

# Engineering Approaches to Create Antibacterial Surfaces on Biomedical Implants and Devices



Ruwen Tan, Jin Yoo, and Yeongseon Jang

**Abstract** Bacterial adhesion and biofilm formation on biomedical surfaces remain the annoying problems in global public health, causing severe infectious diseases and increasing health care costs. Moreover, the continued increase in the number of multidrug-resistant bacteria and their fast evolution induce a serious concern with the lack of development of new antimicrobials. These problems have initiated numerous research efforts to develop more effective antimicrobial surfaces through different engineering approaches to prohibit bacterial adhesion and subsequent biofilm formation. In this review, we summarize the engineering technologies for constructing antibacterial surfaces from the conventional to the cutting-edge strategies. Most of the traditional methods are based on the antifouling coatings and the release of toxic biocides from the chemically modified substrates. Antimicrobial nanoparticles can actively inhibit biofilm formation or other essential processes in the drug resistance mechanisms of bacteria. Thus, the combined use of bactericidal nanoparticles and antifouling polymers for functionalized organic–inorganic platforms has been investigated to enhance antibacterial performance. In recent years, unique surface topographies of antibacterial, natural surfaces have been discovered and studied with the increased understanding of the interaction between bacteria and substrates. We introduce various natural surfaces and artificial implantable biomaterials, which present the bactericidal surface topographies, along with their bactericidal mechanisms and efficiency. The use of biomimetic, nanotextured surfaces is a promising approach to overcome the current challenges for the treatment of multidrug-resistant bacteria.

**Keywords** Antimicrobial · Antifouling · Bactericidal · Implant · Coating · Surface engineering · Functional surface · Nanotechnology · Nanostructure

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R. Tan · Y. Jang (✉)

Department of Chemical Engineering, University of Florida, Gainesville, FL, USA

e-mail: [y.jang@ufl.edu](mailto:y.jang@ufl.edu)

J. Yoo

School of Chemical and Biological Engineering, Seoul National University,  
Seoul, Republic of Korea

## Introduction

Surgical procedures with implantation of biomedical devices have saved and improved the quality of life of numerous patients. The implantable medical devices are being used in many different parts of the body including orthopedic, cardiovascular, ophthalmic, or gastroenterological implants for various applications [1]. Given applications, diverse types of materials used for the medical implants and devices have been developed, ranging from pure metals, metal alloys, ceramics to polymers. Mechanical properties, corrosion resistance and biocompatibility of the materials, as well as fabrication methods and processing costs, are the key parameters to determine the success of the biomedical implants and devices, which the engineers must consider when designing advanced biomaterials.

Despite considerable efforts in developing implantable biomedical devices, the infectious problems persist accompanied by bacterial adhesion and growth on the surfaces. Bacterial infections are considered a challenge in the global health care units, which can lead to life-threatening problems or incurring substantial costs. Therefore, preventing bacterial adhesion and colonization of the surfaces of biomedical implants and devices is essential to mitigate pathogenic bacteria-associated infections. To create antibacterial properties of biomaterials, many researchers mainly focus on the development of surface features that are unfavorable for bacterial attachment and growth by engineering surface chemistry or physical textures. Herein, we review several engineering approaches to develop biomedical implants and devices for antibacterial performance by using diverse surface treatments with chemical or physical ways. The antibacterial surfaces can be achieved by three major categories: (1) sustained release of antibacterial agents, (2) repelling bacterial adhesion (antifouling), and (3) contact-killing.

First, antibacterial coatings with antibiotics, antimicrobial nanoparticles, or antifouling polymers have been widely used as one of the global strategies to inhibit bacterial infections by mitigating colonization [2]. We introduce several surface coatings using functionalized polymers (section “Surface Coatings Using Functionalized Polymers”), antimicrobial nanoparticles, and inorganic-organic hybrids (section “Surface Modification with Antimicrobial Nanoparticles and/or Inorganic–Organic Hybrids”), from traditional to recent approaches. The coating methods with functional molecules aim at preventing bacterial adhesion through antifouling surfaces or the controlled release of antibacterial agents from a chemical point of view. The chemical modification has advantages of the versatility to apply diverse materials, regardless of substrate macrostructure, and relatively easy and low-cost fabrication process. Nonetheless, coatings can have challenges of the possibility of drug resistance, delamination, and/or functionality loss due to thermal, hydrolytic, or solvent-induced degradation.

We can learn the lessons from Nature to design antibacterial surfaces without additional chemical treatments. Indeed, biomimetics has inspired many researchers in an interdisciplinary field of engineering, chemistry, and biology to develop new advanced materials that mimic outstanding biological, natural functions. In section “Biomimicry Toward Advanced Antimicrobial Surfaces,” we review several gripping

natural surfaces (e.g., insect wings, herb leaves, and animal skin), which display excellent antimicrobial properties, and summarize critical features that result in the reduced bacterial adhesion or the increased killing efficacy. We also discuss recent engineering techniques to fabricate artificial structures that mimic such natural surfaces with high antibacterial efficiency in section “Nature-Inspired, Nanostructured Surface Development for Antibacterial Properties.” Several studies to understand the relationship between surface structure and bacterial adhesion are introduced along with the efforts to discover the most appropriate materials and methods for each practical use.

It would be feasible to apply the approaches discussed in this chapter for making a perfectly sterile environment in the surgical operating rooms by realizing desired surface properties of surgical tools and tables, monitoring equipment, injection tubes, and drapes. However, translational studies to utilize the surface engineering strategies for the clinical studies and the practical uses remain, which requires a collaborative effort from material researchers, engineers, medical doctors, and regulatory agencies. The multidisciplinary research and development will be the next step toward advanced antibacterial biomaterials design and application. Next-generation biomedical implants and devices should also exhibit multi-functionalities, long-term stability, and enhanced therapeutic properties, in addition to antibacterial properties. We review the current challenges in the latest generation of antibacterial surfaces and propose future respective in section “Prospective Approaches.”

## **Engineering Strategies to Create Antibacterial Surfaces on Biomedical Implants and Devices**

Advances in biomedical engineering have been driven by the development of new biomaterials including therapeutic agents, implants with desired mechanical properties and improved corrosion resistance, and de novo functional small molecules or polymers. Notably, the biological properties of materials, which include biocompatibility, biofouling effect, biodegradability, or cytotoxicity, are directly linked to the surface properties. In other words, the interaction of bacterial cells with biomaterials at surfaces dictates the cell fates, which controls adhesion, colonization, and the corresponding infections [3]. Given a systematic understanding of the surface–bacteria interactions, we can rationally design new classes of biomedical implants and devices and engineer their surface properties to inhibit bacterial cell adhesion and growth while promoting profitable cell growth.

This chapter reviews a variety of engineering strategies to create antibacterial surfaces on biomedical implants and devices in the two main categories: (1) chemical surface coatings and modifications and (2) physical surface texture developments. We summarize the surface fabrication methods from traditional approaches to recent events with a discussion of possible mechanisms of cell adhesion and growth on the engineered surfaces. Moreover, we highlight several examples of antibacterial surfaces in nature, which inspire to the next-generation engineers for advanced antifouling, bactericidal surface developments on artificial materials.

## ***Surface Coatings Using Functionalized Polymers***

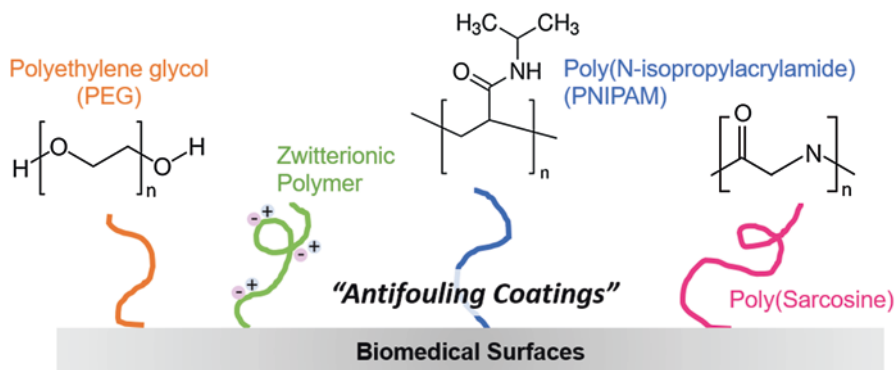
Polymers have been actively explored as advanced coating materials for a myriad of biomedical applications, based on the molecular tunability (i.e., molecular weights, chemical properties of pendent groups, chain flexibility, and so on) and the corresponding diverse functionalities [4]. Several coating techniques of polymers on metals or metal alloys, for instance, layer-by-layer deposition [4], conventional organic coatings (e.g., dipping, spinning, spraying) [5], or brush formation [6], enable functionalization and protection of the surfaces from corrosive or other stimuli attacks.

Proteins are adsorbed on the implanted material surfaces by forming a thin layer in blood, leading to the promotion of bacterial cell attachment. Thus, for an effective antibacterial surface, it is essential to impart antifouling properties that repel proteins and bacteria at the surfaces. First, we highlight widely used polymers as coatings to prevent nonspecific protein adhesions on medical implants in section “Antifouling Polymer Coatings to Prevent Bacterial Adhesion” (i.e., passive approaches). Additionally, we can avoid bacterial infections by coating the surfaces with antibiotics or antimicrobial nanoparticles that can kill adhered, pathogenic microorganisms (i.e., active approaches). Functionalized polymer coatings that release such antibacterial agents can improve the bactericidal performance of the biomedical surfaces. In section “Bactericidal Activity of Functionalized Polymer Coatings,” we introduce surface coating strategies based on functionalized polymers with such active antibacterial properties.

### **Antifouling Polymer Coatings to Prevent Bacterial Adhesion**

To achieve an effective antifouling coating for the bacteria-repellent property, antifouling polymers such as zwitterionic [7], peptidomimetic polymers [8–9], or poly(ethylene glycol) (PEG) [10] have been widely employed, as shown in Fig. 1. The strategy to utilize such antifouling polymers for surface repellency against bacteria can be rationalized by the steric repulsion effect and the formation of the hydration layer [11]. Entropic instability induces the steric repulsion that prevents bacterial adhesion, while the hydrogen bonding interaction with PEG molecules or the electrostatic interaction with zwitterionic molecules forms a hydration layer to deter nonspecific interaction between cell and substrate. The attachment and binding of fouling agents to the surface are energetically unfavorable due to the energy barrier which must be overcome to disrupt the hydration layer [11].

PEG is a nontoxic, non-immunogenic, and uncharged polymer that is soluble in aqueous and many organic solvents, leading to broad utilization in a number of studies [12]. Since the PEG chains are hydrophilic, highly mobile and attain huge exclusion volumes, they prohibit adsorption of cell and protein at the surfaces [13]. Antifouling PEG polymers can be coated on surfaces *via* diverse techniques including self-assembled monolayer (SAM), physical adsorption, or chemical grafting.



**Fig. 1** Representative chemical structures of antifouling polymers commonly used for the surface modification of biomedical devices

Immobilizing PEG through SAM formation is one of the most commonly used approaches to impart passive antifouling activity to a surface. Prime et al. reported that SAMs made from PEG showed remarkable protein resistance [14]. Also, PEG molecules can be chemically grafted on surfaces using grafting-to or grafting-from methods. An important parameter in determining the antifouling performance of the PEG layer is the density of polymer molecules and the chain length. In general, the increase of chain length (i.e., polymer molecular weight) leads to a decreased number of adhering bacterial cells and higher grafting density results in more effective antifouling surfaces [15].

