Strategies to prevent the occurrence of resistance against antibiotics by using advanced materials

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Abstract

Drug resistance occurrence is a global healthcare concern responsible for the increased morbidity and mortality in hospitals, time of hospitalisation and huge financial loss. The failure of the most antibiotics to kill "superbugs" poses the urgent need to develop innovative strategies aimed at not only controlling bacterial infection but also the spread of resistance. The prevention of pathogen host invasion by inhibiting bacterial virulence and biofilm formation, and the utilisation of bactericidal agents with different mode of action than classic antibiotics are the two most promising new alternative strategies to overcome antibiotic resistance. Based on these novel approaches, researchers are developing different advanced materials (nanoparticles, hydrogels, and surface coatings) with novel antimicrobial properties. In this review we summarise the recent advances in terms of engineered materials to prevent bacteria resistant infections according to the antimicrobial strategies underlying their design.

Keywords

Antibiotic resistance, antibiofouling, antimicrobial peptides, quorum sensing, virulence factors, nano-antimicrobial materials

Introduction

Today, antimicrobial resistance (AMR) infections are responsible for 700 thousand deaths annually with an economic burden of, only in the US, over 20 billion dollars per year, and estimations reveal a devastating future by 2050 with 10 million deceased per year unless solutions are found (de Kraker and Stewardson 2016). In the last decade, AMR infections have spread from predominantly hospital and care settings environments towards the wider community, endangering the healthcare advances. Antibiotics are crucial in the modern medicine and the loss of effectiveness jeopardizes not only the fight against microbial infections such as pneumonia, tuberculosis and malaria, but also turns simple wounds or straightforward surgical procedures into a real menace to life (Jasovský and Littmann 2016). Current answers to AMR infections result in higher doses of drugs, treatments with toxic side effects, longer hospital stays, and increased mortality (Lee and Cho 2013;Ventola 2015). For instance, colistin, an antibiotic avoided for many years due to renal and neurological damage, is administered as a last resort treatment for patients with resilient Gram-negative bacterial infections (Karaaslan and Çağan 2016).

The appearance of antibiotic resistances is a naturally occurring phenomenon via natural selection. The antibiotic induces the environmental pressure and those bacteria able to survive and replicate will be the ones with genes that confer antibiotic resistance. Due to the high bacterial replication rate and ability to acquire foreign genetic material coding for resistance determinants through horizontal gene transfer, bacteria can rapidly evolve and adapt to the selective antibiotic pressure with a variety of mechanisms including i) degradation of antibiotics (e.g. beta-lactamase inactivation of penicillins), ii) modification of the drug target (e.g. mutation of the protein rpsL of the 30S ribosomal subunit, which confers resistance to streptomycin), and iii) expression of efflux pumps (e.g. AcrAB-TolC pumps which confer resistance to multiple antibiotics as quinolone, chloramphenicol, florfenicol, and tetracycline (TET)) (Baucheron and Tyler 2004;Carr and Gregory 2005;Frère 1995;Munita and Arias 2016). The current overuse of antibiotics has even enhanced the efficacy of these evolving strategies rendering the emergence of bacterial strains resistant to the clinically relevant antibiotics.

Besides these specific resistance mechanisms, bacteria can adhere to surfaces and grow as biofilms that are tolerant to very high concentrations of multiple antimicrobials. Biofilms comprise a structured and coordinated community of sessile cells embedded within a self-produced extracellular polymeric matrix (Saini and Saini 2011). They can occur on foreign objects inserted into the human body (e.g. orthopaedic prostheses and catheters) as well as in any place in the body where the host defences are compromised (e.g. chronic wounds with impaired blood supply) (Bjarnsholt 2013). Biofilm related infections are difficult to treat and frequently require prolonged treatment or alleviate the burden of diseases (Lebeaux and Ghigo 2014). The high incidence of these infections is related to the progress of the modern medicine and the frequent use of medical devices (Saini and Saini 2011;Shorr and Lodise 2006).

The importance of AMR has fuelled different research initiatives covering from fast diagnostics tools to design of new drugs and advanced materials that tackle bacterial infections and limit the spread of resistance. The novel antimicrobial approaches aim either to interfere with bacterial virulence and biofilm establishment enhancing clearance by the host immune system, or eliminate the pathogens through mechanisms exerting less selective pressure for resistance selection. The present mini review summarises

the recent research focus on the development of novel advanced materials, including nanoparticles (NPs), hydrogels, surface coatings that meanwhile display antimicrobial activities towards common pathogens avoid the appearance of AMR (Figure 1). Unlike previously published reviews focused in a single type of advanced antimicrobial material (Pelgrift and Friedman 2013;Wang and Hu 2017), this review compiles different innovative antimicrobial materials according to the strategy underlying their design and development.

Inhibition of bacterial virulence and biofilm formation

The virulence of a microorganism refers to the measure of its pathogenicity and is directly related to its ability to invade and multiply within the host, avoid the defence mechanisms and cause disease, thanks to the generation of different molecules called virulence factors. These bacteria-associated determinants are classified in i) adhesion factors (pili, flagellae, adhesins), ii) surface components that prevent phagocytosis, iii) enzymes that damage host tissues known as invasins and iv) toxins such as pore-forming toxins (PFTs) (Baron 1996). Once the pathogenic microorganism has avoided clearance by the host immune system and start multiplying, their growth can occur as biofilm. These sessile forms increase the resistance of the pathogenic bacteria to not only the host immune system but also to external agents such as antibiotics up to 1000 times.

The AMR context has driven researchers in the development of ways to prevent bacterial virulence and growth (as biofilm) without killing, thus avoiding the evolutionary pressure towards resistance mechanisms. The inhibition of bacterial virulence and biofilm growth allow the host defence system to eliminate non-cooperating (and hence less virulent) bacteria or substantially increase the effect of co-administered antibiotics at lower dosages (Brackman and Breyne 2016;Hentzer and Givskov 2003). The different strategies to suppress the expression of virulence factors and prevent biofilm growth can be divided into i) anti-quorum sensing (anti-QS), ii) anti-toxins, and iii) antibiofouling. These strategies preclude the design and development of different advanced materials (Figure 1, left side).

