Nanostructures for Antimicrobial Therapy

Nanostructures in Therapeutic Medicine Series

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Series Foreword

Material science and engineering at the nanoscale have brought revolutionary advances to the biomedical sciences, overturning many of the known traditional approaches. Nanotechnology has driven many of the most successful innovative technologies, and their impressive record of accomplishment has made nanostructures promising candidates for future therapy. The advantages that nanomaterials have already provided to therapeutics, such as targeted and controlled delivery, wide accessibility, high specificity, low side effects, improved efficiency, and impressive versatility, are currently considered key elements in designing personalized medicine approaches for prophylaxis, diagnosis, and therapy.

Therapeutic nanostructures can be highly diverse, and their unique properties have led to the development of highly specialized biosensors, more efficient drug delivery vehicles, and controlled release targeting systems to fight severe or incurable diseases, such as cancer, infections, and cardiovascular disease.

In view of the progress made in the field of therapeutic nanotechnology, and its rapidly progressing expansion, this book aims to collect together in one place all the most recent and innovative aspects regarding the impact of nanomaterials in both current and future therapy. The book is organized in five volumes, covering the main areas that are relevant for the design and implementation of nanostructures in medical therapies.

The first volume, *Nanostructures for Novel Therapy: Synthesis, Characterization and Applications*, describes methods to obtain and characterize nanosystems, emphasizing their biomedical applications. Special attention in this volume is paid to modern synthesis methods to reduce side effects and limit the toxicity of nanomaterials in biomedical applications. Numerous examples of nanostructures designed for therapy, as well as the most efficient synthesis and characterization routes for these materials, are clearly described and critically analyzed.

The second volume, entitled *Nanostructures for Drug Delivery*, covers one of the most widely utilized and investigated applications of nanomaterials in the biomedical field, namely, drug delivery. The design of nanoscale agents to specifically and safely carry therapeutic agents to their final destination is an intriguing approach to future targeted therapeutics. This approach could provide a treatment for previously incurable diseases, as well as reducing the side effects of current drugs. Many highly active drugs are severely limited by side effects related to their unspecific sites of action. This book introduces readers to the amazing field of nanomedicine by discussing the versatility and variety of nanovehicles for drug delivery and targeting. Moreover, readers will find numerous examples, and will learn about the currently used or investigational drug delivery agents for therapy, prophylaxis and diagnosis.

Volume 3, *Nanostructures for Antimicrobial Therapy*, highlights the impressive progress made by nanotechnology in the design of novel antimicrobial approaches. Since microbial resistance to antibiotics is a very real and worrying issue growing throughout the world, the development of more efficient antimicrobial agents has a high priority to allow control of infections in the future. Antimicrobial nanosystems have proved to be highly efficient against drug-resistant microorganisms, and are able to fight biofilm-associated infections and control the social behavior of microbial communities. Nanostructures can also reduce microbial virulence factors and reduce pathogenesis mechanisms, thus offering a promising alternative for future therapy.

Volume 4, entitled *Nanostructures for Cancer Therapy*, covers the applications of nanomedicine in cancer diagnosis and treatment. The use of nanoparticles for cancer therapy is not in itself a new approach, but numerous advances have been recently made in this area, and the aim of this book is to cover the most interesting new approaches in the management of this deadly disease. Nanosized drugs are currently believed to represent the most efficient approach in cancer chemotherapy, and this volume provides coverage of the latest novel findings, while also discussing possible improvements in more established types of nanosystems to increase the efficiency of cancer therapy.

Last but not least, Volume 5 of this series, entitled *Nanostructures for Oral Medicine*, covers the progress made in applications of nanotechnology in treating various diseases of the oral cavity and in dentistry. Readers will have the chance to learn about the most efficient modern materials used to treat or prevent widely encountered oral diseases, such as gingivitis, periodontitis, caries, and dental plaque. Moreover, restorative dentistry now makes wide use of nanomaterials.

Overall, this book series will provide a state-of-the-art compendium of knowledge and a crystal ball to see into the future of biomedical nanotechnology and nanomedicine. It will appeal to researchers, clinicians, engineers, pharmacologists, pharmacists, oncologists, infectious disease experts, and dentists. Furthermore, interested general readers may discover the impact, current progress, and future applications of nanotechnology in therapeutics and diagnosis. Taken together, nanoscale approaches will improve the efficiency of personalized medicine for better management of diseases in the 21st century.

