

Recent mitigation strategies in engineered healthcare materials towards antimicrobial applications

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Abstract

The design of material surfaces with antimicrobial properties is highly relevant to the fabrication of medical devices. Biofilm formation with its subsequent infection constitutes a primary reason for device failure. Hence, it is highly relevant to design healthcare materials with antibacterial properties which can efficiently resist biofilm formation and infection. The present current opinion article attempts to give a brief overview of some more recent advances in infection mitigation strategies. A major emphasis has been placed on material science and biological perspectives of biomaterial infection and corresponding mitigation strategies to prevent infection.

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Abbreviations

Gold Nanoparticles, AuNP; Silver Nanoparticles, AgNP; Quorum sensing, QS; Antimicrobial Peptides, AMP; Reactive oxygen species, ROS; Antimicrobial peptides, AMPs; Polycaprolactone, PCL.

Introduction

Bioengineered biomaterials in the body encompass a wide range of medical devices including dental prosthetics, surgical joint replacement implants, indwelling medical devices like pacemakers or catheters, and biodegradable tissues, hydrogels, sutures, and fixators. The placement of these devices produces an environment rich with serum and plasma proteins as well as

other nutrients which attract bacteria to the wound site. As a result, a significant number of these implants or devices become colonized and subsequently infected [1]. US-Centers for Disease Control and Prevention (CDC) reports indicate between 50% and 70% of all hospital-acquired infections can be attributed to medical devices, contributing significantly to morbidity and mortality among patients [2].

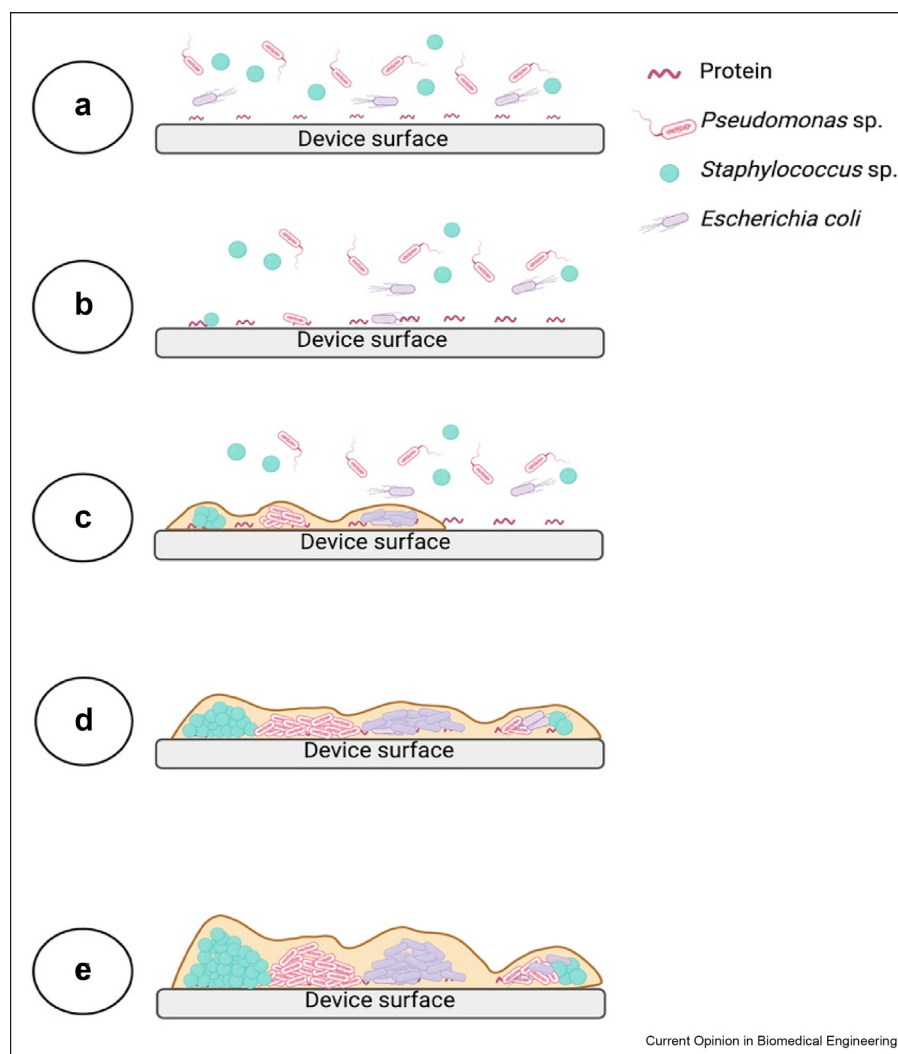
The phases of biofilm development can be reviewed in the following references [1,3,4] with a summary in Figure 1. Antimicrobial activity can be classified in one of two ways (1) a passive strategy in which the material properties of the device deter microorganism growth (also referred to as antifouling strategy) and (2) an active strategy that includes the bactericidal action of released antimicrobial agents that kill the infecting microorganisms (also referred to as bactericidal strategy). Both strategies aim to prevent biofilm formation and subsequent cascades of infection. The following sections discuss in detail regarding the different antimicrobial approaches currently employed for health care materials.

