# Antibacterial Coatings Based on Bioinspired Polymer Systems

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by

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1. Reviewer: Prof. Dr. Nan Ma, Freie Universität Berlin

2. Reviewer: Prof. Dr. Rainer Haag, Freie Universität Berlin

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# 1 Introduction

## 1.1 The requirement for antibacterial materials

Metallic implants are widely used in the clinic. Figure 1 shows a wide variety of implants consisting of orthopaedic implants, maxillofacial bone implants, stents, spine cages, etc.[1] Biofunctional design of the metal surface to optimize the application of implants has drawn a lot of attention. In the last decades, more and more biological functions, such as enhanced biocompatibility, sufficient strength, osteogenic ability, and antibacterial effect, have been introduced to develop innovative implants.[2-5]

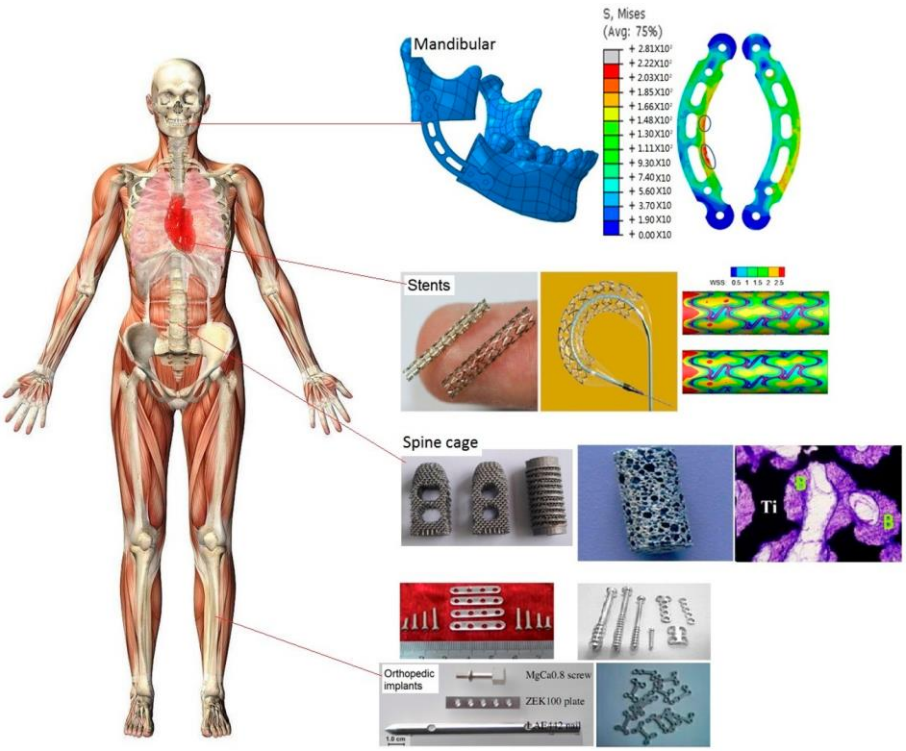



**Figure 1**. Different clinic applications for metal implants. Reprint with permission from ref.[1]. This figure by Yang et al. is licensed under CC BY 4.0.

However, there are always some postsurgical complications occurring after orthopaedic implantation. One major concern is bacterial infection, especially antibiotic-resistant bacterial infections.[6] Bacterial infection usually leads to the failure of the orthopaedic surgery, increasing the cost of the treatment and the patients' suffering. Avoiding this problem has been an urgent task to the researchers worldwide.

In addition to the bacterial infection, implantable device-associated infection is another challenge to the orthopaedic implantation, which results from bacterial adhesion and subsequent biofilm formation (Figure 2) on the implant surface.[7-10] After biofilm formation on the surfaces, the bacteria inside the biofilm have developed more tolerance to the outside environment including the antibiotics, host immune responses, and other external conditions.[8] Therefore, the bacteria within a biofilm are more resistant compared to their planktonic counterparts, increasing the difficulty to eliminate the biofilm. According to the literature, more than 60% of chronic infections are related to biofilm formation.[11, 12] The simplest way to remove the biofilm is to deal with the secondary surgery to remove the implants, which significantly increases both the healthcare cost and patients' debility. To effectively solve this problem, multifunctional materials that can kill the bacteria and meanwhile avoid bacterial adhesion on the surface are urgently needed.

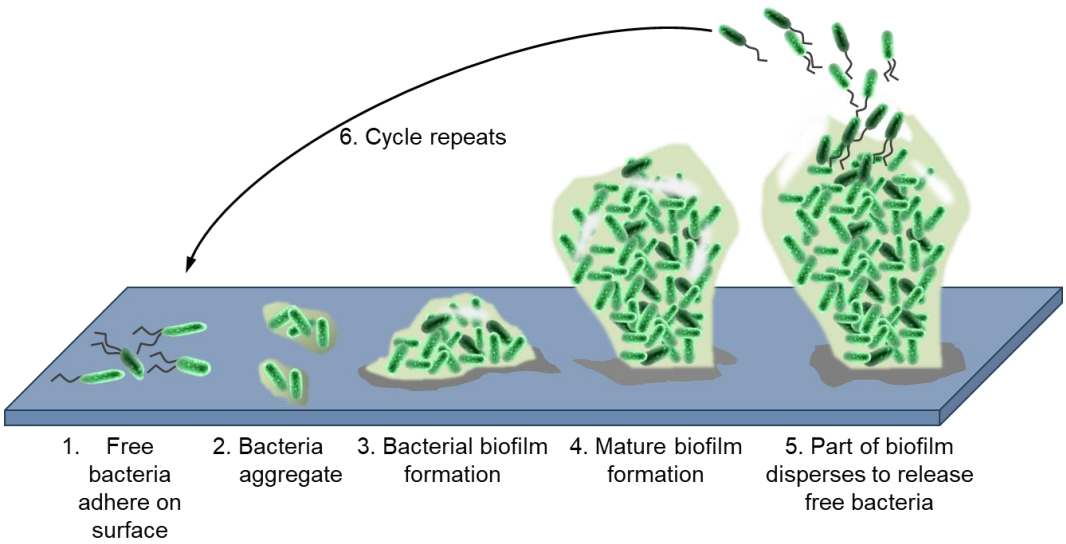



**Figure 2**. Stages of biofilm formation on surfaces.

## 1.2 Typical antibacterial surface treatment methods

There are mainly three strategies of the antibacterial surface treatment, namely, antifouling surfaces, biocide-modified surfaces, and the surfaces with the combination of the last two properties.

### 1.2.1 Antifouling surfaces

Bacterial attachment on the surfaces of implants usually leads to the fouling of the implants, followed by the biofilm formation and bacterial infection.[13] Under these conditions, biofunctional surfaces are blocked and then the biofunctionality of the implants is significantly decreased. Meanwhile, covered by the biofilm, microorganism corrosion occurs on the metal substrate, which significantly reduces the lifetime of the implants. However, by reducing the bacterial attachment, the amount of the bacteria on the surface will be controlled and this fouling problem will be effectively avoided.

Bacterial attachment on the surfaces of biomaterials is typically based on hydrophobic and electrostatic interactions. By controlling the hydrophilicity, roughness, and surface morphology, the surfaces present an antifouling ability.[14, 15] In recent decades, hydrophilic polymers, hydrophobic polymers, featured surfaces, superhydrophobic surfaces, and zwitterionic polymers[16, 17] have been commonly applied in antifouling treatments.[18]

The hydrophilic polymers, such as oligo-/poly(ethylene glycol),[16, 19] oligo-/polyglycerols,[20] polyamides and polysaccharides,[18] are widely used in the antifouling coatings. The poly(ethylene glycol) (PEG)-based polymers were considered as the “gold standard.” A wide variety of PEG polymer based coatings have been studied presenting the antifouling effect (Figure 3).[21, 22] For instance, in Ozcelik et al.’s work, the PEG-based polymer can effectively reduce the bacterial adhesion (Figure 3a). And Tugulu et al. investigated the antifouling ability of PEG derivative based polymer brushes against the nonspecific protein adsorption, shown in Figure 3b.

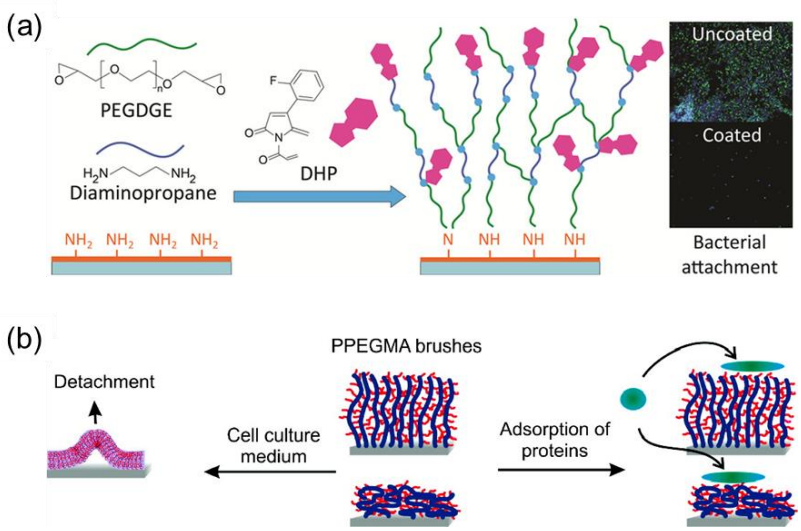



**Figure 3**. (a) PEG-based coatings reduce bacterial adhesion. Reprint with permission from ref. [21]. Copyright 2017 American Chemical Society. (b) Stability and antifouling ability of PEG based polymer brushes. Reprint with permission from ref. [22]. Copyright 2008 American Chemical Society.

In the last few decades, new studies on the alternatives to PEG have attracted more and more interest from the researchers. One of the most important alternatives is polyglycerol (PG).[23] For example, hyperbranched polyglycerol (hPG) is being successfully used for antifouling applications.[24-27] HPG is a highly flexible branched aliphatic polyether backbone with multiple hydrophilic functional groups, based on which hPG works as an alternative for PEG with excellent antifouling properties. A mussel foot protein-inspired hPG derivative that have been modified with amine and catechol groups is easily post-modified and then be applied as various antifouling materials. In the work by Wei et al.,[27] hPG modified with different amounts of catechol groups were applied to form universal antifouling coatings (Figure 4).

