Coordination Chemistry Reviews 460 (2022) 214481

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

journal homepage: www.elsevier.com/locate/ccr

Review

Tailoring supramolecular short peptide nanomaterials for antibacterial applications

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ARTICLE INFO

Article history:
Received 4 November 2021
Accepted 14 February 2022

Keywords:
Short peptides
Antibacterial
Self-assembly
Resistant bacteria
Supramolecular nanomaterials

ABSTRACT

The rise of bacterial resistance to current antibiotics poses a threat to humanity and reinforces the need for new-generation nanomaterials with antibacterial properties and biosafety. Several types of nanomaterials have been shown to hold great potential to combat pathogenic microorganisms. Self-assembly of peptides and proteins, a spontaneous and tunable process, provides a wide range of new routes to construct functional biological nanomaterials with antibacterial properties. In particular, short-peptide-based supramolecular nanomaterials have attained substantial recognition due to their ease of fabrication, favorable physicochemical properties, and structurally diverse functionalities. Here, we present an overview of the recent progress on the design of short peptides, including linear peptides, amphiphilic peptides, and cyclic peptides, for the formation of supramolecular nanostructures as antibacterial agents and their respective therapeutic modes of action. Moreover, supramolecular short peptide composites and biomineralized nanomaterials are discussed, along with their biosafety and antibacterial mechanisms. These nanomaterials hold great promise as antibiotics of the near future due to their biocompatible, biodegradable, and environmentally friendly nature.

Contents

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https://doi.org/10.1016/j.ccr.2022.214481
0010-8545/

1. Introduction

Following the discovery of penicillin, a variety of antibiotics has been developed to tackle microbial infections. However, over time, resistant strains of bacteria evolved due to the malpractice and overuse of medicines [1]. By 2050, around 10 million deaths are expected to occur annually due to the rapid emergence of antimicrobial resistance [2]. The efficacy of antibiotics is determined by their interactions with essential microbial processes such as replicating DNA, synthesis of cell membrane components, and expression of crucial proteins. However, microbes have developed the ability to alter the drug target, produce drug-metabolizing enzymes, and excrete antibiotics via efflux pumps. Hence, there is a need to introduce novel antimicrobial agents that: i) target bacteria more efficiently, ii) overcome the resistance mechanisms, iii) minimize the emergence of multidrug-resistant (MDR) pathogens, and iv) cost-effective and practical [3].

Advances in nanoscience and technology, along with the increased understanding of nano-bio interfaces, have paved the way for the development of alternative antimicrobials [4]. With their versatile physicochemical properties, nano-antimicrobials can overcome multidrug resistance via improved efficacy, controlled drug release, circulation, and targeted delivery [5]. Several synthetic nanomaterials have already been studied for their antibacterial potential, including metal, self-assembling peptides, polymer, carbon-based nanoparticles (NPs), quantum dots, and up-conversion NPs [6–9]. Interestingly, bacterial cells' membrane integrity can be disrupted via targeted attachment of nanomaterials, leading to the leakage of cytoplasmic components. Subsequent membrane penetration of NPs can disrupt the core cellular functions of bacterial cells via binding of the NPs to cellular components, including enzymes, DNA, and ribosomes. Inspired by nature, self-assembled peptide nanomaterials with potential antimicrobial properties also develop as alternatives to synthetic compounds [10]. Self-assembled peptide nanomaterials are biocompatible, chemically diverse, and have a high loading capacity with extended circulation [11]. Many reports have demonstrated the capability of short peptides to generate self-assembled nanomaterials in a controllable fashion, making them new entities for bacterial therapeutics [9,12]. Short peptides are simple in molecular design, easy to self-assemble, and their molecular arrangement in nanomaterials is understandable. There is a growing interest in the interface of self-assembly and antimicrobial activity, mostly as small organic building blocks are now preferred over the naturally occurring, complex antimicrobial peptides. The AMPs need to pass a specific threshold concentration for action, especially for the cationic AMPs, which require higher concentrations [13]. Furthermore, proteolytic enzymes can easily recognize high molecular weight peptides, while small cationic peptides can escape proteolytic degradation [14]. Most of the naturally occurring antimicrobial peptides have rather long sequences, which can compromise their application as commercial drugs due to the high cost of protein production at an industrial scale. Short AMPs represent a chemical class of promising new drugs due to their robust biomimetic mechanisms of action, their relative ease of synthesis, and low production cost when compared to biologicals. Remarkably, the mechanism of antibacterial activity reclined on the membrane disruption, interference in gene regulation, oxidative stress, and phototherapy [15–18]. The nano-bio materials have also been used for the treatment of infections caused by bacterial communities (biofilms) and free-floating (planktonic) bacteria [19].

This review highlights the physical and chemical properties and molecular design strategies of short peptide nanomaterials for therapeutic action against different bacterial pathogens. These physical and chemical properties are vital pillars in designing supramolecular nanomaterials, while biological and physiochemical properties help to understand the antibacterial mode of action. These properties provide information about structure–function relationships of the proposed materials and lead the researcher from design to applications. Intracellular or extracellular targeting and membrane disruption are the primary mechanisms of the antibacterial therapeutic mechanism of the short peptide nanomaterials. Some review articles on self-assembling peptides have been published [9], which have reported for various aspects and do not cover the synthetic procedures of short peptides-based nanomaterials and the antibacterial application. Other than these, some review articles cover the different materials, for example, carbon nanotubes and polymeric nanomaterials [5,20]. Based on the current need of antibiotics, we highlight the short peptide-based nanomaterials for antibacterial applications. First, the physicochemical properties of short peptides are discussed in detail, and the second antibacterial action mechanism is elaborated. In later sections, we cover the molecular design strategies of supramolecular nanomaterials synthesized from the short peptide building

blocks of linear peptides (di-, tri-, and tetra-), cyclic peptides, and amphiphilic peptides. We discuss the nanomaterials formed from the short peptide building blocks conjugated with therapeutic drugs and biomimetic anchoring functional groups to develop tailored functional peptide nanomaterials, which have shown more antibacterial activity as compared to their respective constitutive components. Some metals for example silver and gold have anti-inflammatory properties, thus to make the short peptide nanomaterials more efficient against the bacteria, could be used together with the short peptide's nanomaterials. Therefore, the molecular design strategies of the co-assembled composites nanomaterials and silver and gold incorporated short peptide supramolecular nanomaterials are also discussed based on the application perspective against bacterial strains. Lastly, we underline the obstacles for the current nanomaterials, along with the main challenges and perspectives for designing next-generation short peptide supramolecular nanomaterials.

2. Physicochemical features of short peptide supramolecular nanomaterials

In the last decade, natural antimicrobial peptides (AMPs) have been extensively studied, but due to the development of bacterial drug resistance, the clinical application of AMPs is facing many problems [21]. The artificially designed supramolecular short peptide nanomaterials have shown promising physicochemical properties in materials, and these unique properties further endow peptide nanomaterials with excellent antibacterial activity [22]. This section introduces peptide supramolecular nanomaterials' unique physical and chemical properties that play an essential role in antibacterial effects.

2.1. Peptide sequences

Peptides are composed of twenty basic amino acids and their derivatives. By rationally designing amino acids, the electronegativity, polarity, and chirality of the peptide chain can be adjusted, all of which affect the antibacterial activity.

For example, the peptide chain has a net positive charge due to lysine, arginine, and histidine residues [23]. Most of the antibacterial peptides discovered so far are also cationic peptides. In addition, amino acids can be divided into polar and non-polar ones. Polar amino acids are hydrophilic, while non-polar amino acids are hydrophobic [24]. Therefore, peptides can be designed to be amphiphilic and have both hydrophilic and hydrophobic structures. In terms of chirality, D-amino acids are not degraded very easily by bacterial proteases [25]. Kolodkin-Gal et al. also reported that the production of D-amino acids by Bacillus subtilis is responsible for preventing and breaking down bacterial biofilm [26]. This aspect is also elucidated by a mixture of D-leucine, D-methionine, D-tyrosine, and D-tryptophan. These D-amino acids are responsible for the disruption of amyloid fibers involved in keeping the biofilm intact. The three aspects mentioned above are essential for their antibacterial activity. Besides, natural AMPs can also be optimized through the programming of peptide sequences, including the substitution of D- or non-natural amino acids or truncation of peptide chains to improve antibacterial activity [21].

2.2. Self-assembly and secondary structure

As mentioned above, the chirality, polarity, and electrical properties of the peptide chain and the number of amino acids all modulate the physicochemical properties of peptides. These factors play a decisive role in the self-assembly of short peptides and enhance the interaction of peptides to help self-assembly [27-29].

The self-assembly of peptides has been regarded as an effective way to prepare antibacterial nanomaterials with enhanced antibacterial, improved stability, and reduced cytotoxicity [30]. The self-assembly process is driven by non-covalent interactions comprised of van der Waals forces, electrostatic interactions, hydrophobic interactions, hydrogen bonding, and π–π stacking (aromatic) interactions [31]. Generally, when the peptide sequence exceeds 12 amino acids, the secondary structure (*e.g.* α-helix, β-sheet, turns, and random coil) formed by self-assembly can be observed [24]. Simultaneously, α-helices, β-sheets can be exploited to drive the self-assembly process.

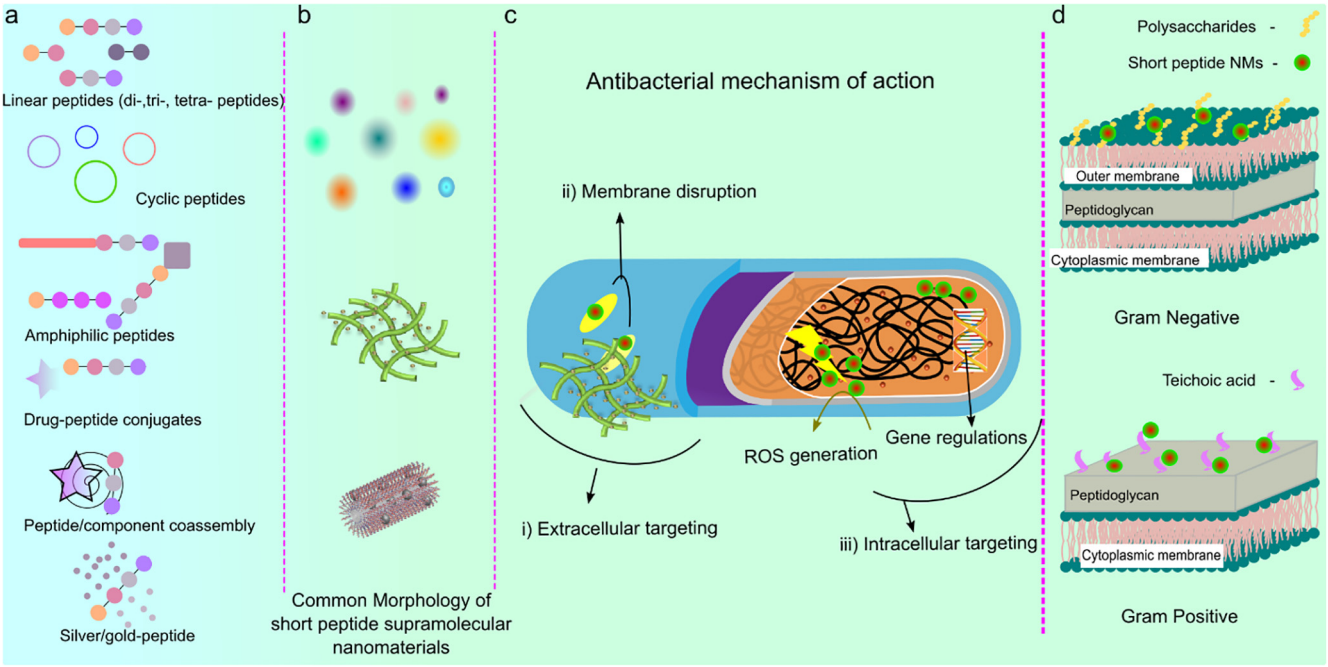
The secondary structure affects the antibacterial activity and cytotoxicity of peptides [32]. For example, many studies have shown that the α-helical structure has a strong relationship with antibacterial activity [33]. Besides this, the cytotoxicity of peptide nanomaterial can be enhanced by introducing the D- amino acids in the sequence of designed peptide building blocks [34]. Not only the D-amino acids contribute to cytotoxicity but also therapeutic drugs, metal ions, and aromatic functional groups also possibly enhance cytotoxicity, which plays a critical role in antibacterial activities [35–37]. However, these cytotoxicity enhanced biomaterials are biocompatible to mammalian cells. In addition, the secondary structure plays an important role in the interaction with the bacterial membrane, and the selectivity to bacteria can be improved by designing conformational switchable self-assembled peptide nanomaterials [32].

2.3. Formation of ordered nanostructures

The nature and structure of peptides provide the flexibility to fabricate various nanomaterials in a controlled fashion. The ordered supramolecular structure of self-assembling peptides can be precisely controlled by encoding peptide sequences to obtain the morphology of spheres, vesicles, micelles, nanofibers, and nanotube structures [24,38]. The ordered nanostructures can be achieved with different bottom-up mechanisms including hierarchical crystallization and traditional Ostwald ripening, where the kinetics and thermodynamics of peptide assembly play crucial roles [39-42]. This organization has resulted from a multitude of non-covalent interactions and could have the potential to play a role in antibacterial activity. The most important aspect of supramolecular peptide nanomaterials is that they are mostly formed in water and with a minute quantity of organic solvent and are often coined as peptide colloidal nanomaterials[43]. This colloidal organization of peptides into nanomaterials as prodrugs makes them more promising candidates especially for biomedical applications including the antibacterial one [43,44].

Short peptides are self-assembled into various nanostructures and have shown excellent antibacterial properties. The nanostructured short antibacterial peptides are also endowed with additional properties, such as nanospheres that encapsulate and deliver drugs and a high aspect ratio of nanofibers and nanotubes that promote the destruction of bacterial morphology [24,45]. In addition, nanofibrous and nanotube structures can reticulate the aqueous media into hydrogels; this kind of antimicrobial peptide hydrogels has also attracted more and more attention in the field of antibacterial. Furthermore, the hydrogel surface exhibited inherent broad-spectrum antibacterial activity when its surface engaged bacteria because the surface of hydrogel destroyed the outer and inner membranes of bacteria [46]. Moreover, with the formulations of 3D peptide hydrogel nanostructures formed as *in-situ* in the targeted region, they are very beneficial for local antibacterial treatment (such as wound antibacterial).

In general, we still need to combine antimicrobial peptide sequence design, secondary structure, and ordered nanostructure



Scheme 1. Illustration of the classification of short peptide-based nanomaterials and mode of action. a) short peptides as linear peptides, cyclic peptides, amphiphilic peptides, drug peptides conjugates, co-assembled peptide composites, and metals(silver/gold) peptides nanomaterials, b) most commonly produced morphology of the nanomaterials from short peptides used in antibacterial studies, c) possible mode of antibacterial action of these nanomaterials, d) interaction sites on the cell wall of the bacteria.

to design a series of intelligent antimicrobial peptide nanomaterials with self-assembling capabilities.

2.4. Drug delivery

The therapeutic efficiency of antibacterial agents/antibiotics can be increased by using the drug carrier, as these transport them to the site of infections [47]. Furthermore, as we mentioned, short peptides are simple in structure, programmable in sequence, and easy to self-assemble; therefore, they have attained a lot of attention in drug delivery [45,48].

Short peptides can self-assemble to form hydrogels, which are excellent carriers for drug delivery, and can improve antibacterial properties through synergistic effects with drugs. The self-assembled hydrogel can not only deliver different components-drugs but also control the drug release process. The formed hydrogel can provide various antibacterial components, including drugs, ROS generators, or silver ions. For example, the designed octapeptide IKFQFHFD can form a dynamic supramolecular hydrogel nanofiber network under the adjustment of pH, and load drug cypate and proline which are photothermal agent and procollagen commpnent respectively [49]. This method uses a synergistic strategy of antibacterial hydrogel, photothermal therapy, and proline to eradicate biofilm and promote the healing of chronic wounds.

