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Responsive Polymeric Nanoparticles for Biofilm-infection Control

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Abstract With the emergence of multidrug resistance (MDR) in many pathogens, bacterial infections are becoming a growing threat to public health. The frightening scenario is due largely to the formation of biofilms, in which the bacteria are extremely recalcitrant to the conventional antibiotic regimens. To address the emergence of MDR and biofilm-associated infections, numerous polymer-based materials have been designed and prepared recently. The subject of this perspective is the recent development of polymer-based materials that have been applied to combat multidrug-resistant pathogens, to prevent the formation of biofilms, or enhance the eradication efficacy to mature biofilms *via* killing biofilm-bacteria or dispersing biofilms. The advantages and shortcomings of these polymer-based materials are discussed, as well as the challenges we are facing in the clinical translation of these systems.

Keywords Antibacterial; Biofilm; Multidrug resistance; Polymeric nanoparticles; Stimuli-responsive

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INTRODUCTION

Bacteria-associated infections are posing an unprecedented threat to human health worldwide.[1] It is estimated that, if no effective measures are taken, bacterial infection will surpass cancer and become the number one cause of human death by 2050.[2] The frightening scenario of multidrug resistance (MDR) was partly promoted by the abuse and misuse of antibiotics and partly promoted by the ineffectiveness of the antibiotic regimens against bacterial biofilms.[3] Biofilms are well-structured bacterial communities in which bacterial cells aggregate in the self-produced extracellular polymeric substances (EPS) consisting of polysaccharides, proteins, glycoproteins, and nucleic acids.[4] The porous nature of an EPS matrix allows the penetration of nutrients and transport of wastes for the metabolic activities of the inhabitants.[5] In the meantime, biofilms protect the inhabitants against the host immune systems and environmental challenges,[4] as well as antibiotic pressure.[3] Hydrophobic antibiotics barely penetrate bacterial biofilms due to their poor solubility. Besides, most of the commonly used antibiotics carry a positive net charge, and thereby, the negatively charged EPS matrix can absorb those cationic antibiotics through electrostatic attractions and hinder their deep penetration in biofilms. For those antibiotics that penetrate in biofilms, they may face the possibility of being pumped out by the over-expressed drug efflux pumps in biofilms[6] or being hydrolysed by the local bacterial enzymes such as β-lactamases.[7] Also, antibiotics are less effective for the bacteria in their biofilm-phenotype that are featured by their reduced metabolic and growth activities compared with their planktonic counterparts. Taken together, all of the above reasons lead to the low efficiency of traditional antibiotics in eradicating biofilms. Usually, up to 1000 times more dosage of antibiotics are required to treat bacteria in biofilms than their planktonic counterparts, ultimately expediting the development of antimicrobial resistance.[8]

The development of new strategies for biofilm-associated infection control is eagerly needed, either to develop new antibiotics or to improve the bactericidal efficacy of the current antibiotic regimens. Unfortunately, the lifetime of new antibiotics is becoming increasingly shorter since the emergence of drug resistance in bacteria. In this regard, the motivation to develop and market new antibiotics with huge research costs is decreasing.[9] To solve the dilemma, over the past decades, numerous nanotechnology-based systems have been designed as antimicrobials and delivery systems to facilitate the penetration and drug release in biofilms, such as metal-based nanocomposites (*e.g.*, metal oxide-, Ag-, and Au-based nanoparticles), carbon-based nanomaterials (*e.g.*, graphene materials, carbon quantum dots), and polymer-based nanoparticles (natural and synthetic polymeric nanoparticles).[10,11] Among them, synthetic polymeric nanoparticles are flourishing, since the development of polymerization methodologies allows the synthesis of polymers with precise structures and molecu-

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lar sizes.[12–15] Also, there are multitudinous functional groups that could be modified on the polymer chains *via* post-polymerization modification, endowing the polymer with different physicochemical properties applicable in the biofilm microenvironment, such as biocompatibility, stimuli-responsiveness and degradability.[16]

Polymer nanosystems can be applied in combating biofilm-associated infections in two major aspects, as summarized in Scheme 1. First, polymers can be used to modify the surfaces of substrates to avoid bacterial adhesion and subsequently prevent biofilm formation, yielding the antifouling surfaces or antibacterial surfaces. Besides, mature biofilms are eradicated by polymer nanosystems from different perspectives. With rational design, bactericidal polymers can be armed with intrinsic antibacterial capacities, for example, quaternary ammonium-containing polymers,[17–21] polycations,[22–26] polysaccharides[27] and antimicrobial peptides (AMPs).[28–30] Moreover, polymeric nanocarriers can deliver antimicrobials deep into biofilms, enhance the penetration and accumulation of antimicrobials, and release the loaded antimicrobials inside biofilms, improving the efficacy of conventional antimicrobials yet minimizing their side effects on normal tissues.[31] Besides, polymeric nanoparticles may serve as a biofilm dispersant, rendering an efficient way to eradicate biofilms. In this regard, once the EPS matrix is dispersed, antimicrobials will exhibit better bactericidal efficacy against the remaining biofilms. In this perspective, we briefly focus on the recent development of polymer-based materials in eradicating biofilm and their potential clinical applications. Also, we discuss the challenges in their clinical translation.

MICROENVIRONMENT AT INFECTION SITES

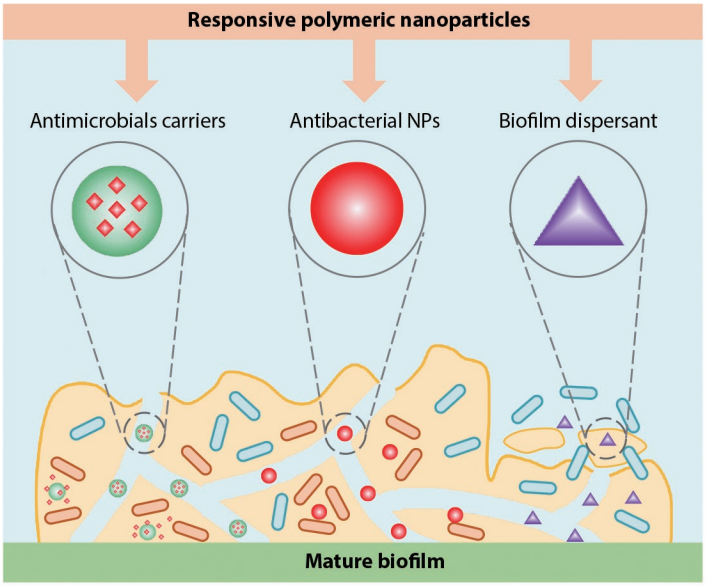
The metabolism activities of microorganisms embedded in infectious biofilms lead to the establishment of unique chemical and physical properties at infection sites, such as the leaky blood vessels, acidic environment, oxygen gradients, diverse enzymes, high levels of H_2O_2, and toxins. These characteristics not only discriminate the infection sites from the normal tissues but also give implications for designing smart antimicrobial systems (Fig. 1). In this section, we focus on the crucial microenvironment at infection sites and their functions in antimicrobial systems.

