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Multifunctional Polymeric Antibacterial Materials: Strategies against Drug-Resistant Bacteria and Biofilms

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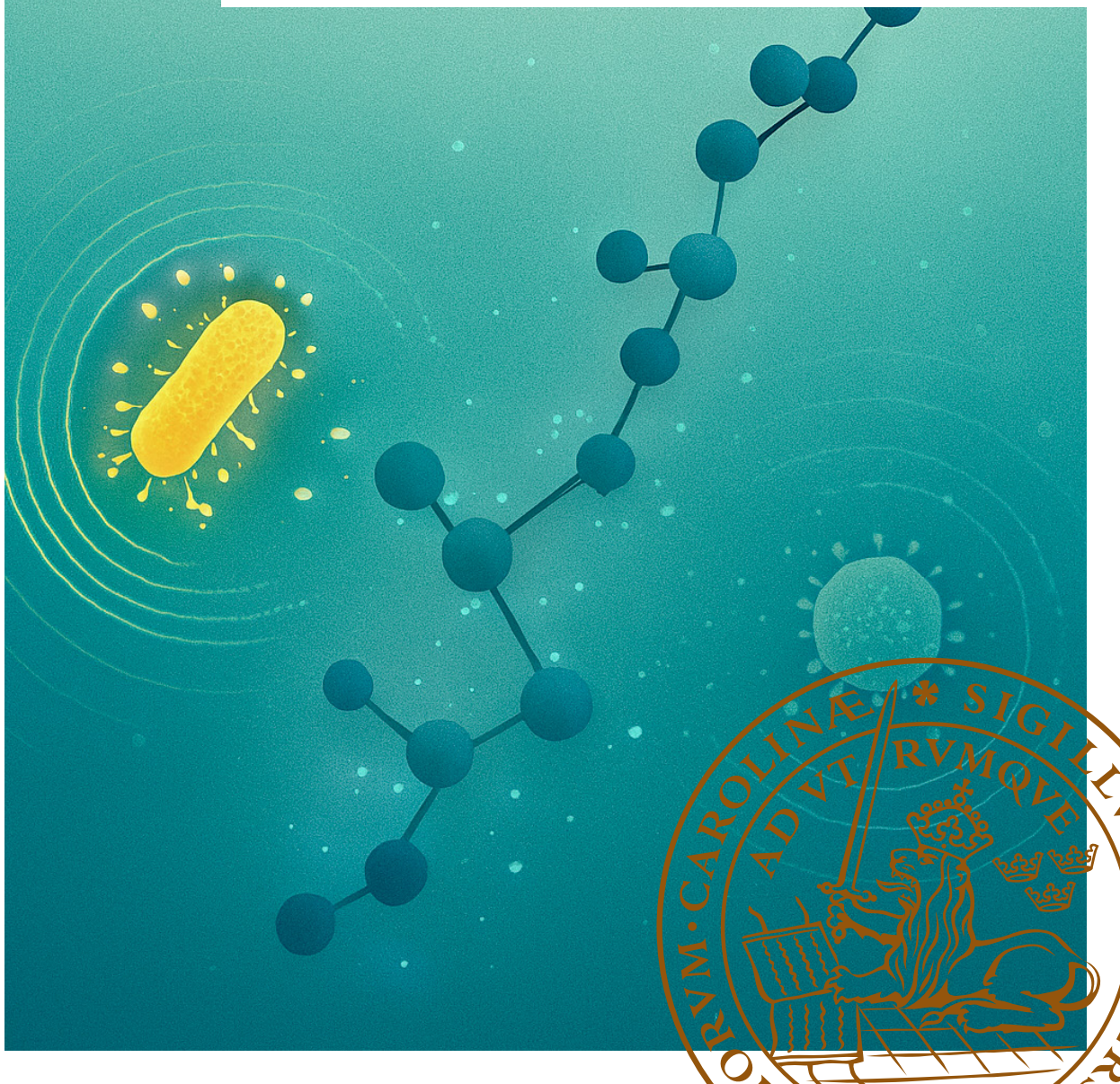
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Multifunctional Polymeric Antibacterial Materials: Strategies against Drug-Resistant Bacteria and Biofilms

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Qicheng Zhang



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DOCTORAL DISSERTATION

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Abstract:

Pathogenic bacterial infections lead to bacterial resistance and biofilm formation, causing significant suffering and presenting an urgent issue to be addressed. Polymer materials have garnered considerable attention in the antibacterial field due to their functional moldability and molecular structure designability. These materials can achieve various antibacterial functions by regulating their monomer composition to avoid resistance issues and remove stubborn biofilms. Additionally, they can acquire functions such as bacterial recognition, hemostasis, and imaging through modification or regulation of the polymer structure. Polymer materials also possess broad-spectrum antibacterial effects and low toxicity, making them ideal antibacterial agents.

In this thesis, we synthesized four different types of functional antibacterial polymer materials and explored their capabilities in various antibacterial scenarios. Firstly, a photothermal antibacterial polymer with molecularly imprinted sites was synthesized for targeted photothermal antibacterial action against *Pseudomonas aeruginosa*. Building on the excellent antibacterial effect of photothermal therapy, a photothermal conjugated polymer was further utilized and combined with chitosan-based cryogel for potential wound hemostasis and bacterial infection treatment. Additionally, photothermal antibacterial therapy was enhanced using molecularly imprinted polymers to improve the photothermal and fluorescence imaging capabilities of aggregation-induced emission molecules for treating methicillin-resistant *Staphylococcus aureus*. Furthermore, a polymer brush with quaternary ammonium salt and Cu-doped quantum dots was employed for bacterial binding, imaging, and synergistic antibacterial action.

In summary, this thesis presents a series of polymer materials designed to address issues such as drug resistance and biofilms caused by bacterial infections. Different techniques such as molecular imprinting, borate affinity, and photothermal antibacterial methods have been employed to meet complex antibacterial requirements. We hope these efforts provide meaningful references and support for the further application and development of polymer materials in antibacterial applications.

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Qicheng Zhang



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To my family

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Popular science summary

Bacteria are the oldest organisms on Earth. Compared to microbes, humans appear more like outsiders. Bacteria-based microorganisms have existed for 80% of the history of life on Earth, resulting in microbial populations that outnumber somatic cells in the human body by hundreds of millions of orders of magnitude. Humans even live in symbiosis with first-class carcinogens, such as *Helicobacter pylori*. Due to the significant impact of bacteria on humans, the Human Microbiome Project was established as an extension of the Human Genome Project to study the gene expression of all human-related microorganisms.

With the development of observation tools, researchers have discovered bacteria in interstitial fluid, blood, the infant's placenta, and even internal organs. This indicates that bacteria have always been present in the human body rather than entering it later. If symbiotic bacteria were harmful, they would have caused humans to go extinct in ancient times, or the human immune system would have evolved to eliminate all bacteria.

This poses a problem: antibacterial methods used by humans will kill both pathogenic and commensal bacteria. It is undeniable that the discovery of penicillin saved countless patients. These early antibiotics, produced by a few microorganisms, animals, and plants, can easily inhibit bacterial growth and reproduction without significantly affecting human bodies. In the past, a slap-sized wound often led to death, but antibiotics can prevent this dire consequence. However, bacteria involved in human life activities are also targeted by antibiotics.

More seriously, most antibiotics are not broad-spectrum. If antibiotics could kill all types of bacteria in the human body, the remaining bacteria would quickly reproduce and occupy the former body sites. But most antibiotics are effective against only one type of bacteria. They kill their target bacteria and allow other unaffected bacteria to grow uncontrollably, disrupting the ecological balance in the human body. This uncontrolled balance allows antibiotic-insensitive bacteria to multiply, which are safe in lower quantities but pathogenic in higher quantities. The rapid growth of bacteria also generates individuals with genetic mutations that possess drug resistance, rendering antibiotics completely ineffective. For example, methicillin-resistant *Staphylococcus aureus* is a typical type of bacteria resistant to several widely used antibiotics. The amount of antibiotics in nature is scarce, but the evolution of bacteria is rapid and relentless. As a result, humans will gradually lose their protection from antibiotics in the face of drug-resistant bacteria. So, what should we do then?

The competition between medical technology and bacteria is an endless "arms race." If medical technology develops more slowly than bacteria mutate, humanity will face great catastrophes. It is crucial to ensure that technological advances keep pace with bacterial mutations. The escalation of antibiotics has become increasingly

challenging in the fight against bacteria. One idea to address this problem is "Magic Must Defeat Magic," which involves using infinitely mutated organisms to combat infinitely mutated bacteria. This means new antimicrobial organisms will continually emerge to fight new bacteria. For example, bacteriophages are viruses that can infect and cause the lysis of microorganisms such as bacteria, fungi, algae, actinomycetes, or spirochetes. They can evolve alongside bacteria to maintain the ecological balance of flora.

Another promising strategy is to increase the targeting efficiency of antibacterial methods, which can significantly reduce the dosage of antibacterial agents and minimize their impact on normal bacteria, thereby maintaining the bacterial ecological balance in the human body. This principle has guided the development of numerous targeted drugs for treating various cancers. Additionally, physical antibacterial tools that are difficult for bacteria to evade through evolution have been invented to protect humans, such as thermal damage and oxidative damage or their combination. For thermal inactivation, some photothermal agents are used to convert light energy into thermal energy, which can denature bacterial proteins through heat.

In this thesis, different types of polymeric materials with various functions were prepared using different methods to achieve high-efficiency bacterial targeting and effective elimination of pathogenic, especially drug-resistant, bacteria. As common materials in our lives, polymers can exist in different forms, such as extremely tiny particles, liquid like glue, and gel state like jelly, with various chemical functional groups. This versatility allows them to be easily modified. For example, molecularly imprinted polymers can be referred to as "artificial locks" that recognize "molecular keys." In this case, components on the surface of bacteria, such as small molecules, carbohydrate chains, or proteins, can serve as "molecular keys" for molecularly imprinted polymers, providing bacterial targeting ability to the polymers. By selecting specific monomer molecules or using polymers to carry heat-producing agents, polymers can also generate heat under light irradiation, and thermal damage has been proven to be an effective sterilization method against drug-resistant bacteria. Additionally, polymers that can destroy the negatively charged cell walls of drug-resistant pathogens through their inherent positive charge and carry other functional materials have also been studied. As a result, this thesis demonstrates the various applications of polymer materials as disinfectant agents against different pathogenic bacteria.

Populärvetenskaplig sammanfattning

Bakterier är de äldsta organismerna på jorden. Jämfört med mikrober framstår människor som mer som outsiders. Bakteriebaserade mikroorganismer har existerat i 80 % av livets historia på jorden, vilket har resulterat i mikrobiella populationer som överstiger somatiska celler i människokroppen med hundratals miljoner storleksordningar. Människor lever till och med i symbios med förstklassiga cancerframkallande ämnen, såsom *Helicobacter pylori*. På grund av bakteriers betydande inverkan på människor etablerades Human Microbiome Project som en förlängning av Human Genome Project för att studera genuttrycket hos alla mänskligt relaterade mikroorganismer.

Med utvecklingen av observationsverktyg har forskare upptäckt bakterier i interstitiell vätska, blod, spädbarnets moderkaka och till och med inre organ. Detta indikerar att bakterier alltid har funnits i människokroppen snarare än att komma in i den senare. Om symbiotiska bakterier var skadliga skulle de ha orsakat att människor dog ut i antiken, eller så skulle det mänskliga immunförsvaret ha utvecklats för att eliminera alla bakterier.

Detta utgör ett problem: antibakteriella metoder som används av människor kommer att döda både patogena och kommensala bakterier. Det är obestridligt att upptäckten av penicillin räddade otaliga patienter. Dessa tidiga antibiotika, producerade av ett fåtal mikroorganismer, djur och växter, kan enkelt hämma bakterietillväxt och reproduktion utan att påverka människokroppen nämnvärt. Förr i tiden ledde ett sår i storleken av ett slag ofta till döden, men antibiotika kan förhindra denna allvarliga konsekvens. Bakterier som är involverade i mänskliga livsaktiviteter är dock också måltavlor för antibiotika.