Apart from PEG, zwitterionic antifouling polymers have attracted significant attention due to their remarkable biofouling resistance, based on the high degrees of ionic hydration [7]. Zwitterionic polymers composed of both cationic and anionic groups with a unique molecular structure exhibit overall charge neutrality with high hydrophilicity. A broad spectrum of zwitterionic polymers can be synthesized with different chemical structures, whereas PEGs share the same repeating units. In this regard, the targeted library of zwitterionic brushes with varying densities of charge, hydration, chain lengths, and grafted chain densities has been quantitatively evaluated for their antifouling properties [16].

A few other hydrophilic polymer brushes have also been developed as antifouling coating materials. For example, poly N-isopropylacrylamide (PIPAAM), a thermo-responsive polymer with the lower critical solution temperature (LCST) behavior, which is grafted on Ti surfaces successfully induced significant detachment of bacteria upon rinsing at room temperature [17]. Polyacrylamide (PAAm) brushes coated on silicon rubber surfaces also showed effective resistance against attachment of proteins and bacteria. Furthermore, peptide-based coatings, such as self-assembled monolayers made from oligopeptide and serum albumin blocking layers, have been proposed for antifouling applications [18, 19].

## Bactericidal Activity of Functionalized Polymer Coatings

Although the passive antifouling approaches have shown broad applicability, inherent limitations to these approaches remain when dealing with proliferative fouling due to their inability to suppress the colonization of bacteria. An alternative strategy is to construct a surface that can actively inhibit microbial colonization by killing bacteria. The active approach can be divided into the controlled release of antimicrobial agents and non-release-based antimicrobial systems.

Antibiotic- or antiseptic-releasing coatings are prepared either by soaking the carrier material coated with polymers in a solution containing antibiotics or by directly impregnating into the coating material. The release of the antibiotics can be controlled by manipulating the composition and concentration of the coating formulation. For example, Hammond and co-workers have used layer-by-layer (LbL) deposition technique to fabricate polyelectrolyte multilayer films containing an antibiotic agent, gentamicin. The LbL multilayered heterostructure was composed of hydrolytically degradable poly( $\beta$ -amino ester), biocompatible polyanionic hyaluronic acid, and gentamicin [20]. The gentamicin loading density, as well as its release rate, can be controlled by tuning of hydrophilicity and electrostatic interactions between the polymeric components in the films. In a similar approach, antimicrobial peptides were incorporated into a microgel by electrostatic interactions. Bactericidal efficiency of the peptide-loaded microgels was achieved *via* both direct contact-killing and release of incorporated peptides. The antimicrobial effects were governed by the release rate of the bactericidal peptides from the microgel, controlled by ionic strength in the solution that affects the electrostatic interactions of the chain scaffold components [21].

Despite many useful applications of the antibacterial systems that release antimicrobial agents, there remains limitation such as the difficulty of long-term use of bleaching agents, i.e., eventual depletion of agents. To circumvent the issues, surface-mounted antibacterial agents that kill bacteria by contact have served as a viable alternative. Cationic polymeric materials with cationic antimicrobial groups (e.g., quaternary ammonium (QA), phosphonium (QP) and guanidinium groups, etc.) have been designed and applied to fabricate surfaces with bacterial contact-killing features [22]. Besides, alkyl pyridinium was reported by Tiller et al. as an active antibacterial agent, resulting in effective contact-killing against bacteria [23]. Specifically, poly(vinyl-*N*-pyridinium bromide) covalently attached to various surfaces was reported to show 99% killing efficiency of both Gram-negative and Gram-positive bacteria [24].

Various bio-based polymers, such as chitosan and cellulose, are well known to have antimicrobial compounds of biological, chemical origins [25]. Coating with nanofibers of such biopolymers has been developed in this field to increase antimicrobial performance with high surface area. Recently, Correia et al. demonstrated that the chitosan nanofiber scaffolds grafted with antimicrobial oligomers induced efficient contact-killing of bacteria [26]. The electrostatic interaction between polycationic chitosan and the anionic exterior surface of microbes leads to the disruption

of the cell membrane and leakage of intracellular components. At the same time, DNA transcription and protein synthesis are interrupted by the penetration of chitosan into the cell membrane [27]. While chitosan shows effectively bactericidal efficacy against both Gram-negative and Gram-positive bacterial cell, chitosan is biocompatible to mammalian cells [25]. Chitosan-based nanofibers can be fabricated by electrospinning technique, which uses electric fields to make fibers in the order of hundreds of nanometers in diameter from charged polymer solutions or melts. Chitosan and its derivatives are successfully electrospun into antibacterial nanofibers as shown in several examples [28–30]. In addition, cellulose-based nanofibers formed *via* electrospinning or surface graft polymerization exhibited antimicrobial property with incorporation of antimicrobial agents or grafted functional groups [31–33]. Besides, diverse nanofibers made from different antimicrobial polymers have been created for bactericidal applications with high surface exposure area [34–36].

In addition to polymeric coatings, some nanomaterials, mainly inorganic nanoparticles including metals and metal oxides can also impart fouling resistance to surfaces. They have also attracted considerable attention because of their superior antibacterial activity with ameliorating the fouling resistance property. We will study the surface modification strategies to utilize antimicrobial inorganic nanoparticles in hybrid form in the next section.

### ***Surface Modification with Antimicrobial Nanoparticles and/or Inorganic–Organic Hybrids***

Bacterial cells primarily exist in robust communities by colonization on surfaces, known as biofilm, which is highly resistant to treatment with antibiotics. Biofilm formation of multidrug-resistant bacteria is a huge issue in a global health care system. Therefore, development of novel engineering approaches to actively prohibit the biofilm formation as well as the related infections is highly in demand rather than conventional antibiotic release from antifouling surfaces. This part focuses on the recent advances in antimicrobial nanoparticles (NPs) and inorganic–organic hybrid platforms, which may offer a promising solution for developing long-lasting antibacterial surfaces.

#### **Antibacterial Nanoparticles**

Antibacterial nanoparticles (NPs) are talent materials, as they can not only combat bacteria by themselves but also play a role as carriers for other biocidal agents. Two general advantages of antibacterial NPs are the distinctive antibacterial efficacy achieved by high surface to volume ratios due to the ultrasmall size and the potential to functionalization with different (bio)molecules [37].

The antimicrobial NPs exert bactericidal activity *via* different and extensive mechanisms. In other words, antibacterial NPs do not present the monotonous actions like standard antibiotics. They can directly interact with the cell wall of bacteria while preventing biofilm formation and triggering immune responses in the body. Ultimately, antibacterial NPs dispersed in a solution phase trigger reactive oxygen species (ROS) generation and intercellular damage of bacterial cells by interactions with nucleic acids and proteins [38].

Among different antibacterial NPs, silver NPs (AgNPs) are considered the most effective antibacterial agent [39]. Several mechanisms have been proposed to explain AgNPs antimicrobial activity [40, 41]. The adsorption of AgNPs leads to the depolarization of the bacterial cell wall, thereby inducing cell membrane disruption. Then, penetration of AgNPs produces ROS that inhibits ATP production and DNA replication. Furthermore, there is an evidence that an oxidative dissolution of AgNPs involves the release of  $\text{Ag}^+$  species, known to exhibit antibacterial activity. Since the  $\text{Ag}^+$  possesses a high affinity with amines, phosphates, and most thiols, it ultimately weakens protein functions that contain amine, phosphates, and thiols by the formation of a quasi-covalent bond. At the same time, AgNP exhibits bactericidal action itself by disrupting cell membranes, in parallel to  $\text{Ag}^+$  release.

Other metallic NPs, such as ZnO,  $\text{TiO}_2$ , Au,  $\text{CeO}_2$ , CaO, and CuO, have also demonstrated bactericidal effects [42–44]. Although some controversy still exists, some studies have utilized AuNPs as antibacterial agents [45–46]. It has been also reported that AuNPs can be utilized as delivery vehicles of antibiotics attributing to nontoxicity for the human body and easy surface modification *via* diverse conjugation chemistry of AuNPs [47, 48]. Metal oxide NPs are also known to effectively inhibit the growth of a wide range of bacteria due to their intrinsic photocatalytic activity, generating ROS.

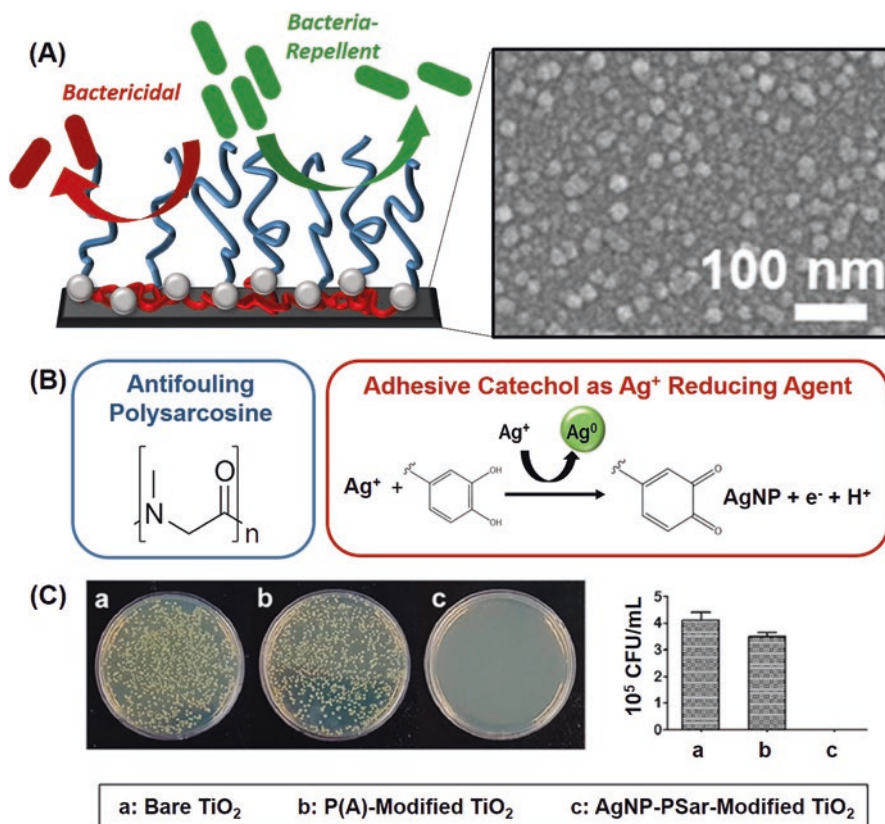
### Inorganic–Organic Hybrids

In section “Antibacterial Nanoparticles,” we highlighted several functional inorganic NPs that exhibit antibacterial properties. Surface modification of biomedical implants and devices with the antimicrobial NPs is useful and productive to prevent biofilm formation of bacteria, mainly presenting high antibiotic resistance. However, decoration of the medical device surfaces only with NPs will have challenges due to easy loss of NPs by adsorption to floating proteins, platelets, dead cells, and cell debris [49]. To resolve the problem, we can integrate the bactericidal inorganic NPs with antifouling organic materials into a single coating platform.

Surface coatings of antifouling polymers combined with antimicrobial NPs can be used for modification of medical implants [50]. Silver-based coatings hybridized with organic materials showed excellent bactericidal activity against both Gram-positive and Gram-negative bacteria. Indeed, many studies regarding organic–inorganic hybrid coatings containing AgNPs have been reported [6, 7, 51, 52].

