https://doi.org/10.59761/RCR5205

Advances of chemistry for the design of antimicrobial biomaterials

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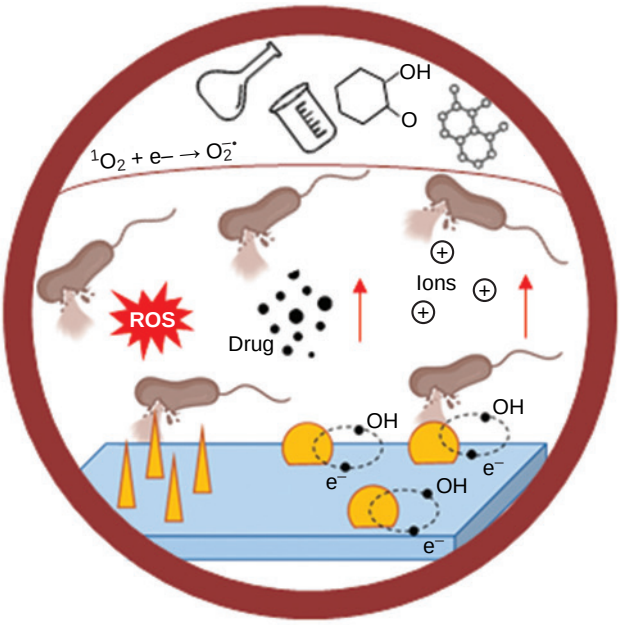
Despite the substantial progress in the understanding of bactericidal mechanisms and the development of novel antimicrobial strategies, infections remain a major threat for the humankind. It is symptomatic that antibiotic-resistant bacterial infections are now the third most common cause of death, being inferior only to stroke and coronary heart disease. Another increasingly serious threat is posed by fungal infections, especially for hospitalized patients with immunodeficiency or those who recover from COVID-19. The main feature of this review is that it provides a unified systematic view on the control of pathogenic microorganisms. The review begins with a historical account and setting of relevant tasks for innovative medical materials and proceeds with a profound analysis of fundamental mechanisms and advanced solutions. The analysis focuses on the key strategies for controlling bacterial and fungal infections, which are considered in detail in relation to metallic and polymeric biomaterials, inorganic nanoparticles and heterogeneous platforms based on them for local therapy. Particular attention is paid to factors that regulate the release of ions and therapeutic agents, generation of reactive oxygen species, and synergistic effects involved in these processes. The review also addresses the antibacterial mechanisms of action of nanoparticles and metal-containing complexes, nanoparticle toxicity and ways to minimize it, and bacterial defence mechanisms against ions and nanoparticles. The achievements of modern chemistry related to surface functionalization and immobilization of therapeutic agents aimed at developing highly effective antimicrobial surfaces are demonstrated. Critical analysis of drawbacks of the existing models for *in vitro* and *in vivo* assays of the antibacterial activity of biomaterials is given.



The bibliography includes 361 references.

Keywords: coatings, nanoparticles, metals, oxides, polymers, bactericidal mechanisms, reactive oxygen species, bactericidal ions.

Contents

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Current research interests: thin films and coatings, surface engineering, metal matrix composites, antibacterial and fungicidal surfaces, nanostructures, heterostructures, nanoparticles, nanofibres, hexagonal boron nitride, catalysis and photocatalysis, plasma polymerization, wound dressings, bactericidal fabrics, water purification sorbents, and delivery systems.
Translation: Z.P.Svitanko

Received 29 September 2025

'Vivere militare est.'
('To live is to fight')
Seneca

1. Brief historical account of the fight against pathogenic microorganisms

Since the dawn of civilization, humankind has been engaged in a continuous struggle against infectious diseases. Even before the beginning of our era, the therapeutic properties of copper, silver, gold, and a number of natural substances were empirically discovered and successfully used for treatment and mummification. The use of copper dates back to between fifth and six thousand years before Christ. Copper could be found as the free metal inside nuggets, which did not require smelting, and later it began to be used to produce brass and bronze. The first medicinal application of copper is mentioned in the Smith Papyrus (year 1500 BC), an ancient medical text,[1] which partly reproduces the text written between the year 2600 and the year 2200 BC and describes the use of copper for sterilization of chest wounds and drinking water. Copper or its compounds were used to treat diseases such as headaches, itching, burns, intestinal worms, and ear infections as well as for general hygiene.[2]

Silver metal was already known to the Chaldeans around 1000 years BC. For thousands of years, silver was used to treat many diseases, even before it was found that infections are caused by microbes.[3] Herodotus (484–425 BC) deemed that Kings of Persia always drank water that was stored and transported only in silver vessels. The ancient Phoenicians, Greeks, Romans, and Egyptians stored water in silver vessels during long military campaigns.[4] An early attempt to treat wound infections with silver plates is attributed to ancient Macedonians. Hippocrates (460–370 BC) used silver dressings to treat ulcers and to accelerate wound healing. There is a hypothesis about the use of silver nitrate in medicine, as it was mentioned in a pharmacopoeia published in Rome in the year 69 BC, and the first mention of the use of silver nitrate for medical purposes dates back to 702–705 AD. Avicenna (980–1037 AD) used silver additives for a blood cleanser and to prevent palpitation and eliminate bad breath.[3] A number of discoveries in 1847–1880 indicating that infections are caused by microorganisms (works of Ignaz Semmelweis, John Snow, Casimir-Joseph Davaine, Louis Pasteur, and Robert Koch)[5] provided a rational base for medicinal use of silver. For example, in the 1880s, the German obstetrician Karl Crede employed dilute solutions of silver nitrate to treat eye infections in newborns. In 1889, William Halstead, the head of the department of surgery in the Johns Hopkins hospital, used silver foil to treat postoperative wound infections.[6] Colloidal silver solutions formed the basis of antimicrobial therapy in the first half of the 20th century, before the advent of antibiotics in the early 1940s. According to a study of the National Aeronautics and Space Administration (NASA) carried out in the mid-1960s, a silver ion concentration of 400 ppb is sufficient for water disinfection.[7] The Soviet spacecrafts Salyut and Mir used ionic silver at a concentration of 0.2 mg L^{-1} (200 ppb) for water treatment.[8]

The medicinal use of gold as a therapeutic agent began in China around 2500 BC. Pure gold was used to treat furuncles, measles, pox, and skin ulcers. Some ancient sources mention the application of gold-containing products for the treatment of joint and lung diseases.[9] Archaeologists are rarely able to discover ancient medicines and, the more so, to determine their chemical composition; therefore, most of information has been derived from ancient manuscripts written by Theophrastus (371–286 BC), Pliny the Elder (1st century BC), and Pedanius Dioscorides (1st century BC). In this regard, of considerable interest are the results of analysis of a tin pyxis (vessel) containing residual medicine that was found on board the Pozzino shipwreck, presumably dating back to 140–130 BC, which showed the presence of zinc compounds.[10]

Many natural and plant-based products have been used in Ayurvedic medicine since around 5000 BC. Ancient healers prepared plant- and animal-based medicines, which were sometimes mixed with soil, minerals, and metals.[11] Over time, herbal, mineral, and metal agents started to occupy an important place in the Ayurvedic pharmacopoeia and have been regularly used in practice in various parts of India for many centuries. The ancient Egyptians also produced various therapeutic means from plants, animal products, and minerals. Detailed information about ancient Egyptian medicine can be found in a review.[12] Modern scientists admire the art of mummification, which used pine resin, myrrh, bee wax, bitumen, onions, lichen, henna, and other natural ingredients.

Despite the fact that the first antibiotic, salvarsan, was used in 1910, and Alexander Fleming discovered penicillin only in 1928, there are numerous examples of antimicrobial drugs entering the bodies of ancient people.[13] For example, traces of tetracycline were found in human skeletal remains in ancient Sudanese Nubia, dating to the years AD 350–550 (Ref. 14, 15) and in thigh bones of the skeletons of the late Roman period from the Dakhla oasis, Egypt.[16] It is assumed that tetracycline entered the body with food and had a protective effect, since the level of infectious diseases in Sudanese Nubia was low, and no traces of bone infections were found in Dakhla. Antibiotics produced by microbes have been used to prevent diseases for thousands of years. For example, poultices made from mouldy bread were used to treat open wounds in Serbia, China, Greece, and Egypt more than 2000 years ago.[17] Mouldy bread and therapeutic soil are mentioned in the Ebers Papyrus dated 1550 BC, which is the oldest surviving medical document.[18] The remedy reconstructed from a recently discovered 1000-year-old Anglo–Saxon prescription has proved to be effective against methicillin-resistant *Staphylococcus aureus* (*S. aureus*).[19] Despite high expectations and the initial high efficacy of antibiotic therapy, especially during World War II, the golden age of antibiotics (1940–1962) turned out to be quite short. Many modern antibiotics are modified versions of previous ones, and today scientists openly speak about a crisis in this field. First of all, this is due to slow introduction of new types of antibiotics into the clinical practice and to the emergence of multidrug resistance (MDR) in pathogens. These and many other problems are described in detail in the book How to Overcome the Antibiotic Crisis.[20] Global estimates of the MDR problem based on systematic data analysis were first published in the Lancet journal in 2022.[21] The six major pathogens, *Escherichia coli* (*E. coli*), *S. aureus*, *Klebsiella pneumoniae* (*K. pneumoniae*), *Streptococcus pneumoniae* (*S. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), and *Pseudomonas aeruginosa* (*P. aeruginosa*) were the cause for 3.57 million MDR-related deaths in 2019. Clinical monitoring data show that the level of antimicrobial resistance of bacteria is alarmingly high, being 51% to penicillin, while the median level of *E. coli* resistance to third-generation cephalosporins is 36%. Moreover, *E. coli* resistance to ciprofloxacin varies from 8.4% to 92.9%, while that for *K. pneumoniae* varies from 4.1 to 79.4%.[22]

In addition to the MDR problem, a new challenge comes from nosocomial fungal infections, which pose an increased

threat to patients with weakened immune systems or those who have had COVID-19. More than 150 million people suffer from severe fungal infections, which cause more than one million deaths annually. Long-term therapy with antifungal drugs, for example, in cancer patients, has led to the emergence of drug-resistant fungi such a *Candida auris* (*C. auris*).[23]

Currently, the design of bactericidal surfaces is a hot topic, with over 23 000 papers published on the subject in 2025 (search for the keywords 'antibacterial activity' in the Scopus database). The main feature of this review is integrated approach to the problem of fight against pathogenic microflora ranging from the historical context and setting of tasks for modern medical materials and products to fundamental mechanisms and advanced developments.

2. The main objectives of fight against an infection as applied to modern medical materials and devices

The global technological and demographic changes in the world such as climate change, environmental pollution, and population growth, increase in the polulation density, and active migration increase the risk of infectious diseases.[24] Materials possessing bactericidal and fungicidal properties are today in-demand for many medical and civilian products such as orthopaedic and dental implants, urological catheters, wound dressings, breathing masks, filters for artificial lung ventilation (ALV), bactericidal fabrics for sportswear and medical personnel protection, and food packaging.

Infection on the implant surface may be caused by previous injury, surgical intervention, or the bacterial entry and spread throughout the body during the installation of catheters or application of dressing materials, the use of ALV devices, or the patient stay in the hospital. In a healthy body, these bacteria carried by the blood are cleared by the host immune system before they reach vulnerable areas. To minimize infection, antibiotics are prescribed, most often, for 2–14 days after the surgery, together with an additional oral preventive treatment. If infection is present, it is often necessary to supplement antibiotic therapy with implant removal and elimination of the infected bone.[25,26] All this gives rise to side effects, additional medical costs, and long-term rehabilitation for the patient.

Infections are usually accompanied by biofilm formation on the implant surface (Fig. 1). Bacteria can exist in the planktonic form or as a biofilm, which is defined as a structured community of bacterial cells enclosed in a self-produced polymer matrix attached to the surface.[27] However, it is noteworthy than not all biofilms develop in this way, especially under clinical conditions *in vivo*, where biofilms often exist as aggregates not attached to the surface.[28]

The biofilm formation includes several stages: first, planktonic bacteria are attached to the surface, which may be facilitated by proteins absorbed from the environment, and then they form microcolonies, which gradually increase in the mass to form extracellular matrix (see Fig. 1).[29] The planktonic cells are attached to the substrate *via* adhesins such as fibronectin-binding proteins. The factors that play the key role in the biofilm formation include the biofilm-associated protein, intercellular polysaccharide adhesin, and some other extracellular polymeric compounds such as extracellular DNA. The implant-associated biofilms formed by Gram-positive *S. aureus* and *Staphylococcus epidermidis* (*S. epidermidis*) strains and Gram-negative *Enterobacter*, *Acinetobacter*, *Klebsiella*, and *Pseudomonas* strains pose a considerable problem throughout the world and account for the increasing rate of failures of implanted devices.[30,31] Bacterial biofilms are much more resistant to antibiotics than planktonic bacteria, as they are protected by the extracellular matrix consisting of polysaccharides, proteins, and nucleic acids.[32] This is due to the fact that attachment of bacteria to the surface leads to rapid changes in the expression of certain genes responsible for the production and maturation of exopolysaccharides and mucus and activation of the protective barrier against the endogenous defence system of the body and external agents such as antibiotics.[33] The antibiotic resistance of biofilms may be due to a delay or absence of antibiotic penetration or to operation of efflux pumps within bacteria that remove antibiotics from the maturing biofilms into the extracellular matrix. Bacteria use signalling molecules (autoinducers) of the quorum sensing (QS) system to exchange information and coordinate various activities within the biofilm; this provides for their protection from the host defence factors

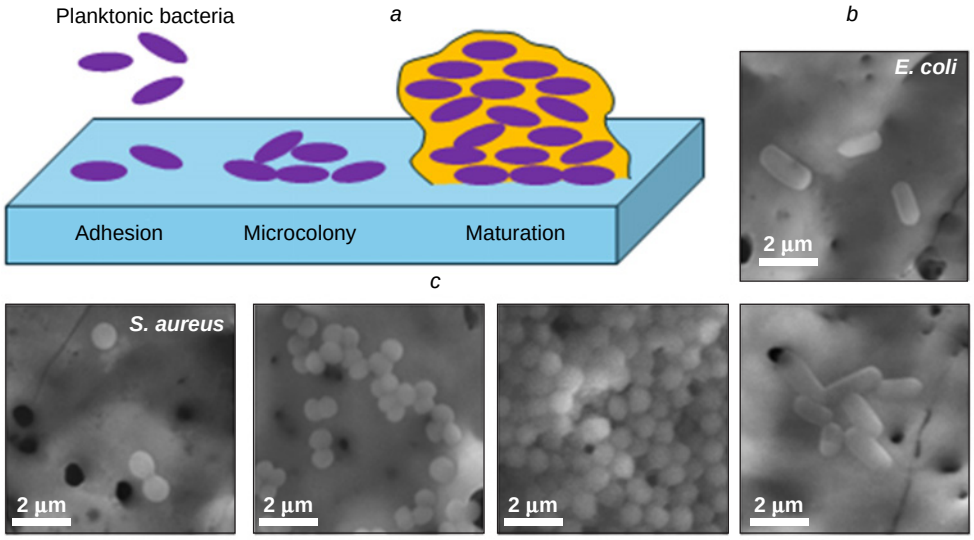


Figure 1. Schematic view of biofilm formation (*a*) and SEM images of single cells and colonies of *E. coli* (*b*) and *S. aureus* (*c*). SEM images were taken from the personal archive of the author.

Table 1. Main bacterial pathogens involved in the biofilm formation on the surface of medical implants.[36]

Bacterial pathogen	Type of implant
S. aureus	Orthopaedic implants Chest and spine implants Heart valve prostheses Cardiac pacemaker Cerebrospinal fluid valves Endotracheal tubes Venous catheter Prostheses for treatment of erectile dysfunction
S. epidermidis	Voice prostheses Orthopaedic implants Chest and spine implants Heart valve prostheses Cerebrospinal fluid valves Endotracheal tubes Urethral catheters Venous catheters Prostheses for treatment of erectile dysfunction
E. coli	Orthopaedic implants
K. pneumoniae	Urethral catheters Venous catheters
Enterococci	Breast implants Orthopaedic implants Venous catheters Urethral catheters Cerebrospinal fluid valves Heart valve prostheses

and antibacterial agents.[34] However, the current understanding of the processes occurring in biofilms is rather limited. To fill this gap, it was recently proposed to use highly efficient imaging and mapping of these structures based on automated scanning electron microscopy (SEM) and an integrated software system that uses neural networks to perform in-depth analysis of biofilms.[35] The main bacterial pathogens involved in biofilm formation on the surface of medical implants are listed in Table 1.

According to predictions, the market of metal orthopaedic implants and medical alloys would nearly double between 2022 and 2030 to reach $30 billion.[37] This is due to increased life expectancy and population ageing [according to the World Health Organization (WHO) data, one in six people on the Earth will be over 60 years old by 2030], development of sports and popularization of extreme sports, and numerous armed conflicts. The success of implantation largely depends on how completely the emergence and growth of pathogenic microflora is prevented in the early stages.