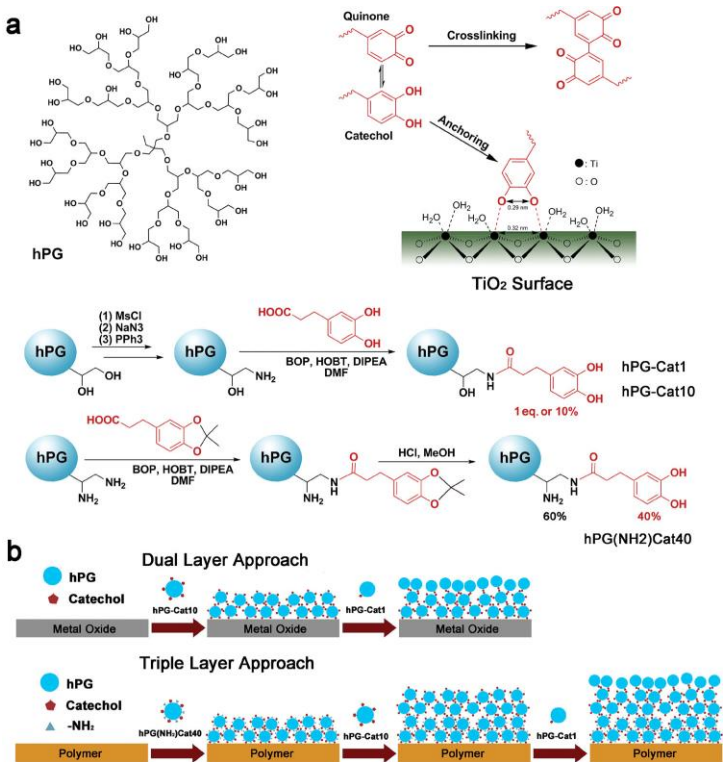



**Figure 4**. (a) Synthesis approach of catechol-modified hPG. (b) Preparation of the multi layers architecture coatings on different substrates. Reprint with permission from ref.[27]. Copyright 2014 WILEY-VCH.

In addition to the hydrophilic polymers, hydrophobic polymers, such as poly(dimethylsiloxane) (PDMS)[28] and poly(N-vinyl-2-pyrrolidone) (PNVP)[29, 30] have also been investigated for antifouling property. There is a highly hydrated layer formed between the interfaces of polymers and external environment. Hydrophilic polymers modified biomaterials reject the adhesion of water or fouling stuff as bacteria and proteins.

Superwetting materials were also studied to show an antifouling effect, such as superhydrophilic, superhydrophobic, and superamphiphobic surfaces.[31-33] A superhydrophobic surface is defined by the water contact angle over 150 ° and a roll-off angle/contact angle hysteresis below 10 °, which resulted from the combination of hydrophobicity and hierarchical surface structure (micro-/nanostructures) (Figure 5a-e).[34-37] In the work of Schlaich et al., superwettable surfaces were synthesized by a layer-by-layer method based on the same mussel-inspired dendritic polyglycerol (MI-dPG) polymer system, showing excellent antifouling properties (Figure 5f).[24]

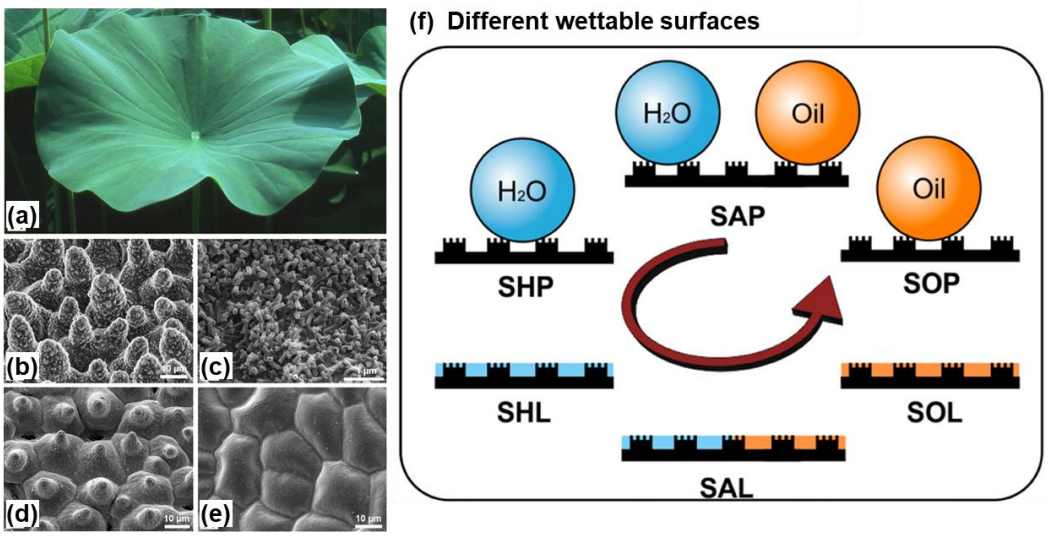



**Figure 5**. (a) Lotus leaves. Scanning electron microscopy (SEM) image of the upper leaf side shows (b) the hierarchical structure, (c) Wax tubules, (d) structure of upper leaf side after critical point drying, (e) structure of leaf underside. Reprint with permission from ref.[37]. The figure by Ensikat et al. is licensed under CC BY 2.0. (f) Illustration of different superwettable surfaces: superhydrophobic (SHP), superhydrophilic (SHL), superamphiphilic (SAL), superoleophilic (SOL), superolephobic (SOP) and superamphiphobic (SAP). Reprint with permission from ref.[24]. Copyright 2017 American Chemical Society.

Another design of an antifouling surface are a zwitterion-modified surface, which show better antifouling effect because zwitterionic materials can tightly bind with water molecules and trap more water molecules.[38-40] There are two main mechanisms for the antifouling effect of the zwitterionic materials. One of these mechanisms is the hydration layer exists between the surface of the zwitterionic surface and the fouling materials, for instance, proteins and bacteria (Figure 6).[39] Based on the electrostatic interactions, the zwitterionic surfaces can trap numerous water molecules to form the hydration layer. Thus, the hydration layer can significantly decrease the contact area between the surfaces and the foulants. The advantage of a zwitterionic polymer compared to PEG based polymers is that the hydration layer existing between zwitterionic surface and the fouling stuff is denser and thicker, the reason being the structure of the two kinds of polymers.[39] The repeat units of PEG and its derivatives are $-CH_2CH_2O-$, and the hydrogen bonding interactions can only combine one water molecule with the repeat unit. However, the repeat unit of zwitterionic based polymer is equally charged unit, and the electrostatic interactions can combine as much as eight water molecules.[41, 42]

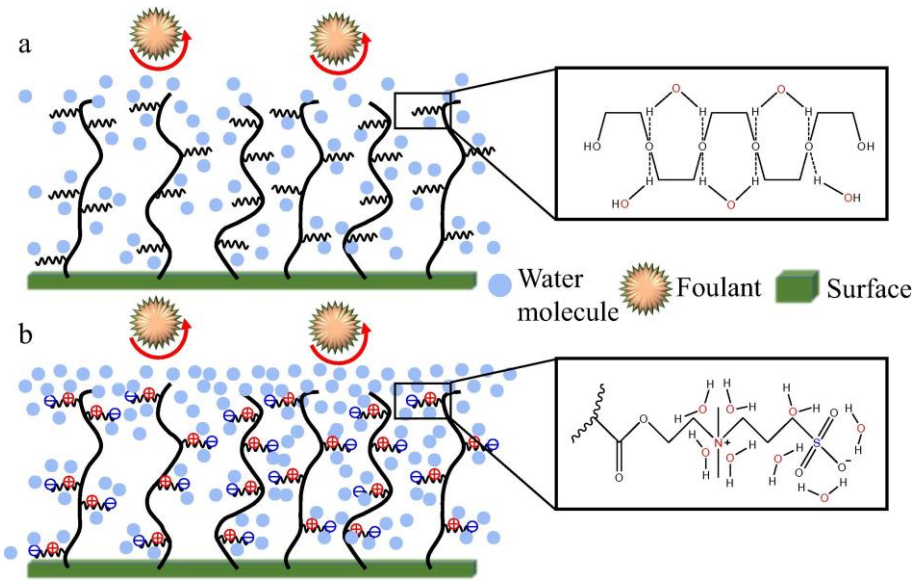



**Figure 6**. Hydration layers formed by the repeat unit of PEG and a zwitterionic polymer, respectively. Reprint with permission from ref.[39]. Copyright 2016 Elsevier.

Another mechanism is steric hindrance (Figure 7).[39, 43, 44] The foulants will compress the polymer chains after contact with the polymer chains; the system's Gibbs free energy can then increase. In the compressed state, the polymer chains are not stable, which makes the polymer chains tend to return to the original state. Based on the steric hindrance effect of all hydrophilic polymer chains, the foulants are rejected.

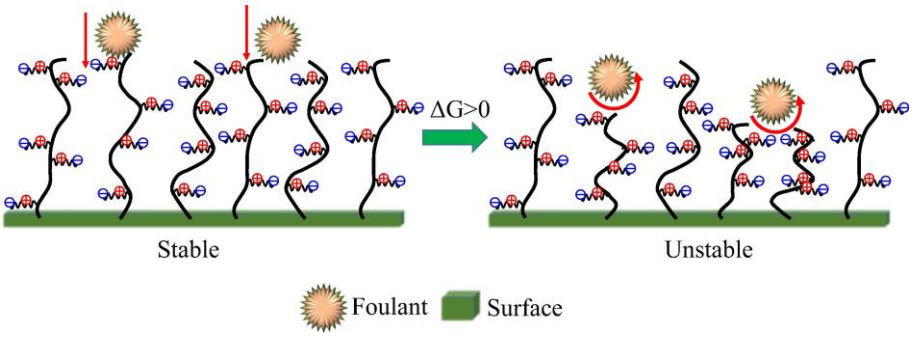



**Figure 7**. Steric hindrance effect produced by antifouling polymers. Reprint with permission from ref.[39]. Copyright 2016 Elsevier.