Using the drug loading strategy, it is expected that in the future, a variety of synergistic antibacterial effects will be exerted based on antibacterial peptides to enhance the effect of antibacterial and anti-infection.

3. The mechanism of action of antibacterial activity

Short peptide-based nanomaterials have an understandable mechanism of their formation because of the simplicity in the structure–function relationship at the molecular level. We classify the antibacterial mechanisms according to the different ways of action of peptide nanofibers on the bacterial structure from the outside to the inside: i) Bacteria extracellular targeting. ii) Membrane damage and disruption. iii) Intracellular targeting. (Scheme 1)

3.1. Bacterial extracellular targeting

When peptide nanomaterials interact with bacteria, they first reach the surrounding microenvironment of the bacteria and encounter cell wall components as shown in scheme 1 d. This makes targeting extracellular components and encapsulating and capturing the entire bacteria become a kind of antibacterial mechanism.

3.1.1. AMPs inhibit the synthesis of extracellular biopolymer

Bacterial extracellular polymers, including peptidoglycan (PGN, in all bacteria) and lipopolysaccharide (LPS, in Gram-negative bacteria) are the main components of the bacterial outer membrane, which can cause an immune response [50]. Unlike most antibiotics, a class of AMPs bind to PGN precursors (such as lipid II) and interfere with the further enzymatic reaction, thereby inhibiting the synthesis of PGN. One of the representative examples is nisin, which can specifically bind to lipid II and interfere with the physiological process of bacteria mainly by inhibiting the PGN mechanism [51]. Other examples include branched tricyclic glycopeptide vancomycin and families of cyclic lipo(glyco)peptides and lipo-glyco-depsi peptides [51].

3.1.2. Self-assembled peptides trap bacteria

Self-assembled peptide hydrogels have an extracellular matrix (ECM) like nanofiber network structure, and researchers have done a lot of studies on using self-assembling peptide building blocks to engineer supramolecular structures which mimic the ECM [52]. Extracellular peptide self-assembly, when forming nanofibers, can lead to bacteria entrapment and prevent cell mobility [53]. For example, the natural human α-defensin 6 (HD6) can form high-order oligomers through self-assembly, thereby trapping bac-

teria and preventing host cell invasion to maintain intestinal homeostasis [54].

Synthetic short peptides can also be designed as ECM mimicking networks, acting as a trap outside the bacteria, and self-assembled into nanofibers on the surface in situ to trap and wrap the bacteria, which mimics the antibacterial process of innate immunity. This antibacterial mechanism effectively inhibits bacterial infections without killing the bacteria. Many studies have recently focused on the novel designs of self-assembled short peptide nanostructures that mimic antibacterial neutrophil extracellular traps (NETs), which we will specifically mention in the design of short peptide materials [55,56].

3.2. Membrane damage and disruption

Membrane destruction is the primary way of killing bacteria and is one of the preferred mechanisms for developing new drugs because it is unlikely to cause drug resistance. For these reasons, the interaction between AMPs and microbial lipid membranes has always been the focus of in-depth research.

3.2.1. Membrane destruction of cationic peptides

Antibacterial peptides or host defense peptides are usually cationic amphiphilic molecules, which disrupt the integrity of bacterial surfaces upon contact [57]. Self-assembled cationic peptides rich in lysine and arginine have polycationic surfaces, and the density of anionic groups in bacterial cell membranes is higher than that in mammalian cells, so the cationic peptides experience more significant electrostatic attraction to the bacterial pathogens [58,59]. The cationic surface shows antibacterial activity against both Gram-positive and negative bacteria by destroying the bacterial cell membrane. Several main modes of action have been recognized for bacterial membrane disruption by peptides, including carpet, barrel-stave, toroidal-pore models, and aggregate mechanism [60].

3.2.2. Secondary structure affects membrane activity

Secondary structure is the essential element of protein-membrane interaction, which also applies to antibacterial peptides. The damage of antibacterial peptides to membranes depends heavily on their secondary structures, especially for those cells that act by barrel-stave and toroidal-pore model [32].

Many studies have found that folding into α-helix structures helps antibacterial peptides insert into cell membranes. At the same time, helix fraying leads to dysfunction [61]. The α-helical antibacterial peptides attach to the negatively charged bacterial membrane through electrostatic interaction and insert their hydrophobic domain into bacterial membranes, causing the membrane to deform [32]. In addition to helical structures, a few β-sheet peptides, such as β-defensin analog and their designed synthetic cyclic derivatives, also affect the membrane activity of antibacterial peptides, but there are few studies [62]. It is worth noting that the selectivity of antibacterial peptides can also be improved by regulating their secondary structures, which is very beneficial for applications [32].

3.2.3. Membrane disruption upon peptide self-assembly

All AMPs cannot self-assemble to form the nanomaterial, the self-assembly of peptides can increase or even impart antibacterial activity to peptides. When self-assembly occurs, the charge and secondary structure of antibacterial peptides may change, which affects the interaction between antibacterial peptides and cell membrane [63,64]. Supramolecular nanomaterials also form the pore in the membrane of bacteria which play a critical role in membrane disruption [65]. Recently, a fluorescent probe-based strategy is also used to kill the bacteria where the probe targets the cell wall of the bacteria [66,67], which may be helpful for design of peptide-based nanomaterials with bacteria-targeting and fluorescent-imaging capabilities.

Most of these types of self-assembled peptides are amphiphilic cationic peptides. Among them, the amphiphilic design of the peptide is responsible for providing self-assembly properties, while the hydrophobic and cationic charge ensure the interaction with phospholipids and membrane insertion, thereby producing antibacterial [53]. In addition, several investigations have utilized the self-assembled nanostructure (such as nanotubes and nanofibers) of peptides to disrupt bacteria's cell membrane to cause the death of bacteria [18,68].

In general, many studies have proved that self-assembly affects the antibacterial activity of peptides. However, the understanding of the specific mechanism of the direct interaction between self-assembly and antibacterial activity still needs more research to clarify.

3.3. Intracellular function inhibition

When peptides enter bacteria, they can inhibit specific key intracellular processes, such as nucleic acid and protein synthesis, or cause cell death through intracellular self-assembly. These are other mechanisms of antibacterial peptides.

3.3.1. Inhibition of intracellular nucleotide and protein synthesis

In addition to destroying membranes, antibacterial peptides can also perform their antibacterial functions by being internalized. Some AMPs (such as buforin II, indolicidin, and microcin B17) can traverse bacterial cell membranes and block intracellular components [50]. For example, the antimicrobial peptide buforin II can traverse cell membranes and inhibit cell function by binding to DNA and RNA of cells, leading to rapid cell death [69]. Proline-rich antimicrobial peptides (Pr-AMP) inhibit protein synthesis by targeting the bacterial ribosomal exit tunnel to achieve antibacterial activity [70,71].

3.3.2. Intracellular aggregation of peptide assemblies

Several studies have reported the rational design of short peptide sequences that self-assemble into toxic aggregates in bacterial cells. For example, Xu et al. smartly designed a tripeptide derivative that enters the bacteria through a diffusion process and then dephosphorylates to self-assembles into toxic nanofibers. This intracellular assembled peptide antibiotic is bacteriostatic [72]. In addition, another study used bacterial genome screening to identify aggregation-prone sequences peptide sequences [73]. The obtained peptides accumulated in the cell and caused bacterial cell death [73].

So far, few studies have designed synthetic peptides for intracellular mechanisms, but it provides ideas for the future development of antimicrobial peptides with new modes of action. However, peptide carriers also have limitations, which may prevent some carriers from being degraded. In the future, more comprehensive development of peptide carriers is needed to carry "cargo" more perfectly and controllably.

Besides, it is possible to induce sequence-specific modifications in peptides at the molecular level, and further functionalize the nanostructures via the incorporation of antibodies, enzymes, and fluorescent compounds [74,75]. A variety of AMPs including dermaspetin S9, protegrin-1, and human α-defensin 6 can self-assemble to form amyloid-like nanostructures to regulate immune systems [76-78].

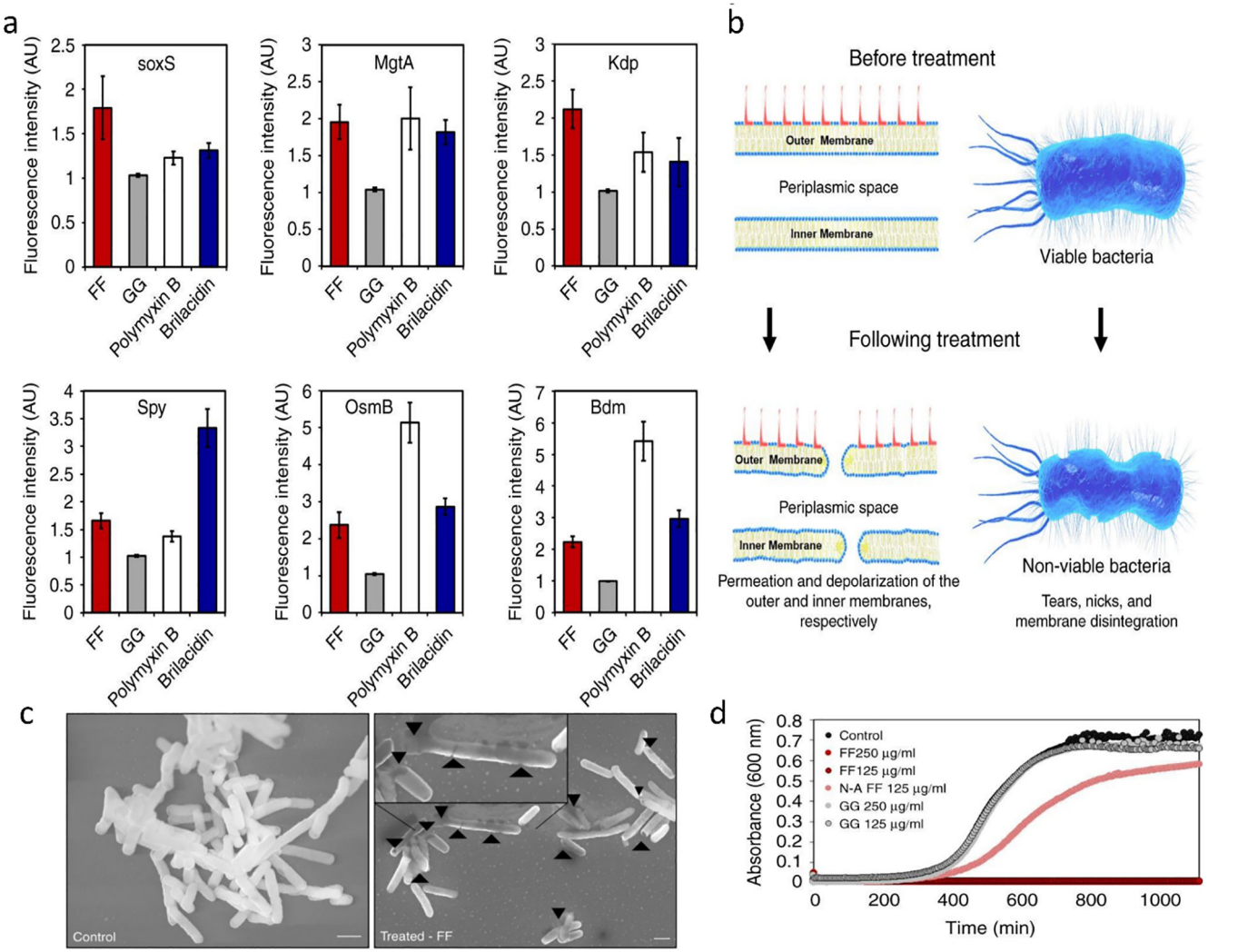


Fig. 1. The antibacterial mechanism of diphenylalanine nanostructures, a) upregulation of cellular stress-related genes after treatment with diphenylalanine nanostructures, b) proposed antibacterial mechanism diphenylalanine nanostructures c) evaluation of the effect of the diphenylalanine nanostructures on bacterial morphology. The scale bar is 1 μm. d) kinetics of the inhibition of bacterial growth. Reproduced with permission from reference [18] Copyright 2017, Springer Nature.

4. Molecular design of antimicrobial short peptide supramolecular nanomaterials

Short peptides are composed of amino acid residues linked via peptide bonds and are able to form self-assembled supramolecular nanomaterials. This section is classified into the short peptide-based nanomaterials on their structural bases, such as dipeptides and cyclic peptides, which have antibacterial activities.

4.1. Linear peptides-based nanomaterials

Linear peptides nanomaterials have been used for various biomedical applications and have the simplest model of self-assembling peptide-based antimicrobial materials. Linear peptides are di-, tri-, tetra-, pentapeptides depending on the number of amino acid residues in the peptide design. Interestingly, the dipeptide diphenylalanine (FF) has received tremendous attention because of its aromaticity, hydrophilic/hydrophobic balance, which plays a decisive role in creating self-assembled nanomaterials [79]. However, dipeptides FF have also shown antibacterial activity, and we believe that other linear peptides could also have the same antibacterial properties. Based on the simplicity of diphenylalanine, we are discussing FF nanotubes for antibacterial applications. Schnaider et al. reported the diphenylalanine nano-assemblies as potential antibacterial agents [18]. Several different morphologies of FF nanomaterials can be formed under different assembly conditions and can be used for nucleotide delivery because of their strong interactions with nucleotides [80]. Therefore, these diphenylalanine nano-assemblies effectively inhibit the growth of bacteria, upregulated stress response regulons, and disrupt the morphology. Furthermore, the peptide assemblies were integrated into tissue scaffolds for the demonstration of membrane-specific interactions. Interestingly, several bacterial species developed modifications in the molecules of their cell membranes. At the same time, they also executed counter-measures like electrostatic repulsion and reduced binding. Due to the hydrophobic and non-cationic nature of diphenylalanine nano-assemblies, bacteria's probability of developing resistance was less than with short cationic peptides. The upregulation was observed in the stress-related genes as shown in Fig. 1.

In the context of antimicrobial resistance, biofilms also present a significant issue to healthcare. Biofilms are made up of surface-attached microbial cells covered by a protective extracellular polysaccharide matrix [19]. Porter et al. demonstrated the biofilm eradication and antibacterial activity of self-assembled peptide nanotubes composed of a diphenylalanine motif [81]. The antibac-

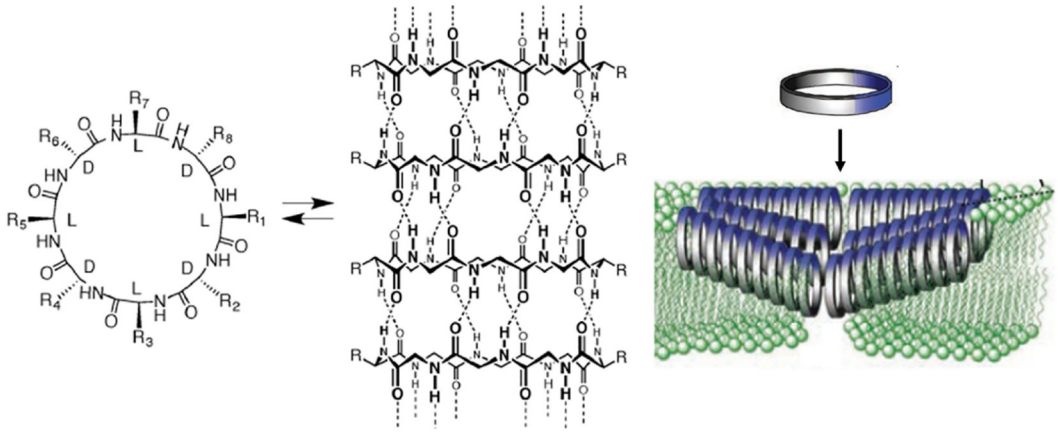


Fig. 2. The chemical structure of cyclic D, L-α-peptide consists of eight amino acid residues, which self-assembled to form tubular nanostructure through hydrogen bonding in the backbone of the cyclic peptide (left panel). Ring-shaped conformation of cyclic D, L-α-peptide nanotubes show the modes of membrane permeation (right panel). Reproduced with permission from reference [84] Copyright 2020, Elsevier.

terial selectivity and toxicity of peptide nanotube to the mammalian cells changed upon modifying the terminal functional groups. Moreover, after 24 h of exposure at the concentration of 10 mg $mL^{-1,}$ the peptide nanotubes cleared the complete biofilm of *Staphylococcus aureus*.