Two-thirds of infections associated with implanted devices are caused by *S. aureus* strains. Titanium and its alloys are most commonly used for implants that contact with bone tissue.[38] Numerous methods for surface modification of titanium and endowing titanium surface with bactericidal properties are discussed in detail in a book by Sánchez-Bodón *et al*.[39] Currently, biodegradable magnesium alloys are considered to be a promising alternative to titanium alloys, despite problems that have not yet been fully solved, such as fast corrosion, hydrogen formation, and the need to excrete harmful magnesium ions; therefore, extensive studies aimed at increasing the antibacterial properties of magnesium are underway.[40]

The WHO considers wound infections, which affect 1–2% of population in developed countries, to be a serious and relevant problem.[41] In the US, infections associated with implants account for approximately 26% of all infections related to healthcare.[42] The cost of treatment of wound infections amounts to approximately 3% of total healthcare costs and, according to predictions, it would reach $18.7 billion by 2027.[43] The biological tissue regeneration process consists of several overlapping stages: hemostasis, inflammation, proliferation, and maturation, which include various cells and endogenous factors.[44] Medical dressings maintain a moist medium for healing, protect the wound surface from bacterial infection, and promote debridement, epithelialization, and restoration of damaged skin areas.[45] Polymer-based hydrogels saturated with medicinal agents or containing bactericidal nanoparticles are considered to be promising for would healing, as they absorb the wound exudate and activate immune cells. In order to extend the scope of applicability of hydrogels, it is necessary to find new methods for chemical and physical cross-linking (click chemistry, enzymatic reactions, crystallization, amphiphilic block copolymers, *etc*.), endowing materials with bactericidal characteristics and enhancing their mechanical properties and adhesion.[44]

Catheter-associated urinary tract infection (UTI) is a highly widespread infection transmitted in healthcare facilities,[46] which gives rise to secondary bloodstream infections. The duration of catheterization plays a key role in the development of bacteriuria, since the catheter surface is prone to biofilm formation. Antibiotic treatment becomes less effective due to MDR bacteria. The hospital-acquired infections related to catheterization are often caused by antibiotic-resistant *Staphylococcus* and *Enterococcus* strains and *Candida* fungus. After insertion of urethral stents/catheters, infection arises in 10–50% of patients within 7 days.[47] Urethral catheters are usually made of polytetrafluoroethylene (Teflon®), polyurethane, polyvinyl chloride, or polyethylene. To modify the surface of inert polymeric items, surface activation is needed; surface properties such as chemical composition and morphology are crucial for cell adhesion and biofilm formation. The best way to prevent the growth and development of pathogenic microflora is to inhibit the initial stage of bacterial attachment and hinder the biofilm formation, which requires the fabrication of bactericidal surfaces. There are three main approaches to surface modification of orthopaedic and dental implants for endowing them with antibacterial properties: (i) change in morphology, roughness, and wettability, (ii) attachment of antibacterial or antifouling agents (antibiotics, antifungal agents, antimicrobial peptides, anti-adhesive molecules, nitroxides, *etc*.), and (iii) deposition of bactericidal coatings.

Hospital patients on ventilators are most vulnerable to bacterial/viral infections, because the contours of the ALV apparatus can be contaminated by pathogenic microflora from the respiratory passages and the environment. The most frequent complication is ventilator-associated pneumonia, a serious hospital-acquired infection that occurs 48 h after endotracheal intubation and is difficult to diagnose and treat.[48] The most common pathogens are Gram-positive *S. aureus* (28.4%) and Gram-negative *P. aeruginosa* (25.2%) and other bacteria (26.6%).[49] Modern filter membranes for ventilators mainly operate on the principles of mechanical and electrostatic filtration, which does not provide the required antibacterial protection.

Cotton fabrics ate widely used in healthcare, the sports industry, and everyday life, but they are prone to microbial growth and, hence, they can carry bacteria and viruses. Cotton fabrics can be endowed with antibacterial properties by immobilization of antimicrobial agents on the fabric surface.[50]

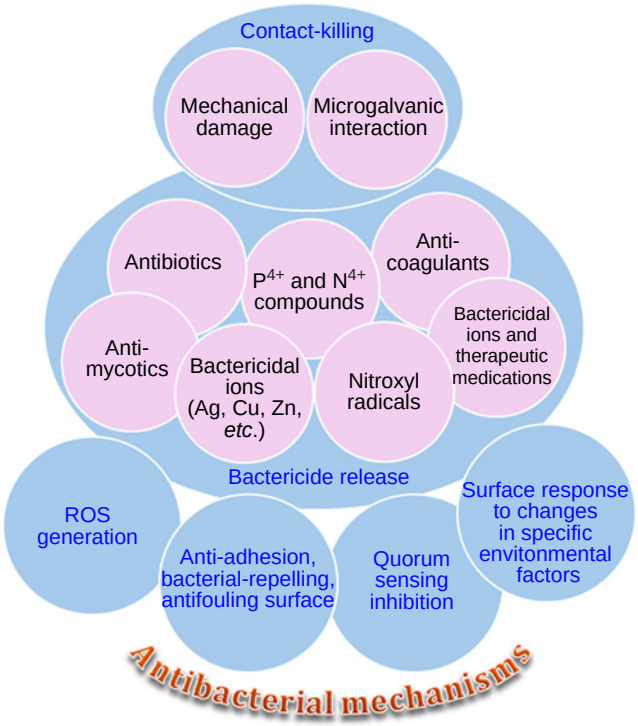
In recent years, this area has actively developed owing to the success of nanoindustry in the production of nanoparticles and nanofibres of bactericidal metals and introduction of these species into fabrics. However, immobilization of nanomaterials is a challenge due to the absence of a strong chemical bond with textile surfaces.[51] It is necessary to introduce a cross-linking agent, in order to improve the ability of a cotton fabric to hold nanoparticles. In addition, the bactericidal properties of textiles are deteriorated after prolonged use as the additives are gradually lost during washing. In a new, recently developed method for copper ion impregnation into a cellulose matrix, copper ions are strongly coordinated to oxygen-containing polar functional groups (*e.g.*, hydroxyl groups) of the cellulose chains.[52]

3. Main mechanisms of prevention of the growth and development of pathogenic microflora

There are several main mechanisms for suppressing the bacterial or fungal infection: (1) treatment with bactericidal ions, therapeutic agents, viruses and/or amino acid residues (antibiotics, antimycotics, bacteriophages, antimicrobial peptides), (2) formation of reactive oxygen species (ROS), which damage the bacterial wall and cause the oxidative stress in bacteria, (3) bacterial wall damage on contact with the implant surface *via* mechanical damage or microgalvanic interactions, (4) prevention of bacterial adhesion *via* formation of an anti-adhesive surface, (5) suppression of the QS system in bacterial films by using bioactive molecules, and (6) surface response to changes in specific environmental factors (Scheme 1).[53–56]

Correspondingly, there are a few strategies for the fabrication of bactericidal surfaces: (i) doping with bactericidal elements (Ag, Cu, Zn, *etc.*),[57,58] (ii) creation of heterogeneous surfaces decorated with bactericidal metal or oxide nanoparticles (NPs),[59–61] (iii) surface modification with various antibiotics, antimycotics, antibacterial peptides, N^{4+} and P^{4+} compounds, anticoagulants, or nitroxides *via* covalent or electrostatic bonds,[61–63] and (iv) generation of a specific surface texture or roughness.[53,64–66] The problems of implant-associated infections and various strategies directed towards growth inhibition of bacterial colonies have been described in detail in the literature.[67,68]

Scheme 1



3.1. Release of bactericidal ions

The most popular method for endowing a surface with antibacterial properties is the introduction of bactericidal metals, among which Ag, Cu, Au, and Zn are most important and studied in most detail. A benefit of the approach based on the release of bactericidal ions such as Ag,[69–71] Cu,[72,73] Au,[74,75] and Zn[76,77] is that the action is local, being concentrated directly near the substrate surface. However, the mechanisms of their action on pathogens are considerably different.[27] The Ag^+ ions have the widest range of action: they damage the bacterial cell membrane and cytoplasmic component, block the transfer of oxygen into bacterial cells, inactivate functions of enzymes, and disrupt the DNA replication.[53] The damage of the *E. coli* outer membrane and cytoplasmic membrane by Ag^+ ions was demonstrated using energy-filtering transmission electron microscopy.[78] An important component of the bacterial cell wall is the heteropolymer peptidoglycan (PG), which acts as a target for Ag^+ ions. It was shown that the Ag^+ ions inhibit the PG elongation in *S. aureus* cells by enhancing the activity of autolysins (amidases and hydrolases). Bacteriolysis and destruction of *E. coli* cell wall by Ag^+ ions is caused by disruption of lipopolysaccharide synthesis and breaking of the outer membrane due to degradation of lipoprotein at the C- and N-termini.[79] The DNA damage is due to the formation of two-coordinate Ag^+ complexes within triple (guanine)≡(cytosine) and double (adenine)=(thymine) hydrogen bonds in DNA base pairs.

The bactericidal action of Cu^{2+} ions is based on their ability to penetrate through the cell membrane and generate ROS, thus inducing oxidative stress. This results in the bacterial cell damage, influx of additional Cu^{2+} ions, and destruction of DNA molecules and bacterial enzymes.[80] The antibacterial activity of Zn^{2+} ions is usually attributed to the generation of ROS, damage of cytoplasmic membrane, which disrupts the enzymatic system, and formation of surface hydroxyl groups, which prevents bacterial adhesion.[81,82] The Zn^{2+} ions can also be absorbed by *E. coli* cells, being thus converted to insoluble ZnO-based nanocomposites, which damage the cell membrane.[83] The excellent antibacterial activity against Gram-positive and Gram-negative bacterial strains and prevention of biofilm formation are attributable to the synergistic effect of Zn^{2+} ions and ROS.[84]

Gold NPs and nanoclusters are most often used in the antibacterial therapy as conjugates with various surface ligands (amino acids, peptides, antibiotics, antibodies, enzymes, DNA, *etc.*).[85] Using *in situ* liquid-cell transmission electron microscopy, it was shown that Au NPs surface-decorated with glutathione ligand were first attached to bacterial membrane *Acetobacter aceti* through physical adsorption and then internalized. The ROS generation caused destruction of the bacterial membrane and induced cell death.[86]

The antimicrobial activity of Ag^+, Cu^{2+}, and Zn^{2+} ions against various strains of bacteria and fungi was confirmed in numerous studies (see, *e.g.*, review[87]). However, the data on the effective concentrations of bactericidal ions are highly scattered (Table 2): 1×10^{-4}–5 ppm (Ag^+), 0.15–450 ppm (Cu^{2+}), and 0.015–770 ppm (Zn^{2+}). It was reported that the ion concentrations of 0.25–1 ppm (Ag^+) and 65–650 ppm (Zn^{2+}

Table 2. Dependence of the antibacterial effect against *E. coli* and *S. aureus* on the type and concentration of ions.

Ions	Ion concentration, ppb	Antibacterial effect, % (time, h)	Bacterial strain	Ref.
Ag^+	30–50	100 (24)	*E. coli* O78	53
Ag^+	0.1–0.3	95 (3) 100 (24) 100 (8)	*E. coli* K261 *E. coli* K261 *S. aureus* ATCC 25923	54
Ag^+	300–1100	100 (3) 100 (3) 100 (24) 100 (8)	*E. coli* K-261 *E. coli* U20 *S. aureus* MW2 *S. aureus* 839	88
Ag^+	30 – 80	100	*S. aureus* and *E. coli*	89
Ag^+	$1–5\times10^3$	97 (12) 87 (12)	*E. coli* *S. aureus*	90
Cu^{2+}	$5.2–8\times10^3$	100 (6) 100 (6) 99.0 (6) 99.9 (24)	*E. coli* K261 *E. coli* U20 *S. aureus* CSA154 *S. aureus* CSA154	91
Cu^{2+}	$256–448\times10^3$	100	*S. aureus* and *E. coli*	89
Cu^{2+}	150–500	95 (12) 82 (12)	*E. coli* *S. aureus*	90
Zn^{2+}	15–30	80 (3) 100 (24) 80 (3) 100 8)	*E. coli* K261 *E. coli* K261 *S. aureus* ATCC 25923 *S. aureus* ATCC 25923	54
Zn^{2+}	300–400	100 (24) 100 (6) 100 (6) 100 (24)	*E. coli* K-261 *E. coli* U20 *S. aureus* CSA154 *S. aureus* ATCC 29213	84
Zn^{2+}	768×10^3	100	*S. aureus* and *E. coli*	89
Zn^{2+}	100–300	96 (12) 80 (12)	*S. aureus* *E. coli*	90

and Cu^{2+}) are effective against *S. aureus* and *E. coli* strains, while exhibiting no cytotoxicity against fibroblast cells.[80] The minimum inhibitory concentrations (MICs) of metal ions released from chitosan nanoparticles saturated with ions against *E. coli* and *S. aureus* strains, respectively, were 4 and 8 ppm (Ag^+), 256 and 448 ppm (Cu^{2+}), and 768 ppm (Zn^{2+}).[92] In relation to *P. aeruginosa*, MIC was 62.5 ppm (Zn^{2+}), 12.5–125 ppm (Cu^{2+}), and 104 ppm (Ag^+).[93] One explanation to this large scatter of data is the difference between methods and conditions of bactericidal assays.[94] The types of used strains (pathogenic or non-pathogenic, collection or clinically isolated, MDR or non-MDR), the initial concentrations of colony-forming units (CFU), which are usually in the $10^4–10^8$ CFU mL^{-1} range, and the growth medium are different. Since bacteria vary in shape, size, cell wall thickness, outer membrane composition, and many other characteristics, the causes for their death can also be different. Some strains exhibit increased resistance to bactericidal ions due to their ability to regulate their cellular uptake.[95] In experiments using physiological saline solution (PSS), the initial cell concentration in the control either remains unchanged or decreases with time, while the culture medium usually promotes cell proliferation.

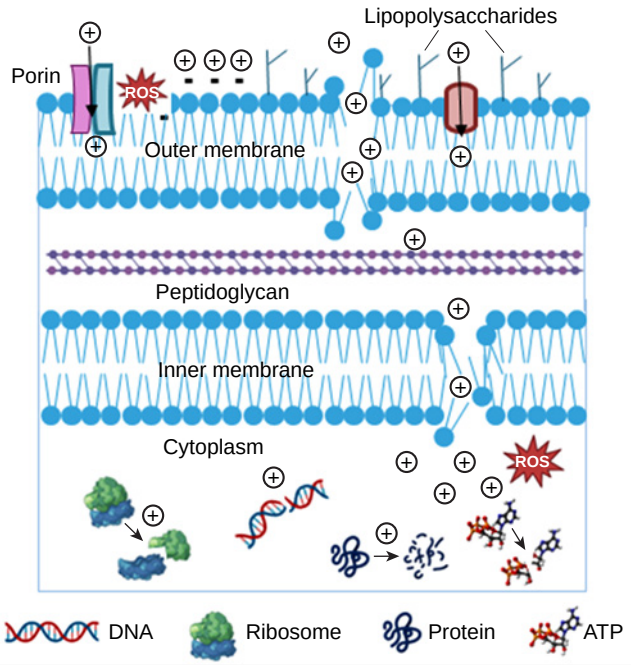
A key challenge in the use of bactericidal ion release strategy is to provide a controlled release of ions. It should be borne in mind that the rate of ion release does not always depend on the concentration of the bactericidal element, and there are additional factors that affect the yield of bactericidal ions, such as the state of metal agglomeration, surface roughness, and surface oxidation kinetics.[53] It was shown that the surface roughness has a more pronounced effect on the release of Ag^+ ions than the silver content in the surface. By appropriate adjustment of the surface roughness, it is possible to considerably increase the release of silver compared to that for smooth surface. For example, after 24 h, the amounts of Ag^+ ions released from the multielement TiCaPCON-Ag coating deposited on the smooth and rough Ti surfaces by magnetron sputtering of the $TiC_{0.5}–Ca_3(PO_4)_2$ target in the Ar–15% N_2 gas mixture differed by a factor of three. The effect of surface topography on Ag^+ release was demonstrated by Ponomarev *et al*.[96] Periodically spaced pillars of 10 and 50 μm diameter and 3, 1, and 0.2 μm height were formed by photolithography on a silver-coated silicon surface. The samples with the greatest pillar height showed the fastest release of Ag^+ ions due to greater specific surface area and the presence of Ag NPs located between the pillars.

An equally important factor influencing the yield of ions is surface oxidation in a biological medium, with the oxidation rate being directly related to the surface roughness. As a rule, the higher the roughness, the greater the specific surface area and the faster the oxidation (see Section 4). An additional contribution is made by the concentration of bactericidal nanoparticles on the surface: the higher the concentration, the slower the surface oxidation. After 7 days, the amount of Ag^+ ions released from the surface of the TiCaPCO–Ag coating deposited in an argon medium that contained 27 at.% oxygen was almost three times higher than that from the surface containing 2 at.% oxygen that was deposited in water.[97] All these factors must be taken into account for temporal control of bactericidal ion release.