The main advantage of using the inorganic–organic hybrid platform is in the versatility to create multi-functionalities of the material surfaces based on the beauty of chemistry. For instance, Yoo et al. have recently demonstrated that a combination of antifouling polymeric brushes and AgNPs on a Ti results in 100% bacterial killing





**Fig. 2** (A) Schematic representation of surface modification with inorganic–organic hybridization on biomedical implants and devices. AgNPs are formed through reduction by catechol groups of polysarcosine (p(Sar)) brushes modified on a TiO<sub>2</sub> surface (inset: a scanning electron micrograph of the inorganic–organic hybrid surface) (B) Representative chemical structure of p(Sar) and catechol-mediated AgNP reduction process. (C) Photographs and the number of *E. coli* colonies with non-modified, p(Sar)-modified, and AgNPs-decorated p(Sar) TiO<sub>2</sub> surfaces. (Reprinted with permission from [6]. Copyright 2018 American Chemical Society)

efficiency. Protein-resistant polysarcosine brushes at the surface played a dual role in inhibiting adsorption of biofoulants and mediating formation of bactericidal AgNPs at the coated surfaces. This approach does not only yield antifouling properties but also introduce a pronounced bactericidal activity, thereby leading to far more improved antibacterial surfaces (Fig. 2) [6]. AgNPs can be conjugated with polymers *via* photoreduction or by using reducing agents. Recently, “green” synthesis of AgNPs using plant extracts as reducing agents has been spotlighted instead of using chemical agents [53, 54]. Similarly, other bacteria-repelling, antifouling polymers (e.g., zwitterionic polymer, per-fluoro polymer, and PEG) can also be demonstrated to improve the prevention efficacy of biofilm formation with the incorporation of AgNPs by the conjugation chemistry.

It would also be worthy to note that we can decorate the surfaces of antimicrobial NPs with organic materials to create a synergistic effect. Metal oxide photocata-

lysts, such as TiO<sub>2</sub>, ZnO, CeO<sub>2</sub>, and so on, generate ROS under light irradiation, thereby resulting in bactericidal effects. However, the surfaces of metal oxides are inherently hydrophilic, which is vulnerable to bacterial colonization. Surface modification of hydrophilic metal oxides with polydimethylsiloxane (PDMS) under UV light enables to create hydrophobic surfaces with retention of the natural photocatalytic activity [55].

Furthermore, biocompatible biopolymers to mammalian cells combined with antimicrobial inorganic NPs can improve the biocompatibility of implantable materials as well as facilitate the controlled release of biocidal agents. For example, the gelatin and ZnO NPs composite films have been applied for food preservation, showing excellent antibacterial activity against foodborne, pathogenic bacteria [56].

### ***Biomimicry Toward Advanced Antimicrobial Surfaces***

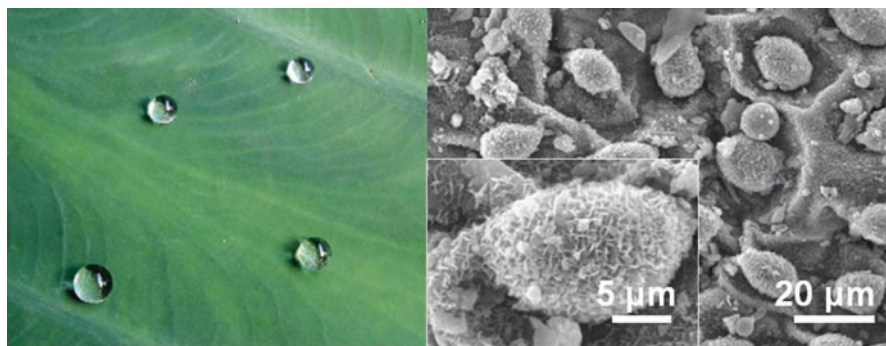
Living organisms in Nature have evolved their structure and functions over a geological period to survive extreme and various environmental conditions, which offer engineering solutions to overcome many challenges in new material development. For instance, the lotus effect, known as self-cleaning properties of surfaces to remove dirt particles with water droplets *via* superhydrophobicity based on hierarchical surface roughness, has inspired researchers in the fields of antifouling paints, clothes, anti-stiction coatings, and low friction surfaces [57].

Indeed, we can easily find functional, natural surfaces from plants, animals, and insects that display antifouling and/or bactericidal properties with the delicate nanostructure. Gecko skin [58], sharkskin [59], many insect wings [60, 61], and plant leaves [62] possess antibacterial properties with unique surface patterns. Also, we recently discovered nanoprotusive natural surfaces, Such as gecko skin [63], cicada wing [64], and dragonfly wings [65], exhibit high bactericidal efficiency.

Motivated by such antifouling and bactericidal surfaces in nature, researchers have been actively trying to mimic and engineer the surface structure of human-made materials used in biomedical implants and devices [66]. In section “Biomimicry Toward Advanced Antimicrobial Surfaces,” we introduce *natural antimicrobial surfaces* classified into two categories based on the resistance mechanism against bacterial cells: (1) reduction of cell attachment (antifouling surfaces), and (2) rupture of the attached cell membrane (bactericidal surfaces).

#### **Natural, Antifouling Surfaces with Reduced Bacterial Adhesion**

Preventing adhesion of contaminants on surfaces can be achieved *via* the creation of superhydrophobic surfaces with nano/micro hierarchical structures that mimic different natural, antifouling surfaces observed in various herbaceous plants [62], insect species [60–65], and animals [58, 59].



**Fig. 3** Antifouling, superhydrophobic taro leaves. A photograph and scanning electron micrographs of taro leaves. (Reprinted from [68] with permission from Elsevier. Copyright 2007 Elsevier)

For examples, rice, lotus, and taro leaves display hierarchical surface layers with dense, nanometer-scale wax crystalloids on micrometer-sized, convex epidermal cells (Fig. 3) [68]. Such unique surface structural and chemical properties of leaves result in very high surface contact angles with low water sliding angles [69]. Hence, bacteria and any contaminant particles can be easily picked up by near water droplets and removed with the rolling-off-droplets on the natural superhydrophobic, antifouling surfaces.

The antifouling effect of superhydrophobic surfaces is based on air traps between the surface structure and bacterial cell membrane. The hierarchical nanostructures on microstructures, which enable retaining the trapped air under water, have a critical role in fluid drag reduction and biofouling prevention [67]. Cassie–Baxter model suggests that the air layer captured under the droplet serves as another substrate in the system, leading to reduced surface tension of solid and vapor [70]. A heterogeneous surface composed of air and solid results in meager adhesive force between water and the solid surface, which induces “self-cleaning, antifouling effect.”

In addition to the plenty of superhydrophobic plant leaves, animal skin also present great antifouling property. Sharkskin is one of the representative examples to demonstrate excellent antifouling efficacy against bacteria, algae, and barnacles. The superior antifouling performance of sharkskin originates from a combination of a unique surface structure composed of micrometer-scale riblets and dermal denticles. In conjunction with the unique surface patterns, superior mechanical flexibility and mucous surface layers of sharkskin significantly reduce friction drag and increase aerodynamics in water [59]. Many research efforts have been devoted to designing a new type of surface to attack bacteria with the sharkskin-mimicking, patterned diamond-like surface texture [71]. We will discuss the engineering approaches developed to mimic natural structure in the next section “Nature-Inspired, Nanostructured Surface Development for Antibacterial Properties” in more detail.

Other interesting natural surfaces that present antifouling effect can be found from a variety of insects living in an extreme environment like dusty soil and damp tropical jungle. Wings of butterflies, moths, alderflies, antlions, fishflies, dobsonflies, or snakeflies presented excellent antifouling properties, which were demonstrated by testing the efficiency to remove particles of different sizes with water droplets during fogging. It was reported that only less than 5% particles, initially applied to the surfaces, remain on the *Lepidoptera* and *Planipennia* wings [61]. Moreover, *Lepidoptera* wings have hierarchical microgrooves on an array of shingle-like structures, which is useful to create engineering surfaces by obtaining a replica of the surface for enhanced antifouling properties [72, 73]. Truly, insects have inspired many researchers to develop marvelous surface structure using advanced nanotechnology toward antifouling surfaces while overcoming the hostile environmental disadvantages.

### **Natural, Bactericidal Surfaces to Induce Membrane Rupture of Bacterial Cell**

Another effective strategy to prevent biofilm formation is to kill and physically interfere interactions of attached microbes with surface protrusive topography. In this regard, cicada (e.g., *Psaltoda claripennis*) and dragonfly wings (e.g., *Diplacodes bipunctata*) have recently received an intense attention due to their antifouling as well as high bactericidal effectiveness. Herein, we summarize several reports of natural surfaces showing the excellent bactericidal performance.

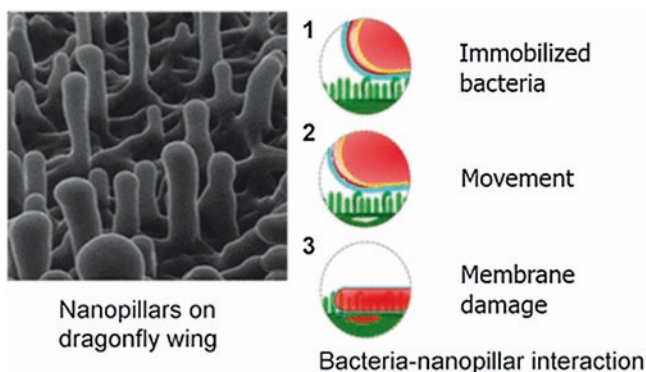
Ivanova et al. reported the first example of natural cicada wings that kill Gram-negative pathogenic bacteria, *Pseudomonas aeruginosa* (*P. aeruginosa*), which causes severe infections at different sites within the body such as urinary and respiratory tracts or wounded skin [64]. The authors demonstrated that the nanopillars on the cicada wings could rupture and penetrate the bacterial membrane within approximately 3 min, resulting in high bactericidal efficiency. The physical and mechanical bactericidal ability was further demonstrated by altering the cicada surface into deposited gold to eliminate the chemical effect, which also confirmed that the nanopillar structure has a significant role to kill the adhered bacteria. A biophysical model to explain the interaction of bacterial cell and surface nanopillar structure supported that mechanical properties, especially rigidity of cells, are the important factors to determine bactericidal efficacy on the cicada wing [74]. These findings provide scientific insights into the bactericidal mechanism underlying natural antimicrobial materials. However, it is worth noting that the cicada wings are only lethal to Gram-negative bacteria but less effective to more rigid Gram-positive bacteria with a thicker layer of peptidoglycan. Also, the bactericidal efficacy on cicada wings varies from different cicada species [75, 76].

Dragonfly wings (*Diplacodes bipunctata*) are effective to kill both Gram-positive and Gram-negative bacterial cells, which originates from the high-aspect ratio nanoprotrusion on the surfaces [65]. The protrusive nanopillars or their clusters on dragonfly wings (e.g. *Hemianax papuensis*, *Sympetrum vulgatum*) are primarily

composed of aliphatic hydrocarbon and a fatty acid outer layer. The size of the nanoscale surface structures varies between 83 and 195 nm in diameter according to species [77, 78]. The bactericidal efficiency is dependent on the topography of the nanoprotrusion on their wings, which implies that different dragonfly species would show different bactericidal efficiency against pathogenic bacteria [79].

The sharp nanopillars on insect wings with high-aspect-ratio exhibit great bactericidal activity while bringing about by cell membrane deformation and lysis. Bandara et al. demonstrated that the cell membrane rupture is caused by a combination of the strong adhesion between nanopillars and extracellular polymeric substance (EPS) of attached bacteria as well as the shear force when immobilized bacterium tries to move on the nanotextured surface (Fig. 4) [80]. Most notably, the nanoprotrusive surface structure does play the main role in the bactericidal performance. A recent study confirmed that the black silicon surfaces which mimic dragonfly wings effectively killed both of Gram-negative and Gram-positive bacteria, despite low production of EPS [81].

