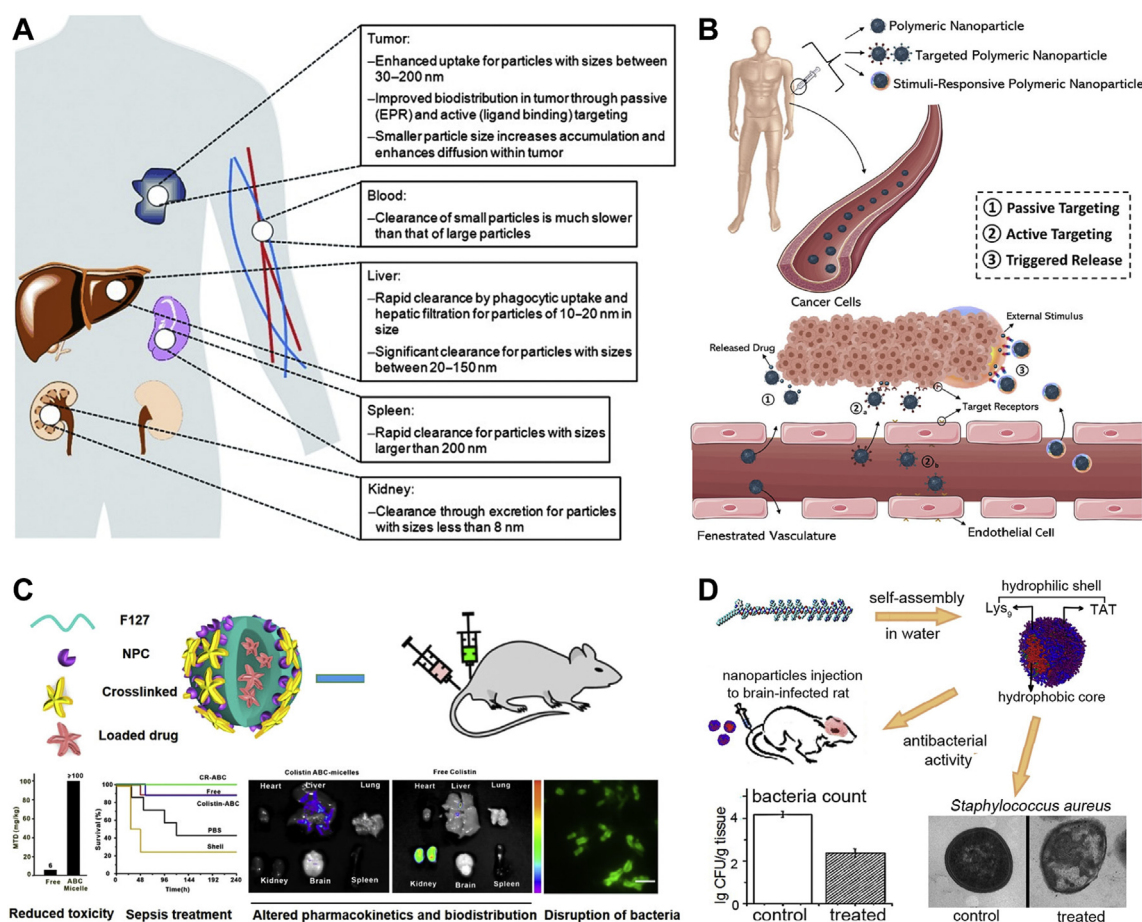
Figure 12 MDPs-based intravenous delivery systems and its application. (A) Biodistribution and clearance of nanoparticles from the human body. Reproduced with permission from Ref. 228. Copyright © 2014, John Wiley and Sons. (B) Schematic illustration of different drug targeting approach. Reproduced with permission from Ref. 229. Copyright © 2021, Frontiers Media S.A. (C) Design of an antibiotic cross-linked micelles for multidrug-resistant bacterial sepsis treatment. Reproduced with permission from Ref. 230. Copyright © 2021, American Chemical Society. (D) Schematic illustration of TAT-modified self-assembled cationic peptide nanoparticles for brain infection treatment. Reproduced with permission from Ref. 231. Copyright © 2018, Elsevier.

targeted delivery of MDPs can easily be achieved by passive or active targeting mechanisms.

Previous research has revealed that the passive targeting efficacy of nanomedicines is associated with properties such as particle size, surface charge, hydrophobicity, stealth coating, and protein binding ability[222,223]. Nanoparticles with diameters larger than 200 nm tend to accumulate in the spleen and liver, where they are processed by mononuclear phagocyte system cells. Due to the large gap between newly produced blood vessels around the tumor, there is poor structural integrity of tumor tissue; nanoparticles can accumulate in tumor tissues by an effect called the EPR effect, resulting in passive targeting activity (Fig. 12A)[224].

Although some passive targeting agents have been well applied in the treatment of diseases such as cancer therapies in humans, these agents suffer from numerous limitations, such as high administration doses and specific organ toxicities. Active targeting is considered an alternative to passive targeting, and is achieved by coupling targeting moieties, ligands, and antibodies onto the surface of the nanoparticles (Fig. 12B)[225−227]. In general, because nano drug delivery systems have the advantages of high bioavailability, low toxicity, and high target numbers, MDP-based nanomedicines can achieve many unique applications through the intravenous delivery route.

4.2.2. Application

Intravenous injection mediated by nanocarriers can significantly improve the bioavailability of drugs for antibacterial and antitumor applications. MDPs with high bioavailability are expected to be used for the treatment of specific diseases, such as sepsis and brain infections. Sepsis is defined as a life-threatening organ dysfunction caused by an aberrant immune response initiated by an invading pathogen, that fails to return to homeostasis, ultimately leading to the pathological syndrome characterized by persistent excessive inflammation and immunosuppression. In sepsis, inflammatory dysregulation is typically triggered by the excessive activation of Toll-like receptors (TLRs). TLRs recognize pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns, such as bacterial toxins, proteins, and nucleic acids[232].

Many previous studies have reported that cationic AMPs and their mimics have great potential for sepsis therapy. PMB has a unique advantage in Gram-negative sepsis therapy, due to its bacterial endotoxin LPS-binding ability[233]. Since 1994, PMB has been well applied for immobilization in columns to remove endotoxins from the bloodstream, for the treatment of severe sepsis and septic shock[234−238]. Recently, the development of nano-drug delivery systems has led to significant improvements in the bioavailability and safety of AMPs *in vivo*. Hence, nanoparticulate LPS scavengers have also been developed for intravenous delivery.

Bae's group[239] developed a cationic antimicrobial decapeptide KSLW (KKVVFWVKFK) and conjugated it with a PEGylated phospholipid to form micelles (PLM-KSLW). They found that PLM-KSLW was not only able to inhibit bacterial growth, it could also improve the survival rate of mouse models with LPS-, bacteria-, and cecal ligation and puncture-induced sepsis without undesired immune responses, while also alleviating LPS-induced severe vascular inflammatory responses. Zhang's group[230] designed drug-cross-linked Pluronic micelles *via* a one-pot synthesis to encapsulate colistin (Fig. 12C). *In vivo* animal studies showed that the micelles altered the pharmacokinetic behavior and biodistribution of colistin, leading to reduced nephrotoxicity and

neurotoxicity. In particular, when rifampicin was co-loaded with colistin, the micelles showed a synergistic antimicrobial effect, leading to significantly improved survival in a murine model of sepsis, as well as a reduced bacterial burden.

Scavenging inflammatory cell-free DNA (cfDNA) has recently become an alternative approach for preventing aberrant TLR activation, in order to treat sepsis without blocking TLR functions. MDP-based systems, such as PEI-functionalized mesoporous silica nanoparticles[240], PEI-functionalized zeolitic imidazolate framework-8 (PEI-*g*-ZIF)[241], and other cationic nanoparticles (cNPs)[242,243], have illustrated the possibility of developing DNA scavenging therapies for cfDNA-associated diseases.

Developing novel formulations for drug delivery to the brain is essential for central nervous system disorder therapy. However, since the brain has a unique blood–brain barrier (BBB) that restricts the entry of neurotoxic substances, the BBB also restricts the permeation of most drugs to the brain. To overcome this obstacle, many nanosystems have been applied to bypass the BBB and facilitate the delivery of therapeutic agents into the brain through intravenous administration. Strategies such as surface modification with targeting peptides [*i.e.*, the human immunodeficiency virus (HIV)-1 transactivator of transcription (TAT) peptide] could provide an additional edge to these nanosystems for brain-targeted drug delivery[244].

He's group[231] developed ~150 nm core−shell nanoparticles, self-assembled by the TAT-conjugated cationic peptide PA-28, for brain infection treatment (Fig. 12D). *In vivo* anti-infective experiments showed that these nanoparticles were able to penetrate the BBB and inhibit the growth of *S. aureus* in infected rat brains. Yang's group[245] reported that cholesterol-conjugated CG_3R_6TAT formed cationic nanoparticles *via* self-assembly. Their results demonstrated that the peptide nanoparticles were able to cross the BBB and suppress *S. aureus*- and *Cryptococcus neoformans*-induced brain infections with high biocompatibility[245,246].

4.3. MDP-based transdermal delivery systems

4.3.1. Challenges and advantages

Transdermal delivery as a non-invasive route of drug administration has been widely used for the treatment of skin disorders, allowing for rapid, pain-free administration either by minimally trained healthcare providers or through self-administration[247]. Moreover, drug delivery *via* the transdermal route can avoid first-pass elimination and digestive enzyme metabolism.

Achieving efficient transdermal MDP delivery may be not easy. The skin is the largest organ in the body and contains two primary layers: the outer epidermis and inner dermis. The stratum corneum is the outermost part of the epidermis. The tight junctions in the stratum corneum form a water-tight barrier, which is impermeable to hydrophilic drugs and molecules with molecular weights larger than 500 kDa[248]. Therefore, the troublesome penetration of macromolecule drugs across the stratum corneum limits drug efficacy.

Constructing a suitable formulation is important to improve the stability of MDPs and mediate stimuli-responsive controlled drug release, because the bioactivities of MDPs are likely weakened by environmental factors such as hydrolysis, oxidation, reduction, and photolysis. For instance, AMPs that contain methionine residues (*e.g.*, pediocin PA-1) may be oxidized, leading to destabilization[249]. In addition, UV irradiation may induce racemization and isomerization of Asp residues in peptides[250]. The high levels of protease within chronic wounds and proteolytic enzymes

associated with bacterial infection and tumor cell metastasis are also responsible for the degradation of MDPs[251]. The pHs of acute wounds and the microenvironment of skin cancer are known to be acidic, while chronic wounds and infected wounds with a high bacterial burden usually exhibit pH values above 7.3[252]. Currently, in order to improve skin permeation and stability of drugs, many transdermal drug delivery systems are currently under investigation, including nano- or micro-particles[253−255], hydrogels[254,256,257], and microneedles[258−261].

4.3.2.   Application
Currently, many nano drug delivery systems have been developed to improve the stability, permeability, and therapeutic efficacy of MDPs. Recently, Takeuchi's group[253] prepared CsA-loaded nanoparticles with a mean diameter of 30 nm using poly(lactic-co-glycolic acid) (PLGA)-PEG-PLGA triblock copolymers. The results showed that the nanoparticles could mediate a more efficient drug delivery into the deep skin, compared to conventional PLGA nanoparticles, which suggested that the application of PLGA-PEG-PLGA triblock copolymers increased the thermodynamic activity and stabilization of CsA, and promoted the diffusion of nanoparticles into the epidermis and dermis layer via hair follicles.

Chereddy's group[262] found that PLGA nanoparticles were beneficial for enhancing the therapeutic effect of LL37 in promoting wound healing. Their results demonstrated the combined effects of lactate and LL37 released from nanoparticles. It was observed that PLGA-LL37 NP-treated wounds clearly achieved higher re-epithelialization, granulation tissue formation, immunomodulation, improved angiogenesis, and modulated inflammatory wound response. In addition to promoting wound healing,

Hernandez's group[263] observed that encapsulated LL37 has the potential to inhibit the growth of bacteria in wounds through sustained LL37 release. MDPs and metal nanocomposites also show potential for wound healing. Mangoni's group[174] developed AMP-coated AuNPs by covalent binding of the frog-skin-derived AMP esculentin-1a via a PEG linker to AuNPs. The systems exhibited increased antimicrobial activity against *P. aeruginosa*, enhanced proteolytic stability, and wound healing activity on a keratinocyte monolayer model.

Zhang's group[264] designed a benign EPL/AgNPs nanocomposite (EPL-g-butyl@AgNPs) (Fig. 13A). Through a combination of EPL-g-butyl and AgNPs, the composite exerted polyvalent and synergistic antibacterial effects, which first bind to bacterial surfaces to disrupt bacterial cell walls and membranes, followed by the penetration of cells and strong inhibition of enzyme activity, ultimately resulting in bacterial apoptosis. In the treatment of diabetic rats with wounds on their backs, the nanocomposites successfully modulated inflammatory cells and thus facilitated wound healing without inducing observable side effects on dermal tissues.

Recently, hydrogels have also been studied as a potential formulation for the transdermal delivery of MDPs, owing to their unique properties, including their high ability to swell in water, high oxygen permeability, improved biocompatibility, ease of loading and release of drugs, and structural diversity[265]. MDP-loaded, stimuli-responsive hydrogels that respond to corresponding stimuli and thus release MDPs can achieve controlled, targeted, and effective treatment. In addition, the solid-like mechanical properties of the hydrogel can protect the wound site from further external damage, which helps to accelerate the healing process.
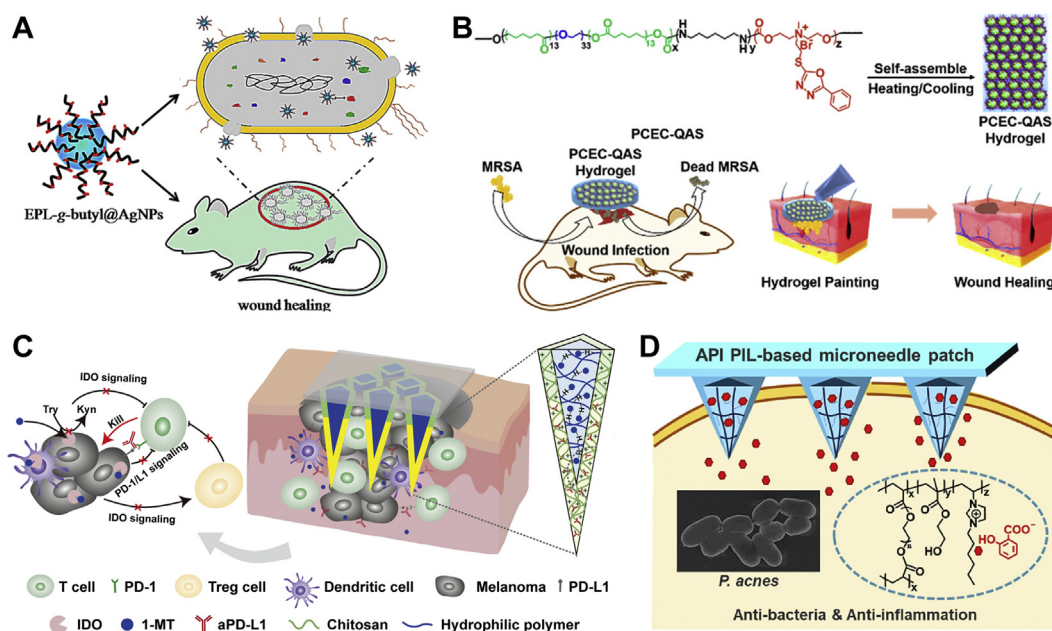
Figure 13   MDPs-based transdermal delivery systems and their applications. (A) The benign EPL/AgNPs nanocomposites with improved wound healing capability. Reproduced with permission from Ref. 264. Copyright © 2016, American Chemical Society. (B) Schematic illustration of PCEC-QAS polymeric antibacterial hydrogel for wound healing. Reproduced with permission from Ref. 229. Copyright © 2020, American Chemical Society. (C) Construction of a core−shell microneedle system for melanoma immunotherapy. Reproduced with permission from Ref. 283. Copyright © 2020, Elsevier. (D) Schematic illustration of PIL-based microneedles for the treatment of skin *Propionibacterium acnes* infection. Reproduced with permission from Ref. 289. Copyright © 2020, Elsevier.

Gholipourmalekabadi's group[266] fabricated an antibacterial wound dressing by loading AMP piscidin-1 into a thermo-responsive CS hydrogel, cross-linked with β-glycerolphosphate disodium salt pentahydrate. The hydrogels formed at 37 °C could mediate controlled release of AMP and displayed excellent antibacterial activity against both standard strains and resistant clinical isolates of *A. baumannii*. Lu's group[267] developed a physically-chemically dual cross-linked hydrogel, which combined a PEG diacrylate (PEGDA) covalent network and a CS ion cross-linked network; it was prepared by a two-step method of photopolymerization and salt solution soaking treatment. After encapsulation with Trp-rich peptides PSI and plasmid Ang-1, the hydrogels can synergistically promote wound healing by inhibiting infection, in order to reduce inflammation and promote microvascular formation.