As noted in some studies[53,98] and was demonstrated above, there is no direct correlation between leaching of bactericidal ions and antibacterial properties. Meanwhile, the cytocompatibility of materials depends on the dose of the bactericide; therefore, the concentration of bactericidal ions should be thoroughly controlled and compared with the results of cytocompatibility assays.[99]

The bactericidal mechanism based on the action of ions is shown in Schemes 2 and 3. Bacterial cells are surrounded by an outer membrane (only in the case of Gram-negative bacteria) containing lipopolysaccharides, lipids, and proteins, cell wall the main component of which is PG (same as murein), and an inner cytoplasmic membrane. The thick PG layer of Gram-positive bacteria decreases the probability of penetration of bactericidal ions. The interaction of ions with bacterial cells often starts with electrostatic attraction between positively charged ions and the negatively charged bacterial surface (Scheme 2). The Ag^+, Cu^{2+}, Zn^{2+}, and Mg^{2+} ions can directly interact with various structural components of the cell wall and membrane such as lipids and amino acids occurring as parts of proteins and PG and change their structure, which leads to damage and denaturation (Scheme 3). In the case of Gram-negative bacteria, ions can penetrate the outer membrane through beta-barrel proteins (porins) or membrane transport proteins. When bactericidal ions get into the cell, they deactivate respiratory enzymes and disrupt the production of adenosine triphosphate (ATP), which provides energy for various biochemical reactions. The reactions of Ag^+ with sulfur and phosphorus in DNA and the action of ROS on DNA are main causes for the disruption of DNA replication. Silver ions can inhibit protein synthesis, which results in ribosome denaturation in the cytoplasm.[100] Copper ions react with proteins depending on the oxidation state: Cu(I) binds to sulfur donors such as

Scheme 2



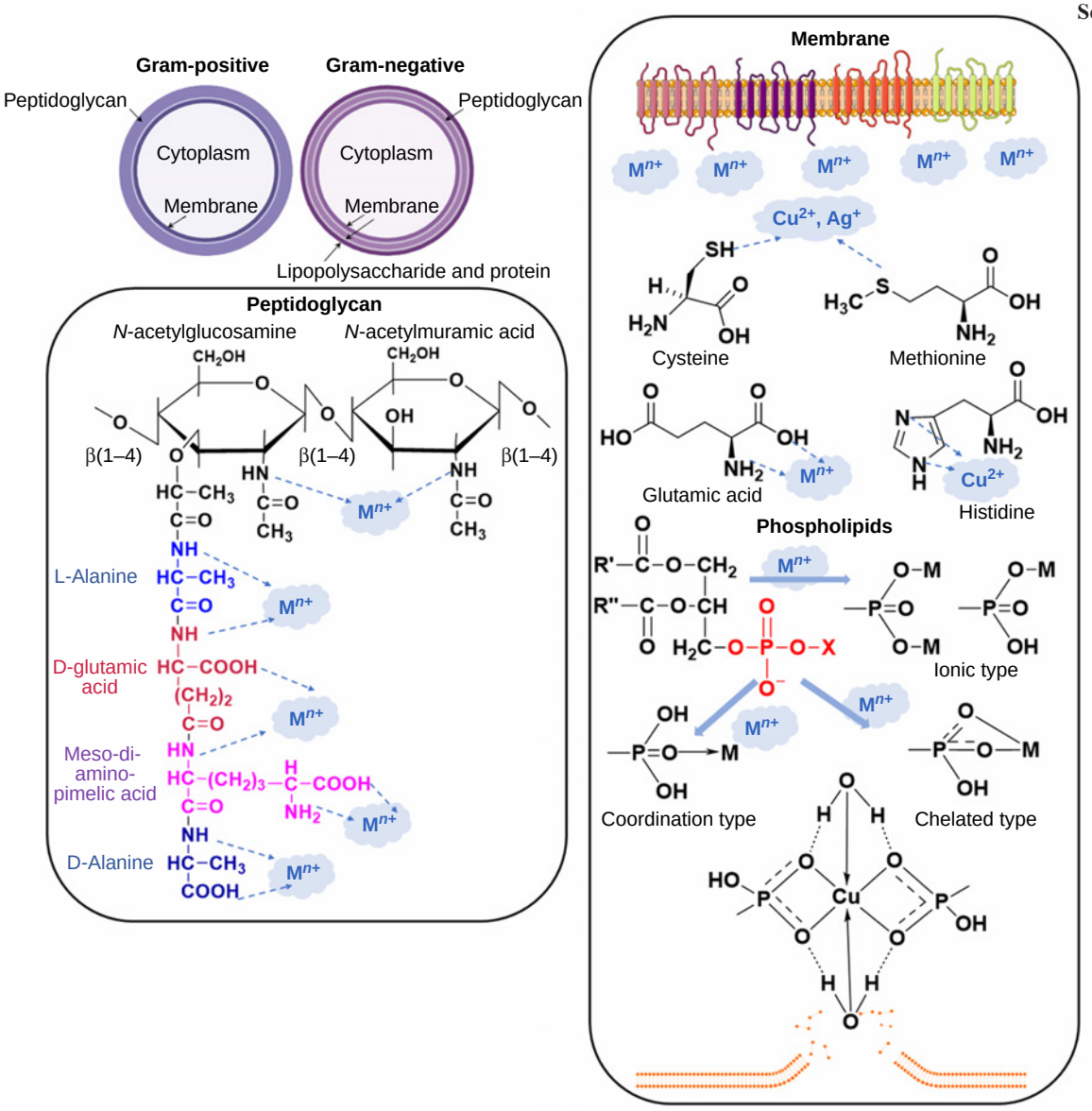
cysteine and methionine, whereas Cu(II) prefers nitrogen donors such as histidine and other amino groups.[101]

In conclusion, it should be noted that the release and transport of bactericidal ions are influenced by the biological medium. The implant surface actively interacts with blood serum proteins such as human serum albumin (HSA), which is the main zinc(II) transporter in blood plasma.[102] The reactions of Ag^+ with extracellular thiols and human blood components prevent the interaction of silver ions with the cells, which reduces the antimicrobial activity. Binding to silver affects the protein structure, thus inducing loss of alpha-helices and a change in the tertiary conformation.[103]

3.2. Release of medications

The strategy based on the release of pharmaceutical agents [antibiotics,[61,104,105] quaternary ammonium compounds,[106] halogen compounds (fluorides[107] and iodides[108]), chlorhexidine,[109] nitric oxide,[110] chitosan,[111] *etc.*) also implies the local action just near the substrate surface, which considerably reduces the therapeutic load. The main benefit of the surface-bound antibiotics and antimycotics is that they suppress the infection over a short period of only a few hours even in low

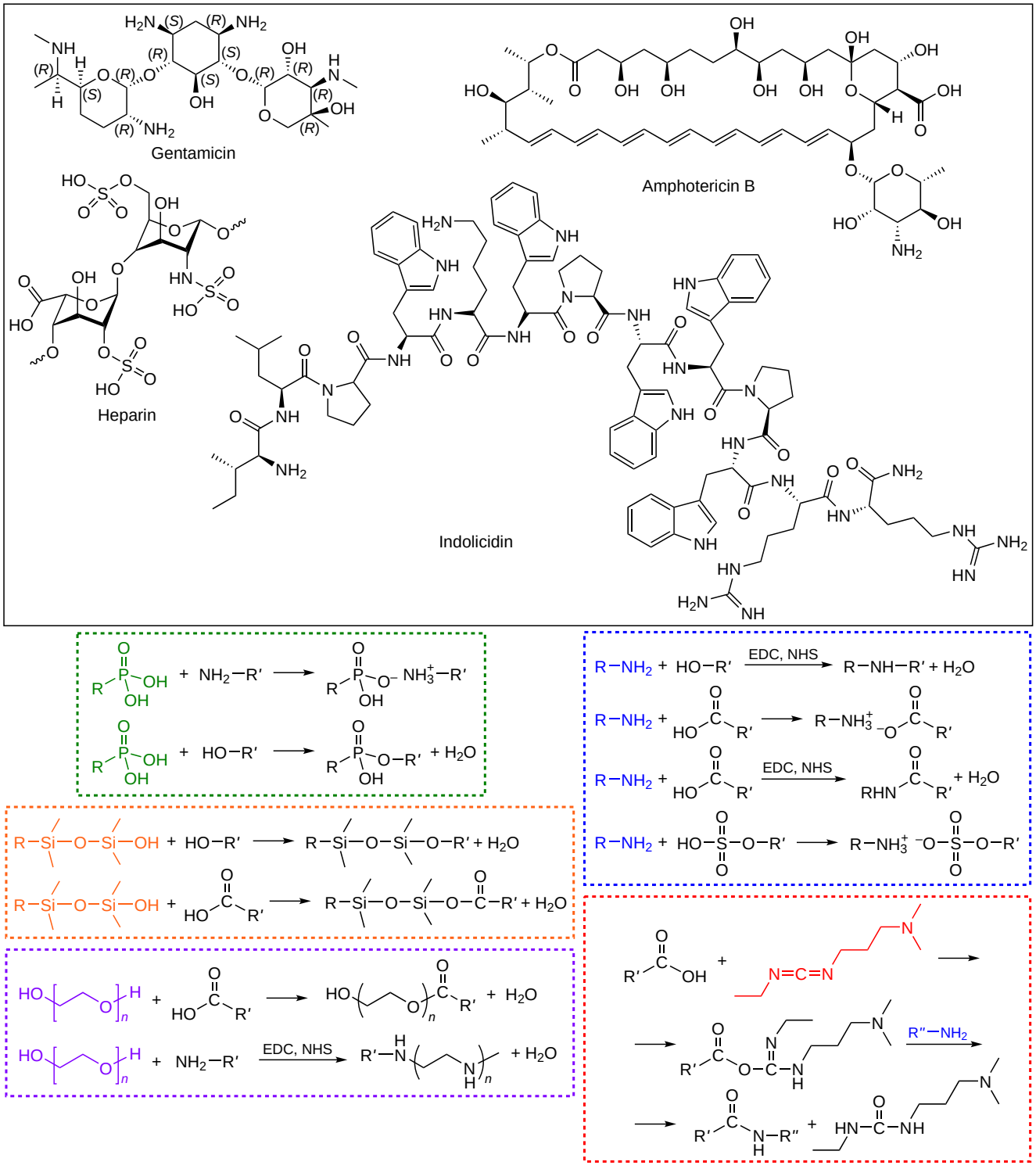
Scheme 3



doses[61,63] and are non-toxic for the surrounding tissues and the whole body. In order to achieve a wider range of action, mixtures of medications can be used.[63] The major drawbacks are the emergence of MDR (and related decrease in the efficacy of antibiotics), limited time of the bactericidal effect due to complete release of the medication over a short period, and undesirable side effects at high therapeutic doses.

A promising approach is to combine the strategies based on the release of antibiotics and bactericidal ions, which follow different kinetics. For example, Ag-containing TiCaPCON coating provided a persistent release of Ag^+ ions for 7 days, while gentamicin (GM) loaded into the specially formed surface relief was released almost completely within 12 h, with accelerated release being observed during the first hour.[63] The possible interactions of therapeutic components should also be taken into account. For example, GM can interact with silver ions and form stable Ag/GM complexes, thus decreasing the concentration of free silver ions in the test solution.[112] The accelerated initial release of the medication in a low dose (in order to avoid side effects) provides fast suppression of the infection, while prolonged release of bactericidal ions provides long-term protection to prevent latent infection.

Scheme 4



A wider range of action can also be achieved by combining various antibiotics, antimycotics, and bactericidal ions. For example, titanium hybrid bioconstructs containing Ag NPs and loaded with a mixture of GM and amphotericin B (ATB) were equally effective against the Gram-negative *E. coli* bacterium and GM-resistant *Neurospora crassa* (*N. crassa*) fungus.[63] This type of fungus is characterized by strong cell walls that act as a barrier against bactericidal Ag^+ ions. The GM- (150 and 300 μg cm^{-2}) and ATB-loaded (100 μg cm^{-2}) hexagonal boron nitride h-BN coatings also effectively inhibited the growth of *E. coli* K-261 and *N. crassa* strains.[55]

The strategies that imply immobilization of therapeutic agents are based on the generation of a surface rich in functional groups to provide a strong adhesion to the substrate surface *via* the formation of covalent bonds (Scheme 4). The titanium surface is activated using carbodiimide chemistry and click-chemistry methods, surface functionalization using thiols, plasma amination (introduction of NH_2 groups), silanization, surface photopolymerization, *etc*.[113]

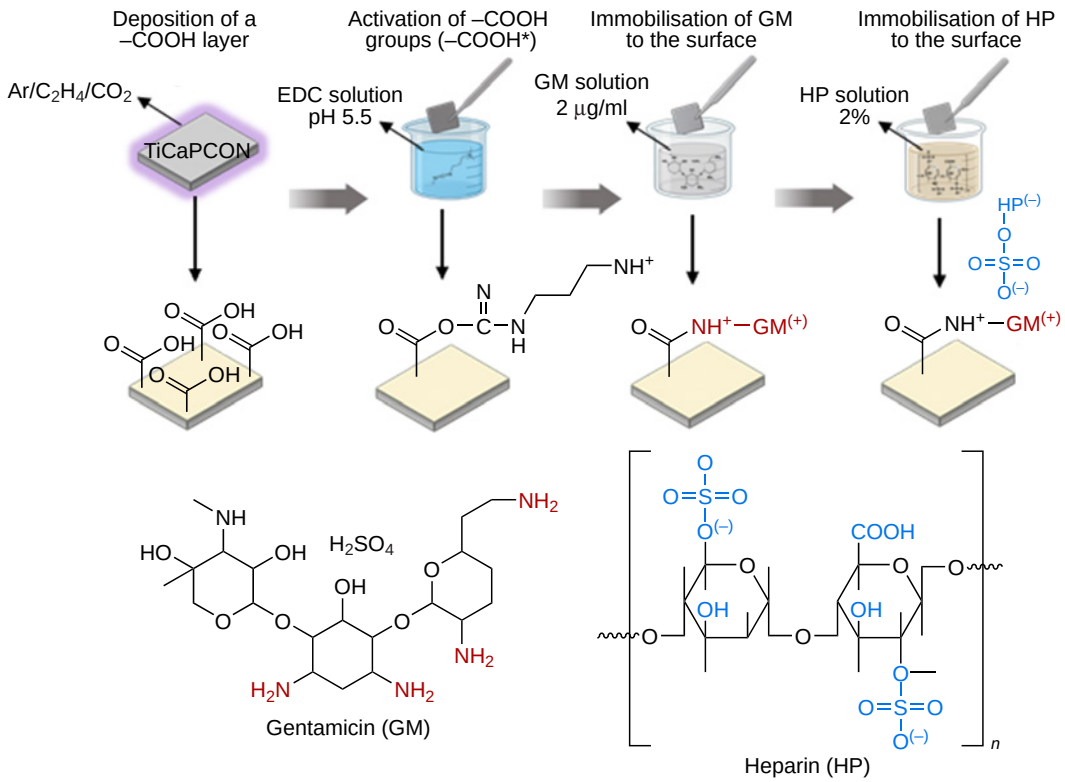
The surface of titanium with the deposited TiCaPCON coating (Ag-loaded or Ag-free) was treated with the $Ar/C_2H_4/CO_2$ radio frequency plasma at a low-pressure of 2–4 Pa in order to form a polymer layer containing COOH groups (Scheme 5).[114] The generation of surface carboxyl groups is commonly used for immobilization of various biomolecules on plasma-treated materials.[115] For the covalent immobilization of GM, the sample was first placed into an aqueous solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), which is often used a carboxyl-activating reagent, and then into a 2% aqueous solution of GM for chemical binding to EDC through amide bonds. Anti-adhesive heparin (HP) molecules were immobilized on the GM surface *via* ionic bonds formed between the positively charged GM amino groups and the negatively charged COOH groups of HP.[114] After 24 h, GM- and GM/HP-loaded samples, as well as the sample with Ag NPs showed 99.999% bactericidal effect against antibiotic-resistant *E. coli* K261 strain.

Low-pressure plasma polymerization and carbodiimide chemistry methods were used to immobilize four different therapeutic agents (antibiotic, GM; antimicrobial peptide, indolicidin; anti-adhesive HP; and nitroxide, 2,2,5,5-tetramethyl-3-carboxyl-pyrrolidin-1-oxyl) on the surface of TiCaPCON coatings *via* ionic or covalent bond to endow the coatings with antibacterial properties.[116] The use of modified coatings markedly decreased the level of antibiotic-sensitive *E. coli* U20 strain and (except for samples with immobilized indolicidin) induced effective inhibition of the antibiotic-resistant *E. coli* K261 strain at an initial concentration of 10^4 CFU mL^{-1}. The coatings bearing covalently attached nitroxide not only exhibited the highest antibacterial activity against *E. coli* K261 cells (99.99% after 8 h), but also prevented the biofilm formation.

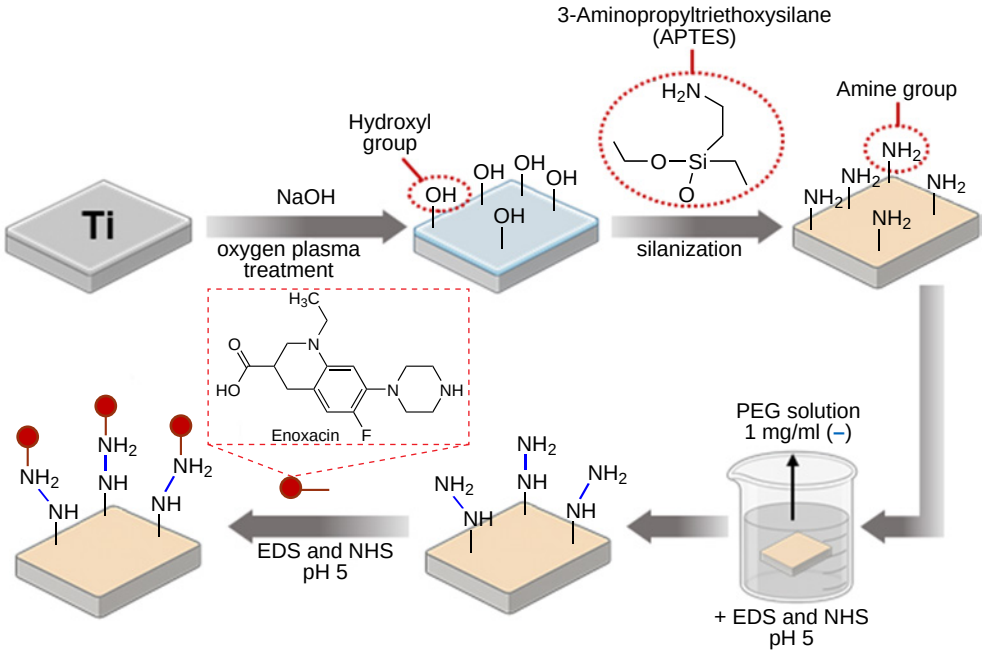
The vancomycin (VM) antibiotic was encapsulated into a polyethylene glycol (PEG)-based hydrogel film that was bound to titanium implants by a covalent bond and then coated with a membrane made of PEG copolymer with the product of polycondensation of lactic acid and caprolactam.[117] In order to retard the drug release, the hydrogel was used as a mixture with cross-linked starch, the porous microstructure of which inhibited the hydrogel swelling. The materials demonstrated stable release of VM for almost 3 weeks *in vitro* and for more than 4 weeks *in vivo*. In the *S. aureus* infection model in rabbits, implants loaded with 4 mg of VM substantially reduced the imflammatory response and showed good antimicrobial activity.