For animal surfaces presenting the bactericidal effect, gecko skin (e.g., *L. steindachneri*) with sub-micro-spaced, hairy spinules on hexagonal-patterned dome-like structures demonstrated the self-cleaning property as well as bactericidal efficacy against both Gram-negative and Gram-positive bacteria [58, 63, 82]. In addition to terrestrial insect and animal surfaces, the cuticle of the aquatic larva of the drone fly (e.g., *Eristalis tenax*) is reported to have a potential bactericidal property [83]. The authors observed the spine-like nanopillars on the cuticle layers made it difficult for bacteria to attach and colonize the surfaces. Considered the larvae living in bacteria-, fungi- and algae-rich environments, mimicking an array of the nanopillars (typically <100 nm in diameter) would facilitate to enhance antibacterial efficiency of engineered surfaces in a harsh environment.



**Fig. 4** SEM image and schematics to show the bactericidal effects of natural dragonfly wings with nano-topography. (Reprinted with permission from [80]. Copyright 2017 American Chemical Society)

## ***Nature-Inspired, Nanostructured Surface Development for Antibacterial Properties***

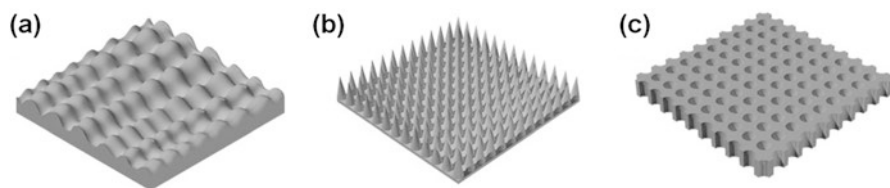
Advances in nanofabrication techniques facilitate the development of such functional, engineered surfaces on various materials. Recently, the creation of biomimetic, antibacterial surfaces using nanotechnology has gathered strong attention in surface sciences, material developments, and biomedical applications. In section “Nature-Inspired, Nanostructured Surface Development for Antibacterial Properties,” we review current engineering approaches to create biomimicking, antibacterial nanostructures, classified into three categories based on the structural characteristics: (1) nano/microscale roughness, (2) nanoprotrusion, and (3) nanopores (Fig. 5).

### **Engineered Surfaces with Surface Roughness or Pattern at the Nano and Micro Scale**

Inspired by the antimicrobial structure in the nature surfaces (e.g., plant leaves, insect wings, and animal skin), researchers have tried to fabricate analogous structures on the surfaces of biomedical implants or devices to prevent bacterial infections. Herein, we highlight widely used engineering techniques to create the nature-mimicking structures on surfaces of artificial materials, in particular, the fabrication methods to make nano/micro surface roughness, hierarchical structure, or regular patterns.

The lotus leaf-inspired hierarchical nanostructure has been created for wettability control on the diverse types of materials by using many advanced engineering techniques including self-assembly, laser processing, etching, and electrodeposition. The approaches to mimic superhydrophobic, antifouling lotus leaves can also be used for modification of biomedical surfaces [69]. Recent work reported that the lotus leaf-mimicking, fluorinated polypropylene surfaces significantly reduced *E. coli* adhesion, compared to the untreated, flat control surface, based on structural and chemical properties [84].

One of the easiest, feasible ways to mimic natural surfaces would be to obtain the direct replication of natural antibacterial surfaces by molding, embossing, and printing of polymers. The polymer replication techniques broadly require the following



**Fig. 5** Schematic representations of engineered surfaces with (a) nano-/microscale roughness, (b) protrusive structures with high-aspect-ratio nanopillars, and (c) pores at the nanometer scale

necessary steps: a master mold (e.g., a natural surface from which replicas are formed), replication of the master using moldable polymer, and transfer and registration of the replica to a functional material (e.g., implants or surgical tools) [85]. Using this technology, engineers have tried to make replicas of sharkskin, rice leaf, and butterfly wing by diverse types of polymeric substrates (e.g., polyurethane, polypropylene, and polydimethylsiloxane), which also demonstrated good antifouling effect against both Gram-positive and Gram-negative bacteria [73, 86]. Notably, some polymeric replicas of sharkskin exhibited a better self-cleaning and antifouling performance against microorganisms including zoospores and *E. coli* than the primary micropattern [87, 88]. The molding or casting methods are useful to fabricate the nature-mimicking surfaces in a high throughput and low cost with a good resolution at the microscale, but they can be limited to the higher resolution of the nanoscale range [66]. This challenge can be overcome with different engineering strategies. For example, polyethylene terephthalate was fabricated into nanocones or sharp nanopillars by colloidal lithography or inductively coupled plasma, which also mitigated bacterial adhesion and colonization activity [89, 90].

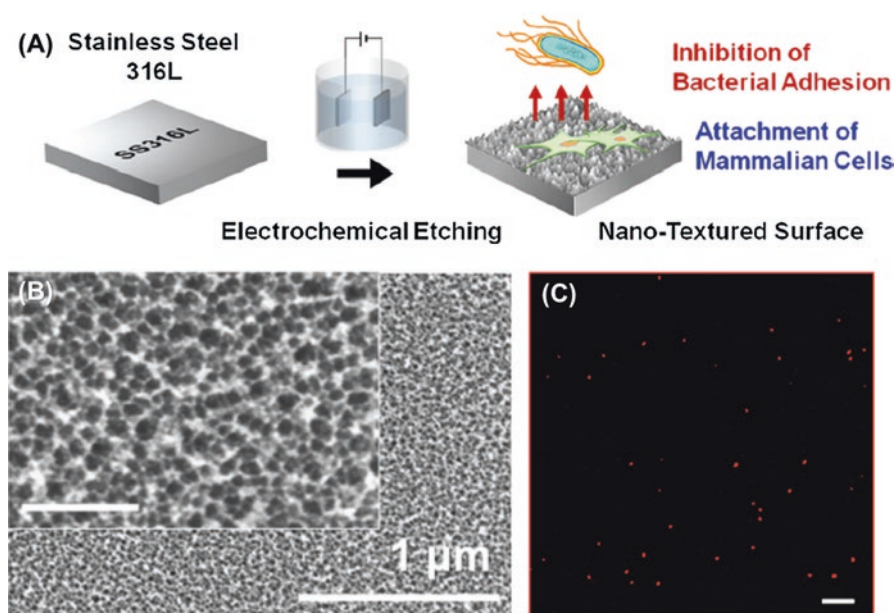
For the direct implementation of surface roughness on implantable metal or metal alloy materials, researchers have tried to apply sputtering or shot peening and tested the antimicrobial properties of the modified surfaces. For example, a titanium alloy ( $Ti_6Al_4V$ ) has been coated with nanocolumnar structures by the glancing angle deposition using magnetron sputtering technique for lotus leaf effect [91]. The nano-roughened Ti alloy surfaces inhibited bacterial attachment and biofilm formation of *S. aureus* while showing good biocompatibility to osteoblasts [91]. The nano-roughened Ti surfaces with nanocolumns reduce the available area for bacterial cells to attach, leading to a limited number of anchoring points between the bacteria and nanorough surface. Nevertheless, nanoroughness on the Ti surface has less impact on osteoblasts due to a more deformable membrane and the large size of mammalian cells.

Such nano-roughened Ti surfaces can also be fabricated by physical vapor deposition. Jandt and others demonstrated the nanorough Ti surfaces reduced adhesion of *E. coli* and *S. aureus* with the increase of surface roughness, which originated from the decrease of adhesion points of the cells to the surfaces [92]. However, the degree of reduction of bacterial attachment on the nanorough surface may vary in an individual bacterial cell type for a given specific surface. The ability of bacterial attachment reduction could be affected by many factors, like shape or spatial distribution of surface features, surface chemistry, and bacterial type [93, 94]. To our best knowledge, up to date, there is no substrate possessing the universal ability to reduce the adhesion of all types of bacteria.

### **Biomimetic Surfaces with Nanoprotrusion**

Since the first report of the antifouling and the bactericidal efficacy of the cicada wings with high-aspect-ratio nanoprotrusion [64], many efforts have been devoted to creating the bioinspired, bactericidal surfaces with nanoprotrusion on medical devices or implants.

Stainless steel 316L (SS316L) is one of the most extensively used metal alloys for food processing equipment and biomedical devices such as implants and surgical tools due to its biocompatibility, corrosion resistance, and mechanical strength [95]. Therefore, it is critical to developing a facile method to attain nano-topography on SS316L surfaces to inhibit bacterial adhesion. Surface-roughened SS316L can be created *via* severe shot peening [96], abrasive flow finishing [97], or electrochemical etching methods [98]. Jang and Choi et al. evaluated the antibacterial nature of nano-textured SS316L surfaces fabricated by electrochemical etching, which possess pronounced, nanoporous, and protrusive structures on the surface (Fig. 6) [98]. The SS316L surfaces with  $\sim 20$  nm pores and protrusive nanopikes exhibited a significant reduction in surface adhesion of both of Gram-negative *E. coli* and Gram-negative *S. aureus*. Compared to other surface finishing techniques, the electrochemical etching process is affordable and scalable as well as has exquisite control of surface structures by electrochemical parameters such as potential and current density. Furthermore, the electrochemical surface modification produced a superior passive film with enrichment of Chromium (Cr) and Molybdenum (Mo) at the SS316L surface for corrosion resistance in physiological solution, which would be another advantage to use this method for biomedical applications.



**Fig. 6** (A) Schematic illustration of development of biocompatible, nanoporous, and protrusive stainless steel 316L (SS316L) surfaces by electrochemical etching to inhibit bacterial adhesion. (B) Scanning electron micrographs of nanotextured SS316L (NT-SS316L) surface. (C) A representative fluorescent micrograph of dead *E. coli* on NT-SS316L. (Reprinted with permission from [98]. Copyrights at American Chemical Society 2018)



Ti and its alloys are also one of the most popular choices of implant materials due to their excellent chemical and corrosion resistance, biocompatibility, and osseointegration [99–101]. Several different engineering approaches have been applied for the fabrication of protrusive structures on implantable Ti surfaces to prevent the microbial-induced infection problems. For instance, a cicada wing-mimicking nanocolumnar structure on Ti was fabricated by glancing angle sputter deposition, leading to selective bactericidal activity with 50% mortality of *E. coli* [102]. Using hydrothermal etching, Bhadra and coworkers created perpendicular-oriented nanowire-like structure on Ti surfaces. The engineered Ti surfaces with nano-patterned arrays, mimicking dragonfly wings, showed high efficiency in killing *P. aeruginosa* [103]. Another nanopillar structure, made from a chlorine-based reactive ion etching on Ti surface, also presented excellent bactericidal efficacy against Gram-negative bacterial cells [104]. In addition, all the aforementioned nanotextured surfaces possess good cytocompatibility allowing the proliferation and growth of mammalian cells. Some other works related to Ti and Ti alloys etched by the hydrothermal process [105], anodization [106], or thermal oxidation [107] also demonstrated specific bactericidal efficacy and good cytocompatibility as well.

Silicon (Si) is a good candidate to fabricate the nanoprotusion, while enabling to control the aspect ratio systematically, with high throughput and low fabrication costs. The nanotextured silicon substrate created *via* reactive ion etching, called “black silicon,” presents sharper, more discretely distributed, and lower clustered nanoprotusive features [81, 108]. The black silicon resulted in higher efficiency to kill endospores, Gram-negative and Gram-positive bacteria than natural dragonfly wings [65]. Besides, *in vivo* implant study demonstrated that the biocompatibility of black silicon surfaces to eukaryotic cells without inflammatory response in ocular and general tissue environment of the host [109].