Antifouling approach to combat infection in engineered healthcare materials

Antifouling approaches mainly focus on the important material properties including surface wettability, surface charge and surface energy [5,6]. Fine-tuning these properties can increase biomaterial resistance to colonization. Surface topography, more specifically nanoscale topography like nanopatterns and nanogrooves, can be exploited to deter bacterial settlement [7–10]. This nanoscale topography also mechanically disrupts bacterial cell membranes [10].

Surface wettability and surface charge are primary influencers in bacterial adhesion to the material surface [5]. These flexible traits can be tweaked to optimize inherent material defense mechanisms [6]. Changes in these parameters such as surface wettability, hydrophilic surfaces, and superhydrophobic are effective in preventing biofilm formation [7–9]. This can be attributed to the protein adsorption and cell attachment process [10]. Studies in surface charge have found that cationic charge-bearing materials are highly resistant to colonization secondary to cell lysis caused by membrane penetration or the release of

Figure 1



Progression of biofilm formation on device surface. Physical surface characteristics and charge dynamics recruit proteins (a) and then bacterial pioneers to settle (b). Microcolonies of bacterial kin, the product of binary fission, are formed and begin to secrete extracellular polymeric substances (EPS) including proteins, extracellular DNA, lipids, and polysaccharides, which build up to form a maturing biofilm (c). Biofilm associated quorum sensing then recruits additional individuals who subsequently settle (d–e).

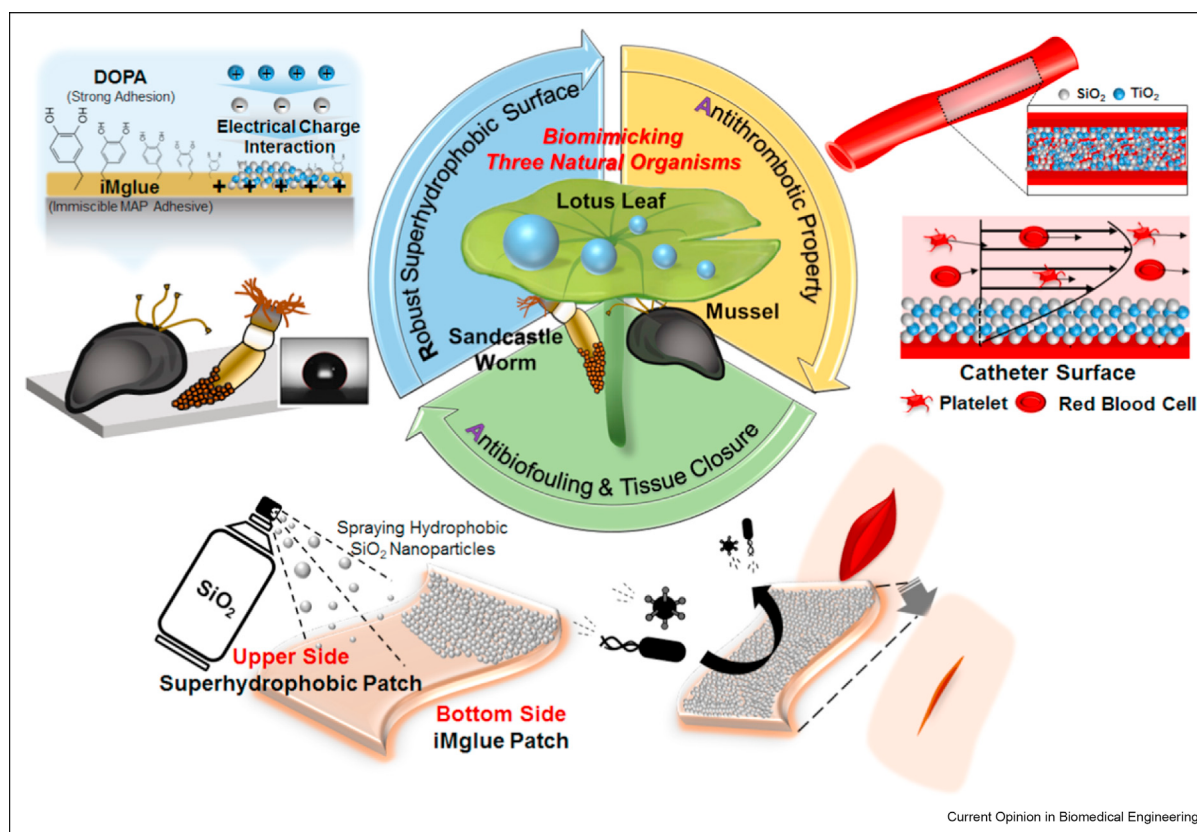
multivalent cations upon contact to a cationic surface [11,12]. Drawbacks to these approaches exist, even superhydrophobic (SH) surface modification, while efficient to prevent bacterial adhesion, lacks the durability necessary for sustained prevention and the toxicity associated with its character seriously limits its practical utility for biomedical applications [13].