The surface of titanium implants was functionalized with 3-aminopropyltriethoxysilane followed by attachment of enoxacin (EX)-linked PEG molecules *via* amino groups (Scheme 6).[118] The EX-bearing titanium surface effectively prevented the bacterial colonization with methicillin-resistant *S. aureus* (MRSA) without deteriorating *in vitro* cell viability, adhesion, or proliferation.

Scheme 5



Scheme 6



GM-loaded biodegradable coatings based on polylactic and glycolic acid polymers or poly(*D*,*L*-lactide) were deposited on the surface of titanium implants, which markedly decreased the frequency of infection and improved the recovery rate after infection compared to systemic GM application.[119–121]

Implant coating by an amphiphilic polymeric material was performed by a new technique involving surface binding of a branched block copolymer of PEG with polyallylmercaptan (PAM) obtained *in situ*,[122] which was effectively chemisorbed on metal surfaces and self-organized to give a uniform coating. The titanium Kirschner wires were immersed into a solution of PAM, PEG thiol (6 mass%), and vancomycin (20 mg mL^{-1}). Then the wet titanium wires were UV-irradiated and dried at room temperature to form PEG-PAM on the sample surface.

Vancomycin and caspofungin were covalently attached to titanium surface pretreated with 3-aminopropyltriethoxysilane. The functionalized titanium samples were placed into a solution (1 mL per disc) of n-heptane/hexamethylene diisocyanate. The *in vitro* formation of *S. aureus* bacterial biofilms and *Candida albicans* (*C. albicans*) fungal pathogen was substantially reduced compared to that in the titanium control sample. In *in vivo* assays, the formation of *S. aureus* biofilms in VM-loaded samples decreased by more than 99.9% and the formation of *C. albicans* biofilms in caspofungin-loaded samples decreased by 89% compared to the control Ti sample.[123]

To suppress local infection, titanium implants were coated with chitosan-based hydrogels loaded with antibiotics such as ciprofloxacin, amoxicillin, and gentamicin[124] or their mixture. After 24-hour subcutaneous implantation of titanium implants coated with antibiotic-loaded chitosan particles in male Sprague–Dawley rats, analysis of SEM images showed that the samples contained less *S. aureus* colonies than the control sample.[125]

Antimicrobial peptides (AMPs) attached to the surface of biomaterials represent a promising alternative to traditional antibiotics for fight against infections.[126] AMPs are molecules formed by amino acid residues connected by peptide (amide) bonds; they exhibit antibacterial activity against negatively charged outer and cytoplasmic membranes of Gram-negative bacteria due to their positive charge (cationic type).[127] A small number of AMPs are anionic owing to the presence of glutamic and aspartic acids (*e.g.*, dermcidin present in sweat); their antibacterial activity is caused by the ability of metal ions to form cationic salt bridges with negatively charged components of bacterial membranes.[128] Antimicrobial peptides interact with bacterial cell membranes, thus destroying them or causing the formation of pores, which results in cell death. AMPs can also be incorporated in the negatively charged cytoplasmic membrane, thus disrupting the cell integrity, and penetrate into the bacterial cytoplasm, binding to DNA and RNA, which also induces cell death.[129] The antimicrobial properties of AMPs, cytocompatibility, molecular structure, and mechanism of antibacterial action have been described in detail in a number of reviews.[130,131]

There are two key strategies for the attachment of AMPs to the implant surface: covalent binding of AMPs to metal surface and non-covalent immobilization. In both cases, the bactericidal effect is achieved through the controlled release of AMPs into the microenvironment surrounding the implant.[132–134] The key factors determining the efficiency of bactericidal protection are the surface density, mobility, and orientation of peptide molecules.[126] A meta-analysis of the available data on *in vivo* AMP modification of implants was published.[135] Synthetic HHC36 and VM were the most common AMPs used for surface modification, while *S. aureus* was the bacterium best studied *in vivo*. The main methods for AMP attachment to the titanium surface included covalent binding to a predeposited polymer surface layer, physical adsorption, and layer-by-layer self-assembly.[136–138] Functional groups present in AMPs such as NH_2, COOH, and SH can react with functional groups on the implant surface, *e.g.*, OH groups formed after alkaline etching or NH_2 groups resulting from silanization.[139,140]

As of September 2025, the AMP database contains 5680 peptides with various antibacterial, antiviral, and antifungal activities.[141] These peptides are constantly expressed in epithelial and phagocytic cells of the body and are activated when host cells detect an active infection or bacterial endotoxin. AMPs effectively kill antibiotic-resistant bacteria such as MRSA, *P. aeruginosa*, and quinoline-resistant *Enterobacteriaceae*.[142] AMPs are classified in terms of length,

charge, structure, concentration of hydrophobic amino acids, and the source of origin.[143]

After diffusion release, AMPs can affect bacteria in two ways: (1) by damaging bacterial membranes or disrupting their vital functions or (2) by direct physical contact between the bacterial cell and cationic AMPs.[144] The practical use of AMPs is limited due to a number of problems, first of all, uncontrolled toxicity, high cost of production on an industrial scale, cytotoxic effect on eukaryotic cells, and degradation by host proteases.[145]

A promising alternative to traditional antibiotic therapy is the use of bacteriophages, that is, viruses that selectively infect bacterial cells to induce cell lysis. An advantage of bacteriophages is that they can selectively infect particular types of bacteria without affecting the bacteria of the normal microbiome flora.[146] After the bacteriophage is attached to specific receptors on the membrane of the target bacterial cell, the genetic material of the bacteriophage is inserted into the host cell. During replication of the virus inside the cell, new phages are formed; they attack new targets and destroy the infected bacterial cell. The bacteriophage can also transmit its own genetic material into the bacterial genome and replicate with each cell division of the infected bacterial cell.[147] The efficiency of bacteriophages was demonstrated against various MDR strains such as *K. pneumoniae*, *P.aeruginosa*, *E. coli*, and *A. baumannii*.

The main benefits of the bacteriophage therapy include high specificity (bacteriophages can affect a specific bacterial strain), the absence of antagonistic effect when bacteriophages are mixed, low toxicity, and the ability to penetrate into biofilms.[148] However, evaluation of the pharmacokinetic behaviour of bacteriophages is a complicated task, since inside bacterial cells, they interact with numerous microbial pathogens that are recognized and suppressed by the human immune system. Determination of the infectious titers of bacteriophages is still labour-consuming, subject to errors, and ineffective.[149] The bioavailability of bacteriophages that are not intravenously administered is considered to be low, while data on intravenous administration are currently limited. Personalized combinations of bacteriophages and antibiotics may be of interest to expand the scope of antibacterial therapy; however, it should be borne in mind that these combinations may give rise to both synergistic[150] and antagonistic effects,[151] depending on the mechanism of inhibition of bacteria by the antibiotic used in combination with the bacteriophage. Furthermore, the use of bacteriophage cocktails does not always provide an advantage over antibiotic therapy.[152]

3.3. Prevention of biofilm formation by generation of an antiadhesive surface and inhibition of the quorum sensing system

Using various chemical methods, it is possible to modify surfaces and endow them with particular functions. Antiadhesive or antifouling coatings prevent bacterial adhesion and may consist of hydrophilic polymers, superhydrophobic materials with low surface energy, or have a structured surface. The antiadhesive properties of a surface depend on several key parameters: topography, roughness, wettability, and charge. Many materials occurring in nature have inspired researchers to design artificial surfaces resistant to bacteria, which may mimic the gecko skin,[153] lotus leaves,[154] and insect wings.[65,155] The antiadhesive properties of a surface are usually due to low contact area; therefore, bacterial adhesion is influenced most appreciably by nanostructures with a high aspect ratio (nanospikes, nanotubes, nanoripples) and structured surfaces with approximately 1 μm structural elements (micro-wells, micro-grooves, submicro-pillars, and micro-protrusions).[156] The effect of surface wettability on the bacterial adhesion is highly ambiguous, and the available data are quite contradictory: readers can find relevant information in recently published reviews.[156–158] The superhydrophilic and superhydrophobic surface characteristics are strongly influenced by bound water and trapped air, which prevent bacteria from direct contact with solid surfaces, which reduces bacterial adhesion.[159]

The repulsion of bacteria from a surface may arise if there is a physical barrier to the proteins in the bacterial cell wall caused by electrostatic interaction or low surface energy. Various types of adhesive polymer materials are described in the literature: hydrophilic polymers, among which PEG is used most commonly; chitosan-based hydrogels; mixtures of peptides and polymers; nanoparticle-doped hydrogels; and poly-zwitter-ion polymers,[137] which belong to the type of materials with equal numbers of cations and anions along polymer chains[160] and contain positively and negatively charged groups, making them highly hydrophilic.[161] The biological fouling of polymers results in the formation of conditioning films (macromolecules), which can grow to form biofilms (microorganisms) and lead to macroscopic biofouling (macroorganisms).[162] Antiadhesive coatings often contain enzymes immobilized on the surface that either prevent bacteria from attaching or can break the biofilm matrix.[163]

The van der Waals forces and electrostatic interactions largely determine the bacterial adhesion to the surface. In view of the fact that bacteria are usually negatively charged due to carboxyl, amino, and phosphate groups on their cell walls, they often have more pronounced adhesion to positively charged surfaces. Meanwhile, numerous facts indicate that bacteria can overcome electrostatic repulsion and strongly bind to negatively charged surfaces.[164]

The free surface energy is a critical initial factor for biofilm formation, but its role is ambiguous. The former paradigm according to which bacteria prefer to be attached to hydrophobic surfaces is largely outdated. In particular, in a biological medium, the surface is instantaneously covered by a layer of organic molecules (proteins, polysaccharides), which changes the initial surface free energy. In addition, bacteria can recognize the surface properties and regulate gene expression where they switch from reversible to irreversible attachment and initiate matrix formation.

A specific biofilm control mechanism is the use of bioactive molecules capable of suppressing the QS system. Over the past two decades, quorum sensing inhibitor (QSI) and quorum sensing quencher (QSC) enzymes have been developed. These enzymes are capable of inhibiting various parts of QS signalling pathway and affecting signalling molecules and their receptors. Synthetic QS inhibitors include derivatives of furanone, benzimidazole, benzothiazole, pyranone, quinolines, pyrrole, indole, pyridine, pyrimidine, thiazole, thiadiazole, thiazolidine-2,4-dione, cinnamaldehyde, and esters.[165] In view of the fact that during evolution, plants have developed chemical mechanisms to combat external pathogens, secondary metabolites of various classes of plants such as terpenes, quinones, coumarins, stilbenes, alkaloids, curcuminoids, flavonoids, phenolic compounds, and their derivatives and analogues are suitable candidates for QS system inhibition.[166]

Bioactive molecules have been used for surface functionalization of biomaterials. For example, the antibacterial and cytocompatible peptoid GN2-Npm9 was electrostatically attached to the chemically pretreated Ti6Al4V surface. In the

presence of the peptioid, the adhesion of *P. aeruginosa* MMA83 bacteria markedly decreased, which was attributed to QS disruption.[167] Quorum sensing inhibitors were also used to prevent the biofilm formation on the surface of catheters.[168,169]

3.4. Formation of reactive oxygen species

Generation of ROS such as hydroxyl radicals (•OH), superoxide anions $O_2^{-\bullet}$, and hydrogen peroxide (H_2O_2) may introduce imbalance (called oxidative stress) between the cellular production and consumption of ROS, which impairs the cell integrity.[170] The oxidation process can lead to the death of microorganisms if it causes oxidative damage to proteins, lipids, and nucleic acids. The $O_2^{-\bullet}$ anion is formed *via* cellular redox metabolism mediated by electron transfer proteins. The dismutation of $O_2^{-\bullet}$ affords H_2O_2, which can be reduced to hydroxyl radicals by the Fenton reaction. In addition, $O_2^{-\bullet}$ can react with nitric oxide radical (•NO) to give reactive nitrogen species.[171]

$$^1O_2 + e^- \longrightarrow O_2^{-\bullet} \quad (1)$$

$$O_2^{-\bullet} + {}^\bullet NO \longrightarrow ONOO^- \quad (2)$$

$$ONOO^- + CO_2 \longrightarrow {}^\bullet NO_2 + CO_3^{\bullet} \quad (3)$$

$$2\,O_2^{-\bullet} + 2\,H^+ \longrightarrow H_2O_2 + O_2 \quad (4)$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + {}^\bullet OH \quad (5)$$

$$Cu^+ + H_2O_2 \longrightarrow Cu^{2+} + OH^- + {}^\bullet OH \quad (6)$$

A combination of ROS and bactericidal ions produces a synergistic antibacterial effect.[55,84] The generation of ROS can be used to prevent the formation of surface biofilm and to kill planktonic bacteria.[172,173] The lifetimes of free radicals such as superoxide ($O_2^{-\bullet}$), hydroxyl ($OH^\bullet$), peroxyl ($ROO^\bullet$), and alkoxyl ($RO^\bullet$) amount to fractions of a second, while hydrogen peroxide (H_2O_2) and organic peroxides (ROOH) can be preserved for a few hours.[174] Current research focuses on the development of heterogeneous materials capable of generating ROS both by themselves and after exposure to various sources of radiation.[175–178] These materials are typically photocatalytic semiconductors that generate ROS as a result of electron transition from the valence band to the conduction band to give holes.[179,180] In order to decrease the band gap and enhance the visible and UV absorption, new composites are being developed or known photoactive materials (TiO_2, CuO, ZnO) are being doped with additional elements (*e.g.*, Zn, Ca, Au, graphene, *etc.*).[181–183] The surface of the material is often decorated with NPs of transition and noble metals (Cu, Ag, Au, Zn, *etc.*) to prevent fast recombination of electrons and holes.[184–186] The electron work function is higher for metal NPs than for semiconductors, which increases the lifetime of the electron–hole pair. The efficiency of this approach was demonstrated in relation to the Ag/TiO_2 and Pt/TiO_2 systems, which efficiently generated ROS on exposure to UV radiation or visible light.[182] Bimetallic Pt–Fe NPs deposited on the surface of Ti(C,N)-based coatings also enhanced the generation of ROS after UV irradiation.[186]

The separation of electrons and holes is usually activated by some external source (ultrasound, radiation).[63,185–192] The most studied type of external action is UV irradiation, which activates transition metal oxides (Ti, Zn, Cu), bimetallic systems (Cu–Bi), nonmetals (graphene nitrides and oxides, polymers), and various composites.[183,186,190–194] However, this method can be used only before the implant placement, for example, during sterilization, as UV radiation does not penetrate into a tissue to a depth more than 1 mm. Inflammation and implant-associated infection can also occur after implantation during the patient rehabilitation period; therefore, the possibility of implant surface activation directly in the implantation area opens up new opportunities for fighting infections.[195]

In recent years, X-ray therapy methods have been increasingly used, since X-rays penetrate deep into tissues. X-ray luminescence is used more and more often for imaging, biosensorics, and theranostics.[196] Soft X-ray irradiation enhances the generation of ROS in mesoporous titanium peroxide used in tumour therapy.[197] The ROS activation with X-rays may be an effective alternative to UV radiation and will allow X-rays to activate the material directly at the site of infection. The available data indicate that X-ray irradiation may give rise to electron–hole pairs in TiO_2.[198]

The current knowledge of the effect of X-rays on the ability of composite coatings to generate ROS is limited; this approach has not been used until recently to combat bacterial infections. Recently, light-sensitive Si-doped TiCaCON films decorated with Fe and Pt NPs possessing ROS-mediated photoinduced antibacterial activity have been developed. After short-term (5–10 s) low-dose X-ray irradiation, the films generated much more ROS than they generated after UV illumination for 1 h. The Fe/TiCaCON–Si films showed enhanced capacity for biomineralization, good cytocompatibility, and excellent antibacterial activity against multidrug-resistant hospital *E. coli* U20 and K261 and MRSA MW2 strains.[199]

The formation of ROS upon X-ray irradiation of a zinc-doped coating produced by plasma electrolytic oxidation (PEO) was reported for the first time by Popova *et al*.[84] The zinc-containing TiO_2-based coating with added Na, Ca, Si, and K provided effective and versatile bactericidal protection without compromising the biocompatibility. The excellent cytocompatibility of PEO–Zn samples was confirmed by three methods: monitoring of MC3T3-E1 cell proliferation, evaluation of the viability of sheep osteoblast cells using calcein-AM staining and fluorescence microscopy, and incubation with spheroids based on primary osteoblasts and NIH3T3 mouse embryonic fibroblasts. After 24 h, the PEO–Zn coatings completely inactivated four types of strains, Gram-positive *S. aureus* CSA154 and ATCC29213 and Gram-negative *E. coli* K261 and U20, and prevented the formation of *E. coli* U20 and K261 biofilms. The excellent antibacterial activity is attributable to the synergistic effect of Zn^{2+} ions in a safe concentration and ROS generated upon UV irradiation or short-term soft X-ray irradiation. The results markedly expand the options for using PEO coatings on the surfaces of titanium implants.

3.5. Destruction of bacteria on contact with a surface due to mechanical damage or microgalvanic interaction

The search for alternative strategies for preventing bacterial colonization, instead of methods based on the release of bactericidal ions or antibiotics, resulted in the development of contact-killing surfaces that do not contain toxic substances. These approaches imply generation of a specific surface nanorelief, incorporation of cationic compounds into the coating, or the use of microgalvanic effects (Fig. 2).