Anti-infective materials with anti-quorum sensing activity

As bacteria multiply, secreted small-molecule signals called autoinducers (AIs) accumulate in the extracellular media and once a threshold is reached, recognition of these signals by membrane receptors activates a regulatory cascade that controls numerous cellular processes. This phenomenon, known as QS, enables single cells to sense the number of bacteria in their environment and when a sufficient number of bacteria is reached, turns on collective behaviours, such as expression of virulence factors and formation of biofilms. Gram-negative bacteria secrete acyl-homoserine lactones (AHLs) that penetrate into the cells and activate the cognate AHL receptor, while Gram-positive bacteria produce autoinducing peptides that interact with a transmembrane histidine kinase receptor activating the target gene expression via autophosphorylation of the transcriptional regulator (Atkinson and Williams 2009).

Interruption of QS has become an attractive strategy to suppress the virulence factors secretion and biofilm establishment, increasing bacterial susceptibility to lower dosages of conventional antimicrobials

and host immune response (Annous and Fratamico 2009;Cvitkovitch and Li 2003;Davies and Parsek 1998;Galloway and Hodgkinson 2010;Li and Tian 2012;Wang and Morohoshi 2008). Anti-QS approaches target the disruption of QS signalling by: i) quorum quenching enzymes (QQE) degrading the AIs in the extracellular environment and ii) QS inhibitors (QSI) competing with QS molecules for binding to the cognate receptors. QQE, such as acylase and lactonase, selectively inactivate the QS signals in Gram-negative bacteria through the hydrolysis of amide bond or lactone ring in the AHLs, respectively (Craigen and Dashiff 2011;Johansen and Falholt 1997). Based on these anti-QS strategies, researchers have generated novel materials to attenuate bacterial virulence and prevent biofilm formation. In our group, the potential of acylase to reduce *Pseudomonas aeruginosa* biofilm formation on catheters, was demonstrated *in vitro* under conditions mimicking the real situation during catheterisation (Ivanova and Fernandes 2015). In another work, the enzyme immobilisation on polyurethane surface resulted also in attenuation of *P. aeruginosa* virulence (Grover and Plaks 2016). Acylase has been used as an anti-biofilm agent after chemical and enzymatic immobilisation on carboxylated polyaniline nanofibers (Lee and Lee 2017). This QQE was also combined with matrix degrading amylase to impart anti-biofilm functionality on catheter surface. The enzymes were deposited in multilayered fashion on silicone material and demonstrated ability to counteract single and dual species biofilms formation by *P. aeruginosa* and *Escherichia coli*. The anti-biofilm activity of the coatings was improved by more than 20 % when the outermost layer was the QQE, initially affecting bacterial communication. QQE lactonase has been coated onto gold NPs to reduce exopolysaccharide production, metabolic activities, and cell surface hydrophobicity of multidrug-resistant *Proteus* species (Vinoj and Pati 2015). This QQE has also been immobilised onto magnetic NPs that were also able to hydrolyse AHL and inhibit QS in Gram-negative bacteria (Beladiya and Tripathy 2015). Lactonase containing gels inhibited the spread of skin pathogens and considerably increased the mice survival after treatment with antibiotic, at very low amounts (Gupta and Chhibber 2015). Except the enzymes for QS signals inactivation, other compounds such as antibodies and NPs have been engineered to interfere with bacterial virulence. For example, silicon dioxide NPs functionalised with β-cyclodextrin demonstrated the ability to quench the signals in *Vibrio fisheri* inhibiting QS regulated genes expression (Miller and Wang 2015).

Innovative anti-QS approaches use analogues of the AIs that recognise and bind with the corresponding bacterial receptors in order to obstruct the QS pathways in Gram-positive or Gram-negative bacteria and therefore reduce toxins production or biofilms formation (Frei and Breitbach 2012). Several anti-QS materials such as nonwoven meshes, tampons or glass surfaces have been coated with cyclic peptides able to disrupt *Staphylococcus aureus* QS. The QS system of *S. aureus* was inactivated by 95 % when using macrocyclic peptide-loaded carboxymethylcellulose materials. *In vitro* tests have shown that these anti-QS coatings also prevent the QS-dependent biofilm formation of *S. aureus* but enabling the normal bacterial growth (Kratochvil and Tal-Gan 2015).

Natural compounds such as heterocyclic organic furanones alter biofilm formation by hindering QS process. Red algae *Delisea pulchra* synthesizes halogenated furanones as secondary metabolite for bleaching protection. This organic compound also influences the interspecies QS communication on *Serratia liquefaciens* and *Proteus mirabilis* altering their biofilm motility (Givskov and de Nys

1996;Gram and de Nys 1996). Furanone (5Z)-4-bromo-5-(bromomethylene)-3-butyl-2(5H) produced by *D. pulchra* can also alter the swarming motility and biofilm formation of *E. coli* by interrupting the QS gene regulation (Ren and Sims 2001). Release efficiency of (5Z-)-4-bromo-5-(bromomethylene)-2(5H)-furanone - loaded poly(L-lactic acid) (PLLA) NPs coated on dental devices have been shown to be effective for prevention of peri-implant infection (Cheng and Wu 2012). The immobilisation of this furanone loaded PLLA NPs on microarc-oxidised titanium implants also inhibited *S. aureus* biofilm formation in the early and intermediate stages (Cheng and Zhao 2015).

Synthetic furanones have been designed to improve the otherwise limited effect of the natural furanones on the QS system of *P. aeruginosa*. These new compounds were tested on mice and results showed their potential to control bacterial virulence without bactericidal or growth inhibition effect (Wu and Song 2004). The immobilisation of derivative 3-(1′-bromohexyl)-5-dibromomethylene-2(5 H)-furanone on the styrene polymer or catheter surface significantly reduced *Staphylococcus epidermidis* formation (Hume and Baveja 2004). Anti-QS compounds were used to develop solid lipid NPs with improved anti-virulence activity against *P. aeruginosa* compared to the free agent (Nafee and Husari 2014). The QSI *S*-phenyl-L-cysteine sulfoxide was encapsulated into zein NPs and inhibited *Streptococcus mutants* biofilm growth (Kasper and Hart 2016). The simultaneous application of either QQE or QSI with antibiotics was shown to significantly attenuate bacterial virulence and inhibit resistant biofilm formation when compared to the active agents alone. This approach opens new avenue for the development of highly effective antibacterial and anti-biofilm materials (Brackman and Cos 2011).