Enhanced Permeability and Retention (EPR) Effect

The EPR effect is a major effect known as that nanoparticles are allowed to accumulate in tumor tissue other than normal tissue.[32] This is because, in normal tissues, the endothelial space of micro-vessels is dense and intact, and nanoparticles are less likely to bypass the vascular wall. However, in those diseased tissues, the vascular wall space is much wider, leading to the permeability and retention of nanomedicines.[33–36] Of note, the EPR effect was observed not only in tumor tissues, but also in bacterial infection, inflammation, and injury sites.[37,38] During bacterial infection, proteases play an important role in forming leaky vascular structures.[39–42] The bradykinin-generating cascade of endogenous proteases is activated by exogenous proteases. Then, the endogenous proteases can activate thrombin, form fibrin and generate kinin, leading to the increase in vascular permeability.[38] Therefore, this vascular change allows nanoparticles to accumulate at the infection sites *via* the EPR effect. Particularly, the EPR effect lay the basis for the selective distribution of nanoparticles in bacterial infection, which can increase efficacy and reduce systemic side effects of conventional antimicrobials.

Acidic Environment

An acidic environment exists in a biofilm, in which the pH value in a biofilm may reach 4.5 or even lower.[43] For example, the



Scheme 1 Schematic illustration of the applications of responsive polymeric nanoparticles in biofilm-associated infection control. Responsive polymeric nanoparticles can be used to deliver antimicrobials, kill bacteria directly, or disperse biofilms to combat mature biofilms.

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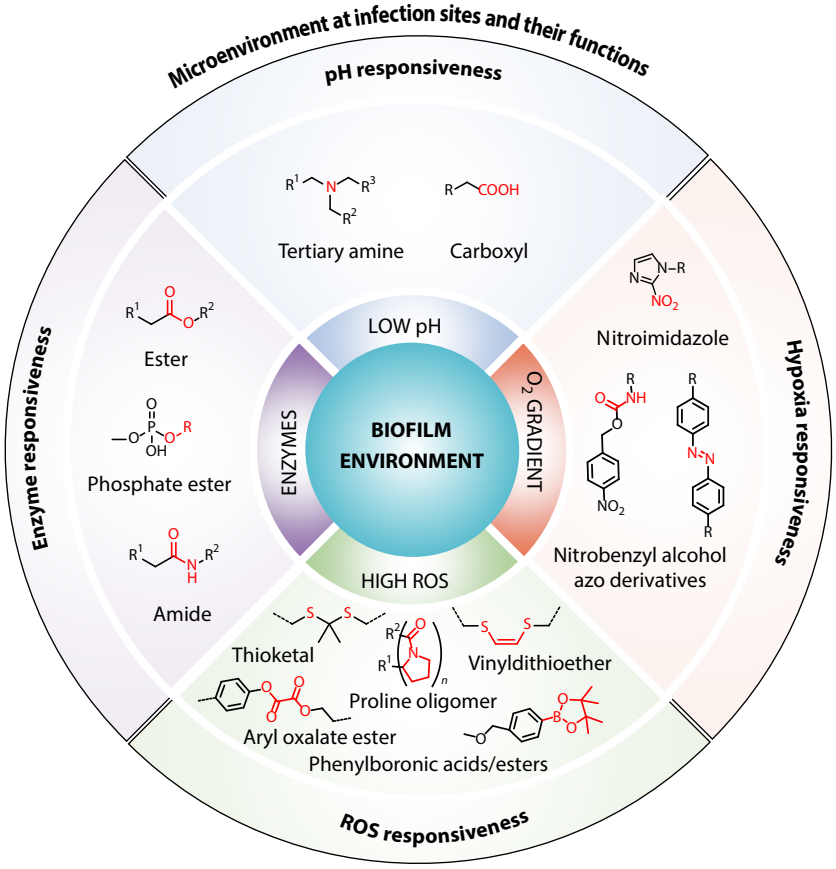

Fig. 1 A summary of the physio-chemical factors in the microenvironment of infection sites and the typical chemical structures that can respond to the corresponding factors.

metabolic activity of acidogenic/acid-tolerant oral bacteria can result in an acidic microenvironment.[44] The anaerobic fermentation of certain microbes, such as *Staphylococcus aureus* (*S. aureus*) or *Streptococcus mutans* (*S. mutans*), can produce and accumulate organic acids in biofilms, leading to an acidic environment.[45] Besides, bacterial infections can induce phagocytosis, during which, the inflammatory cells release lactic acid, lowering the pH at infection sites.[46] The low pH at infection sites is different from the physiological pH of 7.4, which can provide implications for the determination and treatment of bacterial infection.

In principle, several chemical groups can transform between protonation and de-protonation when the pH varies around their pK_a values, such as amines, carboxylates and sulfonic groups.[47] In the meantime, the solubility of these chemical groups will change drastically, ultimately leading to the phase change of the bulk materials. Therefore, this property can be used to design pH-responsive nanomaterials for various purposes.[45]

Oxygen Gradients

The EPS matrix in biofilm leads to the creation of physio-chemical heterogeneities, for example, nutrient and oxygen gradients.[48] The oxygen gradient in a biofilm is attributed to the fact that bacteria in the superficial layers of the biofilm consume oxygen at a rate faster than the diffusion of oxygen, leading to the formation of hypoxia in the bottom layers of a biofilm.[49] This oxygen gradient and local hypoxia are of great importance to the metabolism, virulence, and drug resistance of bacteria.[5] Besides, the local hypoxia of a biofilm implicates the possibility of delivering and releasing antibiotics in an "on-demand" manner. The commonly used hypoxia-responsive moieties include azo crosslinkers, nitroimidazoles, and nitrobenzyl alcohols (Fig. 1).[50] In most cases, they undergo a hydrophobic-to-hydrophilic transition once being reduced under the hypoxia conditions. Those moieties have been extensively applied to design/construct controlled release systems in cancer therapy and immunotherapy.[51] Whereas, the application of hypoxia-responsive systems in combating bacteria-associated infections is still in its infancy. Besides, the oxygen-loaded nanocarriers can relieve the biofilm hypoxia to a certain extent.[52]

Enzymes

Like hypoxia, bacterial enzymes also play crucial roles in the metabolism, biological process, virulence, and drug resistance of bacteria.[53] There are several over-expressed enzymes at the infection sites, such as β-galactosidases,[54] alkaline phosphatases,[29,55] nitroreductases,[56] proteinases,[57] lipases,[58] phospholipases,[59] toxins,[60,61] and hyaluronidases.[62] These enzymes can degrade/hydrolyze specific chemical structures, potentiating their applications in drug delivery.[47]

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Reactive Oxygen Species (ROS)

At the infection sites, the infiltrating immune cells produce an increased amount of ROS, such as hydrogen peroxide (H_2O_2), superoxide (O_2^-), hypochlorite (OCl^-), *etc*. to eradicate the invaded bacteria.[63–65] Therefore, infection sites are often enriched with ROS that can be used to determine and eradicate bacterial infections. In this regard, numerous ROS-responsive systems have been investigated for diverse applications,[65–67] while their application in eradicating bacteria- or biofilm-associated infections remains largely undeveloped.