The bactericidal activity of nanostructured surfaces and their ability to kill bacteria by mechanical interaction with cell walls was demonstrated for various nanomaterials such as black silicon,[200,201] carbon nanostructures,[66,202] zinc oxide

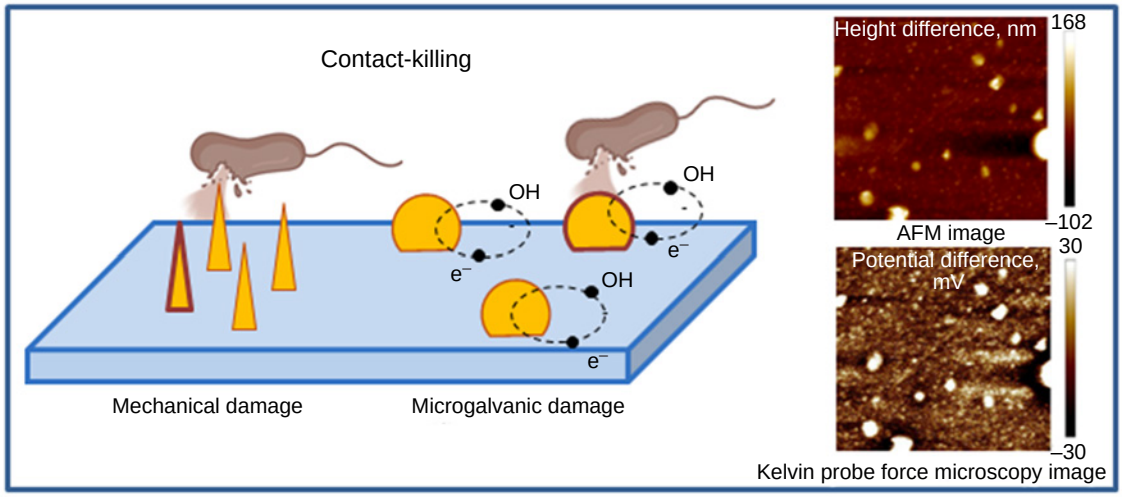


Figure 2. Schematic view of destruction of bacteria upon contact with the surface due to mechanical damage or microgalvanic interaction. The atomic force microscopy image (above) and Kelvin probe force microscopy image (below) of Pt nanoparticles on the surface of TiCaPCON coating were taken from the author's personal archive.

nanorods,[203] copper oxide nanosheets,[204] CuO_x NPs,[205] and hexagonal BN (h-BN) nanosheets/nanoneedles.[55] It was assumed that cell death is caused by the ability of vertically oriented nanotubes to accumulate and release elastic energy upon deformation caused by contact with the cells. A similar mechanism may also be involved in the case of nanosheets. The results of TEM analysis clearly demonstrated that membranes of *E. coli* and *Bacillus subtilis* cells were damaged by the nanostructured surfaces of h-BN[55] and CuO_x NPs,[205] respectively. A comparison of the bactericidal properties of a nanostructured surface and a surface loaded with an antibiotic was first reported by Gudz *et al*.[55] The h-BN coatings formed by nanosheets and nanoneedles were shown to have a high antibacterial activity (>99% after 24 h) against the *E. coli* K-261 strain with an initial concentration of 10^4 CFU mL^{-1}, which is comparable with a GM-loaded h-BN sample (150 μg cm^{-2}). The mechanical damage to the bacterial wall is the first stage of destruction and may be accompanied by the penetration of bactericidal ions or ROS into the cell, thus accelerating the cell death.

Microgalvanic effects on the implant surface may be caused by local electric currents arising due to potential differences between system components (*e.g.*, metal NPs on the surface and the surrounding conductive matrix) in a conductive biological medium. As a result of dissolution of NPs, which act as cathodes in the system, the electrons that are formed in reaction (7) pass through the surface layer of the coating, which acts as an anode, towards metal NPs and are involved in depolarization reactions (8) and in reactions with molecules of the medium (9). The electrical circuit is closed due to transfer of negatively charged ions through the biological medium to the anode. In the case of Ti-based coating, the above-mentioned chemical reactions can be described in the following way:[54]

$$Ti \longrightarrow Ti_1^{n+} + ne^- \quad (7)$$

$$2H_2O + 2e– \longrightarrow H_2 + 2OH^- \quad (8)$$

$$O_2 + 2H_2O + 4e^- \longrightarrow 4OH^- \quad (9)$$

The microgalvanic interaction between the Ag NPs and the Ti matrix was studied by measuring the electrochemical polarization and zeta-potential.[206,207] The Ag-modified samples considerably decreased proliferation of the *S. aureus* and *E. coli* bacteria despite the low Ag content (<10 ppb). It was suggested that proton-depleted regions formed during cathodic reactions disrupt the proton electrochemical gradient in the intermembrane space of bacteria.[207] To intensify the microgalvanic effect, the Ag-modified Ti coatings were doped with zinc.[208,209] Although Ag- and Zn-modified coatings demonstrated an increased bactericidal effect, it is difficult to draw any reasonable conclusions about the contribution of microgalvanic processes, since both elements are bactericides. The antibacterial effect of thin magnesium coatings against *S. epidermidis* was explained by various factors, including microgalvanic interactions.[210,211] Direct experimental evidence for the formation of galvanic couples in the Pt/TiCaPCON system was obtained using Kelvin probe microscopy.[54] Platinum NPs had a more positive potential than the surrounding matrix, with the potential difference being approximately 5–10 mV. Electrochemical study also revealed a considerable difference between the free corrosion potentials of Pt NPs (990 mV) and TiCaPCON coating (150 mV). The resistance of the TiCaPCON coating equal to 29 Ω cm^{-2} implies that it can conduct current. It was show that Pt/Fe NPs, which are positively charged relative to the TiCaPCON matrix (potential difference of ~30 mV), become negatively charged (potential difference of 40–50 mV), after being kept in PSS.[186]

The surface of Gram-positive and Gram-negative cells carries a negative charge, arising upon dissociation or protonation of carboxyl (COOH), phosphate (HPO_4, H_2PO_4, HPO_4^-), and amino (NH_3^+) groups. On approaching the charged surface of an implant, these groups can associate or dissociate on the bacterial surface and thus change their conformation. In the initial stage of interaction of bacteria with the surface, the major role belongs to van der Waals forces and electrostatic interactions.[212] Since the overall bactericidal effect may be caused by simultaneous action of several factors, identification of the contribution of each single factor is a challenging task. Therefore, additional model tests were carried out, which made it possible to exclude the contribution of ions and ROS and confirm that *E. coli* bacteria are inactivated on contact with the surface as a result of microgalvanic interactions.[186] It was shown experimentally that the negative charge is transferred from the substrate (TiN, TiC, or TiCN) to Pt NPs, which gives rise to electron-enriched Pt sites.[213]

3.6. Surface response to changes in specific environmental factors

The release of a bactericidal component from the implant surface may be due to changes in specific factors of the medium such as pH, temperature, enzymatic activity, light, *etc*. For example, chronic wounds form an acidic microenvironment caused by bacterial activity; therefore, biodegradable polymers can release encapsulated AMPs at low pH upon contact with the infected wound bed.[214] The pH-sensitive natural polymers include hyaluronic acid, alginates, and chitosan. The two last-mentioned materials respond also to changes in the ionicity of the environment: Ca^{2+} (alginate) and Mg^{2+} (chitosan); this leads to swelling/dehydration.[215] Other examples are thermosensitive hydrogels, which maintain their integrity at normal body temperature and break down at elevated temperature during inflammation, releasing the therapeutic drug at the site of infection.[216] Thermosensitive and biodegradable hydrogels based on poly(lactic-co-glycolic acid) (PLGA) for drug delivery to various organs have been described in detail in a recent review.[217] A microneedle patch sensitive to near-infrared light and capable of releasing AMPs was developed for the treatment of wound biofilms.[218] The IR780 iodide as a photothermal conversion agent and molecularly engineered W379 peptide were loaded into soluble polyvinylpyrrolidone (PVP) microneedle patch, which was later coated with 1-tetradecanol (TD). After the patch placed onto a wound was exposed to light, the iodide converted light to heat, which induced melting of TD, dissolution of PVP microneedles, and release of the loaded W379 peptide. Also, there is a group of polymers that respond to a change in the electric field [*e.g.*, polypyrrole, polyaniline, poly(3,4-ethylenedioxythiophene), chitosan] or magnetic field (*e.g.*, PEG, dextran, polyvinyl alcohol, polyethyleneimine, *etc*., containing embedded magnetic particles).[215]

The hydrogel that comprised xylane hemicellulose and biodegradable polymer based on acrylic acid and polyethylene glycol diacrylate was functionalized with Fe_3O_4 NPs.[219] The resulting polymer material could release the therapeutic agent both under the influence of magnetic field or upon pH change.

Smart composites responding to pH change were developed for applications in dentistry. Bacteria in dental plaque metabolize sugars, which increases the acidity, while the composites release therapeutic ions that inhibit bacterial growth in response to the decrease in pH.[220] It was demonstrated that the release of bactericidal Zn^{2+} ions from a glass powder composed of SiO_2, ZnO, CaO, and fluorine is accelerated in acidic media at pH 4.5, which can also be used to treat dental caries.[221,222]

4. Factors affecting the release of bactericidal ions and pharmaceuticals; synergistic effect

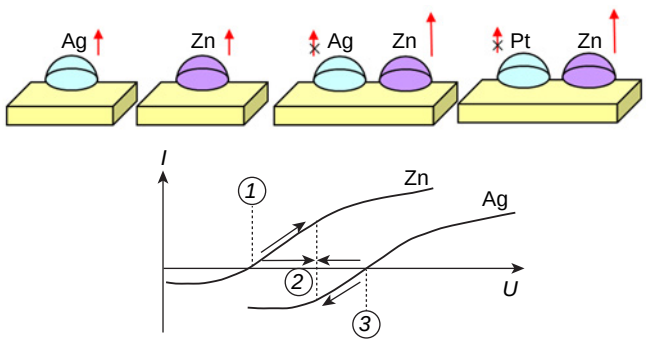
It is known that the synergistic effect implies the enhancement of two or more factors when they act together. Sukhorukova *et al*.[53] considered the synergism in the effects of the chemical composition and surface roughness on the release of bactericidal Ag^+ ions. The authors compared five types of pretreated titanium surfaces (subjected to polishing, sand blasting, pulsed electrospark deposition, and laser treatment in two modes to produce surface grids and holes). The samples were then coated with TiCaPCON–Ag film. It was shown that by changing topographical characteristics of the surface, with the content of the bactericidal element being the same, the release of Ag^+ ions can be both accelerated 2.5-fold and suppressed almost completely. Another important factor that crucially affects the release of ions is the surface oxidation rate. There is an intricate relationship between the density of Ag NPs on the implant surface, surface roughness, and oxidation kinetics. Electrochemical measurements demonstrated that an increase in the concentration of Ag NPs on the surface slows down the growth of the oxide layer, while an increase in the surface roughness accelerates oxidation due to increasing specific surface area, which retards the release of bactericidal ions. The interplay of these factors resulted in the following dependences: for Ti samples coated with TiCaPCON containing 2 at.% Ag, the number of leached Ag^+ ions increased with increasing roughness, while the sample containing 1 at.% Ag followed the opposite trend: an increase in roughness resulted in decreasing leaching of surface Ag^+ ions.

The release of bactericidal ions can also be affected by the presence of a second therapeutic component. For example, the presence of GM retarded leaching of Ag^+ ions from the surface of TiCaPCON–Ag-GM samples into PSS,[63] which may be attributable to GM reaction with silver ions to give stable Ag/GM complexes, which decreases the concentration of free silver ions in the solution.[112] The GM release rate from the TiCaPCON–Ag-GM sample was also lower than that for Ag-free material.

Antibacterial activity assays showed that implants with a cellular surface structure loaded in 4 and 0.4 mg mL^{-1} GM solutions completely suppressed *E. coli* bacteria after 3 and 24 h, respectively. The synergistic effect can be manifested when combinations of antibiotics and bactericidal ions are used. For example, in order to evaluate the bactericidal effect after the active release of the antibiotic and Ag^+ ions in the first 24 h, the samples were initially kept in PSS for 24 h. The coatings containing both GM and Ag demonstrated a strong antibacterial effect (decrease in the CFU count by 99.9%) during incubation with the *S. aureus* for 24 h, whereas samples containing either GM or Ag separately exhibited no antibacterial activity.[63]

The kinetics of bactericidal ion release from the implant surface can be regulated by forming a heterogeneous surface containing various NPs. For example, an equilibrium potential is established between the neighbouring bactericidal Ag (cathode) and Zn (anode) NPs, as shown in Scheme 7. The free corrosion potential of zinc shifts to more positive values, while the potential of silver shifts to the negative side. As a result, Ag NPs are under anodic protection of Zn NPs and do not dissolve until the Zn NPs are completely dissolved.[54] A similar situation is observed in the Pt–Zn NP pair. Meanwhile, in the Ag–Zn and Pt–Zn pairs, cathode NPs accelerate the dissolution of zinc with respect to the dissolution in the absence of cathode nanoparticles.

Scheme 7



Free corrosion potential of Zn (*1*) and Ag (*3*), equilibrium potential of Ag–Zn (*2*)

This strategy makes it possible not only to combine different bactericidal ions, but also to control the rate or time of ion release.

5. Surface modification methods

There are numerous methods for surface modification to endow a surface with bactericidal properties.[223–225] The particular choice of the most appropriate method depends on the type of material (metal, polymer, organic or bioresorbable materials). Conventionally, two groups of methods can be distinguished: (1) wet chemistry methods for deposition of coatings from solutions such as electrochemical deposition [anodization, micro arc oxidation (MAO), PEO], sol–gel process, centrifugation, immersion into a solution and impregnation and (2) vapour deposition of coatings [physical vapour deposition (PVD) and chemical vapour deposition (CVD)]. Each method has its own benefits and drawbacks, with their comparison being beyond the scope of this review; however, note that PVD and CVD methods typically require the use of special expensive equipment.

A modern scientific trend is surface modification of metal implants in order to improve their osseointegration and impart bactericidal properties to them.[226,227] Antibacterial Ag/Cu nanocomposite coatings were deposited on a pretreated titanium surface (after sandblasting and acid etching) by **magnetron sputtering** of single-component Ag and Cu targets.[228] Various antibacterial silver coatings were formed on titanium alloy substrates using **ion implantation** and magnetron sputtering techniques.[229] The ion implantation technique proved to be less effective for the release of antibacterial components or providing direct antibacterial effect; the authors attributed this result to deeper penetration of silver into the substrate. Silver- or silver/copper-doped antimicrobial amorphous carbon coatings fabricated by magnetron sputtering on the key internal components of spacecrafts have been reported.[230] The potential of the magnetron sputtering technique can be expanded by using composite targets produced by self-propagating high-temperature synthesis (SHS).[231] These targets can contain both metal and non-metal elements, and their use for magnetron sputtering may give rise to nanocomposite coatings with a beneficial set of properties. For example, bioactive and bactericidal Ag-containing TiCaPCON coatings were produced by two methods: magnetron sputtering of the $TiC_{0.5}Ca_3(PO_4)_2$ composite target obtained by SHS followed by implantation of Ag^+ ions and simultaneous sputtering of the $TiC_{0.5}Ca_3(PO_4)_2$ composite target and Ag metal target.[96] Silver-doped bioactive and bactericidal TiCaPCO coatings were also deposited by pulsed electrospark alloying using the $TiC–Ti_3PO_x–CaO–Ag$ composite electrode produced by SHS.[98]

Magnetron sputtering and **ion implantation** methods are also promising for modification of nano/submicron polymer fibres to endow them with improved bactericidal properties. Another frequently used method is **electrostatic spinning** in which nanoparticles are dispersed in polymer solutions.[232] The inclusion of metal (Ag, Cu, Au) or oxide (ZnO, FeO_x, CeO_2, CuO, TiO_2) NPs into a biodegradable fibrous material has a beneficial effect on the cell growth and proliferation.[232–235] Nanoparticle-modified nanofibres can be used for the design of various biomedical materials such as artificial heart valves, artificial blood vessels, and scaffolds for tissue engineering.[232] The therapeutic efficacy of polymer scaffolds depends on the presence of antibacterial properties that prevent or retard inflammation. For example, polycaprolactone (PCL)-based membranes, PCL/gelatin/MgO, considerably accelerated healing of diabetic wounds by suppressing inflammatory responses and stimulating angiogenesis.[233] The antibacterial mechanisms of metal oxides (Ti, Ag, Zn, Cu, Mg, Ni), factors influencing the antibacterial activity, and their role in acceleration of wound healing were considered in a review.[234] The formation of ROS and bacterial cell wall damage are the two main interrelated mechanisms. Damage of the membrane changes the membrane potential and induces membrane depolarization and loss of integrity, which in turn causes an imbalance in enzyme transport, respiratory failure, and cell lysis. The ROS generated by NPs themselves or formed due to respiratory chain disorders damage the cell macromolecules, which induces lipid peroxidation, modification of proteins, enzyme inhibition, and damage to RNA and DNA.

Binary oxide coatings (TiO_2, ZnO, Fe_2O_3, MgO, and ZrO_2) containing metal NPs (Ag, Cu, Pt, and Au), and multicomponent coatings ($TiO_2–ZnO$, $TiO_2–ZrO_2$, $ZnO–Al_2O_3$, $TiO_2–Ag$, and $ZnO–Ag$) were produced by **atomic layer deposition** and considered in detail in a review.[236] The atomic layer deposition was used to modify the surface of the superelastic biocompatible Ti-18Zr-15Nb alloy with TiO_2. To endow the material with bactericidal properties, Ag NPs were deposited on the surface by reduction of silver ions from a solution of $AgNO_3$ with sodium borohydride $NaBH_4$.[237] An alternative method of silver deposition was applied to the Ti-18Zr-15Nb alloy, which was etched in a piranha solution (3/4 concentrated H_2SO_4 + 1 H_2O_2)[238] and then immersed into a PEG solution containing $AgNO_3$; the synthesis was carried out under UV irradiation.