Toxin sequestering materials

Bacterial pathogens produce toxins able to create the optimum conditions for bacterial invasion and growth in the host. The role of toxins in damaging the host tissues, for example, via physical disruption, or modulating the host immune response, such as up-regulation of cytokine expression, is well established as part of the infectious processes. Within the framework of anti-virulence therapy, the removal of bacterial offensive weapons is of high interest and despite it has been less explored in comparison to the aforementioned strategies, researchers have designed advanced materials with anti-toxin properties. Using NPs as decoys for PFTs, scientists have design and produced the so-called “nanosponges”, a polymeric NP cores coated with intact red blood cell membranes (Hu and Fang 2013). Thanks to the wrapping membrane, these “nanosponges” display an ideal mimicry to absorb a wide range of PFTs regardless of their molecular structures. On the other hand, the polymeric core stabilizes the membrane shell and prolongs systemic circulation for detoxification in the bloodstream. In further developments, the “nanosponges” have been integrated in hydrogels for the effective treatment of localised bacterial infection in mouse model through subcutaneous injection (Wang and Gao 2015). Moreover, a recent work shows how changing the NPs coating for macrophages membranes allowed the removal of endotoxins, a lipopolysaccharide released in sepsis, that bounds to macrophages and induce changes in immune cell activity (Thamphiwatana and Angsantikul 2017). Therefore, the membrane-coated NPs open a door to the sequestration of different toxins, based on its cell target, as an attractive alternative to prevent infections. Nevertheless, the removal of toxins is not limited to the use of NPs with biological component,

biocompatible synthetic polymer NPs for instance have showed *in vivo* binding affinity against melitin, a cytolytic peptide from bee venom that forms membrane pores (Henry and Neill 2014). These particles were generated from the combinations of hydrophobic, negatively charged and positively charged monomer library thus adjusting the ratio of each component for optimum toxin binding. This systematic approach shows potential used for the generation of NPs with specific binding against bacterial toxins.

Antibiofouling materials and surfaces

Indwelling medical devices and implants, once inserted in the human body, create an environment for pathogenic bacteria to adhere and establish biofilms, resulting in severe chronic infection with associated tissue destruction, as well as systemic dissemination of the pathogen. Bacterial adherence occurs at the so called "surface conditioning layer" which is comprised of proteins (e.g. fibronectin, fibrinogen, and collagen), lipids, polysaccharides and inorganic salts (Zwaal and Comfurius 1977). The nonspecific protein adsorption on the inserted device surface triggers the irreversible bacterial attachment (Denstedt and Wollin 1998;Trautner and Darouiche 2004). Upon adhesion, bacteria start to grow and expand, forming small functional community of cells of the same species or other bacterial species and microorganisms (Hung and Henderson 2009).

Systematic replacement of the contaminated device is not the best option to prevent biofilm related infections, since only provides a new surface for biofilm establishment (Cole and Records 2014). However, the functionalisation with broad-spectrum antibacterial agents (e.g. antibiotics, silver and nitric oxide), despite being an active field of research (Evliyaoğlu and Kobaner 2011;Lellouche and Friedman 2012;Li and Li 2014), implies evolutionary stress for selection of resistant bacteria. For these reasons, the design of novel antibacterial and anti-biofilm materials aims to inhibit the initial adherence of the free floating cells and consequently prevent the biofilm formation on the surface of the inserted medical device.

Surface roughness, charge, degree of hydrophobicity, Lewis acid-base character and hydrogen-bonding capacity are the main factors that influence non-specific reversible microbial attachment, the first step in biofilm growth (Tang and Cao 2009). Low surface roughness and hydrophobicity decrease cell attachment in different surfaces. Hydrophilic polymers such as poly(ethylene glycol) (PEG), poly(L-glutamic acid), poly(acrylic acid) (PAA) grafted PEG, heparin and hyaluronic acid (HA), have been used to increase the surface hydrophilicity forming a highly hydrated layer that serves as a physical and energy barrier for bacterial adherence (Boulmedais and Frisch 2004;Fu and Ji 2005;Saldarriaga Fernández and van der Mei 2007;Schmolke and Demming 2010). Nanofilms of silver and titanium oxide decreased roughness and hydrophobicity of stain steel orthodontic brackets limiting *Streptococcus mutans* biofilm formation (Ghasemi and Arash 2017). Fluoroalkylsilane also reduced *S. epidermidis* adhesion when coated on silicone by reduced roughness and hydrophobicity (Tang and Cao 2009). Although these reported studies exhibit higher bacterial adhesion on hydrophobic surfaces, other works have concluded that hydrophobic surfaces reduced bacterial adhesion when tested *in vivo* (Quirynen and Bollen 1995). Negatively charged surfaces have been reported to prevent biofilm formation due to electrostatic repulsion of the negatively charged bacterial cells. The above-mentioned strategy is feasible for

temporary materials such as sutures, meshes, and drainage tubes, but not very practical to control the occurrence of implant associated infections (Boudou and Crouzier 2010).