Jiang et al. have studied the zwitterion polymer in various applications, as medical devices, tissue scaffolds, drug carriers, and marine coatings. One of the most important functions of a zwitterion polymer is its antifouling ability, which was designed for hydrogels, surface coatings, and switchable polymers.[45-55] The typical structures of zwitterionic polymers used in their works are shown in Figure 8.

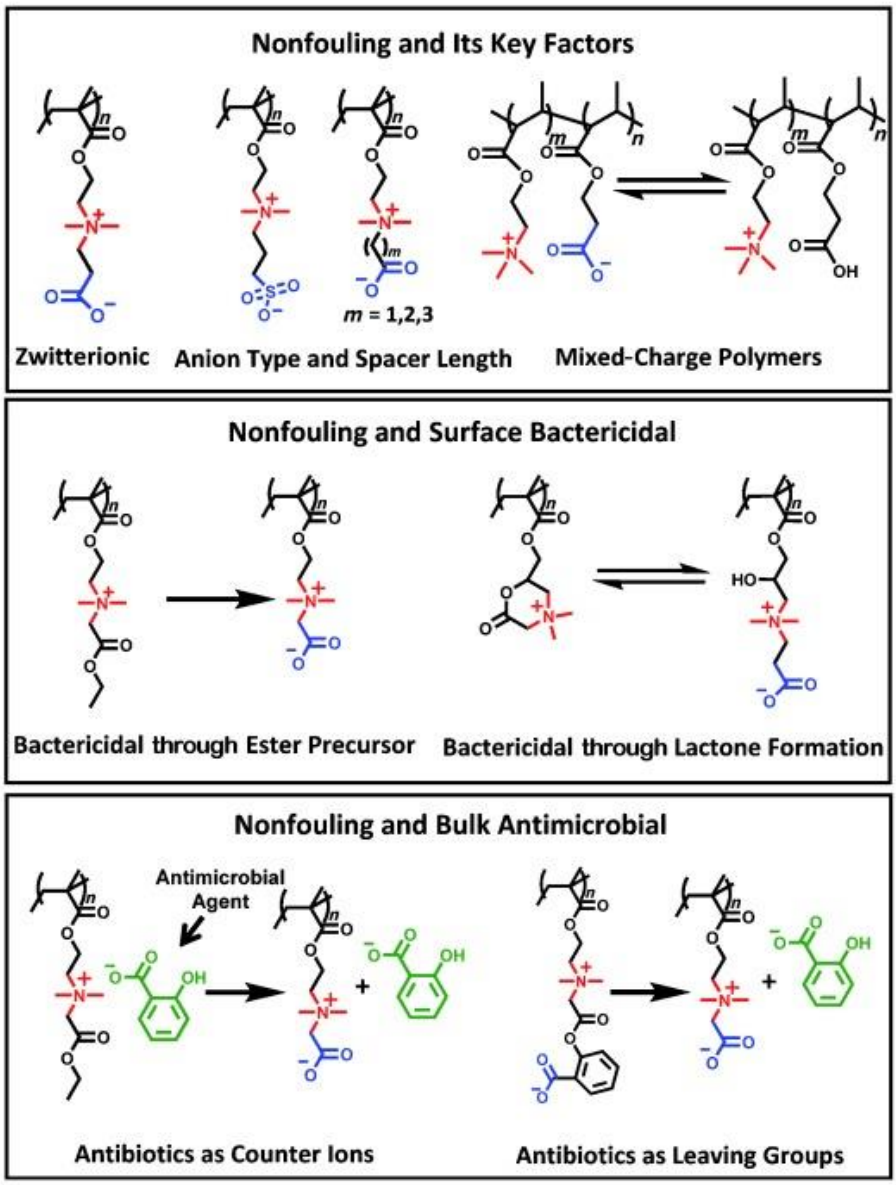



**Figure 8.** Chemical structures of several zwitterionic polymers and their derivatives in Jiang et al.'s work. Reprint with permission from ref.[52]. Copyright 2014 WILEY - VCH.

In addition, as shown in Figure 9a,[56] Kolewe et al. modified the zwitterionic polymer on the surface of an electrospun nanofiber, which demonstrated superior antifouling effect against *Escherichia coli (E. coli)* and *Staphylococcus aureus (S. aureus)*. The zwitterionic polymer coating enhanced the antifouling effect of the nanofiber membranes. This zwitterionic polymer based antifouling surface was also applied in Kuang et al.'s work,[57] which, when combined with the mussel-mimetic polymer it generates an antifouling surface (Figure 9b).

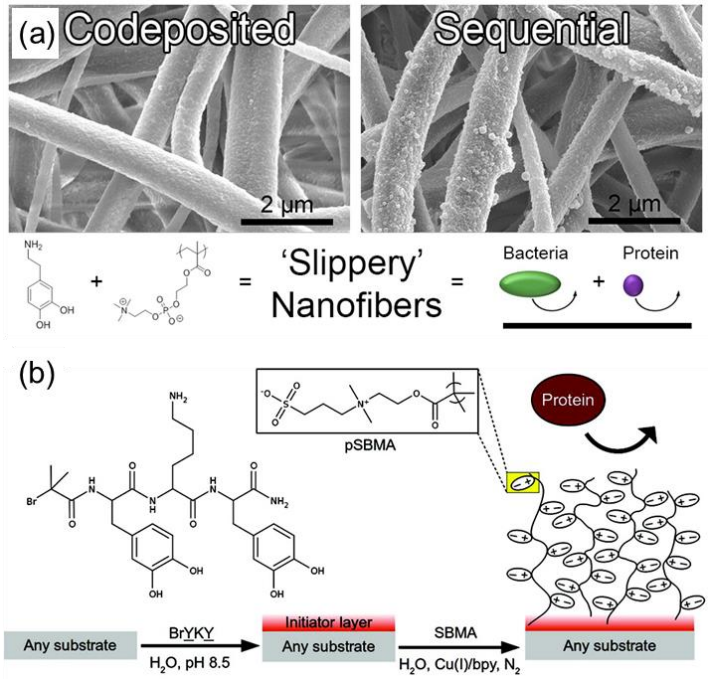



**Figure 9**. (a) Antifouling electrospun nanofiber functionalized with polymer zwitterions. Reprint with permission from ref. [56] (b) Surface independent coatings formed by zwitterionic polymers with antifouling property. Reprint with permission from ref. [57] Copyright 2012 and 2016 American Chemical Society.

## 1.2.2 Biocide-modified materials

In addition to antifouling materials, there is another important method to avoid bacterial infection, namely, antibacterial materials that release or combine biocides during their applications. In recent decades, a wide variety of antibacterial agents have been applied to the biomedical materials, such as antibiotics,[10, 58] antimicrobial peptides,[59, 60] quaternary ammonium compounds,[61-63] some metals (silver, zinc, iron, copper, etc.),[64] and nanoparticles.[65] These biocides have been proven to possess excellent narrow- or broad-spectrum antibacterial ability.

A wide variety of antibiotics have been designed to overcome infectious diseases. For instance, penicillin, methicillin, vancomycin, and zyvox were sequentially used to treat the staphylococcal infections over the latter half of the 20$^{th}$ century.

In addition to injection, another application of antibiotics is the modification on surfaces of biomedical materials to promote the biological function of implants. Vancomycin was commonly used in the antibacterial materials via various approaches. For instance, Lawson et al. designed four polymerizable vancomycin derivatives bearing either

acrylamide or PEG-acrylate, and then the polymers were successfully polymerized to the substrate to form antibacterial surfaces.[66]

However, the new generation of antibiotics was always followed by the resistance of the bacteria against these antibiotics.[67, 68] Drug-resistant bacteria appear after long-term antibiotic treatment. Therefore, various novel antibacterial agents have been designed to overcome this problem. Antimicrobial peptides (AMPs) attracted a lot of attention from the researchers in the last few decades, owing to the broad-spectrum antibacterial abilities and different mechanisms compared to conventional antibacterial agents.[69] Chen et al. designed the AMPs-functionalized titanium implants based on the click chemistry of Cu (I)–catalyzed azide–alkyne cycloaddition (CuAAC), which have shown significant antibacterial activity against *S. aureus* and *E. coli* (Figure 10).[70]

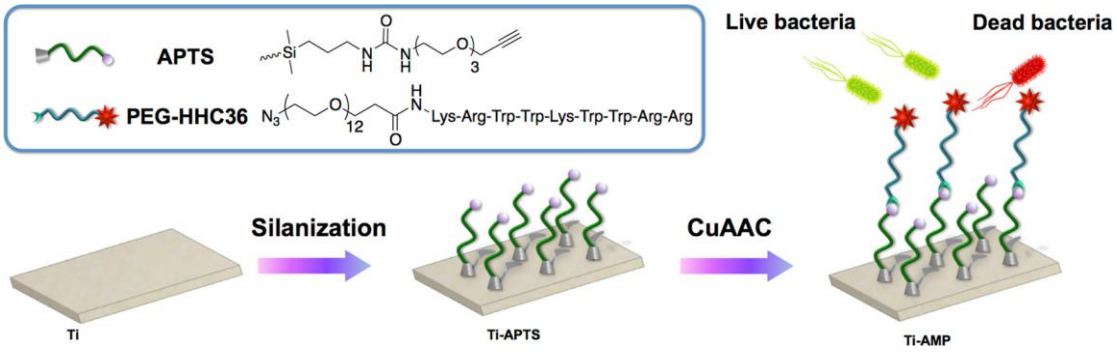



**Figure 10**. AMPs modified titanium surface. Reprint with permission from ref.[70]. Copyright 2019 American Chemical Society.