Ännu allvarligare är att de flesta antibiotika inte har ett bredspektrum. Om antibiotika kunde döda alla typer av bakterier i människokroppen skulle de återstående bakterierna snabbt reproducera sig och ockupera de tidigare kroppsområdena. Men de flesta antibiotika är effektiva mot endast en typ av bakterier. De dödar sina målbakterier och låter andra opåverkade bakterier växa okontrollerat, vilket stör den ekologiska balansen i människokroppen. Denna okontrollerade balans gör att antibiotikaokänsliga bakterier kan föröka sig, vilka är säkra i lägre mängder men patogena i högre mängder. Den snabba tillväxten av bakterier genererar också individer med genetiska mutationer som har läkemedelsresistens, vilket gör antibiotika helt ineffektiva. Till exempel är meticillinresistenta *Staphylococcus aureus* en typisk typ av bakterier som är resistenta mot flera allmänt använda antibiotika. Mängden antibiotika i naturen är knapp, men bakteriernas utveckling är snabb och obevlig. Som ett resultat kommer människor gradvis att förlora sitt skydd mot antibiotika inför läkemedelsresistenta bakterier. Så vad ska vi göra då?

Konkurrensen mellan medicinsk teknik och bakterier är en oändlig "kapprustning". Om medicinsk teknik utvecklas långsammare än bakterier muterar, kommer mänskligheten att stå inför stora katastrofer. Det är avgörande att säkerställa att tekniska framsteg håller jämna steg med bakteriella mutationer. Upptrappningen av antibiotika har blivit alltmer utmanande i kampen mot bakterier. En idé för att ta itu med detta problem är "Magi måste besegra magi", vilket innebär att man använder oändligt muterade organismer för att bekämpa oändligt muterade bakterier. Detta innebär att nya antimikrobiella organismer kontinuerligt kommer att dyka upp för att bekämpa nya bakterier. Bakteriofager är till exempel virus som kan infektera och orsaka lys av mikroorganismer som bakterier, svampar, alger, aktinomyceter eller spiroketer. De kan utvecklas tillsammans med bakterier för att upprätthålla florans ekologiska balans.

En annan lovande strategi är att öka effektiviteten hos antibakteriella metoder, vilket avsevärt kan minska doseringen av antibakteriella medel och minimera deras påverkan på normala bakterier, och därigenom bibehålla den bakteriella ekologiska balansen i människokroppen. Denna princip har väglett utvecklingen av ett flertal riktade läkemedel för behandling av olika cancerformer. Dessutom har fysiska antibakteriella medel som är svåra för bakterier att undvika genom evolutionen uppfunnits för att skydda människor, såsom termisk skada och oxidativ skada eller kombinationer av dessa. För termisk inaktivering används vissa fototermiska medel för att omvandla ljusenergi till termisk energi, vilket kan denaturera bakterieproteiner genom värme.

I denna avhandling framställdes olika typer av polymermaterial med olika funktioner med olika metoder för att uppnå högeffektiv bakteriell målinriktning och effektiv eliminering av patogena, särskilt läkemedelsresistenta, bakterier. Som vanliga material i våra liv kan polymerer existera i olika former, såsom extremt små partiklar, flytande som lim och gelform som gelé, med olika kemiska funktionella grupper. Denna mångsidighet gör att de enkelt kan modifieras. Till exempel kan molekylärt präglade polymerer kallas "artificiella lås" som känner igen "molekylära nycklar". I detta fall kan komponenter på bakteriernas yta, såsom små molekyler, kolhydratkedjor eller proteiner, fungera som "molekylära nycklar" för molekylärt präglade polymerer, vilket ger polymererna bakteriell målinriktningsförmåga. Genom att välja specifika monomermolekyler eller använda polymerer för att bära värmeproducerande ämnen kan polymerer också generera värme under ljusbestrålning, och termisk skada har visat sig vara en effektiv steriliseringsmetod mot läkemedelsresistenta bakterier. Dessutom har polymerer som kan förstöra de negativt laddade cellväggarna hos läkemedelsresistenta patogener genom sin inneboende positiva laddning och bära andra funktionella material också studerats. Som ett resultat av detta visar denna avhandling de olika tillämpningarna av polymermaterial som desinfektionsmedel mot olika patogena bakterier.

Abstract

Pathogenic bacterial infections lead to bacterial resistance and biofilm formation, causing significant suffering and presenting an urgent issue to be addressed. Polymer materials have garnered considerable attention in the antibacterial field due to their functional moldability and molecular structure designability. These materials can achieve various antibacterial functions by regulating their monomer composition to avoid resistance issues and remove stubborn biofilms. Additionally, they can acquire functions such as bacterial recognition, hemostasis, and imaging through modification or regulation of the polymer structure. Polymer materials also possess broad-spectrum antibacterial effects and low toxicity, making them ideal antibacterial agents.

In this thesis, we synthesized four different types of functional antibacterial polymer materials and explored their capabilities in various antibacterial scenarios. Firstly, a photothermal antibacterial polymer with molecularly imprinted sites was synthesized for targeted photothermal antibacterial action against *Pseudomonas aeruginosa*. Building on the excellent antibacterial effect of photothermal therapy, a photothermal conjugated polymer was further utilized and combined with chitosan-based cryogel for potential wound hemostasis and bacterial infection treatment. Additionally, photothermal antibacterial therapy was enhanced using molecularly imprinted polymers to improve the photothermal and fluorescence imaging capabilities of aggregation-induced emission molecules for treating methicillin-resistant *Staphylococcus aureus*. Furthermore, a polymer brush with quaternary ammonium salt and Cu-doped quantum dots was employed for bacterial binding, imaging, and synergistic antibacterial action.

In summary, this thesis presents a series of polymer materials designed to address issues such as drug resistance and biofilms caused by bacterial infections. Different techniques such as molecular imprinting, borate affinity, and photothermal antibacterial methods have been employed to meet complex antibacterial requirements. We hope these efforts provide meaningful references and support for the further application and development of polymer materials in antibacterial applications.

List of Papers

This thesis is based on the following scientific papers, which will be referred to in the text by their Roman numerals. The publications and manuscripts are appended at the end of the thesis.

Paper I

Qicheng Zhang, Ming Zhang, Zheng Huang, Yi Sun, and Lei Ye, Molecularly imprinted polymers for targeting lipopolysaccharides and photothermal inactivation of *Pseudomonas aeruginosa*. *ACS Applied Polymer Materials*, 2023, 5, 3055-3064.

Paper II

Qicheng Zhang, Si Chen, Xiaoting Xue, Solmaz Hajizadeh, Tomohiko Yamazaki, and Lei Ye, Cationic polymer brushes functionalized with carbon dots and boronic acids for bacterial detection and inactivation. *ACS omega*, 2025, 10, 14536-14546.

Paper III

Qicheng Zhang, Zhurun Fang, Jiarong Zhang, Qifei Yang, Ming Zhang, and Lei Ye, Photothermal cryogels for rapid hemostasis and antibacterial treatment in potential chronic wound application. *Manuscript*

Paper IV

Qicheng Zhang, Ming Zhang, and Lei Ye, Protein-imprinted polymer nanoparticles equipped with aggregation-induced emission for enhanced photothermal therapy against MRSA. *Manuscript*

Publications not included in this thesis:

Paper I

Man Zhang, Qicheng Zhang, and Lei Ye. Colorimetric aptasensing of microcystin-LR using DNA-conjugated polydiacetylene. *Analytical and Bioanalytical Chemistry*, 2024, 416, 7131-7140.

Paper II

Lei Ye, Tong Zhang, and Qicheng Zhang. Molecular recognition polymer microspheres and nanoparticles for nonseparation assays: the Mosbach imprint. *TrAC Trends in Analytical Chemistry*, 2025, 194, 118370.

My contributions to the papers

Paper I

I designed most of the experiments with the help of coauthors, performed most of the experiments and analyzed all the experimental data with the assistance of coauthors. I wrote the first draft of the paper and made revisions together with other coauthors.

Paper II

I designed the experiments with the assistance of coauthors, performed most of the experiments and analyzed all the experimental data. I wrote the first version of the manuscript and revised it together with other coauthors.

Paper III

I designed the experiments, performed most of the experiments and all the experimental analysis. I wrote the first draft of the paper and made initial revisions together with other coauthors.

Paper IV

I designed the experiments, performed all the experiments and the experimental analysis. I wrote the first draft of the paper and made initial revisions to it.

Abbreviations

ACQ	Aggregation-caused quenching
AIE	Aggregation-induced emission
ARS	Alizarin red S
CDs	Carbon dots
CDC	Centers for Disease Control and Prevention
CHX	Chlorhexidine
CP NPs	Conjugated polymers nanoparticles
D-A	Donor-acceptor
<i>E. coli</i>	<i>Escherichia coli</i>
EPS	Extracellular polymeric substance
FDA	Food and Drug Administration
GMA	Glycidyl methacrylate
LPS	Lipopolysaccharide
METAC	[2-(methacryloyloxy)-ethyl]trimethylammonium chloride
MIPs	Molecularly imprinted polymers
MOFs	Metal-organic frameworks
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NIH	National Institutes of Health
NIR	Near-infrared
PDA	Polydopamine
Ppy	Polypyrrole
PS	Polystyrene
<i>P. aeruginosa</i>	<i>Pseudomonas aeruginosa</i>
PTAs	Photothermal agents
PTT	Photothermal therapy
QACs	Quaternary ammonium compounds
QS	Quorum sensing

ROS	Reactive oxygen species
SI-ATRP	Surface-initiated atom transfer radical polymerization
SPA	Staphylococcal Protein A
WHO	World Health Organization

Chapter 1 Introduction

1.1 Background

Bacteria are among the most well-known and ancient microorganisms, having existed on Earth for approximately 3.5 billion years. Due to their strong adaptability, species diversity, and ease of variation, bacteria are ubiquitous in our environment, found in food, air, water, soil, animals, and plants.^{1,2} Bacteria have co-evolved with humans since the dawn of life and play a crucial role in promoting human health. For instance, certain bacterial populations coexist with human organs or tissues, participating in metabolism and immune regulation. Remarkably, while the human body comprises billions of cells, it harbors a similar number of bacteria in areas such as the eyes, enamel, and gut.^{3,4}

Despite their beneficial roles, bacteria are often associated with negative images due to their responsibility for numerous animal and plant diseases, as well as food spoilage. Only a small fraction of bacteria are beneficial to humans; most bacterial populations are pathogenic and can invade the human body, causing infections that significantly impact health. Bacterial invasion can lead to symptoms ranging from mild conditions like the common cold and fever to severe complications such as sepsis, pneumonia, gastritis, and other systemic issues, posing serious threats to human life.^{5,6}

Although antibiotics, notably penicillin, have saved countless lives from bacterial infections since their discovery in 1928, their misuse has led to decreased effectiveness and the emergence of bacterial resistance. This resistance includes not only single-drug resistance but also the development of "super bacteria" resistant to multiple antibiotics, which poses a significant threat to global public health.^{7,8} Studies by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) indicate that at least 700,000 people worldwide die from bacterial infections annually, with more than half of these deaths caused by bacteria resistant to commonly used antibiotics.^{9,10} Furthermore, excessive bacterial invasion can lead to the formation of bacterial biofilms, which help bacteria resist antibiotics and the host's immune system, resulting in prolonged wound healing.¹¹

To address the challenge of bacterial infections and drug-resistant bacteria, various types of materials have been developed for antibacterial applications under different conditions. These materials include natural biological antimicrobials, inorganic

antimicrobials, organic antimicrobials, and composite antimicrobials. Typically, these antimicrobials interfere with or disrupt the normal metabolic activities of microorganisms through physical or chemical methods, thereby affecting their growth and reproduction.