To bridge this gap, Han et al. have reported a combinatorial biomimicking strategy using lotus leaf, mussel, and sandcastle worm [14]. Their objective was to design more stable and biocompatible SH coatings that could be applied to medical devices (Figure 2). This robust naturally inspired coating was created using a mussel

adhesive protein (iMglue), and $\text{SiO}_2(\text{TiO}_2/\text{SiO}_2)_2$ nanoparticles through a process called solution-based electrical charge-controlled layer-by-layer growth of nanoparticles. The coating was then applied to the inner diameter of a catheter tube and clearly displayed both antibacterial and antithrombotic effects.

In another interesting study, Facchi et al. have reported a cationic polyelectrolyte multilayer which can prevent the growth of the two detrimental healthcare pathogens, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [15]. Specifically, the cationic multilayer was prepared by the combination of cationic tannin derivative, iota-carrageenan and pectin and exhibited both antiadhesive and antimicrobial action against *S. aureus* and *P. aeruginosa*.

Figure 2



Comprehensive summary and biomedical multifunctionality of the robust superhydrophobic surface with water-immiscible underwater adhesive. "Adapted with permission from Han *et al.* [14]. Copy right (2019) American Chemical Society."

The common antibacterial mechanism reported in all these approaches focuses on tailoring surface energy, surface charge and surface topography to deter the bacterial growth.

In general, tailoring material properties such as surface energy and surface charge is a good strategy for fabricating antifouling surfaces, it still faces some major challenges. More specifically, the mutation and emergence of resistant bacterial strains and the long-term stability concerns of the modified surface properties of the materials. This makes it highly challenging to fabricate efficient and stable antifouling materials. This necessitates the development of more effective bactericidal approach where the active bactericidal agent can prevent the growth of different bacterial strains in much efficient manner.

Bactericidal approach to combat infection in engineered healthcare materials

With bactericidal approaches, antibacterial capability is conferred to the device by the incorporation of different agents, primarily metallic nanoparticles, antimicrobial peptides (AMPs) and biological agents (including

quorum sensors, bacteriophages, lysins, and bacteriocins). The following section discuss in more detail regarding these bactericidal agents.