4.2. Cyclic peptides nanostructures

Cyclic peptides can be formed from two to several amino acids in a circular shape in their polypeptide backbone via a typical peptide bond. As we discuss in the physicochemical features of short peptide nanomaterials (section 2.1), the amino acids in peptide sequence and conformation play a significant role in antibacterial activity. Usually, cyclic peptides are formed from the combination of the D- and L- forms of amino acids, and the D- form is considered unnatural. D, L-α-peptides also limited the temporal acquirement of drug resistance by bacteria based on the unnatural structure. Therefore, we just highlighted one example of the cyclic peptides, which have been used as an antibacterial agent in their solution form, not in a self-assembled structure. Igarashi et al. discovered cyclic peptide pargamicin A while screening potential antibiotics against *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis/faecium* [82].

Contrary to the cyclic peptide used as antibacterial agents in solutions, the self-assembled cyclic peptide nanotubes have shown a tremendous effect against the bacterial strain because of their intact arrangement enhancing cellular penetration. The cyclic peptides with D and L residues at alternative positions in the backbone sequence can effectively trigger the assembly process [83]. Therefore, in a pioneering study, Fernandez-Lopez reported antimicrobial activity of six- and eight- residual cyclic D, L-α-peptides, which formed flat ring-like structures and stacked into hollow tubes of the bacterial membrane [34]. The cyclic D, L-α-peptides were shown to be highly effective against methicillin-resistant *Staphylococcus aureus*. They monitored the D, L-α peptide-mediated depolarization of intact bacteria incorporating a dye in *Staphylococcus aureus* membranes. The fast antibacterial activity of cyclic peptide nanomaterials and their ability to target the integrity of membranes rather indicates that it is hard for bacteria to develop resistance. To confirm this hypothesis, Barbara et al. carried out the study to investigate the self-assembled nanotubes (left panel in Fig. 2) with the lipid bilayers, a biomimetic membrane of a bacterial cell, which shows the strong electrostatic interactions with membrane and ultimately cause a disruption of the membrane (right panel in Fig. 2) [84]. This disruption is also dependent on the charges present on the membrane and cyclic peptide nanotubes.

4.3. Amphiphilic short peptide-based nanomaterials

Amphiphilic short peptides have received considerable attention to design supramolecular peptide nanomaterials from the desired perspective of applications. Amphiphilic peptides are also referred to as surfactant-like peptides and they can have diverse physical and chemical properties, which have shown the potential role in the assembly process and different applications [85]. With a hydrophobic tail and hydrophilic head, short amphiphilic peptides can form the self-assembled nanostructures in aqueous solutions analogous to surfactants [86]. This section provides the physical and chemical properties of nanomaterials of short peptides, which are chemically modified with functional groups of alkyl chains, cholesterol moieties, and any other biological motifs.

4.3.1. Amphiphilic short peptides

This section considered the short peptide amphiphiles with hydrophilic and hydrophobic parts made of amino acids. Chen et al. studied the structure–function relationship of short amphiphilic peptides for their tendency to form nanostructures and the antibacterial activity as revealed in Fig. 3. [16] The structure–function relationship increased with increasing the length of the hydrophobic tail, which increases the membrane disruption ability. The ease of synthesis and structural simplicity of the short amphiphilic peptides can offer technological advantages in purification and mass production.

Gong et al. reported the self-assembly of amphiphilic peptide Ac-VVVVVVKKK-NH_2 (V_6K_3) to form the nanoparticles, hydrophobic tail inside the core hydrophilic part is exposed towards the solvent [87]. The enzyme, plasma amine oxidase (PAO), induces the transformation in morphology from nanoparticles to nanofibers; because of the least polarity, nanoparticles are converted to nanofibers. This transformation in morphology from nanoparticles to nanofibers plays a significant role in enhancing the antibacterial activity of V_6K_3 as presented in Fig. 3f.

4.3.2. Alkyl chain modified peptides

Recently, the chemistry of short peptide amphiphiles has been tuned with bioactive epitopes, which can form nanofibrous structures and target specific molecules. Beter et al. utilized short cationic self-assembled peptide nanofibers for potential antibacterial activity [88]. Compared to soluble peptide solution, self-

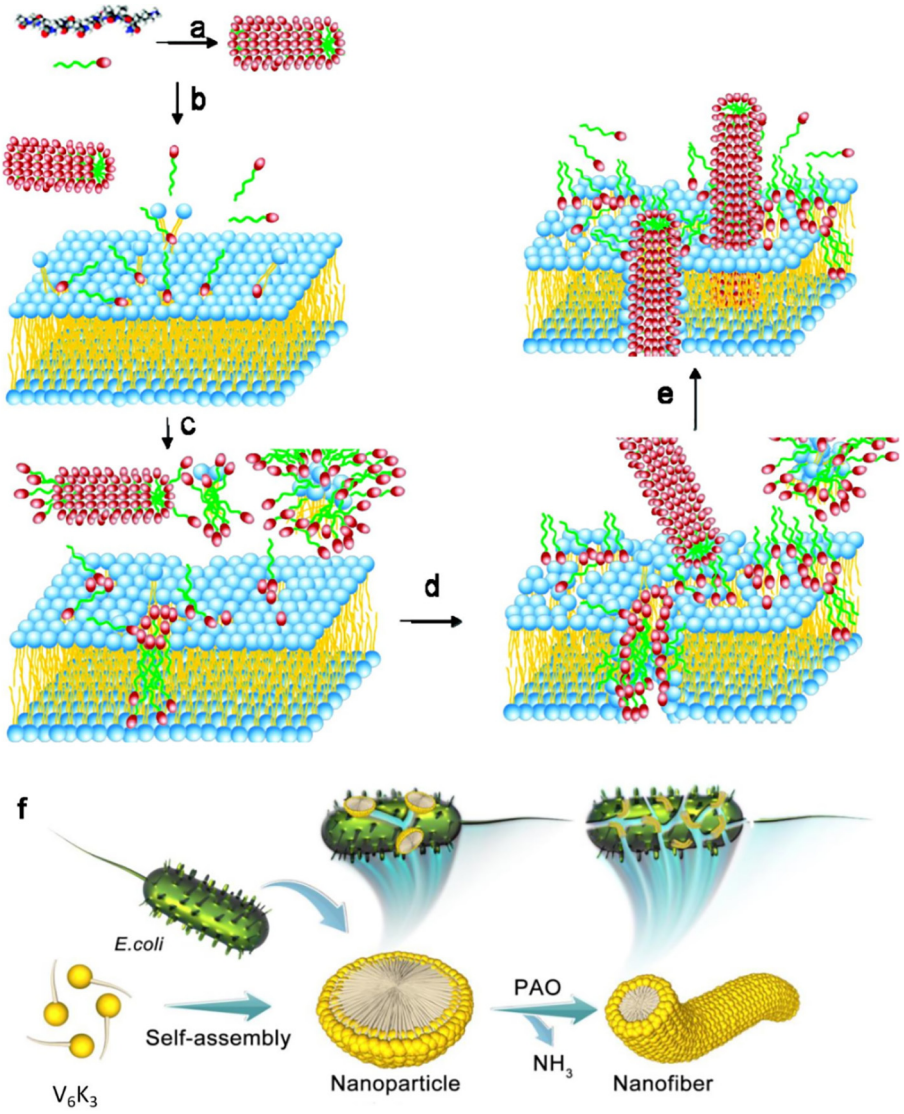


Fig. 3. Schematic illustrations of actions of A_9K leading toward bacterial membrane permeation and disruption. a) A_9K molecules self-assemble into nanorods (red) with the positive charges outside the rod. b) A_9K molecules flap onto the outer membrane surface through charge affinity and may be inserted in the membrane through a hydrophobic effect. c) They can then flip to enter into the membrane's inner leaf and make a "through barrel" or micelles to cause leakage or lysis. d) Nanorods might associate with the cell membrane surface directly through charge interaction. e) become inserted subsequently due to different effects, including electrostatic and hydrophobic interactions. Reproduced with permission from reference [16] Copyright 2010, American Chemical Society, f) Self-assembly of short amphiphilic peptide V_6K_3 into nanoparticles and transformation into nanofiber because of the enzymatic effect. Reproduced with permission from reference [87]. Copyright 2020, American Chemical Society. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

assembled peptide nanofibers demonstrated more antibacterial activity, even with identical amino acid sequences. The study validated the presentation of bioactive epitopes plays a vital role in the design of next-generation amphiphilic short peptides for antibacterial activity. Interestingly, the accumulation of bacteria was much higher on the self-assembled peptide nanofibers, leading to enhanced bacterial membrane disruption. Recently, supramolecular peptide-based hydrogels have emerged as potential antimicrobial agents owing to their bio-functionality [17,89]. Nandi et al. designed a series of synthetic peptide amphiphiles (general chemical formula $[H_2N–(CH_2)_nCONH\text{-}Phe\text{-}CONHC_{12}]$ (n = 1–5, C_{12} = dodecyl amine) without lysine or arginine residues and determined their potential antibacterial activity against *Staphylococcus aureus, Bacillus subtilis and Escherichia coli* [90]. The selected peptide amphiphiles demonstrated non-cytotoxic nature in dose-dependent cell-viability studies. Furthermore, the amphiphilic peptides have shown resistance to enzyme proteinase K and chymotrypsin because of their hydrophobic nature of the long alkyl or aromatic head groups.

4.3.3. Cholesterol head modified peptides

The functional groups with specific biological features play a decisive role in designing various nanomaterials for antibacterial activity when introduced in short peptides. The cell-penetrating minimal peptide sequence YGRKKRRQRRR (TAT) has the potential for membrane translocation due to its biological origin, derived from the TAT protein of the human immunodeficiency type 1 virus [91,92]. Their cellular uptake could also be enhanced by conjugating it to molecules carrying genetic information (RNA) and proteins [93,94]. A new building block ($CholG_3Arg_6TAT$) was designed with hydrophilic (TAT) and additional cationic amino acids (Arg_6) as a cationic part, as both play a role in cell adhesion and translocation.

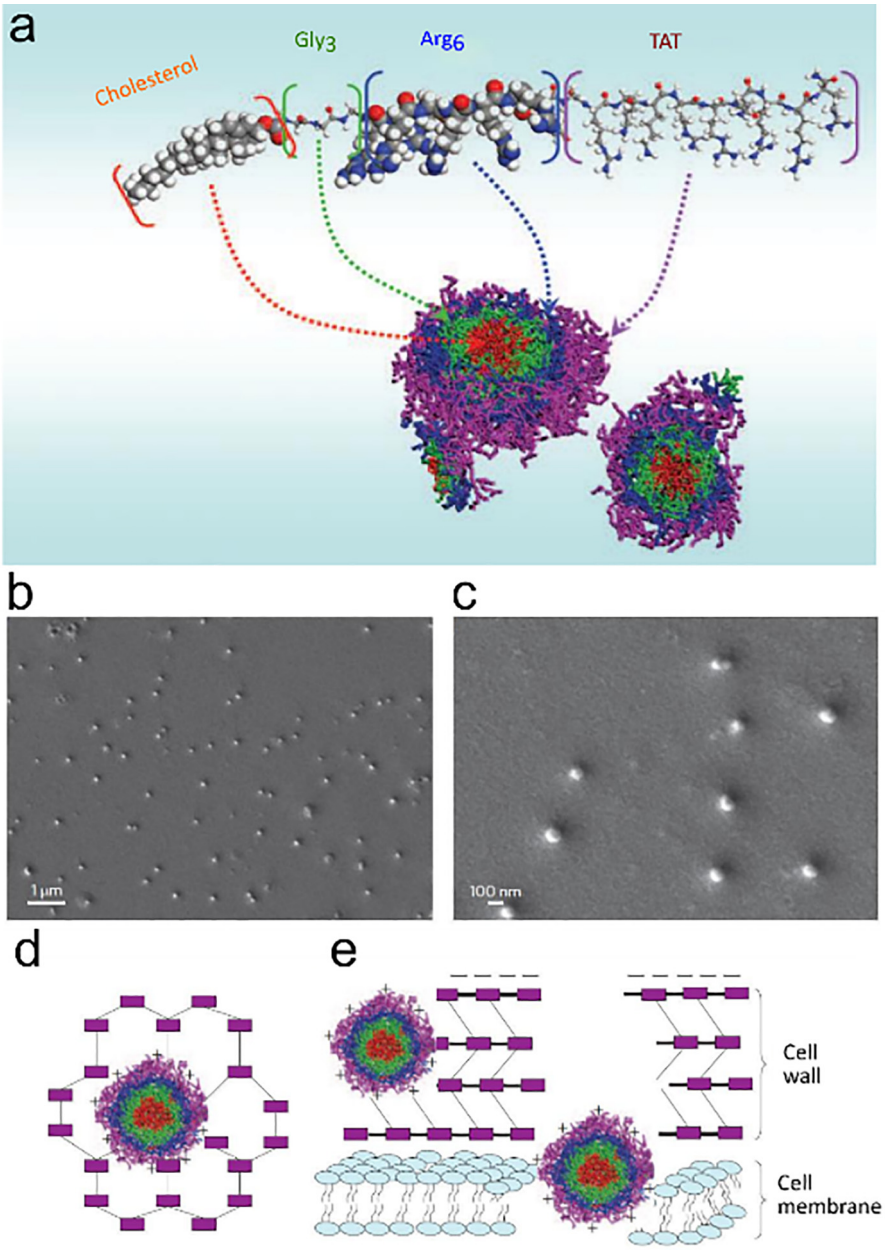


Fig. 4. Illustration of design strategy, characterization, antibacterial mechanism, and activity. a) Molecular representation of components involved in the synthesis of building blocks and self-assembled micelles. b, c) Scanning electron micrographs of nanoparticles at different scales bars. d) Top view for the electrostatic binding of nanoparticles with the cell wall. e) A cross-sectional view of nanoparticles interacting with the cell wall and cell membrane. Reproduced with permission from reference [95]. Copyright 2009, Springer Nature.

The cholesterol (Chol) in the design is a hydrophobic part that improves cell permeability and a function to accelerate the self-assembly and three residues of glycine act as a spacer between hydrophobic and hydrophilic blocks. The self-assembly of CholG_3-Arg_6TAT resulted in core–shell nanoparticles. The hydrophobic part of cholesterol is towards to core; the hydrophilic part forms a shell for the nanoparticles and faces out to the external environment as shown in Fig. 4a. The local charge density and mass of peptides could play a role in enhancing antimicrobial activity.

In contrast, TAT peptide on the surface of nanoparticles makes them more efficient in crossing the Blood-Brain Barrier (BBB) to mitigate brain infections. These self-assembled nanoparticles show potential antimicrobial properties against various pathogens, such as bacteria, fungi, and yeast. The authors observe the inhibition in the growth of *staphylococcus aureus* in mice and rabbits and effectively work against the bacterial treatment present in the brain [95]. The antimicrobial activity of self-assembled nanoparticles is to disintegrate the cell wall via a membrane disruption mechanism. A relatively significant volume of nanoparticles, along with the physical properties of its components, helped permeate membranes as clearly shown in Fig. 4d-e.