PREVENTION OF BIOFILM FORMATION

Bacteria need to adhere to the surface of tissues or implants and to initiate the growth of biofilms thereafter.[68,69] Therefore, the easiest and most convenient way to avoid biofilm-associated infections is to prevent biofilm formation. In general, there are two major approaches to prevent bacterial adhesion and subsequent formation of biofilms on a surface, namely to "attack" or to "defend".[70] The "attack" strategy is to kill the bacteria using antibiotics or antimicrobial cationic polymers,[71–73] since the cell membranes of bacteria are negatively charged because of the ample anionic lipids, like phosphatidylglycerols and cardiolipins.[74] However, the dead bacteria will remain on these surfaces, which can trigger the immune response and induce side effects such as inflammation and sepsis. In the meanwhile, the "defend" strategy is to form a non-fouling surface using polymers such as poly(ethylene glycol) (PEG) and zwitterionic polymers.[75,76] In particular, these polymers can form a hydration periphery that can largely avoid the interactions of bacteria with the surface of a substratum. Of note, some recent developments realize the design of multifunctional surfaces. For example, zwitterionic surfaces formed by an equal amount of quaternary ammonium and carboxyl groups were able to achieve the "attract-and-release" of bacteria.[76,77] The zwitterionic surface is positively charged at pH below 4.5 due to the partial protonation of carboxyl groups, enabling the attraction of bacteria. While under neutral and basic conditions, the zwitterionic surface becomes neutral owing to the deprotonation of acids. Thus, the attenuated interaction between surface and bacteria leads to the release of the captured bacteria.[77] However, the pH variation only allows the switch of surfaces from bacteria-adhesive to bacteria-resistant, and the surfaces do not induce the lysis of bacterial cells. Subsequently, Jiang *et al.* developed a surface modified with ester-containing quaternary ammoniums to achieve the "kill-and-release" property.[78] The antibacterial surface possessed a strong positive charge that kills the attached bacteria by damaging the bacteria cell membrane. In the meantime, the released esterases from the killed bacteria could hydrolyze the ester groups, leading to the formation of a zwitterionic and non-fouling surface that liberates the dead bacteria.[78] However, the hydrolysis of ester groups is not reversible, and the surface cannot turn back its "kill" state to maintain its non-fouling nature. To solve this problem, in their subsequent study, a surface capable of switching between attacking and defending functions was developed. The surfaces can transform the cationic *N*,*N*-dimethyl-2-morpholinone into the zwitterionic carboxy betaine under the trigger of bacterial enzyme-triggered hydrolysis.[70]

Apart from the chemical modification of surfaces to prevent bacterial adhesion, the roughness and topography of substrate surfaces also influence bacterial adhesion, as reviewed elsewhere.[79,80] Polymer-based nanoparticles, such as nanogels, can form the antifouling nanogel coating on the surface of a substratum to reduce bacterial attachment *via* its unique topography and stiffness, as well as hydration property.[81] For example, poly(*N*-isopropylmetacrylamide) (pNIPMAM) nanogel coatings were used to prevent the adhesion of bacteria and subsequently prevent the formation of biofilms.[82] However, in most cases, only repelling the bacterial attachment is not enough to prevent the formation of biofilms.[83] To address this issue, antimicrobials are applied as additives to enhance the bactericidal efficacy and the ability to prevent biofilm formation. Antimicrobials can be loaded, chemically conjugated, or coordinated into the polymeric hydration layer or nanogels that coat on a surface. For example, Xu *et al.* designed porous hydroxyapatite (HA) implants functionalized *via* ethylenediamine-modified poly(glycidyl methacrylate) brushes, which further conjugated gentamicin sulfate (GS), yielding the antibacterial HA implants (HA-GS).[84] The local acidic microenvironment can trigger the release of GS *via* the hydrolysis of the acid-sensitive linkers between GS and polymer brushes. HA-GS exhibited excellent anti-infection activity *in vivo* in an infected bone defect rabbit model. Taken together, all the above-mentioned strategies provide powerful arsenals for preventing bacterial adhesion and subsequent biofilm formation.

BIOFILM ERADICATION

Besides preventing biofilm formation, eradicating the established biofilm is also a huge task. There are two main strategies to eradicate biofilm. On the one hand, polymer nanosystems can be used as carriers for traditional antibiotics or serve as nano-antibiotics to kill bacteria in biofilms. On the other hand, polymer nanoparticles can be used as biofilm dispersants to destroy the architectures of biofilms, making the remaining bacterial more susceptible to other antibacterial therapies, such as antibiotics. In this section, recent developments of polymer-based materials that have been applied in eradicating mature bacterial biofilms will be discussed.

Antibiotics Delivery Systems

Free antibiotics are easily cleared through blood circulation *via* renal filtration or inactivated by the various enzymes in tissues such as livers. Furthermore, as we mentioned above, the penetration of free antibiotics in biofilms is remarkably poor, greatly attenuating the anti-biofilm efficacy of antibiotic regimens and resulting in serious side effects. To solve this problem, conventional antibiotics can be loaded in polymeric nanoparticles. The drug-encapsulated polymeric systems possess the following advantages. First, after being encapsulated, conventional antibiotics are temporarily protected by the polymeric peripheries, thereby enhancing the stability and biocompatibility of antibiotics during blood circulation. Besides, certain polymeric carriers can respond to the bacterial infection microenvironments and target the infection sites. Moreover, with rational design, polymeric carriers can enhance the

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penetration of antibiotics in biofilms, and release their cargoes to eradicate the biofilms in an on-demand manner. Both hydrophilic and hydrophobic antibiotics can be loaded by choosing different polymer systems.