Recently, zwitterionic polymers have appeared as very promising antifouling materials bearing both positively and negatively charged groups (Zhang and Finlay 2009). The adhesion of *E. coli* and *P. mirabilis* was reduced on silicone coated with zwitterions phosphorylcholines delaying biofilm formation compared with uncoated surfaces. The substitution of the phosphorylcholine group by sulfobetaine and carboxybetaine has generated antifouling materials able to prevent microbial and protein adhesion (Chen and Li 2010;Zhang and Chiao 2015). Immobilisation of zwitterionic poly(carboxybetaine methacrylate) on glass material decreased significantly the adhesion of non-specific fibrinogen, preventing *P. aeruginosa* attachment (Cheng and Li 2009). Sulfobetaine polymer brushes prevented bovine serum albumin (BSA) adsorption and attachment of *E. coli* and *S. aureus* onto a variety of medically relevant surfaces (Guo and Jańczewski 2015). Polysulfobetaine coatings on central venous catheters, using a redox polymerisation process, have reduced thrombus aggregation and consequent bacterial attachment better than unmodified catheter surface (Smith and Zhang 2012). Poly(sulfobetaine methacrylate) (PSBMA), polyphenol and tannic acid (TA) coatings have been generated in a multi-layered fashion forming stable and protein-resistant materials. These $(TA/PSBMA)_n$ layers were stable between pH 4–10, and at 0.05 to 1 M sodium chloride and urea solutions. Moreover, 20 bilayers of TA and PSBMA were highly hydrophilic, reducing the adsorption of BSA, lysozyme and haemoglobin (Ren and Yang 2015). However, these zwitterionic coatings easily dissolve in water, limiting their long-term safe applicability. The introduction of double bonds into the PSBMA structure has generated a more stable antifouling material to coat polyutherane (Wang and Lu 2016). In our group, sulfobetaine metacrylate monomers were coated on silicone developing urinary catheters with antifouling properties. This coating prevented *P. aeruginosa* and *S. aureus* biofilm growth on the urinary catheters longer than their lifetime (Diaz Blanco and Ortner 2014). Other strategies involve the degradation of the biofilm extracellular polymeric matrix components, weakening and dispersing the biofilm. The observation that different enzymes can degrade the matrix components of the biofilm with its subsequent dispersion has revealed potential tools to generate antibiofouling and anti-biofilm enzyme based materials (Craigen and Dashiff 2011;Johansen and Falholt 1997). In this sense, the enzyme deoxyribonuclease I (DNase I) that degrades the extracellular deoxyribonucleic acid (DNA), a key component of *P. aeruginosa* biofilm matrix, was immobilised on ciprofloxacin-loaded poly(lactic-co-glycolic acid) NPs to reduce the mass, size and living cell density in *P. aeruginosa* biofilms (Baelo and Levato 2015). Co-immobilisation of DNase I and the antimicrobial peptide (AMP) Palm onto polydimethylsiloxane material, using dopamine chemistry, generated a bifunctional antimicrobial and anti-biofilm surface against *S. aureus* and *P. aeruginosa* (Alves and Magalhães 2016). On the other hand, polysaccharides, another structural component of the biofilm, can also be targeted with the use of enzymes. Disersin B from *Aggregatibacter actinomycetemcomitans,* which degrades poly-N-actylglucosamine (Izano and Wang 2007), have been used to generate a silicone surface that inhibits the biofilm of two *S. epidermidis* clinical strains through its layer-by-layer deposition (Pavlukhina and Kaplan 2012). Promising anti-biofilm activities against Gram-positive and negative pathogenic bacteria, have also been observed using the glycosyl hydrolase (Kalpana and Aarthy 2012).

Advanced antibacterial materials

The discovery of antimicrobial drugs has revolutionised the medicine and changed the paradigm in treating severe bacterial infections (Munita and Arias 2016). Their introduction in the clinical practice have made possible the complex medical approaches such as cutting edge surgical procedures, solid organ transplantation and even management of patients with cancer. However, the antibiotics overuse and misuse has led to the appearance of multi-drug resistant pathogens that can survive at unfavourable growth conditions, impeding the successful outcomes of critically ill patients (Cantas and Shah 2013). The introduction of new antibiotic analogues with similar structural and functional characteristics to the original drug is only a short-term antibacterial strategy. Therefore, there is an urgent need of finding an alternative solution that relies on more than just the development of next generation antibiotic drugs. In this section, special focus is given on the novel antibiotic alternatives for the development of advanced materials aimed at killing pathogens via non-specific mechanisms related to membrane damage, oxidative stress and interaction with genetic material and protein, reducing the possibility of inducing resistance in bacteria. The antibiotic alternatives used to generate the advanced antibacterial materials span from molecules such as enzymes or peptides to polymers and more complex nanostructured materials (Figure 1, right side).

Antibacterial enzymes

Besides of targeting the degradation or inactivation of essential biofilm components, enzymes may elicit antimicrobial activity through the production of hydrogen peroxide, which destroys the invading pathogens. In general, hydrogen peroxide kills bacterial cells through peroxidation and disruption of cell membranes, oxidation of oxygen scavengers and thiol groups, and disruption of protein synthesis (McDonnell and Russell 1999). Hydrogen peroxide-producing enzymes such as glucose oxidase and cellobiose dehydrogenase (CDH) can significantly reduce the growth of both Gram-positive and Gram-negative bacteria and therefore they are widely exploited in the food industry (Ge and Zhao 2012;Nyanhongo and Sygmund 2013;Walker and Fourgialakis 2007). CDH oxidises cello-oligosaccharides, which are not considered essential compounds for the pathogens, and produce bactericidal hydrogen peroxide. A novel *in situ* antibacterial approach based on CDH was used to produce hydrogen peroxide in presence of cellobiose or other biofilm exopolysaccharides and inhibit bacterial growth and biofilm formation on silicone catheters. CDH produced by *Myriococcum thermophilum* inhibited the growth of common urinary pathogens including the multidrug-resistant *E. coli*, *S. aureus*, *S. epidermidis*, *P. mirabilis*, *Stenotrophomonas maltophilia*, *Acinetobacter baumannii* and *P. aeruginosa* in presence of cellobiose. CDH combination with glycoside hydrolases demonstrated enhanced antimicrobial and anti-biofilm activity by the larger amount of released hydrogen peroxide. The enzyme incorporation in lubricants led to significant reduction of bacterial biofilms on catheter surface (Thallinger and Argirova 2014). Furthermore, urinary catheters chemically functionalised with antimicrobial CDH, resisted *S. aureus* biofilm formation under static and dynamic conditions. CDH NP-coating onto silicone material have been generated *in situ* using ultrasound sonochemistry to reduce the amount of viable *S.*

aureus cells and the total biomass on urinary catheters (Lipovsky and Thallinger 2015). Myeloperoxidase, lactoperoxidase and haloperoxidase are another type of antibacterial enzymes that use hydrogen peroxide as a substrate to oxidise halide/pseudohalide to even more active antimicrobials. For instance, horseradish peroxidase and glucose oxidase have been incorporated in polyurethane electrospun fibers that inhibited the *E. coli* and *S. aureus* growth (Amitai and Andersen 2009). However, the enzymes may also contribute to the unwanted degradation of biological compounds present in the surrounding of the material.