Antibacterial polymer coatings obtained by **chemical deposition methods** are addressed in a number of recent reviews (see, for example, Shu *et al*.[239]). The CVD methods are based on the action of a chemically reactive vapour on a substrate, which eliminates the risk of damaging the substrate by organic solvents. The adhesion of CVD coatings is usually achieved through physical adsorption of gas monomers and van der Waals interactions.

In recent years, increased attention has been paid to **treatment of materials in low-temperature plasma**, which is a reactive gas medium consisting of a mixture of ions, electrons, radicals, and neutral species.[240] Depending on the plasma treatment conditions, there are four main processes: plasma sputtering (physical degradation and removal of the thin external layer, removal of surface contaminants, and deposition of thin coatings), plasma etching (removal of the surface layer, cross-linking of surface polymer chains, and generation of surface functional groups), plasma ion implantation (charged species present in the plasma directly react with the polymer surface, thus inducing the formation of new chemical groups such as amino, hydroxy, and other groups), and plasma polymer deposition (a thin polymer-like film is formed on the surface of the polymer substrate.).[241] Plasma treatment may give rise to various types of bactericidal surfaces: anti-adhesive, contact-killing, and antibiotic-releasing surfaces. For example, black silicon nanostructures were prepared by reactive plasma etching in SF_6 and O_2 (Ref. 201) or Cl_2/O_2 and O_2/SF_6 gas mixtures.[242] The nanostructures obtained by Ivanova *et al*.[201] demonstrated high antibacterial activity against various Gram-negative and Gram-positive bacterial strains, while the needle-shaped nanostructures prepared by Hazell *et al*.[242] were effective only against Gram-negative *E. coli*.

Inert gases such as argon or helium are often used for plasma surface activation and generation of free radicals, while cold gas discharge plasma in N_2, O_2, or NH_3 atmosphere is utilized to introduce oxygen- or nitrogen-containing functional groups on

the surface.[243] Some free radicals generated upon plasma activation can form covalent bonds with liquid or vapour monomers/precursors fed into the plasma discharge region; various reactions and recombinations can take place in the plasma, which can lead to the deposition of a plasma polymer layer. Precursors can be either applied on the surface prior to plasma treatment or introduced directly into the plasma discharge area. For example, the plasma-polymerized coating on silicon substrates prepared by injection of the 2-methyl-2-oxazoline monomer into atmospheric pressure helium plasma provided a 80% decrease in the adhesion of *S. epidermidis*.[244] Ho *et al*.[245] first performed plasma deposition of monomers (allylamine and diallylamine) on silicon wafers, and then the amine surfaces were treated with gaseous NO at elevated pressure. During the treatment, the primary and secondary amino groups of the base coating reacted with NO molecules to form diazeniumdiolate as NO donor. The resulting coatings showed continuous NO release for more than 48 h and effectively reduced the adhesion and biofilm formation of Gram-negative and Gram-positive pathogens. The use of plasma-treated PCL scaffolds with immobilized platelet-rich plasma markedly improved wound healing in diabetic mice.[246] In order to enhance antibacterial properties of curdlan/chitosan-based foam materials, a solution of $AgNO_3$ was added during polymerization, and then silver was reduced on exposure to UV radiation. According to *in vivo* assays, the addition of Ag considerably enhanced the skin tissue regeneration in mice with type II diabetes compared to foam material without Ag.[247]

Ag NPs were immobilized on the plasma-treated surface of biodegradable PCL nanofibres, which were immersed into a solution of $AgNO_3$, and then reduction induced by UV irradiation was carried out. The plasma-deposited polymer layer containing carboxyl groups provided a uniform distribution of Ag NPs on the surface of nanofibres.[248] The ZnO NP-modified PCL nanofibres were obtained by plasma treatment of the nanofibre surface in the $Ar/CO_2/C_2H_4$ gas mixture followed by immersion of the fibres into a colloidal ZnO solution to immobilize ZnO NPs. The resulting materials exhibited enhanced antibacterial and fungicidal activity.[249] Wound dressings based on PCL nanofibres with CuO NPs were obtained by electrospinning. For immobilization of wound-healing antibiotic Baneocin, a polymer layer containing COOH groups was formed on the surface of PCL nanofibres by plasma treatment in the $Ar/CO_2/C_2H_4$ gas mixture.[250] The introduction of carboxyl, amide, and EDC-activated carboxyl groups onto the PCL surface increased the ability to bind the antibiotic through the formation of a hydrogen bond network. The presence of Baneocin covalently bound to the PCL surface *via* a layer of COOH groups improved the surface wettability and retarded the release of Cu^{2+} ions, thus ensuring the long-term and stable leaching of bactericidal ions. The modified nanofibres exhibited excellent bactericidal and fungicidal activities against the bacterial strains *S. aureus* BAA1707 (MW2), *P. aeruginosa* C3945/23, *E. faecium* Ya253, *E. coli* U20, and *A. baumannii* C66627/23 and the fungal strain *C. auris* KA10.

A promising approach is the use of **PEO** and **anodization (ANO)** methods, which fit well in the paradigm of fabrication of biologically safe metal implants possessing bactericidal properties. The bioactive properties of the materials were generated by surface deposition of a finishing layer based on hydroxyapatite and chitosan by electrophoresis (Fig. 3). The fundamentals and characteristic features of **PEO** as applied to various oxide-forming metals have been reported in detail in recent reviews.[251–254] By using PEO and ANO methods, it is possible to form porous and durable biocompatible coatings with increased hardness, improved wear resistance and corrosion resistance, and high adhesion strength to the surface of complex-shaped titanium implants, without subjecting the internal part of the material to elevated temperatures. As compared with the most popular plasma spraying[255] and magnetron sputtering[256] techniques, PEO and ANO methods imply the use of relatively simple equipment, have no restrictions on the sample size or shape, and, therefore, they are easily scalable. The choice of electrolyte composition and PEO process parameters (treatment temperature and time, electrical process parameters) have a considerable effect on the thickness, roughness, porosity, microstructure, and phase composition of the coatings.[257,258] The PEO and ANO layer usually consists of titanium oxide polymorphs such as anatase and rutile,[251] while in the case of using complex electrolyte or suspension compositions, it can contain Ca–P-based amorphous regions and nanoparticle inclusions.[91,259,260] The porous structure of PEO coatings containing Ca and P promotes formation of bone tissue and demonstrates improved osseointegration *in vivo*.[261] The concept of PEO using complex electrolytes is directed towards incorporation of functional elements providing enhanced bioactivity (Ca, P, Mn, K, and Si) and bactericidal protection (Ag, Cu, Zn, and B) into the coating. There are two main approaches to incorporation of bioactive and bactericidal components into PEO coatings: addition of soluble salts to the electrolyte or the use of particle suspensions.[262] The incorporation of Ca and P markedly enhances the bioactivity of the materials.[185] Antibacterial metal ions such as Ag^+, Zn^{2+}, and Cu^{2+} are effective against two clinically significant types of bacteria (*E. coli* and *S. aureus*) without apparent cytotoxicity against fibroblast cells in the concentration ranges of 0.1–0.3, 0.65–6.5, and 0.63–6.3 ppm, respectively.[63] However, although Ag and Cu ions provide effective and extensive protection against many types of bacterial strains, they can cause toxicity at high concentrations.

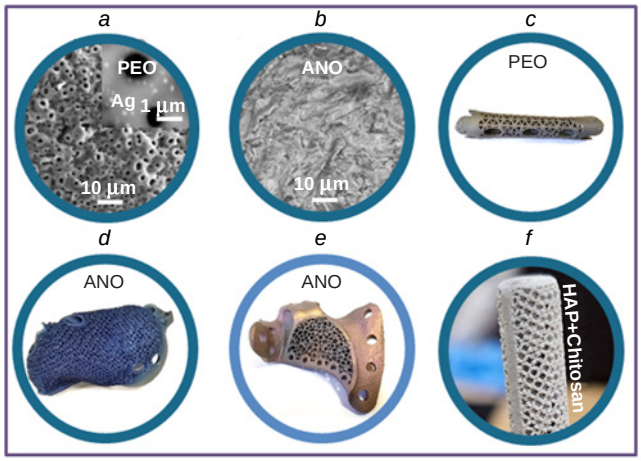


Figure 3. SEM images of PEO (*a*) and ANO (*b*) coatings and optical images of implants with PEO (*c*), ANO (*d*, *e*), and HAP + chitosan (*f*) coatings. The SEM images were taken from the author's personal archive.

Silver and CaP NPs were electrophoretically deposited on TiO_2 nanotubes formed by electrochemical anodization of titanium.[263] The CaP NPs were stabilized by polyethyleneimine (PEI). The simultaneous presence of Ag and CaP NPs on the TiO_2 surface induced a considerable decrease in the bacterial activity of *S. aureus* compared to non-modified TiO_2 surface;

apart from the action of bactericidal silver ions, this was attributed to the presence of PEI, which contains quaternary ammonium groups active against bacteria due to either pore formation in the cell wall and membrane or membrane depolarization.

Open porosity is an important benefit of PEO coatings. Micropores not only increase the degree of mechanical osseointegration, but can also serve as reservoirs for loading of various biologically active substances (growth factors, bactericides, *etc*.). For example, saturation of a porous titanium dioxide layer with the bone morphogenetic protein BMP-2 promoted differentiation of osteogenic cells.[264] Recently, it was shown that the introduction of BMP-2 into the surface of porous PEO and PEO – Cu coatings substantially increases the osteoconductivity and provides pronounced osteogenesis.[91]

Lately, a lot of attention has been given to bioresorbable materials, which are designed for temporary replacement of damaged areas followed by resorption and replacement by newly formed bone tissue. A key representative of the family of bioresorbable materials is magnesium the density and elastic modulus of which are very close to those of bone tissue. However, despite the obvious attractiveness of this approach, there are still a few unsolved problems: high corrosion rate exceeding the rate of bone tissue regeneration, formation of large amounts of magnesium ions and hydrogen gas, and increase in the alkalinity of the environment. The methods used to increase the bactericidal properties of magnesium alloys include surface laser modification, friction stirring, PEO, layer-by-layer assembly, electrophoretic deposition, chemical conversion, and hydrothermal and sol – gel processes, which are surveyed in a recent review.[40] The use of electrolytes with Zn-, Ag-, and Cu-containing additives in PEO technology for magnesium alloys has been described in detail.[265]

The demand for fabrics and textiles with antibacterial protection is constantly growing, especially in relation to the COVID-19 pandemic.[266] Textile materials are widely used in a variety of areas, including sportswear, everyday clothing, shoe insoles, medical gowns and masks, and bed linen. The use of NPs to modify the surface of cotton fabric is a promising approach to endow the material with a set of desired characteristics, which can markedly extend the functionality, wearing comfort, and service life of textile products. As a rule, bactericidal nanoparticles such as TiO_2 (Ref. 267) or Ag and Au[268] NPs are introduced into fabrics. Cotton fabric coated with h-BN NPs modified with maleic anhydride (MA) and diethylenetriamine (DETA) in order to increase the stability of h-BN suspensions and enhance the adhesive strength between the particles and the cloth exhibited high antibacterial effect against *E. coli* and *S. aureus* and completely prevented the formation of *E. coli* biofilm, which was attributed to the release of boron and formation of boric acid.[269] Polyamide fabrics impregnated with (3-glycidyloxypropyl)trimethoxysilane-modified ZnO NPs demonstrated high antibacterial activity against *E. coli* and *S. aureus*.[270] The antibacterial properties of polyamide fabrics were retained after 20 wash cycles.

Nanoparticles are widely used in the food industry, usually as part of polymer and biopolymer coatings, to prevent bacterial growth and extend the shelf life of perishable products. Antibacterial coatings based on alginate, PLA, cellulose, chitosan, polylactic acid, low-density polyethylene, and other polymer matrices with added plant extracts and Ag, Cu, ZnO, TiO_2, Cu_2S, and other NPs have been used for packaging of cheese, fish and meat products, and fresh vegetables and have proved to be effective against major food pathogens such as *E. coli*, *S. aureus*, *Listeria monocytogenes*, *Pseudomonas aeruginosa*, *Streptococcus oralis*, *Salmonella typhimurium*, *etc*.[271]

The active development of additive technologies has not gone without the design of bactericidal materials. For example, 3D printing was used to fabricate Ag microstructures that can be used as an antibacterial filter.[272] The 3D frameworks are endowed with antibacterial properties using antibiotics, polymers, peptides, graphene, metals/ceramics/glass, and antibacterial coatings.[273] 3D-printed polymer composites based on thermoplastic elastomers doped with carbon quantum dots completely suppressed the growth of *S. aureus* and *E. coli* after 1 h of exposure to blue light due to generation of singlet oxygen.[274] 3D-printed plastics based on poly(hexamethylene-biguanide) and photocurable liquid resins proved to be effective against *S. aureus*, *E. coli*, and *K. pneumoniae* strains.[275]

6. Bactericidal nanoparticles and heterogeneous platforms based on them for local therapy

The antibacterial action of NPs is based on the following mechanisms: destruction of the cell membrane and electron transport chain; damage of proteins, DNA, and efflux pumps; inhibition of ribosome translation; generation of ROS; and release of bactericidal ions.[276] Nanoparticles of metals such as Ag,[277,278] Cu,[279,280] and Au[281] and oxides such as CuO,[282,283] FeO_x,[284] AlO_x,[285] ZnO,[286] TiO_2,[287] and CeO_2,[288] which exhibit antibacterial effect against a wide range of pathogens even at a low dose, are often utilized for local antibacterial therapy.[289] The main mechanisms of action of NPs are reduced to bacterial wall destruction, release of bactericidal ions, and generation of ROS. The potential of metal and oxide NPs as antimicrobial agents is described in a review.[290] The same review gives detailed information on MIC, minimum bactericidal concentration (MBC), half-maximal inhibitory concentration (IC_{50}), and inhibition zone for various strains depending on the particle type and size. Table 3 gives brief information only on MICs.

As for different types of ions (see Table 2), a large scatter of the values is observed, which cannot always be explained by differences in the particle size or in the type of bacterial strain. Even for the same type of NPs of approximately the same size and the same strain, MIC values can vary by two orders of magnitude. In a number of studies, it is noted that MIC is lower for smaller particles.

It is important to note that MIC values for a particular type of bacteria may increase after repeated treatment, which attests to emergence of resistance. For example, the *E. coli* K-12 MG1655 strain was shown to have specific resistance to sub-inhibitory concentrations of Ag NPs accompanied by mutation of cusS gene responsible for the silver ion efflux.[291]

Table 3. Dependence of MIC on nanoparticle type and size.[290]

NPs	Size, nm	MIC, mg mL^{-1}
Ag	1 – 70	0.4 – 600
Au	2 – 200	4 – 256
Cu	9 – 350	20 – 200
CuO	20 – 300	1.5 – 3.1
TiO_2	23 – 362	10 – 100
ZnO	8 – 800	1.2 – 18

Atomic/zerovalent silver (Ag^0) is relatively inert and is primarily a source of ions released *via* oxidation:

$$4\,Ag^0 + O_2 + 2\,H_2O \longrightarrow 4\,Ag^+ + 4\,OH^- \quad (10)$$

Although the prevailing opinion stated in the literature is that Ag^+ ions are the main biocidal agent responsible for most antibacterial effects, it is possible that NPs come into direct physical contact with the bacterial membrane, resulting in the destruction of the membrane, or that NPs are captured by the cell in which silver ions are rapidly released, leading to cell death. There are four key mechanisms of the antibacterial activity of Ag NPs: (i) NP adhesion to the cell wall/membrane followed by destruction, (ii) intracellular penetration and damage, (iii) oxidative stress, and (iv) modulation of signal transduction pathways.[292] A detailed comparison of the action of Ag^+ ions and Ag NPs can be found in a review by Chernousova and Epple.[293]

Bismuth NPs show a high antibacterial activity against common pathogenic strains such as *E. coli* and *S. aureus*.[294] The main mechanism of the antibacterial activity is the formation of ROS *via* separation of electrons and holes in the particles on exposure to radiation. However, Bi NPs can inhibit the growth of not only prokaryotic, but also eukaryotic cells.