In addition, supramolecular antibacterial materials are another popular approach to overcome the drug-resistant bacteria. These supramolecular materials are formed by small molecules via noncovalent interactions, electro-static, hydrogen bonding, metal-ligand coordination, van der Waals, π–π stacking interactions, and the hydrophobic effect.[71, 72] These self-assembled systems present potential application in the biofunctional materials, such as cell culture and tissue engineering, drug delivery, and cancer therapy, etc.[73, 74] Researchers have increasingly studied antibacterial applications. Various antibacterial agents were combined with the supramolecular materials, for instance, antibiotics, cationic polymers, antibacterial peptides, metals, and so on.[75-77] In the work of Li et al., an antibiotic delivery system was realized by the core–shell supramolecular gelatin nanoparticles (Figure 11). Vancomycin was used as an antibiotic to be encapsulated inside the nanoparticle, and the vancomycin was released after the gelatin nanoparticle degraded by the gelatinase overexpressed in the infection microenvironment. The

supramolecular system shows the potential to reduce the generation of antibiotic resistance.[78]

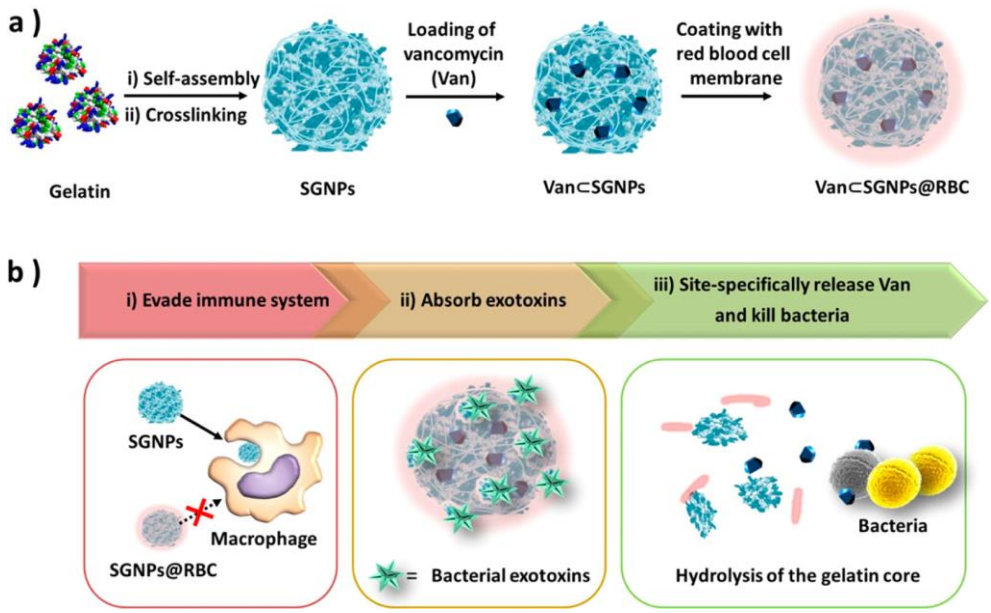



**Figure 11.** (a) Preparation of vancomycin encapsulated supramolecular gelatin nanoparticles. (b) Schematic representation in the treatment of a bacterial infection. Reprinted with permission from ref.[78]. Copyright 2014 American Chemical Society.

Furthermore, metal elements, such as Ag and Cu, have been studied in the field of antibacterial biomedical materials. It has been reported that silver nanoparticles (Ag NPs) showed broad-spectrum antibacterial ability and can subsequently inhibit biofilm formation.[79-81] Wang et al. embedded the Ag NPs on the surface of titanium substrate via plasma immersion ion implantation.[82] The electron transfer exists between the Ag NPs and titanium substrate that enhances the amount of reactive oxygen species (ROS) produced by Ag NPs. By producing ROS and the release of silver ions, this approach can effectively kill the bacteria adhered on the surface of biomedical materials as well as planktonic bacteria. Grohmann et al. designed the novel antibacterial coating modified with silver and ruthenium (AGXX, Largentec GmbH, Berlin, Germany), producing micro-galvanic elements, which showed enhanced antibacterial ability compared with the conventional silver surfaces (Figure 12).[83]

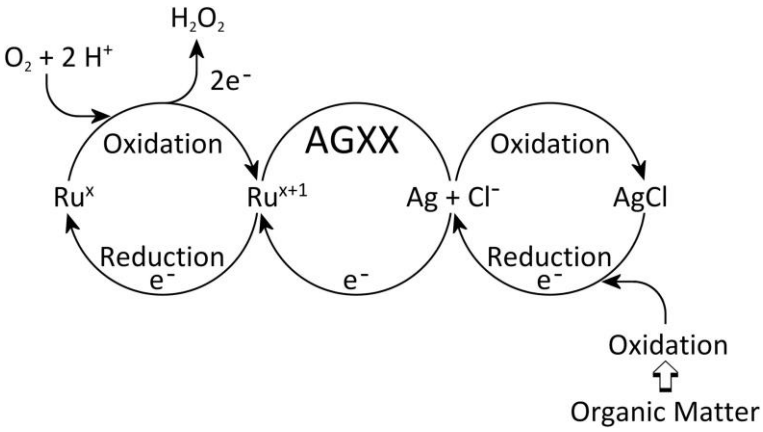



**Figure 12.** Redox-cycling and self-renewal of this antibacterial surface coating. AGXX (Largentec GmbH, Berlin, Germany) refers to the antibacterial agent used in Grohmann et al.'s work. Reprint with permission from ref.[83] Copyright 2017 Elsevier.

One more important metal element applied in antibacterial agents is copper. Besides the broad-spectrum antibacterial ability, copper is also an essential trace element in the human body.[84] Copper plays a crucial role in the function of various enzymes *in vivo*. What's more, copper ions showed additional biological functions, such as angiogenic effects. Thus copper was widely applied in various biomedical materials, as copper ions,[85] copper nanoparticles,[86] and copper oxide nanoparticles (CuO NPs).[87] In the work of Li et al., the Cu NPs were incorporated on universal surfaces by the *in-situ* reduction of the mussel-inspired polymers, showing significant antibacterial activity against *E. coli*, *S. aureus*, and kanamycin-resistant *E. coli*.[88]

Recently, one new efficient approach to enhance the efficiency of antibacterial ability was studied by researchers, which is the integration of the multiple antibacterial agents, for instance, the synergistic effect of Ag NPs and various antibiotics, two species of antibiotics, etc. In the study from Bakhshandeh et al., the silver ions and vancomycin were simultaneously loaded onto highly porous titanium implants by the chitosan and gelatin compound through electrophoretic deposition (Figure 13a).[89] In Zheng et al.'s work, the antimicrobial hybrid formed through conjugating silver nanoclusters with daptomycin presented enhanced antibacterial ability (Figure 13c).[90] In addition, the Ag/Cu bimetallic nanoparticle was introduced in Perdikaki et al.'s work (Figure 13b),[91] and the Ag/Ag@AgCl/ZnO hybrid nanostructures were designed in Mao et al.'s work (Figure 13d).[92]

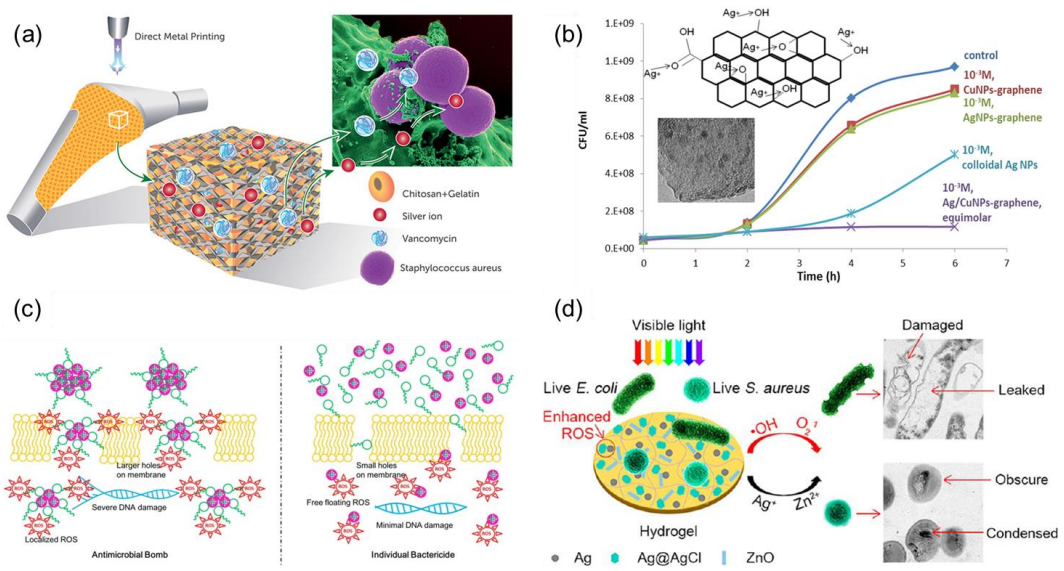



**Figure 13**. (a) Multiple antibacterial agents are loaded to strongly eradicate planktonic and adherent *S. aureus*. Reprint with permission from ref. [89]. (b) Ag/Cu bimetallic nanoparticle modified graphene composites show increased antibacterial property. Reprint with permission from ref. [91]. (c) Silver nanoclusters packed with daptomycin. Reprint with permission from ref. [90]. (d) Photo-inspired hydrogel encapsulated with Ag/Ag@AgCl/ZnO nanostructures. Reprint with permission from ref. [92]. Copyright 2016 and 2017 American Chemical Society.

### 1.2.3 Combination of the biocide and antifouling ability

Although these biocide-modified coatings have shown excellent antibacterial ability in multiple works, several drawbacks appear, including cytotoxicity, narrow antimicrobial spectrum, limited effective time, and increased multi-drug resistance of bacteria. Moreover, the antifouling property is rarely considered, which results in the situation where the protein and microorganisms could easily cover the. The surface-tethered antibacterial agents become blocked, which leads to a decrease of the antibacterial effectiveness. Furthermore, antifouling materials can only inhibit the bacteria that adhere on the surface, while the amount of the bacteria cannot be reduced.

In this context, there is an urgent trend to combine the biocide-modified and antifouling property, making it possible to produce dual functional materials.[93, 94] Dual functional materials have been realized by combining the antifouling agent and the antibacterial agent. The antibacterial agents can be tethered to nonfouling (super)hydrophilic/hydrophobic polymers or an anti-adhesive layer (Figure 14),[95] for instance, the combination of PEG and Ag NPs,[96] polyglycerol and Cu NPs.[88] This dual functional material effectively avoids the biofilm formation on the surface of implants

and meanwhile kills the bacteria existing in the surrounding environment, which is a promising way to avoid bacterial infection.