Loading hydrophobic antibiotics

The most prevalent polymeric nanocarriers for hydrophobic antibiotics are polymeric micelles. In recent years, our group have made a lot of efforts to research polymer assembly behavior and its applications.[85–91] In particular, polymeric micelles are core-shell-structured nano-assemblies that self-assembled from amphiphilic copolymers. Therefore, the hydrophobic cores of polymeric micelles are the ideal containers for hydrophobic antibiotics, such as triclosan,[92] curcumin,[93] isoniazid,[94] and bedaquiline.[95] There are several approaches for the preparation of the hydrophobic antimicrobial-loaded polymeric micelles, which have been reviewed elsewhere.[16,47] This is not the subject of our article. We merely focus on the utility of polymeric micelles in overcoming the physical barrier of biofilm during antibiotic treatments. For example, triclosan could be loaded in mixed-shell-polymeric-micelles (MSPMs), which are self-assembled from two diblock copolymers, namely poly(ethylene glycol)-*block*-poly(*ε*-caprolactone) (PEG-*b*-PCL) and poly(*ε*-caprolactone)-*block*-poly(*β*-amino ester) (PCL-*b*-PAE) (Fig. 2).[92] The shells of MSPMs are formed by the hydrophilic PEG and the pH-responsive PAE,[96] while PCL forms the lipase-sensitive micelle core that can encapsulate hydrophobic triclosan. The mixed shell allows the stability and long circulation of MSPMs, since the PAE block is negatively charged and hydrophobic under normal physiological pH 7.4, and the whole micelles were stabilized by the PEG shell.[92] Once being exposed to the acidic microenvironment of infection sites, the PAE block would be protonated and become hydrophilic and positively charged, enhancing their interactions with the negatively charged bacteria in biofilms through electrostatic attractions. Upon the deep penetration of the drug-loaded MSPMs in biofilms, the micellar cores would be hydrolyzed by the bacterial lipases, releasing the loaded triclosan to kill the bacteria embedded in biofilms. In contrast, non-loaded triclosan and the triclosan encapsulated in single-shell-polymeric-micelles (SSPMs) consisting of only PEG-*b*-PCL exhibited poor biofilm eradication efficacy. This study renders an efficient pathway to overcome the biofilm barrier.

Subsequently, we used MSPMs to encapsulate protoporphyrin IX (PpIX), a photosensitizer that produces singlet oxygen using tissue oxygen under light irradiation, for biofilm eradication. Our MSPMs greatly enhanced the penetration of the hydrophobic PpIX in biofilms and the ability to produce singlet oxygen thereafter.[97] Since singlet oxygen induces bacterial lysis using its oxidative stress on bacterial lipids and biomacromolecules, bacteria are less likely resistant to this mechanism. Therefore, these photosensitizer-based bactericidal systems are ready to be applied in combating biofilms constructed from drug-resistant bacteria.

The above-mentioned antibiotics are loaded into nanocarriers expediently through hydrophobic interactions, which are weak and usually cannot prevent the drug premature leakage during storage and blood circulation.[98,99] Conjugating antibiotics in polymers, also named as polyprodrug, is a promising option to circumvent this problem. For instance, we conjugated triclosan onto a PEG-*b*-PAE block polymer *via* ester bonds. The triclosan-conjugated PEG-*b*-PAE forms stable polymeric micelles in water and possesses PEG shells that enable long blood circulation after being injected.[100] Triclosan is less likely to be released during blood circulation due to its chemical conjugation. While the PAE domain can be proton-

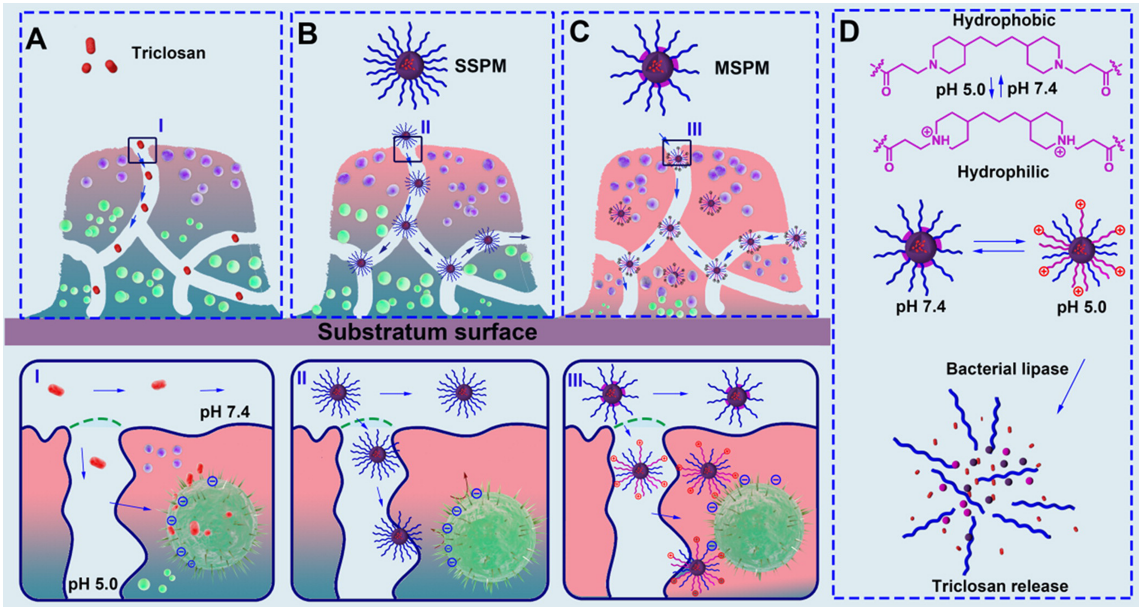

Fig. 2 Schematic illustration of the process of triclosan-loaded MSPMs in eradicating bacterial biofilms. (A) Free triclosan is less likely to penetrate biofilms. (B) SSPMs can assist the penetration of triclosan in biofilms, while they cannot interact with EPS matrixes of biofilms. (C) MSPMs allow the full penetration of biofilms and kill most of the embedded bacteria in biofilms. (D) The charge conversion PAE in MSPMs upon the switch of pH and bacterial lipase-triggered micelle core degradation and triclosan release. (Reproduced with permission from Ref. [92]; Copyright (2016) American Chemical Society.)

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ated at lower pH in a biofilm, facilitating the interactions between micelles and biofilm matrix and allowing the retention of micelles inside biofilms. The local bacterial lipases triggered the triclosan release to eradicate the biofilm-bacteria (Fig. 3).[100] PEG-PAE-Triclosan micelles could not only eradicate subcutaneous drug-resistant *S. aureus* infection in mice but also preferentially kill cariogenic oral pathogen *S. mutans* that secrete lipases in oral biofilms.

Loading hydrophilic antibiotics

Most of the commonly used antibiotics are hydrophilic because hydrophilic ones are more easily administered *via* oral or injection pathways. However, free hydrophilic antibiotics often suffer from shortcomings such as short blood retention, poor biodistribution, poor biofilm penetration, and potential side effects. To avoid these defects, diverse drug carriers such as hydrogels[101–109] and vesicles[110] have been developed. To be more specific, the focus of this section is the polymer-based delivery systems for hydrophilic antibiotics.