A. Material-based bactericidal agents

Metallic nanoparticles such as gold (AuNp) and silver (AgNp) nanoparticles have received considerable attention as antimicrobials [16,17]. The rise in multi-drug resistance stresses the importance of metallic nanoparticles in infection treatment [18]. These particles offer desirable physio-chemical properties that make them suitable for the detection and treatment of bacterial infections [19]. These properties strongly depend on the composition, size, and shape of the prepared nanoparticles [20–22]. For instance, the mechanistic action of AuNp can be attributed to the inhibition of the binding process of ribosome subunits with the transport RNA [16,23]. Another important AuNp mechanism is the production of large amount of reactive oxygen species (ROS) [23]. They are more efficient for the treatment of infections caused by bacterial strains such as *Escherichia coli*, *Candida albicans*, and *S. aureus* [16]. The improved performance of the silver nanoparticles can be attributed to the release of

silver ions and subsequent production of excess ROS species [24].

A current study by Zhao et al. has succeeded in addressing device failures in polyurethane (PU)-based materials [30]. Polyurethane is particularly susceptible to bacterial colonization which seriously compromises device success. To counteract PU susceptibility, Zhao et al. coated PU devices with a gold nanorod-PEG layer, conferring bactericidal qualities to the material (Figure 3).

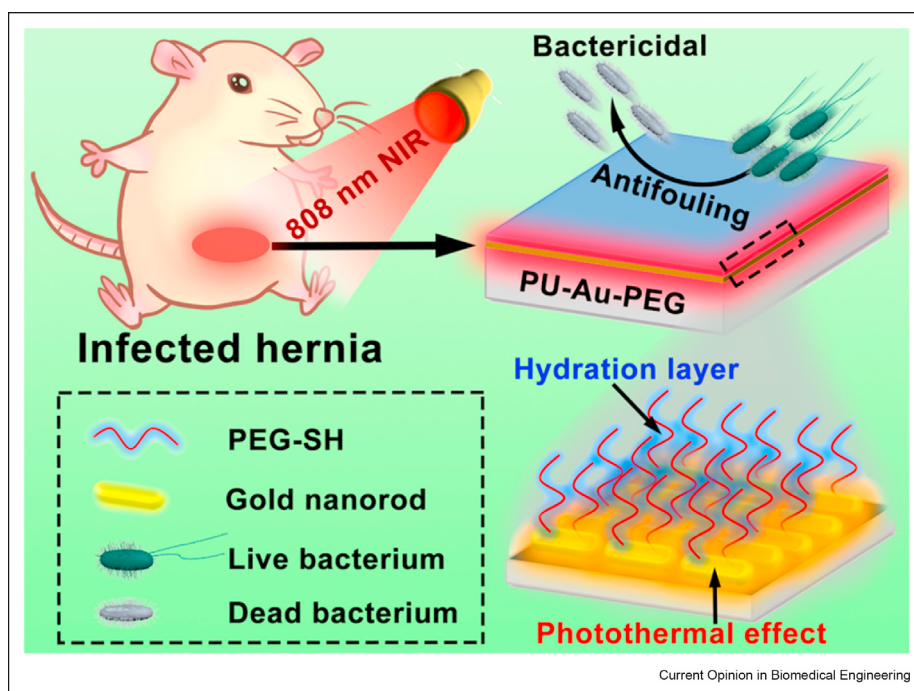
The bactericidal nature of gold nanorods lies in its near infra-red (NIR) characteristics, which act a photo-thermal deterrent. This study clearly establishes the potential of gold nanorods as an antimicrobial device coating.

Another interesting study conducted by Abdelaziz et al. reported the use of surface-embedded AgNp in polycaprolactone-based electrospun fibers to enhance fiber resistance to microbial colonization [26]. The results have shown the excellent antibacterial performance of the fibers. All these reported metallic nanoparticles-based bactericidal approaches rely on the detrimental effects of the metallic ions to the bacterial cells which prevents the biofilm formation.

Even though metallic nanoparticles exhibited good antibacterial performance, the emergence of resistant bacterial strains is one of the major concerns [18]. ESKAPE pathogens in particular demonstrate multi-drug resistance and represent a growing threat [27]. This necessitated the development of new material-based bactericidal agents. In this regard, antimicrobial peptides (AMPs) represent a promising material-based bactericidal agents for treating infections [28]. The mechanism of action of these peptides comprises of disrupt cell membranes, cell signaling, degrade EPS, and inhibit the stringent response [27]. AMPs also possess immunomodulatory and anticancer properties and are used for both tissue engineering and drug delivery [28]. The plethora of recent research is a testament to the functionality of these proteins to address current and future infection crises.