Among these, polymeric antimicrobials, a type of high molecular weight organic antimicrobials, are widely used in the design of antimicrobial materials due to their significant advantages, such as functional controllability and molecular structure designability. Depending on the preparation method, there are currently three main design approaches for polymeric organic antimicrobials: (1) Directly polymerizing organic monomers with antimicrobial functions to form polymeric organic antimicrobials. (2) Introducing molecules or materials with antimicrobial activity into the polymer backbone through side-chain grafting *via* covalent or coordination bonds. (3) Using non-antimicrobial monomers to form polymers that can exhibit antimicrobial activity through physical interactions, such as the photothermal inactivation effect of polydopamine (PDA).

Additionally, the unique physicochemical properties of polymers make them easy to endow with other functions, such as targeting and imaging capabilities. Therefore, polymeric organic antimicrobials are considered one of the most ideal antimicrobial materials due to their broad-spectrum and highly efficient antibacterial ability, low toxicity, high safety, and high functional structure tunability.

1.2 Aim and scope of the thesis

The aim of this thesis is to design and synthesize antibacterial materials of various types and functions based on potent polymers, targeting the elimination of different kinds of pathogenic bacteria, particularly drug-resistant bacteria under diverse conditions. To achieve this goal, the synthetic polymer materials focus primarily on bacterial binding functions and photothermal antibacterial abilities, which can efficiently eliminate bacteria without being hindered by drug resistance and can even impact biofilm formation. Additionally, this thesis also discusses sterilization methods related to electrostatic interactions and oxidative stress-induced membrane disruption. By designing polymers with diverse structures and forms and integrating molecules or nanomaterials with different functions into polymer materials, this research aims to provide a theoretical foundation and innovative approaches for polymer-based antibacterial materials to address bacterial infections and drug resistance.

Paper I describes the development of lipopolysaccharide (LPS)-imprinted photothermal molecularly imprinted polymers (PMIPs) for the efficient capture and elimination of *Pseudomonas aeruginosa* (*P. aeruginosa*). These PMIPs were synthesized using polydopamine (PDA) as the supporting core and imprinting

matrix with LPS from *P. aeruginosa* as the template. The resulting molecularly imprinted polymers (MIPs) were evaluated for their photothermal effect and bacteria recognition behaviors using LPS and *P. aeruginosa* as models. The biocompatibility and biofilm removal capacity were also explored.

Paper II describes multifunctional nanocomposites designed for simultaneous bacterial binding, fluorescence labeling, and synergistic antibacterial treatment. These nanocomposites were created by introducing Cu-doped carbon dots (CDs) modified with boronic acid and monomers containing quaternary ammonium compounds (QACs) onto copolymers generated by surface-initiated atom transfer radical polymerization (SI-ATRP). The study investigated the results of bacterial fluorescence labeling from boronic acid, imaging from CDs, and deactivation from the positive charge of QACs and reactive oxygen species (ROS) of CDs.

Paper III describes the development of rapidly hemostatic and efficiently photothermal antibacterial cryogels (CP@Gel) for potential chronic wound healing. These cryogels were achieved by combining 980 nm-laser-responsive photothermal conjugated polymer nanoparticles (CP NPs) with chitosan-based cryogels. CP NPs were immobilized into cryogels *via* nanoprecipitation, followed by grafting using a column-flow method. The hemostatic behavior and photothermal effect were studied on methicillin-resistant *Staphylococcus aureus* (MRSA) and mature MRSA-formed biofilms.

Paper IV describes the creation of Staphylococcal Protein A (SPA)-imprinted polymer NPs equipped with aggregation-induced emission (AIE) for enhanced photothermal therapy (PTT) for MRSA. The fluorescence intensity and photothermal effect of AIE molecules were enhanced after being loaded into polystyrene (PS) nanospheres, attributed to the molecular motion affected by PS. The imprinted polymer shell was further formed on the PS nanospheres using the microemulsion polymerization method to bind SPA on the surface of MRSA.

Chapter 2 Bacteria and their risks

2.1 Basic information of bacteria

To effectively address the problem of bacteria, it is essential to first understand their basic characteristics. Microorganisms are a general term for a class of tiny organisms that can only be observed with the aid of a microscope. They are widely present in nature and are closely related to human production and life. Based on their cellular structure, degree of differentiation, and chemical composition, microorganisms can be classified into three major categories (**Figure 1**):

- **Non-cellular structural microorganisms:** These have the simplest structure, consisting only of a single nucleic acid (RNA or DNA) and a protein capsid. They must survive within obligate living cells to proliferate.
- **Prokaryotic cell-type microorganisms:** Their main characteristic is the presence of a nucleoid formed by coiled DNA, without a nucleolus or nuclear membrane. The ribosome is the only organelle within the cell.
- **Eukaryotic cell-type microorganisms:** These can be single-celled or multi-celled and possess nucleoli, nuclear membranes, typical nuclear structures, and well-developed organelles.¹²⁻¹⁴

Bacteria are a type of prokaryotic single-celled organism and are the most numerous among all living things.^{15, 16} They were first observed by the Dutchman Antonie van Leeuwenhoek using a homemade single-lens microscope.¹⁷ Subsequently, Louis Pasteur used the swan-neck flask experiment to demonstrate that bacteria are produced by existing bacteria in the environment rather than occurring spontaneously. Based on this discovery, he invented the famous "Pasteurization method" and is hailed as the "father of microbiology."¹⁸

Bacteria have a significant impact on human activities. On one hand, many diseases are caused by bacteria, including influenza, diarrhea, tuberculosis, plague, and anthrax.^{19, 20} On the other hand, many aspects of human production and life are also dependent on bacteria. For instance, a large number of bacteria in the human body are essential for maintaining basic physiological functions.²¹ Additionally, humans also utilize bacteria to produce cheese, yogurt, and alcohol. Recent research even explores the use of engineered bacteria to purify wastewater, generate electricity, and treat diseases.²²⁻²⁴

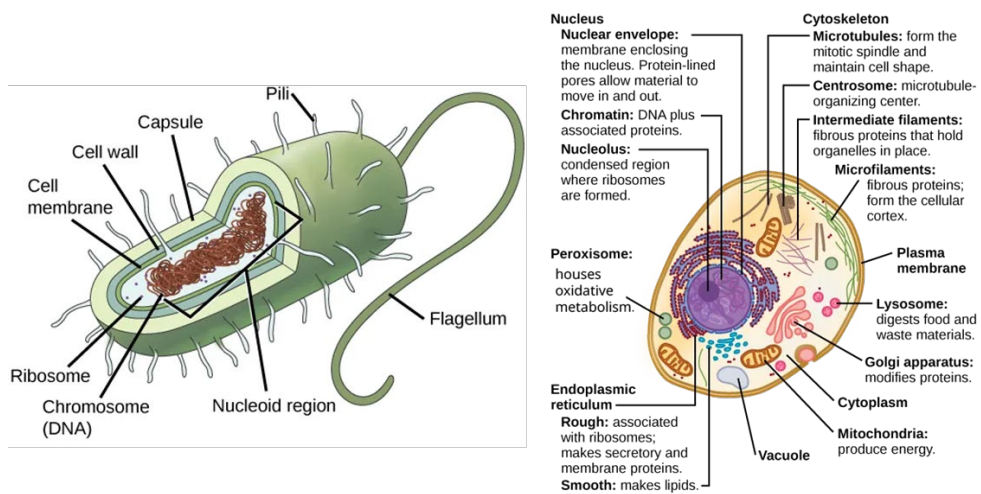


Figure 1. Structure and contents of prokaryotic and eukaryotic cells.²⁵ Reproduced with permission from reference 25. Adapted from OpenStax, Biology 2e, CC BY 4.0.

2.1.1 Classification

Bacteria have a long history and are prone to mutation, resulting in a wide variety of types. Based on their shapes, bacteria can be classified into three categories: cocci, bacilli, and spirals (including spirillum and spirochetes) (**Figure 2**):

- **Cocci:** These bacteria have an oval or spherical shape. Depending on their arrangement, they can be further divided into single cocci, diplococci, streptococci, staphylococci, etc.²⁶
- **Bacilli:** These bacteria have a rod-like shape and can be classified into short rods with similar length and width, and long rods with significant differences in length and width. Based on their cellular arrangement, they can also be divided into diplobacilli, streptobacilli, and spore-formers.^{27, 28}
- **Spirilla:** These bacteria can be classified into vibrio, spirillum, and spirochetes according to the degree of curvature of their bodies.²⁹

In addition to shape, bacteria can be classified based on their lifestyle:

- **Autotrophic bacteria:** These bacteria produce their own food.
- **Heterotrophic bacteria:** These bacteria rely on external sources of organic carbon. Heterotrophic bacteria include saprophytic bacteria (which feed on dead organic matter) and parasitic bacteria (which feed on living hosts).^{30, 31}

Bacteria can also be classified based on their response to oxygen:

- **Aerobic bacteria:** These bacteria can only grow in the presence of oxygen.
- **Anaerobic bacteria:** These bacteria can only grow in the absence of oxygen.
- **Facultative anaerobic bacteria:** These bacteria can grow in both aerobic and anaerobic environments.³²

Additionally, some bacteria can thrive in extreme environments, such as thermophilic bacteria in hot springs, psychrophilic bacteria in glaciers, and acidophilic or alkaliphilic bacteria in acidic or alkaline environments.^{33, 34}

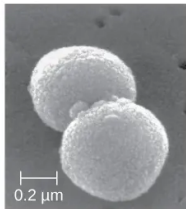
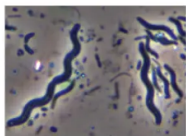
Common Prokaryotic Cell Shapes			
Name	Description	Illustration	Image
Coccus (pl. cocci)	Round		
Bacillus (pl. bacilli)	Rod		
Vibrio (pl. vibrios)	Curved rod		
Coccobacillus (pl. coccobacilli)	Short rod		
Spirillum (pl. spirilla)	Spiral		
Spirochete (pl. spirochetes)	Long, loose, helical spiral		

Figure 2. Classification of bacteria on the basis of shape.³⁵ Reproduced with permission from reference 35. Adapted from OpenStax, Microbiology, CC BY 4.0.

2.1.2 Structure

The main components of bacteria include the cell wall, cell membrane, cytoplasm, and nucleoid. Some bacteria also possess appendages such as flagella, capsules, and spores.^{36, 37} The cell wall, located at the outermost layer of the bacterial structure, protects the shape of bacteria and facilitates material exchange. The components of the cell wall are complex, and its structure varies among different bacteria.³⁸ Based on differences in the cell wall, bacteria can be classified into two types using the Gram staining method: Gram-positive bacteria have a dense cell wall and stain purple, while Gram-negative bacteria have a loose cell wall structure and stain red.³⁹

As shown in **Figure 3**, the cell wall structure of Gram-positive bacteria is simple, with 90% of the outer layer being peptidoglycan and 10% being phospholipase. In typical *Staphylococcus aureus*, there are also surface proteins such as SPA that can be used for specific targets and immunological research.^{40, 41} The cell wall of Gram-negative bacteria is thinner and more complex than that of Gram-positive bacteria, consisting of multiple components such as LPS, bacterial outer membrane, lipoprotein, and peptidoglycan from the outside to the inside.⁴² Among these, the endotoxin mainly composed of LPS is the main virulence factor of Gram-negative bacteria and can be further divided into O antigen, core polysaccharide, and lipid A, which can also be used as specific targets for bacterial recognition.