When it comes to the mechanism of bactericidal efficacy, the mechanical rupture of the cell membrane caused by the interaction between the cell membrane and surface topography is generally accepted as reported in several papers [74, 110–112]. The effect of topographic geometry on bactericidal efficiency has been systematically investigated by tuning the surface protrusion dimension (i.e., height, tip sharpness, and pillar diameter) and testing the various material surfaces, such as silicon, polymer, and metals [81, 105–114]. The nanoprotusive surface topography and the bacterial motility are believed as the two paramount factors to result in the bactericidal efficacy [115, 116]. For the bactericidal effect underlying bacterial motility, several recent studies indicated that the strong focal adhesion of bacterial cells on the tips of nanopillars, enabled by the generation of extracellular polymeric substances (EPS), enhances the cell membrane tension during movement, thereby leading to the death of the bacterial cell [80, 114]. However, no universal mechanism regarding all the factors affecting the bactericidal properties of a nanotextured surface is reported so far. There are some controversial studies regarding the cell rupture mechanism emerged [80, 81, 115], which imply that we need more comprehensive studies to understand the universal mechanism behind bacteria adhesion on the engineered surfaces with nanoprotusive structure.

## Antifouling Nanoporous Surface Formation

An alternative strategy to enhance the antibacterial property is to lower the bacterial attachment *via* nanopore formation on the substrates. The nanoporous surface tends into more hydrophobic based on the Cassie–Baxter model, which leads to the reduction of attached bacterial cells with the increased wettability.

Anodized aluminum oxide with nanoscale pores in diameters of 15 and 20 nm displayed a significant reduction of bacterial attachment and biofilm formation of *E. coli* and *Listeria innocua*. The nanoporous surfaces inhibited flagella-dependent attachment of *E. coli* by suppressing expression of appendages. The antifouling effect of nanoporous surfaces can be explained by the increased net repulsion forces between bacterial cell and substrate, in combination with electrostatic repulsion and surface effective free energy [117]. The report about simple and robust anodizing method to develop nanoporous structure on alumina surfaces brought significant scientific benefits for understanding antibacterial mechanism of the surfaces with nanopores. However, porous anodic aluminum oxide is not applicable for biomedical implants or devices due to its toxicity, mechanical weakness, and low corrosion resistance as compared to other materials.

Implantable polymeric material, polymethyl methacrylate (PMMA), has been tested with the nanoporous surface structure fabricated by nanoimprint lithography for antibacterial properties. The nanoimprinted PMMA surfaces demonstrated the reduced attachment of bacteria as compared to the flat surfaces [118]. However, only a few works have been demonstrated in this area up to date. Some studies of the influence of pore size on the bacterial adhesion yielded conflicting results according to the types of materials and cells [90]. Therefore, development of potential fabrication methods to create nanopores on other biocompatible materials in tunable scale is worth to be investigated, along with a systematic study to understand the adhesion of different types of bacteria.

In section “Nature-Inspired, Nanostructured Surface Development for Antibacterial Properties,” we highlighted several different engineering approaches to create nature-inspired, nanostructured surfaces for antibacterial activities, ranging from the nano- or microscale roughness/patterns, protrusion, and to pores. According to the material types of biomedical surfaces and target functionalities, we need to design the surface engineering methods rationally. Herein, we summarize the types of materials, fabrication methods, characteristic surface features, and corresponding antibacterial properties in Table 1.

## Prospective Approaches

While many advances toward developing antibacterial surfaces have been achieved for several decades, the practical applications of the surfaces for *in vivo* implants or industrial fabrications are still in early stages. So far, material scientists have focused on the development of new surface properties of implantable biomaterials and dem-

**Table 1** A summary of engineering approaches to create biomimetic antibacterial surfaces on diverse types of materials used for biomedical devices

	Nano/micro roughness	Nanoprotusions	Nanopores
<b>Materials</b>	<p><b>Polymer:</b>                      Polypropylene [84, 86] Polyurethane [73]                      Polydimethylsiloxane (PDMS) [87, 88]                      Polyethylene terephthalate (PET) [90]</p> <p><b>Metal:</b>                      Titanium [91, 92]</p>	<p><b>Polymer:</b>                      Epoxy resin [63]                      Polymethyl methacrylate [113]                      Silicon [65, 81, 108, 109]</p> <p><b>Metal:</b>                      Stainless steel [98]                      Titanium [102–107]</p>	<p><b>Polymer:</b>                      Polymethyl methacrylate [118]</p> <p><b>Metal:</b>                      Alumina [117]</p>
<b>Fabrication methods</b>	Reactive ion etching (RIE) [84] Soft lithography [73, 86] Micro-molding [87, 88] Inductively coupled plasma etching [90] Glancing angle deposition [91] Physical vapor deposition [92]	Soft lithography [63] Nanoimprint lithography [113] RIE [65, 81, 104, 108, 109] Electrochemical etching [98] Glancing angle sputter deposition [102] Hydrothermal etching [103, 105] Anodization [106] Thermal oxidation [107]	Nanoimprint lithography [118] Anodization [117]
<b>Surface features</b>	Lotus, Rice leaf-mimicking hierarchical structure [73, 84, 86] Sharkskin riblet-like structure [73, 87, 88] Butterfly wing-mimicking shingle-like structure [73] Nanopillars with low aspect ratios [90, 92]	Gecko skin-mimicking hierarchical hairy structure [63] Insect wing-mimicking nanopillars with various dimensions (diameters: 20 nm–2 µm, Spacing gaps: 50 nm–1800 nm, Heights: 210 nm–2 µm) [65, 80, 98, 102, 104, 106, 108, 109, 113] Protusive nanopikes [107]	Nanopores with diameters from tens to hundreds of nanometers [117, 118]
<b>Antifouling/bactericidal activities against</b>	<p><b>Gram-positive bacteria:</b>  <i>S. aureus</i> [86, 90–92]</p> <p><b>Gram-negative bacteria:</b>  <i>E. coli</i> [84, 86, 87, 90, 92]  <i>H. pylori</i> [90]</p> Others: Zoospore [88], Silicon carbide particles [73]	<p><b>Gram-positive bacteria:</b>  <i>S. mutans</i> [63]  <i>S. aureus</i> [65, 98, 103, 104, 106, 109]  <i>B. subtilis</i> [65]  <i>M. smegmatis</i> [104]</p> <p><b>Gram-negative bacteria:</b>  <i>P. gingivalis</i> [63]  <i>E. coli</i> [81, 98, 102, 104, 107, 108, 113]  <i>P. aeruginosa</i> [65, 81, 103–105, 108, 109]</p>	<p><b>Gram-positive bacteria:</b>  <i>L. innocua</i> [117]</p> <p><b>Gram-negative bacteria:</b>  <i>E. coli</i> [118]  <i>P. aeruginosa</i> [118]</p>
<b>Summary</b>	Nano-roughened or patterned surfaces can reduce the bacterial adhesion, but the efficiency varies from materials and dimension of surface structures	Nanoprotusive surfaces can kill both Gram-negative and Gram-positive bacteria by increasing cell membrane stress. The bactericidal efficiency is dependent on the dimension and geometry of protusive structures	Nanoporous surfaces can inhibit bacterial adhesion while showing excellent antifouling efficacy. More case studies are necessary to understand the relationship between porous dimension and bacterial adhesion with different cell types

onstration of antibacterial properties in lab scale. The biological, fundamental studies on the interactions between microorganisms and surfaces have been conducted separately. Meanwhile, medical doctors have faced challenges to find applicable medical devices that present advanced antibacterial properties without frequent replacement or additional antibiotic treatments. Moving forward, we believe that the multidisciplinary, cooperative efforts will be the primary focus of continued research. Engineers need to advance strategies to create functional surfaces with target antibacterial properties of biomedical devices in a practical scale by active discussions with surgeons and biomedical industry, as well as to improve understanding of the bacteria–surface interactions with collaboration with microbiologists.

The recent accomplishments in mimicking the excellent bactericidal, antifouling natural surfaces *via* different surface treatment techniques offer futuristic biomedical implants and devices. We have reviewed the diverse structural features of the natural surfaces displaying antibacterial activities (i.e., plant leaves, insect wings, and animal skins) on account of the relationship between the surface nanostructure and bactericidal mechanism. We realize that significant variations in the structural dimension and configuration of these natural surfaces, which implies that there is no universal surface structure to exhibit antimicrobial property against all types of bacteria. Current understanding on the pathogenesis of bacteria adhered on the nanotextured surfaces is still limited, and the biomimetic approaches have been recently suggested in this field. Since the future of biomimicking surfaces is promising, establishing the surface–bacteria correlation will be necessary while varying surface structure systematically and testing multiple microorganisms. Also, studies about the long-term effects of the surface textures on biomedical implants in the body are essential before the new methods can be used to inhibit bacterial adhesion.

Given the fast evolution of microorganisms with increasing antibiotic resistance, the development of functional surfaces inspired by nature is of great significance to inhibit pathogenic bacteria adhesion and growth without antibiotic or other chemical treatments. We will need a more comprehensive investigation to develop engineering methods to create the biomimetic structure in large-scale and rapid production for clinical demonstration. Ultimately, such cumulative attempts toward advanced antibacterial surfaces created *via* different engineering approaches will serve not only to enable the development of practical biomedical devices displaying excellent antimicrobial performance but also enhance our understanding of the complex bacteria–surface interactions.

## Summary

We have discussed many facets of surface engineering approaches to create antibacterial properties for biomedical implants and devices, highlighting chemical and physical aspects to inhibit bacterial adhesion and growth, through this chapter.

Traditionally, surface coatings of antifouling polymers using PEG, PNIPAAm, or zwitterionic polymers have been widely employed to prevent protein adsorption ultimately leading to reduced bacterial attachment. However, these polymer coating

approaches can have inherent limitations due to the lack of long-term suppression ability against bacterial colonization. For contact-killing of adhered bacteria, researchers have also developed functionalized polymer coatings that release antibiotics or bleaching agents *via* several different surface modification techniques, which include layer-by-layer deposition, brush formation, and electrospinning. Recent advances in the synthesis of new types of functional polymers or peptides are promising to develop chemically active antimicrobial surfaces with enhanced performance. The fast evolution of bacteria that show high resistance to antibiotics is a growing problem. As another engineering approach to actively inhibit biofilm formation of multidrug-resistant bacteria, we have highlighted several antibacterial inorganic nanoparticles (e.g., Ag, ZnO, CuO, and TiO<sub>2</sub>) and their bactericidal mechanisms. To carry the antimicrobial functions of nanoparticles at the surfaces of biomedical devices, engineers have developed several strategies for designing inorganic–organic hybrid platforms that can present dual activities of antifouling and contact-killing.

The challenges of chemical coatings of the delamination and functionality loss by degradation can be overcome through physical approaches to develop antibacterial physical structure at the surfaces. Inspired by living organisms in nature, which have evolved their structure to survive extreme conditions, we can establish new engineering strategies toward advanced antibacterial materials. Thus, we have reviewed various natural surfaces that present excellent antifouling and bactericidal properties, such as plant leaves, insect wings, and animal skins. Depending on the dimension and configuration of the natural surface structures, they presented bacterial-resistant mechanisms by inhibiting adhesion and rupturing the attached cell membranes. The biomimetic attempts and advances in nanofabrication techniques in recent years have recently accelerated the development of antibacterial surfaces on biomedical implants and devices while gathering intense attention in surface and materials science and engineering. We have reviewed cutting-edge reports in this field to create antifouling, bactericidal surfaces with biomimicking nanostructures (i.e., nano-/microscale roughness, hierarchical structure, protrusive nanopillars, and nanopores) *via* different types of surface treatment methods. Considerable efforts to advance diverse surface engineering approaches will facilitate the development of the next-generation implantable biomedical devices perfectly preventing bacterial infections.