In contrast to the previous strategy of loading MDPs into hydrogels to acquire antibacterial effects, researchers recently constructed antibacterial hydrogels using MDPs as matrix materials to achieve a higher loading capacity of MDPs[268−273]. For example, Jan's group[274] reported a polypeptide/heparin composite hydrogel using linear PLL and star-shaped PLL polypeptides cross-linked with genipin. The antibacterial polypeptides were chosen owing to not only their cationic characteristics in binding bacteria and heparin, but also the ease of regulating the physical and mechanical properties of the as-prepared hydrogels simply by varying the polypeptide topology and chain length. Wang's group[275] developed a synthetic polymeric antibacterial hydrogel *via* the spontaneous self-assembly of PCEC-QAS polymeric micelles in water, and the subsequent noncovalent nanoparticle stacking at a high polymer concentration gave rise to the formation of an irreversible gelatin-to-solution hydrogel after heating−cooling treatment (Fig. 13B). The PCEC-QAS hydrogel is degradable *in vivo* to release the antibacterial PCEC-QAS copolymer, thus showing broad-spectrum antimicrobial activity and inducing acceleration of MRSA-infected cutaneous wound healing. Li's group[276] designed a pH-switchable antimicrobial hydrogel based on the self-assembly of the AMP IKFQFHFD at neutral pH. The hydrogel disassembles and possesses activated antimicrobial activity at acidic pH. Thus, it is suitable to deliver cyapte (a PTA for biofilm EPS damage) and proline (procollagen component for improved cell proliferation) for synergistic biofilm eradication and subsequent healing cascade activation. Furthermore, hydrogels that used EPL or its derivative as the main matrix materials also exhibit high drug encapsulation and superior antimicrobial efficacy in promoting wound healing[277−279].

Microneedle patches that consist of miniaturized needles, generally 100−1000 μm in length, have emerged as promising tools for bypassing the skin stratum corneum barrier and effectively delivering therapeutic agents into deep skin layers in a minimally invasive manner[280,281]. Therefore, microneedle-mediated transdermal delivery is a viable option for promoting the transdermal delivery of MDPs to combat skin infections and cancer[282−285]. Recently, Xie's group[286] reported a fabricated Janus-type antimicrobial dressing, consisting of AMP-loaded electrospun nanofiber membranes and dissolvable microneedle arrays, for the eradication of biofilms in chronic wounds. The microneedle array successfully enhanced the penetration of AMP to both inside and outside biofilms, exhibiting superior activity in the removal of *P. aeruginosa* and MRSA dual-species biofilms in an *ex vivo* human skin infection model.

Chen and co-workers[287] used a CS-PEI copolymer as a biocompatible antimicrobial agent to fabricate microneedle patches for treating deep cutaneous fungal infections. Compared to the conventional topical drug application, the microneedle patches exhibited superior therapeutic effectiveness, with high bioavailability and sustained synergistic actions from both CS−PEI and the antifungal drug amphotericin B, in a mouse model of fungal infection. Because of the natural antibacterial property of CS, Wang's group[288] also illustrated the potential of CS-based microneedle patches for promoting wound healing.

Recently, MDPs have been found to have the potential to facilitate tumor immunotherapy[284,285]. Taking advantage of the ability of CS to enhance penetration and carry anion drugs, Wu's group[290] encapsulated an ICG PS into CS nanoparticles (ICG-NPs) and further co-delivered the photosensitizer with an IDO blockade 1-methyl-tryptophan (1-MT). Their research illustrated that their constructed binary cooperative microneedle array could be used to amplify photoimmunotherapy for eliciting antitumor immunity and the abscopal effect. In another study, Wu's group[283] developed a highly drug-concentrated hybrid core−shell microneedle system for the co-delivery of checkpoint inhibitors anti-PD-L1 antibody (aPD-L1) and 1-MT (Fig. 13C). They found that aPD-L1/1-MT loaded CS-based core−shell microneedles (CS-CSMN) could mediate higher cumulative skin permeation rates than sodium alginate-based or shell-less microneedles, and could also increase the infiltration of immune cells into the tumor site, leading to a decrease in the tumor weight. A more recent study from the same group further found that the co-administration of ICG-NP MNs and the aPD-L1/1-MT CSMNs could combine instant ablation of tumor cells from PTT and the persistent antitumor immune response of immunotherapy, displaying superior antitumor efficacy compared to PTT or immunotherapy alone[285].

Furthermore, studies have shown that microneedle administration is a potential route to achieve systemic delivery, in place of intravenous injection[291]. Dillon's group[292] used a polyvinyl pyrrolidone PVP/trehalose hybrid matrix to prepare a dissolving microneedle system for transdermal and subsequent systemic delivery of PMB. The study showed that the microneedle system successfully delivered PMB through porcine skin at a faster initial rate, and the antimicrobial activity of PMB was retained after incorporation into the microneedle system and delivery.

Recently, PILs, an innovative class of polyelectrolytes comprised of polymeric backbones and IL species in each repeating unit, have attracted considerable attention. Among them, a variety of cationic PILs have been developed for antimicrobial applications because of their biocompatibility, bacterial cell membrane disruption, and transdermal permeability. Since PILs usually display a low glass transition temperature (T_g), they can exist in a gel or solid state at room temperature, ideal for fabricating a new class of unique topical formulations for antimicrobials[99−101,293−295].

For example, to address the poor penetration of antimicrobial agents in the biofilm of infected skin, Wu's group[296] developed a pH-responsive superporogen combined with PDT, based on the conjugation of poly Ce6 IL to SiO_2 nanoparticles (SiO_2-PCe6-IL) to combat MRSA biofilm infection. In the acidic microenvironment of biofilm infection, SiO_2-PCe6-IL, with a positive charge, can interact with the negatively charged bacterial membrane and rapidly release PSs to the biofilm by creating holes on it, thus

dramatically improving the PDT efficacy against MRSA biofilm infection. In order to increase the mechanical properties and stability of PILs for preparing first-rate antibacterial wound dressings, composite hydrogel-like PIL/poly(vinyl alcohol) (PVA)[295], PIL/montmorillonite clay[294], and PIL/lignin were developed.

To further facilitate the transdermal delivery of drugs and bypass the skin stratum corneum barrier, Yan and coworkers[289] developed PIL-based microneedle patches with salicylic acid loaded onto a microneedle, *via* electrostatic interactions between the salicylic acid anion and imidazolium cation (Fig. 13D). The use of microneedles improved the transdermal efficiency of salicylic acid and enhanced the treatment effect in *P. acnes*-treated mice, and is active not only against bacteria but also against inflammation.

Recent studies have found that some MDPs have the ability to permeabilize the skin and promote skin penetration of other therapeutic drugs[48]. Prausnitz's group found that magainin can increase skin permeability by disrupting the lipid structure of the stratum corneum[297,298]. A formulation containing magainin and the surfactant chemical enhancer *N*-lauroylsarcosine in 50% ethanol could synergistically increase skin permeability to fluorescein by 47-fold. There are many other transdermal delivery systems for MDPs, having also been incorporated into cream[299],

ointment[300], and wafer[301], which have made good attempts for their clinical application.

4.4. MDP-based pulmonary delivery systems

4.4.1. Challenges and advantages

In recent years, pulmonary delivery has attracted growing interest as an efficient and patient-friendly route for drug administration. In the treatment of pulmonary diseases, direct delivery of drugs to the target site *via* the pulmonary route is beneficial for increasing the local concentration of drugs, thereby lowering the therapeutic dose and reducing systemic side effects[302]. As the lungs have more than 300 million alveoli, large contact surface area (*ca.* 100 m^2), thin alveolar epithelium (0.1−0.2 μm), and high membrane permeability, drugs can be absorbed into the bloodstream to achieve a rapid onset action of systemic drug delivery and avoid first-pass metabolism[303].

The lung airways are highly branched, including the trachea, bronchi, bronchioles, and alveolar air sacs, and the path becomes narrower with increasing generations, as shown in Fig. 14A. Microparticles are deposited in the lungs *via* several mechanisms, namely impaction, sedimentation, diffusion, interception, and electrostatic precipitation (Fig. 14B). The first three are

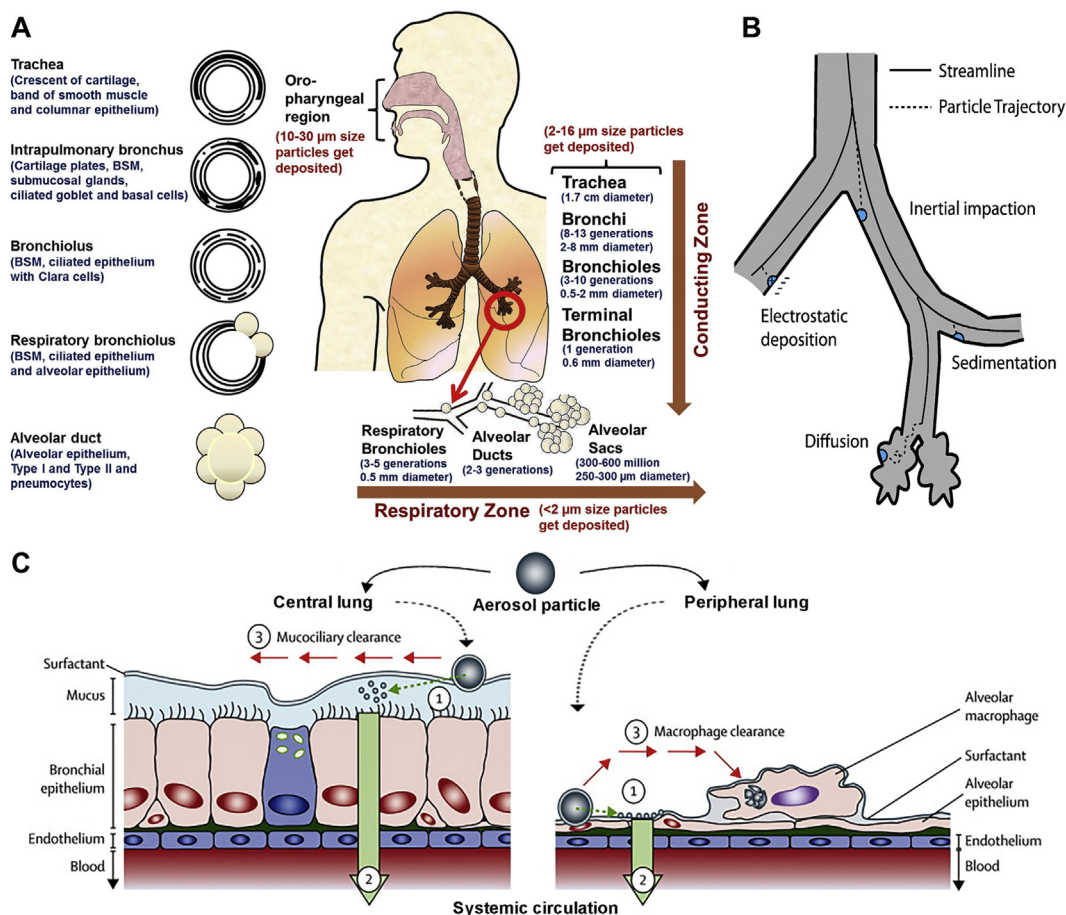**Figure 14** Challenges of pulmonary delivery. (A) The structure of adult lung airways. Reproduced with permission from Ref. 306. Copyright © 2013, Elsevier. (B) Different mechanisms of deposition in lung airways. Reproduced with permission from Ref. 309. Copyright © 2015, Elsevier. (C) Physiological barriers and different clearance mechanisms of lung. Reproduced with permission from Ref. 307. Copyright © 2014, Elsevier.

mainly affected by the size and density of particles, whereas interception depends largely on the shape of the particle. The electrostatic deposition of particles is dependent on the electrostatic precipitation of charged particles on the oppositely charged lung surface.

When inhaled, the parameters of particles, mainly aerosolization diameter, determine their deposition behavior and deposition regions in the respiratory tract[304,305]. Because particles with diameters larger than 10 μm are suitable for deposition in the oropharynx and those with diameters smaller than 0.5 μm are likely to be exhaled, the aerosolization diameter of microparticles should be in the range of 1−5 μm to achieve effective pulmonary deposition[306].

Once deposited in the lungs, these particles still need to fight against physiological barriers and different clearance mechanisms (Fig. 14C). For example, the mucus layer covering the surface of the bronchial epithelium can capture large particles that settle in the upper airway and prevent their penetration into the lung epithelium, to be subsequently eliminated by mucociliary clearance. Even though they reach the alveoli, smaller particles are susceptible to phagocytosis and are eliminated by alveolar macrophages[307,308].

All obstacles mentioned above must be overcome to develop an effective pulmonary delivery system for MDPs. Three types of aerosol devices are available for pulmonary delivery: nebulizers, pressurized metered dose inhalers (pMDIs), and dry powder inhalers (DPIs). Nebulizers were the first devices developed for the inhalation therapy market and are used to provide drugs that are available and chemically stable in liquid form. Nebulizers have some drawbacks, such as low efficiency, poor reproducibility, and great variability[310]. The emergence of portable pMDIs has brought great convenience to users, but the use of chlorofluorocarbon propellants in pMDIs limits their development and application to some degree[311]. Recently, DPIs are advantageous due to their portability, free of propellants, formulation stability and less need for patient coordination[312,313]. Thus, DPIs have become a hot spot in the application for pulmonary delivery, especially for peptide and protein delivery.

In order to meet the previously discussed size range for sufficient deposition in lung airways, several methods have been developed to produce appropriate particle sizes, such as spray drying[314], jet milling[315] and ultrasonic spray freeze drying[316]. In addition, a novel ultra-fine particle processing system (UPPS) reported by Wu's group[317−319] was applied as an alternative technology for microparticle preparation, due to its ability to produce microparticles under mild temperature conditions, wide range viscosity, and high encapsulation efficiency.

In recent years, nanoparticle-containing micron-sized particles, also termed nano-embedded microparticles (NEMs), have been widely applied to release primary nanoparticles after reaching the deep lung, activating upon the dissolution of the inert carrier in the lung lining fluid[320]. Drug-loaded nanoparticles are generally prepared using various carrier systems first, followed by the addition of excipients to form dry microparticles[320,321].

4.4.2. Application

Directly delivering MDPs to a lesion site through pulmonary administration may achieve a better therapeutic effect than intravenous delivery. Di's group[322] reported that the AMP WLBU2 could remarkably reduce bacterial burden and bacteria-induced inflammation in a murine model of *P. aeruginosa* infection *via* the pulmonary route. Rivas-Santiago's group[323] also reported 3−10-fold reductions in bacterial load in a virulent model of *Mycobacterium tuberculosis* lung infection after intratracheal therapeutic application of AMPs.

Furthermore, Forde's group[324] investigated the physical characteristics and antimicrobial activity of AMPs before and after nebulization using a vibrating mesh nebulizer, and found that the nebulized AMPs displayed appropriate aerosol characteristics, in both models of spontaneously breathing and models of mechanically ventilated patients, with maintained antibacterial effects.

In addition, pMDIs can also be used for the pulmonary delivery of MDP-based therapeutic agents. As reported by Rocha's group[325], a PEGylated PAMAM-DOX conjugate (G3NH2-mPEG-nDOX) induced significant cell death in alveolar cancer cells (Fig. 15A). The aerosol characteristics of the resulting pMDI
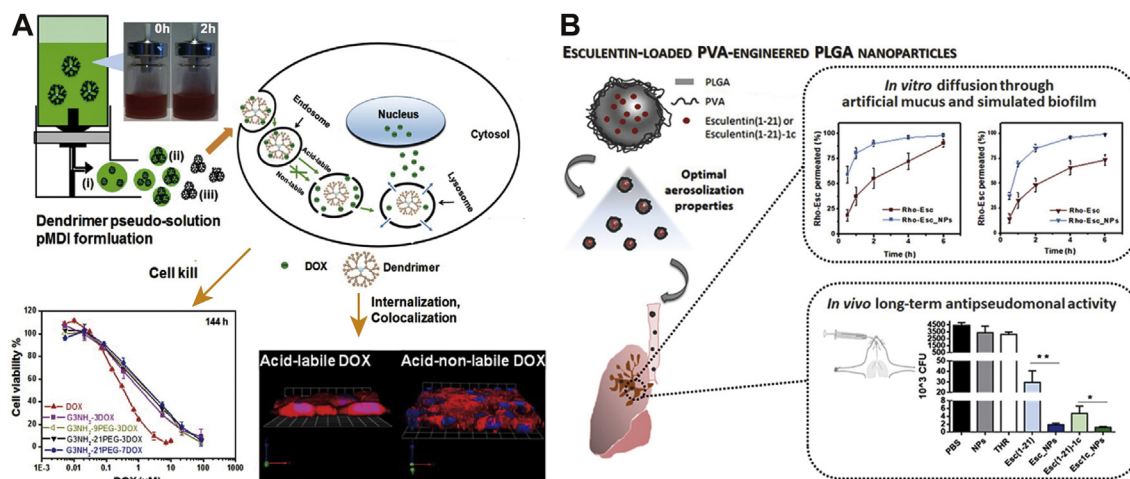
Figure 15 MDPs-based pulmonary delivery systems and their applications. (A) PAMAM-DOX conjugates formulated in pMDIs with enhanced aerosol characteristics and cancer cell-killing ability. Reproduced with permission from Ref. 325. Copyright © 2016, American Chemical Society. (B) Schematic illustration of AMP-loaded PLGA nanoparticles for lung infection treatment. Reproduced with permission from Ref. 326. Copyright © 2020, American Chemical Society.

formulations were shown to be exceptional, with respirable fractions as high as 82% and fine particle fraction up to 78%.

Bearing in mind the limitations of the physicochemical properties of MDPs and the intricate biological structure of the lungs, the construction of corresponding delivery systems for pulmonary delivery is necessary to improve bioavailability. For example, consider the cationic characteristics of MDPs. When administered *via* the pulmonary route, the positively charged MDPs interact electrostatically with anionic proteins (*e.g.*, mucin) or other polysaccharides (*e.g.*, bacterial alginates or glycosaminoglycans) in the extracellular lung environment, which results in strongly hampered activity and rapid clearance from the body[327,328]. Therefore, many nanoparticle-based delivery systems have been developed to address these problems.