4.3.4. Aromatic group modified peptides

Aromatic moieties have also been used to make the short peptide amphiphilic. Usually, these aromatic moieties are Fmoc (9-fuorenylmethyloxycarbonyl) (F_{moc}), aromatic drugs, and small aromatic molecules, which ultimately change the hydrophobicity of the overall short peptide building. These aromatic groups act as a hydrophobic head like the alkyl chain does in amphiphilic peptides, and other parts of the peptide can be used as hydrophilic

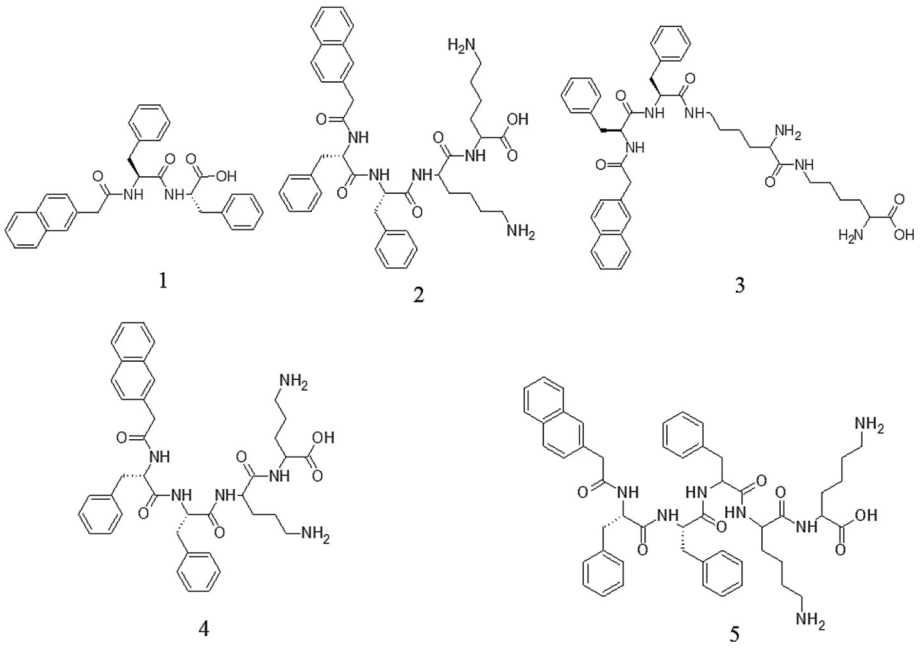


Fig. 5. Chemical structures of Nap conjugated short peptides. Reproduced with permission from reference [35] Copyright 2014, American Chemical Society.

parts. However, it depends on the composition of amino acids in that designer peptide. Fmoc is one of the commonly used hydrophobic motifs which have been used to tune the assembly process. Debnath et al showed the design of Fmoc linked amino acids and amphiphilic peptides with the pyridinium group, which self-assembled further through pi-pi and hydrogen bonding interactions [96]. These hydrogelators when turn into assembled state show antibacterial activity through the cell membrane penetration [97]. Fmoc coupled amino acids, di- tri-peptides not only show antibacterial activity in their assembled state but also have shown such ability in the solution phase. Interestingly, the hydrogel of these peptide conjugates can also be used for antibacterial coatings to prevent the spread of bacteria [98]. Recently, naphthalene is getting attention to be used as an aromatic group for the assembly of short peptides and it has been used to modify diphenylalanine (FF) to form self-assembled nanomaterials. In one study, researchers designed the five dipeptides (FF) conjugates Nap-FF, Nap-FFKK, Nap-FFK'K', Nap-FFOO, and Nap-FFFKK as shown in Fig. 5. These conjugates have a minimum difference in chemical structures. This difference arose because of the lysine (K), Ornithine (O), and epsilon-linked lysine, which can tune the hydrophobicity and antibacterial activity [35]. The hydrophobic-hydrophilic balance in the chemical structure governs the assembly process.

In contrast, in the same fashion, the hydrophobic-charge balance determines antimicrobial efficiency. The inclusion of positively charged amino acids increases the selectivity for negatively charged membranes and cell walls of bacteria rather than the neutral phospholipids bilayers. The introduction of third phenylalanine (F) in Nap-FFFKK is not beneficial in the assembly process; undoubtedly, it has increased the hydrophobicity and decreased the hydrophobic/hydrophilic balance. Thus, such a change in physical property induced a shift in the assembly process.

The ability of supramolecular peptide hydrogels of Nap-peptide derivatives to reduce the viability of bacterial biofilms was demonstrated in four different species: Gram-positive *Staphylococcus epidermidis* and *Staphylococcus aureus,* and the Gram-negative pathogens *Pseudomonas aeruginosa* and *Escherichia coli*. Antibacterial activity increased with the increasing concentration of the peptide derivatives. The ultrashort peptide containing the two-lysine amino acids Nap-FFKK and Nap-FFFKK supramolecular hydrogel showed significant anti-biofilm activity against bacterial strains used in the study.

Another significant aspect of aromatic residues linked short peptides; by changing, the hydrophobicity with decreasing the methylene units in two peptide conjugates resulted in antibacterial activity. This concept was proved by Nap-FFOO, where the ornithine has less methylene unit on the side-chain than lysine. Such a minor difference in molecular structure has little effect on the formation of the nanomaterials but it makes a significant difference in the antibiofilm activity. The antibacterial mechanism is based on the electrostatic interaction between positively charged free amine of peptides and negatively charged bacterial membranes. Thus, the lack of free amine in the designed building blocks of peptides decreased the antibacterial efficiency.

5. Functionalizing short peptide nanomaterials to achieve antimicrobial activity

Short peptides can be easily modified through covalent bonding with functional groups and therapeutic agents for different biomedical applications, enhancing therapeutic efficiency against the bacteria [99,100]. Covalently modified short peptide conjugates promise candidates to construct nanomaterials and treat bacterial infections [101]. Therefore, researchers have started to design and synthesize single multifunctional molecules with self-assembly and pharmacology pre-defined properties. Recently, short peptides with a defined number of amino acids in the range of 2–10 are also termed ultrashort peptides [89] and these are exciting candidates for future pharmaceutical applications as they are proven to be highly biocompatible and cost-effective relative to their protein and longer peptide counterparts [35].

5.1. Therapeutic drug conjugated short peptides-based nanomaterials

The self-assembling molecules linked with drugs to construct supramolecular biomaterials have shown several advantages. For example, such conjugated molecules can reduce the use of drug carriers, which may exhibit biodegradability constraints and acute

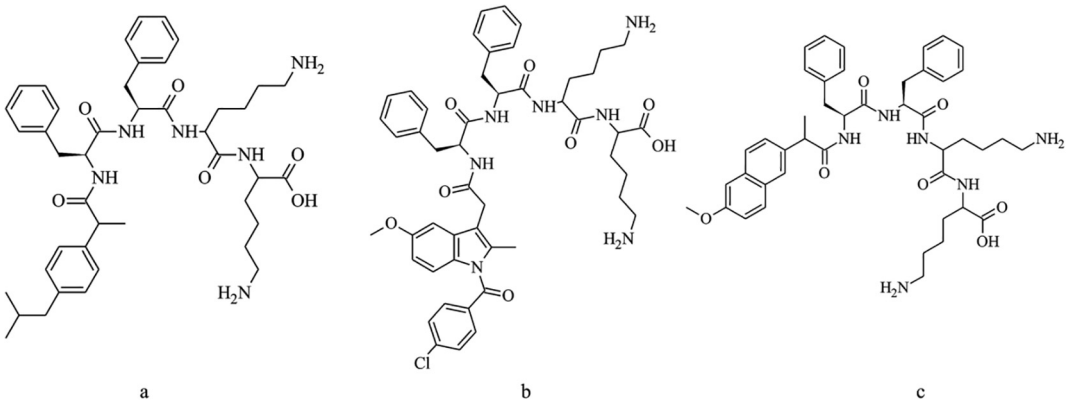


Fig. 6. Chemical structures of therapeutic drugs ibuprofen (Ibu), indomethacin (Ind), and naproxen (Npx) linked with short peptide FFKK. Reproduced with permission from reference [36] Copyright 2016, Royal Society of Chemistry.

toxicity. These biological concerns thus hamper achieving the results expected from the designer nanomaterials [102]. The drug carriers may have side effects because of stimuli nature to physiological parameters, for example, enzymes and pH-responsive, and acid production, which may further contribute to inflammation [103]. The functionalization of short peptide building blocks with therapeutic drugs has become a promising alternative approach because it can enhance the selectivity of those drugs, thus increasing the efficiency via nanotechnology. McCloskey et al. reported the short peptide conjugates consisting of diphenylalanine-dilysine (FFKK) covalently linked with Nonsteroidal anti-inflammatory drugs (NSAID) to form the nanosponges abbreviated as Npx-FFKK, which replaced the traditional self-assembling aromatic motifs such as Fmoc (9-fuorenylmethyloxycarbonyl), carboxybenzyl, and 2-naphthoyl (Nap) [104,105]. The two main advantages of using NSAIDs with peptides;1) This limits the need for the aromatic residue to tailor the hydrophobic interactions for creating the self-assembled nanomaterials, 2) are the aromatic groups of NSAIDs acting as self-assembling motifs and acute pain relievers (ibuprofen and naproxen) the antibacterial activity [36].

By keeping the aforementioned advantages of therapeutic drugs in mind, FFKK peptides were linked with ibuprofen (Ibu), indomethacin (Ind), and naproxen (Npx) as multifunctional motifs for the fabrication of hydrogel biomaterials and chemical structures are given in Fig. 6(a-c). The central role of NSAIDs is to improve the hydrogel mechanical properties by increasing the hydrophobicity of molecules and inducing the enzymatic inhibitory properties in the particles. The significant difference in the formation of biomaterials from three NSAIDs peptides stemmed from the difference in chemical structures, which changed the non-covalent interactions required to establish supramolecular biomaterials. These presumably physical properties also change the viscoelastic properties, morphology, and secondary structures of short peptide biomaterials. The lysine-based cationic peptides show inhibition in bacterial growth because of electrostatic interactions with anionic hydroxylated phospholipids. Finally, it creates the detergent-like chemical environment that induces the cell-lysis and leads to death [23,35]. Therefore, the authors employed these biomaterials on four different bacterial strains (*Staphylococcus epidermidis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa, Escherichia coli*) using the colony counting method, which represented the significant reduction in viability of bacterial growth. Significant inhibition of cyclooxygenase (COX-2) enzymes was observed in the case of NSAIDs peptides in comparison to without NSAIDs. The Npx-FFKK conjugates show more efficiency against all four bacterial strains. It has established a promising reduction of the bacterial viability and selectivity in inhibition COX-2 because of the enhanced viscoelastic properties.

Xu and coworkers reported the strategy based on antibiotic prodrug with dipeptides to enhance the efficiency of peptides against Gram-negative bacteria. They manipulated the chemistry of ester-bond hydrolysis to release the drug inside the bacterial cell [106]. The conjugated prodrug chloramphenicol succinate (CLsu) with dipeptide diglycine (GG) was more effective against *Escherichia coli* than only CLsu, which reveals the antibacterial activity of dipeptide. The enzymes such as BioH and YjfP present in the bacterial cells catalyze the hydrolysis to make the release faster, which thus enhanced the activity of the conjugates of the prodrug. Functionalization with the therapeutic drug enhances antibacterial efficiency and improves the cytotoxicity of the conjugates of the prodrug. The modulation of antibiotic prodrugs with short peptides can provide a platform to enhance the efficacies against bacteria [106].

On the one hand, peptides and functional nanomaterials are coupled through chemical bonds to enhance the antibacterial activity of the peptides. For example, conjugating peptides onto one-dimensional rodlike nanoparticles can enhance the activity against gram-negative bacteria [107], and conjugating AMPs and gold nanoparticles can resist trypsin digestion without affecting the antibacterial activity of peptides [108].

5.2. Peptide-photothermal agent composite nanomaterial for antibacterial phototherapy

The diversity in physical and chemical properties, coupled with advantages in biodegradability and biocompatibility, makes composite nanomaterials promising candidates in nanomedicine [29]. Based on their biological nature, short peptides have gained considerable attention due to their well-understood assembly mechanism, the ease of use for the surface modification of various metal-based nanostructures, and the co-assembling motifs for inorganic nano-agents to enhance the biocompatibility [27,109]. Inorganic components, metals, or photosensitive dyes are usually intended to play a role in the photothermal and photodynamic inactivation of bacteria. Besides that, the simplicity in the change of chemical structures also makes them a favorable biological entity for covalent conjugation with certain functionalities or targeted motifs to trigger the assembly process and increase the efficacy of these biomaterials for nanomedicine [110,111].

Supramolecular composites can be formed by combining two or more components, including short peptides and the non-covalent interactions between those components that play a role in the assembly process of composites [112,113]. However, the compos-

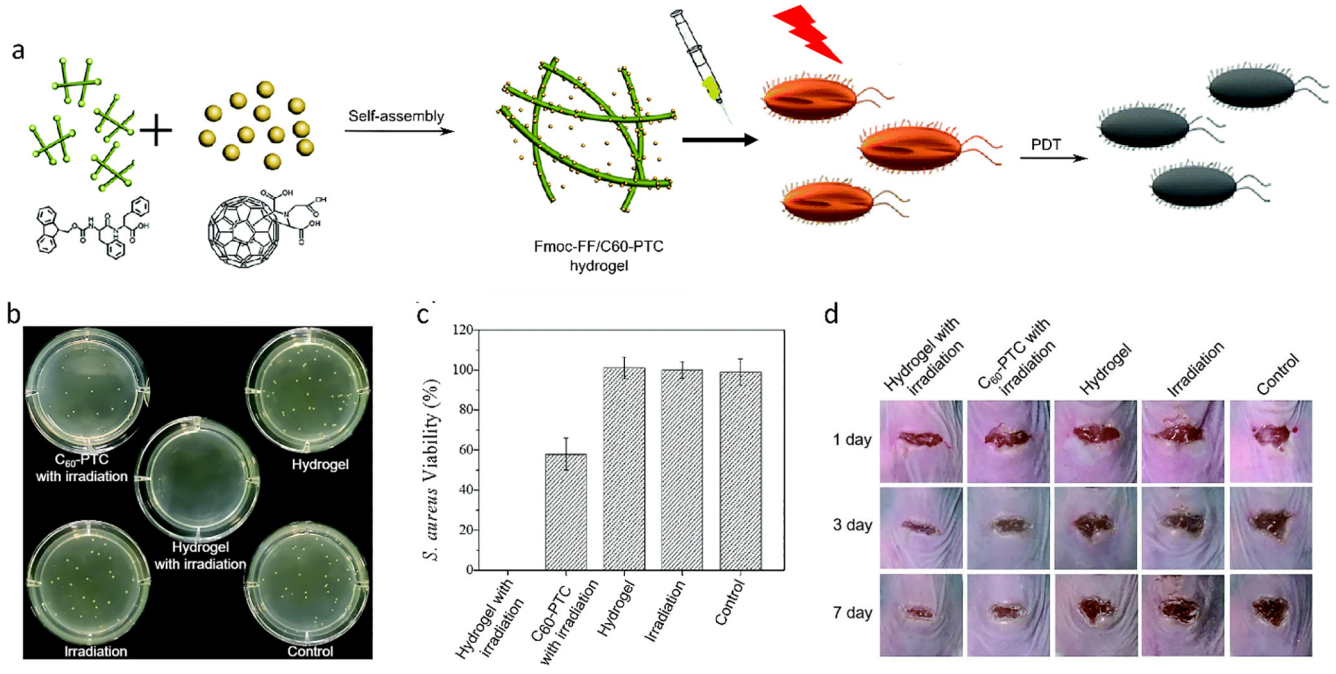


Fig. 7. Schematic diagram of self-assembly of dipeptide, fullerene, photodynamic therapy of bacteria, a), the chemical structure of short peptide and fullerene, and the self-assembled peptide-fullerene hybrid nanostructures. b, c), Photographs of photodynamic antibacterial therapy *in-vitro,* and the corresponding bacteria viability of *Staphylococcus aureus* colonies grown on agar plates (n = 3). d) *In-vivo* photodynamic antibacterial treatment of mice, the wound images at different days of treatments. Reproduced with permission from reference [122] Copyright 2019, Royal Society of Chemistry.

ite nanomaterials could have different physical and chemical properties from their parent components and show promising characteristics that make them valuable candidates in nanomedicine [114,115]. These composite nanomaterials are used for nanomedicine and received huge attention for their application in the biomedical field. The physicochemical properties of composites nanomaterials make them promising to achieve maximum efficiency [116-118]. The size, surface potential, and stability of nanoparticles synthesized via a bottom-up approach are fundamental features that play a role in drug delivery carriers' antimicrobial activity and efficiency. Furthermore, these factors enhance the therapeutic effectiveness, precision and increase drug payloads [119]. Peptide supramolecular nanomaterials like hydrogels and nanocomposites have been reported as antibacterial therapeutic agents, which may conclude that short peptides are crucial entities for the fabrication of highly biocompatible nanostructures [90,120,121].