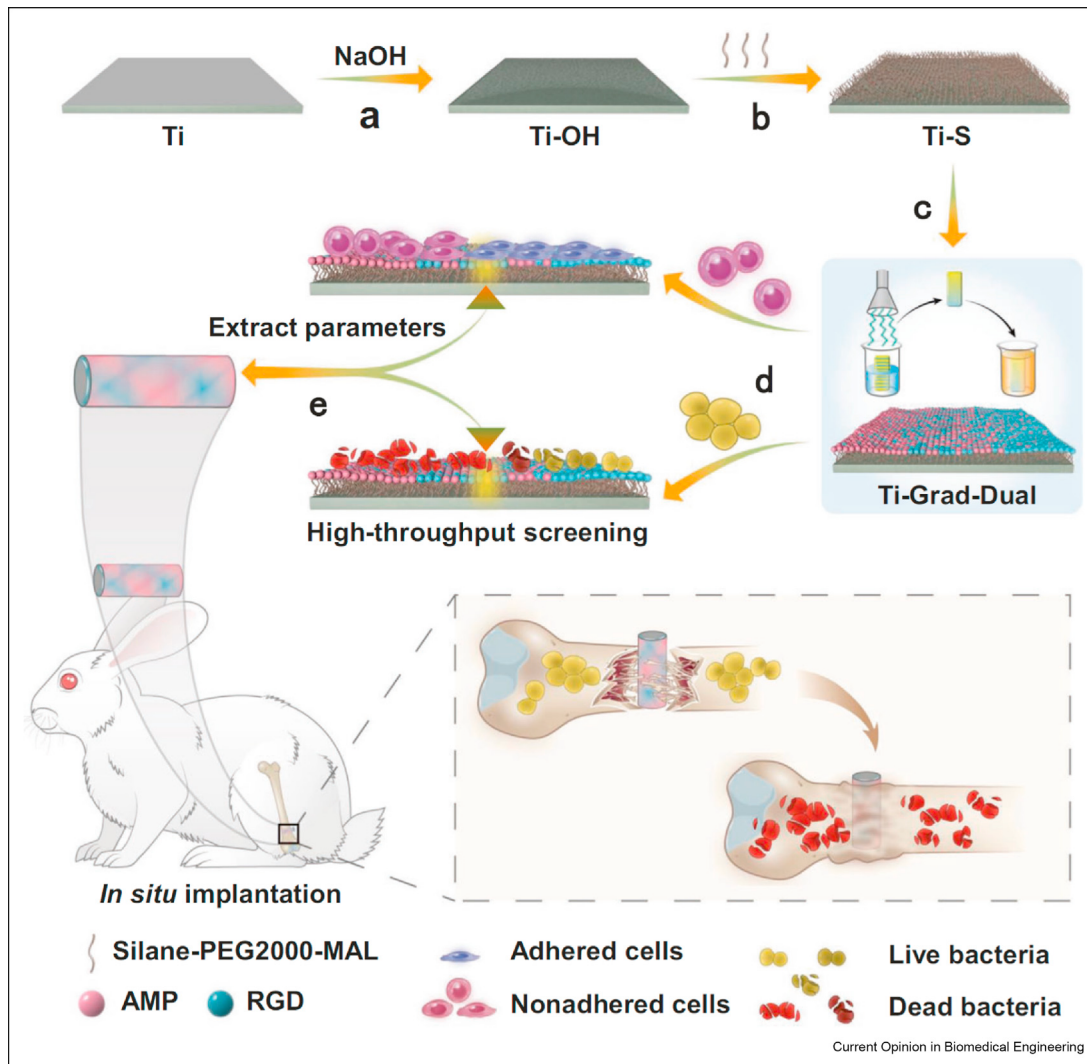
How can these AMPs be better administrated and employed? A common theme from recent studies ties the concentration of these peptides to their efficacy as well as their cytotoxicity and delayed wound healing [29]. In response, Fang et al. designed a high-throughput strategy for optimizing peptide densities/ratios and preparation parameters on material surfaces [30]. Titanium, a widely used orthopedic material, was selected as the model biomaterial (Figure 4). By

Figure 3



NIR-Responsive PU-Au-PEG surface with antifouling and photothermal bactericidal properties. "Adapted with permission from Zhao et al. [25]. Copy right (2020) American Chemical Society."