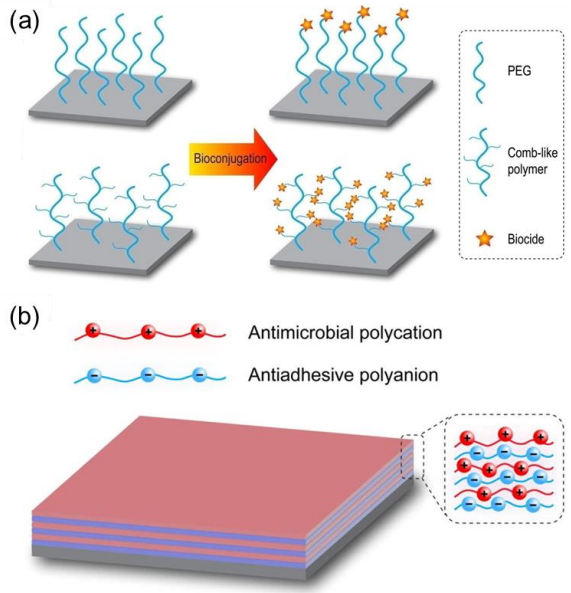



**Figure 14**. (a) Hydrophilic polymers immobilized with biocides. (b) Multilayer film embedded with antimicrobial and antiadhesive agents. Reprint with permission from ref. [95]. Copyright 2015 Elsevier.

## 1.3 Multifunctional materials

### 1.3.1 Optimization of orthopaedic implant materials

Besides of the bacterial infection mentioned above, there are some more surgery related problems that are important concerns for the success of the orthopaedic surgery, such as mechanical integrity, biocompatibility, bacterial infection, osteogenic integration, shelf life, etc. Optimization of the implant coatings is in an urgent need to improve the success of the implant surgeries. Various coatings have been studied each year to optimize the biomaterials.[97-101]

Pan et al. designed two different mussel-inspired bioactive peptides, by which the titanium implants could realize dual biofunctionalization (Figure 15a).[102] This coating promotes human bone marrow-derived mesenchymal stem cells' adhesion and enhances the osteogenicity. In addition, in the work from Hu et al., the aptamer-bilayer scaffold was designed and it can efficiently recruit mesenchymal stem cells (MSCs) to the defect and promote the directional differentiation of MSCs (Figure 15b).[103]

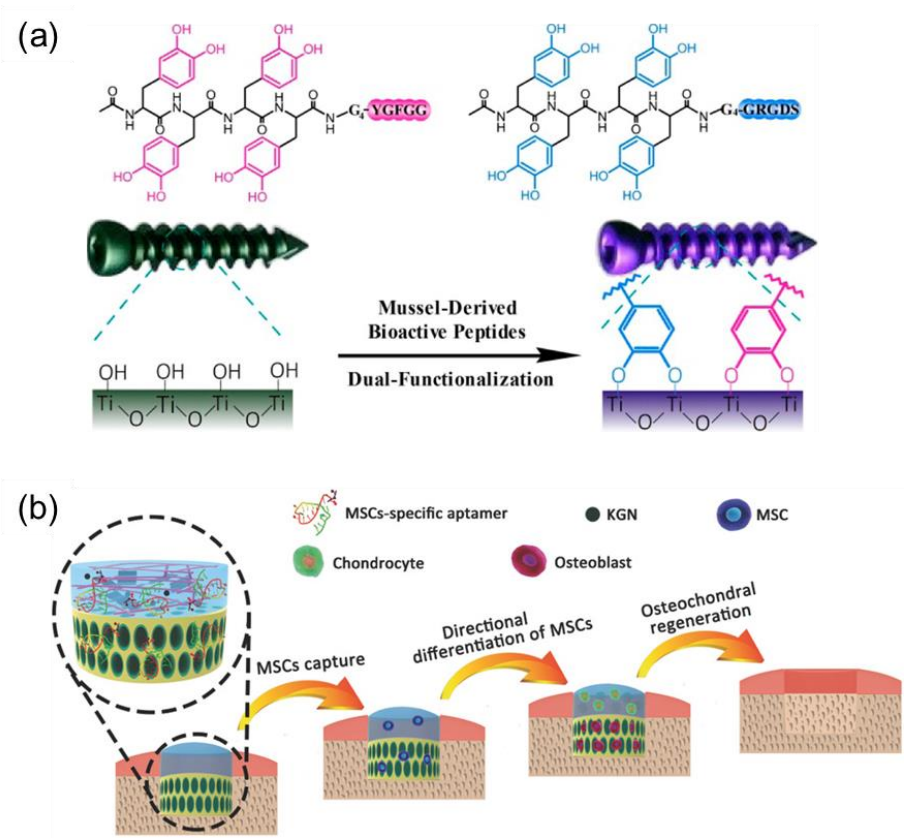



**Figure 15**. (a) Surface modification of Ti implant (a cortical bone screw) via mussel-inspired peptides, $(DOPA)_4$-$G_4$-GRGDS and $(DOPA)_4$-G4-YGFGG. Reprint with permission from ref. [102]. (b) Aptamer-bilayer scaffold in osteochondral defect repair. Reprint with permission from ref. [103]. Copyright 2016 American Chemical Society, 2017 WILEY-VCH.

However, none of the coatings could simultaneously fulfil all the criteria. Therefore, combination coatings with multifunction were designed to address these shortcomings. Among the surgery-related problems, bacterial infection and osteogenic integration are the two that need to be more carefully addressed. These two problems are the common reasons for the failure of the implant surgeries. In this thesis, the two main problems are discussed in detail and the coatings have been designed mainly to solve these two problems. There are different ways to categorize the biofunctional coatings according to the previous literature, for instance, by fabrication methods (e.g., layer by layer, electrospinning, vacuum-deposited), by biofunctions (e.g., antibacterial coating, antifouling coating, enhanced osteogenic integration coating) (Figure 16), by type of coatings (e.g., polymer, hydrogel), etc.[9] Coatings in the thesis were categorized by their function.

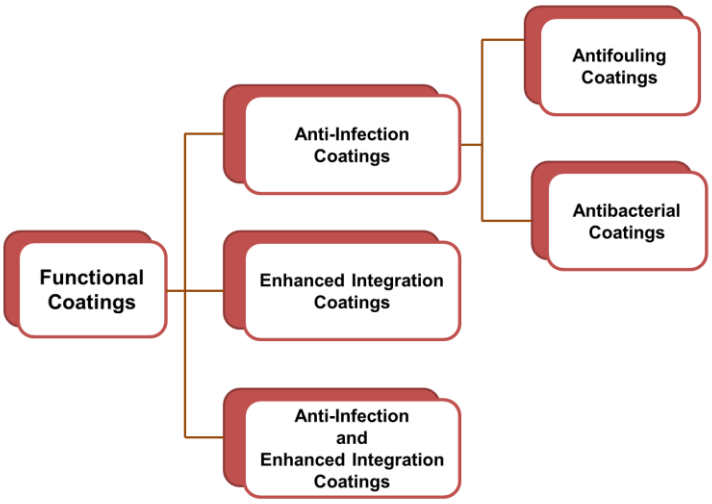



**Figure 16**. Classification scheme used to categorize multifunctional coatings in this thesis. Coatings are defined by their biological functions.

## 1.3.2 Enhanced anti-infection and osteogenic integration materials

Bacterial infection and osteogenic integration are the formidable clinical challenges, and the effective treatment to solve this problem is to design an implant material with both the antibacterial and osteogenic ability.[104, 105] In this context, bioactive moieties such as growth factors, peptides, and some metal ions (silver, zinc and copper) have been applied to modify the implants to enhance implant-bone interactions by promoting osteogenic differentiation.[106-110] Researchers have reported various ways to combine the antibacterial agents and enhanced osteogenic integration agents to fabricate the dual functional coatings.[111-113]

Min et al. have designed dual therapy nanolayered implant coatings (Figure 17).[104] The antibiotic (gentamicin) and the osteoinductive growth factor (BMP-2) were sequentially loaded in different layers. The antibiotic contained in the top layer was released at the early stage to eliminate the bacterial infection. Then the BMP-2 was released in the next stage to induce the bone regeneration.

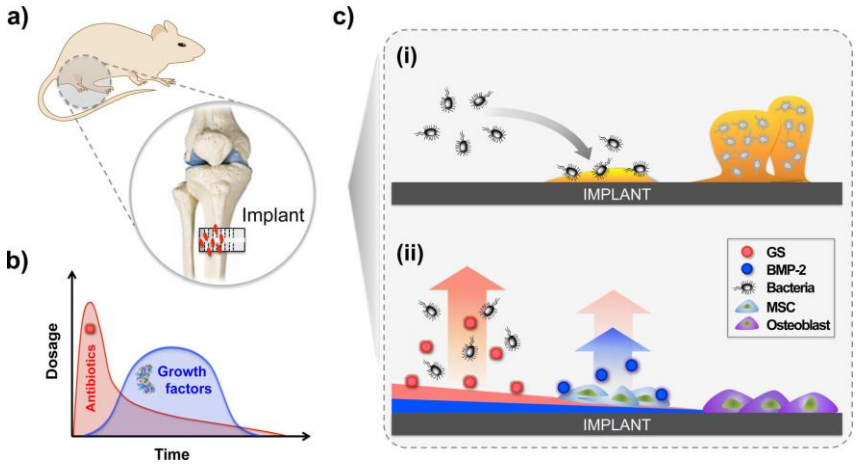



**Figure 17**. Dual functional therapy strategy. (a) The model of rat tibia with induced osteomyelitis. (b) Expected release profile of an antibiotic and a growth factor. (c) Possible applications. Reprint with permission from ref. [104]. Copyright 2016 American Chemical Society.

Cui et al. synthesized and immobilized PEGMA500-Phosmer to Ti6Al4V surfaces,[114] producing a coating which could significantly reduce the bacteria adhesion and meanwhile showed good compatibility to MC3T3-El cells (Figure 18). The PEG brushes inhibited bacterial adhesion and the bacteria of *E. coli*, *Staphylococcus epidermidis and Streptococcus Mutans* were tested. The phosphate segment here functioned as a binding site to promote the MC3T3-El cells that were attached to the surface.