5.2.1. Short peptide/fullerene composite

Taking into account the above mention properties, Yan and co-workers have reported peptide modulated supramolecular hybrids with fullerenes for photodynamic antibacterial therapy [122]. The phototherapies, photodynamic (PDT), and photothermal therapy (PTT) exhibit similar mechanisms for antitumor and antibacterial activities [123,124]. Generally, the mechanism underlying phototherapy involves two steps: the first is to deliver the therapeutic agent to tumor sites, while the second is to activate the agent, as it is non-toxic in the dark. The therapeutic agent generates reactive oxygen species, including singlet oxygen and other oxygen radicals, which kill pathogens. Photodynamic therapy is a non-invasive, more selective, and efficient therapy, which may ultimately replace the conventional modalities of cancer treatments like chemotherapy and radiation therapy. The invention of nanotechnology has made photodynamic therapy even more targeted and one step closer to the clinic. Nanoparticles have additional advantages, like enhancing selectivity through surface modification with targeted ligands and by their enhanced permeability and retention (EPR) effect [125,126].

These favorable properties have led to peptide and protein-based self-assembled nanomaterials being widely used for cancer treatments by phototherapies. This can ensure the better biocompatibility and biodegradability of compounds to overcome the severe biological issues of metallic nanoparticles for the body [127,128]. The fullerene is a class of closed-cage carbon nanomaterials with an extended pi conjugation system, enabling them to absorb visible light and generate reactive oxygen species upon light illumination, supporting the idea to use it as a photodynamic therapy candidate. Due to its strong hydrophobicity and susceptibility for aggregation, there is a need to functionalize short peptides with cationic or anionic functional groups to enhance its water solubility and biocompatibility interactions with bacterial cells [129]. Therefore, other than the covalent conjugation, the co-assembly approach, where the short peptides act as the central motif to create nanostructures, is introduced. In this design, the small amphiphilic peptides Fmoc-FF and C_{60}-PTC (C_{60} pyrrolidine tris-acid) were used to make hybrid or composite type new supramolecular biomaterials through non-covalent interactions, including pi-pi stacking, hydrogen bonding, and electrostatic interactions for antibacterial photodynamic therapy as presented in Fig. 7a. C_{60}-PTC in the form of nanoparticles is entangled in the fibrous peptide network, which inhibits the aggregation of fullerenes. The mechanical properties of peptide hydrogel composites were improved after the incorporation of the photo-responsive component. This also enhanced the production of reactive oxygen species in comparison to C_{60}-PTC alone. The authors employed these peptide/fullerene composites for the *in-vitro* and *in-vivo*

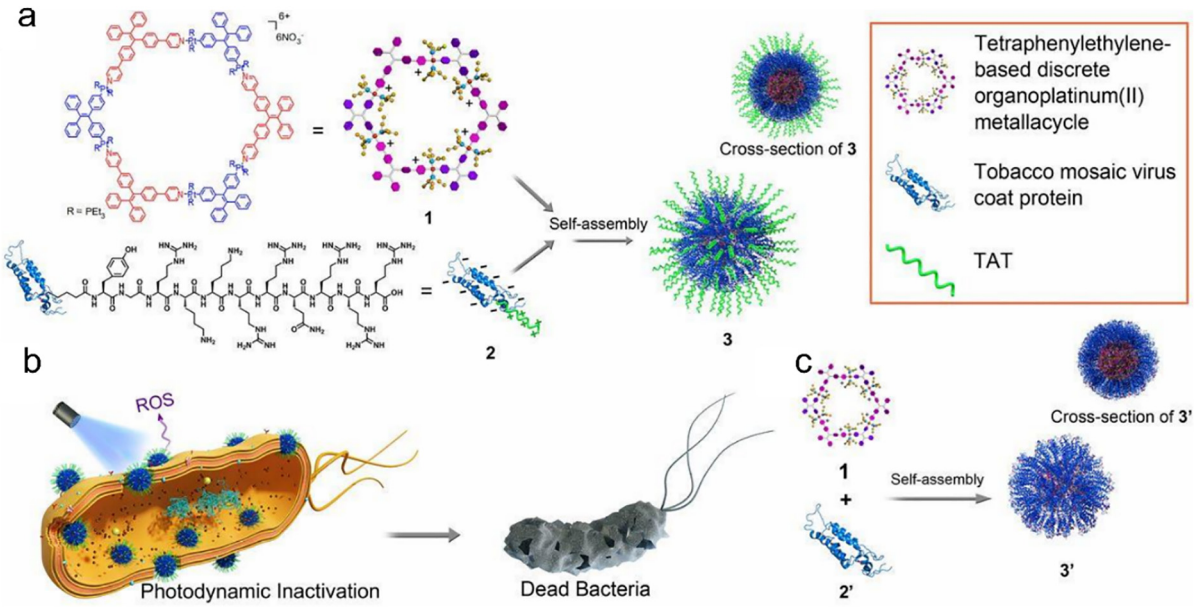


Fig. 8. Chemical design and photodynamic inactivation of bacteria. a) Chemical structures and annotation of arrangements for the building blocks for self-assembled nanospheres, b) Photodynamic inactivation of bacterial cells through intercalation and generation of ROS, c) Self-assembly of two components to fabricate the nanospheres and cross-sectional insights. Reproduced with permission from reference [130] Copyright 2019, United States National Academy of Sciences.

application of antibacterial photodynamic therapy. The results show the significance of this strategy against the multi-antibiotic resistance strains as indicated in Fig. 7b-d.

5.2.2. Aggregation induced emission (AIE) motifs/short peptide composites

The intercalation of nanostructures into membranes for the efficiency of bacterial activity is a critical challenge in designing nanomaterial formulations. Gao and co-workers reported a comparatively new strategy using a transacting activator of transduction (TAT) peptide-decorated on a virus coat protein and a tetra-phenyl-ethylene-based discrete organoplatinum (II) metallacycle through non-covalent presumably electrostatic interactions [130]. The tetraphenyl ethylene acts as a photosensitizer with aggregation-induced emission to produce reactive oxygen species (ROS). This strategy has been used to generate ROS and intercalation-to-bacterial membranes to enhance the photodynamic inactivation (PDI) efficiency. After entry into the cellular membrane, the self-assembled nanostructure 3′ decreased the survival rate of Gram-negative *Escherichia coli* up to almost zero and for Gram-positive *Staphylococcus aureus* to around 30 %, followed by the treatment and ROS generation on light irradiation as shown in Fig. 8.

5.3. Biomimetic short peptide nanomaterials mimicking the antibacterial effect of the immune system

Building blocks that engineer self-assembled biomimetics nanomaterials with responsive, functional groups could be essential for drug delivery and it can regulate the molecular recognition which could help to control the drug release at a targeted site [131]. The control over the formation of nanomaterials from functionalized building blocks via the *in-situ* self-assembly process, which usually is triggered by the environmental conditions lying inside the cells, has attracted attention in recent days. Huang et al. exploited the *in-situ* supramolecular assembly approach to design a biomimetic system that mimics the natural immune process Neutrophil extracellular traps (NETs) [56]. This biomimetic design of small molecule gelators, with their responsive nature, inhibit infection with methicillin-resistant *staphylococcus epidermidis* (MRSE). They synthesized a quinazolinone motif with a linker of aryl boronate immolative, which is linked with the tetra-peptide of GGFF (BQA-GGFF). This small molecule is responsive to oxidative environments which are shown in Fig. 9a. Glucose and glucose oxidase (Gox) were used to produce hydrogen peroxide as the reactive oxygen species (ROS). The small molecule BQH-GGFF has shown the propensity to form hydrogels under the oxidative environment of ROS and emit green fluorescence, as shown in Fig. 9c. When this hydrogel was incubated with MRSE, the nanofibers of the hydrogel strongly entangled the bacterial cells and significantly inhibit their growth *in-vitro* through transcriptome alterations. This strategy was further employed *in-vivo* using a mouse model to test the efficacy of this design by monitoring the appearance of fluorescence at the infection site. The trapping of bacteria inside the nanofibers halted their movement and increased the survival rate of mice. Furthermore, BQA-GGFF acted as a scavenger in the assembly process of nanofibers, which reduced the inflammatory damage of tissues by consuming the excess amount of ROS. Such a new biomimetic strategy can thus be used for countering the multidrug resistance to bacterial infections.

The barriers to transporting self-assembling peptides to the bacterial invasion region can be addressed adequately by trapping the bacteria into in-situ formed fibrous scaffolds at the *in-vivo* level. Therefore, a programmable design of Human defensin-6 mimic peptide (HDMP), inspired by the peptide/protein self-assembly approach, was reported recently to inhibit bacteria via trapping *in-vivo* [55]. This design consists of three main parts; 1) A peptide sequence RLYLRIGRR as a ligand-target to bind with lipoteichoic acid (LTA), which is a unique component of Gram-positive bacteria, 2) the KLVFF as a short peptide motif designed for the β-sheet fibrous structures that also mimic the β-sheet structure of HD6 network, 3) the aromatic bis-pyrenes (BP) used to track the synthesis of HDMP in a particular form and provide the signal of transporting it through intravenous administration by aggregation-induced emission (AIE) of BP as shown in Fig. 10 a-d. The mechanism of this design is proposed to be as follows—first, HDMP is self-assembled to form nanoparticles (NPs) that can bind with *Staphylococcus aureus.* Upon binding, the NPs are transformed

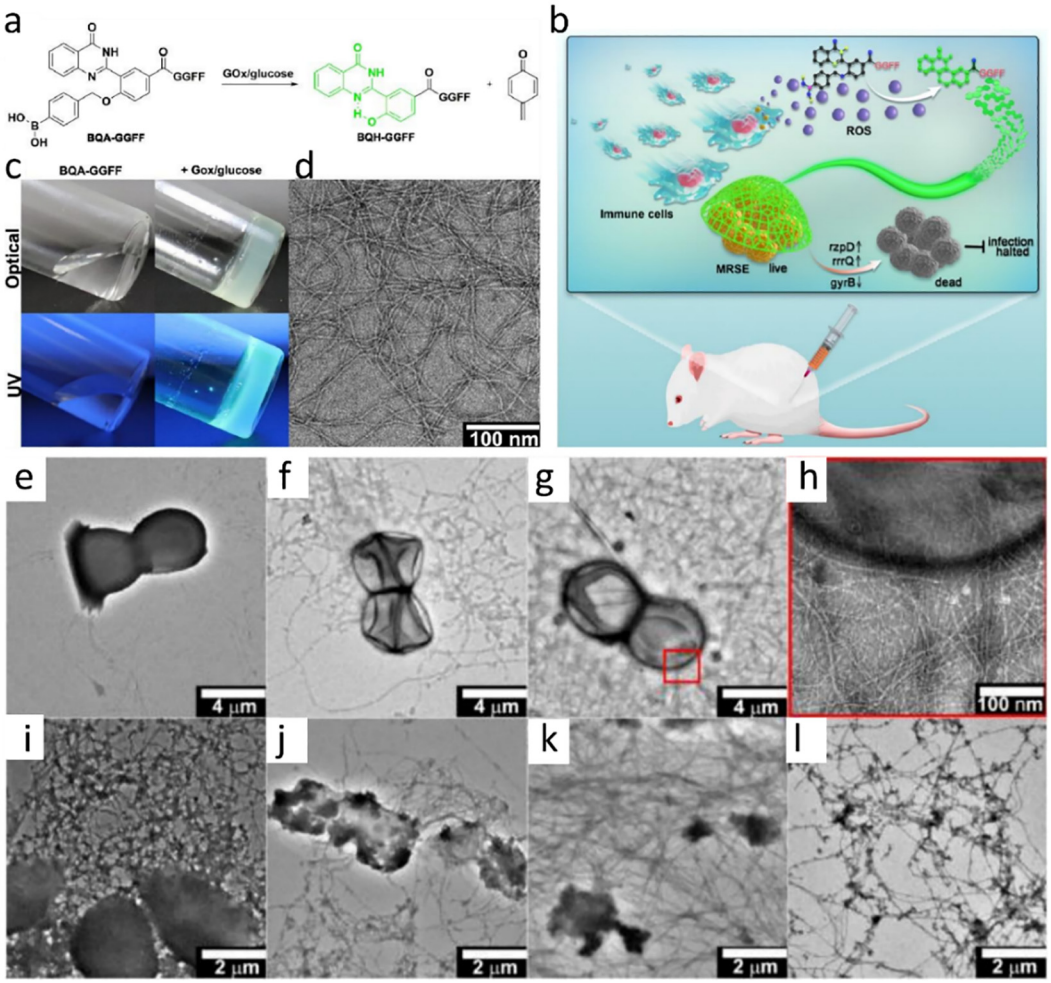


Fig. 9. Chemical structure, responsive nature, and characterization. a) chemical structure, b) schematic diagram of *in-vivo* trapping of MRSC bacteria inside the natural immune mimicking process of Neutrophil extracellular traps (NETs), c) responsiveness of small molecules and green fluorescence, d) TEM image of nanofibers of hydrogel, e-f) adhesion of MRSC bacterial cells to nanofibers of the hydrogel at 2.5 mM, 5.0 mM, and 10.0 mM, g-h) HR-TEM image of trapping, i-l) morphology changes of MRSC cells at different incubation time such as TEM images of the morphology change of MRSE cells. Reproduced with permission from reference [56]. Copyright 2020, Elsevier Ltd. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

into nanofibers (NFs) that developed a fibrous scaffold. The self-assembly is triggered by ligand-receptor interactions and further supported and stabilized by pi-pi stacking and hydrogen bonding. The fibrous network can trap the bacteria and ultimately inhibit bacterial growth as shown in Fig. 11a-h. Altogether, this is a promising combinatorial approach of using three components with particular targets capable of programmable self-assembly, mimicking the HD6 process, and effectively and safely inhibiting the infection of Gram-positive bacteria *in-vivo*.

6. Silver/gold incorporated short peptide nanomaterials

Metal (silver/gold) peptide coordination chemistry is one of the established approaches to form the peptide supramolecular nanomaterials for various applications[110,132]. The use of short peptides to create mineralized biomaterials is one of the green methods for constructing nanomaterials. Metal salts usually require very toxic chemical agents as reducing or capping agents to form nanomaterials[133]. A polyethylene glycol (PEG) water-soluble polymer with a catechol functional group is used to reduce the Ag^+ to Ag (0) and produce silver nanoparticles [134]. Importantly, the controlled release of Ag^+ also showed the ability to enhance antibacterial activity[135]. Another study showed the reduction of silver during polymer hydrogel formation using the reducing agent sodium borohydride. However, PEG is not considered versatile and amenable to living systems. Reithofer et al. used the biomineralization strategy to report the *in-situ* generation of stable, size-controlled silver nanoparticles in peptide hydrogels. The hexameric ultrashort peptides Ac-LIVAGK-NH_2 (Ac-LK_6-NH_2), which can form hydrogels at physiological conditions, are employed to generate silver nanoparticles within the matrix under mild exposure to UV light. Silver nitrate is a source of $Ag^{+,}$ which is reduced to form the nanoparticles without using external stimuli for reduction. Furthermore, the silver nanoparticles increased the mechanical properties of the hydrogel, as the silver nanoparticles were entangled in the gaps of the nanofibrous hydrogel. The silver mineralized peptide hydrogel is biocompatible and showed enhanced activity against bacterial strains of *Escherichia coli*, *Pseudomonas aeruginosa,* and *Staphylococcus aureus* [136]. The size of the silver nanoparticles was less than 20 nm, which is suitable for the penetration of bacterial membranes [137]. Recently, photoionization, a green method was developed to make the silver-peptide nanoparticles in solution, where tetramer short peptide was used as reducing and capping agent. These composite nanoparticles have shown promising antibiofilm activity against gram-positive and gram-negative bacteria [138].