The cell membrane of bacteria is a common double-layer biological membrane, mainly composed of phospholipids, with a thickness of about 8-10 nm.^{43, 44} In the nucleoid area of bacteria, a nuclear body composed of a circular double-stranded DNA molecule carries genetic information, and the cytoplasm contains ribosomes for protein synthesis, plasmids for self-replication, and cytoplasmic granules for temporary storage of nutrients. Additionally, some bacteria have capsules for defense against white blood cell phagocytosis, flagella for movement, bacterial invasion and adhesion, and spores for reproduction in adverse environments.^{45, 46}

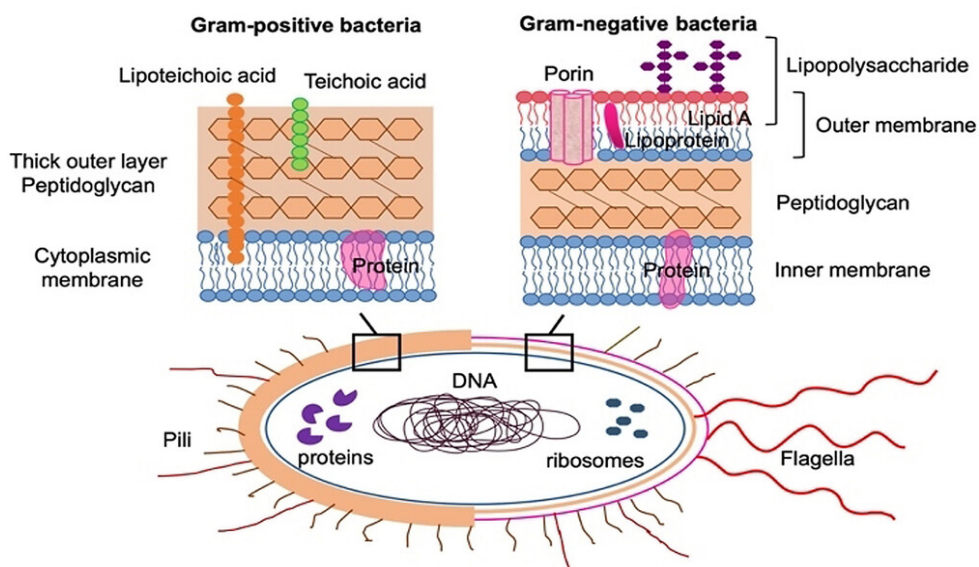


Figure 3. Main structures of Gram-positive and Gram-negative bacteria cell walls and basic cell structure of bacteria.⁴⁷ Reproduced with permission from reference 47. Copyright 2022 John Wiley and Sons.

2.2 Bacterial infection issues

Bacterial infections are primarily caused by pathogenic bacteria invading the human body through the respiratory tract or mosquito bites, leading to infections and potentially infectious diseases. Pathogenic bacteria can breach the human immune system's defenses, rapidly multiply, spread, and secrete bacterial toxins that damage the body.^{48, 49} Bacterial toxins are classified into two types: exotoxins and endotoxins:

- **Exotoxins:** These are toxic substances produced by bacteria in the external environment during their growth. They are mainly composed of proteins, which have relatively weak heat resistance but strong toxicity.
- **Endotoxins:** These are LPS associated with the cell wall of Gram-negative bacteria. Endotoxins are released only when the bacteria are destroyed, and they have strong heat resistance but relatively weak toxicity.⁵⁰⁻⁵²

As bacteria continue to multiply and evolve within the human body, more complex issues such as biofilms and drug resistance can arise.

2.2.1 Biofilm

Research conducted by the National Institutes of Health (NIH) in the United States indicates that over 75% of bacterial infection cases originate from biofilms.⁵³ Infections caused by biofilms are extremely difficult to treat and often result in chronic infections, posing a long-term threat to human health. Bacterial biofilms are bacterial colonies formed when bacteria embed themselves within the extracellular polymeric substance (EPS) matrix that they synthesize during the process of infecting the human body. This matrix is composed of proteins, polysaccharides, peptidoglycan, and DNA, and its production and diffusion are mainly regulated by quorum sensing (QS).⁵⁴⁻⁵⁶

The EPS acts like glue, binding the bacteria in the biofilm together and forming a dense and thick barrier around the bacteria. This barrier not only protects the bacteria from the host immune system and environmental influences but also prevents the diffusion and penetration of antibacterial drugs or materials. Additionally, the bacterial cells within the biofilm exhibit significant heterogeneity in metabolic state and gene expression, contributing to their drug resistance.⁵⁷⁻⁵⁹

The formation of bacterial biofilms consists of several stages (**Figure 4**):

- **Initial Stage:** Bacteria in a reversible adhesion stage attach to the host surface and release EPS, making the attachment on the substrate more stable and entering the irreversible adhesion aggregation stage.
- **Stabilization:** After stabilization, the bacteria rapidly proliferate and form colonies within the peptidoglycan membrane, entering the mature stage of the biofilm and providing a bacterial reservoir for systemic chronic infections.
- **Maturation:** The mature biofilm releases free bacteria to form new biofilms on the substrate surface.^{60, 61}

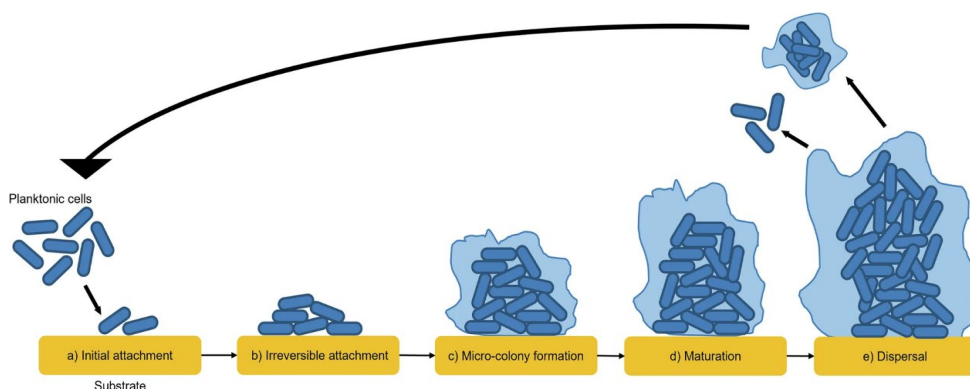


Figure 4. The process of biofilm formation: bacteria initially adhere to substrate, followed by irreversible attachment, cell growth, biofilm maturation and redispersion of bacteria.⁶² Reproduced with permission from reference 62. Copyright 2024 Springer Nature.

2.2.2 Drug-resistance

Bacterial resistance can be fundamentally classified into two types: intrinsic and acquired resistance.⁶³ Intrinsic resistance refers to the inherent ability of bacteria to be insensitive or selectively permeable to antibiotics. Gram-negative bacteria exhibit stronger intrinsic resistance than Gram-positive bacteria due to their more complex outer membrane.^{64, 65}

Acquired resistance, which is more common due to the overuse of antibiotics, occurs when bacteria evolve multidrug resistances to various antibiotics that they were originally sensitive to. Acquired resistance mainly arises through genetic mutations in bacterial populations and the acquisition of genes transferred from adjacent drug-resistant bacteria.⁶⁶ The molecular mechanisms of acquired resistance include (**Figure 5**):

1. Producing enzymes that can degrade or bind to antibiotic molecules, preventing antibiotics from binding to the bacteria.
2. Overexpressing proteins (efflux pumps) that actively extrude antibiotics from bacterial cells, reducing the antibiotic concentration.
3. Altering the permeability of the bacterial outer membrane to reduce the uptake of antibiotics.
4. Adjusting genes to change the original target sites of bacteria that can be recognized by antibiotics or generating new binding sites to reduce the binding effect of drugs to the original target.⁶⁷⁻⁷⁰

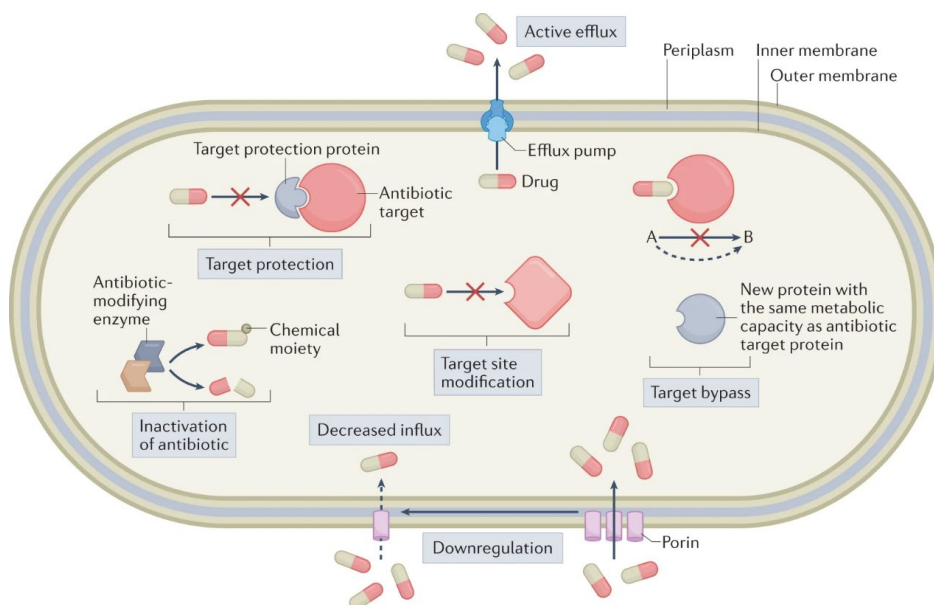


Figure 5. Overview of the molecular mechanisms of antibiotic resistance.⁷¹ Reproduced with permission from reference 71. Copyright 2022 Springer Nature.

Chapter 3 Antibacterial strategies and materials

3.1 Antibacterial strategies

To address the various issues related to bacterial infections, current antibacterial strategies primarily follow two directions. The first approach involves the continuous development of new antibiotics that have not yet encountered drug resistance, while also reducing drug dosages but still ensure therapeutic efficacy. The second approach focuses on developing new antibacterial agents based on non-antibiotic methods, which can prevent the occurrence of drug resistance by employing novel antibacterial mechanisms.^{72, 73} Currently, antibacterial methods can be broadly classified into three categories: physical, chemical, and biological processes.

Physical antibacterial methods primarily aim to kill bacteria through physical means such as temperature changes and radiation. These methods can be divided into non-thermal and thermal antibacterial methods. Non-thermal antibacterial methods include adsorption, filtration, ultraviolet light, microwaves, and radiation. However, these methods have limited application scenarios and are mostly used in external environments such as food processing and hospital disinfection, making *in vivo* applications challenging.⁷⁴⁻⁷⁶ In recent years, photodynamic and sonodynamic antibacterial therapies based on nano antibacterial agents have been widely used for *in vivo* antibacterial research because they can generate reactive oxygen species (ROS) under physical stimulation, which poses no risk of resistance.^{77, 78} Thermal antibacterial methods involve using physical means such as flames, steam, and lasers to raise the temperature of bacteria to destroy them. The photothermal antibacterial method, which generates local heat through photothermal agents (PTAs) under near-infrared (NIR) irradiation, also shows promising application prospects.⁷⁹⁻⁸¹

Chemical antibacterial methods primarily utilize chemical drugs that can directly kill bacteria or materials that produce bacteria-sensitive chemical substances to eliminate them. Antibiotics, as one of the most typical chemical antibacterial agents, can kill bacteria by inhibiting the synthesis of bacterial cell walls, altering the permeability of the cell membrane, hindering bacterial protein synthesis, and

interfering with bacterial nucleic acid replication.⁸² Additionally, other common chemical antibacterial substances, including various metal ions, ROS, and positively charged substances, can effectively damage bacterial structures or interfere with bacterial growth processes. These substances have also been widely used for *in vivo* antibacterial applications.^{83, 84}

Biological antibacterial methods utilize bacteria or engineered bacteria, viruses, or biological organisms that produce polypeptides to kill or inhibit the reproduction of harmful bacteria. For example, probiotics or engineered bacteria can compete with pathogenic bacteria for nutrients and living space, thereby inhibiting their growth and regulating the balance of intestinal flora. Bacteriophages, a type of virus, can specifically parasitize bacteria, using the bacterial metabolic system for self-replication and ultimately lysing the bacteria. Antibacterial peptides are small polypeptide molecules produced in the body that can interact with bacterial membranes, alter their permeability, and cause the leakage of intracellular substances, leading to bacterial death.⁸⁵⁻⁸⁷ The following sections will provide a detailed introduction to one physical, chemical, and biological antibacterial method, respectively.