Liposomes are composed of self-assembled microscopic vesicles consisting of an aqueous solution core, surrounded by one or more lipid bilayers. Liposomes are usually prepared from materials that are endogenous to the lungs, such as cholesterol and phospholipids[303]. These characteristics endow liposomes with an excellent encapsulation capacity for both lipophilic and hydrophilic MDPs, high biocompatibility, and sustained drug release properties for pulmonary drug delivery. Suntres's group[329] developed a liposomal PMB for *P. aeruginosa*-induced lung infection therapy. They demonstrated that the availability of PMB at the site of infection was increased, and superior antimicrobial activity was achieved after intratracheal administration to the lungs.

Polymer nanoparticles have become an increasingly attractive delivery system for drug inhalation due to their excellent biocompatibility, as well as the possibility of tailoring the nanoparticle size and modifying the surface for enhanced drug bioavailability[330]. It has been reported that polymer nanoparticles, such as PLGA[331] and dextran[332] nanoparticles, have a high MDP encapsulation capacity, which is beneficial for enhancing the local concentration and persistence of drugs in the lung, overcoming biodistribution issues, and reducing toxicity.

In order to further enhance therapeutic efficacy and overcome physiological barriers, surface modification of nanoparticles holds great promise for facilitating AMP-loaded nanoparticle transport through mucus. Mangoni's group[326] developed PVA-coated PLGA nanoparticles for AMP Esc(1-21) delivery, which provides a neutral hydrophilic surface that favors translocation through lung mucus and biofilm (Fig. 15B). They studied the aerosol performance of the PVA-engineered PLGA nanoparticle dispersion upon delivery through a liquid jet nebulizer, and found that the nanoparticles have great potential to assist the delivery of AMPs in the conductive airways, as well as to extend and increase their therapeutic efficacy against acute *P. aeruginosa* lung infection. Subsequently, Mangoni's group[328] further developed surface engineering of PLGA nanoparticles with CS, and found that the loaded colistin diffusion through artificial mucus was facilitated, which may be attributed to the mucus fiber collapse and generation of large channels that may promote the penetration of the cationic nanoparticles. Schuster's group[333] found that PEG-coated particles exhibit enhanced transport in airway mucus, likely because the dense PEG coating reduces particle adhesion to the mucus network. This suggests that PEG-coating may also be an approach to enhance the transportation in mucus of MDP-based nanoparticles.

Depending on the therapeutic purpose, a drug delivery system can be customized to avoid or enhance internalization by alveolar macrophages[334]. Some diseases necessitate localized delivery of

drugs and prolonged therapeutic effects, which can be achieved by escaping macrophage uptake, thereby increasing the residence time in the lung. Studies have verified that the PEGylation of NPs prolongs the lung retention time of drugs and significantly reduces particle recognition and uptake by macrophages, likely due to the absence of PEG-specific receptors on their surface[335,336].

Macrophages may also be the primary site of a disease or may participate in disease progression *via* various immunological and physiological pathways. They are involved in the progression of numerous diseases, including asthma, chronic obstructive pulmonary disease, cancer, HIV, and bacterial infection[334]. Thus, when macrophages serve as specific targets for drug delivery, optimization of the physicochemical properties of particles and surface modification through the attachment of specific ligands may be desirable, in order to increase the recognition and internalization of particles by alveolar macrophages.

Recently, many successful examples of MDP-loaded DPI formulations have been reported in the literature[314,337−339]. Among them, the development of DPI formulations for the co-delivery of MDP and other drugs has gradually become a research hotspot, not only because of their potential to afford enhanced therapeutic effects but also because of their potential to increase the aerosol performance of formulations.

Zhou's group[338] developed a liposomal DPI formulation for the co-delivery of ciprofloxacin and colistin against multidrug-resistant Gram-negative lung infections. They found that the liposomal formulation of colistin and ciprofloxacin demonstrated superior antibacterial activity compared to monotherapy, with negligible cytotoxicity, and the liposomal DPI formulations prepared by the ultrasonic spray-freeze-drying technique exhibited satisfactory aerosol performance for the treatment of MDR Gram-negative lung infections. In another study, Zhou's group[337] found that co-spray drying ciprofloxacin with colistin could improve aerosolization through the surface enrichment of colistin, thereby acquiring combinational DPI formulations of ciprofloxacin and colistin for the treatment of respiratory infections.

In order to simultaneously treat cystic fibrosis and its complications, such as multidrug-resistant Gram-negative lung infections, Zhou's group[339] recently reported a novel, inhalable nanocomposite microparticle formulation for co-delivery of colistin and ivacaftor. The authors demonstrated that colistin could work not only as a synergistic antimicrobial agent, but also as a unique matrix material for reducing the use of excipients for high-dose medications, improving the dissolution rate of ivacaftor, and increasing the aerosol performance of formulations.

4.5. MDP-based oral delivery systems

4.5.1. Challenges and advantages

Oral delivery is the most common route of therapeutic administration, with ease of medication, low cost, and high patient compliance. To exert their therapeutic effect locally or systemically, orally administered drugs must overcome numerous metabolic and physicochemical barriers imposed by the gastrointestinal tract, as shown in Fig. 16A.

Oral drug delivery systems play a crucial role in increasing the stability and efficacy of MDPs (Fig. 16B)[340]. When administered orally, MDPs are initially exposed to a series of pH changes from highly acidic conditions in the stomach (pH levels of 1.2−3.0) to neutral and slightly basic environments (pH levels of 6.5−8.0) in the intestinal tract[341]. In addition, various hydrolytic and metabolic enzymes also cause oxidation, de-amidation, as well as acid-
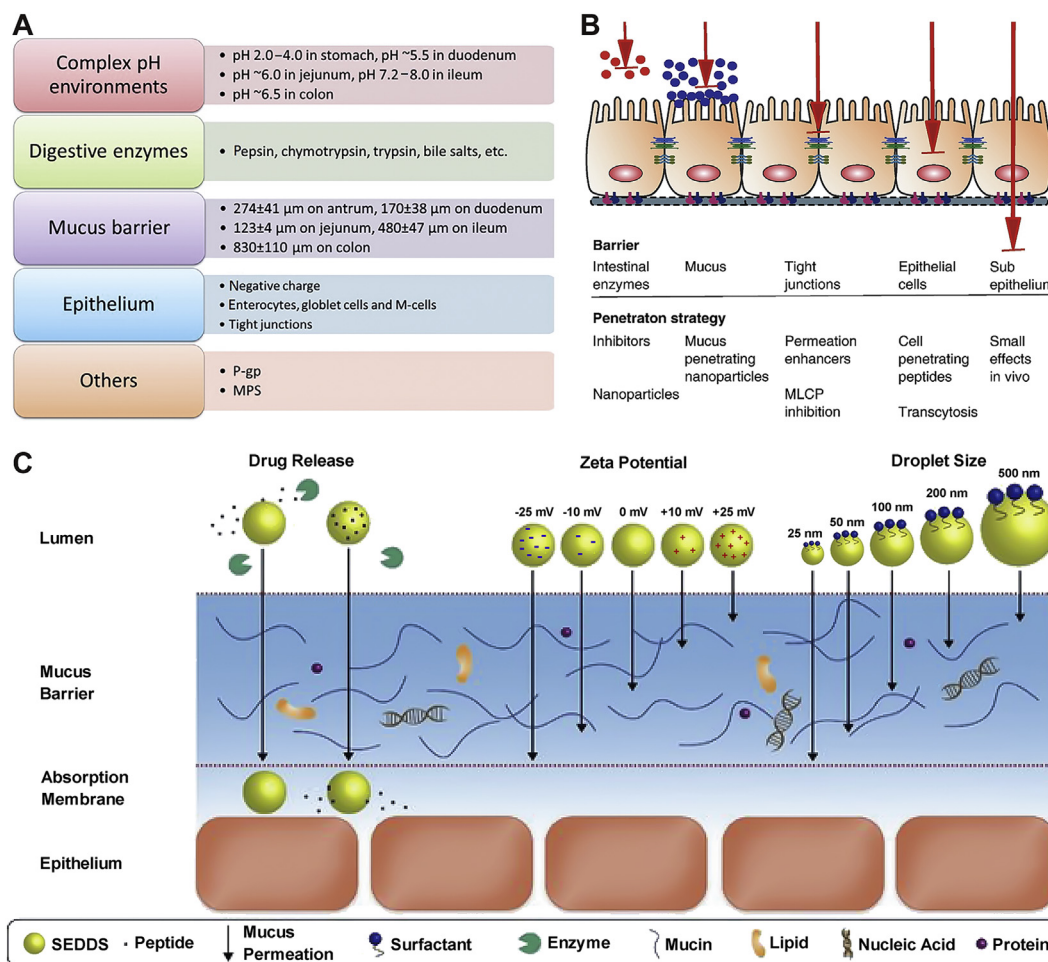
Figure 16 Challenges of oral delivery. The physiological barriers in gastrointestinal tract of oral delivery (A) and the corresponding penetration strategies (B). Reproduced with permission from Ref. 345. Copyright © 2019, Elsevier; and Ref. 340. Copyright © 2016, Elsevier. (C) Self-emulsifying peptide drug delivery systems with different mucus permeating ability. Reproduced with permission from Ref. 346. Copyright © 2018, Elsevier.

or base-catalyzed hydrolysis[342]. When MDPs enter the small intestine, they need to penetrate the mucus layer to reach intestinal epithelial cells, and then must be well transported by epithelial cells to avoid enterocyte-based efflux or metabolism[340,343,344]. Therefore, strategies need to be developed to improve the oral bioavailability of AMPs and their mimics.

4.5.2. Application

Conventional formulations, such as tablets, have been widely applied to enhance the oral bioavailability of different agents and meet different medication purposes, such as controlled or sustained release, taste masking, colon targeting, and administration flexibility. Although biotherapeutics based on peptides and proteins are sensitive to enzymes and pH, oral delivery has been proven to be a possible delivery route *via* appropriate drug delivery system design.

Wu's group[347] designed and developed a self-nanoemulsifying osmotic pump tablet to protect the cyclic peptide cyclosporine A from degradation of the gastrointestinal tract. Taking advantage of the absorption-enhancing effect of self-nanoemulsifying delivery systems and the release rate-controlling capacity of the osmotic pump tablets, pharmacokinetic results showed that the osmotic

pump tablets displayed steady and prolonged blood cyclosporine A levels in beagle dogs.

In recent years, micro- and nanotechnology have been widely applied and developed to improve the oral bioavailability of therapeutic drugs[345,348−350]. To protect MDPs from chemical and enzymatic degradation, well-designed carrier systems, such as mesoporous silica matrices or pellets, along with lipid nanocapsules, have been used to encapsulate and endow them with resistance to harsh environments in the gastrointestinal tract.

Hudson's group[351] demonstrated that loading bactofencin A onto a silica mesoporous matrix can significantly protect bactofencin A against enzymatic degradation and improve its activity against *S. aureus*. Furthermore, they found that the chemical functionality and pore size of mesoporous silicates had a large influence on the loading capacity, release rate, activity, and protection from enzymatic degradation[352]. In addition, Saulnier's group[353] developed a type of reverse micelle-lipid nanocapsules, in which AMP-loaded reverse micelles were developed and incorporated into lipid nanocapsules by a phase inversion process. This formulation effectively protects AMP AP138 from degradation by proteases and preserves its antimicrobial activity against bacteria.

The size and surface properties of particles have been reported to regulate their pharmacokinetic behavior and the absorption sites of nanoparticles in the small intestine[345,354]. In order to penetrate the mucus layer, drugs have to overcome the barrier from mucus, which covers epithelial cells of the mucosa consisting of mucin fiber proteins. This fibrous structure is covered by proteoglycans, which results in the mucus layer carrying a strong negative charge. The continuous secretion of mucus leads to the removal of drug cargo sticking on the surface.

It is well known that classical mucoadhesive carriers tend to be entrapped in the loosely adherent mucus layer and are quickly cleared before reaching the adsorption sites, and the mesh size of mucus ranges from 20 to 200 nm[355,356]. Therefore, nanomedicines have great potential for efficient permeation through human mucus. Recently, Bernkop-Schnürch's group[346] developed self-emulsifying peptide drug delivery systems (SEDDS), which spontaneously form emulsions after getting into contact with body fluids, and illustrated how the size and zeta potential of nanomedicines affects their ability to penetrate the mucus layer (Fig. 16C). They found that the smaller the SEDDS, the higher the mucus permeating properties, and the negatively charged SEDDS demonstrated a better intestinal permeability than the positively charged one, attributed to the tendency of positively charged nanoparticles to get stuck within the negatively charged mucus. Similarly, Mao's group[357] found that the nanocomplex with negative alginate coating had 1.6–2.5 times higher mucus penetration ability than that of positively charged chitosan–peptide nanocomplexes. In addition, PEG has been reported to provide more hydrophilicity for nanoparticles to pass through the mucus and prevent aggregation[345].

Nevertheless, cationic bioadhesive molecules, such as CS, which electrostatically interact with mucin (negatively charged), have also been used to increase the system permanence time at the target site, and thus the bioavailability. Recently, Rishi's group[358] explored a nanoencapsulated cryptdin-2 formulation using CS and tripolyphosphate. The nano-encapsulation system was composed of CS that could be used to modulate the intestinal tight junctions, thereby enhancing the paracellular transport process and its bioadhesive nature. Studies have shown that the cryptdin-2-loaded nanoparticles can efficiently reduce the *Salmonella enterica* load in the liver and intestine, as well as increase the survival rate of infected mice after oral administration.

Furthermore, once the pathogens invade mammalian cells and establish intracellular infection, therapy would become more intractable due to the poor permeability of many antibacterial agents. In this situation, conjugation of cell-penetrating peptides or proteins may be necessary. Loretz and co-workers[359] developed bioinspired liposomes for the oral delivery of colistin to combat intracellular infections by *S. enterica*. Liposomes were surface-functionalized with an extracellular adherence protein, which promoted liposome cellular uptake, enhanced the intracellular antibacterial activity of colistin, and significantly reduced the intracellular bacterial load, suggesting that the liposomes can invade epithelial cells and efficiently release the payload to exert pharmacological effects.

Apart from the previously mentioned applications, MDP-based formulations offer significant potential for the prevention and treatment of oral infectious diseases[360]. For example, Duque's group[361] reported a β-defensin-3 peptide fragment-loaded liquid crystalline system (D1–23-loaded LCS) for dental caries treatment. The bioadhesive property of D1–23-loaded LCS helps to maintain a high concentration of the peptide at the site of action for a long period and protect them from degradation, thus displaying better therapeutic efficacy against *Streptococcus* mutans biofilm. Al-Ghananeem's group[362] formulated an effective antimicrobial and antiplaque chewing gum containing an AMP, which significantly promoted biofilm susceptibility to KSL-W and produced a synergistic effect in killing biofilm-forming bacteria. As applied in the treatment of peri-implantitis, Wang's group[363] fabricated KSL-W-loaded PLGA/CS composite microspheres with prolonged antimicrobial effects against *Fusobacterium nucleatum*. The surface coating of CS shells prevented protein aggregation and denaturation caused by the locally acidic environment associated with PLGA hydrolysis, thus achieving long-term sustained release of KSL-W and a high concentration of antibacterial agent at the site of the oral cavity.

5.   Conclusions and future outlook

In summary, this review provides an overview of the recent advances of MDPs and their delivery systems to combat bacteria and cancer in the drug-resistant era. MDPs are recognized as promising therapeutic agents and adjuvants to combat bacterial infections with high activity and selectivity. In addition, MDPs demonstrate excellent capabilities to inhibit tumor cell growth, mitigate resistance development *via* direct membranolytic effect, and mediate other non-membranolytic mechanisms. Owing to the inherent physicochemical properties of MDPs, the fabrication of appropriate delivery systems is essential for the translation of MDPs into practical applications. The physiological barriers and challenges of different delivery strategies are discussed, and recent advances in MDP-based formulations with enhanced efficacy and reduced toxicity are summarized.

In addition to the four main administration routes aforementioned, MDP-based delivery systems have also been proposed for subcutaneous[207], nasal[364,365], ocular[366,367] and intratumoral[368] applications, which are worthy of consideration for further investigation and development. While MDPs and their formulations have been extensively investigated in antimicrobial applications, their antitumor applications are still in infancy and rarely studied. MDPs provide unique opportunities and challenges not only for bacterial infection but also for cancer therapy[11,369]. Therefore, great efforts are needed for the design and optimization of MDP-based therapeutics to expand their applications and to convert their "potential" applications to "practical" applications.

Author contributions

Chao Lu, Xin Pan and Chuanbin Wu conceived the review. Liming Lin wrote the manuscript with assistance of Jiaying Chi, Yilang Yan, Rui Luo, Xiaoqian Feng, Yuwei Zheng, Dongyi Xian and Xin Li. Chao Lu, Guilan Quan and Daojun Liu revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Ma YX, Wang CY, Li YY, Li J, Wan QQ, Chen JH, et al. Considerations and caveats in combating ESKAPE pathogens against nosocomial infections. *Adv Sci* 2020;**7**:1901872.

2. Rosini R, Nicchi S, Pizza M, Rappuoli R. Vaccines against antimicrobial resistance. *Front Immunol* 2020;**11**:1048.

3. Gold K, Slay B, Knackstedt M, Gaharwar AK. Antimicrobial activity of metal and metal-oxide based nanoparticles. *Adv Ther* 2018;**1**: 1700033.