Among the polymer-based delivery systems for hydrophilic antibiotics, polymeric vesicles are of great importance. Just like polymeric micelles, polymeric vesicles are also assembled from amphiphilic copolymers. Notably, the difference is that the proportion of the hydrophobic domains in the amphiphilic copolymers used to construct polymeric vesicles is greater than that of copolymers used to build polymeric micelles. Compared to vesicles made of lipids, polymeric vesicles are usually more stable against the continuous dilution in the blood. Generally, the cores of the as-prepared polymeric vesicles are hydrophilic and the intermediate layers are hydrophobic. Thus, hydrophilic antibiotics are allowed to be loaded in the cores of polymeric vesicles, and hydrophobic antibiotics can be loaded in the intermediate layers at the same time. As a consequence, a great number of antibiotics could be loaded in vesicles, such as amikacin,[111] gentamicin,[111,112] tobramycin,[113–115] vancomycin,[116,117] azithromycin,[118] metronidazole,[119] oxacillin,[120] daptomycin,[121] doxycycline,[122] and antimicrobial peptides.[123] It is worth noting that the bilayer of vesicles can fuse with the structure of bacterial cell

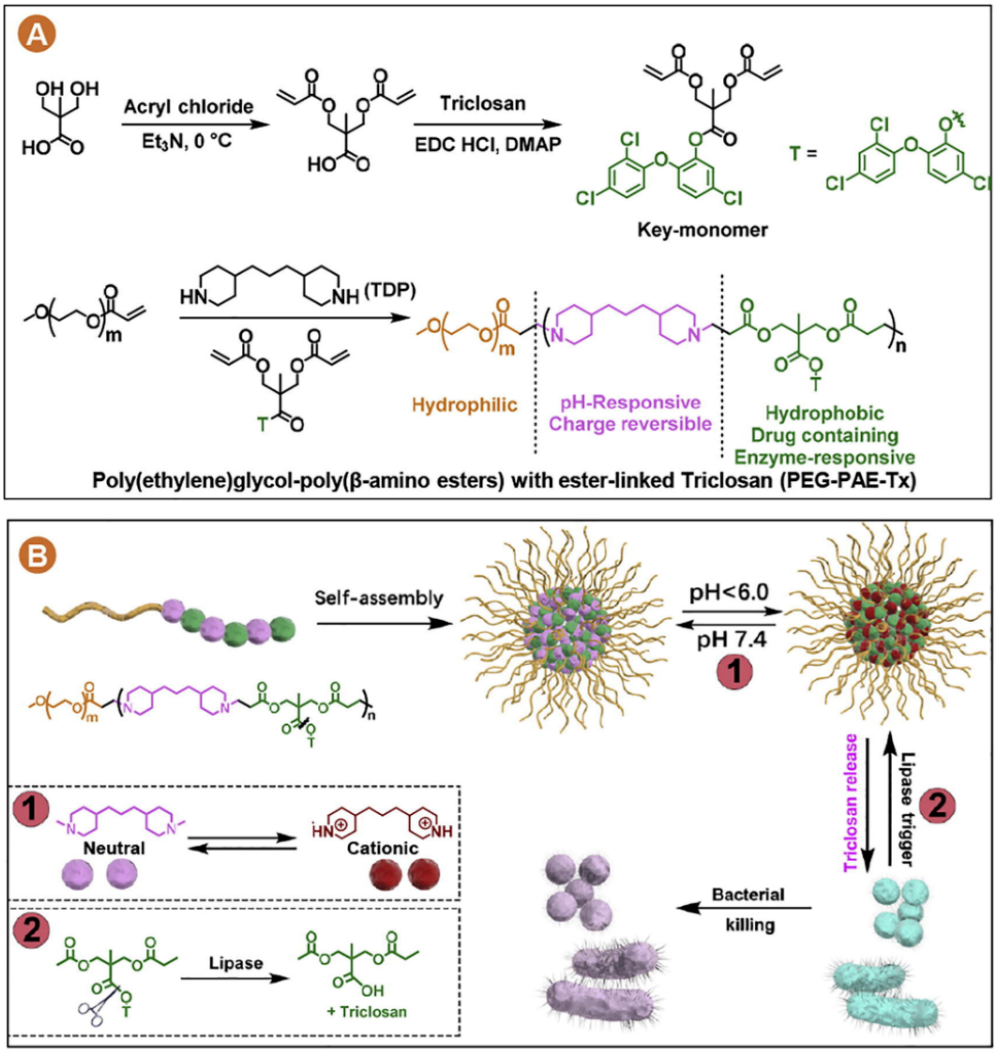

Fig. 3 Schematic illustration of (A) the synthetic route of PEG-PAE-Triclosan, (B) self-assembly, pH-adaptiveness of PEG-PAE-Triclosan micelles, and lipase-triggered Triclosan release and bacterial killing. (Reproduced with permission from Ref. [100]; Copyright (2018) Elsevier.)

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membranes, leading to plenty of antibiotics releasing once inside the biofilm.[110,124] However, different from the inhomogeneous features of bio-membranes, conventional synthetic polymer vesicles usually possess a homogeneous membrane, which significantly limited their versatility. Recently, Du *et al.* reviewed the recent advances and the future perspectives of design principles, synthesis, and biomedical applications of polymer vesicles with inhomogeneous membranes, which endow the vesicle with multi-functionality for various applications including drug delivery.[125] For example, Du *et al.* designed a multifunctional ciprofloxacin-loaded dual corona vesicle with intrinsic antibacterial activity for effective eradication of biofilm, which was made of two block copolymers, namely poly(ε-caprolactone)-*block*-poly(lysine-*stat*-phenylalanine) [PCL-*b*-P(Lys-*stat*-Phe)] and poly(ethylene oxide)-*block*-poly(ε-caprolactone) [PEO-*b*-PCL] (Fig. 4).[126] Similar to PEG, the stealthy property of PEO made vesicles repel the protein during blood circulation, and P(Lys-*stat*-Phe) enabied vesicles with positive charges, endowing them with targeting ability and bacterial membrane damaging ability.[126] After being encapsulated in vesicles, the dosage of ciprofloxacin could be reduced by 50% for the eradication of biofilms. Therefore, this work rendered an efficient approach to overcoming the biofilm barrier using polymeric vesicles.