Despite the biocide producing enzymes that kill bacteria via other mechanisms have also been reported. For examples, lysostaphin is an antibacterial enzyme acting on the cross-linking pentaglycine bridges in the *Staphylococci* cell wall. The enzyme has been immobilised onto a variety of surfaces, which were able to kill hospital strains of *S. aureus* (Yeroslavsky and Girshevitz 2015). Lysostaphin–carbon nanotube conjugates have been developed to reduce protein adsorption and bacterial adhesion (Glinel and Thebault 2012;Pangule and Brooks 2010). Coatings comprised of lysozyme, an antibacterial enzyme that degrades the bacterial cell wall, have been designed to inhibit planktonic and sessile growth of Gram-positive and Gram-negative bacteria (Minier and Salmain 2005;Muszanska and Busscher 2011;Yuan and Wan 2011). Multilayer constructs of lysozyme and negatively charged gold NPs, DNA or pectin inhibited the growth of different medically relevant bacterial species (Nepal and Balasubramanian 2008;Zhang and Zhou 2015;Zhou and Li 2014). Although the enzyme-based antibacterial strategies are very promising, the proteins activity after surface immobilisation and their *in vivo* stability and efficacy is the main concern for further clinical application (Chen and Yu 2013).

Antimicrobial peptides

AMPs are oligopeptides with a broad spectrum antibacterial activity towards bacteria, fungi, viruses, and parasites (Bahar and Ren 2013). They interact with negatively charged bacterial cell membrane, cause membrane disruption or trans-membrane pore formation and lead to cells lysis and death (Brogden 2005). The disruption of bacterial membranes by AMPs is non-specifically and therefore the possibility of inducing resistance in bacteria is considerably low. AMPs have been used for development of broad spectrum antibacterial materials and surfaces (Chen and Zhu 2017;Costa and Carvalho 2011;Holmberg and Abdolhosseini 2013). For instance, polyurethane catheters coated with AMPs inhibited *in vivo* planktonic and sessile forms of Gram-positive and -negative bacteria (Yu and Lo 2017). Antibacterial hydrogels with fast jellification and strong adherence to various medical devices or surfaces have been engineered using the AMP cateslytin (Mateescu and Baixe 2015). In another study, HA has been functionalised with the AMP cateslytin and then used to develop self-defensive multilayer coatings (Cado and Aslam 2013). Coating of the broad spectrum AMP, Tet213, have been assembled onto titanium surface that demonstrated sustained antimicrobial activity and limited early biofilm formation of both a Gram-positive aerobe (*S. aureus*) and a Gram-negative anaerobe (*Porphyromonas gingivalis*) for up to one month (Shi and Liu 2015). In another study, homopolymer of methacrylamide bearing (oxidised) 3,4-dihydroxyphenylalanine was used to engineer durable antibacterial-peptide based coatings (Faure and Lecomte 2011;Zhu and Jun Loh 2015). Stable antimicrobial coating of cecropin-melittin functionalised gold NPs with bactericidal activity towards multi-drug resistant bacteria Gram-positive and -negative

bacteria have been reported (Rai and Pinto 2016). Recently, dual coating of AMPs covalently bonded to hydroxyapatite surface, followed by deposition of electrostatically bound AMPs has been reported as very efficacious in preventing S. *aureus, S. epidermidis* and *P. aeruginosa* colonisation, while decreasing the side effect to human cells (Townsend and Williams 2017). The main drawbacks limiting the practical application of AMPs is their uncontrolled toxicity, ability to affect the eukaryotic cells, high cost for large scale synthesis, and rapid degradation by the human proteases (Huang and He 2014).

Cationic Antibacterial Polymers

Cationic compounds including natural or synthetic polymers and lipids have become very attractive antibiotic alternatives in addressing challenges posed by the drug-resistant bacterial infections with decreased potential for resistance development. Antimicrobial polymers have been grafted or self-assembled onto variety of surfaces to interact with the intrinsically anionic bacterial cell wall and cause cells death [101]. Chitosan, the naturally occurring cationic polymer, has been applied on silicon wafer as chitosan/κ-carrageenan multilayers observing an antibacterial activity against clinically relevant *Enterococcus faecalis* strains (Bratskaya and Marinin 2007). Assemblies of chitosan and anionic lentinan sulphate onto polyurethane surface decreased the pathogenic *P. aeruginosa* growth, without affecting human cells viability (Wang and Hong 2012). Functional finishing of cotton fabric via the deposition of the oppositely charged chitosan and sodium tripolyphosphate resulted in the successful elimination of both Gram-positive and Gram-negative species (Shirvan and Nejad 2014). Nevertheless, the innate cationic charge of chitosan, the differences in assembly conditions frequently defines the amount of the active agent deposited on the surface, the coating thickness and rigidity, and therefore affects the final antibacterial performance of the material. To overcome these drawbacks, quaternary ammonium salts bearing positive charge independent on the pH have been introduced to design surfaces with better bactericidal properties (Carmona-Ribeiro and de Melo Carrasco 2013;Séon and Lavalle 2015;Tischer and Pradel 2012). Quaternary ammonium salt of chitosan have been assembled with PAA on a plasma-treated poly(ethylene terephthalate) to eliminate the *E. coli* and *S. aureus* (Graisuwan and Wiarachai 2012). Quaternary ammonium and/or phosphonium salts of pyridoxine, alanine-derived gemini and fatty acids have also been introduced as potent broad spectrum antibiotic alternatives against bacterial pathogens and viruses (Bakhshi and Yeganeh 2013;Kayumov and Nureeva 2015;Nikitina and Zeldi 2015;Obłąk and Piecuch 2014;Wong and Li 2010).

Synthetic polyethers, polymethacrylates, polynorbornenes, polycarbonates and poly-β-lactams polymers have also been developed to mimic the structure of the AMPs and kill bacteria (Engler and Tan 2013). The introduction of both cationic and hydrophobic moieties into the polymers improves the interaction with bacterial cells, leading to irreparable membrane damage and bacterial death (Paslay and Abel 2012;Smriti Rekha and Ashwani Kumar 2015). Triblock polycarbonate polymers composed of antifouling PEG, antimicrobial cationic polycarbonate, and a tethering or adhesive functional block have been synthesised and then covalently grafted on catheter surface. Depending on the position of the adhesive block, the coatings demonstrated antibacterial and antifouling properties for both Gram-positive *S. aureus* and Gram-negative *E. coli* under conditions simulating the device lifetime (1 week) (Voo and

Khan 2015). Antimicrobial cationic polycarbonate/PEG hydrogels with strong broad-spectrum antimicrobial activities against clinically isolated multidrug-resistant microbes have been generated (Liu and Yang 2012). The hydrophobicity of the synthetic AMPs mimics is thought to be crucial not only for their antimicrobial activity but also for the toxicity to mammalian cells (Timofeeva and Kleshcheva 2011). Numerous variations in the cationic−hydrophobic balance have been examined aiming to design antibacterial compounds. Recently, a very different approach for developing membrane active antimicrobials has been reported. This strategy uses spherical and rod-like polymer molecular brushes that mimic the two basic structural motifs of bacteriophages. The polymers induced an unusual topological transition of bacterial but not mammalian membranes to form pores and as such represent a valuable alternative to design advanced materials or surfaces (Jiang and Zheng 2017).