4. Klein EY, Tseng KK, Pant S, Laxminarayan R. Tracking global trends in the effectiveness of antibiotic therapy using the drug resistance index. *Bmj Glob Health* 2019;**4**:e001315.

5. De Oliveira DMP, Forde BM, Kidd TJ, Harris PNA, Schembri MA, Beatson SA, et al. Antimicrobial resistance in ESKAPE pathogens. *Clin Microbiol Rev* 2020;**33**:3.

6. Dagenais GR, Leong UP, Rangarajon S. Variations in common diseases, hospital admissions, and deaths in middle-aged adults in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* 2020;**395**. 784-784.

7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209−49.

8. World Health Organization. Global health estimates 2020: deaths by cause, age, sex, by country and by region, 2000−2019. Geneva: World Health Organization; 2020. Available from: who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death.

9. Engler AC, Wiradharma N, Ong ZY, Coady DJ, Hedrick JL, Yang YY. Emerging trends in macromolecular antimicrobials to fight multi-drug-resistant infections. *Nano Today* 2012;**7**: 201−22.

10. Brogden NK, Brogden KA. Will new generations of modified antimicrobial peptides improve their potential as pharmaceuticals?. *Int J Antimicrob Agents* 2011;**38**:217−25.

11. Tan J, Tay J, Hedrick J, Yang YY. Synthetic macromolecules as therapeutics that overcome resistance in cancer and microbial infection. *Biomaterials* 2020;**252**:120078.

12. Ong ZY, Wiradharma N, Yang YY. Strategies employed in the design and optimization of synthetic antimicrobial peptide amphiphiles with enhanced therapeutic potentials. *Adv Drug Deliv Rev* 2014;**78**: 28−45.

13. Li YM, Xiang Q, Zhang QH, Huang YD, Su ZJ. Overview on the recent study of antimicrobial peptides: origins, functions, relative mechanisms and application. *Peptides* 2012;**37**:207−15.

14. Melo MN, Ferre R, Castanho MARB. Antimicrobial peptides: linking partition, activity and high membrane-bound concentrations. *Nat Rev Microbiol* 2009;**7**:245−50.

15. Jiang YJ, Chen YY, Song ZY, Tan ZZ, Cheng JJ. Recent advances in design of antimicrobial peptides and polypeptides toward clinical translation. *Adv Drug Deliv Rev* 2021;**170**:261−80.

16. Giuliani A, Pirri G, Nicoletto SF. Antimicrobial peptides: an overview of a promising class of therapeutics. *Cent Eur J Biol* 2007;**2**: 1−33.

17. Dang XL, Tian JH, Yang WY, Wang WX, Ishibashi J, Asaoka A, et al. Bactrocerin-1: a novel inducible antimicrobial peptide from pupae of oriental fruit fly *Bactrocera dorsalis* Hendel. *Arch Insect Biochem Physiol* 2009;**71**:117−29.

18. Carballar-Lejarazu R, Rodriguez MH, Hernandez-Hernandez FD, Ramos-Castaneda J, Possani LD, Zurita-Ortega M, et al. Recombinant scorpine: a multifunctional antimicrobial peptide with activity against different pathogens. *Cell Mol Life Sci* 2008;**65**: 3081−92.

19. Kodama T, Ashitani JI, Matsumoto N, Kangawa K, Nakazato M. Ghrelin treatment suppresses neutrophil-dominant inflammation in airways of patients with chronic respiratory infection. *Pulm Pharmacol Therapeut* 2008;**21**:774−9.

20. Koo HB, Seo J. Antimicrobial peptides under clinical investigation. *Pep Sci* 2019;**111**:e24122.

21. Bonnel C, Legrand B, Simon M, Clavié M, Masnou A, Jumas-Bilak E, et al. Tailoring the physicochemical properties of antimicrobial peptides onto a thiazole-based γ-peptide foldamer. *J Med Chem* 2020;**63**:9168−80.

22. Bechinger B, Gorr SU. Antimicrobial peptides: mechanisms of action and resistance. *J Dent Res* 2017;**96**:254−60.

23. Ahmed TAE, Hammami R. Recent insights into structure−function relationships of antimicrobial peptides. *J Food Biochem* 2019;**43**: e12546.

24. Makovitzki A, Avrahami D, Shai Y. Ultrashort antibacterial and antifungal lipopeptides. *Proc Natl Acad Sci U S A* 2006;**103**: 15997−6002.

25. Teixeira V, Feio MJ, Bastos M. Role of lipids in the interaction of antimicrobial peptides with membranes. *Prog Lipid Res* 2012;**51**:149−77.

26. Lee TH, Hall KN, Aguilar MI. Antimicrobial peptide structure and mechanism of action: a focus on the role of membrane structure. *Curr Top Med Chem* 2016;**16**:25−39.

27. Wu HF, Niu YH, Padhee S, Wang RSE, Li YQ, Qiao Q, et al. Design and synthesis of unprecedented cyclic γ-AApeptides for antimicrobial development. *Chem Sci* 2012;**3**:2570−5.

28. Zhang MZ, Zhao J, Zheng J. Molecular understanding of a potential functional link between antimicrobial and amyloid peptides. *Soft Matter* 2014;**10**:7425−51.

29. Langenegger N, Nentwig W, Kuhn-Nentwig L. Spider venom: components, modes of action, and novel strategies in transcriptomic and proteomic analyses. *Toxins* 2019;**11**:611.

30. Schmitt P, Rosa RD, Destoumieux-Garzon D. An intimate link between antimicrobial peptide sequence diversity and binding to essential components of bacterial membranes. *Biochim Biophys Acta Biomembr* 2016;**1858**:958−70.

31. Duquesne S, Destoumieux-Garzon D, Peduzzi J, Rebuffat S. Microcins, gene-encoded antibacterial peptides from *enterobacteria*. *Nat Prod Rep* 2007;**24**:708−34.

32. Morrison DC, Jacobs DM. Binding of polymyxin B to the lipid A portion of bacterial lipopolysaccharides. *Immunochemistry* 1976;**13**: 813−8.

33. Harder J, Bartels J, Christophers E, Schroder JM. A peptide antibiotic from human skin. *Nature* 1997;**387**:861.

34. Sass V, Schneider T, Wilmes M, Korner C, Tossi A, Novikova N, et al. Human β-defensin 3 inhibits cell wall biosynthesis in Staphylococci. *Infect Immun* 2010;**78**:2793−800.

35. Schneider T, Kruse T, Wimmer R, Wiedemann I, Sass V, Pag U, et al. Plectasin, a fungal defensin, targets the bacterial cell wall precursor lipid II. *Science* 2010;**328**:1168−72.

36. Wang GS, Li X, Wang Z. APD3: the antimicrobial peptide database as a tool for research and education. *Nucleic Acids Res* 2016;**44**: D1087−93.

37. Zheng MC, Pan M, Zhang WC, Lin HC, Wu SL, Lu C, et al. Poly(α-L-lysine)-based nanomaterials for versatile biomedical applications: current advances and perspectives. *Bioact Mater* 2021;**6**:1878−909.

38. Baltzer SA, Brown MH. Antimicrobial peptides—promising alternatives to conventional antibiotics. *J Mol Microbiol Biotechnol* 2011; **20**:228−35.

39. Giangaspero A, Sandri L, Tossi A. Amphipathic alpha helical antimicrobial peptides—a systematic study of the effects of structural and physical properties on biological activity. *Eur J Biochem* 2001; **268**:5589−600.

40. Brogden KA. Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria?. *Nat Rev Microbiol* 2005;**3**:238−50.

41. Li P, Zhou C, Rayatpisheh S, Ye K, Poon YF, Hammond PT, et al. Cationic peptidopolysaccharides show excellent broad-spectrum antimicrobial activities and high selectivity. *Adv Mater* 2012;**24**: 4130−7.

42. Chen L, Harrison SD. Cell-penetrating peptides in drug development: enabling intracellular targets. *Biochem Soc Trans* 2007;**35**: 821−5.

43. Mookherjee N, Lippert DND, Hamill P, Falsafi R, Nijnik A, Kindrachuk J, et al. Intracellular receptor for human host defense peptide LL-37 in monocytes. *J Immunol* 2009;**183**:2688−96.

44. Boman HG, Agerberth B, Boman A. Mechanisms of action on *Escherichia coli* of cecropin P1 and PR-39, two antibacterial peptides from pig intestine. *Infect Immun* 1993;**61**:2978−84.

45. Hsu CH, Chen CP, Jou ML, Lee AYL, Lin YC, Yu YP, et al. Structural and DNA-binding studies on the bovine antimicrobial peptide, indolicidin: evidence for multiple conformations involved in binding to membranes and DNA. *Nucleic Acids Res* 2005;**33**: 4053−64.

46. Mardirossian M, Grzela R, Giglione C, Meinnel T, Gennaro R, Mergaert P, et al. The host antimicrobial peptide bac7(1-35) binds to bacterial ribosomal proteins and inhibits protein synthesis. *Chem Biol* 2014;**21**:1639−47.

47. Nishikata M, Kanehira T, Oh H, Tani H, Tazaki M, Kuboki Y. Salivary histatin as an inhibitor of a protease produced by the oral bacterium *Bacteroides gingivalis*. *Biochem Biophys Res Commun* 1991;**174**:625−30.

48. Splith K, Neundorf I. Antimicrobial peptides with cell-penetrating peptide properties and *vice versa*. *Eur Biophys J Biophy* 2011;**40**: 387−97.

49. Tavares TD, Antunes JC, Ferreira F, Felgueiras HP. Biofunctionalization of natural fiber-reinforced biocomposites for biomedical applications. *Biomolecules* 2020;**10**:148.

50. Scott MG, Davidson DJ, Gold MR, Bowdish D, Hancock REW. The human antimicrobial peptide LL-37 is a multifunctional modulator of innate immune responses. *J Immunol* 2002;**169**:3883−91.

51. Brown KL, Hancock REW. Cationic host defense (antimicrobial) peptides. *Curr Opin Immunol* 2006;**18**:24−30.

52. Ma XT, Xu B, An LL, Dong CY, Lin YM, Shi Y, et al. Vaccine with β-defensin 2-transduced leukemic cells activates innate and adaptive immunity to elicit potent antileukemia responses. *Cancer Res* 2006; **66**:1169−76.

53. Palermo EF, Vemparala S, Kuroda K. Antimicrobial polymers: molecular design as synthetic mimics of host-defense peptides. *ACS Symp Ser* 2013;**1135**:319−30.

54. Shen W, He P, Xiao CS, Chen XS. From Antimicrobial peptides to antimicrobial poly(α-amino acid)s. *Adv Healthcare Mater* 2018;**7**: 1800354.

55. Lu C, Quan GL, Su M, Nimmagadda A, Chen WD, Pan M, et al. Molecular architecture and charging effects enhance the in vitro and in vivo performance of multi-arm antimicrobial agents based on star-shaped poly(L-lysine). *Adv Ther* 2019;**2**:1900147.

56. Pan M, Lu C, Zheng MC, Zhou W, Song FL, Chen WD, et al. Unnatural amino-acid-based star-shaped poly(L-ornithine)s as emerging long-term and biofilm-disrupting antimicrobial peptides to treat Pseudomonas aeruginosa-infected burn wounds. *Adv Healthcare Mater* 2020;**9**:2000647.

57. Wang J, Lu C, Shi Y, Feng XQ, Wu BY, Zhou GL, et al. Structural superiority of guanidinium-rich, four-armed copolypeptides: role of multiple peptide-membrane interactions in enhancing bacterial membrane perturbation and permeability. *ACS Appl Mater Interfaces* 2020;**12**:18363−74.

58. Liu RH, Chen XY, Hayouka Z, Chakraborty S, Falk SP, Weisblum B, et al. Nylon-3 polymers with selective antifungal activity. *J Am Chem Soc* 2013;**135**:5270−3.

59. Liu RH, Chen XY, Falk SP, Masters KS, Weisblum B, Gellman SH. Nylon-3 polymers active against drug-resistant *Candida albicans* biofilms. *J Am Chem Soc* 2015;**137**:2183−6.

60. Kuroda K, Caputo GA, DeGrado WF. The role of hydrophobicity in the antimicrobial and hemolytic activities of polymethacrylate derivatives. *Chem Eur J* 2009;**15**:1123−33.

61. Ivanov I, Vemparala S, Pophristic V, Kuroda K, DeGrado WF, McCammon JA, et al. Characterization of nonbiological antimicrobial polymers in aqueous solution and at water-lipid interfaces from all-atom molecular dynamics. *J Am Chem Soc* 2006;**128**: 1778−9.

62. Sovadinova I, Palermo EF, Huang R, Thoma LM, Kuroda K. Mechanism of polymer-induced hemolysis: nanosized pore formation and osmotic lysis. *Biomacromolecules* 2011;**12**:260−8.

63. Palermo EF, Sovadinova I, Kuroda K. Structural determinants of antimicrobial activity and biocompatibility in membrane-disrupting methacrylamide random copolymers. *Biomacromolecules* 2009;**10**: 3098−107.

64. Gabriel GJ, Maegerlein JA, Nelson CE, Dabkowski JM, Eren T, Nusslein K, et al. Comparison of facially amphiphilic *versus* segregated monomers in the design of antibacterial copolymers. *Chem Eur J* 2009;**15**:433−9.

65. Zhou M, Qian YX, Xie JY, Zhang WJ, Jiang WN, Xiao XM, et al. Poly(2-oxazoline)-based functional peptide mimics: eradicating MRSA infections and persisters while alleviating antimicrobial resistance. *Angew Chem Int Ed* 2020;**59**:6412−9.

66. Krumm C, Harmuth S, Hijazi M, Neugebauer B, Kampmann AL, Geltenpoth H, et al. Antimicrobial poly(2-methyloxazoline) s with bioswitchable activity through satellite group modification. *Angew Chem Int Ed* 2014;**53**:3830−4.

67. Qiao Y, Yang C, Coady DJ, Ong ZY, Hedrick JL, Yang YY. Highly dynamic biodegradable micelles capable of lysing Gram-positive and Gram-negative bacterial membrane. *Biomaterials* 2012;**33**:1146−53.

68. Liu SQ, Yang C, Huang Y, Ding X, Li Y, Fan WM, et al. Antimicrobial and antifouling hydrogels formed *in situ* from polycarbonate and poly(ethylene glycol) *via* michael addition. *Adv Mater* 2012;**24**: 6484−9.

69. Ilker MF, Nusslein K, Tew GN, Coughlin EB. Tuning the hemolytic and antibacterial activities of amphiphilic polynorbornene derivatives. *J Am Chem Soc* 2004;**126**:15870−5.

70. Lienkamp K, Madkour AE, Musante A, Nelson CF, Nusslein K, Tew GN. Antimicrobial polymers prepared by ROMP with unprecedented selectivity: a molecular construction kit approach. *J Am Chem Soc* 2008;**130**:9836−43.

71. Wu YM, Xia GX, Zhang WW, Chen K, Bi YF, Liu SQ, et al. Structural design and antimicrobial properties of polypeptides and saccharide-polypeptide conjugates. *J Mater Chem B* 2020;**8**:9173−96.

72. Uppu DSSM, Akkapeddi P, Manjunath GB, Yarlagadda V, Hoque J, Haldar J. Polymers with tunable side-chain amphiphilicity as non-hemolytic antibacterial agents. *Chem Commun* 2013;**49**:9389−91.

73. Uppu DSSM, Samaddar S, Hoque J, Konai MM, Krishnamoorthy P, Shome BR, et al. Side chain degradable cationic-amphiphilic polymers with tunable hydrophobicity show *in vivo* activity. *Biomacromolecules* 2016;**17**:3094−102.

74. Uppu DSSM, Konai MM, Baul U, Singh P, Siersma TK, Samaddar S, et al. Isosteric substitution in cationic-amphiphilic polymers reveals an important role for hydrogen bonding in bacterial membrane interactions. *Chem Sci* 2016;**7**:4613−23.

75. Karlsson AJ, Pomerantz WC, Weisblum B, Gellman SH, Palecek SP. Antifungal activity from 14-helical β-peptides. *J Am Chem Soc* 2006; **128**:12630−1.

76. Wang M, Feng X, Gao R, Sang P, Pan X, Wei L, et al. Modular design of membrane-active antibiotics: from macromolecular antimicrobials to small scorpionlike peptidomimetics. *J Med Chem* 2021; **64**:9894−905.

77. Sang P, Shi Y, Teng P, Cao AN, Xu H, Li Q, et al. Antimicrobial AApeptides. *Curr Top Med Chem* 2017;**17**:1266−79.

78. Niu YH, Padhee S, Wu HF, Bai G, Qiao Q, Hu YG, et al. Lipo-γ-AApeptides as a new class of potent and broad-spectrum antimicrobial agents. *J Med Chem* 2012;**55**:4003−9.

79. Zhou M, Zheng MM, Cai JF. Small molecules with membrane-active antibacterial activity. *ACS Appl Mater Interfaces* 2020;**12**:21292−9.

80. Li YQ, Wu HF, Teng P, Bai G, Lin XY, Zuo XB, et al. Helical antimicrobial sulfono-γ-AApeptides. *J Med Chem* 2015;**58**:4802−11.

81. Timofeeva L, Kleshcheva N. Antimicrobial polymers: mechanism of action, factors of activity, and applications. *Appl Microbiol Biotechnol* 2011;**89**:475−92.