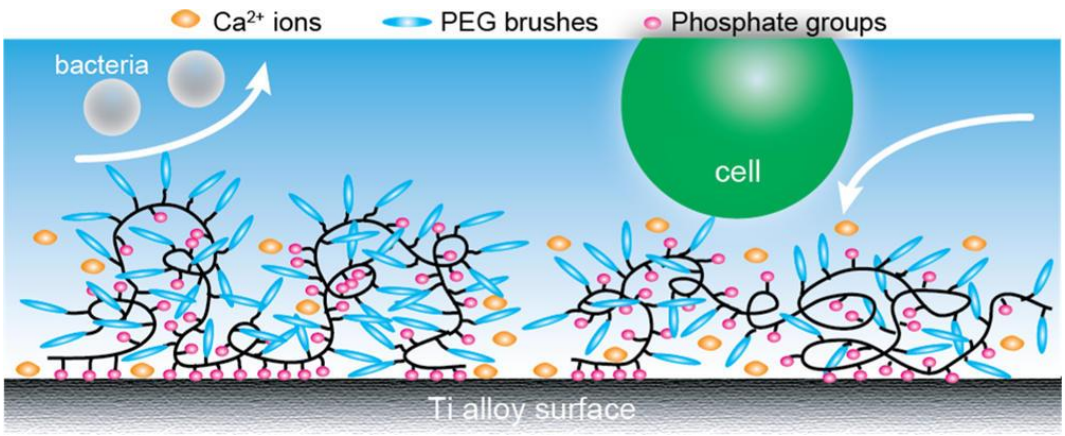



**Figure 18**. Bacteria antiadhesion and osteoblast adhesion on poly(PEGMA-r-Phosmer) modified Ti alloy surfaces. Reprint with permission from ref. [114]. Copyright 2018 American Chemical Society.

However, the antibacterial ability and the biocompatibility are sometimes contradictory. Therefore, balancing between the antibacterial ability and the biocompatibility becomes very important in the design of the implants. Multi-biofunctional materials showing antibacterial ability and osteogenic differentiation function will be addressed in this thesis.

### 1.3.3 Mussel-inspired polymers

Mussels can attach to virtually versatile substrates, such as glass, metal, ceramic, etc. Therefore, the structural mimic of mussel foot protein is widely applied in later studies especially in the biomedical materials.[115-117]

One important factor that help the mussels adhere on the versatile substrates are the byssus, which could secret the proteins and help to resist the lift and drag of waves.[118, 119] The potential reasons for this attachment ability lie on the amino acid composition of proteins found near the plaque-substrate interface (Figure 19).[118] Mytilus byssus contains roughly 25–30 different proteins, and the 3, 4-dihydroxy-L-phenylalanine (DOPA) and lysine amino acids are the main components inside the proteins.[120] Mussel foot protein (mfp)-5 is the mostly adhesive protein between the plaques and the substrates, because mfp-5 contains the most DOPA with the content of 28 mol%. The catechol (DOPA) adheres to the surfaces by covalent or noncovalent interactions. In the meantime, the crosslinking between the catechol (DOPA) and amine (lysine) groups help the mussel-inspired polymers form the strong adhesion on the versatile substrates.[121, 122]

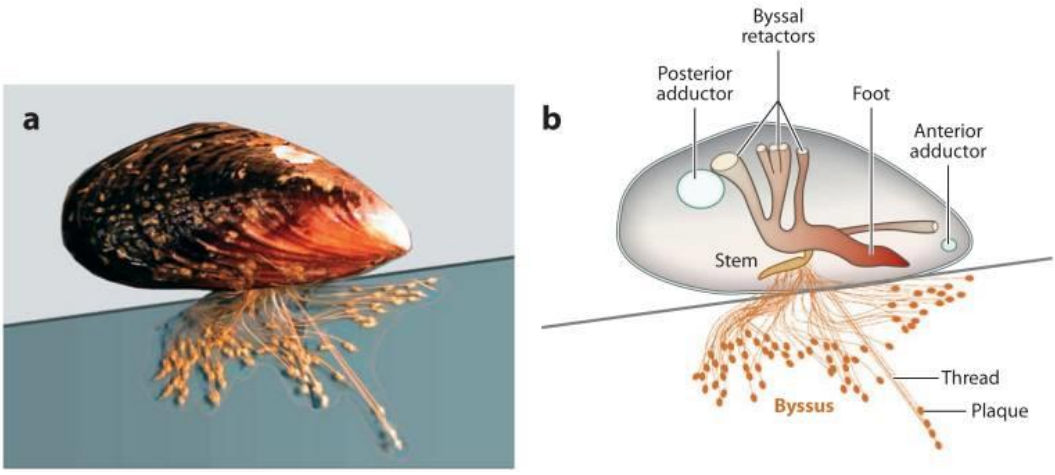



**Figure 19**. Illustration of mussel *Mytilus californianus* adhesion. (a) Byssus adhesion on a mica surface. (b) Schematic a half-shell of mussel. Reprint with permission from ref. [118]. Copyright 2011 ANNUAL REVIEWS, INC.

Mussel-inspired polymers were frequently studied in the last two decades. Polydopamine attracted many researchers due to its rapid and strong adhesion, simple and versatile coating method, and easy post-modification.[123-129] One significant application for mussel-inspired polymer is adhesives that bind with the surfaces. A wide variety of biofunctional

coatings synthesized by mussel-inspired polymers have been reported, for instance, antifouling coating, antibacterial coatings, osteogenetic coatings, and the coatings with the combinational biofunctions.[119, 130-132]

MI-dPG with different modification amounts of catechol and amine groups will be applied in this thesis. MI-dPG was firstly designed by Wei et al.[133] The highly branched dendritic polyglycerol (dPG) was used as the scaffold to highly increase the content of the amine and catechol groups to obtain the MI-dPG. The MI-dPG mimics not only the functional groups but also the molecular weight and molecular structure of mfp-5, of which the average molecular weight is about 10 kDa (Figure 20). Via a simple dip-coating approach, the MI-dPG could easily form a stable coating on versatile substrates.[133]

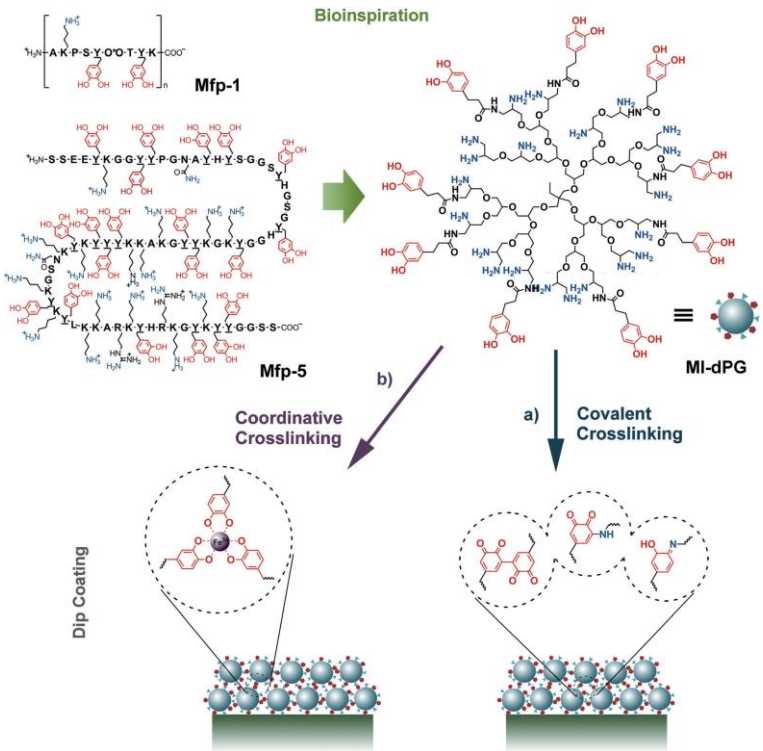



**Figure 20**. Top left: Structures of the mussel foot proteins mfp-1 and mfp-5, and the amino acids that contain amine (blue) and catechol (red) groups. Top right: the chemical structure of MI-dPG. Bottom: covalent and coordinative crosslinking for universal substrates. Reprint with permission from ref. [133]. Copyright 2014 WILEY-VCH.

Moreover, MI-dPG could construct surfaces with different roughness by controlling coating time, layers, polymer concentration, pH value of buffer, etc. Inspired by the water-repellent lotus leaf, different wettabilities could be achieved by controlling the

roughness.[134, 135] Micro- and nanometer roughened surfaces can be obtained based on adjusting of the parameters. As shown in (Figure 5a-e), the upper epidermis of the lotus leaves contains a great amount of agglomerated wax tubules, which is the basis of the lotuslike hierarchical structure.[37] This characterization-based coatings have been reported in various works to show superhydrophilicity. Schlaich et al. combined two separate biomimetic approaches, mussel-inspired and lotus leaf-inspired approaches, and designed a universal approach for constructing different superwetting systems on versatile substrates.[24] Various layer-by-layer surfaces with different wettability were prepared, such as (super)hydrophilic coating, (super)hydrophobic coating, (super)amphiphobic coating, etc. (Figure 5f). [134]

In addition, the MI-dPG coatings containing amine and catechol groups are easily post-modified, making it possible to possess the great potential application on the biomedical materials (Figure 21). The antibacterial agents, such as silver ions and copper ions, could be in-situ reduced to nanoparticles by the free catechol-groups in MI-dPG.[88, 136] The coatings with the combination of different wettability and antibacterial agents reported.[23] These dual-functional coatings with antifouling and antibacterial abilities will be studied in this work.


**Figure 21**. Different postmodification methods for the MI-dPG-coated surfaces, achieving antifouling and antibacterial properties. Reprint with permission from ref. [136]. Copyright 2018 WILEY-VCH.