Besides, hydrophilic antimicrobials can be conjugated in polymers and applied as a prodrug as well. For example, Ji *et al.* conjugated azithromycin on amino-ended poly(amidoamine) dendrimer (PAMAM) as a prodrug (PAMAM-AZM NPs) and subsequently assembled them with 2,3-dimethyl maleic anhydride (DA) modified poly(ethylene glycol)-*block*-polylysine (PEG-*b*-PLys) to form nanoparticles (AZM-DA NPs) through electrostatic complexation (Fig. 5).[127] At low pH in a biofilm, the amide bond between PEG-*b*-Plys and DA is hydrolyzed and the positive net charge of the Plys domain is recovered, resulting in the dissociation of AZM-DA NPs and the release of PAMAM-AZM NPs. With a small size and positive charge, PAMAM-AZM NPs can penetrate and accumulate inside biofilms, exhibiting excellent antibiofilm activity. This research is promising for the treatment of biofilm-caused chronic infections.

Antimicrobial Nanosystems

Although many antibiotics delivery systems have been investigated and great progress has been made, polymeric systems with intrinsic bactericidal activities are still urgently

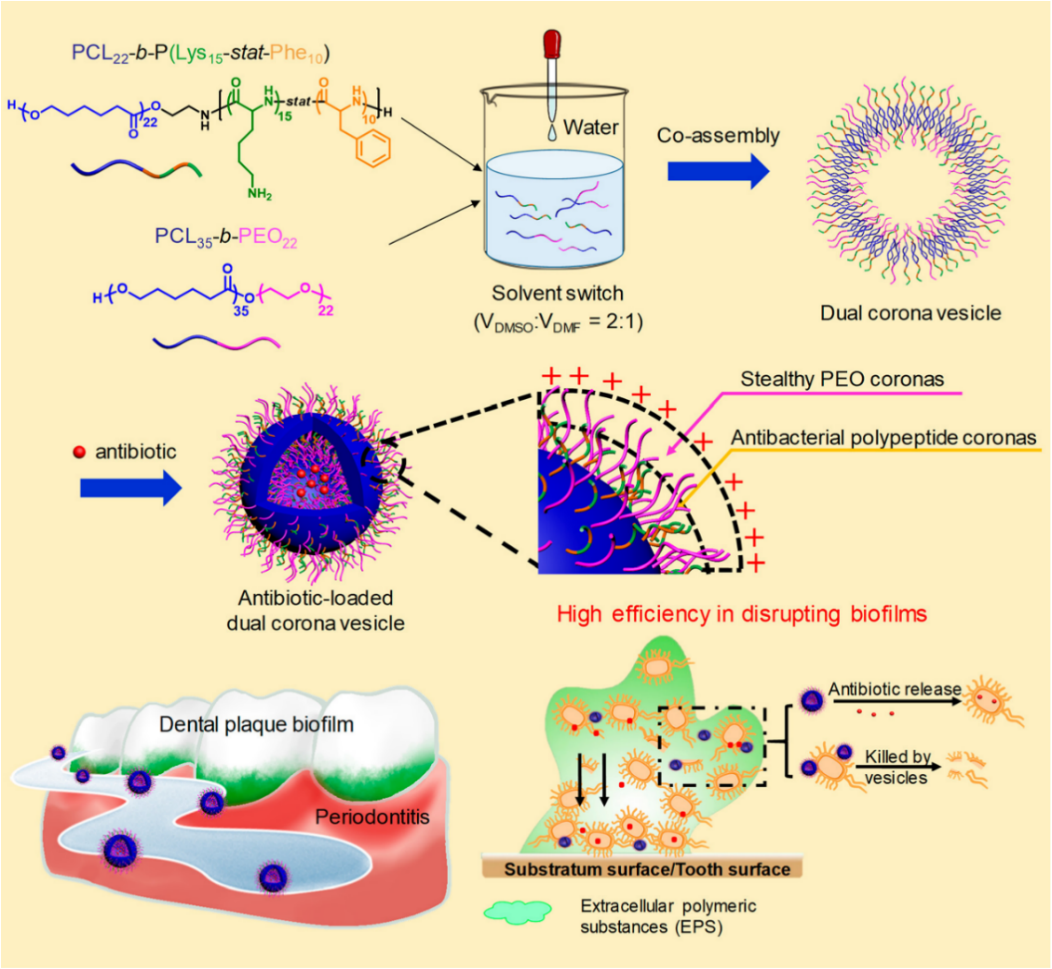

Fig. 4 Schematic illustration of the chemical structures of the copolymers used and procedure to construct the antibiotic-loaded dual corona vesicle, as well as the mechanism in treating periodontitis biofilms. (Reproduced with permission from Ref. [126]; Copyright (2019) American Chemical Society.)

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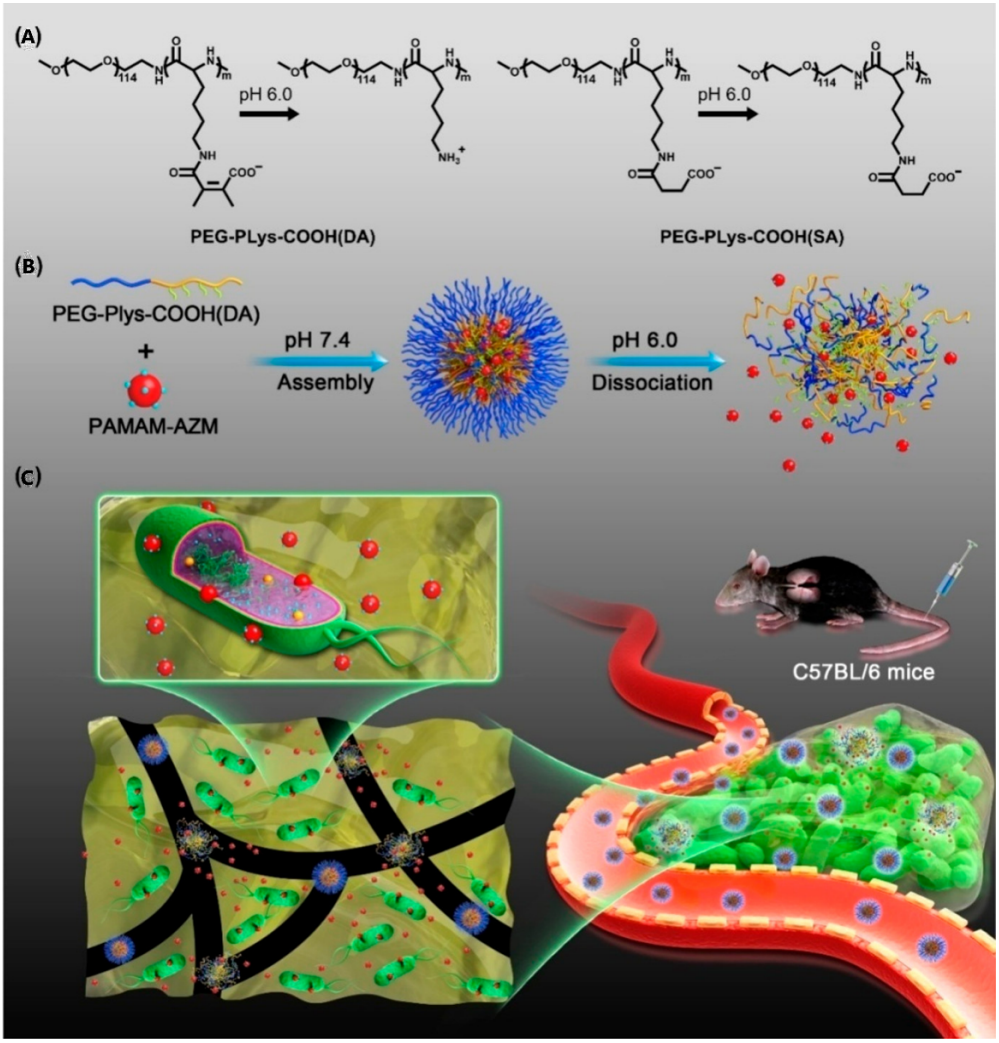