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Series Preface

In our permanently changing world, novel therapeutic strategies are constantly required to manage the health and wellbeing of the population. Although numerous diseases are currently considered incurable, massive progress made in biomedicine, but also associated fields, such as chemistry, physics, engineering, pharmacology, and materials science, offers a new solution to the therapeutics domain. In this context, most physicists and researchers believe that a personalized and adequate treatment may significantly improve the outcome of severe diseases and ensure faster healing. Nanotechnology offers great perspectives for personalized medicine; nanostructures proved their efficiency, versatility, and sensibility in therapy, prophylaxis, and diagnosis. The dynamic field of nanosized materials has numerous applications in the biomedical field, especially in therapy. This series of five volumes emerged from the need to learn about recent progress in the science of nanostructured materials to improve current therapy and lead to the next level. The books offer an interesting and updated perspective regarding applications of nanomaterials in therapy of most investigated and difficult-to-treat diseases, such as cancer and severe infections. The presentation style of each chapter contained in those five volumes is clear and easy to understand both by specialized and unspecialized readers and is interesting for biomedical doctors, researchers, and engineers. The series is organized in an attractive manner for students and academics in the field, starting with a volume dealing with synthesis, characterization, and main applications of nanostructures, emphasizing their impact in therapy. The next volume reveals the most recent progress made in a much investigated field, considered a key element in personalized medicine and future therapy, namely, nanostructured drug delivery systems. Their impact in antimicrobial therapy is also widely discussed and suggestive examples are given and explained. Moreover, a whole volume is dedicated to the management of the disease of the century—cancer—revealing the huge value added by the utilization of nanosystems in the therapy of this deadly disease. Important aspects related to improved diagnosis and prophylaxis are highlighted. In the last volume, the progress and novel applications of nanotechnology in oral medicine are dissected. The field of oral diseases represents a wide interest and a priority field since both physicists and researchers believe that they can be prevented and treated more easily with targeting systems and nanofunctional prosthetics. All chapters are clearly illustrated to highlight important or more difficult-to-understand aspects, and suggestive examples are often enumerated in organized tables, which are explained and discussed. Overall, the series contains very recent but accessible information regarding the progress of nanostructures in therapeutics and gives a novel perspective on the future therapy of severe diseases.

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Preface

Volume 3 of the series *Therapeutic Nanostructures* is entitled *Nanostructures for Antimicrobial Therapy*. In this volume recent information regarding different types of nanostructured antimicrobial agents, their fabrication, and main properties are revealed. The main focus of the volume is to discuss the most frequent problems caused by resistant microorganisms and difficult-to-treat bacteria and to highlight the impact of recently developed antimicrobial nanosystems. Various methods to obtain efficient nanomaterials with antimicrobial properties are described. Moreover, their advantages, challenges, and main applications are revealed in the chapters of this volume. The design of targeting antimicrobial therapeutics able to specifically detect pathogenic microorganisms and to act in a very specific manner still represents a much investigated concept. Although numerous approaches were developed to control severe infections, the ability of microbes to adapt and select resistance still represents a major challenge in the design of alternative antimicrobial agents. This volume also presents the progress made in the design of nanostructured drugs containing natural antimicrobials, which are considered more effective in limiting the selection of resistant mutants, as compared to classical antibiotics, and are regarded as environmentally safe. Nonetheless, the progress made in the case of particularly difficult-to-reach infections, such as intracellular pathogens and biofilm-associated infections, is separately discussed, innovation made in the detection and therapy by using nanoscale materials being highlighted. Volume 3 contains 30 chapters, prepared by outstanding international researchers from the United States, Argentina, Italy, Poland, Romania, Russia, Turkey, Iran, India, Czech Republic, Slovakia, Spain, Germany, Portugal, Greece, Brazil, the United Kingdom, and Slovenia.