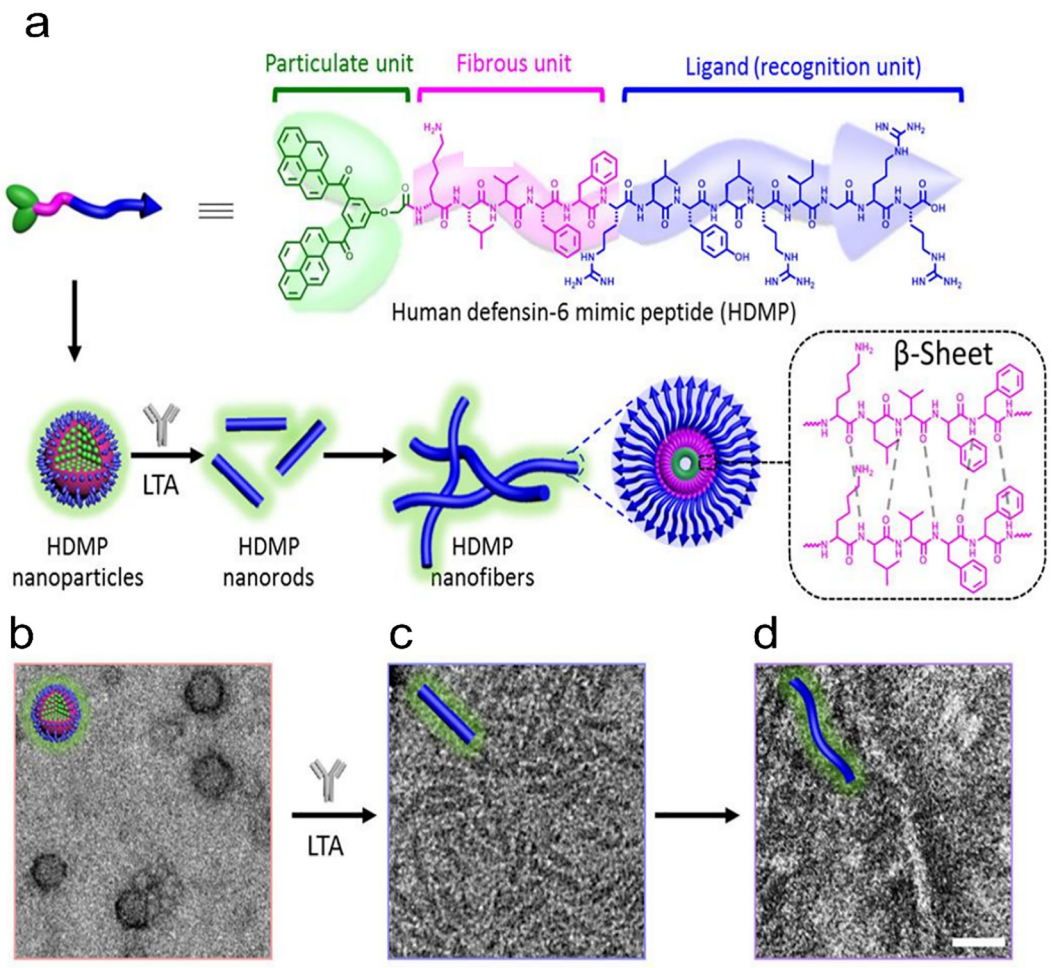


Fig. 10. Molecular design, preparation of HDMP NPs, and transformation into nanofibers, a) Chemical structure of functionalized building block of Human defensin-6 mimic peptide (HDMP) and schematic diagram of self-assembly of HDMP into nanoparticles (NPs), transformation into nanorods, and then finally into nanofibers (NFs) upon the incubation with lipoteichoic acid (LTA), b-d) Transmission electron microscope (TEM) images of HDMP NPs, HDMP nanorods, and NFs respectively. Reproduced with permission from reference [55] Copyright 2020, American Association for Advancement of Science.

Despite this, Stupp and co-workers designed the amphiphilic peptides with a propensity to form self-assembled nanofibers. The toxicity of capping or reducing agents and the complex nature of surfactants or polymers can be avoided using peptide motifs to overcome the aforementioned issues in the synthesis of metallic nanoparticles [17]. Therefore, the authors reported the two amphiphilic peptides with minor differences in the chemical structure, one with an aldehyde functional group and another lacking the aldehyde group. Based on the chemical design, both peptide conjugates formed supramolecular nanofibers in water. The aldehyde group is used to control the nucleation of the silver nanoparticles because it is a well-known functional group to reduce two silver ions to form the Ag_2 cluster and, at the same time, oxidize the carboxylic acid group without any external additives or reducing agents. The modified N-terminus of the peptide was exposed at the surface of the nanofibers to reduce the silver ions as is presented in Fig. 12a. The silver nanoparticles generated in this strategy are tested from typical plasmonic peaks of silver nanoparticles in UV–VIS spectra. The size of the nanoparticles was about 4 nm confirmed by TEM. The nanoparticles were tested for biocompatibility on eukaryotic cells and were 30 times less toxic than they are to bacterial cells and less toxic than silver nitrate solution. Significant inhibition in the growth of bacteria was observed by using the metalized nanofibers.

Furthermore, the antibacterial activity against *Escherichia coli* was investigated. The inhibition profile of the bacterial growth for *Escherichia coli* in the presence of silver decorated peptide nanofibers up to 16 h, and silver concentration varied from 0, 100, 250, 500, 750 nM, 1, 1.5, and 2 μM as shown in Fig. 12b. The results demonstrate that the silver nano-decorated peptide nanofibers have a promising inhibition of the growth of bacterial colonies.

Metal nanoparticles, especially silver nanoparticles (AgNPs) as broad-spectrum antimicrobial agents, exhibit intense antibacterial activity yet low resistance against the antibiotics and small molecule bactericidal agents [139]. There is no doubt about the enormous potential of AgNPs as antibacterial agents. However, the individual AgNPs are not able to replace the antibiotics due to the accumulation of AgNPs in healthy tissues and the adverse side effects of Ag^+ at high dosages or long terms use, like cellular toxicity, skin staining, and allergic reactions [140-142]. The aromatic modified amphiphilic amino acids like proline, and leucine, have anti-inflammatory and antibacterial properties. However, supramolecular hydrogels formed from these motifs are not stable enough alone for use as antibacterial dressings. Combined with the reinforcing silver NPs, composite hydrogels open new avenues to form biocompatible, stable hydrogels from simple amino acid derivatives [143,144]. Yan and the team introduced the strategy based on Fmoc-amino acids and silver through coordinated self-

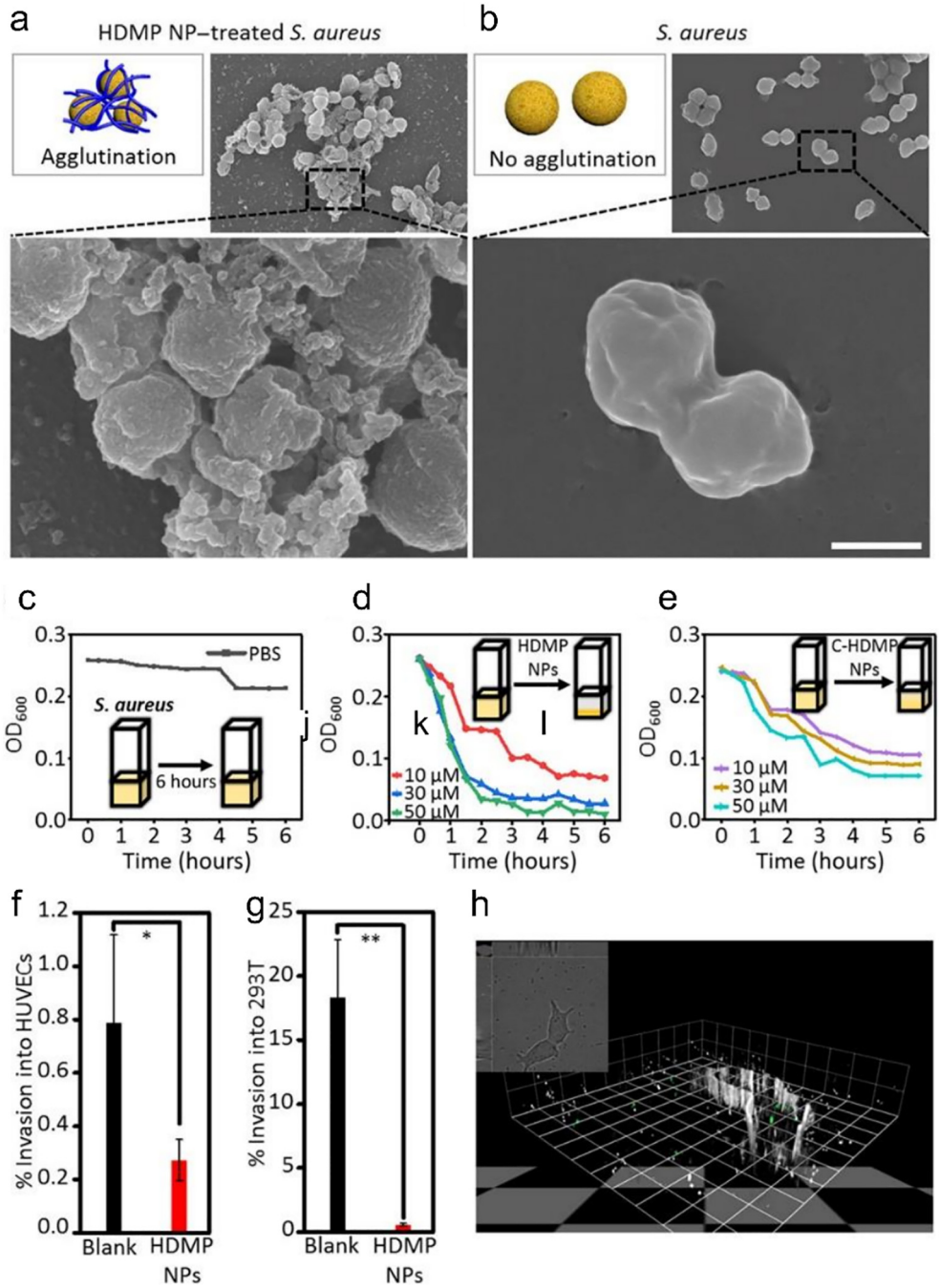


Fig. 11. The antibacterial mechanism, a-b) trapping of *staphylococcus aureus* in the nanofibers of HDMP and untreated *staphylococcus aureus* by Scanning electron microscope (SEM), Scale bar, 1 μm., c-e) *in-vitro* time-dependent inhibition assay for *Staphylococcus aureus* at different concentrations of NPs, f-h) invasion of human umbilical vein endothelial cells (HUVECs) and human embryonic kidney 293 (293 T) cells, a 3D confocal image of invasion of 293 T cells. Reproduced with permission from reference [55] Copyright 2020, American Association for Advancement of Science.

assembly, resulting in a hydrogel decorated with silver nanoparticles on the hydrogel nanofibers as shown in Fig. 13. The hydrophobic amino acid derivatives are released from the metallic-hydrogel and interact with the cell wall due to hydrophobic interactions [145]. As a result, both the AgNPs and silver ions (Ag^{+}) entered the bacterial membrane. There was an excellent inhibition in *Escherichia coli* and *Staphylococcus aureus* growth monitored for up to seven days. Metallic-hydrogels satisfy the biocompatibility concerns. Moreover, the disintegration of bacterial membranes was confirmed by the TEM, followed by the fusing and clumping of bacterial membranes.

The short peptide sequence FFECG with hydrophobic and hydrophilic functionality, additionally connected with aromatic moiety Fmoc (Fmoc-FFECG), was used to create self-assembled nanofibrous hydrogel [146]. In this strategy, the hydrophobic part fosters aggregation, which can help the encapsulation of hydrophobic drugs [147]. On the other hand, the hydrophilic groups such as carboxylic acid and thiol groups at the surface of nanofibers serve as nucleation sites to form stable and monodisperse AgNPs. Due to their molecular recognition capability and biocompatible nature, silver mineralized peptide nanofibers (Ag-Pep NFs) showed long-term antibacterial activity against both *Bacillus*

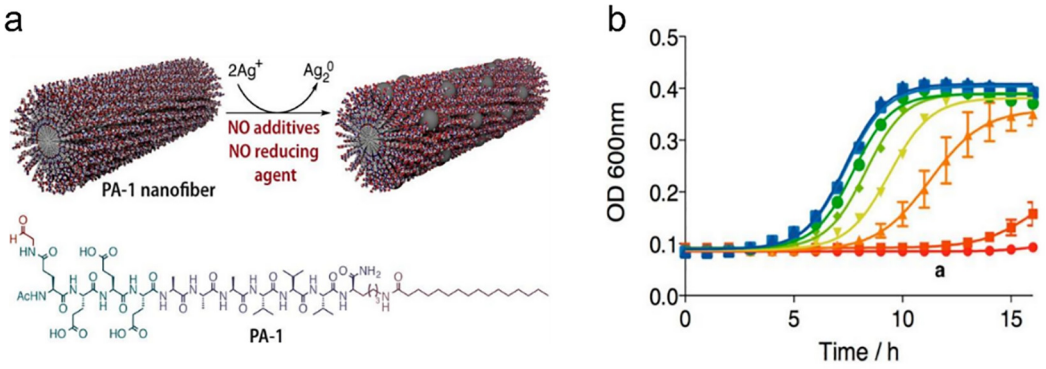


Fig. 12. Schematic diagram of amphiphilic peptide and antibacterial activity. a) Rationally designed chemical structure of amphiphilic peptide with modification of aldehyde functional group, the self-assembled nanofiber, and silver decorated supramolecular peptide amphiphilic nanofibers. b) the inhibition profile of the bacterial growth for *Escherichia coli* in the presence of silver decorated peptide nanofibers up to 16 h and silver concentration varies from 0, 100, 250, 500, 750 nM; 1, 1.5, and 2 mM. Reproduced with permission from reference [17] Copyright 2019, American Chemical Society.

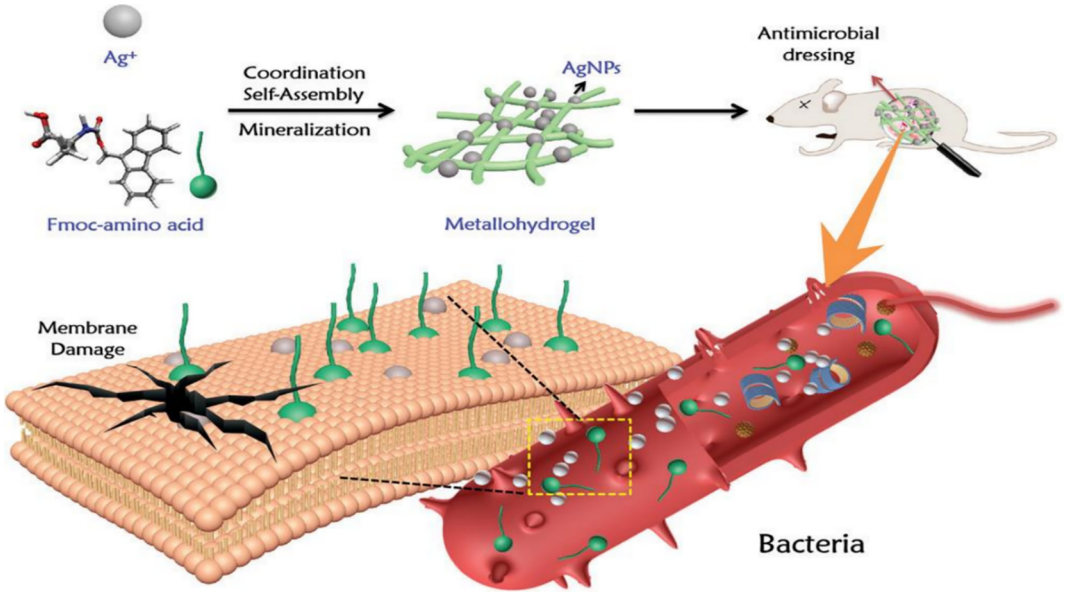


Fig. 13. A schematic diagram of Fmoc-amino acids, metal coordinated self-assembly, and mineralization to construct hydrogel with embedded silver nanoparticles (AgNPs) and antimicrobial dressing. The biocompatible metal nanoparticles embedded in hydrogel showed enhanced antibacterial activity due to the synergy of amphiphilic amino acids and AgNPs. The hydrophobic nature of amphiphilic amino acids supports permeation to the cell wall through hydrophobic interactions and disrupts the bacterial morphology. Reproduced with permission from reference [145] Copyright 2020, Wiley.

subtilis and *Escherichia Coli.* The inhibition in the growth of bacterial strains is demonstrated at 10 μg mL^{-1} concentration of Ag-Pep NFs nanocomposites. In contrast, only AgNPs with the same silver concentration did not show any significant inhibition in the proliferation of bacteria [148]. Furthermore, Fmoc-FF/Ag nanocomposites with enhanced antibacterial activity and inhibition in biofilm formation can be used in wound dressings.