Fig. 5 Scheme illustration of (A) reaction of DA modified PEG-*b*-PLys at low pH; (B) the assembly and dissociation of AZM-DA NPs under different pH conditions; (C) the mechanisms of AZM-DA NPs in eradication biofilm infection. (Reproduced with permission from Ref. [127]; Copyright (2020) American Chemical Society.)

needed. In nature, antimicrobial peptides (AMPs) exhibit excellent antibacterial activities.[128–133] Most AMPs are amphiphilic and possess cationic and hydrophobic moieties. Besides, they often possess an *α*-helical or *β*-sheet-like tubular secondary confirmation. Once interact with bacteria, the cationic moiety attracts negatively charged bacteria, and the hydrophobic moiety inserts into the lipophilic cell membrane domain, rupturing the cell membrane of bacteria.[134] This physical damage antibacterial mechanism is less likely to develop resistance.[135] Though AMPs are promising antimicrobials, low stability, high toxicity and expensive production limit their antibacterial application. To overcome these drawbacks, synthetic polymeric AMP mimics have been developed because of their facial synthesis with the key properties of AMPs.[22–25,135,136] Basically, these AMP mimics bearing positively charged domains such as primary amines, ammoniums, guanidiniums, thiazoliums, triazoliums, and phosphoniums on either main-chains or side-chains.[137] Also, they usually possess a rigid spatial configuration that regulates their bactericidal efficacy.[138] In certain cases, the secondary structures of the synthetic AMP mimics are transitionable under the trigger of stimuli. For example, Cheng *et al.* developed series of AMPs that could realize helix-coil conformation transition for regulating the antibacterial efficacy versus the cell lysis property of the polymers.[30,139,140] Moreover, synthetic AMP polymers can assemble into antimicrobials nanoparticles, thus increasing the local concentration of AMPs. Qiao *et al.* developed the synthesis of structurally nanoengineered antimicrobial peptide polymers (SNAPPs), which were unimolecular, forming star nanoparticles.[135] These SNAPPs showed superior antibacterial activity with several different antimicrobial mechanisms. Compared to the unimolecular AMPs, these nano-antimicrobials might be more stable during blood circulation and have greater biofilm penetration ability. Together with their multivalentcy effect, these nanoscale antimicrobials usually possess enhanced antibacterial activity.

Biofilm Dispersal

In a biofilm, the EPS matrix holds the embedded bacteria together like glue and limits the penetration of antibiotics.

Therefore, dispersing the biofilm is another way to combat biofilm-related infections. In recent years, many kinds of molecular biofilm dispersants have been reported,[141–143] such as enzymes,[144–146] ROS,[147–150] nitric oxide (NO),[151] peptides,[152–155] molecules that regulate signaling pathways,[156,157] amino acids,[158] and biosurfactants.[159,160] But these molecular biofilm dispersants have disadvantages, limiting their applications. For example, DNase is easily inactivated by many factors, such as low pH and proteinases. Also, natural peptides are prone to be proteolyzed. Additionally, there were no beneficial effects of NO observed *in vivo* experiments because of the metabolic consumption.[161] The cytotoxicity of some dispersants has not been investigated. Fortunately, a combination of biofilm dispersants with nanoparticles can enhance their efficiency yet ameliorate their adverse effects.

After being loaded in polymer nanoparticles, the dispersants are protected in blood circulation,[162] and their stability is improved.[163] Also, with rational design, the loaded cargoes could be released in response to stimuli.[164–167] For example, when dispersion B was loaded with chitosan nanoparticles, the thermal stability and storage time were greatly improved.[168] Apart from encapsulation, the dispersants can be decorated on the surfaces of nanoparticles. For example, DNase I could be conjugated on the amino groups of chitosan nanoparticles.[169] Antimicrobials are often co-administered with these nano-dispersants to achieve desirable biofilm eradication efficacy. For example, ciprofloxacin was co-loaded into the DNase I-modified nanoparticles, and the simultaneous release of both DNase I and ciprofloxacin synergistically enhanced the biofilm eradication efficacy.

Besides, some polymer nanoparticles possess an intrinsic biofilm-dispersal property. Most of these biofilm-dispersal nanoparticles are cationic micelles or peptides because of their strong interactions with the negative bacteria and EPS.[170] However, the positive charge makes them easily cleared during blood circulation and has cytotoxicity to healthy cells.[171] Recently, we designed self-targeting zwitterionic MSPM (ZW-MSPM), which were self-assembled from PEG-*b*-PCL and poly(ε-caprolactone)-*block*-poly(quaternary-amino-ester) to address the above-mentioned issue.[172] Zwit-