82. Lam SJ, O'Brien-Simpson NM, Pantarat N, Sulistio A, Wong EHH, Chen YY, et al. Combating multidrug-resistant Gram-negative bacteria with structurally nanoengineered antimicrobial peptide polymers. *Nat Microbiol* 2016;**1**:16162.

83. Lienkamp K, Kumar KN, Som A, Nusslein K, Tew GN. Doubly selective" antimicrobial polymers: how do they differentiate between bacteria?. *Chem Eur J* 2009;**15**:11710−4.

84. Epand RF, Mowery BP, Lee SE, Stahl SS, Lehrer RI, Gellman SH, et al. Dual mechanism of bacterial lethality for a cationic sequence-random copolymer that mimics host-defense antimicrobial peptides. *J Mol Biol* 2008;**379**:38−50.

85. Al-Badri ZM, Som A, Lyon S, Nelson CF, Nusslein K, Tew GN. Investigating the effect of increasing charge density on the hemolytic activity of synthetic antimicrobial polymers. *Biomacromolecules* 2008;**9**:2805−10.

86. Song AR, Walker SG, Parker KA, Sampson NS. Antibacterial studies of cationic polymers with alternating, random, and uniform backbones. *ACS Chem Biol* 2011;**6**:590−9.

87. Chin W, Zhong GS, Pu QQ, Yang C, Lou WY, De Sessions PF, et al. A macromolecular approach to eradicate multidrug resistant bacterial infections while mitigating drug resistance onset. *Nat Commun* 2018;**9**:917.

88. Palermo EF, Kuroda K. Structural determinants of antimicrobial activity in polymers which mimic host defense peptides. *Appl Microbiol Biotechnol* 2010;**87**:1605−15.

89. Rahman A, Jui MS, Bam M, Cha YJ, Luat E, Alabresm A, et al. Facial amphiphilicity-induced polymer nanostructures for antimicrobial applications. *ACS Appl Mater Interfaces* 2020;**12**:21221−30.

90. Eren T, Som A, Rennie JR, Nelson CF, Urgina Y, Nusslein K, et al. Antibacterial and hemolytic activities of quaternary pyridinium functionalized polynorbornenes. *Macromol Chem Phys* 2008;**209**:516−24.

91. Rahman MA, Bam M, Luat E, Jui MS, Ganewatta MS, Shokfai T, et al. Macromolecular-clustered facial amphiphilic antimicrobials. *Nat Commun* 2018;**9**:5231.

92. Xiong M, Lee MW, Mansbach RA, Song Z, Bao Y, Peek RM, et al. Helical antimicrobial polypeptides with radial amphiphilicity. *Proc Natl Acad Sci U S A* 2015;**112**:13155−60.

93. Wiradharma N, Sng MYS, Khan M, Ong ZY, Yang YY. Rationally designed α-helical broad-spectrum antimicrobial peptides with idealized facial amphiphilicity. *Macromol Rapid Commun* 2013;**34**:74−80.

94. Ergene C, Yasuhara K, Palermo EF. Biomimetic antimicrobial polymers: recent advances in molecular design. *Polym Chem* 2018;**9**:2407−27.

95. Palermo EF, Kuroda K. Chemical structure of cationic groups in amphiphilic polymethacrylates modulates the antimicrobial and hemolytic activities. *Biomacromolecules* 2009;**10**:1416−28.

96. Alvarez-Paino M, Munoz-Bonilla A, Lopez-Fabal F, Gomez-Garces JL, Heuts JPA, Fernandez-Garcia M. Effect of glycounits on the antimicrobial properties and toxicity behavior of polymers based on quaternized DMAEMA. *Biomacromolecules* 2015;**16**:295−303.

97. Kenawy ER, Abdel-Hay FI, El-Shanshoury AERR, El-Newehy MH. Biologically active polymers: synthesis and antimicrobial activity of modified poly(glycidyl methacrylate-co-2-hydroxyethyl methacrylate) derivatives with quaternary ammonium and phosphonium salts. *J Polym Sci A Polym Chem* 2002;**40**:2384−93.

98. Chang HI, Yang MS, Liang M. The synthesis, characterization and antibacterial activity of quaternized poly(2,6-dimethyl-1,4-phenylene oxide)s modified with ammonium and phosphonium salts. *React Funct Polym* 2010;**70**:944−50.

99. Shi J, Wang MY, Sun Z, Liu YY, Guo JN, Mao HL, et al. Aggregation-induced emission-based ionic liquids for bacterial killing, imaging, cell labeling, and bacterial detection in blood cells. *Acta Biomater* 2019;**97**:247−59.

100. Zhang TK, Guo JN, Ding YY, Mao HL, Yan F. Redox-responsive ferrocene-containing poly(ionic liquid)s for antibacterial applications. *Sci China Chem* 2019;**62**:95−104.

101. Zheng ZQ, Guo JN, Mao HL, Xu QM, Qin J, Yan F. Metal-containing poly(ionic liquid) membranes for antibacterial applications. *ACS Biomater Sci Eng* 2017;**3**:922−8.

102. Su YJ, Tian L, Yu M, Gao Q, Wang DH, Xi YW, et al. Cationic peptidopolysaccharides synthesized by 'click' chemistry with enhanced broad-spectrum antimicrobial activities. *Polym Chem* 2017;**8**:3788−800.

103. Lan TY, Guo QQ, Shen XC. Polyethyleneimine and quaternized ammonium polyethyleneimine: the versatile materials for combating bacteria and biofilms. *J Biomater Sci Polym Ed* 2019;**30**:1243−59.

104. Hyldgaard M, Mygind T, Vad BS, Stenvang M, Otzen DE, Meyer RL. The antimicrobial mechanism of action of epsilon-poly-L-lysine. *Appl Environ Microbiol* 2014;**80**:7758−70.

105. Liu JN, Chang SL, Xu PW, Tan MH, Zhao B, Wang XD, et al. Structural changes and antibacterial activity of epsilon-poly-L-lysine in response to pH and phase transition and their mechanisms. *J Agric Food Chem* 2020;**68**:1101−9.

106. Dathe M, Nikolenko H, Klose J, Bienert M. Cyclization increases the antimicrobial activity and selectivity of arginine-and tryptophan-containing hexapeptides. *Biochemistry* 2004;**43**:9140−50.

107. Rodriguez-Vazquez N, Ozores HL, Guerra A, Gonzalez-Freire E, Fuertes A, Panciera M, et al. Membrane-targeted self-assembling cyclic peptide nanotubes. *Curr Top Med Chem* 2014;**14**:2647−61.

108. Fernandez-Lopez S, Kim HS, Choi EC, Delgado M, Granja JR, Khasanov A, et al. Antibacterial agents based on the cyclic D,L-α-peptide architecture. *Nature* 2001;**412**:452−5.

109. Rozek A, Powers JPS, Friedrich CL, Hancock REW. Structure-based design of an indolicidin peptide analogue with increased protease stability. *Biochemistry* 2003;**42**:14130−8.

110. Kawano Y, Jordan O, Hanawa T, Borchard G, Patrulea V. Are antimicrobial peptide dendrimers an escape from ESKAPE?. *Adv Wound Care* 2020;**9**:378−95.

111. Calabretta MK, Kumar A, McDermott AM, Cai CZ. Antibacterial activities of poly(amidoamine) dendrimers terminated with amino and poly(ethylene glycol) groups. *Biomacromolecules* 2007;**8**:1807−11.

112. Chen CZS, Cooper SL. Interactions between dendrimer biocides and bacterial membranes. *Biomaterials* 2002;**23**:3359−68.

113. Chen CZS, Beck-Tan NC, Dhurjati P, van Dyk TK, LaRossa RA, Cooper SL. Quaternary ammonium functionalized poly(propylene imine) dendrimers as effective antimicrobials: structure-activity studies. *Biomacromolecules* 2000;**1**:473−80.

114. Polcyn P, Jurczak M, Rajnisz A, Solecka J, Urbanczyk-Lipkowska Z. Design of antimicrobially active small amphiphilic peptide dendrimers. *Molecules* 2009;**14**:3881−905.

115. Stach M, Siriwardena TN, Kohler T, van Delden C, Darbre T, Reymond JL. Combining topology and sequence design for the discovery of potent antimicrobial peptide dendrimers against multidrug-resistant pseudomonas aeruginosa. *Angew Chem Int Ed* 2014;**53**:12827−31.

116. Siriwardena TN, Stach M, He RZ, Gan BH, Javor S, Heitz M, et al. Lipidated peptide dendrimers killing multidrug-resistant bacteria. *J Am Chem Soc* 2018;**140**:423−32.

117. Siriwardena TN, Capecchi A, Gan BH, Jin X, He RZ, Wei DW, et al. Optimizing antimicrobial peptide dendrimers in chemical space. *Angew Chem Int Ed* 2018;**57**:8483−7.

118. Gide M, Nimmagadda A, Su M, Wang MH, Teng P, Li CP, et al. Nano-sized lipidated dendrimers as potent and broad-spectrum antibacterial agents. *Macromol Rapid Commun* 2018;**39**:1800622.

119. Pu YJ, Hou Z, Khin MM, Zamudio-Vazquez R, Poon KL, Duan HW, et al. Synthesis and antibacterial study of sulfobetaine/quaternary ammonium-modified star-shaped poly[2-(dimethylamino)ethyl methacrylate]-based copolymers with an inorganic core. *Biomacromolecules* 2017;**18**:44−55.

120. Wiradharma N, Liu SQ, Yang YY. Branched and 4-arm starlike α-helical peptide structures with enhanced antimicrobial potency and selectivity. *Small* 2012;**8**:362−6.

121. Chen YF, Lai YD, Chang CH, Tsai YC, Tang CC, Jan JS. Star-shaped polypeptides exhibit potent antibacterial activities. *Nanoscale* 2019;**11**:11696−708.

122. Li YM, Yu HS, Qian YF, Hu JM, Liu SY. Amphiphilic star copolymer-based bimodal fluorogenic/magnetic resonance probes for concomitant bacteria detection and inhibition. *Adv Mater* 2014;**26**:6734−41.

123. Liu H, Zhang X, Zhao ZY, Yang FP, Xue RZ, Yin LC, et al. Efficient synthesis and excellent antimicrobial activity of star-shaped cationic polypeptides with improved biocompatibility. *Biomater Sci* 2021;**9**:2721−31.

124. Sun S, Chen Q, Tang ZD, Liu C, Li ZJ, Wu AG, et al. Tumor microenvironment stimuli-responsive fluorescence imaging and synergistic cancer therapy by carbon-dot-Cu^{2+} nanoassemblies. *Angew Chem Int Ed* 2020;**59**:21041−8.

125. Wang ST, Fang Y, Zhang ZQ, Jin Q, Ji J. Bacterial infection microenvironment sensitive prodrug micelles with enhanced photodynamic activities for infection control. *Colloid Interface Sci Commun* 2021;**40**:100354.

126. Hu DF, Zou LY, Yu WJ, Jia F, Han HJ, Yao K, et al. Relief of biofilm hypoxia using an oxygen nanocarrier: a new paradigm for enhanced antibiotic therapy. *Adv Sci* 2020;**7**:2000398.

127. Xiu WJ, Gan SY, Wen QR, Qiu Q, Dai SL, Dong H, et al. Biofilm microenvironment-responsive nanotheranostics for dual-mode imaging and hypoxia-relief-enhanced photodynamic therapy of bacterial infections. *Research* 2020;**2020**:9426453.

128. Nicol M, Alexandre S, Luizet JB, Skogman M, Jouenne T, Salcedo SP, et al. Unsaturated fatty acids affect quorum sensing communication system and inhibit motility and biofilm formation of acinetobacter baumannii. *Int J Mol Sci* 2018;**19**:214.

129. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. *Nat Rev Microbiol* 2016;**14**:563−75.

130. Mangwani N, Kumari S, Das S. Bacterial biofilms and quorum sensing: fidelity in bioremediation technology. *Biotechnol Genet Eng Rev* 2016;**32**:43−73.

131. Xiong MH, Bao Y, Xu X, Wang H, Han ZY, Wang ZY, et al. Selective killing of helicobacter pylori with pH-responsive helix-coil conformation transitionable antimicrobial polypeptides. *Proc Natl Acad Sci USA* 2017;**114**:12675−80.

132. Xiong MH, Han ZY, Song ZY, Yu J, Ying HZ, Yin LC, et al. Bacteria-assisted activation of antimicrobial polypeptides by a random-coil to helix transition. *Angew Chem Int Ed* 2017;**56**:10826−9.

133. Xu LL, He C, Hui LW, Xie YT, Li JM, He WD, et al. Bactericidal dendritic polycation cloaked with stealth material *via* lipase-sensitive intersegment acquires neutral surface charge without losing membrane-sisruptive activity. *ACS Appl Mater Interfaces* 2015;**7**:27602−7.

134. Qi GB, Zhang D, Liu FH, Qiao ZY, Wang H. An "on-site transformation" strategy for treatment of bacterial infection. *Adv Mater* 2017;**29**:1703461.

135. Takahashi H, Yumoto K, Yasuhara K, Nadres ET, Kikuchi Y, Buttitta L, et al. Anticancer polymers designed for killing dormant prostate cancer cells. *Sci Rep* 2019;**9**:1096.

136. Gaspar D, Veiga AS, Castanho MRB. From antimicrobial to anticancer peptides: a review. *Front Microbiol* 2013;**4**:294.

137. Izzi V, Heljasvaara R, Pihlajaniemi T. Understanding the extracellular matrix in acute myeloid leukemia. *Haematologica* 2017;**102**:1807−9.

138. Li XY, Shen B, Chen Q, Zhang XH, Ye YQ, Wang FM, et al. Antitumor effects of cecropin B-LHRH' on drug-resistant ovarian and endometrial cancer cells. *BMC Cancer* 2016;**16**:251.

139. Deslouches B, Di YP. Antimicrobial peptides with selective anti-tumor mechanisms: prospect for anticancer applications. *Oncotarget* 2017;**8**:46635−51.

140. Cruciani RA, Barker JL, Zasloff M, Chen HC, Colamonici O. Antibiotic magainins exert cytolytic activity against transformed cell lines through channel formation. *Proc Natl Acad Sci U S A* 1991;**88**:3792−6.

141. Huang TC, Chen JY. Proteomic analysis reveals that pardaxin triggers apoptotic signaling pathways in human cervical carcinoma HeLa cells: cross talk among the UPR, c-Jun and ROS. *Carcinogenesis* 2013;**34**:1833−42.

142. Lee JH, Kim IW, Kim SH, Yun EY, Nam SH, Ahn MY, et al. Anticancer activity of CopA3 dimer peptide in human gastric cancer cells. *BMB Rep* 2015;**48**:324−9.

143. Zhou H, Forveille S, Sauvat A, Yamazaki T, Senovilla L, Ma Y, et al. The oncolytic peptide LTX-315 triggers immunogenic cell death. *Cell Death Dis* 2016;**7**:e2134.

144. Leuschner C, Hansel W. Targeting breast and prostate cancers through their hormone receptors. *Biol Reprod* 2005;**73**:860−5.

145. Kuriyama I, Miyazaki A, Tsuda Y, Yoshida H, Mizushina Y. Inhibitory effect of novel somatostatin peptide analogues on human cancer cell growth based on the selective inhibition of DNA polymerase β. *Bioorg Med Chem* 2013;**21**:403−11.

146. Koskimaki JE, Karagiannis ED, Tang BC, Hammers H, Watkins DN, Pili R, et al. Pentastatin-1, a collagen IV derived 20-mer peptide, suppresses tumor growth in a small cell lung cancer xenograft model. *BMC Cancer* 2010;**10**:29.

147. González-Montoya M, Cano-Sampedro E, Mora-Escobedo R. Bioactive peptides from le-gumes as anticancer therapeutic agents. *Int J Cancer Clin Res* 2017;**4**:81.

148. Park NH, Cheng W, Lai F, Yang C, de Sessions PF, Periaswamy B, et al. Addressing drug resistance in cancer with macromolecular chemotherapeutic agents. *J Am Chem Soc* 2018;**140**:4244−52.

149. Shen W, Zhang Y, Wan PQ, An L, Zhang P, Xiao CS, et al. Antineoplastic drug-free anticancer strategy enabled by host-defense-peptides-mimicking synthetic polypeptides. *Adv Mater* 2020;**32**:2001108.

150. Mader JS, Hoskin DW. Cationic antimicrobial peptides as novel cytotoxic agents for cancer treatment. *Expet Opin Invest Drugs* 2006;**15**:933−46.

151. Felicio MR, Silva ON, Goncalves S, Santos NC, Franco OL. Peptides with dual antimicrobial and anticancer activities. *Front Chem* 2017;**5**:5.

152. Duffy C, Sorolla A, Wang E, Golden E, Woodward E, Davern K, et al. Honeybee venom and melittin suppress growth factor receptor activation in HER2-enriched and triple-negative breast cancer. *NPJ Precis Oncol* 2020;**4**:24.

153. Skerlavaj B, Gennaro R, Bagella L, Merluzzi L, Risso A, Zanetti M. Biological characterization of two novel cathelicidin-derived peptides and identification of structural requirements for their antimicrobial and cell lytic activities. *J Biol Chem* 1996;**271**:28375−81.

154. Yang QZ, Wang C, Lang L, Zhou Y, Wang H, Shang DJ. Design of potent, non-toxic anticancer peptides based on the structure of the antimicrobial peptide, temporin-1CEa. *Arch Pharm Res* 2013;**36**:1302−10.

155. Huang YB, He LY, Jiang HY, Chen YX. Role of helicity on the anticancer mechanism of action of cationic-helical peptides. *Int J Mol Sci* 2012;**13**:6849−62.