The incorporation process with various metals, especially silver and gold, is more frequently used in biomedical applications[37]. Therefore, Manish et al., who found AgNPs with dipeptide have more antibacterial activity than AgNPs alone, to native dipeptides and AuNPs with dipeptide, studied the combinatorial effect of silver and gold nanoparticles stabilized with the short peptides. Moreover, L-His-L-Arg-OMe capped AgNPs were found to be more effective than antibiotics [149].

7. Conclusion and future perspectives

We have summarized the supramolecular nanomaterials based on short peptides, including dipeptides, cyclic peptides, amphiphilic peptides, silver-peptide nanostructures, and peptide co-assembled nanostructures with an emphasis on their antibacterial efficiency and mode of action against bacterial pathogens. Short peptides are simple biomolecules that can form supramolecular nanostructures through self-assembly, which is a nature-inspired process. Until now, self-assembling short peptides have demonstrated promising results for applications in nanomedicine. These short peptide building blocks have been used to engineer supramolecular nanostructures through non-covalent interactions, with or without other motifs such as metal ions and other co-assembling components. Besides that, the flexibility in inter-and

intramolecular interactions and in-built physicochemical properties of the short peptides create a room at the bottom to fabricate supramolecular nanostructures for various applications, including nanomedicine. Furthermore, the structural importance of peptide building blocks and the formulation strategies of antibacterial agents by using self-assembling short peptides show the merits of improved efficacy and significantly decrease possible issues with toxicity. The selectivity of antibacterial agents can be achieved by tailoring strategies for supramolecular nanomaterials based on short peptide building blocks.

Recently, the phase separating short peptides and even simple amino acid derivatives have been developed, which could have the ability to form the liquid-like droplets and in some cases dynamic evolution into soft supramolecular hydrogels spontaneously with the assistance of a multitude of non-covalent interactions [150,151]. Though, these phase separating peptides with kinetically-trapped mesostable structures have not yet been explored for antibacterial applications. However, their physicochemical properties are very promising to be used for antibacterial and antibiofilm properties. As they show the phase separation *in vitro*, we believe these short peptide and amino acid derivatives can also adapt to the phase separation *in vivo* to arrest the bacterial cells.

The cytotoxicity and complexity of biodegradability of many cationic polymers have led to severe concerns, which hinder their adoption as antibiotic agents against pathogenic microorganisms. Besides this, many antibacterial agents have innate accumulation issues in healthy tissues and have adverse side effects like skin staining and allergic reactions, long-term treatment, and the need for high dosages of existing nanomaterials for antibacterial activity. Although inorganic nanomaterials, especially carbon-based ones, have shown low toxicity, biosafety concerns such as neuro- and reproductive toxicity cannot be overlooked because they can cross biological barriers [152,153]. The cyclic peptide nanotubes have emerged as antibacterial nanomaterials used *in-vitro* and *in-vivo* for bacterial infections. The most frequently observed antibacterial mechanism is the electrostatic interaction between peptide nanotubes and negatively charged bacterial membranes, leading to a disruption of the membranes [154]. However, the relatively high production cost could prevent their use as antibacterial agents in creams, and other cosmetics products are not practical. With this in mind, the quest is to formulate new strategies structurally based on highly biocompatible entities that can replace conventional antibiotics for different bacteria strains. However, there remains a need for additional research to find promising nanomaterials for bacterial treatments. In our perspective, short peptide supramolecular nanomaterials will be potent candidates to remove critical barriers met at the clinical level.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

M.A acknowledges financial support from the European Union's Horizon 2020 program under grant 839177 (PEPREP). The authors acknowledge financial support from the National Natural Science Foundation of China (Project Nos. 22025207, 22072154), the National Natural Science Fund BRICS STI Framework Programme (No. 51861145304), and Innovation Research Community Science Fund (No. 21821005), as well as the Natural Science Foundation of Hebei Province of China (B2020103025).

References

[1] V.L. Simpkin, M.J. Renwick, R. Kelly, E. Mossialos, J. Antibiot. Res. 70 (2017) 1087–1096.
[2] L. Piddock, Lancet Infect. Dis. 16 (2016) 767–768.
[3] B. Jamil, M. Imran, Crit. Rev. Microbiol. 44 (2018) 79–94.
[4] A.J. Huh, Y.J. Kwon, J. Control. Release 156 (2011) 128–145.
[5] A. Gupta, S. Mumtaz, C.H. Li, I. Hussain, V.M. Rotello, Chem. Soc. Rev. 48 (2019) 415–427.
[6] M.J. Hajipour, K.M. Fromm, A.A. Ashkarran, D. Jimenez de Aberasturi, I.R. de Larramendi, T. Rojo, V. Serpooshan, W.J. Parak, M. Mahmoudi, Trends Biotechnol. 30 (2012) 499–511.
[7] D. Botequim, J. Maia, M.M. Lino, L.M. Lopes, P.N. Simoes, L.M. Ilharco, L. Ferreira, Langmuir 28 (2012) 7646–7656.
[8] K. Hadinoto, W.S. Cheow, Colloids Surf. B 116 (2014) 772–785.
[9] L. Lombardi, A. Falanga, V. Del Genio, S. Galdiero, Pharmaceutics 11 (2019) 166.
[10] H. Zazo, C.I. Colino, J.M. Lanao, J. Control. Release 224 (2016) 86–102.
[11] L. Zhao, Q. Zou, X. Yan, Bull Chem. Soc. Jpn. 92 (2019) 70–79.
[12] B. Mojsoska, H. Jenssen, Pharmaceuticals 8 (2015) 366–415.
[13] M.N. Melo, R. Ferre, M.A.R.B. Castanho, Nat. Rev. Microbiol. 7 (2009) 245–250.
[14] D.J. Craik, D.P. Fairlie, S. Liras, D. Price, Chem. Biol. Drug Des. 81 (2013) 136–147.
[15] U. Chitgupi, Y. Qin, J.F. Lovell, Nanotheranostics 1 (2017) 38–58.
[16] C. Chen, F. Pan, S. Zhang, J. Hu, M. Cao, J. Wang, H. Xu, X. Zhao, J.R. Lu, Biomacromolecules 11 (2010) 402–411.
[17] E. Pazos, E. Sleep, C.M.R. Perez, S.S. Lee, F. Tantakitti, S.I. Stupp, J. Am. Chem. Soc. 138 (2016) 5507–5510.
[18] L. Schnaider, S. Brahmachari, N.W. Schmidt, B. Mensa, S. Shaham-Niv, D. Bychenko, L. Adler-Abramovich, L.J.W. Shimon, S. Kolusheva, W.F. DeGrado, E. Gazit, Nat. Commun. 8 (2017) 1–10.
[19] H.-C. Flemming, J. Wingender, U. Szewzyk, P. Steinberg, S.A. Rice, S. Kjelleberg, Nat. Rev. Microbiol. 14 (2016) 563–575.
[20] Q. Xin, H. Shah, A. Nawaz, W. Xie, M.Z. Akram, A. Batool, L. Tian, S.U. Jan, R. Boddula, B. Guo, Adv. Mater. 31 (2019) 1804838.
[21] W. Li, F. Separovic, N.M. O'Brien-Simpson, J.D. Wade, Chem. Soc. Rev. 50 (2021) 4932–4973.
[22] X. Li, H. Bai, Y. Yang, J. Yoon, S. Wang, X. Zhang, Adv. Mater. 31 (2019) 1805092.
[23] B. Findlay, G.G. Zhanel, F. Schweizer, Antimicrob. Agents Chemother. 54 (2010) 4049–4058.
[24] P. Zou, W.-T. Chen, T. Sun, Y. Gao, L.-L. Li, H. Wang, Biomater. Sci. 8 (2020) 4975–4996.
[25] M. Chen, S. Zhang, Z. He, A.C.S. Appl, Bio Mater. 3 (2020) 6343–6350.
[26] I. Kolodkin-Gal, D. Romero, S. Cao, J. Clardy, R. Kolter, R. Losick, Science 328 (2010) 627–629.
[27] W. Ji, C. Yuan, S. Zilberzwige-Tal, R. Xing, P. Chakraborty, K. Tao, S. Gilead, X. Yan, E. Gazit, ACS Nano 6 (2019) 7300–7309.
[28] H.G. Cui, A.G. Cheetham, E.T. Pashuck, S.I. Stupp, J. Am. Chem. Soc. 136 (2014) 12461–12468.
[29] Z.Y. Ong, N. Wiradharma, Y.Y. Yang, Adv. Drug Deliv. Rev. 78 (2014) 28–45.
[30] Y. Yan, Y. Li, Z. Zhang, X. Wang, Y. Niu, S. Zhang, W. Xu, C. Ren, Colloids Surf. B 202 (2021) 111682.
[31] A. Dehsorkhi, V. Castelletto, I.W. Hamley, J. Pept. Sci. 20 (2014) 453–467.
[32] Y. Liang, X. Zhang, Y. Yuan, Y. Bao, M. Xiong, Biomater. Sci. 8 (2020) 6858–6866.
[33] S. Park, J.A. Jackman, N.J. Cho, Langmuir 35 (2019) 9934–9943.
[34] S. Fernandez-Lopez, H.S. Kim, E.C. Choi, M. Delgado, J.R. Granja, A. Khasanov, K. Kraehenbuehl, G. Long, D.A. Weinberger, K.M. Wilcoxen, M.R. Ghadiri, Nature 414 (2001) 329.
[35] G. Laverty, A.P. McCloskey, B.F. Gilmore, D.S. Jones, J. Zhou, B. Xu, Biomacromolecules 15 (2014) 3429–3439.
[36] A.P. McCloskey, S.M. Gilmore, J. Zhou, E.R. Draper, S. Porter, B.F. Gilmore, B. Xu, G. Laverty, RSC Adv. 6 (2016) 114738–114749.
[37] M. Abbas, A. Atiq, R. Xing, X. Yan, J. Mater. Chem. B 9 (2021) 4444–4458.
[38] S. Fleming, R.V. Ulijn, Chem. Soc. Rev. 43 (2014) 8150–8177.
[39] C. Yuan, W. Ji, R. Xing, J. Li, E. Gazit, X. Yan, Nat. Rev. Chem. 3 (2019) 567–588.
[40] J. Wang, K. Liu, R. Xing, X. Yan, Chem. Soc. Rev. 45 (2016) 5589–5604.
[41] L. Zhao, S. Li, Y. Liu, R. Xing, X. Yan, CCS Chem. (2019) 173–180.
[42] S. Li, W. Zhang, R. Xing, C. Yuan, H. Xue, X. Yan, Adv. Mater. 33 (2021) 2100595.
[43] R. Xing, Q. Zou, X. Yan, Acta. Phys. Sin. 36 (2020) 1909048.
[44] R. Chang, Q. Zou, R. Xing, X. Yan, Adv. Ther. 2 (2019) 1900048.
[45] X. Wang, Z. Song, S. Wei, G. Ji, X. Zheng, Z. Fu, J. Cheng, Biomaterials (2021) 120913.
[46] D.A. Salick, J.K. Kretsinger, D.J. Pochan, J.P. Schneider, J. Am. Chem. Soc. 129 (2007) 14793–14799.
[47] L. Chu, H. Gao, T. Cheng, Y. Zhang, J. Liu, F. Huang, C. Yang, L. Shi, J. Liu, ChemComm 52 (2016) 6265–6268.
[48] N. Habibi, N. Kamaly, A. Memic, H. Shafiee, Nano Today 11 (2016) 41–60.
[49] J. Wang, X.Y. Chen, Y. Zhao, Y. Yang, W. Wang, C. Wu, B. Yang, Z. Zhang, L. Zhang, Y. Liu, X. Du, W. Li, L. Qiu, P. Jiang, X.Z. Mou, Y.Q. Li, ACS Nano 13 (2019) 11686–11697.
[50] H. Moravej, Z. Moravej, M. Yazdanparast, M. Heiat, A. Mirhosseini, M.M. Moosazadeh, R. Mirnejad, Microb. Drug Resist. 24 (2018) 747–767.