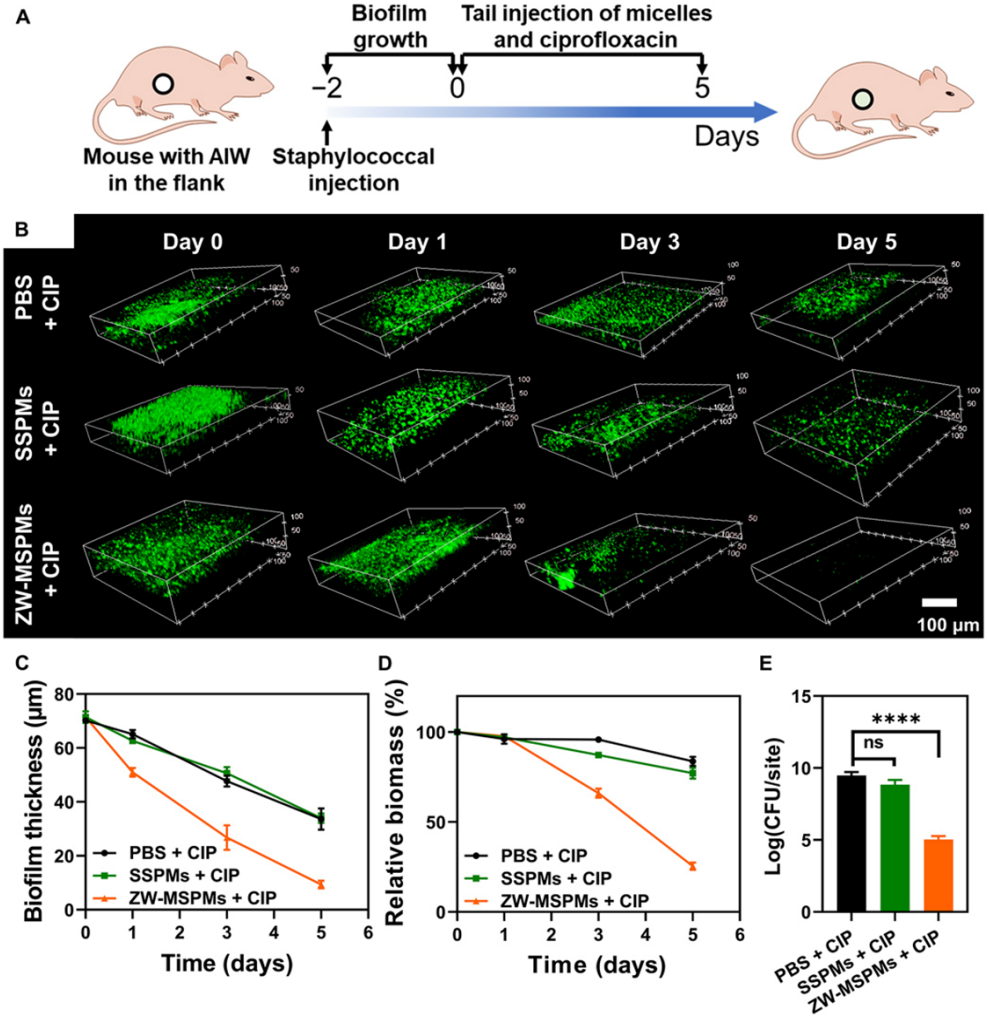

Fig. 6 Scheme illustration of (A) workflow of AIW model construction and treatment in mice. (B) 3D intravital images of biofilms during the different treatment periods. (C) The thickness of staphylococcal biofilms. (D) The biomass of staphylococcal biofilms. (E) The number of *S. aureus* CFUs after 5-day treatments. (Reproduced with permission from Ref. [172]; Copyright (2021) Science.)

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terionic micelles are negatively charged at physiological conditions (pH 7.4) but transformed to a positive charge at low pH in a bacterial biofilm. This property endows the micelles with targeting ability *in vivo*. And the positive charge facilitates the micelles to penetrate and accumulate in biofilms, and subsequently disperse the biofilm. The *in vivo* efficacy of ZW-MSPM was observed in mice by growing staphylococcal biofilm underneath an intravital abdominal imaging window (AIW) (Fig. 6).[172]

To address the issue of delivering gaseous biofilm dispersants, Ji *et al.* developed a NO delivery system for the eradication of biofilms.[173] In this work, NO was conjugated on glutathione-responsive *α*-cyclodextrin (*α*-CD) as a prodrug, and integrated into a pH-sensitive block polypeptide copolymer together with *α*-CD-chlorin e6, forming supramolecular nanocarrier. Once inside biofilms, NO was rapidly released stimulated by the overexpressed glutathione in biofilms, which could synergistically eradicate biofilm with photodynamic therapy. This strategy may offer great possibilities for the eradication of biofilm-associated infections.

CONCLUSIONS AND FUTURE PERSPECTIVES

Biofilm-associated infections are posing a great threat to global human health. The demand and requirements for new antibiotic regimens remain largely unmet. The recent developments of polymer-based nanomaterials are of great potential in addressing the above-mentioned issues. Polymer-based nanosystems have been used to prevent bacterial adhesion and subsequent biofilm formation, as well as to eradicate the mature biofilms. Although polymer-based nanosystems possess numerous advantages, in our opinion, more efforts should be made on the following prospects:

(1) Polymer synthesis and characterizations. Until now, it is still quite challenging to synthesize polymers with exact molecular weights or with a narrow distribution. Besides, the synthesized polymers often differ in molecular weights and even chemical properties from batch to batch. Most of the synthesized polymers were characterized *via* nuclear magnetic resonance spectra and gel permeation chromatography measurements, *etc*, which, to some extent, are not enough to illustrate the chemical structures and properties due to the limitation of the apparatuses used. For example, the peaks of polymers in their NMR spectra are quite broad and the signal will be low if the polymers are not completely soluble.

(2) Currently, most of the polymeric nano-assemblies are formed by the driving forces of electrostatic attraction or hydrophobic interaction, which cannot fully prevent drug leakage during storage or circulation in the blood. Some strategies like cross-linking should be applied to reinforce the stability of nano-assemblies.[174]

(3) At present, most nanomaterials elucidated their antibacterial activity on biofilms that grow for 1 or 2 days. However, in clinical, the pathogenetic biofilms are formed over a long period with multiple bacterial species. Therefore, the anti-biofilm efficacy of the polymer-based materials should be evaluated on old biofilms that are more similar to real clinical situations in the future.

(4) Moreover, bacteria can also grow in mammalian cells. Most antibiotics cannot penetrate the mammalian cell membranes to eradicate these intracellular pathogens, causing chronic infections. Hence, nanosystems capable of targeting penetrate and across infected cell membranes should be taken into consideration. For example, our group recently have reported a macrophage membrane-coated antimicrobial nanoparticle, which could selectively enter into infected macrophages and wipe out the intracellular bacteria.[175]

(5) Despite many nanosystems have improved the efficiency of antibiotics, it is still at risk of developing drug resistance. Future infection control strategies should concentrate more on non-antibiotic-containing systems, such as photodynamic therapy, photothermal therapy, and systems based on cascade reactions.[176]

BIOGRAPHY

Yong Liu obtained his PhD degree from Nankai University, Tianjin, China, in 2016 under the supervision of Prof. Linqi Shi, majoring in polymer chemistry and physics. After that, he joined the Department of Biomedical Engineering at the University Medical Center Groningen/University of Groningen, the Netherlands, to work on novel nanotechnology-based infection control strategies. In 2019, he was an associate professor at FUNSOM, Soochow University. He joined Wenzhou Institute, University of Chinese Academy of Sciences in 2021. Currently, his research interest is focused on using polymer-based materials to control the emergence of multidrug resistance in microbes.

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