3.1.1 Photothermal therapy

PTT is a novel antibacterial strategy that utilizes PTAs to convert light energy into heat energy under NIR light irradiation, thereby killing bacteria through high temperatures. It is generally believed that the fluidity of bacterial cell membranes changes and the bacteria become inactive when the temperature exceeds 50°C.^{88, 89} Therefore, the excellent photothermal antibacterial effect and the absence of drug resistance issues make PTT widely studied in the antibacterial field.

PTT also has the advantages of low invasiveness, few side effects, and high spatiotemporal selectivity, making it a safe and efficient antibacterial method.^{90, 91} The PTT induced by NIR light (700-1400 nm) can locally destroy the cell membrane, cause the cell wall to rupture, and denature proteins and enzymes, thereby inducing bacterial cell death.⁹² Light in this wavelength range not only has good tissue penetration but also causes no photodamage to normal tissues, making it suitable for *in vivo* applications and approved by the US Food and Drug Administration (FDA) for clinical use.⁹³ Additionally, PTT can be combined with other treatment methods, such as ROS or metal ions, to perform mild high-temperature (>43°C) antibacterial treatment, minimizing tissue damage to the greatest extent (**Figure 6**).^{94, 95}

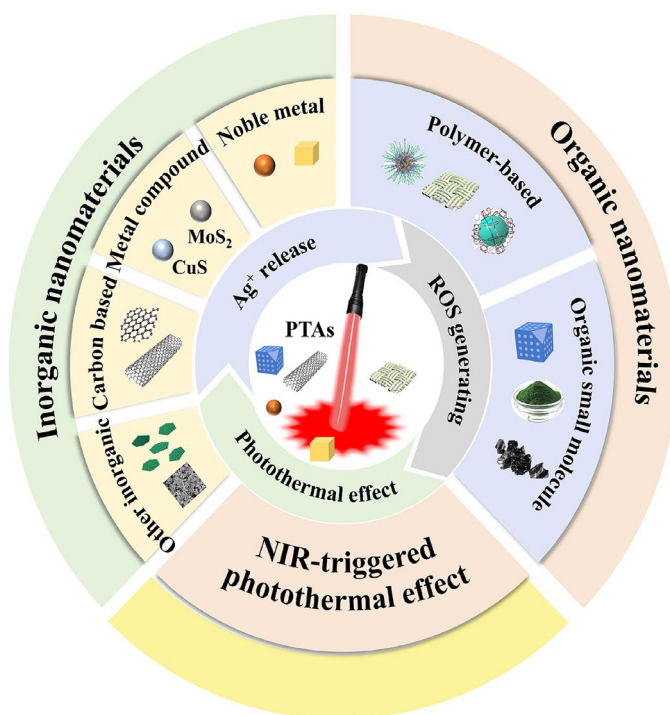


Figure 6. Overview of photothermal antibacterial nanomaterials.⁹⁶ Reproduced with permission from reference 96. Copyright 2024 Oxford University Press.

In addition to sterilization, PTT can also damage mature biofilms and inhibit the formation of new biofilms by regulating the genes involved in biofilm formation. Xu et al. found that genes involved in arginine biosynthesis and arginine catabolism, such as *argF*, *argH*, *arcC*, *arcA*, and *arcD*, were significantly upregulated after photothermal treatment of mature biofilms, which inhibited biofilm formation and facilitated their dissociation. PTT also shows potential immunomodulatory capabilities.⁹⁷ Some studies have demonstrated effective regulation of inflammatory factors using mild high temperatures (approximately 40°C). These studies combined activated heat shock protein 1 with the 5'-untranslated region of the inflammatory factor TNF- α to significantly inhibit TNF- α expression. Conversely, higher levels of PTT can induce inflammatory responses and promote the production of pro-inflammatory cytokines. Some researchers used the photothermal agent polypyrrole (Ppy) to induce PTT activation of the complement receptor system, effectively regulating the phagocytic function of macrophages.^{98, 99}

3.1.2 Cationic antibacterial agents

Because the surface of bacteria usually exhibits a negative charge, it is easy for bacteria to adsorb positively charged antibacterial materials (such as polymers and metals) through electrostatic interactions to achieve an antibacterial effect.¹⁰⁰ For Gram-negative bacteria, their cell membrane surface contains a large amount of negatively charged LPS, which can be adsorbed and bound by positively charged antibacterial materials. Subsequently, these antibacterial materials can compete with Ca^{2+} and Mg^{2+} in the LPS and replace the binding sites, thereby neutralizing the surface charge of the bacteria and changing their surface hydrophobicity. Ultimately, the outer membrane of the bacteria will rupture or perforate, forming transmembrane ion channels, causing the substances inside the bacteria to leak out and resulting in bacterial death.¹⁰⁰⁻¹⁰³

For Gram-positive bacteria, negatively charged substances such as muramic acid, glucuronic acid, and phospholipids on the cell membrane surface also make the cell membrane surface negatively charged, allowing them to bind to positively charged antibacterial materials. In addition to the mechanism described above that kills cells by targeting the cell membrane, some positively charged antibacterial materials can enter the interior of the cell membrane and combine with intracellular macromolecules, thereby rendering their functions ineffective and causing bacterial death (**Figure 7**).^{104, 105}

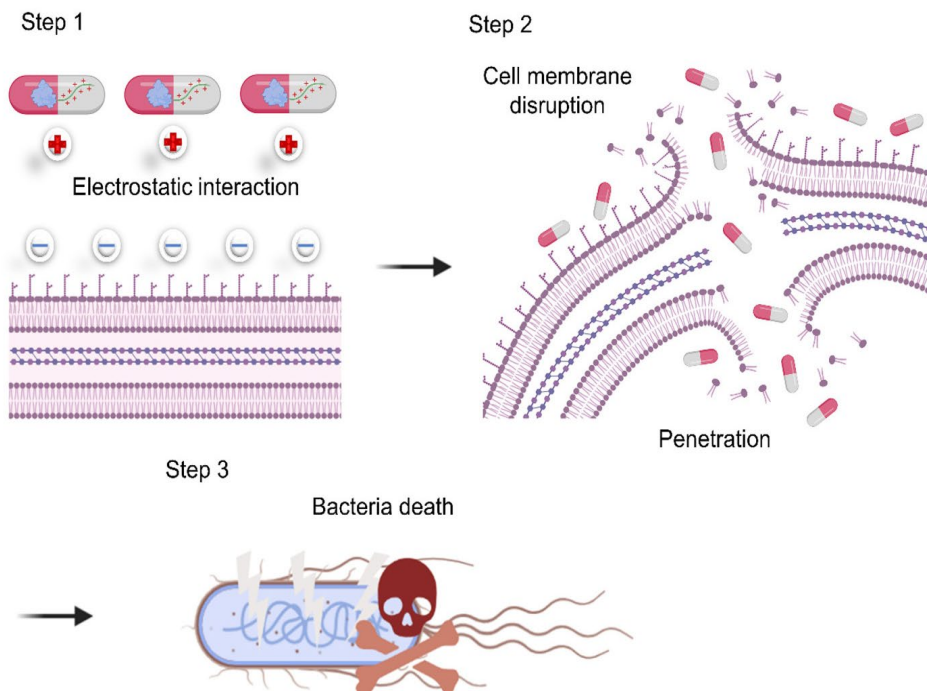


Figure 7. The antibacterial mechanism of cationic polymers.¹⁰⁶ Reproduced with permission from reference 106. Copyright 2022 American Chemical Society.

3.1.3 Antimicrobial peptides

Antimicrobial peptides are natural antibacterial agents found in living organisms. Typically composed of 7 to 100 amino acids, they are emerging as a new generation of antibacterial drugs due to their low toxicity, high efficiency, and high selectivity.^{107, 108} Natural antimicrobial peptides are widely distributed in nature and come in various types, extracted from insects, plants, microorganisms, and various animals. Besides their antibacterial properties, they can also be used for antifungal, antiviral, anti-cancer, and anti-inflammatory purposes.^{109, 110}

Commonly used antimicrobial peptides are mainly cationic compounds, and their antibacterial mechanism is similar to that of positively charged antibacterial materials. They kill bacteria by targeting the cell wall, interacting with the cell membrane, and interfering with the activities of intracellular organelles or destroying the bacterial structure. Due to the various action pathways of antimicrobial peptides, bacterial resistance can be significantly reduced, making them a promising antibacterial agent.^{111, 112}

Additionally, various artificially designed and synthesized antimicrobial peptide analogues are constantly emerging, inspired by the unique structure and antibacterial mechanism of natural antimicrobial peptides. Compared to natural antimicrobial peptides, these analogues usually have better protease stability, stronger permeability, lower flexibility, and higher selectivity (**Figure 8**).^{113, 114}

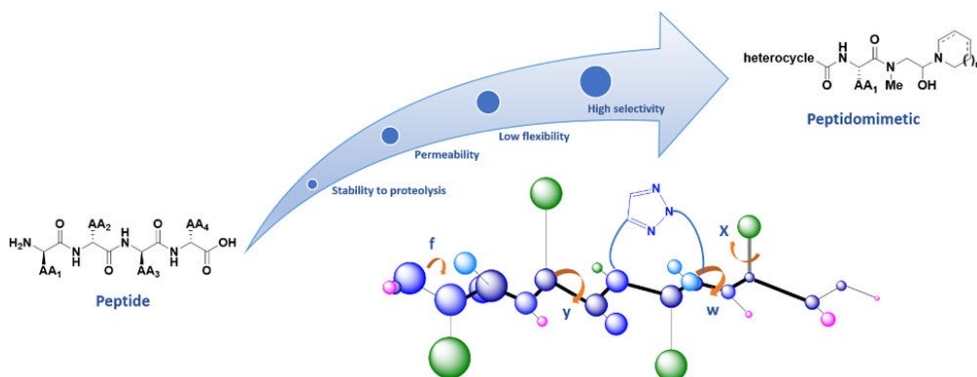


Figure 8. The advantages of antimicrobial peptide analogues.¹¹⁵ Reproduced with permission from reference 115. Copyright 2022 American Chemical Society.

3.1.4 Other antimicrobial materials

In recent years, with the continuous development of nanotechnology, nanoscale antibacterial materials have been extensively explored, leading to significant progress in various synergistic antibacterial methods based on these materials. For instance, ultrasound has been used to activate antibacterial peptides and generate ROS for synergistic antibacterial effects, while antibiotics have been combined with PTT to reduce the dosage of antibiotics.^{88, 116} By combining multiple antibacterial methods, various complex and challenging multi-drug-resistant bacterial infections can be effectively addressed.

3.2 Antibacterial materials

Because most antibacterial methods rely on antibacterial materials to be effective, various types of these materials have been extensively studied. Antibacterial materials can be mainly classified into natural antibacterial agents, inorganic antibacterial agents, organic antibacterial agents, and composite antibacterial agents.¹¹⁷ Generally speaking, these materials can interfere with the normal metabolic activities of microorganisms or directly damage their physiological structures through physical, chemical, or biological means, thereby affecting their

growth and reproduction. Some antibacterial materials can also be used as delivery carriers to promote the penetration and controlled release of antibacterial drugs to bacteria, thereby improving antibacterial efficiency. Furthermore, some antibacterial materials are designed as platforms that can integrate multiple antibacterial functions, significantly reducing the probability of bacterial resistance.^{118, 119}

3.2.1 Natural antibacterial materials

Natural antibacterial materials are organic substances with antibacterial activity extracted from animals, plants, and microorganisms. Among them, the most common animal-derived antibacterial agent is chitosan, which is obtained through the alkaline deacetylation of chitin. Chitosan has high antibacterial activity, good biocompatibility, and hemostatic effects, making it widely used in wound dressing research.^{120, 121}

Antibacterial agents derived from plants mainly include natural terpenoids, alkaloids, anthraquinones, flavonoids, tannic acids, and coumarins. These substances enable plants or their powders to exhibit antibacterial effects.¹²² Additionally, antibiotics, antibacterial peptides, bacteriophages, and other antibacterial substances extracted from microorganisms such as bacteria, fungi, and viruses are also among the most effective sterilization materials.¹²³

3.2.2 Inorganic antibacterial materials

Inorganic antibacterial materials are primarily composed of antibacterial agents made from metals such as silver, copper, zinc, and titanium, along with their derivatives.¹²⁴ These agents offer advantages such as high thermal stability, effective antibacterial properties, and no risk of drug resistance. However, they also face challenges like high cost, significant toxic side effects, and difficulty in biological applications.