156. Wu BY, Fu JT, Zhou YX, Shi Y, Wang J, Feng XQ, et al. Metal-organic framework-based chemo-photothermal combinational system

for precise, rapid, and efficient antibacterial therapeutics. *Pharmaceutics* 2019;**11**:463.

157. Sullivan GJ, Delgado NN, Maharjan R, Cain AK. How antibiotics work together: molecular mechanisms behind combination therapy. *Curr Opin Microbiol* 2020;**57**:31−40.

158. Chellat MF, Raguz L, Riedl R. Targeting antibiotic resistance. *Angew Chem Int Ed* 2016;**55**:6600−26.

159. Ding X, Yang C, Moreira W, Yuan PY, Periaswamy B, de Sessions PF, et al. A macromolecule reversing antibiotic resistance phenotype and repurposing drugs as potent antibiotics. *Adv Sci* 2020;**7**:2001374.

160. Brochado AR, Telzerow A, Bobonis J, Banzhaf M, Mateus A, Selkrig J, et al. Species-specific activity of antibacterial drug combinations. *Nature* 2018;**559**:259−63.

161. Wu XZ, Li Z, Li XL, Tian YM, Fan YZ, Yu CH, et al. Synergistic effects of antimicrobial peptide DP7 combined with antibiotics against multidrug-resistant bacteria. *Drug Des Dev Ther* 2017;**11**:939−46.

162. Ng VWL, Ke XY, Lee ALZ, Hedrick JL, Yang YY. Synergistic co-delivery of membrane-disrupting polymers with commercial antibiotics against highly opportunistic bacteria. *Adv Mater* 2013;**25**:6730−6.

163. Zhang M, Liu EG, Cui YN, Huang YZ. Nanotechnology-based combination therapy for overcoming multidrug-resistant cancer. *Cancer Biol Med* 2017;**14**:212−27.

164. Al-Jamal KT, Al-Jamal WT, Wang JTW, Rubio N, Buddle J, Gathercole D, et al. Cationic poly-L-lysine dendrimer complexes doxorubicin and delays tumor growth *in vitro* and *in vivo*. *ACS Nano* 2013;**7**:1905−17.

165. Muchintala D, Suresh V, Raju D, Sashidhar RB. Synthesis and characterization of cecropin peptide-based silver nanocomposites: its antibacterial activity and mode of action. *Mat Sci Eng C Mater* 2020;**110**:110712.

166. Hemeg HA. Nanomaterials for alternative antibacterial therapy. *Int J Nanomed* 2017;**12**:8211−25.

167. Oktar FN, Yetmez M, Ficai D, Ficai A, Dumitru F, Pica A. Molecular mechanism and targets of the antimicrobial activity of metal nanoparticles. *Curr Top Med Chem* 2015;**15**:1583−8.

168. Slavin YN, Asnis J, Hafeli UO, Bach H. Metal nanoparticles: understanding the mechanisms behind antibacterial activity. *J Nanobiotechnol* 2017;**15**:65.

169. Godoy-Gallardo M, Eckhard U, Delgado LM, de Roo Puente YJ, Hoyos-Nogués M, et al. Antibacterial approaches in tissue engineering using metal ions and nanoparticles: from mechanisms to applications. *Bioact Mater* 2021;**6**:4470−90.

170. Mei L, Lu ZT, Zhang XG, Li CX, Jia YX. Polymer-Ag nanocomposites with enhanced antimicrobial activity against bacterial infection. *ACS Appl Mater Interfaces* 2014;**6**:15813−21.

171. Zheng YK, Liu WW, Chen Y, Li CM, Jiang H, Wang XM. Conjugating gold nanoclusters and antimicrobial peptides: from aggregation-induced emission to antibacterial synergy. *J Colloid Interface Sci* 2019;**546**:1−10.

172. Ruden S, Hilpert K, Berditsch M, Wadhwani P, Ulrich AS. Synergistic interaction between silver nanoparticles and membrane-permeabilizing antimicrobial peptides. *Antimicrob Agents Chemother* 2009;**53**:3538−40.

173. Smekalova M, Aragon V, Panacek A, Prucek R, Zboril R, Kvitek L. Enhanced antibacterial effect of antibiotics in combination with silver nanoparticles against animal pathogens. *Vet J* 2016;**209**:174−9.

174. Casciaro B, Moros M, Rivera-Fernandez S, Bellelli A, de la Fuente JM, Mangoni ML. Gold-nanoparticles coated with the antimicrobial peptide esculentin-1a (1-21)NH₂ as a reliable strategy for antipseudomonal drugs. *Acta Biomater* 2017;**47**:170−81.

175. Zhou SN, Ji HX, Fu YQ, Yang Y, Lu CL. Mussel-inspired fabrication of cationic polymer modified rGO supported silver nanoparticles hybrid with robust antibacterial and catalytic reduction performance. *Appl Surf Sci* 2020;**506**:144655.

176. Lin JQ, Zhang HW, Chen Z, Zheng YG. Penetration of lipid membranes by gold nanoparticles: insights into cellular uptake, cytotoxicity, and their relationship. *ACS Nano* 2010;**4**:5421−9.

177. Rajchakit U, Sarojini V. Recent developments in antimicrobial-peptide-conjugated gold nanoparticles. *Bioconjugate Chem* 2017;**28**:2673−86.

178. Jelinkova P, Mazumdar A, Sur VP, Kociova S, Dolezelikova K, Jimenez AMJ, et al. Nanoparticle-drug conjugates treating bacterial infections. *J Control Release* 2019;**307**:166−85.

179. Yang P, Pageni P, Rahman MA, Bam M, Zhu TY, Chen YP, et al. Gold nanoparticles with antibiotic-metallopolymers toward broad-spectrum antibacterial effects. *Adv Healthcare Mater* 2019;**8**:1800854.

180. Pallavicini P, Dona A, Taglietti A, Minzioni P, Patrini M, Dacarro G, et al. Self-assembled monolayers of gold nanostars: a convenient tool for near-IR photothermal biofilm eradication. *Chem Commun* 2014;**50**:1969−71.

181. Spagnul C, Turner LC, Boyle RW. Immobilized photosensitizers for antimicrobial applications. *J Photochem Photobiol, B* 2015;**150**:11−30.

182. Wei T, Yu Q, Chen H. Responsive and synergistic antibacterial coatings: fighting against bacteria in a smart and effective way. *Adv Healthcare Mater* 2019;**8**:1801381.

183. Feng YH, Liu L, Zhang J, Aslan H, Dong MD. Photoactive antimicrobial nanomaterials. *J Mater Chem B* 2017;**5**:8631−52.

184. Bai HT, He W, Chau JHC, Zheng Z, Kwok RTK, Lam JWY, et al. AIEgens for microbial detection and antimicrobial therapy. *Biomaterials* 2021;**268**:120598.

185. Ren YW, Liu HP, Liu XM, Zheng YF, Li ZY, Li CY, et al. Photo-responsive materials for antibacterial applications. *Cell Rep Phys Sci* 2020;**1**:10025.

186. Xu DX, Li ZD, Li LS, Wang J. Insights into the photothermal conversion of 2D MXene nanomaterials: synthesis, mechanism, and applications. *Adv Funct Mater* 2020;**30**:2000712.

187. He DF, Yang T, Qian W, Qi C, Mao L, Yu XZ, et al. Combined photothermal and antibiotic therapy for bacterial infection *via* acidity-sensitive nanocarriers with enhanced antimicrobial performance. *Appl Mater Today* 2018;**12**:415−29.

188. Zhou TT, Hu R, Wang LR, Qiu YP, Zhang GQ, Deng QY, et al. An AIE-active conjugated polymer with high ROS-generation ability and biocompatibility for efficient photodynamic therapy of bacterial infections. *Angew Chem Int Ed* 2020;**59**:9952−6.

189. Li J, Liu XM, Tan L, Cui ZD, Yang XJ, Liang YQ, et al. Zinc-doped prussian blue enhances photothermal clearance of *Staphylococcus aureus* and promotes tissue repair in infected wounds. *Nat Commun* 2019;**10**:4490.

190. Zhu YW, Xu C, Zhang N, Ding XK, Yu BR, Xu FJ. Polycationic synergistic antibacterial agents with multiple functional components for efficient anti-infective therapy. *Adv Funct Mater* 2018;**28**:1706709.

191. Mohammadpour R, Safarian S, Buckway B, Ghandehari H. Comparative endocytosis mechanisms and anticancer effect of HPMA copolymer- and PAMAM dendrimer-MTCP conjugates for photodynamic therapy. *Macromol Biosci* 2017;**17**:1600333.

192. Owens DE, Peppas NA. Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. *Int J Pharm* 2006;**307**:93−102.

193. Tong F, Tang XY, Luo L, Li X, Xia WQ, Lu C, et al. Sustained delivery of insulin-loaded block copolymers: potential implications on renal ischemia/reperfusion injury in diabetes mellitus. *Biomed Pharmacother* 2017;**91**:534−45.

194. Lu C, Jiang L, Xu WJ, Yu FY, Xia WQ, Pan M, et al. Poly(ethylene glycol) crosslinked multi-armed poly(ε-benzyloxycarbonyl-L-lysine)s as super-amphiphiles: synthesis, self-assembly, and evaluation as efficient delivery systems for poorly water-soluble drugs. *Colloids Surf, B* 2019;**182**:110384.

195. Wen T, Quan GL, Niu BY, Zhou YX, Zhao YT, Lu C, et al. Versatile nanoscale metal-organic frameworks (nMOFs): an emerging 3D nanoplatform for drug delivery and therapeutic applications. *Small* 2021;**17**:2005064.

196. Kanchanapally R, Nellore BPV, Sinha SS, Pedraza F, Jones SJ, Pramanik A, et al. Antimicrobial peptide-conjugated graphene oxide membrane for efficient removal and effective killing of multiple drug resistant bacteria. *RSC Adv* 2015;**5**:18881−7.

197. Fu XC, Bai HT, Lyu FT, Liu LB, Wang S. Conjugated polymer nanomaterials for phototherapy of cancer. *Chem Res Chinese* 2020; **36**:237−42.

198. Teixeira MC, Carbone C, Sousa MC, Espina M, Garcia ML, Sanchez-Lopez E, et al. Nanomedicines for the delivery of antimicrobial peptides (AMPs). *Nanomaterials* 2020;**10**:560.

199. Wu QL, Feng DS, Huang ZW, Chen ML, Yang D, Pan X, et al. Supersaturable organic-inorganic hybrid matrix based on well-ordered mesoporous silica to improve the bioavailability of water insoluble drugs. *Drug Deliv* 2020;**27**:1292−300.

200. Zhang L, Zhao ZL, Wei XH, Liu JH. Preparation and *in vitro* and *in vivo* characterization of cyclosporin A-loaded, PEGylated chitosan-modified, lipid-based nanoparticles. *Int J Nanomed* 2013;**8**: 601−10.

201. Wang CH, Feng SL, Qie JK, Wei XL, Yan HS, Liu KL. Polyion complexes of a cationic antimicrobial peptide as a potential systemically administered antibiotic. *Int J Pharm* 2019;**554**:284−91.

202. Severino P, Chaud MV, Shimojo A, Antonini D, Lancelloti M, Santana MHA, et al. Sodium alginate-cross-linked polymyxin B sulphate-loaded solid lipid nanoparticles: antibiotic resistance tests and HaCat and NIH/3T3 cell viability studies. *Colloids Surf, B* 2015; **129**:191−7.

203. Insua I, Majok S, Peacock AFA, Krachler AM, Fernandez-Trillo F. Preparation and antimicrobial evaluation of polyion complex (PIC) nanoparticles loaded with polymyxin B. *Eur Polym J* 2017;**87**: 478−86.

204. Lawrence SM, Alpar HO, McAllister SM, Brown MR. Liposomal (MLV) polymyxin B: physicochemical characterization and effect of surface charge and drug association. *J Drug Target* 1993;**1**:303−10.

205. Peng XQ, Zhu L, Guo JY, Sun ZL, Zhao MM, Zhan XB. Enhancing biocompatibility and neuronal anti-inflammatory activity of polymyxin B through conjugation with gellan gum. *Int J Biol Macromol* 2020;**147**:734−40.

206. Gounani Z, Asadollahi MA, Meyer RL, Arpanaei A. Loading of polymyxin B onto anionic mesoporous silica nanoparticles retains antibacterial activity and enhances biocompatibility. *Int J Pharm* 2018;**537**:148−61.

207. Shi Y, Feng X, Lin L, Wang J, Chi J, Wu B, et al. Virus-inspired surface-nanoengineered antimicrobial liposome: a potential system to simultaneously achieve high activity and selectivity. *Bioact Mater* 2021;**6**:3207−17.

208. Li YW, Xu N, Zhu WH, Wang L, Liu B, Zhang JX, et al. Nanoscale melittin@zeolitic imidazolate frameworks for enhanced anticancer activity and mechanism analysis. *ACS Appl Mater Interfaces* 2018; **10**:22974−84.

209. Lu XM, Liu JJ, Gou L, Li JL, Yuan B, Yang K, et al. Designing melittin-graphene hybrid complexes for enhanced antibacterial activity. *Adv Healthcare Mater* 2019;**8**:1801521.

210. Xiao SF, Lu XM, Gou L, Li JL, Ma YQ, Liu JJ, et al. Graphene oxide as antibacterial sensitizer: mechanically disturbed cell membrane for enhanced poration efficiency of melittin. *Carbon* 2019;**149**:248−56.

211. Jiang L, Su C, Wen YY, Zhu ZJ, Liu J, He SR, et al. Antibacterial activity and long-term stable antibacterial performance of nisin grafted magnetic GO nanohybrids. *Mat Sci Eng C-Mater* 2020;**111**: 110809.

212. Gao YF, Wang J, Chai MY, Li X, Deng YY, Jin Q, et al. Size and charge adaptive clustered nanoparticles targeting the biofilm microenvironment for chronic lung infection management. *ACS Nano* 2020;**14**:5686−99.

213. Zhao ZW, Yan R, Wang JH, Wu H, Wang YH, Chen AH, et al. A bacteria-activated photodynamic nanosystem based on polyelectrolyte-coated silica nanoparticles. *J Mater Chem B* 2017;**5**: 3572−9.

214. Bessa LJ, Eaton P, Dematei A, Placido A, Vale N, Gomes P, et al. Synergistic and antibiofilm properties of ocellatin peptides against multidrug-resistant Pseudomonas aeruginosa. *Future Microbiol* 2018;**13**:151−63.

215. Liu XW, Li Z, Wang XD, Chen YJ, Wu FB, Men K, et al. Novel antimicrobial peptide-modified azithromycin-loaded liposomes against methicillin-resistant *Staphylococcus aureus*. *Int J Nanomed* 2016;**11**:6781−94.

216. Jiang YJ, Han M, Bo Y, Feng YJ, Li WM, Wu JR, et al. Metaphilic" cell-penetrating polypeptide-vancomycin conjugate efficiently eradicates intracellular bacteria *via* a dual mechanism. *ACS Cent Sci* 2020;**6**:2267−76.

217. Costley D, Nesbitt H, Ternan N, Dooley J, Huang YY, Hamblin MR, et al. Sonodynamic inactivation of Gram-positive and Gram-negative bacteria using a rose bengal-antimicrobial peptide conjugate. *Int J Antimicrob Agents* 2017;**49**:31−6.

218. Mozhi A, Ahmad I, Okeke CI, Li C, Liang XJ. pH-sensitive polymeric micelles for the co-delivery of proapoptotic peptide and anti-cancer drug for synergistic cancer therapy. *RSC Adv* 2017;**7**: 12886−96.

219. Lim C, Kang JK, Won WR, Park JY, Han SM, Le TN, et al. Co-delivery of D-(KLAKLAK)(2) peptide and chlorin e6 using a liposomal complex for synergistic cancer therapy. *Pharmaceutics* 2019; **11**:293.

220. Xiang YC, Chen LQ, Zhou R, Huang Y. Enhanced intracellular and intranuclear drug delivery mediated by biomimetic peptide SVS-1 for anticancer therapy. *Int J Pharm* 2019;**570**:118668.

221. Hormann K, Zimmer A. Drug delivery and drug targeting with parenteral lipid nanoemulsions—a review. *J Controlled Release* 2016;**223**:85−98.

222. Sabio RM, Meneguin AB, dos Santos AM, Monteiro AS, Chorilli M. Exploiting mesoporous silica nanoparticles as versatile drug carriers for several routes of administration. *Microporous Mesoporous Mater* 2021;**312**:110774.

223. Tan LW, Peng JR, Zhao Q, Zhang L, Tang XC, Chen LJ, et al. A novel MPEG-PDLLA-PLL copolymer for docetaxel delivery in breast cancer therapy. *Theranostics* 2017;**7**:2652−72.

224. Albanese A, Tang PS, Chan WCW. The effect of nanoparticle size, shape, and surface chemistry on biological systems. *Annu Rev Biomed Eng* 2012;**14**:1−16.

225. Gao HL, He Q. The interaction of nanoparticles with plasma proteins and the consequent influence on nanoparticles behavior. *Expet Opin Drug Deliv* 2014;**11**:409−20.

226. Aggarwal P, Hall JB, McLeland CB, Dobrovolskaia MA, McNeil SE. Nanoparticle interaction with plasma proteins as it relates to particle biodistribution, biocompatibility and therapeutic efficacy. *Adv Drug Deliv Rev* 2009;**61**:428−37.

227. Mukherjee B, Satapathy BS, Mondal L, Dey NS, Maji R. Potentials and challenges of active targeting at the tumor cells by engineered polymeric nanoparticles. *Curr Pharmaceut Biotechnol* 2013;**14**: 1250−63.