Various NPs are used for wound dressings, surface modification of catheters to prevent the biofilm formation, water purification filters, breathing masks, automotive filters, food packaging materials, clothing, *etc*.[99,295,296] It was shown that combination of CuO and Ag NPs may increase the antibacterial effect severalfold compared to that of Ag NPs alone against a broad range of bacteria, including the antibiotic-resistant strains. The main synergistic mechanisms include the positive charge of Cu NPs, faster release of Ag^+ ions from Ag NPs, and lower binding of Ag^+ ions to incubation medium proteins in the presence of Cu^{2+} ions.[297]

Recent studies identified a large potential of SiO_2 NPs and core@shell particles based on them in the antibacterial therapy.[298] The antibacterial activity of ZnO@SiO_2 is due, first of all, to the ability to generate ROS,[299] while the porous structure allows for the effective introduction of antibacterial agents.[300] Functionalization of SiO_2 NPs with appropriate ligands not only increases their stability and dispersion in various media, but also enhances their antibacterial activity.[301]

Polyester, oligosaccharide, and biodegradable polymeric NPs, including PEG, polylactic acid (PLA), PCL, PLGA, cyclodextrins and other NPs loaded or functionalized with active bactericidal components have been addressed in numerous studies.[302–306] However, these systems cannot always ensure the combination of the desired specific properties such as immunogenicity, surface charge, high pharmaceutical activity, prolonged release, appropriate mechanical properties, and long-term physicochemical stability. A detailed analysis of various antibacterial agents containing NPs can be found in a recently published review.[307]

Chitosan-based polymer NPs acquire increasing popularity owing to their high biocompatibility and biodegradability. Chitosan was used both by itself to impart antibacterial properties to the materials [due to the presence of protonated positively charged amino groups, which ensure enhanced cell penetrability or the ability to inhibit messenger ribonucleic acid (mRNA) by being bound to DNA] and in combination with specific metal oxides or with AMP for higher efficiency.[308] Hydrophilic-modified chitosan is a suitable material for gel dressings and film packaging for food products owing to good gel-forming properties, film-forming ability, and antibacterial and antioxidant properties.[38,309]

The search for new effective and safe nanocarrier materials for the delivery of bactericidal agents to inflammation sites has a great scientific and practical importance. The biomedical applications of h-BN NPs are constantly expanding. According to a number of studies, h-BN NPs in concentrations lower than 0.1 mg mL^{-1} are safe for medicinal purposes.[310,311] GM-loaded h-BN NPs demonstrated high bactericidal activity against *S. aureus*, *P. aeruginosa*, and 38 *E. coli* strains.[312] Nanohybrids containing Ag NPs exhibited excellent bactericidal activity against other 11 *E. coli* strains. Antibiotic-free Ag/h-BN nanohybrids and ATB-loaded Ag/h-BN and h-BN NPs showed high fungicidal activity against *C. albicans*, *C. auris*, *C. parapsilosis*, and *N. crassa* strains. The theoretic modelling methods are used for understanding of the mechanisms of antibiotic attachment to NPs. For example, using density functional theory calculations, it was shown that GM and ATB bind to h-BN and Ag surfaces in different ways, which determines the dose of the loaded antibiotic. For GM molecule, it is energetically more favourable to attach to h-BN than to Ag, whereas in the case of ATB molecule, the attachment to h-BN and Ag is equally energetically favourable.

Different NPs can be connected into a single system to achieve a synergistic effect. For example, TiO_2 and Ag NPs were combined *in situ* to fabricate the TiO_2–Ag nanoplatform with low Ag content possessing synergistic antibacterial effect due to the presence of hydroxyl radicals.[313] To increase the stability of colloidal aqueous solutions, (3-mercaptopropyl) trimethoxysilane and sodium 3-mercapto-1-propanesulfonate were used as stabilizers for covalent binding to TiO_2 (*via* the Ti–O–Si bond) and Ag (*via* the Ag–S bond) surfaces, respectively.

The combination of Ag NPs with AMP proved to be efficient against antibiotic-resistant bacteria. A synergistic antibacterial effect was observed when sodium oleate-stabilized Ag NPs were used in combination with protegrin-1 and when acetylcysteine-containing Ag NPs were combined with protegrin-1, ricecilin, and shuchin-4.[314]

Macrocyclic cavitands such as cucurbituril are used to develop new-generation bactericidal NPs. The pumpkin-shaped cucurbituril molecule can encapsulate other molecules, serve as a reservoir for metal ions, and provide for metal ion transport in biological systems. Recently, Au NPs functionalized with cucurbit[7]uril (CB7) were developed to modulate the activity of the antibiotic levofloxacin.[315]

A promising strategy is to use metal-containing complexes in which an important role is played by metal ions capable of binding to DNA, proteins, and enzymes, suppressing their functions and inducing apoptosis and necrosis. Examples of high antibacterial and fungicidal activities of palladium (Pd^{II}) complexes, exceeding the activity of antibiotics and antifungal drugs widely used in clinical practice, can be found in the literature.[316] A limiting factor is that determination of the mechanism of antibacterial, antifungal, and cytotoxic activities of metal-containing complexes is a complicated task: minor structural changes may induce a pronounced change in the biological activity of the complexes, and currently there is no clear understanding of the relationship between their structure and properties.

In relation to the growing MDR problem and the threat of environmental pollution with antibiotics, it would be promising to use NPs in broiler farms instead of antibiotics or probiotics. For example, it was shown that the chitosan/Ag hybrid NPs not only exhibit much better antibacterial effect against *E. coli* than CuO or Ag NPs, but also act as growth promoters in broilers.[317]

As a rule, an increase in the surface-area-to-volume ratio of NPs enhances their ability to interact with bacterial components, penetrate into bacterial cells, and exhibit antimicrobial behaviour. However, bacteria have two main defence mechanisms against small and large NPs.[318] Bacteria can produce the extracellular matrix (a globular protein, flagellin), which can alter the zeta-potential of NPs that are larger than 10 nm and cause them to agglomerate, thus preventing the direct contact between bacteria and NPs. The mechanisms responsible for preventing the antimicrobial effect of NPs smaller than 10 nm and silver ions released by larger NPs involve changes in gene expression and conformations and mutations (*e.g.*, inhibition of porins or changes in membrane fluidity) that decrease the range of possible pathways for NP penetration into bacteria. Higher ROS concentrations stimulate expression of short-term and long-term defence mechanisms in bacteria. The activation of expression of ROS-neutralizing enzymes allows bacteria to maintain a short-term balance. The long-term adaptation implies the activation of antioxidant mechanisms and DNA repair processes.

The ion and lipid pumps of bacteria (P-type ATPases or E1-E2 ATPases) are important factors for the bacterial resistance to copper, as they provide copper efflux from the cell. Also, many bacteria have QS regulation systems, which are involved in the active copper efflux from the cells.[319] *E. coli* has a two-component system of transenvelope efflux of excess metal cations from the periplasm: Cus system for the removal of Cu(I) and Ag(I).[320] Among the 193 investigated strains, there were nine Ag^+ ion-resistant strains including *K. pneumoniae* (5 strains) and *Enterobacter hormaechei* (4 strains).[321]

In the body, NPs interact with blood serum proteins, giving rise to protein corona (PC), which may considerably influence their antibacterial activity.[322] For example, the antibacterial activity of Pt, Ag, and Au NPs against *E. coli* strains was markedly enhanced in the presence of HSA protein corona, with the temperature increasing during photoexcitation.[323] The PC affects the colloid stability, cell interactions, and cell viability and can also hinder the interaction of the target ligands with tissue-specific receptors and prevent the targeted delivery of therapeutic agents. Some surface-bound proteins can activate the immune system, causing premature elimination of NPs or promoting the release of anti-inflammatory cytokines. The composition and quantity of proteins bound to NPs vary depending on their size and surface nature and curvature. In addition, PC can markedly change when the protein concentration changes.

In order to prevent the PC formation, the NP surface is coated with PEG, poly(2-oxazolines), zwitter-ionic polymers, polyglycerols, polysaccharides, and low-molecular-weight chitosan and its water-soluble derivatives. These examples represent only a limited subset of surface modifications of NPs that are used to prevent the PC formation. Interested readers can find more information in detailed reviews addressing the surface modification of NPs to prevent PC formation[324,325] and NP functionalization with ligands that interact with cells.[326] Note that coatings on the NP surface can alter both the biophysical interactions with proteins and the cytotoxicity of the particles.[327]

Despite the promising therapeutic potential, the use of NPs poses certain health risks.[328] Nanoparticles can have a toxic effect on the respiratory, nervous, endocrine, immune, and reproductive systems and also cause cancer.[329] For example, Ag NPs have high reactivity and can be accumulated in the lungs, spleen, kidneys, liver, and brain and induce side effects.[330] TiO_2 NPs can also be accumulated in various organs and induce DNA damage, genetic instability, and pneumonia.[331] In addition, TiO_2 NPs can penetrate the blood–brain barrier and induce apoptosis of human hippocampal neurons and exhibit genotoxic effects, which can result in apoptosis and chromosomal instability. The release of metal ions and the associated oxidative stress may cause of a wide range of physiological disorders.[332] Metal NPs can also have an adverse effect on the central nervous system.[333] There is still no clear understanding of the NP toxicity. It is believed that the toxicity of NPs depends on quite a few factors: size, shape, surface chemistry and charge, concentration, degree of agglomeration, and immunogenicity and on the mechanisms of their absorption and interaction with cells. In each particular case, all factors should be thoroughly analyzed and taken into account for the safe use of NPs to combat infections.

Owing to the large surface-area-to-volume ratio, smaller particles can be more toxic because of enhanced redox activity and the ability to avoid phagocytosis and more easily penetrate into cells. Ultrasmall NPs can bind to cell receptors and influence various signalling mechanisms. A change in the surface chemistry by functionalization can considerably reduce the toxicity intensity. For example, functionalization of the NP surface with sodium citrate, PVP, or surfactants markedly reduces their immunogenicity and toxicity.[334]

The shape of NPs affects their bioaccumulation, reactivity, and toxicity. Sharp-edged particles with high aspect ratios and large specific surface areas are usually more biologically active; they circulate in the blood for longer periods, accumulate more efficiently in certain organs, and are potentially more toxic.[335]

The surface charge markedly affects the interaction between NPs and cells. Positively charged NPs tend to be more toxic, as they can more effectively interact with negatively charged cell membranes, which leads to more intense cellular uptake of NPs. For example, only positively charged polystyrene NPs could induce *in vivo* dose-dependent decrease in the viability of *Caenorhabditis elegans*.[336] According to a recent study, the surface charge has a more pronounced effect on the cytotoxicity and cellular uptake of Ag NPs than the formation of PC.[337] The positively charged Ag NPs are better taken up by cells, which induces a more pronounced cytotoxic effect. Recently, it was hypothesized that the toxicity of NPs is determined by the number of atoms/ions/molecules per NP and that NPs of different shapes and sizes with different physicochemical properties would have different toxicity to the test organism.[338] The solubility and the surface charge are also important characteristics of NPs that make a substantial contribution to the overall toxicity.

7. Models *in vitro* and *in vivo*

The screening methods and antimicrobial activity assays are subdivided into *in vitro* and *in vivo* ones. The existing *in vitro* assays have been described in detail;[94] they can be subdivided into diffusion methods [agar diffusion method, concentration gradient diffusion assay in agar medium (E_{test}), *etc.*]; thin layer chromatography (direct and immersion bioautography); dilution methods, which are perfectly suited for the quantitative determination of the antibacterial activity; determination of time or concentration dependence of the bactericidal effect; and analysis of bioluminescence of adenosine triphosphate produced by bacterial and fungal cultures (Scheme 8). It is still an open question to what extent these different conditions of *in vitro* assays bring us closer to *in vivo* conditions. An infection may already be present in the body before treatment, or may be introduced during the implant placing, or may get into the

patient's body in the post-surgery period during hospital stay. Therefore, extrapolation of the *in vitro* results obtained using various models would not necessarily reflect the actual bactericidal behaviour of the material in the body.

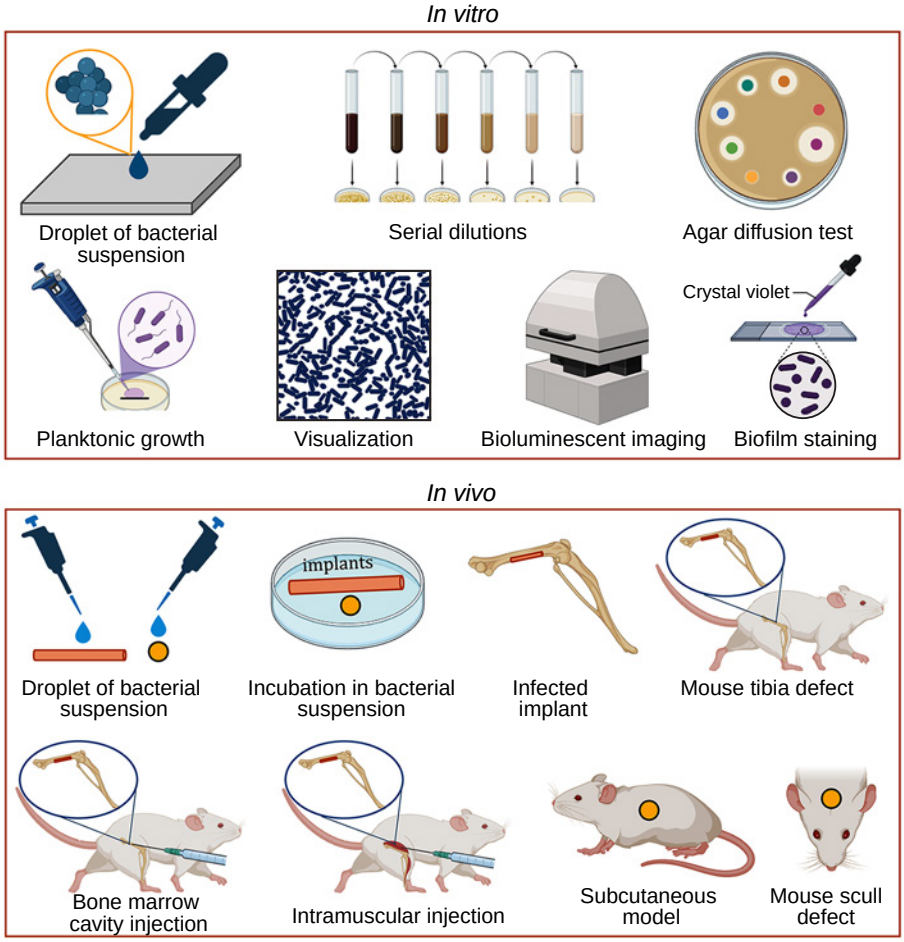
Recently, Sheveyko *et al*.[87] reported a comparison of various models *in vitro* (i) application of a droplet of bacterial suspension on the sample surface, (ii) biofilm formation (SEM imaging and quantitative estimation of the biofilm by staining with crystal violet), and (iii) planktonic growth in a culture medium and PSS.[87] The results showed that preliminary screening of the antibacterial activity may be performed using both phosphate buffer and PSS as a medium for experiments to prevent bacterial growth on a rich culture medium. However, *in vitro* experiments carried out in a culture medium resemble more closely the *in vivo* conditions, because the bacterial cells are provided with nutrients and energy sources that enable them to actively eliminate toxic compounds, repair damaged cell components, and be multiplied. The most pronounced bactericidal effect was observed in a model where droplets of *S. aureus* cells in a culture medium were deposited on the implant surface, which resulted in complete bactericidal effect for both Ag^+ and Cu^{2+} ions for the initial bacterial concentration of 4.5×10^5 CFU mL^{-1}, which greatly exceeds the average bacterial contamination during a surgery where several hundred bacteria per cm^2 can, on average, settle on the wound surface during one hour of surgery. For comparison, complete suppression of *S. aureus* was also observed when implants were incubated with 10^8 CFU mL^{-1} of bacteria in PSS. The experimental results on the formation of *S. aureus* biofilm and growth of planktonic bacteria in the presence of a culture medium appear to better reflect the processes that occur over long periods of time *in vivo*. However, preservation of viable cells in the culture medium surrounding the implant indicates that the long-distance antibacterial effect of ions released from the implant surface is limited and the residual infection in surrounding tissues is more than likely.

It is known that pathogenic bacteria differ from non-pathogenic strains by the presence of virulence factors (set of biological characteristics able to infect and destroy the human body).[339] Bacterial virulence factors are crucial for overcoming the host immune system. The emergence and wide distribution of antibiotic-resistant bacteria severely complicates antibiotic therapy. MDR bacteria may restrict the drug uptake, inactivate a drug *via* chemical binding, or eliminate the antibiotic from the bacterial cell.[340] Therefore, both antibiotic-sensitive and antibiotic-resistant strains should be used for an integrated evaluation of the bactericidal activity.

The growth rate of microorganisms on the implant surface *in vivo* is a critical factor that largely determines the success of implantation. Quantitative measurements of microbial growth rates *in vivo* are few in number, while factors that determine this rate, such as availability of essential nutrients, chemical microenvironment at the site of infection, and diffusion of bactericidal ions, remain insufficiently investigated.[341]

In mouse and rat models, bacterial infection can be initiated by inoculating a bacterial suspension into the implantation site or by using a precolonized implant (Scheme 8). For *in vivo* tests, a 2-mm hole was drilled in the tibia of male New Zealand rabbits.[117] A suspension (0.1 mL) of *S. aureus* (ATCC29213, 3×10^8 CFU mL^{-1}) was injected into the bone marrow cavity, and the hole was sealed with bone wax. A sterilized titanium foil strip surface modified with VM was attached to the tibia. The concentration of VM in muscle tissue adjacent to the titanium

Scheme 8



foil was measured using high-performance liquid chromatography. The inflammatory response was evaluated by monitoring the body temperature and white blood cell level for the animals. Macroscopic X-ray images and microscopic histological examinations showed that the antibiotic-modified Ti plates provided a faster recovery of rabbits compared to the control groups.

Titanium rods modified with enoxacin using PEG were implanted into the femoral bone of 12-week old female Sprague-Dawley rats. After 1 day and 3 weeks, X-ray images were taken to evaluate the degree of destruction of the cortical bone.[118] The CFU count on the Ti rods and in the surrounding bone tissue were successively determined by seeding on plates and by serial dilutions on agar plates. The bacterial colonization of the Ti rod surface *in vivo* was studied by scanning electron microscopy. The degree of bone destruction was evaluated by microcomputer tomography and histological examination. The *in vivo* experiments showed the absence of MRSA infection of the enoxacin-modified Ti surface.

Silver-containing Ti implants were mounted in the intramedullary canal of the tibia of 14-week-old male Sprague – Dawley rats.[342] The infection was caused either by injecting 10 μL of the bacterial inoculum into the bone marrow cavity or by incubation of samples *in vitro* for 1 min in the prepared bacterial inoculum (1 mL). In the former case, the presence of the Ag – Ti implant did not affect the course of the infection, which indicates that this model is not suited for evaluation of the antibacterial activity. However, when the infection was induced by inoculation of the implants *in vitro* prior to implantation, the number of CFU bound to the Ag – Ti sample was much lower than in the case of the Ti implant.