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## References

1. Arsiwala A, Desai P, Patravale V (2014) Recent advances in micro/nanoscale biomedical implants. *J Control Release* 189:25–45. <https://doi.org/10.1016/j.jconrel.2014.06.021>
2. Cloutier M, Mantovani D, Rosei F (2015) Antibacterial coatings: challenges, perspectives, and opportunities. *Trends Biotechnol* 33:637–652. <https://doi.org/10.1016/j.tibtech.2015.09.002>

3. Tuson HH, Weibel DB (2013) Bacteria-surface interactions. *Soft Matter* 9:4368–4380. <https://doi.org/10.1039/c3sm27705d>
4. Jang Y, Park S, Char K (2011) Functionalization of polymer multilayer thin films for novel biomedical applications. *Kor J Chem Eng* 28:1149–1160. <https://doi.org/10.1007/s11814-010-0434-x>
5. Son H, Jang Y, Koo J, Lee JS, Theato P, Char K (2016) Penetration and exchange kinetics of primary alkyl amines applied to reactive poly(pentafluorophenyl acrylate) thin films. *Polym J* 48:487–495. <https://doi.org/10.1038/pj.2016.6>
6. Yoo J, Birke A, Kim J, Jang Y, Song SY, Ryu S, Kim BS, Kim BG, Barz M, Char K (2018) Cooperative catechol-functionalized polypept(o)ide brushes and Ag nanoparticles for combination of protein resistance and antimicrobial activity on metal oxide surfaces. *Biomacromolecules* 19:1602–1613. <https://doi.org/10.1021/acs.biomac.8b00135>
7. Xie Y, Tang C, Wang Z, Xu Y, Zhao W, Sun S, Zhao C (2017) Co-deposition towards mussel-inspired antifouling and antibacterial membranes by using zwitterionic polymers and silver nanoparticles. *J Mater Chem B* 5:7186–7193. <https://doi.org/10.1039/c7tb01516j>
8. Lau KHA, Ren C, Park SH, Szeleifer I, Messersmith PB (2012) An experimental-theoretical analysis of protein adsorption on peptidomimetic polymer brushes. *Langmuir* 28:2288–2298. <https://doi.org/10.1021/la203905g>
9. Rosu C, Jang Y, Jiang L, Champion J (2018) Nature-Inspired and “Water-Skating” Paper and Polyester Substrates Enabled by the Molecular Structure of Poly( $\gamma$ -stearyl- $\alpha$ , 1-glutamate) Homopolymer peptide. *Biomacromolecules* 19:4617–4628. <https://doi.org/10.1021/acs.biomac.8b01312>
10. Chen L, Zeng R, Xiang L, Luo Z, Wang Y (2012) Polydopamine-graft-PEG antifouling coating for quantitative analysis of food proteins by CE. *Anal Methods* 4:2852–2859. <https://doi.org/10.1039/c2ay25129a>
11. Zhang RN, Liu YN, He MR, Su YL, Zhao XT, Elimelech M, Jiang ZY (2016) Antifouling membranes for sustainable water purification: strategies and mechanisms. *Chem Soc Rev* 45:5888–5924. <https://doi.org/10.1039/c5cs00579e>
12. Banerjee I, Pangule RC, Kane RS (2011) Antifouling coatings: recent developments in the design of surfaces that prevent fouling by proteins, bacteria, and marine organisms. *Adv Mater* 23:690–718. <https://doi.org/10.1002/adma.201001215>
13. Kingshott P, Thissen H, Griesser HJ (2002) Effects of cloud-point grafting, chain length, and density of PEG layers on competitive adsorption of ocular proteins. *Biomaterials* 23:2043–2056. [https://doi.org/10.1016/S0142-9612\(01\)00334-9](https://doi.org/10.1016/S0142-9612(01)00334-9)
14. Prime KL, Whitesides GM (1993) Adsorption of proteins onto surfaces containing end-attached oligo(ethylene oxide)—a model system using self-assembled monolayers. *J Am Chem Soc* 115:10714–10721. <https://doi.org/10.1021/ja00076a032>
15. Roosjen A, van der Mei HC, Busscher HJ, Norde W (2004) Microbial adhesion to poly(ethylene oxide) brushes: influence of polymer chain length and temperature. *Langmuir* 20:10949–10955. <https://doi.org/10.1021/la0484691>
16. Lau KHA, Sileika TS, Park SH, Sousa AML, Burch P, Szeleifer I, Messersmith PB (2015) Molecular design of antifouling polymer brushes using sequence-specific peptoids. *Adv Mater Interfaces* 2:1400225. <https://doi.org/10.1002/Admi.201400225>
17. Lee SJ, Heo DN, Lee HR, Lee D, Yu SJ, Park SA, Ko WK, Park SW, Im SG, Moon JH, Kwon IK (2015) Biofunctionalized titanium with anti-fouling resistance by grafting thermo-responsive polymer brushes for the prevention of peri-implantitis. *J Mater Chem B* 3:5161–5165. <https://doi.org/10.1039/c5tb00611b>
18. Chelmowski R, Koster SD, Kerstan A, Prekelt A, Grunwald C, Winkler T, Metzler-Nolte N, Terfort A, Woll C (2008) Peptide-based SAMs that resist the adsorption of proteins. *J Am Chem Soc* 130:14952–14953. <https://doi.org/10.1021/ja8065754>
19. Le NCH, Gubala V, Gandhiraman RP, Daniels S, Williams DE (2011) Evaluation of different nonspecific binding blocking agents deposited inside poly(methyl methacrylate) microfluidic flow-cells. *Langmuir* 27:9043–9051. <https://doi.org/10.1021/la2011502>

20. Chuang HF, Smith RC, Hammond PT (2008) Polyelectrolyte multilayers for tunable release of antibiotics. *Biomacromolecules* 9:1660–1668. <https://doi.org/10.1021/bm800185h>
21. Nystrom L, Stromstedt AA, Schmidtchen A, Malmsten M (2018) Peptide-loaded microgels as antimicrobial and anti-inflammatory surface coatings. *Biomacromolecules* 19:3456–3466. <https://doi.org/10.1021/acs.biomac.8b00776>
22. Kaur R, Liu S (2016) Antibacterial surface design—contact kill. *Prog Surf Sci* 91:136–153. <https://doi.org/10.1016/j.progsurf.2016.09.001>
23. Tiller JC, Liao C-J, Lewis K, Klibanov AM (2001) Designing surfaces that kill bacteria on contact. *Proc Natl Acad Sci* 98:5981–5985. <https://doi.org/10.1073/pnas.111143098>
24. Tiller JC, Lee SB, Lewis K, Klibanov AM (2002) Polymer surfaces derivatized with poly(vinyl-N-hexylpyridinium) kill airborne and waterborne bacteria. *Biotechnol Bioeng* 79:465–471. <https://doi.org/10.1002/bit.10299>
25. Wang J, Vermerris W (2016) Antimicrobial nanomaterials derived from natural products—a review. *Materials (Basel)* 9:255. <https://doi.org/10.3390/ma9040255>
26. Correia VG, Ferraria AM, Pinho MG, Aguiar-Ricardo A (2015) Antimicrobial contact-active oligo(2-oxazoline)s-grafted surfaces for fast water disinfection at the point-of-use. *Biomacromolecules* 16:3904–3915. <https://doi.org/10.1021/acs.biomac.5b01243>
27. Rabea EI, Badawy MET, Stevens CV, Smagghe G, Steurbaut W (2003) Chitosan as antimicrobial agent: applications and mode of action. *Biomacromolecules* 4:1457–1465. <https://doi.org/10.1021/bm034130m>
28. Ohkawa K, Minato KI, Kumagai G, Hayashi S, Yamamoto H (2006) Chitosan nanofiber. *Biomacromolecules* 7:3291–3294. <https://doi.org/10.1021/bm0604395>
29. Elsabee MZ, Naguib HF, Morsi RE (2012) Chitosan based nanofibers, review. *Mater Sci Eng C* 32:1711–1726. <https://doi.org/10.1016/j.msec.2012.05.009>
30. Torres-Giner S, Ocio MJ, Lagaron JM (2008) Development of active antimicrobial fiber based chitosan polysaccharide nanostructures using electrospinning. *Eng Life Sci* 8:303–314. <https://doi.org/10.1002/elsc.200700066>
31. Fernandes SCM, Sadocco P, Alonso-Varona A, Palomares T, Eceiza A, Silvestre AJD, Aki Mondragon I, Freire CSR (2013) Bioinspired antimicrobial and biocompatible bacterial cellulose membranes obtained by surface functionalization with aminoalkyl groups. *ACS Appl Mater Interfaces* 5:3290–3297. <https://doi.org/10.1021/am400338n>
32. Roemhild K, Wiegand C, Hipler U, Heinze T (2013) Novel bioactive amino-functionalized cellulose nanofibers. *Macromol Rapid Commun* 34:1767–1771. <https://doi.org/10.1002/marc.201300588>
33. Roy D, Knapp JS, Guthrie JT, Perrier S (2008) Antibacterial cellulose fiber via RAFT surface graft polymerization. *Biomacromolecules* 9:91–99. <https://doi.org/10.1021/bm700849j>
34. Heunis T, Bshena O, Klumperman B, Dicks L (2011) Release of bacteriocins from nanofibers prepared with combinations of poly(D,L-lactide) (PDLLA) and poly(ethylene oxide) (PEO). *Int J Mol Sci* 12:2158–2173. <https://doi.org/10.3390/ijms12042158>
35. Viana JFC, Carrijo J, Freitas CG, Paul A, Alcaraz J, Lacorte CC, Migliolo L, Andrade CA, Falcão R, Santos NC, Gonçalves S, Otero-González AJ, Khademhosseini A, Dias SC, Franco OL (2015) Antifungal nanofibers made by controlled release of sea animal derived peptide. *Nanoscale* 7:6238–6246. <https://doi.org/10.1039/c5nr00767d>
36. Gatti JW, Smithgall MC, Paranjape SM, Rolfes RJ, Paranjape M (2013) Using electrospun poly(ethylene-oxide) nanofibers for improved retention and efficacy of bacteriolytic antibiotics. *Biomed Microdevices* 15:887–893. <https://doi.org/10.1007/s10544-013-9777-5>
37. Baptista PV, McCusker MP, Carvalho A, Ferreira DA, Mohan NM, Martins M, Fernandes AR (2018) Nano-strategies to fight multidrug resistant bacteria—“A Battle of the Titans”. *Front Microbiol* 9:1441. <https://doi.org/10.3389/fmicb.2018.01441>
38. Wang L, Hu C, Shoa L (2017) The antimicrobial activity of nanoparticles: present situation and prospects for the future. *Int J Nanomed* 12:1227–1249. <https://doi.org/10.2147/IJN.S121956>
39. Le Ouay B, Stellacci F (2015) Antibacterial activity of silver nanoparticles: a surface science insight. *Nano Today* 10:339–354. <https://doi.org/10.1016/j.nantod.2015.04.002>
40. Ramalingam B, Parandhaman T, Das SK (2016) Antibacterial effects of biosynthesized silver nanoparticles on surface ultrastructure and nanomechanical properties of gram-negative bac-