In Chapter 1, entitled "Antimicrobials: Meeting Challenges of Antibiotic Resistance Through Nanotechnology," Bhaskar Das et al. highlight the current advances underlying emergence of antibiotic-resistant pathogens and endorse the use of nanomaterials to counteract antimicrobial resistance and delivery of antimicrobial drugs.

Chapter 2, prepared by Josef Jampílek, entitled "Nanoantimicrobials: Activity, Benefits, and Weaknesses," focuses on the methods of incorporation of active ingredients into different types of nanocarriers for targeted biodistribution/controlled release, discussing the antimicrobial effectiveness of these formulations. In addition, weaknesses of the application of nanoantimicrobials in clinical practice and potential health risks related to the application of nanoformulations are discussed.

Chapter 3, written by Nurgul K. Bakirhan et al., entitled "Sensitive and Selective Assay of Antimicrobials on Nanostructured Materials by Electrochemical Techniques," presents an up-to-date overview of the classification of nanoantimicrobial agents and their used fields, nanostructured material types applied for a specific infection, and applications in the determination of antimicrobials (on nanostructured materials) by sensitive and selective electrochemical techniques.

In Chapter 4, entitled "Antimicrobial Polymeric Nanostructures," Nelson Vargas Alfredo et al. discuss alternative strategies to prepare nanostructured antimicrobial polymeric materials. Also the authors review the generation of materials exhibiting nanostructured interfaces that reduce or prevent the adhesion of microorganisms.

Chapter 5, entitled "Thin Degradable Coatings for Optimization of Osteointegration Associated With Simultaneous Infection Prophylaxis" and prepared by Anke Bernstein et al., presents novel approaches related to prevention of prosthetic joint infection. Both antibiotic prophylaxis and faster osteointegration can be obtained by the incorporation of bactericidal active metals in degradable calcium and phosphorus-containing coatings.

Chapter 6, entitled "Nanostructure and Nanomedicine of Antimicrobial Agents for Neuroinfections of Neurodegenerative Diseases: Current and Future Perspectives," prepared by Arunachalam Muthuraman et al., gives an overview of the mechanisms involved in the antimicrobial activity of nanomaterials, i.e., (1) destruction of peptidoglycan layer; (2) release of toxic metal ions; (3) alteration of cellular pH via proton efflux pumps; (4) generation of reactive oxygen species; (5) damage of nuclear materials; and (6) loss of ATP production. Also, this chapter focuses on the current perspectives of nanostructures and nanomedicine in the development if improved antimicrobial agents for the possible management of infection-associated neurodegenerative disorders.

Burcu Devrim and Asuman Bozkir in Chapter 7, entitled "Nanocarriers and Their Potential Application as Antimicrobial Drug Delivery," focus on the properties of various nanocarriers including liposomes, solid lipid nanoparticles, polymeric nanoparticles, dendrimers, and metal nanoparticles as promising tools for antimicrobial drugs. The potential application of these nanoparticles in the management of infections is also reviewed.

Teixeira M.C. et al. in Chapter 8, "Delivery of Antimicrobials by Chitosan-Composed Therapeutic Nanostructures," review the current progress of theoretical concepts and current advances related to the development of chitosan-based nanostructures for antimicrobial peptides delivery.

Roxana-Cristina Popescu et al. in Chapter 9, "Antimicrobial Thin Coatings Prepared by Laser Processing," review some recent examples of antimicrobial coatings obtained using laser processing, focusing on pulsed laser deposition and matrix-assisted pulsed laser deposition. The ion implantation approach is also discussed, as it is becoming increasingly used in the modification of implants and medical device surfaces to obtain improved antimicrobial properties.

Reza Fekrazad et al. in Chapter 10, entitled "Antimicrobial Photodynamic Therapy With Nanoparticle Versus Conventional Photosensitizer in Oral Diseases," discuss the advantages and disadvantages of conventional photodynamic therapy by means of chemical photosensitizers compared to nanoparticle-based photodynamic therapy in the management of oral microbial diseases.