Figure 4



Schematic illustration of a platform for high-throughput screening and rational design of the biofunctionalized surfaces with optimized biocompatibility and antimicrobial activity. "Adapted with permission from Fang *et al.* [30]. Copy right (2021) Springer Nature."

applying the screening method, two optimal peptides were identified and successfully applied to the titanium surface, simultaneously improving the biomaterial's antibacterial character as well as its biocompatibility.

Yet another novel study by Najmi *et al.* reported the usage of Nisin and LL-37 peptides for the prevention of bacterial infection and the acceleration of articular cartilage healing [31]. Competitive experiments on 3D spheroid models of cartilage cells in a bioreactor between the Nisin peptide and LL-37 showed Nisin's superior antibacterial action and increased cytocompatibility. All these approaches rely on the detrimental action of AMP on the bacterial cells which prevents the biofilm formation.

It was clear that the usage of metallic nanoparticles and AMP-based bactericidal agents have clearly demonstrated excellent antibacterial responses; however, it is worth to mention that they are not able to completely overcome all the challenges needed for making clinical translation. For example, it is highly necessary that the material used for killing the bacterial strains should not elicit any toxicity concerns to our body. While using metallic nanoparticles like silver nanoparticles, this is one of the major concerns. Then regarding the antimicrobial peptides, the synthesis of these peptides is tedious and expensive which makes it challenging to use. Hence, careful optimization should be required to address these challenges for making an impact for clinical applications.

B. Biological bactericidal agents

There are many biological biocidal agents used for deterring the growth of bacterial growth. The following section will discuss more on the biological agents currently used. Quorum sensing (QS) is a process defined as the cell-to-cell communication between individual bacterium during the formation of biofilm [32]. As the number of individuals in a colony increases, the concentration of QS molecules increases. Over time this triggers subsequent bacterial settlement that grows and more firmly establishes the biofilm environment [32]. This has inspired researchers to explore new therapeutic strategies that target QS molecules produced by bacteria.

One such exploratory study conducted by Dapunt et al. reported the use of avian IgY antibodies against Gram-positive *Staphylococci* species which communicate via QS molecules such as AtlE, PIA, and GroEL [33]. The findings showed that IgY antibodies were very efficient to inhibit the production and secretion of all the QS molecules, consequently preventing biofilm formation. This study clearly indicates the futuristic potential of QS inhibitors towards the development of infection resistant biomaterials.

Bacteriophages, known simply as phages, have historically been used by medical practitioners to treat a variety of infections [4]. With the growing specter of antibiotic resistance, however, optimizing phage efficacy as an antimicrobial has experienced a renaissance. Challenges in phage therapies are sweeping. Most bacteria host resistance mechanisms like CRISPR, restriction modification, and abortive infection systems, to name a few [34,35]. Site specific delivery of phages also presents a barrier to treatment efficacy. Finally, extinction of host bacteria is counter-intuitive to phage survival, which leads to a steady state equilibrium that enables both predator and prey to persist [4]. Thus far, the addition of phage to biomaterials has focused mainly on biosensor and pathogen capture assays. These same techniques, most of which use physisorption, covalent bonding, electrostatic, or ligand-binding, have the potential to be modified as therapies for infection control and treatment [36,37]. Despite the discrepancy in focus, there do exist a select few studies that target infecting bacteria. In one such study by Nogueira et al., electrospun polycaprolactone (PCL) fibers were activated and then functionalized with vB_Pae_Kakheti25 phages which infect *P. aeruginosa*. By orienting phages tail side out on the fibers, researchers established that immobilized phages on this textile-based wound dressing were able to first adsorb and then successfully kill infecting bacteria [38].