- teria viz *Escherichia coli* and *Pseudomonas aeruginosa*. *ACS Appl Mater Interfaces* 8:4963–4976. <https://doi.org/10.1021/acsami.6b00161>
41. Duran N, Marcato PD, De Conti R, Alves OL, Costa FTM, Brocchi M (2010) Potential use of silver nanoparticles on pathogenic bacteria, their toxicity and possible mechanisms of action. *J Braz Chem Soc* 21:949–959. <https://doi.org/10.1590/S0103-50532010000600002>
  42. Salem W, Leitner DR, Zingl FG, Schratler G, Prassl R, Goessler W, Reidl J, Schild S (2015) Antibacterial activity of silver and zinc nanoparticles against *Vibrio cholerae* and enterotoxigenic *Escherichia coli*. *Int J Med Microbiol* 305:85–95. <https://doi.org/10.1016/j.ijmm.2014.11.005>
  43. Hemeg HA (2017) Nanomaterials for alternative antibacterial therapy. *Int J Nanomedicine* 12:8211–8225. <https://doi.org/10.2147/IJN.S132163>
  44. Slavin YN, Asnis J, Hafeli UO, Bach H (2017) Metal nanoparticles: understanding the mechanisms behind antibacterial activity. *J Nanobiotechnol* 15:56. <https://doi.org/10.1186/s12951-017-0308-z>
  45. Cui Y, Zhao YY, Tian Y, Zhang W, Lu XY, Jiang XY (2012) The molecular mechanism of action of bactericidal gold nanoparticles on *Escherichia coli*. *Biomaterials* 33:2327–2333. <https://doi.org/10.1016/j.biomaterials.2011.11.057>
  46. Shamaila S, Zafar N, Riaz S, Sharif R, Nazir J, Naseem S (2016) Gold nanoparticles: an efficient antimicrobial agent against enteric bacterial human pathogen. *Nanomaterials* 6:71. <https://doi.org/10.3390/nano6040071>
  47. Rastogi L, Kora AJ, Arunachalam J (2012) Highly stable, protein capped gold nanoparticles as effective drug delivery vehicles for amino-glycosidic antibiotics. *Materials Science and Engineering: C* 32(6):1571–1577. <https://doi.org/10.1016/J.MSEC.2012.04.044>
  48. Roshmi T, Soumya KR, Jyothis M, Radhakrishnan EK (2015) Effect of biofabricated gold nanoparticle-based antibiotic conjugates on minimum inhibitory concentration of bacterial isolates of clinical origin. *Gold Bulletin* 48(1–2):63–71. <https://doi.org/10.1007/s13404-015-0162-4>
  49. Zeng Q, Zhu Y, Yu B, Sun Y, Ding X, Xu C, Wu YW, Tang Z, Xu FJ (2018) Antimicrobial and antifouling polymeric agents for surface functionalization of medical implants. *Biomacromolecules* 9:2805–2811. <https://doi.org/10.1021/acs.biomac.8b00399>
  50. Qayyum S, Oves M, Khan AU (2017) Obliteration of bacterial growth and biofilm through ROS generation by facilely synthesized green silver nanoparticles. *PLoS One* 12:e0181363. <https://doi.org/10.1371/journal.pone.0181363>
  51. Jankauskaite V, Lazauskas A, Griskonis E, Lissauskaite A, Zukiene K (2017) UV-curable aliphatic silicone acrylate organic-inorganic hybrid coatings with antibacterial activity. *Molecules* 22:964. <https://doi.org/10.3390/molecules22060964>
  52. Xu DQ, Su YL, Zhao LL, Meng FC, Liu C, Guan YY, Zhang JY, Luo JB (2017) Antibacterial and antifouling properties of a polyurethane surface modified with perfluoroalkyl and silver nanoparticles. *J Biomed Mater Res Pt A* 105:531–538. <https://doi.org/10.1002/jbm.a.35929>
  53. Prasannaraj G, Venkatchalam P (2017) Enhanced antibacterial, anti-biofilm and antioxidant (ROS) activities of biomolecules engineered silver nanoparticles against clinically isolated gram positive and gram negative microbial pathogens. *J Clust Sci* 28:645–664. <https://doi.org/10.1007/s10876-017-1160-x>
  54. Gupta K, Barua S, Hazarika SN, Manhar AK, Nath D, Karak N, Namsa ND, Mukhopadhyay R, Kalia VC, Mandal M (2014) Green silver nanoparticles: enhanced antimicrobial and anti-biofilm activity with effects on DNA replication and cell cytotoxicity. *RSC Adv* 4:52845–52855. <https://doi.org/10.1039/c4ra08791g>
  55. Woo S, Butt HJ (2017) A photocatalytically active lubricant-impregnated surface. *Angew Chem Int Ed* 56:4965–4969. <https://doi.org/10.1002/anie.201611277>
  56. Shankar S, Teng XN, Li GB, Rhim JW (2015) Preparation, characterization, and antimicrobial activity of gelatin/ZnO nanocomposite films. *Food Hydrocoll* 45:264–271. <https://doi.org/10.1016/j.foodhyd.2014.12.001>
  57. Solga A, Cerman Z, Striffler BF, Spaeth M, Barthlott W (2007) The dream of staying clean: lotus and biomimetic surfaces. *Bioinspir Biomim* 2:S126–S134. <https://doi.org/10.1088/1748-3182/2/4/S02>



58. Watson GS, Green DW, Schwarzkopf L, Li X, Cribb BW, Myhra S, Watson JA (2015) A gecko skin micro/nano structure—a low adhesion, superhydrophobic, anti-wetting, self-cleaning, biocompatible, antibacterial surface. *Acta Biomater* 21:109–122. <https://doi.org/10.1016/j.actbio.2015.03.007>
59. Bixler GD, Bhushan B (2013) Fluid drag reduction with shark-skin riblet inspired microstructured surfaces. *Adv Funct Mater* 23:4507–4528. <https://doi.org/10.1002/adfm.201203683>
60. Watson GS, Cribb BW, Watson JA (2010) How micro/nanoarchitecture facilitates anti-wetting: an elegant hierarchical design on the termite wing. *ACS Nano* 4:129–136. <https://doi.org/10.1021/nn900869b>
61. Wagner T, Neinhuis C, Barthlott W (1996) Wettability and contaminability of insect wings as a function of their surface sculptures. *Acta Zool* 77:213–225. <https://doi.org/10.1111/j.1463-6395.1996.tb01265.x>
62. Neinhuis C, Barthlott W (1997) Characterization and distribution of water-repellent, self-cleaning plant surfaces. *Ann Bot* 79:667–677. <https://doi.org/10.1006/ANBO.1997.0400>
63. Li X, Cheung GS, Watson GS, Watson JA, Lin S, Schwarzkopf L, Green DW (2016) The nanotipped hairs of gecko skin and biotemplated replicas impair and/or kill pathogenic bacteria with high efficiency. *Nanoscale* 8:18860–18869. <https://doi.org/10.1039/c6nr05046h>
64. Ivanova EP, Hasan J, Webb HK, Truong VK, Watson GS, Watson JA, Baulin VA, Pogodin S, Wang JY, Tobin MJ, Löbbecke C, Crawford RJ (2012) Natural bactericidal surfaces: mechanical rupture of *Pseudomonas aeruginosa* cells by cicada wings. *Small* 8:2489–2494. <https://doi.org/10.1002/smll.201200528>
65. Ivanova EP, Hasan J, Webb HK, Gervinskis G, Juodkazis S, Truong VK, Wu AHF, Lamb RN, Baulin VA, Watson GS, Watson JA, Mainwaring DE, Crawford RJ (2013) Bactericidal activity of black silicon. *Nat Commun* 4:2838. <https://doi.org/10.1038/ncomms3838>
66. Jaggessar A, Shahali H, Mathew A, Yarlagadda PKDV (2017) Bio-mimicking nano and micro-structured surface fabrication for antibacterial properties in medical implants. *J Nanobiotechnol* 15:64. <https://doi.org/10.1186/s12951-017-0306-1>
67. Ma J, Sun Y, Gleichauf K, Lou J, Li Q (2011) Nanostructure on Taro Leaves Resists Fouling by Colloids and Bacteria under Submerged Conditions. *Langmuir* 27 (16):10035–10040
68. Guo Z, Liu W (2007) Biomimic from the superhydrophobic plant leaves in nature: binary structure and unitary structure. *Plant Sci* 172:1103–1112. <https://doi.org/10.1016/j.plantsci.2007.03.005>
69. Feng L, Li S, Li Y, Li H, Zhang L, Zhai J, Song Y, Liu B, Jiang L, Zhu D (2002) Superhydrophobic surfaces: from natural to artificial. *Adv Mater* 14:1857–1860. <https://doi.org/10.1002/adma.200290020>
70. Cassie ABD, Baxter S (1944) Wettability of porous surfaces. *Trans Faraday Soc* 40:546–551. <https://doi.org/10.1039/tf9444000546>
71. Dunder Arisoy F, Kolewe KW, Homyak B, Kurtz IS, Schiffman JD, Watkins JJ (2018) Bioinspired photocatalytic shark-skin surfaces with antibacterial and antifouling activity via nanoimprint lithography. *ACS Appl Mater Interfaces* 10:20055–20063. <https://doi.org/10.1021/acsami.8b05066>
72. Bixler GD, Bhushan B (2015) Rice and butterfly wing effect inspired low drag and antifouling surfaces: a review. *Crit Rev Solid State Mater Sci* 40:1–37. <https://doi.org/10.1080/10408436.2014.917368>
73. Bixler GD, Bhushan B (2012) Bioinspired rice leaf and butterfly wing surface structures combining shark skin and lotus effects. *Soft Matter* 8:11271–11284. <https://doi.org/10.1039/c2sm26655e>
74. Pogodin S, Hasan J, Baulin VA, Webb HK, Truong VK, Phong Nguyen TH, Boshkovikj V, Fluke CJ, Watson GS, Watson JA, Crawford RJ, Ivanova EP (2013) Biophysical model of bacterial cell interactions with nanopatterned cicada wing surfaces. *Biophys J* 104:835–840. <https://doi.org/10.1016/j.bpj.2012.12.046>
75. Hasan J, Webb HK, Truong VK, Pogodin S, Baulin VA, Watson GS, Watson JA, Crawford RJ, Ivanova EP (2013) Selective bactericidal activity of nanopatterned superhydrophobic cicada *Psaltoda claripennis* wing surfaces. *Appl Microbiol Biotechnol* 97:9257–9262. <https://doi.org/10.1007/s00253-012-4628-5>