[51] N. Malanovic, K. Lohner, Pharmaceuticals 9 (2016) 59.
[52] L. Li, J. Li, J. Guo, H. Zhang, X. Zhang, C. Yin, L. Wang, Y. Zhu, Q. Yao, Adv. Funct. Mater. 29 (2018) 1807356.
[53] P. Cardoso, H. Glossop, T.G. Meikle, A. Aburto-Medina, C.E. Conn, V. Sarojini, C. Valery, Biophys. Rev. (2021) 1–35.
[54] P. Chairatana, H. Chu, P.A. Castillo, B. Shen, C.L. Bevins, E.M. Nolan, Chem. Sci. 7 (2016) 1738–1752.
[55] Yu Fan, Xiang-Dan Li, Ping-Ping He, Xiao-Xue Hu, Kuo Zhang, Jia-Qi Fan, Pei-Pei Yang, Hao-Yan Zheng, Wen Tian, Zi-Ming Chen, Lei Ji, Hao Wang, L. Wang, Sci. Adv., 6 (2020) eaaz4767.
[56] Z. Huang, Y. Liu, L. Wang, A. Ali, Q. Yao, X. Jiang, Y. Gao, Biomaterials 253 (2020) 120124.
[57] R.E.W. Hancock, H.-G. Sahl, Nat. Biotechnol. 24 (2006) 1551–1557.
[58] M.R. Yeaman, N.Y. Yount, Pharmacol. Rev. 55 (2003) 27–55.
[59] R.M. Epand, H.J. Vogel, Biochim. Biophys. Acta – Biomembr. 1462 (1999) 11–28.
[60] N. Mookherjee, M.A. Anderson, H.P. Haagsman, D.J. Davidson, Nat. Rev. Drug Discov. 19 (2020) 311–332.
[61] M.J. McKay, F. Afrose, R.E. Koeppe, D.V. Greathouse, Biochim. Biophys. Acta – Biomembr. 1860 (2018) 2108–2117.
[62] O. Scudiero, E. Nigro, M. Cantisani, I. Colavita, M. Leone, F.A. Mercurio, M. Galdiero, A. Pessi, A. Daniele, F. Salvatore, S. Galdiero, Int. J. Nanomed. 10 (2015) 6523–6539.
[63] X. Tian, F. Sun, X.R. Zhou, S.Z. Luo, L. Chen, J. Pept. Sci. 21 (2015) 530–539.
[64] S. Malekkhaiat Häffner, M. Malmsten, Curr. Opin. Colloid Interface Sci. 38 (2018) 56–79.
[65] H. Gill, M.R. Gokel, M. McKeever, S. Negin, M.B. Patel, S. Yin, G.W. Gokel, Coordin Chem Rev 412 (2020) 213264.
[66] W. Liu, L. Miao, X. Li, Z. Xu, Coordin Chem Rev 429 (2021) 213646.
[67] Y. Huang, W. Chen, J. Chung, J. Yin, J. Yoon, Chem. Soc. Rev. 50 (2021) 7725–7744.
[68] C. Ren, H. Wang, X. Zhang, D. Ding, L. Wang, Z. Yang, ChemComm 50 (2014) 3473–3475.
[69] C.B. Park, H.S. Kim, S.C. Kim, Biochem. Biophys. Res. Commun. 244 (1998) 253–257.
[70] A.C. Seefeldt, F. Nguyen, S. Antunes, N. Perebaskine, M. Graf, S. Arenz, K.K. Inampudi, C. Douat, G. Guichard, D.N. Wilson, C.A. Innis, Nat. Struct. Mol. Biol. 22 (2015) 470–475.
[71] R.N. Roy, I.B. Lomakin, M.G. Gagnon, T.A. Steitz, Nat. Struct. Mol. Biol. 22 (2015) 466–469.
[72] Z. Yang, G. Liang, Z. Guo, Z. Guo, B. Xu, Angew. Chem. Int. Ed. 46 (2007) 8216–8219.
[73] N.G. Bednarska, J. van Eldere, R. Gallardo, A. Ganesan, M. Ramakers, I. Vogel, P. Baatsen, A. Staes, M. Goethals, P. Hammarstrom, K.P. Nilsson, K. Gevaert, J. Schymkowitz, F. Rousseau, Mol. Microbiol. 99 (2016) 849–865.
[74] C.M.R. Pérez, N. Stephanopoulos, S. Sur, S.S. Lee, C. Newcomb, S.I. Stupp, Ann. Biomed. Eng. 43 (2015) 501–514.
[75] L. Yu, Y. Yang, C. Wang, Adv. Exp. Med. Biol. 1174 (2019) 35–60.
[76] H. Chu, M. Pazgier, G. Jung, S.-P. Nuccio, P.A. Castillo, M.F. de Jong, M.G. Winter, S.E. Winter, J. Wehkamp, B. Shen, N.H. Salzman, M.A. Underwood, R. M. Tsolis, G.M. Young, W. Lu, R.I. Lehrer, A.J. Baeumler, C.L. Bevins, Science 337 (2012) 477–481.
[77] H. Jang, F.T. Arce, M. Mustata, S. Ramachandran, R. Capone, R. Nussinov, R. Lal, Biophys. J. 100 (2011) 1775–1783.
[78] O.S. Makin, E. Atkins, P. Sikorski, J. Johansson, L.C. Serpell, Proc. Natl. Acad. Sci. U.S.A. 102 (2005) 315–320.
[79] X. Yan, P. Zhu, J. Li, Chem. Soc. Rev. 39 (2010) 1877–1890.
[80] X. Yan, Q. He, K. Wang, L. Duan, Y. Cui, J. Li, Angew. Chem. Int. Ed. 119 (2007) 2483–2486.
[81] S.L. Porter, S.M. Coulter, S. Pentlavalli, T.P. Thompson, G. Laverty, Acta Biomater. 77 (2018) 96–105.
[82] M. Igarashi, R. Sawa, N. Kinoshita, H. Hashizurne, N. Nakagawa, Y. Homma, Y. Nishimura, Y. Akamatsu, J. Antibiot. 61 (2008) 387–393.
[83] Y. Zhao, L.J. Leman, D.J. Search, R.A. Garcia, D.A. Gordon, B.E. Maryanoff, M.R. Ghadiri, ACS Cent. Sci. 3 (2017) 639–646.
[84] B. Claro, E. González-Freire, M. Calvelo, L.J. Bessa, E. Goormaghtigh, M. Amorín, J. R. Granja, R. Garcia-Fandiño, M. Bastos, Colloids Surf. B 196 (2020) 111349.
[85] J. Li, J. Wang, Y. Zhao, P. Zhou, J. Carter, Z. Li, T.A. Waigh, J.R. Lu, H. Xu, Coordin Chem Rev 421 (2020) 213418.
[86] F. Qiu, Y. Chen, C. Tang, X. Zhao, Int. J. Nanomed. 13 (2018) 5003–5022.
[87] Z. Gong, Y. Shi, H. Tan, L. Wang, Z. Gao, B. Lian, G. Wang, H. Sun, P. Sun, B. Zhou, J. Bai, ACS Appl. Mater. Interfaces 12 (2020) 4323–4332.
[88] M. Beter, H.K. Kara, A.E. Topal, A. Dana, A.B. Tekinay, M.O. Guler, Mol. Pharm. 14 (2017) 3660–3668.
[89] W.Y. Seow, C.A.E. Hauser, Mater. Today 17 (2014) 381–388.
[90] N. Nandi, K. Gayen, S. Ghosh, D. Bhunia, S. Kirkham, S.K. Sen, S. Ghosh, I.W. Hamley, A. Banerjee, Biomacromolecules 18 (2017) 3621–3629.
[91] E. Vives, Priscille Brodin, B. Lebleu, J. Biol. Chem. 272 (1997) 16010–16017.
[92] A. Ho, S.R. Schwarze, S.J. Mermelstein, G. Waksman, S.F. Dowdy, Cancer Res. 61 (2001) 474–477.
[93] S. Fawell, J. Seery, Y. Daikh, C. Moore, L.L. Chen, B. Pepinsky, J. Barsoum, Proc. Natl. Acad. Sci. U.S.A. 91 (1994) 664–668.
[94] J.J. Turner, S. Jones, M.M. Fabani, G. Ivanova, A.A. Arzumanov, M.J. Gait, Blood Cells Mol. Dis. 38 (2007) 1–7.
[95] L. Liu, K. Xu, H. Wang, P.K. Tan, W. Fan, S.S. Venkatraman, L. Li, Y.Y. Yang, Nat. Nanotechnol. 4 (2009) 457–463.
[96] S. Debnath, A. Shome, D. Das, P.K. Das, J. Phys. Chem. 114 (2010) 4407–4415.
[97] A.Y. Gahane, P. Ranjan, V. Singh, R.K. Sharma, N. Sinha, M. Sharma, R. Chaudhry, A.K. Thakur, Soft matter 14 (2018) 2234–2244.
[98] M. Criado-Gonzalez, M.H. Iqbal, A. Carvalho, M. Schmutz, L. Jierry, P. Schaaf, F. Boulmedais, Front. bioeng. biotechnol. 8 (2020) 938.
[99] T. Diehl, M.T.S. Krause, S. Ueberlein, S. Becker, A. Trommer, G. Schnakenburg, M. Engeser, Dalton Transl. 46 (2017) 2988–2997.
[100] X.Y. Zhang, Y.Q. Zhao, Y.D. Zhang, A.Z. Wang, X.K. Ding, Y. Li, S. Duan, X.J. Ding, F.J. Xu, Biomacromolecules 20 (2019) 4171–4179.
[101] C.D. Spicer, C. Jumeaux, B. Gupta, M.M. Stevens, Chem. Soc. Rev. 47 (2018) 3574–3620.
[102] F. Zhao, M.L. Ma, B. Xu, Chem. Soc. Rev. 38 (2009) 883–891.
[103] M.J. Webber, J.B. Matson, V.K. Tamboli, S.I. Stupp, Biomaterials 33 (2012) 6823–6832.
[104] R. Orbach, L. Adler-Abramovich, S. Zigerson, I. Mironi-Harpaz, D. Seliktar, E. Gazit, Biomacromolecules 10 (2009) 2646–2651.
[105] D.M. Ryan, S.B. Anderson, F.T. Senguen, R.E. Youngman, B.L. Nilsson, Soft Matter 6 (2010) 475–479.
[106] J. Wang, D.L. Cooper, W. Zhan, D. Wu, H. He, S. Sun, S.T. Lovett, B. Xu, Angew. Chem. Int. Ed. 58 (2019) 10631–10634.
[107] G. Xie, S. Gao, J. Ou, M. Zhu, M. Wu, X. Ju, Z. Li, Y. Tian, Z. Niu, Nano Lett. 21 (2021) 1722–1728.
[108] P. Wadhwani, N. Heidenreich, B. Podeyn, J. Burck, A.S. Ulrich, Biomater. Sci. 5 (2017) 817–827.
[109] Z. Wang, R. Levy, D.G. Fernig, M. Brust, Bioconjug. Chem. 16 (2005) 497–500.
[110] M.W. Cao, R.R. Xing, R. Chang, Y. Wang, X.H. Yan, Coordin Chem Rev 397 (2019) 14–27.
[111] R. Chang, X. Yan, Small Struct. 1 (2020) 2000068.
[112] G. Fabregat, B. Teixeira-Dias, L.J. del Valle, E. Armelin, F. Estrany, C. Aleman, ACS Appl. Mater. Interfaces, 6 (2014) 11940-11954.
[113] G.A. Buckholtz, N.A. Reger, W.D. Anderton, P.J. Schimoler, S.L. Roudebush, W. S. Meng, M.C. Miller, E.S. Gawalt, Mater. Sci. Eng. C 65 (2016) 126–134.
[114] M.S. Ekiz, G. Cinar, M.A. Khalily, M.O. Guler, Nanotechnology 27 (2016) 402002.
[115] C.Y. Yu, W. Huang, Z.P. Li, X.Y. Lei, D.X. He, L. Sun, Curr. Top. Med. Chem. 16 (2016) 281–290.
[116] R.R. Xing, C.Q. Yuan, S.K. Li, J.W. Song, J.B. Li, X. Yan, Angew. Chem. Int. Ed. 57 (2018) 1537–1542.
[117] J.W. Ko, W.S. Choi, J. Kim, S.K. Kuk, S.H. Lee, C.B. Park, Biomacromolecules 18 (2017) 3551–3556.
[118] Q.L. Zou, K. Liu, M. Abbas, X.H. Yan, Adv. Mater. 28 (2016) 1031–1043.
[119] Y.X. Li, Q.L. Zou, C.Q. Yuan, S.K. Li, R.R. Xing, X. Yan, Angew. Chem. Int. Ed. 57 (2018) 17084–17088.
[120] Y.H. Wu, Y.B. Long, Q.L. Li, S.Y. Han, J.B. Ma, Y.W. Yang, H. Gao, A.C.S. Appl, Mater. Interfaces 7 (2015) 17255–17263.
[121] Y.M. Mohan, K. Lee, T. Premkumar, K.E. Geckeler, Polymer 48 (2007) 158–164.
[122] Y.K. Zhang, H. Zhang, Q.L. Zou, R.R. Xing, T.F. Jiao, X.H. Yan, J Mater Chem B 6 (2018) 7335–7342.
[123] J.W. Xu, K. Yao, Z.K. Xu, Nanoscale 11 (2019) 8680–8691.
[124] Z.Z. Yang, Z.R. Sun, Y. Ren, X. Chen, W. Zhang, X.H. Zhu, Z.W. Mao, J.L. Shen, S. N. Nie, Mol Med Rep 20 (2019) 5–15.
[125] P. Agostinis, K. Berg, K.A. Cengel, T.H. Foster, A.W. Girotti, S.O. Gollnick, S.M. Hahn, M.R. Hamblin, A. Juzeniene, D. Kessel, M. Korbelik, J. Moan, P. Mroz, D. Nowis, J. Piette, B.C. Wilson, J. Golab, CA: Cancer, J. Clin. 61 (2011) 250–281.
[126] P. Babilas, S. Karrer, A. Sidoroff, M. Landthaler, R.M. Szeimies, Photodermatol Photo 21 (2005) 142–149.
[127] M. Abbas, Q. Zou, S. Li, X. Yan, Adv. Mater. 29 (2017) 1605021.
[128] M.J. Kogan, I. Olmedo, L. Hosta, A.R. Guerrero, L.J. Cruz, F. Albericio, Nanomedicine (Lond) 2 (2007) 287–306.
[129] M.R. Hamblin, Photoch. Photobio. Sci. 17 (2018) 1515–1533.
[130] S. Gao, X. Yan, G. Xie, M. Zhu, X. Ju, P.J. Stang, Y. Tian, Z. Niu, Proc. Natl. Acad. Sci. U.S.A. 116 (2019) 23437–23443.
[131] A. Pizzi, C. Pigliacelli, G. Bergamaschi, A. Gori, P. Metrangolo, Coordin. Chem. Rev. 411 (2020) 213242.
[132] M. Abbas, H.H. Susapto, C.A. Hauser, ACS Omega 7 (2022) 2082–2090.
[133] Y.M. Mohan, K. Vimala, V. Thomas, K. Varaprasad, B. Sreedhar, S.K. Bajpai, K. M. Raju, J. Colloid Interf. Sci. 342 (2010) 73–82.
[134] D.E. Fullenkamp, J.G. Rivera, Y.K. Gong, K.H.A. Lau, L.H. He, R. Varshney, P.B. Messersmith, Biomaterials 33 (2012) 3783–3791.
[135] Z. Qin, Y. Zheng, Y. Wang, T. Du, C. Li, X. Wang, H. Jiang, Coordin. Chem. Rev. 449 (2021) 214218.
[136] M.R. Reithofer, A. Lakshmanan, A.T.K. Ping, J.M. Chin, C.A.E. Hauser, Biomaterials 35 (2014) 7535–7542.
[137] F. Martinez-Gutierrez, P.L. Olive, A. Banuelos, E. Orrantia, N. Nino, E.M. Sanchez, F. Ruiz, H. Bach, Y. Av-Gay, Nanomed.: Nanotechnol. Biol. Med. 6 (2010) 681–688.
[138] K.A. Seferji, H.H. Susapto, B.K. Khan, Z.U. Rehman, M. Abbas, A.-H. Emwas, C.A. Hauser, ACS Appl. Bio Mater. 4 (2021) 8522–8535.
[139] L. Rizzello, P.P. Pompa, Chem. Soc. Rev. 43 (2014) 1501–1518.
[140] P.Y. Yuan, X. Ding, Y.Y. Yang, Q.H. Xu, Adv. Healthc. Mater. 7 (2018) 1701392.
[141] E. Weir, A. Lawlor, A. Whelan, F. Regan, Analyst 133 (2008) 835–845.
[142] V. Alt, T. Bechert, P. Steinrucke, M. Wagener, P. Seidel, E. Dingeldein, E. Domann, R. Schnettler, Biomaterials 25 (2004) 4383–4391.
[143] G.X. Meng, A. Grabiec, M. Vallon, B. Ebe, S. Hampel, W. Bessler, H. Wagner, C.J. Kirschning, J. Biol. Chem. 278 (2003) 39822–39829.

[144] R.M. Burch, M. Weitzberg, N. Blok, R. Muhlhauser, D. Martin, S.G. Farmer, J.M. Bator, J.R. Connor, C. Ko, W. Kuhn, B.A. Mcmillan, M. Raynor, B.G. Shearer, C. Tiffany, D.E. Wilkins, Proc. Natl. Acad. Sci. U.S.A. 88 (1991) 355–359.
[145] J. Song, C. Yuan, T. Jiao, R. Xing, M. Yang, D.J. Adams, X. Yan, Small (2020) e1907309.
[146] Y. Wang, L. Cao, S. Guan, G. Shi, Q. Luo, L. Miao, I. Thistlethwaite, Z. Huang, J. Xu, J. Liu, J. Mater. Chem. 22 (2012) 2575–2581.
[147] M.O. Guler, R.C. Claussen, S.I. Stupp, J. Mater. Chem. 15 (2005) 4507–4512.
[148] F. Paladini, S.T. Meikle, I.R. Cooper, J. Lacey, V. Perugini, M. Santin, J. Mater. Sci.: Mater. Med. 24 (2013) 2461–2472.
[149] M. Bajaj, S.K. Pandey, T. Nain, S.K. Brar, P. Singh, S. Singh, N. Wangoo, R.K. Sharma, Colloids Surf. B 158 (2017) 397–407.
[150] C. Yuan, A. Levin, W. Chen, R. Xing, Q. Zou, T.W. Herling, P.K. Challa, T.P. Knowles, X. Yan, Angew. Chem. Int. Ed. 131 (2019) 18284–18291.
[151] M. Abbas, W.P. Lipiński, K.K. Nakashima, W.T. Huck, E. Spruijt, Nat. Chem. (2021) 1–9.
[152] M. Zheng, S. Ruan, S. Liu, T. Sun, D. Qu, H. Zhao, Z. Xie, H. Gao, X. Jing, Z. Sun, ACS Nano 9 (2015) 11455–11461.
[153] L. Yan, F. Zhao, S. Li, Z. Hu, Y. Zhao, Nanoscale 3 (2011) 362–382.
[154] T. Ganz, Nature 412 (2001) 392–393.

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