Advanced nanostructured materials

Nanomaterials including NPs, nanospheres and nanocapsules have been widely used in engineering: i) functional coatings of medical devices and surfaces that prevent bacterial infections and promote healing, ii) drug carriers for delivering the antibacterial agents at the site of infection and iii) vaccines. The nano-sized materials possess unique physical and chemical properties and frequently demonstrate improved antibacterial features than their bulk counterparts (Wang and Gupta 2016). Numerous inorganic (e.g. metal and metal oxides) and hybrid (e.g. biopolymer/polymer and metal) NPs have been generated to inhibit planktonic and biofilm growth of medically relevant Gram-positive and Gram-negative bacterial strains (Petkova and Francesko 2014;Sirelkhatim and Mahmud 2015;Wang and Gupta 2016;Wang and Hu 2017). The mechanisms underlying the metal NPs action, for example, in most cases occur simultaneously and comprise oxidative stress induction, metal ion release, and non-oxidative mechanisms including cell membrane disruption, penetration in bacterial cells and interactions with DNA, ribonucleic acid and proteins (Feng and Wu 2000;Pelgrift and Friedman 2013). The multiple bactericidal mechanisms require multiple simultaneous gene mutations and therefore for bacteria is very difficult to develop resistance (Pelgrift and Friedman 2013). For example, silver NPs (AgNPs), synthesised from the cell-free filtrate of fungus *Rhizopus Oryzae*, were able to interact with bacterial membrane, changing its penetrability (Ramalingam and Parandhaman 2016). In addition, the generated reactive oxygen species (ROS) interfered with the antioxidant defence system in bacteria, leading to damage of the *E. coli* and *P. aeruginosa* cells membrane (Ramalingam and Parandhaman 2016). Implants functionalized with antibacterial AgNPs resisted bacterial cells attachment *in vivo* demonstrating their potential in controlling bacterial infection (Secinti and Özalp 2011). ZnO NPs-coated medical textiles with durable antibacterial activity towards Gram-positive *S. aureus* and Gram-negative *E. coli* have been reported (Petkova and Francesko 2016). ZnO and copper oxide (CuO) NPs have been generated to inhibit planktonic or biofilm growth of *E. coli*, *S. aureus* and *Bacillus subtilis* and fungus *Candida albicans* via generation of ROS (Eshed and Lellouche 2012). CuO NPs been used for the development of broad-spectrum durable antibacterial coating towards *E. coli*, *S. aureus* and kanamycin-resistant *E. coli* (Li and Gao 2017). Zn-doped CuO NPs with synergistic efficacy towards multidrug-resistant *S. aureus* and *E. coli* have been generated *in situ* and then deposited on silicone catheters (Malka and Perelshtein 2013;Shalom and Perelshtein 2017). In another work, ZnO/gold NPs generated increased ROS levels and demonstrated

improved antibacterial activity (He and Kim 2014). Doping the ZnO with fluorine also led in more ROS generation than the ZnO NPs and consequently greater bactericidal activity on *S. aureus* (99.99%) and *E. coli* (99.87%) (Podporska-Carroll and Myles 2017). Stable magnesium fluoride (MgF_2) NPs coatings have been developed on silicone catheters and inhibited the *E. coli* and *S. aureus* biofilms (Lellouche and Friedman 2012). MgF_2 NPs have been further combined with ZnO NPs and synergistically inhibited the resistant biofilm growth of S*treptococcus pneumoniae* and *S. aureus* on cochlear implants (Natan and Edin 2016). Antibacterial NPs of cationic biopolymer showed promising antibacterial activities. Thiolated chitosan and aminocellulose NPs showed increased cationic charge density and improved the bactericidal efficacy of the biopolymers towards Gram-negative pathogens (Fernandes and Francesko 2014). Furthermore, the NPs deposition either in layer-by-layer fashion or via chemical grafting onto silicone surface led to stable antibacterial and anti-biofilm active coatings (Fernandes and Ivanova 2017;Francesko and Fernandes 2016).

Nowadays, the design of hybrid polymer/biopolymer-metal NPs have appeared as attractive way to improve metal NPs biocompatibility, stability and efficacy in a safety-by-design way (Marambio-Jones and Hoek 2010). PEG-capped ZnO NPs with higher antimicrobial efficacy have been reported. ZnO NPs alone and in combination with the polymer killed the common pathogens and inhibited the resistant biofilm formation (Meruvu and Vangalapati 2011). Medical textiles have been coated with hybrid NPs of ZnO and the biopolymer chitosan to impart higher antibacterial functionality than the individual ZnO and chitosan coatings. Importantly, the inclusion of the biocompatible polymer in the hybrid NP coatings diminished the side effect of the metal to human cells in a safe manner (Petkova and Francesko 2014). Polymer-Ag bromide NPs and hydrogels loaded with AgNPs have been generated to completely inhibit the planktonic and biofilm bacterial growth (Agnihotri and Mukherji 2012;Sambhy and MacBride 2006). Enzymatically grafted hybrid Ag/chitosan NP coating inhibited *S. aureus* and *E. coli* bacterial growth and attachment onto cork surface (Francesko and Blandón 2015).

Nevertheless the high antibacterial activity and the improved biocompatibility *in vitro*, the *in vivo* application of the aforementioned hybrid nanomaterials is scarcely studied. Nanotransformation of the existing antibiotics could be a facile approach to give new life to these old antibacterials instead of screening for new drugs. Unlike the most common strategies that rely on analogues with similar structural and functional characteristics to the original drug, the nano-sized transformation will improve the actives antibacterial efficacy by a mechanism comprised of a mechanical disruption of bacterial membrane and specific antibiotic activity.