228. Sun TM, Zhang YS, Pang B, Hyun DC, Yang MX, Xia YN. Engineered nanoparticles for drug delivery in cancer therapy. *Angew Chem Int Ed* 2014;**53**:12320−64.

229. Gagliardi A, Giuliano E, Venkateswararao E, Fresta M, Bulotta S, Awasthi V, et al. Biodegradable polymeric nanoparticles for drug delivery to solid tumors. *Front Pharmacol* 2021;**12**:601626.

230. Yang XY, Ren H, Zhang H, Liu GQ, Jiang Z, Qiu Q, et al. Antibiotic cross-linked micelles with reduced toxicity for multidrug-resistant bacterial sepsis treatment. *ACS Appl Mater Interfaces* 2021;**13**: 9630−42.

231. He B, Ma SY, Peng GF, He DH. TAT-modified self-assembled cationic peptide nanoparticles as an efficient antibacterial agent. *Nanomed-Nanotechnol* 2018;**14**:365−72.

232. Van der Poll T, van de Veerdonk FL, Scicluna BP, Netea MG. The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol* 2017;**17**:407−20.

233. Vesentini S, Soncini M, Zaupa A, Silvestri V, Fiore GB, Redaelli A. Multi-scale analysis of the toraymyxin adsorption cartridge—Part I: molecular interaction of polymyxin B with endotoxins. *Int J Artif Organs* 2006;**29**:239−50.

234. Tani T, Shimizu T, Tani M, Shoji H, Endo Y. Anti-endotoxin properties of polymyxin B-immobilized fibers. *Adv Exp Med Biol* 2019;**1145**:321−41.

235. Shimizu T, Miyake T, Tani M. History and current status of polymyxin B-immobilized fiber column for treatment of severe sepsis and septic shock. *Ann Gastroent Surg* 2017;**1**:105−13.

236. Ruberto F, Pugliese F, D'Alio A, Martelli S, Bruno K, Marcellino V, et al. Clinical effects of direct hemoperfusion using a polymyxin-B immobilized column in solid organ transplanted patients with signs of severe sepsis and septic shock. A pilot study. *Int J Artif Organs* 2007;**30**:915−22.

237. Shoji H. Extracorporeal endotoxin removal for the treatment of sepsis: endotoxin adsorption cartridge (Toraymyxin). *Ther Apher Dial* 2003;**7**:108−14.

238. Davies B, Cohen J. Endotoxin removal devices for the treatment of sepsis and septic shock. *Lancet Infect Dis* 2011;**11**:65−71.

239. Lee W, Park EJ, Min G, Choi J, Na DH, Bae JS. Dual functioned PEGylated phospholipid micelles containing cationic antimicrobial decapeptide for treating sepsis. *Theranostics* 2017;**7**:3759−67.

240. Dawulieti J, Sun MD, Zhao YW, Shao D, Yan HZ, Lao YH, et al. Treatment of severe sepsis with nanoparticulate cell-free DNA scavengers. *Sci Adv* 2020;**6**:eaay7148.

241. Liu F, Sheng S, Shao D, Xiao YQ, Zhong YL, Zhou J, et al. A cationic metal-organic framework to scavenge cell-free DNA for severe sepsis management. *Nano Lett* 2021;**21**:2461−9.

242. Liang HY, Peng B, Dong C, Liu LX, Mao JJ, Wei S, et al. Cationic nanoparticle as an inhibitor of cell-free DNA-induced inflammation. *Nat Commun* 2018;**9**:4291.

243. Wu JJ, Liang HY, Li YC, Shi Y, Bottini M, Chen YM, et al. Cationic block copolymer nanoparticles with tunable DNA affinity for treating rheumatoid arthritis. *Adv Funct Mater* 2020;**30**:2000391.

244. Patel MM, Patel BM. Crossing the blood-brain barrier: recent advances in drug delivery to the brain. *CNS Drugs* 2017;**31**:109−33.

245. Wang HY, Xu KJ, Liu LH, Tan JPK, Chen YB, Li YT, et al. The efficacy of self-assembled cationic antimicrobial peptide nanoparticles against cryptococcus neoformans for the treatment of meningitis. *Biomaterials* 2010;**31**:2874−81.

246. Liu LH, Xu KJ, Wang HY, Tan PKJ, Fan WM, Venkatraman SS, et al. Self-assembled cationic peptide nanoparticles as an efficient antimicrobial agent. *Nat Nanotechnol* 2009;**4**:457−63.

247. Uchida N, Yanagi M, Hamada H. Physical enhancement? Nanocarrier? Current progress in transdermal drug delivery. *Nanomaterials* 2021;**11**:335.

248. Bos JD, Meinardi MMHM. The 500 dalton rule for the skin penetration of chemical compounds and drugs. *Exp Dermatol* 2000;**9**:165−9.

249. Johnsen L, Fimland G, Eijsink V, Nissen-Meyer J. Engineering increased stability in the antimicrobial peptide pediocin PA-1. *Appl Environ Microbiol* 2000;**66**:4798−802.

250. Cai S, Fujii N, Saito T, Fujii N. Simultaneous ultraviolet B-induced photo-oxidation of tryptophan/tyrosine and racemization of neighboring aspartyl residues in peptides. *Free Radical Bio Med* 2013;**65**:1037−46.

251. McCrudden MTC, McLean DTF, Zhou M, Shaw J, Linden GJ, Irwin CR, et al. The host defence peptide LL-37 is susceptible to proteolytic degradation by wound fluid isolated from foot ulcers of diabetic patients. *Int J Pept Res Therapeut* 2014;**20**:457−64.

252. Jones EM, Cochrane CA, Percival SL. The effect of pH on the extracellular matrix and biofilms. *Adv Wound Care* 2015;**4**:431−9.

253. Takeuchi I, Kagawa A, Makino K. Skin permeability and transdermal delivery route of 30-nm cyclosporin A—loaded nanoparticles using PLGA-PEG-PLGA triblock copolymer. *Colloids Surf, A* 2020;**600**:124866.

254. Sun MH, Zhu CN, Long JY, Lu C, Pan X, Wu CB. PLGA microsphere-based composite hydrogel for dual delivery of ciprofloxacin and ginsenoside Rh2 to treat *Staphylococcus aureus*-induced skin infections. *Drug Deliv* 2020;**27**:632−41.

255. Hasan M, Khatun A, Fukuta T, Kogure K. Noninvasive transdermal delivery of liposomes by weak electric current. *Adv Drug Deliv Rev* 2020;**154−155**:227−35.

256. Chen J, Wang H, Mei L, Wang B, Huang Y, Quan G, et al. A pirfenidone loaded spray dressing based on lyotropic liquid crystals for deep partial thickness burn treatment: healing promotion and scar prophylaxis. *J Mater Chem B* 2020;**8**:2573−88.

257. Yuan LP, Pan M, Lei MY, Zhou XL, Hu DR, Liu QY, et al. A novel composite of micelles and hydrogel for improving skin delivery of hydrocortisone and application in atopic dermatitis therapy. *Appl Mater Today* 2020;**19**:100593.

258. Hou AL, Quan GL, Yang BB, Lu C, Chen ML, Yang D, et al. Rational design of rapidly separating dissolving microneedles for precise drug delivery by balancing the mechanical performance and disintegration rate. *Adv Healthcare Mater* 2019;**8**:1900898.

259. Yang D, Chen ML, Sun Y, Jin YP, Lu C, Pan X, et al. Microneedle-mediated transdermal drug delivery for treating diverse skin diseases. *Acta Biomater* 2021;**121**:119−33.

260. Wei SH, Quan GL, Lu C, Pan X, Wu CB. Dissolving microneedles integrated with pH-responsive micelles containing AIEgen with ultra-photostability for enhancing melanoma photothermal therapy. *Biomater Sci* 2020;**8**:5739−50.

261. Dubey D, Malviya R, Sharma PK. Advancement in microsponge drug delivery system: preparation methods, patents and commercial utility. *Recent Pat Drug Deliv Formulation* 2014;**8**:101−10.

262. Chereddy KK, Her CH, Comune M, Moia C, Lopes A, Porporato PE, et al. PLGA nanoparticles loaded with host defense peptide LL37 promote wound healing. *J Controlled Release* 2014;**194**:138−47.

263. Garcia-Orue I, Gainza G, Girbau C, Alonso R, Aguirre JJ, Pedraz JL, et al. LL37 loaded nanostructured lipid carriers (NLC): a new strategy for the topical treatment of chronic wounds. *Eur J Pharm Biopharm* 2016;**108**:310−6.

264. Dai XM, Guo QQ, Zhao Y, Zhang P, Zhang TQ, Zhang XG, et al. Functional silver nanoparticle as a benign antimicrobial agent that eradicates antibiotic-resistant bacteria and promotes wound healing. *ACS Appl Mater Interfaces* 2016;**8**:25798−807.

265. Xu WG, Dong SJ, Han YP, Li SQ, Liu Y. Hydrogels as antibacterial biomaterials. *Curr Pharmaceut Des* 2018;**24**:843−54.

266. Rezaei N, Hamidabadi HG, Khosravimelal S, Zahiri M, Ahovan ZA, Bojnordi MN, et al. Antimicrobial peptides-loaded smart chitosan hydrogel: release behavior and antibacterial potential against antibiotic resistant clinical isolates. *Int J Biol Macromol* 2020;**164**:855−62.

267. Huang L, Zhu ZY, Wu DW, Gan WD, Zhu SS, Li WQ, et al. Antibacterial poly(ethylene glycol) diacrylate/chitosan hydrogels enhance mechanical adhesiveness and promote skin regeneration. *Carbohydr Polym* 2019;**225**:115110.

268. Bai JK, Chen CX, Wang JX, Zhang Y, Cox H, Zhang J, et al. Enzymatic regulation of self-assembling peptide A_9K_2 nanostructures and hydrogelation with highly selective antibacterial activities. *ACS Appl Mater Interfaces* 2016;**8**:15093−102.

269. Salick DA, Kretsinger JK, Pochan DJ, Schneider JP. Inherent antibacterial activity of a peptide-based β-hairpin hydrogel. *J Am Chem Soc* 2007;**129**:14793−9.

270. Veiga AS, Sinthuvanich C, Gaspar D, Franquelim HG, Castanho MARB, Schneider JP. Arginine-rich self-assembling peptides as potent antibacterial gels. *Biomaterials* 2012;**33**:8907−16.

271. Liu YF, Yang YL, Wang C, Zhao XJ. Stimuli-responsive self-assembling peptides made from antibacterial peptides. *Nanoscale* 2013;**5**:6413−21.

272. Zhou CC, Li P, Qi XB, Sharif ARM, Poon YF, Cao Y, et al. A photopolymerized antimicrobial hydrogel coating derived from epsilon-poly-L-lysine. *Biomaterials* 2011;**32**:2704−12.

273. Li P, Poon YF, Li WF, Zhu HY, Yeap SH, Cao Y, et al. A polycationic antimicrobial and biocompatible hydrogel with microbe membrane suctioning ability. *Nat Mater* 2011;**10**:149−56.

274. Hsu FM, Hu MH, Jiang YS, Lin BY, Hu JJ, Jan JS. Antibacterial polypeptide/heparin composite hydrogels carrying growth factor for wound healing. *Mat Sci Eng C-Mater* 2020;**112**:110923.

275. Liu WS, Wenbin OY, Zhang C, Wang QS, Pan XB, Huang PS, et al. Synthetic polymeric antibacterial hydrogel for methicillin-resistant *Staphylococcus aureus*-infected wound healing: nanoantimicrobial self-assembly, drug- and cytokine-free strategy. *ACS Nano* 2020;**14**: 12905−17.

276. Wang JH, Chen XY, Zhao Y, Yang YM, Wang WJ, Wu C, et al. pH-switchable antimicrobial nanofiber networks of hydrogel eradicate biofilm and rescue stalled healing in chronic wounds. *ACS Nano* 2019;**13**:11686−97.

277. Sun A, He XY, Li L, Li T, Liu QY, Zhou XL, et al. An injectable photopolymerized hydrogel with antimicrobial and biocompatible properties for infected skin regeneration. *NPG Asia Mater* 2020;**12**:1−11.

278. Liu S, Liu X, Ren YH, Wang PH, Pu YJ, Yang R, et al. Mussel-inspired dual-cross-linking hyaluronic acid/epsilon-polylysine hydrogel with self-healing and antibacterial properties for wound healing. *ACS Appl Mater Interfaces* 2020;**12**:27876−88.

279. Wang SQ, Zheng H, Zhou L, Cheng F, Liu Z, Zhang HP, et al. Nanoenzyme-reinforced injectable hydrogel for healing diabetic wounds infected with multidrug resistant bacteria. *Nano Lett* 2020; **20**:5149−58.

280. Yang J, Liu XL, Fu YZ, Song YJ. Recent advances of microneedles for biomedical applications: drug delivery and beyond. *Acta Pharm Sin B* 2019;**9**:469−83.

281. Wu BY, Fu JT, Zhou YX, Luo SL, Zhao YT, Quan GL, et al. Tailored core-shell dual metal-organic frameworks as a versatile nanomotor for effective synergistic antitumor therapy. *Acta Pharm Sin B* 2020; **10**:2198−211.

282. Jamaledin R, Yiu CKY, Zare EN, Niu LN, Vecchione R, Chen GJ, et al. Advances in antimicrobial microneedle patches for combating infections. *Adv Mater* 2020;**32**:2002129.

283. Yang PP, Lu C, Qin WB, Chen ML, Quan GL, Liu H, et al. Construction of a core-shell microneedle system to achieve targeted co-delivery of checkpoint inhibitors for melanoma immunotherapy. *Acta Biomater* 2020;**104**:147−57.

284. Chen ML, Yang D, Sun Y, Liu T, Wang WH, Fu JT, et al. *In situ* self-assembly nanomicelle microneedles for enhanced photo-immunotherapy *via* autophagy regulation strategy. *ACS Nano* 2021; **15**:3387−401.

285. Yang PP, Chen ML, Qin WB, Shi CN, Bai XQ, Quan GL, et al. Effective photothermal therapy mediated by indocyanine green nanoparticle tip-loaded microneedles to enhance checkpoint inhibitor immunotherapy for melanoma treatment. *ACS Appl Nano Mater* 2021;**4**:5921−31.

286. Su YJ, Mainardi VL, Wang HJ, McCarthy A, Zhang YS, Chen SX, et al. Dissolvable microneedles coupled with nanofiber dressings eradicate biofilms *via* effectively delivering a database-designed antimicrobial peptide. *ACS Nano* 2020;**14**:11775−86.

287. Zan P, Than A, Duong PK, Song JH, Xu CH, Chen P. Antimicrobial microneedle patch for treating deep cutaneous fungal infection. *Adv Ther* 2019;**2**:1900064.

288. Chi JJ, Zhang XX, Chen CW, Shao CM, Zhao YJ, Wang YG. Antibacterial and angiogenic chitosan microneedle array patch for promoting wound healing. *Bioact Mater* 2020;**5**:253−9.

289. Zhang TK, Sun B, Guo JN, Wang MY, Cui HQ, Mao HL, et al. Active pharmaceutical ingredient poly(ionic liquid)-based microneedles for the treatment of skin acne infection. *Acta Biomater* 2020; **115**:136−47.

290. Chen M, Quan G, Wen T, Yang P, Qin W, Mai H, et al. Cold to hot: binary cooperative microneedle array-amplified

291. photoimmunotherapy for eliciting antitumor immunity and the abscopal effect. *ACS Appl Mater Interfaces* 2020;**12**:32259−69.

291. Yao GT, Quan GL, Lin SQ, Peng TT, Wang QQ, Ran H, et al. Novel dissolving microneedles for enhanced transdermal delivery of levo-norgestrel: *in vitro* and *in vivo* characterization. *Int J Pharm* 2017; **534**:378−86.

292. Dillon C, Hughes H, O'Reilly NJ, McLoughlin P. Formulation and characterisation of dissolving microneedles for the transdermal delivery of therapeutic peptides. *Int J Pharm* 2017;**526**:125−36.

293. Qian WJ, Texter J, Yan F. Frontiers in poly(ionic liquid)s: syntheses and applications. *Chem Soc Rev* 2017;**46**:1124−59.

294. Zhou C, Sheng CJ, Gao LL, Guo J, Li P, Liu B. Engineering poly(ionic liquid) semi-IPN hydrogels with fast antibacterial and anti-inflammatory properties for wound healing. *Chem Eng J* 2021;**413**: 127429.

295. Fang H, Wang JH, Li L, Xu LQ, Wu YX, Wang Y, et al. A novel high-strength poly(ionic liquid)/PVA hydrogel dressing for antibacterial applications. *Chem Eng J* 2019;**365**:153−64.

296. Wang CL, Chen P, Qiao YB, Kang Y, Yan CR, Yu Z, et al. PH responsive superporogen combined with PDT based on poly Ce6 ionic liquid grafted on SiO2 for combating MRSA biofilm infection. *Theranostics* 2020;**10**:4795−808.

297. Kim YC, Ludovice PJ, Prausnitz MR. Transdermal delivery enhanced by magainin pore-forming peptide. *J Controlled Release* 2007;**122**:375−83.

298. Kim YC, Ludovice PJ, Prausnitz MR. Transdermal delivery enhanced by antimicrobial peptides. *J Biomed Nanotechnol* 2010;**6**:612−20.

299. Haisma EM, Goblyos A, Ravensbergen B, Adriaans AE, Cordfunke RA, Schrumpf J, et al. Antimicrobial peptide p60.4ac-containing creams and gel for eradication of methicillin-resistant *Staphylococcus aureus* from cultured skin and airway epithelial surfaces. *Antimicrob Agents Chemother* 2016;**60**:4063−72.