The recognized antibacterial mechanisms of metal-based antibacterial materials are mainly as follows:

- **Metal Dissolution and Ion Production.** The surface of these materials undergoes metal dissolution, producing metal ions or metal NPs with bacterial toxicity. These ions bind to the bacterial cell membrane *via* electrostatic interaction, damaging its structure and causing the leakage of intracellular substances. The free metal antibacterial agents can further penetrate the bacterial membrane, entering the bacteria to destroy their DNA and proteins, leading to bacterial death.^{84, 125, 126}
- **ROS Production.** The surface of metal materials reacts with substances in the environment to produce ROS, triggering oxidative stress in bacteria and resulting in oxidative damage to bacterial organelles (**Figure 9**).¹²⁷ For example, compared to

Ag and Au, Cu-based antibacterial materials have lower costs and simpler preparation processes. Cu ions, being one of the essential elements for mammals, offer better biological safety. In terms of antibacterial activity, Cu-based materials can trigger oxidative stress reactions to produce ROS and can dissolve and release Cu^{2+} more quickly, causing the disintegration of bacterial cell membranes or the inactivation of intracellular substances.^{128, 129}

Moreover, a series of new inorganic antibacterial materials have been developed, including carbon-based materials (such as carbon quantum dots, graphene, and carbon nanotubes) and antibacterial nanoenzymes (such as metal oxides and sulfides), all of which exhibit excellent antibacterial behavior.^{130, 131}

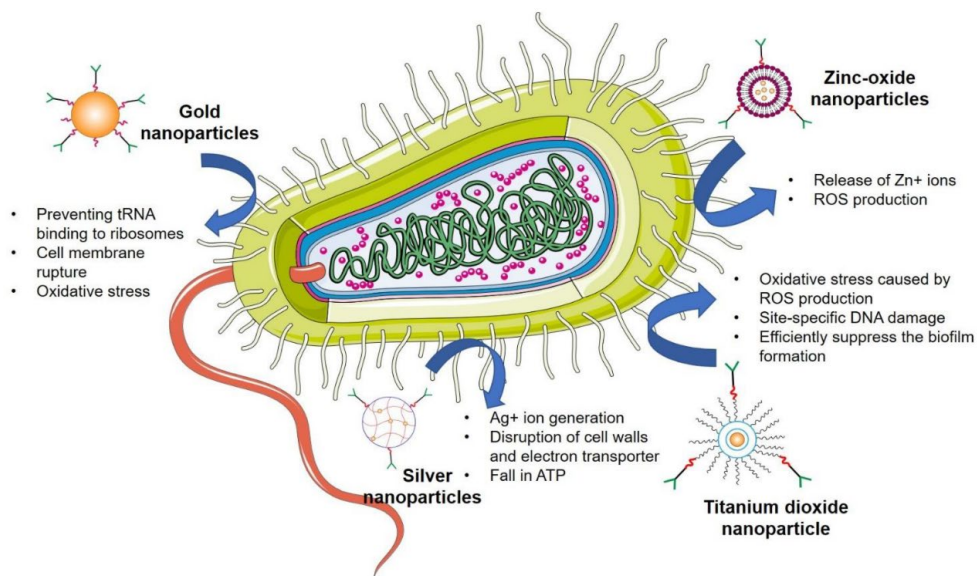


Figure 9. The antibacterial mechanism of common inorganic antibacterial materials.¹³² Reproduced with permission from reference 132. Adapted from MDPI, CC BY 4.0.

3.2.3 Organic antibacterial materials

Organic antibacterial materials consist of a series of antibacterial agents based on organic molecules or polymers. These organic molecules mainly include glycidyl compounds, alcohols, and phenols. Their antibacterial mechanisms rely more on interfering with bacterial intracellular organelles and biochemical pathways rather than just electrostatic interactions between positively charged compounds and negatively charged bacterial membranes.^{117, 133, 134}

As shown in **Figure 10**, chlorhexidine (CHX) kills bacteria by attacking the phospholipids and LPS of the bacteria and affecting their metabolic regulation

processes, while triclosan interferes with lipid synthesis by acting as a synthesis inhibitor. Compared to low-molecular weight organic antibacterial agents, high-molecular weight antibacterial agents offer advantages such as greater control, plasticity, and design flexibility for molecular structures. Common design concepts include directly polymerizing organic monomers that carry antibacterial groups through homopolymerization or copolymerization to form polymer substances, and introducing antibacterial active groups or materials with antibacterial activity through covalent grafting to form polymeric antibacterial agents within the polymer framework.^{135, 136}

Polymeric antibacterial agents can also exist in various forms to meet different antibacterial requirements, such as polymer brushes for antibacterial layers, hydrogels for treating wound infections, and polymer NPs for treating internal inflammation caused by bacteria.¹³⁷⁻¹³⁹

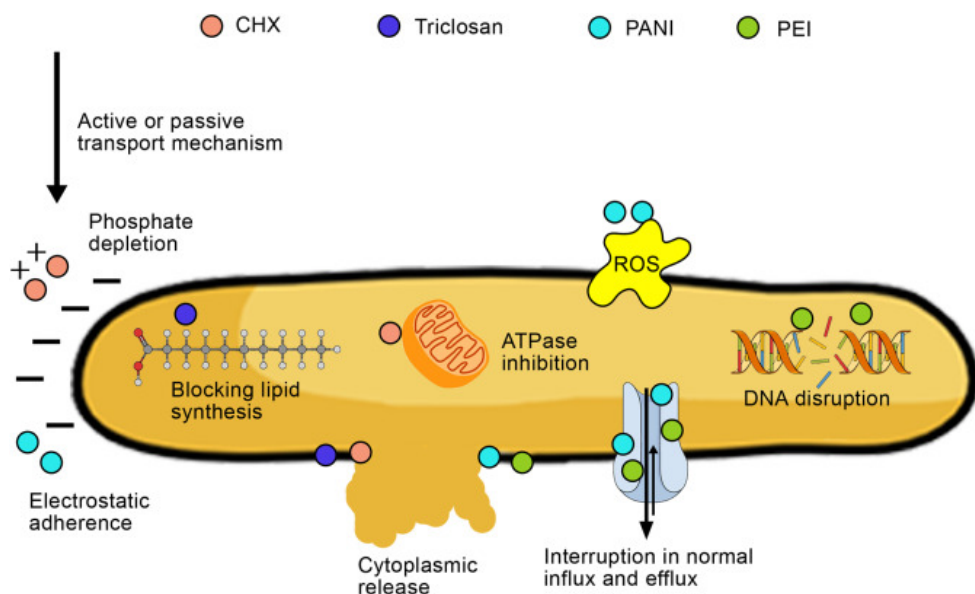


Figure 10. The antibacterial mechanism of some common organic antibacterial materials.¹⁴⁰ Reproduced with permission from reference 140. Copyright 2021 Elsevier B.V.

3.2.4 Composite antibacterial materials

Composite antibacterial materials refer to antibacterial agents synthesized by combining multiple inorganic or organic materials using physical or chemical methods. Compared to single antibacterial agents, composite antibacterial agents can exert synergistic antibacterial effects resulting from the combination of different agents and provide additional functions (such as targeting and anti-inflammatory

abilities). This enhances the antibacterial effect, expands the antibacterial spectrum, and allows adaptation to various complex antibacterial environments.

In recent years, metal-organic frameworks (MOFs) have emerged as a new type of composite antibacterial material. MOFs are formed by combining metal ions or metal clusters with polydentate organic ligands and have shown great potential in antibacterial applications. Compared to other materials, MOFs can be designed to possess different antibacterial mechanisms by adjusting the ratios of different metal nodes and organic linkers.^{141, 142} Therefore, MOFs exhibit multiple antibacterial mechanisms, including physical sterilization, stimulus-responsive sterilization, oxidative stress sterilization, photothermal sterilization, and synergistic sterilization. Additionally, MOFs have the characteristics of low toxicity and degradability, making composite antibacterial materials show broad application prospects in the antibacterial field.

Chapter 4 Antibacterial polymeric materials

4.1 Molecularly imprinted photothermal polydopamine

PTT has been proven to be a broad-spectrum antibacterial agent with no risk of drug resistance. Consequently, many photothermal polymers, such as polyaniline and Ppy, have been developed for photothermal antibacterial applications. However, their antibacterial effects are limited by thermal damage to normal tissues and the absorption of heat by the environment.^{143, 144} Therefore, it is urgent to develop precise photothermal polymers to improve their antibacterial efficiency.

MIPs are polymers with targeting abilities, capable of achieving specific recognition of template molecules through the technology of customizing "artificial locks (MIPs)" that specifically recognize "keys (templates)".¹⁴⁵ The preparation process of MIPs mainly includes three stages: first, functional monomers are mixed with template molecules to form covalent complexes or non-covalent addition products. Then, the mixture is polymerized to fix the template molecules in the three-dimensional network of the polymer. After removing the template molecules, cavities are formed that can recognize molecules with similar size, geometric shape, and functional groups to the template molecules through covalent bonds, hydrogen bonds, ionic interactions, van der Waals forces, and π - π stacking.^{146, 147} Currently, this technology has been widely applied in the biological field for the identification of small drug molecules, biomacromolecules, and even entire bacterial cells.

In Paper I, we used the boronate controllable affinity surface imprinting method to coat a new PDA imprinting polymer layer on PDA microspheres for precise targeting of *P. aeruginosa*. This method fixed the template molecules on the base microspheres by forming a boronic acid ester structure between boronic acid and *cis*-diol, thereby better forming the directional cavities of the template molecules and facilitating their adsorption and dissociation through the regulation of the boronic acid ester structure. Since the LPS part of *P. aeruginosa* contains a *cis*-diol structure that can be used for boronic acid fixation (D-rhamnose residues in the O-antigen), *P. aeruginosa* was selected as the model bacterium.

The PDA microspheres were first synthesized by self-assembly, and the amino groups on the PDA surface were used to immobilize the boronic acid molecules through the Schiff base reaction. Then, LPS was introduced on the microsphere surface, and a new PDA coating was formed. After removing the LPS template molecules, the polymer materials could precisely bind to *P. aeruginosa* and significantly increase the heat release of PTT to the bacteria (**Figure 11**).

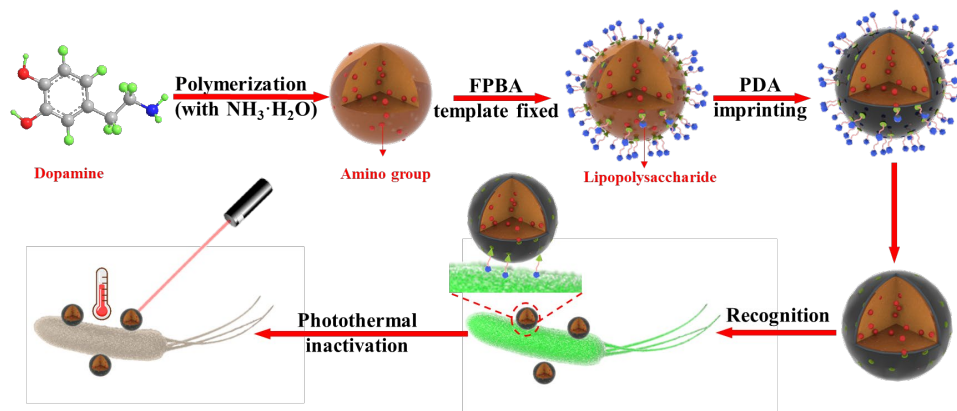


Figure 11. Schematic illustration for the preparation of PMIP, and specific recognition and photothermal inactivation of *P. aeruginosa* using PMIP.