Similar to using phage, endolysins (also known as lysins) are enzymes produced by phage at the end of

the lytic cycle which hydrolyze the bacterial cell wall [39]. Numerous studies have explored the applications of these enzymes as antimicrobials to treat infections in the urinary tract to the skin to the respiratory system [39–42]. Examples of lysins in use today include lysostaphin, which is effective against methicillin-resistance *Staphylococcus* as well as KZ144, effective against *Pseudomonas*. Lysins exist, however, for most every bacterial species. Mechanism of action is common and includes degradation of the peptidoglycan layer from inside the cell which disrupt cell membrane integrity, precipitating cell lysis. Benefits of lysins include a short half-life [43], demonstrated kill kinetics with persister cells, high specificity which leaves collateral microbiome cells unaffected, absence of bacterial resistance and finally no cytotoxicity as eukaryotic cells are unaffected by bacterial lysins [41]. Of course, their rapid mode of action, short half-life and specificity can all be seen a constraint to the use of these biologicals. There also exist challenges in translocating these enzymes across the outer membrane (OM) in Gram-negative bacteria, especially in external administration.

For this, researches have paired lysins with bacteriocins to produce what is known as a lysocin. Bacteriocins are small stable ribosomally synthesized antimicrobial peptides produced by both Gram-positive and Gram-negative bacteria [44] for niche competition. These AMPs are capable of crossing the bacterial OM and bringing with them their attached lysin. Heselpoth et al. combined two domains from the S-type pyocin (PyS2) with a lysin GN4 which then effected intracellular delivery of the lysin itself. The engineered antimicrobial is demonstrably thermostable, and bactericidal with a minimum inhibitory concentration $\geq 0.1 \mu\text{g/mL}$ against limited pseudomonal strains. Mechanism of action for this lysocin exploits the ferripyoverdine receptor FpvAI, which allows for sequestration of the small siderophore in iron deficient environments [45].

A final class of biologically synthesized antimicrobials which also target bacteria specific receptors are tailocins. Tailocins are bactericidal proteins synthesized by bacteria and which closely resemble a *Myo*- or Siphoviridae phage tail. These proteins are target site specific, binding to the surface of a bacterium and causing cell lysis from without. Mechanism of action is membrane depolarization as a result of puncture and dissipation of the proton motive force [46]. Tailocins are primarily produced by gram-negative bacteria [44] and are effective against closely related bacteria living in community.

A common drawback to all these biologically based antimicrobials, whether phage, lysins, bacteriocins, or tailocins, is their high specificity. Most infections, while dominated by a single species, are comprised of multiple

species infecting together. To kill off the primary offender does not equate with infection resolution but oftentimes means another offender takes its place. As such, cocktails would be necessary to fully treat the encroaching growth. Additionally, there exists the risk of resistance. This is commonly seen in phage treatment and occurs for any biocidal which targets receptor specific sites. A single point mutation is all that is needed to convert a susceptible cell to a resistant one.

Antimicrobial products for biomedical applications

The different antibacterial strategies explained above, both antifouling and bactericidal, are utilized to fabricate different biomedical products such as hydrogels, bone cements, and polymer scaffolds [47–49]. In general, these materials are widely utilized in tissue engineering applications for bone, skin, and heart. Biofilm formation and subsequent infection are a major hurdle faced by these materials for clinical translation. Addressing these challenges with multifaceted materials is important to leverage these technologies for the common good. Our group at UAB Polymers & Healthcare Materials/Devices [50], recently reviewed plasma process including plasma electrolytic oxidation (PEO) for nanostructured implant for antibacterial properties. Although additional studies are needed to both marry biologically based biocidals to biomaterials and to explore their efficacy when paired, the intersection represents a perfect union between material science and biology which offer prospective hopes for the threat of antibiotic resistance.

Conclusions and future directions

The role of antimicrobial strategies to improve the performance and life span of healthcare devices is unquestionable. While the current technologies discussed have greatly contributed, no one solution has presented itself far superior to the others. Major hurdles to overcome include (i) toxicity associated with the metallic nanoparticles and peptides, (ii) scalability and cost related issues with quorum sensing inhibitors and phage therapy, (iii) specificity which limits application to monoculture populations, and (iv) resistant mechanisms, which render treatment ineffective. The coming decade may witness new strategies that can address these different challenges. This will be highly important for the successful clinical translation of infection resistant medical devices. An interdisciplinary approach which includes scientists, engineers, microbiologists, and physicians will be needed to accomplish this goal.

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 article.

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- ** of outstanding interest

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