76. Kelleher SM, Habimana O, Lawler J, O'reilly B, Daniels S, Casey E, Cowley A (2016) Cicada wing surface topography: an investigation into the bactericidal properties of nanostructural features. *ACS Appl Mater Interfaces* 8:14966–14974. <https://doi.org/10.1021/acsami.5b08309>
77. Ivanova EP, Nguyen SH, Webb HK, Hasan J, Truong VK, Lamb RN, Duan X, Tobin MJ, Mahon PJ, Crawford RJ (2013) Molecular organization of the nanoscale surface structures of the dragonfly *Hemianax papuensis* wing epicuticle. *PLoS One* 8:e67893. <https://doi.org/10.1371/journal.pone.0067893>
78. Selvakumar R, Karuppanan KK, Pezhinkattil R (2012) Analysis on surface nanostructures present in hindwing of dragon fly (*Sympetrum vulgatum*) using atomic force microscopy. *Micron* 43:1299–1303. <https://doi.org/10.1016/J.MICRON.2011.10.017>
79. Mainwaring DE, Nguyen SH, Webb H, Jakubov T, Tobin M, Lamb RN, Wu AHF, Marchant R, Crawford RJ, Ivanova EP (2016) The nature of inherent bactericidal activity: insights from the nanotopology of three species of dragonfly. *Nanoscale* 8:6527–6534. <https://doi.org/10.1039/c5nr08542j>
80. Bandara CD, Singh S, Afara IO, Wolff A, Tesfamichael T, Ostrikov K, Oloyede A (2017) Bactericidal effects of natural nanotopography of dragonfly wing on *Escherichia coli*. *ACS Appl Mater Interfaces* 9:6746–6760. <https://doi.org/10.1021/acsami.6b13666>
81. Linklater DP, Juodkazis S, Rubanov S, Ivanova EP (2017) Comment on “Bactericidal effects of natural nanotopography of dragonfly wing on *Escherichia coli*”. *ACS Appl Mater Interfaces* 9:29387–29393. <https://doi.org/10.1021/acsami.7b05707>
82. Watson GS, Cribb BW, Schwarzkopf L, Watson JA (2015) Contaminant adhesion (aerial/ground biofouling) on the skin of a gecko. *J R Soc Interface* 12:20150318. <https://doi.org/10.1098/rsif.2015.0318>
83. Hayes MJ, Levine TP, Wilson RH (2016) Identification of nanopillars on the cuticle of the aquatic larvae of the drone fly (diptera: Syrphidae). *J Insect Sci* 16:1–7. <https://doi.org/10.1093/jisesa/iew019>
84. Kayes MI, Galante AJ, Stella NA, Haghanifar S, Shanks RMQ, Leu PW (2018) Stable lotus leaf-inspired hierarchical, fluorinated polypropylene surfaces for reduced bacterial adhesion. *React Funct Polym* 128:40–46. <https://doi.org/10.1016/J.REACTFUNCTPOLYM.2018.04.013>
85. Wolfe DB, Love JC, Whitesides GM (2004) Nanostructures replicated by polymer molding. Marcel Dekker, New York
86. Jafari Nodoushan E, Ebrahimi NG, Ayazi M (2017) An anti-bacterial approach to nanoscale roughening of biomimetic rice-like pattern PP by thermal annealing. *Appl Surf Sci* 423:1054–1061. <https://doi.org/10.1016/J.APSUSC.2017.06.193>
87. Munther M, Palma T, Angeron IA, Salari S, Ghassemi H, Vasefi M, Beheshti A, Davami K (2018) Microfabricated biomimetic placoid scale-inspired surfaces for antifouling applications. *Appl Surf Sci* 453:166–172. <https://doi.org/10.1016/j.apsusc.2018.05.030>
88. Carman ML, Estes TG, Feinberg AW, Schumacher JF, Wilkerson W, Wilson LH, Callow ME, Callow JA, Brennan AB (2006) Engineered antifouling microtopographies—correlating wettability with cell attachment. *Biofouling* 22:11–21. <https://doi.org/10.1080/08927010500484854>
89. Liu W, Liu X, Fangteng J, Wang S, Fang L, Shen H, Xiang S, Sun H, Yang B (2014) Bioinspired polyethylene terephthalate nanocone arrays with underwater superoleophobicity and anti-bioadhesion properties. *Nanoscale* 6:13845–13853. <https://doi.org/10.1039/c4nr04471a>
90. Jin L, Guo W, Xue P, Gao H, Zhao M, Zheng C, Zhang Y, Han D (2015) Quantitative assay for the colonization ability of heterogeneous bacteria on controlled nanopillar structures. *Nanotechnology* 26:055702. <https://doi.org/10.1088/0957-4484/26/5/055702>
91. Izquierdo-Barba I, García-Martín JM, Álvarez R, Palmero A, Esteban J, Pérez-Jorge C, Arcos D, Vallet-Regí M (2015) Nanocolumnar coatings with selective behavior towards osteoblast and *Staphylococcus aureus* proliferation. *Acta Biomater* 15:20–28. <https://doi.org/10.1016/J.ACTBIO.2014.12.023>

92. Lüdecke C, Roth M, Yu W, Horn U, Bossert J, Jandt KD (2016) Nanorough titanium surfaces reduce adhesion of *Escherichia coli* and *Staphylococcus aureus* via nano adhesion points. *Colloids Surf B Biointerfaces* 145:617–625. <https://doi.org/10.1016/J.COLSURFB.2016.05.049>
93. Wu S, Zhang B, Liu Y, Suo X, Li H (2018) Influence of surface topography on bacterial adhesion: a review (review). *Biointerphases* 13:060801. <https://doi.org/10.1116/1.5054057>
94. Desrousseaux C, Sautou V, Descamps S, Traoré O (2013) Modification of the surfaces of medical devices to prevent microbial adhesion and biofilm formation. *J Hosp Infect* 85:87–93. <https://doi.org/10.1016/J.JHIN.2013.06.015>
95. DEWIDAR MM, KHALIL KA, LIM JK (2007) Processing and mechanical properties of porous 316L stainless steel for biomedical applications. *Trans Nonferrous Met Soc Chin* 17:468–473. [https://doi.org/10.1016/S1003-6326\(07\)60117-4](https://doi.org/10.1016/S1003-6326(07)60117-4)
96. Bagherifard S, Hickey DJ, de Luca AC, Malheiro VN, Markaki AE, Guagliano M, Webster TJ (2015) The influence of nanostructured features on bacterial adhesion and bone cell functions on severely shot peened 316L stainless steel. *Biomaterials* 73:185–197. <https://doi.org/10.1016/j.biomaterials.2015.09.019>
97. Sundararaj K, Bangaru M, Mohan B (2017) In vitro biocompatibility study on stainless steel 316L after nano finishing. ASME Paper No. IMECE2017-72606: V003T04A064. <https://doi.org/10.1115/IMECE2017-72606>
98. Jang Y, Choi WT, Johnson CT, García AJ, Singh PM, Breedveld V, Hess DW, Champion JA (2018) Inhibition of bacterial adhesion on nanotextured stainless steel 316L by electrochemical etching. *ACS Biomater Sci Eng* 4:90–97. <https://doi.org/10.1021/acsbiomaterials.7b00544>
99. Lin Y, Gallucci GO, Buser D, Bosshardt D, Belser UC, Yelick PC (2011) Bioengineered periodontal tissue formed on titanium dental implants. *J Dent Res* 90:251–256. <https://doi.org/10.1177/0022034510384872>
100. Michelle Grandin H, Berner S, Dard M (2012) A review of titanium zirconium (TiZr) alloys for use in endosseous dental implants. *Materials (Basel)* 5:1348–1360. <https://doi.org/10.3390/ma5081348>
101. Neoh KG, Hu X, Zheng D, Kang ET (2012) Balancing osteoblast functions and bacterial adhesion on functionalized titanium surfaces. *Biomaterials* 33:2813–2822. <https://doi.org/10.1016/j.biomaterials.2012.01.018>
102. Sengstock C, Lopian M, Motemani Y, Borgmann A, Khare C, Buenconsejo PJS, Schildhauer TA, Ludwig A, Köller M (2014) Structure-related antibacterial activity of a titanium nanostructured surface fabricated by glancing angle sputter deposition. *Nanotechnology* 25:195101. <https://doi.org/10.1088/0957-4484/25/19/195101>
103. Bhadra CM, Khanh Truong V, Pham VTH, Al Kobaisi M, Seniutinas G, Wang JY, Juodkazis S, Crawford RJ, Ivanova EP (2015) Antibacterial titanium nano-patterned arrays inspired by dragonfly wings. *Sci Rep* 5:16817. <https://doi.org/10.1038/srep16817>
104. Hasan J, Jain S, Chatterjee K (2017) Nanoscale topography on black titanium imparts multi-biofunctional properties for orthopedic applications. *Sci Rep* 7:41118. <https://doi.org/10.1038/srep41118>
105. Tsimbouri PM, Fisher L, Holloway N, Sjöstrom T, Nobbs AH, Meek RMD, Su B, Dalby MJ (2016) Osteogenic and bactericidal surfaces from hydrothermal titanium nanowires on titanium substrates. *Sci Rep* 6:36875. <https://doi.org/10.1038/srep36857>
106. Hizal F, Zhuk I, Sukhishvili S, Busscher HJ, Van Der Mei HC, Choi CH (2015) Impact of 3D hierarchical nanostructures on the antibacterial efficacy of a bacteria-triggered self-defensive antibiotic coating. *ACS Appl Mater Interfaces* 7:20304–20313. <https://doi.org/10.1021/acsami.5b05947>
107. Sjöström T, Nobbs AH, Su B (2016) Bactericidal nanospine surfaces via thermal oxidation of Ti alloy substrates. *Mater Lett* 167:22–26. <https://doi.org/10.1016/j.matlet.2015.12.140>
108. Wang X, Bhadra CM, Yen Dang TH, Buividas R, Wang J, Crawford RJ, Ivanova EP, Juodkazis S (2016) A bactericidal microfluidic device constructed using nano-textured black silicon. *RSC Adv* 6:26300–26306. <https://doi.org/10.1039/c6ra03864f>

109. Pham VTH, Truong VK, Orłowska A, Ghanaati S, Barbeck M, Booms P, Fulcher AJ, Bhadra CM, Buividas R, Baulin V, James Kirkpatrick C, Doran P, Mainwaring DE, Juodkakis S, Crawford RJ, Ivanova EP (2016) Race for the surface: eukaryotic cells can win. *ACS Appl Mater Interfaces* 8:22025–22031. <https://doi.org/10.1021/acsami.6b06415>
110. Li X (2015) Bactericidal mechanism of nanopatterned surfaces. *Phys Chem Chem Phys* 18:1311–1316. <https://doi.org/10.1039/c5cp05646b>
111. Xue F, Liu J, Guo L, Zhang L, Li Q (2015) Theoretical study on the bactericidal nature of nanopatterned surfaces. *J Theor Biol* 385:1–7. <https://doi.org/10.1016/j.jtbi.2015.08.011>
112. Nowlin K, Boseman A, Covell A, LaJeunesse D (2014) Adhesion-dependent rupturing of *Saccharomyces cerevisiae* on biological antimicrobial nanostructured surfaces. *J R Soc Interface* 12:20140999. <https://doi.org/10.1098/rsif.2014.0999>
113. Dickson MN, Liang EI, Rodriguez LA, Vollereaux N, Yee AF (2015) Nanopatterned polymer surfaces with bactericidal properties. *Biointerphases* 10:021010. <https://doi.org/10.1116/1.4922157>
114. Michalska M, Gambacorta F, Divan R, Aranson IS, Sokolov A, Noirot P, Laible PD (2018) Tuning antimicrobial properties of biomimetic nanopatterned surfaces. *Nanoscale* 10:6639–6650. <https://doi.org/10.1039/c8nr00439k>
115. Lin N, Berton P, Moraes C, Rogers RD, Tufenkji N (2018) Nanodarts, nanoblades, and nanospikes: mechano-bactericidal nanostructures and where to find them. *Adv Colloid Interface Sci* 252:55–68. <https://doi.org/10.1016/j.cis.2017.12.007>
116. Elbourne A, Crawford RJ, Ivanova EP (2017) Nano-structured antimicrobial surfaces: from nature to synthetic analogues. *J Colloid Interface Sci* 508:603–616. <https://doi.org/10.1016/j.jcis.2017.07.021>
117. Feng G, Cheng Y, Wang SY, Hsu LC, Feliz Y, Borca-Tasciuc DA, Worobo RW, Moraru CI (2014) Alumina surfaces with nanoscale topography reduce attachment and biofilm formation by *Escherichia coli* and *Listeria* spp. *Biofouling* 30:1253–1268. <https://doi.org/10.1080/08927014.2014.976561>
118. Kim S, Jung UT, Kim SK, Lee JH, Choi HS, Kim CS, Jeong MY (2015) Nanostructured multifunctional surface with antireflective and antimicrobial characteristics. *ACS Appl Mater Interfaces* 7:326–331. <https://doi.org/10.1021/am506254r>