For example, NPs of β-lactam antibiotic penicillin have been produced using ultrasound sonochemistry. The NPs showed great antibacterial activity against clinical isolate of *S. aureus* (Yariv and Lipovsky 2015). The nano-sized transformation of another antibiotic TET also improved its bactericidal activity, killing both TET sensitive and resistant bacteria (Shimanovich and Lipovsky 2015). Sonochemically synthesised graphene oxide/TET nanocomposites demonstrated enhanced activity against both sensitive and resistant *S. aureus* when compared to the same concentration of non-transformed antibiotic (Mishra and Segal 2015). TET loaded in protein microspheres showed high bactericidal effect against *E. coli* and *S. aureus* (Avivi and Nitzan 2003). Liposomes have also been used as carriers to improve the antibacterial

or anti-biofilm efficiency of several antibiotics, such as amikacin (Okusanya and Bhavnani 2009), ciprofloxacin, meropenem, and gentamicin (Gubernator and Drulis-Kawa 2007). However, the effective drug delivery by liposomes, which are composed on membrane phospholipids is very challenging task, due to drug leakage, temperature sensitivity, and short shelf-life. Several studies have shown that superior efficacy of *in vivo* cellular delivery, enhanced biocompatibility and prolonged circulation time can be achieved by lipid–polymer hybrid NPs compared with delivery without polymeric NPs or by liposomes. For instance, lipid-polymer hybrid NPs of norfloxacin have been prepared to eliminate *S aureus* and *P. aeruginosa* (Dave and Yadav 2017).

Conclusions

Overall, the development of effective strategies to fight bacterial infection while limiting the appearance of new drug resistant strains is a very challenging task. Despite we described very promising examples (summarised in Table 1), a better understanding of the antibacterial mechanism is required especially within the *in vivo* context in order to reach the final end users. Within the host environment, the uncontrolled protein adsorption onto the material can modify its physicochemical properties and antimicrobial efficacy by hindering its targeting capacity or inducing rapid clearance. Moreover, most of the highly effective antibacterial show low biocompatibility, which arises the need for development of a new generation of hybrid materials with strong antimicrobial/antifouling activities and improved biocompatibility generated in a "safety by design" manner. Finally, considering the bacterial genetic plasticity to evolve rapidly and survive hostile conditions a deep understanding of how bacteria can overcome the new antimicrobials is necessary to avoid its rapid obsolescence ending up once again without responses against resistant bacteria.

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Conflict of interest

The authors declare no competing financial interests.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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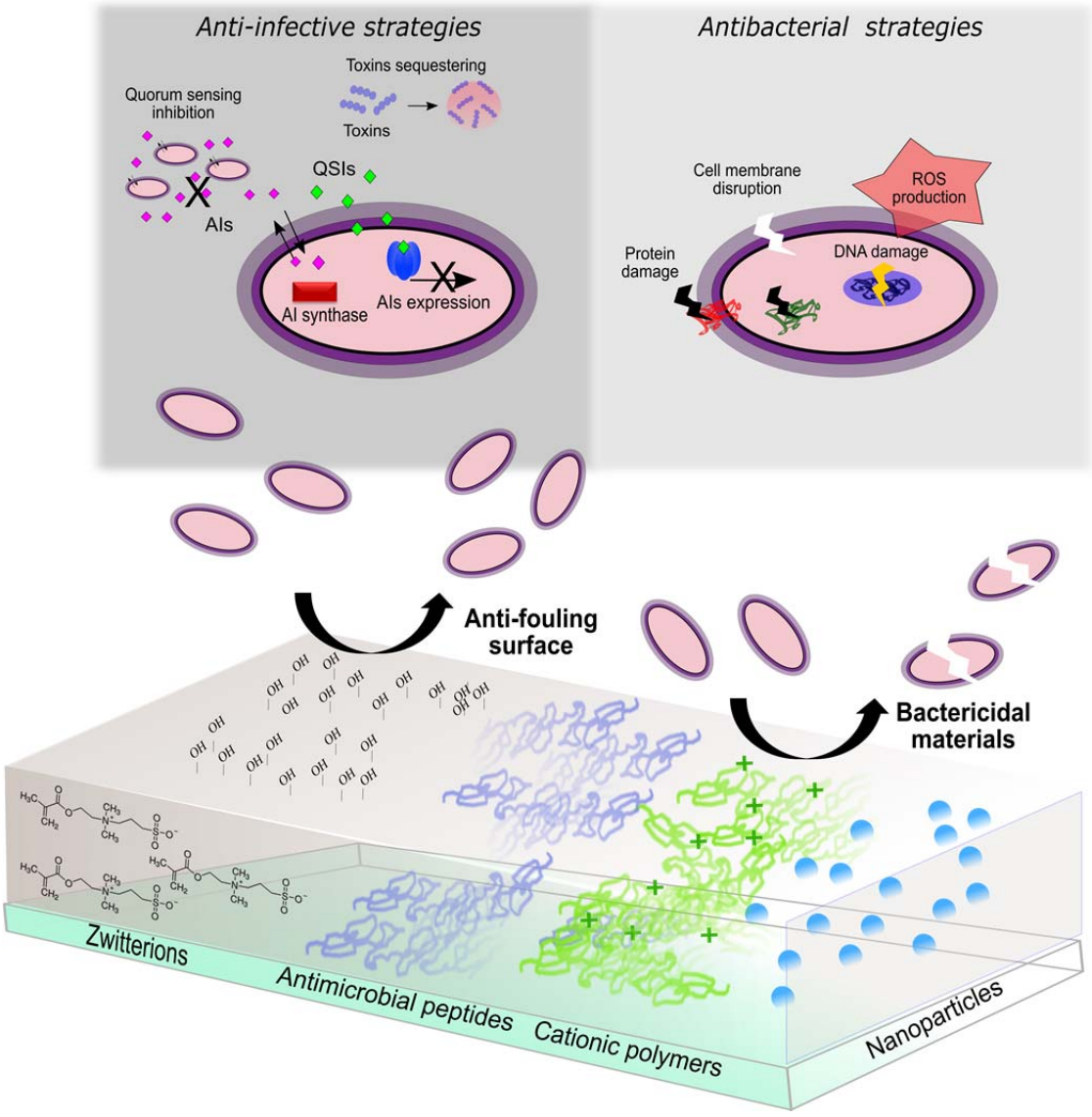

Figures 1 Strategies to prevent AMR precluding the design and development of different advanced materials. Anti-infective strategies to suppress the expression of virulence factors and prevent biofilm growth can be divided into i) anti-quorum sensing (anti-QS), ii) anti-toxins, and iii) antibiofouling (left side). Novel antibiotic alternatives aimed at killing pathogens via non-specific mechanisms related to

membrane damage, oxidative stress and interaction with genetic material and protein, reducing the possibility of inducing resistance in bacteria (right side).