Implants like K-shaped pins (Kirschner wires) surface-modified by the VM antibiotic were placed into either the distal right femur or the L4 spinous process of the lumbar spine of 12-week old male C57BL/6 wild type mice.[122] The infection (1×10^3 CFU) was inoculated to the implant using the bioluminescent *S. aureus* Xen36 strain, which emits blue-green light only in the metabolically active state. Bioluminescence imaging was performed *in vivo*; in order to confirm that the bioluminescence signals corresponded to the bacterial load, the amount of bacteria attached to the implants and surrounding tissues were separated by ultrasonic treatment and then CFU were counted.

Subcutaneous implantation models were also used to evaluate the antibacterial activity of surface-modified metal implants. For example, Ti discs surface-modified by VM or caspofungin (CF) were subcutaneously implanted into female BALB/c mice.[123] A bacterial or fungal inoculate was subcutaneously introduced into the area around the disc. *In vivo* experiments showed a more than 99.9% decrease in the formation of *S. aureus* biofilms on VM-Ti and a 89% decrease in the *C. albicans* biofilm formation on the CF-Ti substrates compared to that on the control Ti samples.

Titanium implants bearing surface chitosan particles loaded with aspirin, amoxicillin, or aspirin + amoxicillin were subcutaneously implanted to male Sprague – Dawley rats.[125] A bacterial suspension of *S. aureus* was introduced into the implantation site by depositing droplets on the sample surface. The antibacterial activity was evaluated by counting CFU after bacteria were removed from the implant by ultrasonic treatment in PSS and by SEM analysis. When drug-loaded samples were used, the number of *S. aureus* colonies on the surface of titanium tablets markedly decreased.

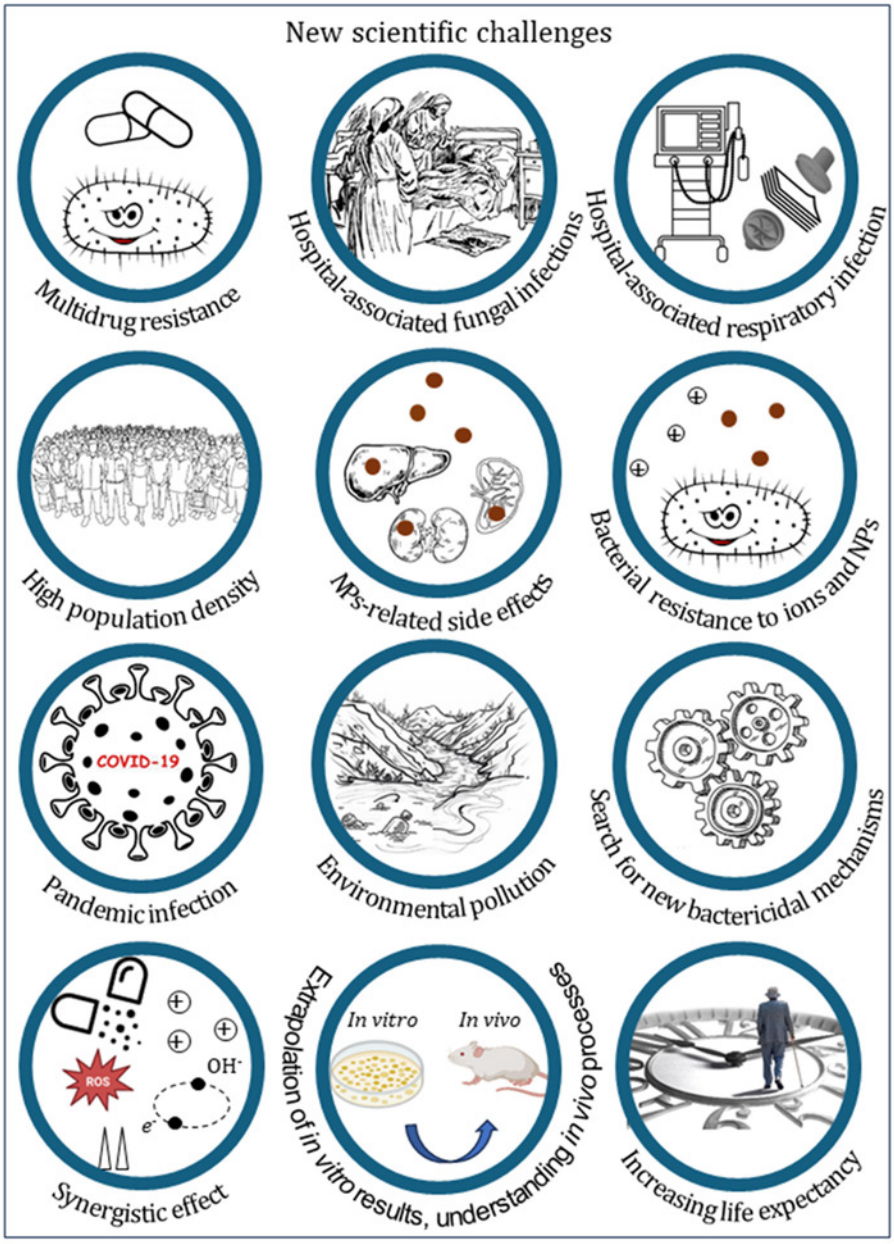
8. Conclusion (unresolved issues and outlook to the future)

Considerable progress in various fields of chemistry and materials science, such as physical and inorganic chemistry, macromolecular compounds, the chemistry of new metal, ceramic, composite, and nano-sized materials, and computer simulation of complex chemical systems and materials, has enabled significant advances in the development of bactericidal nanomaterials and coatings. New methods of chemical and physical cross-linking, low-pressure plasma polymerization, and carbodiimide chemistry appeared. There have been substantial achievements in the chemistry of heterocyclic compounds used for drug production[343] and in the synthesis of new derivatives of polyene macrolide antibiotics by chemical modification and genetic engineering methods.[344] A new compound, (aryloxy)cyclotriphosphazene, containing β-carboxyethenylphenoxy groups, which bind silver as cinnamates, thus providing antimicrobial effect, was used to prevent silver aggregation in a gel wound dressing.[345]

The number of nanohybrid and surface-functionalized nanomaterials is steadily growing. However, in view of emerging scientific challenges such as appearance of new viruses and MDR bacteria and hospital-associated fungal infections, environmental pollution, the release of pharmaceutical waste into the environment, and increasing population density in large cities, the fight against infections not only actively continues (*Vivere militare est* meaning 'to live is to fight'; Seneca, no earlier than 8 BC to 65 AD), but also calls for a new scientific and technological level (Scheme 9). Most studies use the known principles of combating infections based on generation of ROS or delivery of therapeutic agents, bactericidal ions, or NPs. Considering slow development of new antimicrobial drugs with novel mechanisms of action, both these strategies remain highly promising for the control of MDR bacteria. A benefit of these approaches is that they are targeted and local, which makes it possible to avoid high concentrations of ROS and bactericidal components dangerous for eukaryotes. Eukaryotic cells have a more complex internal structure and a stronger plasma membrane, which protects their DNA and metabolic mechanisms from the adverse effects of bactericidal ions. Antibiotics act on specific structures and processes (cell wall, ribosomes, and enzymes responsible for unique metabolic pathways) that are inherent only in bacteria using the selective toxicity principle. Eukaryotic cells generally do not have such targets. Nevertheless, biocompatibility assays are necessary.

It is known that apart from emergence of resistance, high doses of antibiotics reduce the microbial diversity in the intestine, thus leading to dysbiosis. Meanwhile, excess concentrations of metal ions may lead to numerous disorders in the body functions, as ions are involved in electron transport chains, especially in mitochondria (Cu^{2+} and Fe^{2+}/Fe^{3+}), DNA replication and repair (Zn^{2+} and Mg^{2+}), synthesis of neurotransmitters (Cu^{2+} and Zn^{2+}), and development and activity of immune cells (Zn^{2+} and Se^{2+}); in addition, they are components of antioxidant enzymes that help to neutralize ROS (Cu^{2+} and Mn^{2+}).[346] The safety of low concentrations of silver for osteoblast cells has recently been confirmed. The release of Ag^+ ions from Ag-containing Ti6Al4V alloy and the effect of Ag^+ ions on the primary human osteoblast cells (Hob) was studied. Over a period of 1 – 7 days, the Ag^+ concentration was 0.78 – 1.67 ppm in a cell-free medium and 0.70 – 1.37 ppm in a cell-containing medium. The Ag concentration in cell homogenates on the 7th day was approximately ~ 0.1 μg per mg

Scheme 9



of protein. The absence of silver toxicity to osteoblasts was confirmed by the normal morphology and cell growth to confluence and by the absence of a decrease in lactate dehydrogenase and alkaline phosphatase activities.[347]

Comparison of different bactericidal strategies in terms of their efficacy, safety, cost, and scalability is a fairly complicated task. In the near-term outlook, one can expect the introduction of technologies that, first of all, do not require high costs, use inexpensive feedstock, and, in addition, provide reproducible results. These technologies include PEO, ion implantation, electrophoresis, electrospinning, and 3D printing. However, it is necessary to gain more in-depth understanding of the mechanisms of interaction of bactericidal ions and NPs with cells and the causes of microbial resistance. The relatively new mechanisms such as microgalvanic interaction or mechanical damage to bacteria by nanostructures, although thoroughly documented, are inferior in efficiency to the action of bactericidal ions, antibiotics, and ROS. It is wrong to believe that using only one therapeutic component or involvement of only one cell destruction mechanism can provide an extensive protection against various bacterial and fungal infections. An approach based on combination of two or more therapeutic components was successfully implemented in a number of studies.[54,63,281,348–350] This strategy is directed either towards extension of the antibacterial and antifungal activity to more types of pathogens or towards attaining a synergistic effect. However, the introduction of innovative bactericidal materials is held up by long time periods needed to carry out clinical trials.

Special mention should be made of the unsolved resistance problem. Bacteria have learned to develop various mechanisms to suppress bactericidal ions and NPs. In order to overcome these mechanisms, it is necessary to use multi-target strategies, including those aimed at interfering into the QS system to regulate efflux/uptake, inhibit metal-binding enzymes, and disrupt the production of extracellular polymers or other biofilm components.[351]

Despite the wide range of biological activities (antimicrobial, antibiofilm, antiviral, and anti-inflammatory effects), AMPs still have quite a few limitations such as complex mechanisms of action, cytotoxicity, immunogenicity, and unsatisfactory pharmacokinetic properties (short half-life and inability to maintain effective therapeutic concentrations *in vivo*).

Furthermore, the industrial production of AMPs would be unprofitable due to high cost of raw materials, complicated process engineering, and low yields.[352]

Of special concern is the use of NPs, which can be accumulated in various organs and bring about adverse consequences (see Scheme 9). Considering the large number of bactericidal nanoparticles and hybrid nanomaterials based on them, the number of experiments demonstrating the safety of NPs for the body is obviously insufficient. The effect of NPs on the antibiotic resistance of bacteria is a debatable issue, as both stimulation and inhibition have their supporters.[353–355] Adherents of the former hypothesis believe that microorganisms can adapt to NPs by altering the expression of their proteins and inducing mutations in resistance genes. The lack of understanding of NP characteristics and transformations in the surrounding medium was recognized to be the key issue responsible for the lack of agreement. In addition, it is not entirely clear whether NPs can cause changes in ROS production in cells and affect cell membrane permeability. The lack of comprehensive studies of NP systems for intracellular infections and the limited use of *in vivo* models reveal substantial blind spots in the current research.

It should also be borne in mind that bacteria quickly develop various mechanisms that enable them to evade the bactericidal activity of different types of NPs.[356] Moreover, bacteria can counteract physical impacts such as contact with nanorods or nanoneedles. Therefore, it is important to develop approaches that would prevent the emergence of various types of resistance in the clinical application of NPs. One such strategy may consist in the use of NPs functionalized with antibiotics, antimycotics, AMPs, bioactive molecules, bacteriophages, or bacteriocins. However, this would not only inevitably lead to a pronounced complication of the structures of hybrid nanosystems and methods for their production, but would also require more versatile biosafety tests.

If the bactericidal effect is due the release of ions, it is difficult to distinguish between their action and accompanying mechanisms such as ROS generation, direct contact of bacteria with the material, and microgalvanic interaction, which can expand the antimicrobial spectrum of bactericidal ions (see Scheme 9). The continuous release of antibacterial elements to the medium may give rise to drug resistance of bacteria; therefore, surface nanostructuring may be a promising method for the control of bacterial colonization.[357]

The search for new mechanisms for suppression of bacterial and fungal infections and synergistic effects would also remain relevant in the future. The number of studies addressing the prolonged bactericidal effect of ions *in vivo* is still insufficient. The question of how long the implant should retain antibacterial activity remains open. Extrapolation of *in vitro* results obtained using various models does not necessarily correspond the actual bactericidal behaviour of the material in the body (see Schemes 8 and 9). There is insufficient data on the growth of microorganisms *in vivo* near the implant surface releasing bactericidal ions, antibiotics, or ROS and on the influence of the microenvironment at the site of infection on the diffusion of bactericidal agents. In this connection, a new amperometric method for the measurement of ROS level near the implant surface appears promising. This method proved to be effective in *in vitro* models and holds promise for the transfer to *in vivo* models.[84,91,199] The integrated method using SEM images and neuronal network, able to reveal the differences between antibiotics and antimicrobial compounds used to inhibit biofilms, is of interest for more in-depth understanding of the inhibition of QS system and for development of new strategies of combating infections.[35]

It is noteworthy that little attention is paid to the purity of developed biomaterials, which may contain impurities harmful to health at the ppb level. It is important that the amount of bacteria in the body of an adult is 3.8×10^{13} or approximately 200 g, most of which are the intestinal and oral microflora or populate the skin.[358] Therefore, while using bactericidal materials in the maxillofacial surgery, gastrointestinal tract, and as wound dressing, it is important not to harm non-pathogenic bacteria. Also, it should be taken into account that the bacterial flora in the treatment of domestic and sports injuries or severe gunshot and blast osteomuscular injuries is usually considerably different; therefore, apart from the widely used *E. coli* and *S. aureus* strains, it is necessary to perform tests for *P. aeruginosa*, *Enterococcus faecalis*, *A. baumannii*, *K. pneumoniae*, *etc*. The key problems related to dental materials are the narrow range of microorganisms used to test the antimicrobial effect (mainly *Streptococcus mutans*, *Enterococcus faecalis*, *C. albicans*) and predominance of *in vitro* studies over clinical studies.[359]

The use of bacteriophages that do not disrupt the body's natural flora is becoming a promising new approach to combating MDR bacteria.[360] However, the current laboratory practice does not make it possible to easily substantiate the clinical use of bacteriophages and, before phages would become widely available for treatment, it is necessary to perform additional clinical trials to demonstrate their efficacy or safety. Cocktails of bacteriophages that are active against a wide range of pathogens must contain a large number of different phages and are still difficult to develop and produce. Progress can be expected from the development and extensive application of artificial intelligence (AI). For example, experimental testing of AI-generated genomes yielded 16 viable bacteriophages with considerable evolutionary novelty that may be effective against rapidly evolving bacterial pathogens.[361]

Acknowledgements

This review was prepared with the support of Ministry of Education and Science (Agreement No. 075-15-2023-469) as applied to surface-modified highly porous titanium-based implants and the Russian Science Foundation (Agreement No. 25-19-00458) as applied to analysis of various bactericidal mechanisms. The author is grateful to Yu.A.Makarets and E.S.Chikanova for the help in the preparation of figures. The figures and schemes were drawn using elements of the BioRender.com platform.

9. List of abbreviations and symbols

A. baumannii — *Acinetobacter baumannii*,
AI — artificial intelligence,
ALV — artificial lung ventilation,
AMP — antimicrobial peptides,
ANO — anodization,
ATB — amphotericin B,
ATP — adenosine triphosphate,
h-BN — hexagonal boron nitride,
C. albicans — *Candida albicans*,
C. auris — *Candida auris*,
CF — caspofungin,
CFU — colony-forming units,
CVD — chemical vapour deposition,
DETA — diethylenetriamine,
DNA — deoxyribonucleic acid,
E. coli — *Escherichia coli*,
EDC — 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,

EX — enoxacin,
PSS — physiological saline solution,
GM — gentamicin,
HP — heparin
HSA — human serum albumin,
K. pneumoniae — Klebsiella pneumoniae,
MA — maleic anhydride,
MAO — microarc oxidation,
MDR — multi-drug resistance,
MIC — minimal inhibitory concentration,
MRSA — methicillin-resistant *S. aureus*,
NASA — National Aeronautics and Space Administration,
N. crassa — Neurospora crassa,
NPs — nanoparticles,
P. aeruginosa — Pseudomonas aeruginosa,
PAM — polyallylmercaptan,
PC — protein corona,
PCL — polycaprolactam,
PEG — polyethylene glycol,
PEI — polyethyleneimine,
PEO — plasma electrolytic oxidation,
PG — peptidoglycan,
PLA — polylactic acid,
PLGA — poly(lactic-co-glycolic acid),
ppb — parts per billion,
ppm — parts per million,
PSS — physiological saline solution,
PVD — physical vapour deposition,
PVP — polyvinylpyrrolidone,
QS — quorum sensing,
RNA — ribonucleic acid,
ROS — reactive oxygen species,
S. aureus — Staphylococcus aureus,
S. epidermidis — Staphylococcus epidermidis,
S. pneumoniae — Streptococcus pneumoniae,
TEM — transmission electron microscopy,
TD — 1-tetradecanol,
SHS — self-propagating high-temperature synthesis,
UTI — urinary tract infection,
VM — vancomycin,
WHO — World Health Organization.

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