The prepared photothermal molecularly imprinted polymers (PMIP) exhibited excellent photothermal properties. When the concentration of PMIP reached 200 $\mu\text{g/mL}$, the temperature could rise to 52.7°C within ten minutes under laser irradiation at 2 W/cm^2 . By adjusting the imprinting time, PMIP showed an obvious recognition ability for LPS with an imprinting factor of approximately 2. Based on the photothermal effect of PMIP and its affinity for LPS, PMIP demonstrated significant targeting ability and antibacterial effects against *P. aeruginosa*. Due to the presence of rhamnose components in the *P. aeruginosa* biofilm, PMIP also aggregated within the biofilm and effectively destroyed it (**Figure 12**).

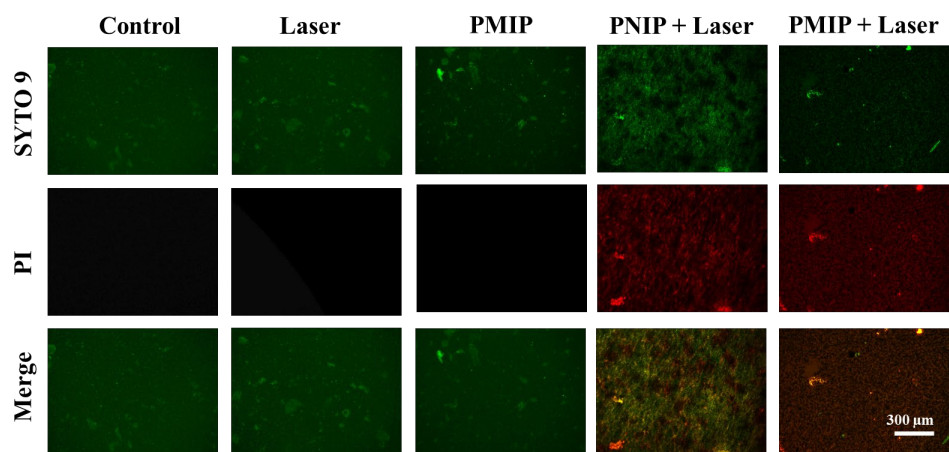


Figure 12. Fluorescent images of biofilms after different treatments.

4.2 Cationic polymer brushes functionalized with carbon dots and boronic acids

In addition to bacterial binding and sterilization capabilities, the bacterial detection ability of antibacterial materials is also of great significance. To simultaneously endow antibacterial materials with affinity, detection, and antibacterial capabilities, polymer brushes are a promising candidate because they can form block copolymers by copolymerizing different functional units onto a single polymer chain.

In Paper II, an antibacterial platform that combines fluorescence detection, borate affinity, and synergistic antibacterial properties was developed for the capture, detection, and destruction of bacteria. As shown in **Figure 13**, SI-ATRP was used to prepare block copolymers on the surface of SiO₂ NPs modified with initiators. Cationic monomers containing QACs, [2-(methacryloyloxy)ethyl]-trimethylammonium chloride (METAC), and a tunable functional glycidyl methacrylate (GMA) monomer were selected to form the two units of the block copolymer. Subsequently, Cu-doped aminated CDs were introduced into the polymer chain through a ring-opening reaction between epoxy groups and amino groups. Finally, borate functional groups were modified onto the CDs to form Schiff bases between the aldehyde group and the amino group. The resulting composite material (Si@co@BA) can achieve fluorescence imaging of bacteria from CDs, affinity to bacteria from borate, and synergistic antibacterial properties from CDs and QACs.

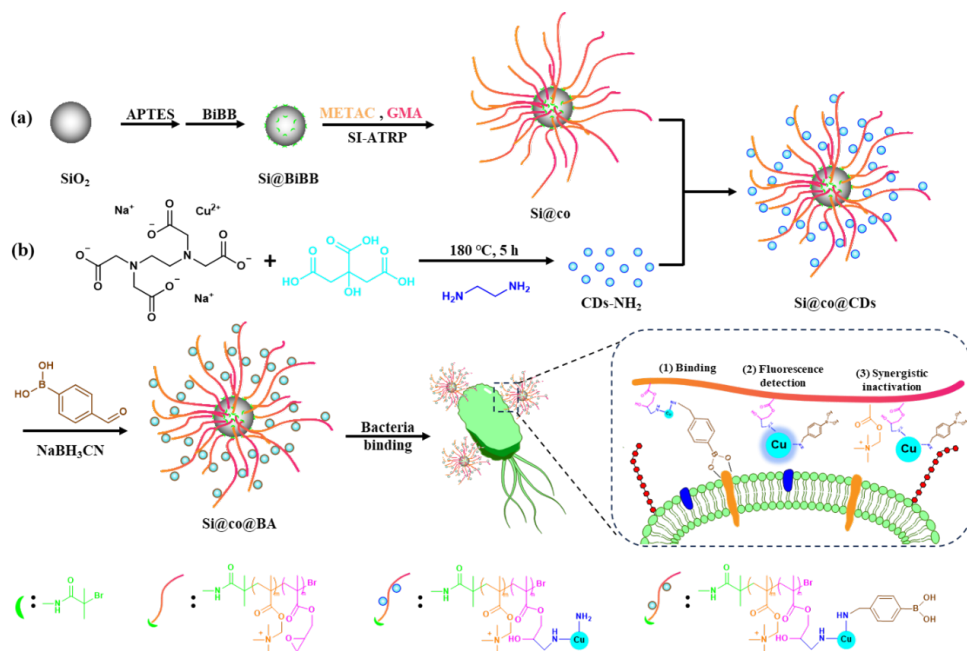


Figure 13. Schematic illustration for the synthesis of the multifunctional nanocomposite Si@co@BA, and application of the material for binding, detection, and inactivation of bacteria.

After the introduction of METAC, Si@co@BA exhibited a surface charge of up to 40 mV. The NMR results indicated that the ratio of METAC to GMA in the polymer chain was approximately 1:1.6, and the TGA test showed that the average molecular weight of the polymer was approximately 14000 Da. Moreover, the fluorescence spectrum showed that Si@co@BA had the same emission peak at 470 nm as CDs, and the Alizarin Red S (ARS) experimental data confirmed the presence of boronic acid in Si@co@BA.

The antibacterial activity, bacterial targeting, and imaging ability of Si@co@BA were studied using *Escherichia coli* (*E. coli*). The colony count experiment showed that the minimum inhibitory concentration of Si@co@BA was 1 mg/mL, with QACs and CDs exerting a synergistic effect in the antibacterial process (**Figure 14**). The bacterial binding experiment, tested using bacterial TEM and sedimentation experiments, showed that the presence of boronic acid significantly increased the attachment of Si@co@BA to bacteria. The fluorescence imaging and bacterial flow cytometry experiments demonstrated that Si@co@BA successfully labeled the bacteria, causing them to exhibit blue fluorescence.

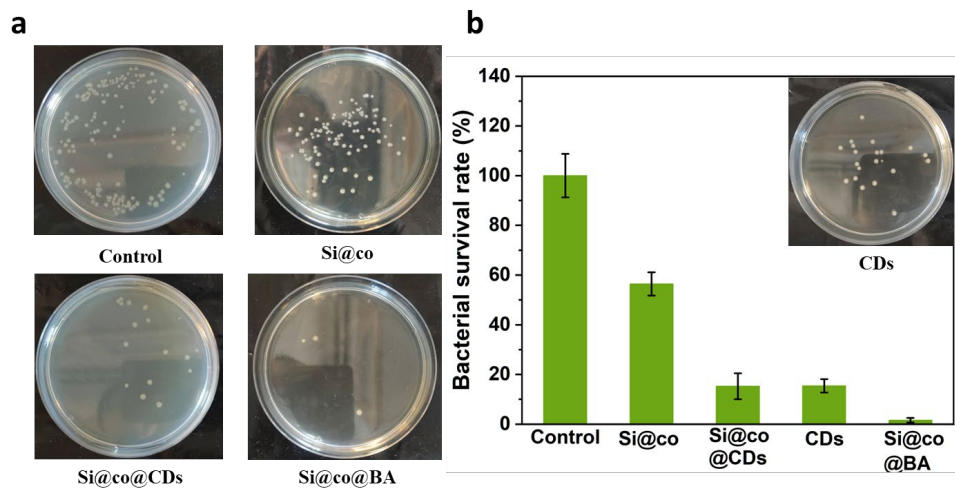


Figure 14. (a) Photographs and (b) corresponding cell survival rate of *E. coli* treated with 1 mg/mL of Si@co, Si@co@CDs, Si@co@BA and 200 μ g/mL of CDs.

4.3 Chitosan cryogel loaded with conjugated polymers

Considering that the main biological application scenarios of antibacterial materials are wound healing, where bacterial infection and bleeding are the two main problems of chronic wounds, cryogel is a promising type of wound dressing due to its large pore structure, which can promote the absorption of blood and the loading of antibacterial materials. Chitosan-based cryogel can help aggregate red blood cells, activate platelets, and accelerate hemostasis, making it an ideal hemostatic material.¹⁴⁸

In addition, the numerous antibacterial advantages of photothermal antibacterial materials were mentioned above, and CP is an excellent PTA. CP can overcome the problems of low biocompatibility and long-term biotoxicity of inorganic PTAs, and its donor-acceptor (D-A) structures can be adjusted to enhance its photothermal conversion efficiency and move its excitation wavelength to the NIR II region to improve tissue penetration.^{149, 150}

In Paper III, a chitosan-based cryogel for loading CP (CP@Gel) was developed. CP NPs were encapsulated into DSPE-PEG₂₀₀₀-COOH by ultrasonic precipitation to increase their hydrophilicity, and the cryogel was formed by freezing chitosan at -12°C. Subsequently, a column-flow method was used to introduce CP NPs into the cryogel by forming amide bond between amino and carboxyl groups. The column-flow method allowed to continuously react the CP NPs with cryogel, increasing the efficiency of NP conjugation (**Figure 15**). For comparison, cryogel loaded with CP NPs was synthesized by directly adding CP NPs to the chitosan solution before the freezing process.

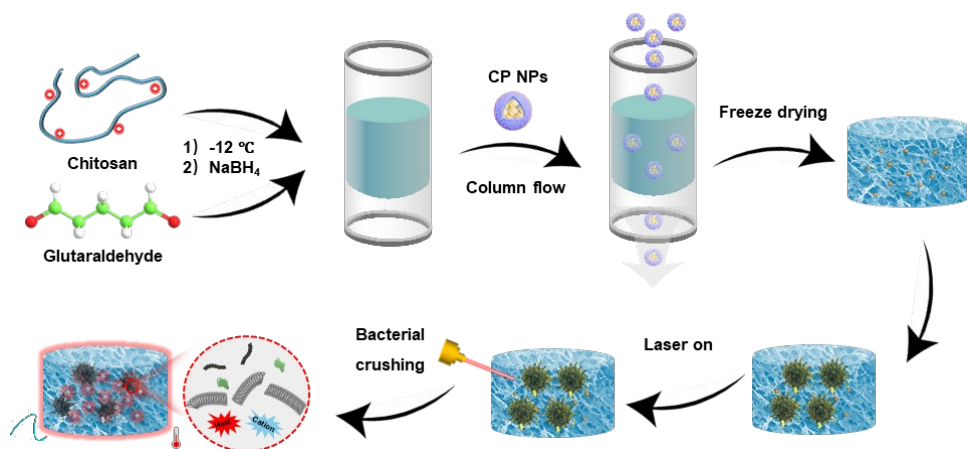


Figure 15. Schematic illustration of the preparation of CP@Gel and its photothermal antibacterial mechanism against MRSA.