Table 1: Advanced anti-infective and antibacterial strategies

Anti-infective strategies			
Approach	Actives	Target	References
Anti-quorum sensing	QQE: acylase and lactonase	Gram-negative bacteria	Johansen and Falholt 1997 Craigen and Dashiff 2011 Ivanova and Fernandes 2015 Grover and Plaks 2016
	Autoinducers analogues	*S. aureus*	Kratochvil and Tal-Gan 2015
	β-cyclodextrin functionalised NPs	*V. fisheri*	Miller and Wang 2015
	Heterocyclic organic furanones*:* free form and encapsulated	*S. liquefaciens*, *P. mirabilis*, *E. coli* and *S. aureus*	Givskov and de Nys 1996 Gram and de Nys 1996 Ren and Sims 2001 Cheng and Wu 2012 Cheng and Zhao 2015
	Synthetic furanones	*P. aeruginosa* and *S. epidermidis*	Wu and Song 2004 Hume and Baveja 2004
Toxin sequestering materials	Polymer NPs coated with red blood cell membrane	*S. aureus*, *E. coli*, *S. pneumoniae*,	Henry and Neill 2014 Wang and Gao 2015 Thamphiwatana and Angsantikul 2017

Anti-infective strategies			
Approach	Actives	Target	References
Antibiofouling and antibiofilm surfaces	Silver and titanium oxide nanofilms	*S. mutans*	Ghasemi and Arash 2017
	Fluoroalkylsilane	*S. epidermidis*	Tang and Cao 2009
	Negatively charged surfaces	Gram-negative and -positive bacteria	Boudou and Crouzier 2010
	Zwitterionic polymers	*E. coli*, *P. mirabilis, P. pseudomonas*, *S. aureus*	Cheng and Li 2009 Chen and Li 2010 Zhang and Chiao 2015 Guo and Jańczewski 2015 Diaz Blanco and Ortner 2014 Alves and Magalhães 2016
	Deoxyribonuclease I	*P. aeruginosa* and *S. aureus*	Baelo and Levato 2015 Alves and Magalhães 2016
	Disersin B	*S. epidermidis*	Pavlukhina and Kaplan 2012

Antibacterial strategies			
Approach	Actives	Target	References
Antibacterial enzymes	Cellobiose dehydrogenase	Gram-positive and -negative bacteria, including multidrug-resistant strains	Walker and Fourgialakis 2007 Ge and Zhao 2012 Nyanhongo and Sygmund 2013 Thallinger and Argirova 2014 Lipovsky and Thallinger 2015
	Horseradish peroxidase	*E. coli* and *S. aureus*	Amitai and Andersen 2009
	Glucose oxidase	*E. coli* and *S. aureus*	Amitai and Andersen 2009
	Lysostaphin	*Staphylococci* genus	Yeroslavsky and Girshevitz 2015
	Lysozyme	Gram-positive and -negative bacteria	Minier and Salmain 2005 Muszanska and Busscher 2011 Yuan and Wan 2011
Antimicrobial peptides	Cateslytin functionalized HA	*S. aureus* and *C. albicans*	Cado and Aslam 2013
	Tet213	*S. aureus* and *P. gingivalis*	Shi and Liu 2015
	Cecropin-melittin NPs	*E. coli*, *S. aureus*, *P. aeruginosa*, *Klebsiella Pneumoniae*, multidrug resistant *E. coli* and *Staphylococcus haemolyticus*	Rai and Pinto 2016
	Defensin-based AMP	*S. aureus, S. epidermidis and P. aeruginosa*	Townsend and Williams 2017

Antibacterial strategies			
Approach	Actives	Target	References
Cationic polymers	Chitosan	Clinically relevant *E. faecalis strains, P. aeruginosa* Gram-positive and –negative bacteria	Bratskaya and Marinin 2007 Wang and Hong 2012 Shirvan and Nejad 2014
	Quaternary ammonium salt of chitosan	*E. coli* and *S. aureus*	Graisuwan and Wiarachai 2012
	Triblock polycarbonate polymer combined with PEG and a tethering or adhesive functional block	*E. coli* and *S. aureus*	Voo and Khan 2015
	Polycarbonate/PEG hydrogels	Clinically isolated multidrug-resistant bacteria	Liu and Yang 2012
Advanced nanostructured materials	Silver NPs	*E. coli, S. aureus* and *P. aeruginosa*	Ramalingam and Parandhaman 2016 Petkova and Francesko 2016
	ZnO NPs	*E. coli*, *S. aureus*, *B. subtilis* and *C. albicans*	Eshed and Lellouche 2012
	CuO NPs coatings	*E. coli, S. aureus and kanamycin-resistant E. coli*	Li and Gao 2017
	Zn-doped CuO NPs	Multidrug-resistant *E. coli* and *S. aureus*	Malka and Perelshtein 2013 Shalom and Perelshtein 2017

Antibacterial strategies			
Approach	Actives	Target	References
Advanced nanostructured materials	Fluorine-doped ZnO NPs	*S. aureus* and *E. coli*	Podporska-Carroll and Myles 2017
	MgF_2 coatings	*E. coli* and *S. aureus*	Lellouche J, Friedman A, Lahmi R, Gedanken A, Banin E 2012
	Hybrid MgF_2/ZnO NPs	S. *pneumoniae* and *S. aureus*	Natan and Edin 2016
	Thiolated chitosan and aminocellulose NPs	*E. coli* and *P. aeruginosa*	Fernandes and Francesko 2014 Francesko and Fernandes 2016 Fernandes and Ivanova 2017
	Hybrid polymer/biopolymer-metal NPs	*S. aureus* and *E. coli*	Kishen and Shi 2008 Francesko and Blandón 2015 Petkova and Francesko 2014
	Penicillin NPs	Clinical isolate of *S. aureus*	Yariv and Lipovsky 2015
	TET nanoformulations	Drug resistant and sensitive Gram-positive and Gram-negative bacteria	Avivi and Nitzan 2003 Shimanovich and Lipovsky 2015 Mishra and Segal 2015
	Lipid-polymer hybrid NPs of norfloxacin	*S aureus* and *P. aeruginosa*	Dave and Yadav 2017