# 2 Scientific Goals

Bacterial infection has become a serious problem in the clinical surgeries. One important concern during the antibacterial procedure was the biomedical device-associated infection. The planktonic bacteria and the subsequent biofilm formation on the surface of the biomaterials have led to surgery failures, which have resulted in high treatment costs and patient debility. Thus it is really important to avoid the biofilm formation on the surfaces of the biomedical materials, which is a crucial factor leading to the failure of the surgery.

In this work, the two above factors were considered to optimize biomaterials. Antibacterial coatings, antibacterial supramolecular, and multifunctional coating with antibacterial and antifouling properties were designed.

## 2.1 Mussel-inspired polyglycerol works as a universal coating in combination with antibacterial agent

The first aim of this work was to design an antibacterial coating on versatile substrates. There were two goals in designing this research work. One goal of this work was to provide a universal coating by applying the MI-dPG polymer. The amine and catechol groups could form coatings on the universal substrates via a covalent reaction. In addition, the free catechol group could *in situ* reduce the copper ions into Cu NPs on the surface of the initial coating. The second goal of this work was antibacterial function. The Cu NPs modified on the coating surfaces showed excellent antibacterial ability. Therefore they have great potential in the antibacterial biomedical devices.

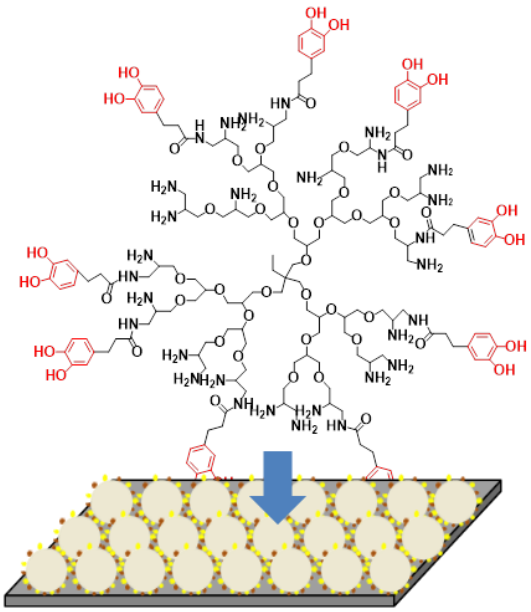


**Figure 22.** Universal coatings formed by MI-dPG

## 2.2 Mussel-inspired, polyglycerol-based coatings with antifouling ability

In this work, the antifouling ability was considered to address the bacterial adhesion problem. Antifouling effect was increasingly studied, and the approach of the antifouling effect in this work was realized by the antifouling polymer (hyperbranched polyglycerol (hPG)) or by controlling the roughness.

In the area of passive anti-biofouling surfaces, extreme wettability has drawn a lot of attention. We will study MI-dPG-based polymer in this work to investigate the relationship of the antifouling effect with wettability. The same MI-dPG-based polymer can be achieved with a different roughness of the multilayer coating, which made it more comparable. By changing the adjusting pH, polymer concentration, and immersion depth, different roughnesses were obtained. Followed by the *in situ* reduction of the silver ions, the antibacterial agent (Ag NPs) was introduced to the surface of these multilayer coatings. Based on this approach, the antibacterial and antifouling coatings are combined in this work.

One more approach in this work is to combine the antifouling polymer with Cu NPs. The antifouling polymer (hPG) modified with 10% catechol group (hPG-Cat 10) will be

applied in this work, therefore playing two roles in this work. One function of the hPG-Cat 10 is to form the coating on the universal substrate. Another function is to *in-situ* reduce the copper ions to Cu NPs on the surfaces of the substrate.

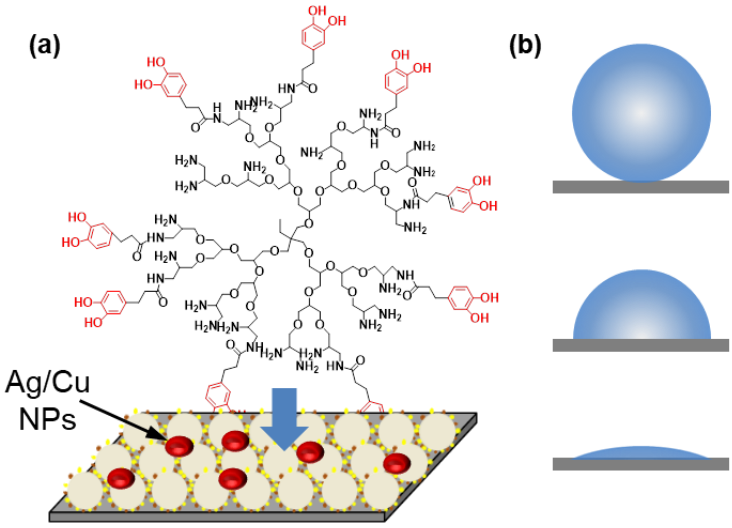



**Figure 23.** (a) Mussel-inspired antibacterial and antifouling coatings surface combined with different wettability. (b) The corresponding contact angles.

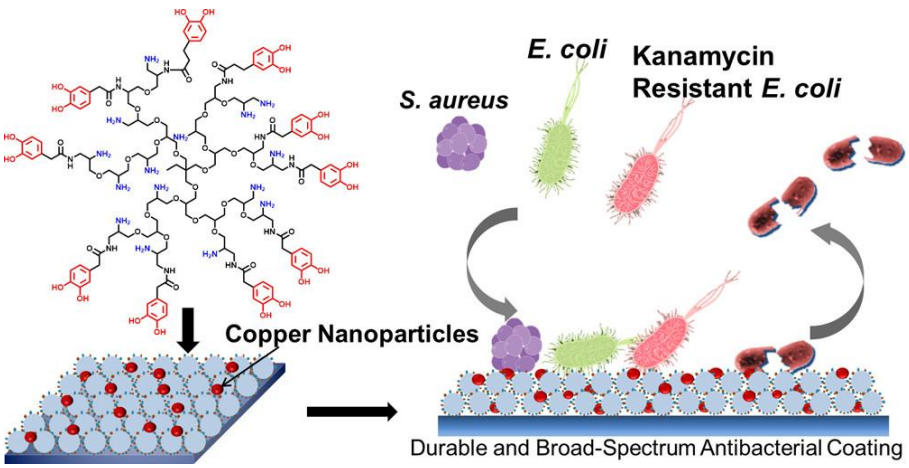
## 2.3 The application of mussel-inspired polyglycerol based coatings in tissue engineering

The purpose of this project is on the design of the multi-functional materials in the tissue engineering. The osteogenic ability shall be incorporated in the surfaces and extended to the antibacterial activity. Besides the antibacterial infection, bone integration of the implant are always important concerns in surgery. Whether the MSCs could proliferate and differentiate on the surfaces of implants is a key factor on the success of the surgery. In order to promote the implant materials, the biofunctions of antibacterial ability and osteogenic ability were both considered in this work.

Cu NPs have been studied to show the antibacterial ability in the previous work. Additionally, copper is an essential trace element in the human body that promotes bone regeneration which has been rarely studied in recent decades. Cu NPs simultaneously showing antibacterial ability and antifouling ability shall be used in this work.

# 3. Publications

## 3.1 Construction of functional coatings with durable and broad-spectrum antibacterial potential based on mussel-inspired dendritic polyglycerol and *in-situ* formed copper nanoparticles



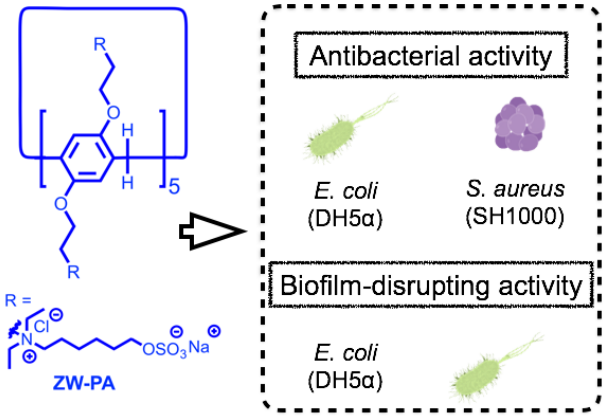

**Mingjun Li**, Lingyan Gao*, Christoph Schlaich, Jianguang Zhang, Ievgen S. Donskyi, Guozhi Yu, Wenzhong Li, Zhaoxu Tu, Jens Rolff, Tanja Schwerdtle, Rainer Haag* and Nan Ma*

*ACS Appl. Mater. Interfaces*, **2017**, 9, 35411–35418
https://doi.org/10.1021/acsami.7b10541

**Author Contribution**

Mingjun Li designed the project, performed the main experiments, and wrote the paper. Christoph Schlaich supported to synthesize the polymer. Jianguang Zhang, Wenzhong Li, Guozhi Yu and Jens Rolff supported the bacterial experiments. Ievgen S. Donskyi performed the X-ray photoelectron spectroscopy (XPS) experiment. Zhaoxu Tu performed the TEM experiment. Tanja Schwerdtle supported the experiment of copper ions release profile. Lingyan Gao, Rainer Haag and Nan Ma supervised the project.

## 3.2 Positively charged nanoaggregates based on zwitterionic pillar[5]arene that combat planktonic bacteria and disrupt biofilms



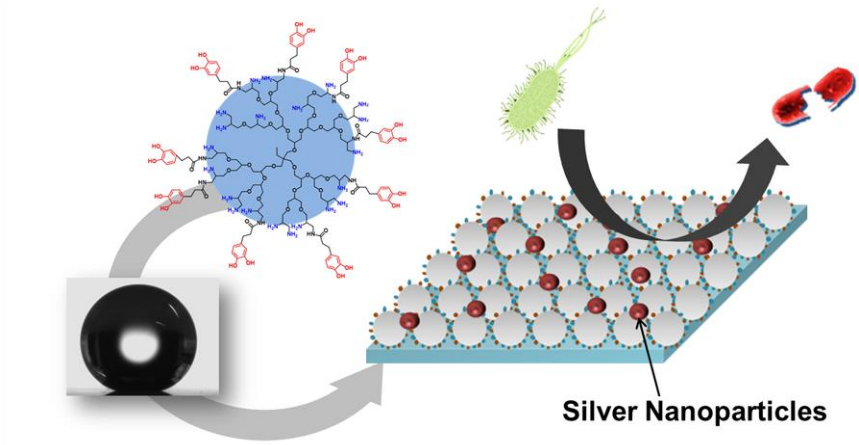

Lingyan Gao,[#] **Mingjun Li**,[#] Svenja Ehrmann, Zhaoxu Tu, and Rainer Haag*
[#] These authors contributed equally to this work.