By using the column-flow method to load the NPs, more NPs were attached to the surface of the gel. As a result, CP@Gel exhibited a stronger photothermal effect than CP/Gel under 980 nm laser irradiation. Additionally, CP@Gel showed a hemolysis rate lower than 5% and a clotting index nearly the same as that of commercial band-aids.

To verify the antibacterial effect of CP@Gel against drug-resistant bacteria, MRSA was selected as the bacterial model. Benefiting from the natural antibacterial effect of chitosan and the photothermal antibacterial effect of CP, 99% of the bacteria were eliminated in the CP@Gel group, which also showed a good clearance effect on the biofilm formed by MRSA.

The antibacterial mechanism of CP@Gel was further studied, and the results indicated that CP@Gel mainly caused the rupture of bacterial cell membranes, leading to the leakage of internal proteins and nucleic acid substances, resulting in the death of MRSA. The antibiofilm mechanism of CP@Gel was investigated using RT-PCR, and the results showed that the CP@Gel group significantly upregulated the gene levels that inhibit biofilm formation and promote biofilm decomposition (**Figure 16**).

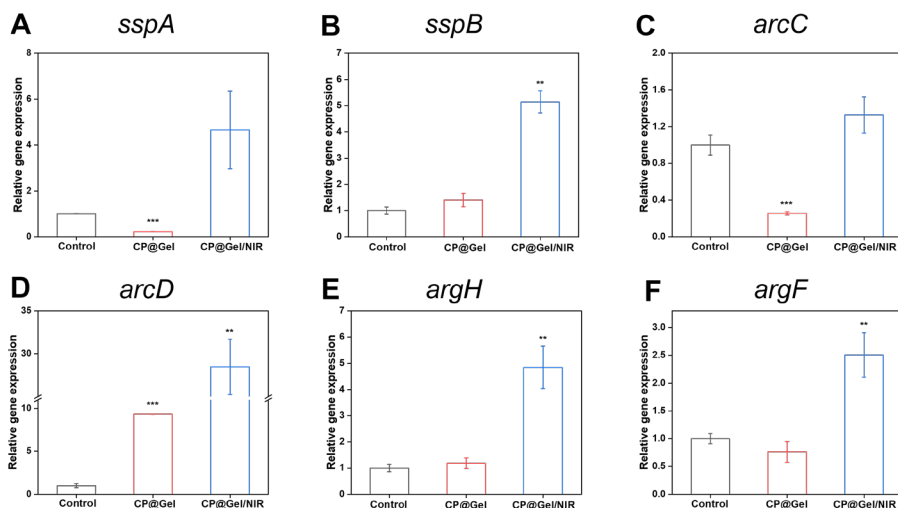


Figure 16. The expression levels of typical genes. RT-PCR results of typical genes encoding extracellular proteases (a,b) and involved in arginine biosynthesis and arginine catabolism (c-f) (n = 3). Statistical significance is indicated with * ($p \leq 0.05$), ** ($p \leq 0.01$), *** ($p \leq 0.001$).

4.4 Combining molecularly imprinted polymers with aggregation-induced emission molecules

Given the excellent photothermal antibacterial effect, the main issue we need to consider next is how to further enhance the photothermal efficiency of PTAs, endow them with more functions, and expand their application scope. AIE molecules can provide efficient photothermal performance through D-A engineering design. They also possess aggregation-induced luminescence functions, which can be used for molecular diagnosis and treatment in biological systems without the problem of aggregation-caused quenching (ACQ) that occurs with conventional molecular dyes for imaging.^{151, 152}

Interestingly, it has been reported that AIE molecules can utilize the polymer network of PS carriers to limit molecular motion, thereby increasing the fluorescence quantum yield.¹⁵³ The main framework of MIPs is a polymer network, which might not only enhance the fluorescence intensity of AIE molecules but also endow them with bacterial targeting ability, further improving the photothermal antibacterial effect.

In Paper IV, SPA-imprinted polymer NPs equipped with AIE molecules were designed for enhanced PTT of MRSA. As shown in **Figure 17**, a PS seed emulsion was prepared by emulsion polymerization, and then the PS seed was used to load AIE molecules by the swelling method. Afterwards, SPA protein template and MAA were added to the emulsion to form a polymer layer that imprinted SPA on the surface of the PS seed. After removing the template, the surface of the NPs was modified with amino groups to make it positively charged, promoting the particles to penetrate the biofilm (AIE@MIPs). Moreover, AIE@MIPs can target and eliminate MRSA since SPA is a protein on the surface of MRSA.

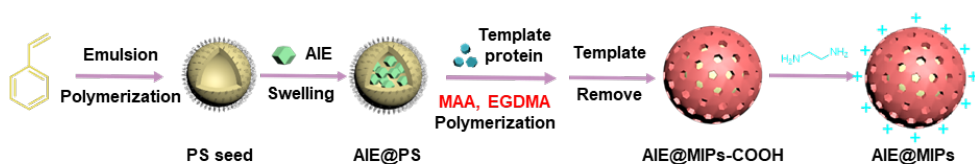


Figure 17. Schematic illustration of the preparation of AIE@MIPs.

The particle size of the AIE@MIPs obtained was approximately 251 nm, while the PS seeds before imprinting were around 127 nm. Due to the thermal swelling effect of the PS seeds during the imprinting process, the imprinting thickness should be less than 80 nm, and the final imprinting factor was approximately 1.66. Using the AIE molecules wrapped with DSPE-PEG₂₀₀₀-NH₂ as a comparison, NIR imaging

and penetration experiments showed that AIE@MIPs significantly increased the fluorescence quantum yield of the AIE molecules. Additionally, the photothermal effect of the AIE molecules was also improved to a certain extent, which might be due to the swelling effect of PS during heating, resulting in enhanced thermal motion within the AIE molecules.

In the antibacterial experiment using MRSA as a bacterial model, the excellent photothermal antibacterial effect and targeting ability of AIE@MIPs ensured that most bacteria were eliminated. Finally, owing to the positively charged surface of AIE@MIPs and its affinity for the surface proteins of MRSA, AIE@MIPs exhibited a faster dispersion speed in the MRSA-formed biofilm, and the biofilm was also significantly disrupted (**Figure 18**).

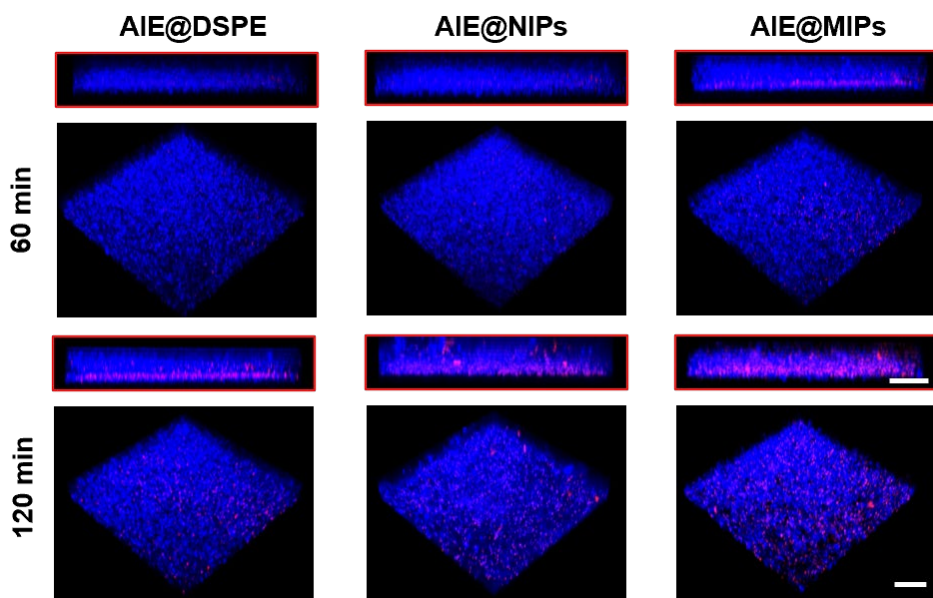


Figure 18. CLSM images and corresponding z-stack images of MRSA biofilms treated with Cy5.5-labeled NPs for 60 and 120 min. Blue: bacteria stained with DAPI, Red: Cy5.5-labeled NPs.

Chapter 5 Conclusion and future outlooks

Polymer materials have attracted widespread attention as potential antibacterial agents due to their multiple antibacterial mechanisms and simple functional tunability. Antibacterial polymer materials can take various forms, each with different antibacterial mechanisms and functions to meet complex practical requirements. In this thesis, different antibacterial polymer materials with various antibacterial methods, especially photothermal antibacterial capabilities, were developed to explore the potential of polymers in the antibacterial field. Various functions, particularly bacterial targeting, were verified, and different types of bacteria such as *P. aeruginosa*, *E. coli*, and MRSA were investigated.

In Paper I, for the first time, we combined molecular imprinting technology with photothermal antibacterial materials to prepare a photothermal antibacterial polymer that imprinted the LPS of *P. aeruginosa*. This polymer material exhibited strong affinity for *P. aeruginosa* and excellent photothermal properties, thereby concentrating heat around *P. aeruginosa* to cause its thermal death. Additionally, the PTT used showed certain targeting and thermal damage properties for the polysaccharide substances surrounding the biofilm area. Therefore, the photothermal antibacterial material with molecular imprinting ability is a promising antibacterial material that can overcome drug resistance and biofilm problems caused by pathogenic bacteria.

In Paper II, the antibacterial polymer was endowed with imaging functions beyond bacterial targeting and antibacterial properties. A new polymer brush composed of METAC and GMA was prepared and combined with Cu-doped CDs, followed by modification with boronic acid. The resulting polymer material successfully achieved targeted binding of *E. coli*, fluorescence imaging, and synergistic antibacterial effects, attributed to boronic acid, CDs, Cu in CDs, and METAC. This work expands the application of multifunctional polymers in the antibacterial field. In the future, the molecular weight of this polymer brush can be further optimized, and the supporting substrate can be removed to enhance its application scenarios.

In Paper III, to make photothermal antibacterial polymer materials more applicable to practical use, a chitosan-based cryogel loaded with photothermal CP was

developed for the treatment of bleeding and bacterial infections in chronic wounds. The obtained antibacterial gel demonstrated significant promotion of blood coagulation and synergistic antibacterial ability. Meanwhile, the photothermal effect also regulated the biofilm-forming genes of MRSA and inhibited the growth of biofilms. This photothermal gel was further explored for the antibacterial effects of different forms of polymers, and antibacterial research was conducted on actual drug-resistant MRSA strains, suggesting the potential application of photothermal polymers in chronic wounds. In the future, this can be further expanded to animal studies.

In Paper IV, we further combined the imaging function with photothermal antibacterial polymer materials and designed MIPs that could enhance the photothermal and imaging capabilities of AIE molecules for targeted antibacterial action against MRSA. This polymer material can recognize the SPA protein on the surface of MRSA and achieve photothermal antibacterial effects. Moreover, the PS polymer structure in the MIPs can enhance the fluorescence quantum yield and photothermal efficiency of the AIE molecules. Due to the positive charge modification on the material surface, the NPs can disperse more rapidly in the biofilm. Future plans include conducting *in vivo* studies on the NPs to further explore the effect of enhanced fluorescence in animal models.

In summary, this thesis presented a series of antibacterial polymer materials that also possess other functions to address bacterial resistance and biofilm issues, meeting complex practical antibacterial requirements. We started with photothermal antibacterial MIPs, then expanded to photothermal antibacterial hemostatic gels, and finally to photothermal enhanced antibacterial MIPs for imaging. At the same time, cationic antibacterial polymers and metal-doped antibacterial agents were also investigated. During this process, we achieved significant antibacterial results and bacterial recognition effects, and the issues of drug resistance and biofilms were also discussed. In the future, *in vivo* studies can be conducted to explore the practical applications of these antibacterial polymer materials.

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