300. Nibberinga PH, Goblyos A, Adriaans AE, Cordfunke RA, Ravensbergen B, Rietveld MH, et al. Eradication of meticillin-resistant *Staphylococcus aureus* from human skin by the novel LL-37-derived peptide P10 in four pharmaceutical ointments. *Int J Antimicrob Agents* 2019;**54**:610−8.

301. O'Driscoll NH, Labovitiadi O, Cushnie TPT, Matthews KH, Mercer DK, Lamb AJ. Production and evaluation of an antimicrobial peptide-containing wafer formulation for topical application. *Curr Microbiol* 2013;**66**:271−8.

302. Peichl NK, Guzmán EAT, Wang ZM, Meenach SA. Routes of administration for nanocarriers. In: Chung EJ, Leon L, Rinaldi C, editors. *Nanoparticles for biomedical applications*; 2020. p. 67−87.

303. Ngan CL, Asmawi AA. Lipid-based pulmonary delivery system: a review and future considerations of formulation strategies and limitations. *Drug Deliv Transl Res* 2018;**8**:1527−44.

304. Agarwal V, Bajpai M, Sharma A. Patented and approval scenario of nanopharmaceuticals with relevancy to biomedical application, manufacturing procedure and safety aspects. *Recent Pat Drug Deliv Formulation* 2018;**12**:40−52.

305. Agarwal V, Bansal M. Chronomodulated delivery system: a tailored cap to fit different heads. *Recent Pat Drug Deliv Formulation* 2012;**6**: 171−80.

306. Nahar K, Gupta N, Gauvin R, Absar S, Patel B, Gupta V, et al. *In vitro*, *in vivo* and *ex vivo* models for studying particle deposition and drug absorption of inhaled pharmaceuticals. *Eur J Pharmaceut Sci* 2013;**49**:805−18.

307. Carvalho CDS, Daum N, Lehr CM. Carrier interactions with the biological barriers of the lung: advanced *in vitro* models and challenges for pulmonary drug delivery. *Adv Drug Deliv Rev* 2014;**75**:129−40.

308. Cui YT, Huang Y, Zhang XJ, Lu XY, Xue Jun, Wang GL, et al. A real-time and modular approach for quick detection and mechanism exploration of DPIs with different carrier particle sizes. *Acta Pharm Sin B* 2021. Available from: https://doi.org/10.1016/j.apsb.2021.06.011.

309. Dubsky S, Fouras A. Imaging regional lung function: a critical tool for developing inhaled antimicrobial therapies. *Adv Drug Deliv Rev* 2015;**85**:100−9.

310. Pilcer G, Amighi K. Formulation strategy and use of excipients in pulmonary drug delivery. *Int J Pharm* 2010;**392**:1−19.

311. Forte R, Dibble C. The role of international environmental agreements in metered dose inhaler technology changes. *J Allergy Clin Immunol* 1999;**104**:S217−20.

312. Hoppentocht M, Hagedoorn P, Frijlink HW, de Boer AH. Technological and practical challenges of dry powder inhalers and formulations. *Adv Drug Deliv Rev* 2014;**75**:18−31.

313. Zhang XJ, Cui YT, Liang RF, Wang GL, Yue X, Zhao ZY, et al. Novel approach for real-time monitoring of carrier-based DPIs delivery process *via* pulmonary route based on modular modified Sympatec HELOS. *Acta Pharm Sin B* 2020;**10**:1331−46.

314. Kwok PCL, Grabarek A, Chow MYT, Lan Y, Li JCW, Casettari L, et al. Inhalable spray-dried formulation of D-LAK antimicrobial peptides targeting tuberculosis. *Int J Pharm* 2015; **491**:367−74.

315. Suzuki H, Ueno K, Mizumoto T, Seto Y, Sato H, Onoue S. Self-micellizing solid dispersion of cyclosporine A for pulmonary delivery: physicochemical, pharmacokinetic and safety assessments. *Eur J Pharmaceut Sci* 2017;**96**:107−14.

316. Ye TT, Yu JQ, Luo QH, Wang SJ, Chan HK. Inhalable clarithromycin liposomal dry powders using ultrasonic spray freeze drying. *Powder Technol* 2017;**305**:63−70.

317. Wen XG, Peng XS, Fu H, Dong YX, Han K, Su JF, et al. Preparation and *in vitro* evaluation of silk fibroin microspheres produced by a novel ultra-fine particle processing system. *Int J Pharm* 2011;**416**: 195−201.

318. Zhu CN, Peng TT, Huang D, Feng DS, Wang XY, Pan X, et al. Formation mechanism, *in vitro* and *in vivo* evaluation of dimpled exenatide loaded PLGA microparticles prepared by ultra-fine particle processing system. *AAPS PharmSciTech* 2019;**20**:64.

319. Zhu CE, Huang Y, Zhang XY, Mei LL, Pan X, Li G, et al. Comparative studies on exenatide-loaded poly (D,L-lactic-*co*-glycolic acid) microparticles prepared by a novel ultra-fine particle processing system and spray drying. *Colloids Surf, B* 2015;**132**:103−10.

320. Baghdan E, Duse L, Schuer JJ, Pinnapireddy SR, Pourasghar M, Schafer J, et al. Development of inhalable curcumin loaded nano-in-microparticles for bronchoscopic photodynamic therapy. *Eur J Pharmaceut Sci* 2019;**132**:63−71.

321. Ni R, Zhao J, Liu QY, Liang ZL, Muenster U, Mao SR. Nanocrystals embedded in chitosan-based respirable swellable microparticles as dry powder for sustained pulmonary drug delivery. *Eur J Pharmaceut Sci* 2017;**99**:137−46.

322. Chen C, Deslouches B, Montelaro RC, Di YP. Enhanced efficacy of the engineered antimicrobial peptide WLBU2 *via* direct airway delivery in a murine model of Pseudomonas aeruginosa pneumonia. *Clin Microbiol Infect* 2018;**24**:547.e1−8.

323. Rivas-Santiago B, Rivas Santiago CE, Castaneda-Delgado JE, Leon-Contreras JC, Hancock RE, Hernandez-Pando R. Activity of LL-37, CRAMP and antimicrobial peptide-derived compounds E2, E6 and CP26 against *Mycobacterium tuberculosis*. *Int J Antimicrob Agents* 2013;**41**:143−8.

324. Forde E, Kelly G, Sweeney L, Fitzgerald-Hughes D, MacLoughlin R, Devocelle M. Vibrating mesh nebulisation of pro-antimicrobial peptides for use in cystic fibrosis. *Pharmaceutics* 2019;**11**:239.

325. Zhong Q, da Rocha SRP. Poly(amidoamine) dendrimer-doxorubicin conjugates: *in vitro* characteristics and pseudosolution formulation in pressurized metered-dose inhalers. *Mol Pharm* 2016;**13**:1058−72.

326. Casciaro B, d'Angelo I, Zhang XP, Loffredo MR, Conte G, Cappiello F, et al. Poly(lactide-*co*-glycolide) nanoparticles for prolonged therapeutic efficacy of esculentin-1a-derived antimicrobial peptides against *Pseudomonas aeruginosa* lung infection: *in vitro* and *in vivo* studies. *Biomacromolecules* 2019;**20**:1876−88.

327. Felgentreff K, Beisswenger C, Griese M, Gulder T, Bringmann G, Bals R. The antimicrobial peptide cathelicidin interacts with airway mucus. *Peptides* 2006;**27**:3100−6.

328. D'Angelo I, Casciaro B, Miro A, Quaglia F, Mangoni ML, Ungaro F. Overcoming barriers in Pseudomonas aeruginosa lung infections: engineered nanoparticles for local delivery of a cationic antimicrobial peptide. *Colloids Surf, B* 2015;**135**:717−25.

329. Omri A, Suntres ZE, Shek PN. Enhanced activity of liposomal polymyxin B against Pseudomonas aeruginosa in a rat model of lung infection. *Biochem Pharmacol* 2002;**64**:1407−13.

330. Ungaro F, d' Angelo I, Miro A, La Rotonda MI, Quaglia F. Engineered PLGA nano- and micro-carriers for pulmonary delivery: challenges and promises. *J Pharm Pharmacol* 2012;**64**:1217−35.

331. Water JJ, Smart S, Franzyk H, Foged C, Nielsen HM. Nanoparticle-mediated delivery of the antimicrobial peptide plectasin against *Staphylococcus aureus* in infected epithelial cells. *Eur J Pharm Biopharm* 2015;**92**:65−73.

332. Falciani C, Zevolini F, Brunetti J, Riolo G, Gracia R, Marradi M, et al. Antimicrobial peptide-loaded nanoparticles as inhalation therapy for Pseudomonas aeruginosa infections. *Int J Nanomed* 2020;**15**: 1117−28.

333. Schuster BS, Suk JS, Woodworth GF, Hanes J. Nanoparticle diffusion in respiratory mucus from humans without lung disease. *Biomaterials* 2013;**34**:3439−46.

334. Patel B, Gupta N, Ahsan F. Particle engineering to enhance or lessen particle uptake by alveolar macrophages and to influence the therapeutic outcome. *Eur J Pharm Biopharm* 2015;**89**:163−74.

335. Avgoustakis K. PEGylated poly(lactide) and poly(lactide-*co*-glycolide) nanoparticles: preparation, properties and possible applications in drug delivery. *Curr Drug Deliv* 2004;**1**:321−33.

336. Patel B, Gupta V, Ahsan F. PEG-PLGA based large porous particles for pulmonary delivery of a highly soluble drug, low molecular weight heparin. *J Controlled Release* 2012;**162**:310−20.

337. Shetty N, Ahn P, Park H, Bhujbal S, Zemlyanov D, Cavallaro A, et al. Improved physical stability and aerosolization of inhalable amorphous ciprofloxacin powder formulations by incorporating synergistic colistin. *Mol Pharm* 2018;**15**:4004−20.

338. Yu SH, Wang SN, Zou PZ, Chai GH, Lin YW, Velkov T, et al. Inhalable liposomal powder formulations for co-delivery of synergistic ciprofloxacin and colistin against multi-drug resistant Gram-negative lung infections. *Int J Pharm* 2020;**575**:118915.

339. Zhu CN, Chen JT, Yu SH, Que CL, Taylor LS, Tan W, et al. Inhalable nanocomposite microparticles with enhanced dissolution and superior aerosol performance. *Mol Pharm* 2020;**17**:3270−80.

340. Lundquist P, Artursson P. Oral absorption of peptides and nanoparticles across the human intestine: opportunities, limitations and studies in human tissues. *Adv Drug Deliv Rev* 2016;**106**: 256−76.

341. Evans DF, Pye G, Bramley R, Clark AG, Dyson TJ, Hardcastle JD. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. *Gut* 1988;**29**:1035−41.

342. Woodley JF. Enzymatic barriers for GI peptide and protein delivery. *Crit Rev Ther Drug Carrier Syst* 1994;**11**:61−95.

343. Ndayishimiye J, Popat A, Blaskovich M, Falconer JR. Formulation technologies and advances for oral delivery of novel nitroimidazoles and antimicrobial peptides. *J Controlled Release* 2020;**324**:728−49.

344. Werle M, Makhlof A, Takeuchi H. Oral protein delivery: a patent review of academic and industrial approaches. *Recent Pat Drug Deliv Formulation* 2009;**3**:94−104.

345. Han Y, Gao ZG, Chen LQ, Kang L, Huang W, Jin MJ, et al. Multifunctional oral delivery systems for enhanced bioavailability of therapeutic peptides/proteins. *Acta Pharm Sin B* 2019;**9**:902−22.

346. Griesser J, Hetenyi G, Kadas H, Demarne F, Jannin V, Bernkop-Schnurch A. Self-emulsifying peptide drug delivery systems: how to make them highly mucus permeating. *Int J Pharm* 2018;**538**: 159−66.

347. Zhang X, Yi YN, Qi JP, Lu Y, Tian ZQ, Xie YC, et al. Controlled release of cyclosporine A self-nanoemulsifying systems from osmotic pump tablets: near zero-order release and pharmacokinetics in dogs. *Int J Pharm* 2013;**452**:233−40.

348. Lu C, Li X, Xia WQ, Lu SH, Luo HJ, Ye DY, et al. Poly(ε-benzyloxycarbonyl-L-lysine)-grafted branched polyethylenimine as efficient nanocarriers for indomethacin with enhanced oral

bioavailability and anti-inflammatory efficacy. *Acta Biomater* 2017; **49**:434−43.

349. Li C, Wang JC, Wang YG, Gao HL, Wei G, Huang YZ, et al. Recent progress in drug delivery. *Acta Pharm Sin B* 2019;**9**:1145−62.

350. He HS, Lu Y, Qi JP, Zhu QG, Chen ZJ, Wu W. Adapting liposomes for oral drug delivery. *Acta Pharm Sin B* 2019;**9**:36−48.

351. Durack E, Mallen S, O'Connor PM, Rea MC, Ross RP, Hill C, et al. Protecting bactofencin A to enable its antimicrobial activity using mesoporous matrices. *Int J Pharm* 2019;**558**:9−17.

352. Flynn J, Mallen S, Durack E, O'Connor PM, Hudson SP. Mesoporous matrices for the delivery of the broad spectrum bacteriocin, nisin A. *J Colloid Interface Sci* 2019;**537**:396−406.

353. Groo AC, Matougui N, Umerska A, Saulnier P. Reverse micelle-lipid nanocapsules: a novel strategy for drug delivery of the plectasin derivate AP138 antimicrobial peptide. *Int J Nanomed* 2018;**13**:7565−74.

354. Griffin BT, Guo JF, Presas E, Donovan MD, Alonso MJ, O'Driscoll CM. Pharmacokinetic, pharmacodynamic and biodistribution following oral administration of nanocarriers containing peptide and protein drugs. *Adv Drug Deliv Rev* 2016;**106**:367−80.

355. Ensign LM, Cone R, Hanes J. Oral drug delivery with polymeric nanoparticles: the gastrointestinal mucus barriers. *Adv Drug Deliv Rev* 2012;**64**:557−70.

356. Lai SK, O'Hanlon DE, Harrold S, Man ST, Wang YY, Cone R, et al. Rapid transport of large polymeric nanoparticles in fresh undiluted human mucus. *Proc Natl Acad Sci U S A* 2007;**104**:1482−7.

357. Zhang X, Cheng HB, Dong W, Zhang MX, Liu QY, Wang XH, et al. Design and intestinal mucus penetration mechanism of core-shell nanocomplex. *J Control Release* 2018;**272**:29−38.

358. Rishi P, Bhogal A, Arora S, Pandey SK, Verma I, Kaur IP. Improved oral therapeutic potential of nanoencapsulated cryptdin formulation against Salmonella infection. *Eur J Pharmaceut Sci* 2015;**72**:27−33.

359. Menina S, Eisenbeis J, Kamal MAM, Koch M, Bischoff M, Gordon S, et al. Bioinspired liposomes for oral delivery of colistin to combat intracellular infections by *Salmonella enterica*. *Adv Healthc Mater* 2019;**8**:1900564.

360. Liang YX, Luan XH, Liu XH. Recent advances in periodontal regeneration: a biomaterial perspective. *Bioact Mater* 2020;**5**:297−308.

361. Aida KL, Kreling PF, Caiaffa KS, Calixto GMF, Chorilli M, Spolidorio DMP, et al. Antimicrobial peptide-loaded liquid crystalline precursor bioadhesive system for the prevention of dental caries. *Int J Nanomed* 2018;**13**:3081−91.

362. Al-Ghananeem AM, Leung KP, Faraj J, DeLuca PP. Development of a sustained antiplaque and antimicrobial chewing gum of a decapeptide. *AAPS PharmSciTech* 2017;**18**:2240−7.

363. Li YY, Na RW, Wang XM, Liu HY, Zhao LY, Sun XD, et al. Fabrication of antimicrobial peptide-loaded PLGA/chitosan composite microspheres for long-acting bacterial resistance. *Molecules* 2017;**22**:1637.

364. Popescu R, Ghica MV, Dinu-Pirvu CE, Anuta V, Lupuliasa D, Popa L. New opportunity to formulate intranasal vaccines and drug delivery systems based on chitosan. *Int J Mol Sci* 2020;**21**: 5016.

365. Goblyos A, Schimmel KJM, Valentijn ARPM, Fathers LM, Cordfunke RA, Chan HL, et al. Development of a nose cream containing the synthetic antimicrobial peptide P60.4Ac for eradication of methicillin-resistant *Staphylococcus aureus* carriage. *J Pharm Sci-US* 2013;**102**:3539−44.

366. Huang JF, Zhong J, Chen GP, Lin ZT, Deng YQ, Liu YL, et al. A hydrogel-based hybrid theranostic contact lens for fungal keratitis. *ACS Nano* 2016;**10**:6464−73.

367. Malakooti N, Alexander C, Alvarez-Lorenzo C. Imprinted contact lenses for sustained release of polymyxin B and related antimicrobial peptides. *J Pharm Sci-US* 2015;**104**:3386−94.

368. Jiang YC, Meng XY, Wu ZH, Qi XL. Modified chitosan thermosensitive hydrogel enables sustained and efficient anti-tumor therapy *via* intratumoral injection. *Carbohydr Polym* 2016;**144**: 245−53.

369. Wang C, Hong TT, Cui PF, Wang JH, Xia J. Antimicrobial peptides towards clinical application: delivery and formulation. *Adv Drug Deliv Rev* 2021;**175**:113818.