*Angew. Chem. Int. Ed.* **2019**, 58, 3645-3649
https://doi.org/10.1002/anie.201810314

**Author Contribution**

Mingjun Li contributed to the design of the project, the main experiments, and the writing of the paper. Svenja Ehrmann performed the experiment of cryogenic transmission electron microscopy. Zhaoxu Tu performed the experiment of transmission electron microscopy. Lingyan Gao and Rainer Haag supervised this project.

## 3.3 Mussel-inspired coatings with tunable wettability, for enhanced antibacterial efficiency and reduced bacterial adhesion




**Mingjun Li**,[#] Christoph Schlaich,[#] Michaël Willem Kulka, Ievgen S. Donskyi, Tanja Schwerdtle, Wolfgang E.S. Unger, and Rainer Haag*

[#] These authors contributed equally to this work.

*J. Mater. Chem. B*, **2019**

https://doi.org/10.1039/C9TB00534J

**Author Contribution**

Mingjun Li and Christoph Schlaich contributed to the design of the project, the main experiments, and the writing of the paper. Michaël Willem Kulka supported the polymer of linear polyglycerol. Ievgen S. Donskyi and Wolfgang E.S. Unger performed the XPS experiment. Tanja Schwerdtle supported the experiment of silver release profile. Rainer Haag supervised the project.

# 4. Conclusions and outlook

This work mainly focuses on the antibacterial treatment of the biomedical materials based on the mussel-inspired polymers. In the last few decades, there has been a tremendous interest in the study of the antibacterial materials. However, due to the emergence of drug resistant bacteria, the design of antibacterial materials has met with more challenges. In this work, the silver and Cu NPs were applied as antibacterial materials combined with the mussel-inspired polymers. In addition, a new supramolecular material was developed as good alternative to antibacterial compounds. The positively charged nanoaggregates based on zwitterionic pillar[5]arene were designed in this work combating the planktonic bacteria and disrupting the biofilm.

In the first project, a Cu NPs-incorporated MI-dPG coating was designed. Based on the antibacterial tests, surface characterization, and stability test, the universal coating presented excellent antibacterial ability against the Gram-negative bacteria (*E. coli, DH5α*), Gram-positive bacteria (*S. aureus, SH1000*), and the drug resistant bacteria (*kanamycin resistant E. coli, MG1655*). This coating approach can be realized by a simple dip-coating method. Furthermore, the coating is available on versatile substrates, such as ceramic, metal, polymers, etc.

In the second project, the zwitterionic Pillar[5]arene presented excellent antibacterial ability against the Gram-negative bacteria (*E. coli, DH5α*), Gram-positive bacteria (*S. aureus, SH1000*). This supramolecular system can self-assemble into weakly positively charade nanoaggregates. Pillar[5]arene combined with the zwitterion showed excellent antibacterial ability. Meanwhile, it also presented the ability to eradicate both the young biofilm and pre-established biofilm, which did not lead to rapid generation of resistance.

In the third project, the antibacterial and antifouling surfaces based on the antibacterial agent (Ag NPs) and antifouling surfaces with superwettability were produced. One important advantage of the work is that the system was based on the same polymer, MI-dPG, which makes the different wettability more comparable. The comparison between different wettability showed that the Ag NPs incorporated onto the superamphiphobic surface presented better stability. This study demonstrated that the superamphiphobic wettability helped stabilize the Ag NPs incorporated on the surface because there was an

air film between the surface and the outside environment, which could reduce the release of the Ag NPs.

In summary, the work aimed to modify the biomedical materials with antibacterial ability based on the bio-inspired polymers. Besides the antibacterial effect, more biological functions were meanwhile combined (antifouling, osteogenic ability) in the later study to promote the integration of the biomaterials. The simple and rapid fabrication of antibacterial surfaces showed great potential in the biofunctional materials and need to be further tested *in vivo*.

# 5. Kurzzusammenfassung

Diese Arbeit konzentriert sich hauptsächlich auf die antibakterielle Behandlung biomedizinischer Materialien auf Basis der von Muscheln-inspirierten Polymeren. In den letzten Jahrzehnten gab es ein großes Interesse an der Erforschung solcher antibakterieller Materialien. Durch die Entstehung von medikamentenresistenten Bakterien wurde das Design antibakterieller Materialien jedoch vor immer größeren Herausforderungen gestellt. In dieser Arbeit wurden deshalb Silber- und Kupfer Nanopartikel in die antibakteriellen Materialien in Kombination mit den muschelinspirierten Polymeren aufgebracht. Darüber hinaus war das supramolekulare Material auch eine gute Alternative zu den antibakteriellen Verbindungen. Diese positiv geladenen Nanoaggregate auf Basis der zwitterionischen Pillar[5]arene wurden zur Bekämpfung der planktonischen Bakterien und zur Störung des Biofilms entwickelt.

Im ersten Projekt wurde die mit Cu NPs integrierte MI-dPG-Beschichtung entworfen. Basierend auf den antibakteriellen Tests, der Oberflächencharakterisierung und dem Stabilitäts-Test wies die Universalbeschichtung eine ausgezeichnete antibakterielle Wirkung gegen die gramnegativen Bakterien (*E. coli, DH5α*), grampositive Bakterien (*S. aureus, SH1000*) und die medikamentenresistenten Bakterien (kanamycinresistent *E. coli, MG1655*) auf. Dieser Beschichtungsansatz kann durch ein einfaches Tauchverfahren realisiert werden. Darüber hinaus ist die Beschichtung auf vielseitigen Substraten wie Keramik, Metall, Polymeren usw. möglich.

Im zweiten Projekt zeigte die zwitterionische Pillar[5]arene eine ausgezeichnete antibakterielle Wirkung gegen die gramnegativen Bakterien (*E. coli, DH5*α), grampositive Bakterien (*S. aureus, SH1000*). Dieses supramolekulare Material kann sich selbst zu schwach positiv geladenen Nanoaggregaten zusammenfügen. Pillar[5]arene zeigte auf Grund seiner zwitterionischen Beschaffenheit eine ausgezeichnete antibakterielle Fähigkeit, und stellte unterdessen die Fähigkeit zur Beseitigung sowohl der jungen Biofilm und vorab etablierten Biofilm, welcher nicht zu einer schnellen Generierung von Resistenzen führen wird.

Im dritten Projekt wurden die antibakteriellen und bewuchsverhindernden Oberflächen auf Basis des antibakteriellen Wirkstoffs (Silber NPs; Ag NPs) und der bewuchsverhindernden-Oberfläche (Superbenetzbarkeit) hergestellt. Ein nicht zu

vernachlässigender Vorteil der Arbeit ist, dass das System auf dem gleichen Polymer MI-dPG basierte, was die unterschiedliche Benetzbarkeit besser vergleichbar machte. Der Vergleich zwischen den unterschiedlichen Benetzbarkeiten zeigte, dass die Ag NPs mit einer superamphiphoben Oberfläche eine höhere Stabilität aufwiesen. Diese Untersuchung zeigte, dass die superamphiphobische Benetzbarkeit dazu beiträgt, die auf den Oberflächen eingebauten Ag NPs zu stabilisieren, da ein Luftfilm zwischen der Oberfläche und der Außenumgebung vorhanden ist, der die Freisetzung der Ag NPs reduziert.

Zusammenfassend lässt sich sagen, dass diese Arbeit darauf abzielt, die biomedizinischen Materialien mit antibakterieller Wirkung auf der Grundlage der bio-inspirierten Polymere zu modifizieren. Neben der antibakteriellen Wirkung wurden weiterführend zwischen den beiden biologischen Funktionen (Antifouling, osteogene Fähigkeit) kombiniert, um die Integration der Biomaterialien zu fördern. Die einfache und schnelle Herstellung antibakterieller Oberflächen bietet großes Potenzial für die weitere Verwendung als biofunktionale Materialien und sollte weiter *in vivo* untersucht werden.

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# 7. Abbreviations

| | |
|---|---|
| SEM | Scanning electron microscopy |
| XPS | X-ray photoelectron spectroscopy |
| CuAAC | Cu (I)–catalyzed azide–alkyne cycloaddition |
| PEG | poly(ethylene glycol) |
| *E. coli* | *Escherichia coli* |
| *S. aureus* | *Staphylococcus aureus* |
| PDMS | poly(dimethylsiloxane) |
| AMPs | antimicrobial peptides |
| Ag NPs | silver nanoparticles |
| Cu NPs | copper nanoparticles |
| CuO NPs | copper oxide nanoparticles |
| ROS | reactive oxygen species (ROS) |
| MSC | mesenchymal stem cell (MSC) |
| SHP | superhydrophobic |
| SHL | superhydrophilic |
| SAL | superamphiphilic |
| SOL | superoleophilic |
| SOP | superolephobic |
| SAP | superamphiphobic |

# 8. Publications from this PhD work

[6] M. Li, C. Schlaich, M. W. Kulka, I. S. Donskyi, T. Schwerdtle, W. E. S. Unger and R. Haag, *J. Mater. Chem. B*, **2019**, in press, DOI:10.1039/C9TB00534J.

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[1] M. Li, L. Gao, C. Schlaich, J. Zhang, I. S. Donskyi, G. Yu, W. Li, Z. Tu, J. Rolff, T. Schwerdtle, R. Haag and N. Ma, *ACS Appl. Mater. Interfaces*, **2017**, *9*, 35411-35418.

## Poster Presentation

[1] **M. Li**, L. Gao, R. Haag
Copper nanoparticles-incorporated mussel-inspired dendritic polyglycerol monolayer as a new broad-spectrum antimicrobial coating,
100th Anniversary of Georg Manecke, International Symposium 2016 “Functional Biointerfaces”

# 9. Curriculum vitae

Der Lebenslauf ist aus Gründen des Datenschutzes nicht enthalten.