Chapter 11, prepared by Dorota Bartusik, entitled "Applications of ^{19}F Magnetic Resonance Spectroscopy and Imaging for the Study of Nanostructures Used in Antimicrobial Therapy," summarizes diagnostic and therapeutic applications of ^{19}F magnetic resonance spectroscopy and ^{19}F magnetic resonance imaging techniques to nanomedicine in antimicrobial therapy. The authors provide an overview of the known examples of the synthesis of fluorine-containing compounds by the use of bacteria species and their analysis by ^{19}F nanomagnetic resonance.

Chapter 12, prepared by Mariana Carmen Chifiriuc et al., entitled "Essential Oils and Nanoparticles: New Strategy to Prevent Microbial Biofilms," gives an up-to-date overview of the aspects related to the manufacturing, characterization, and antibiofilm activity of essential oils—loaded nanoparticles, highlighting aspects of the organo-inorganic and bioorganic nanostructured systems based on essential oils with antibiofilm activity.

Chapter 13, entitled "Nanocarrier-Assisted Antimicrobial Therapy Against Intracellular Pathogens," prepared by Lalit Kumar et al., gives an overview of the impact of intracellular pathogens against human health, problems in the eradication of intracellular infection, and different nanocarrier systems being used to deliver antimicrobial agents for targeted eradication of intracellular pathogens.

Chapter 14, "Preparation and Antimicrobial Activity of Inorganic Nanoparticles: Promising Solutions to Fight Antibiotic Resistance," prepared by Marius Boboc et al., is focused on applications and properties of inorganic nanostructured materials and discusses the main advantages and risks of using different metal and metal oxide nanoparticles, such as silver nanoparticles, gold nanoparticles, zinc oxide nanoparticles, magnetite nanoparticles, and copper oxide nanoparticles as antimicrobial agents.

Chapter 15, prepared by Rakesh Chander YashRoy, entitled "Outer Membrane Vesicles of Gram-Negative Bacteria: Nanoware for Combat Against Microbes and Macrobes," focuses on the outer membrane vesicles (OMVs) produced exclusively by Gram-negative organisms. OMVs contain hydrolytic enzymes for breaking down lipid, peptidoglycan, and proteins, thereby enabling bacteria to lyse competing microbes and digest and absorb food reserves available nearby. OMVs are so versatile that bacteria deploy them as combat arsenal for their survival and spread. Isolated OMVs are also being pitted for use as organism-free vaccines in nanosize.

Jan Sobczyński et al. in Chapter 16, entitled "Organic Nanocarriers for the Delivery of Antiinfective Agents," present the requirements for nanoparticulated dental delivery systems and the advantages of various delivery strategies for enhanced efficiency for particular infections.

Oguz Bayraktar et al. in Chapter 17, "Nanocarriers for Plant-Derived Natural Compounds," discuss nanoencapsulation methods and advances in carrier systems for plant-derived natural compounds.

Chapter 18, entitled "Fullerene Derivatives in Photodynamic Inactivation of Microorganisms," prepared by Mariana B. Spesia et al., presents novel approaches related to cationic molecular architectures bearing fullerene C_{60} that are interesting photosensitizers with potential applications in photodynamic inactivation of microorganisms. Also fullerenes combined with tetrapyrrolic macrocycles represent attractive molecular structures to form permanent antimicrobial surfaces activated by visible light.

M. Kannan et al. in Chapter 19, entitled "Silver Iodide Nanoparticles as an Antibiofilm Agent—A Case Study on Gram-Negative Biofilm-Forming Bacteria," highlight the inhibitory properties of biosynthesized AgI nanoparticles to modulate biofilm-related infections.

Chapter 20, "Nanoformulations for the Therapy of Pulmonary Infections," prepared by Sagar Dhoble et al., reports the current status of the various microbial infections afflicting the respiratory system followed by an overview of the formulations for the therapy of the same with special emphasis on the use of biomedical nanostructures.

Jan Sobczyński et al. in Chapter 21, entitled "Nanocarriers for Photosensitizers for Use in Antimicrobial Photodynamic Therapy," present the advantages of various nanoscale delivery systems for the design of photosensitizers and also review different delivery strategies.

Chapter 22, prepared by Iulia Ioana Lungu, entitled "Zinc Oxide Nanostrucures: New Trends in Antimicrobial Therapy," reveals the main synthesis routes to offer particular properties to biomedical ZnO nanoparticles and how they can be modulated to obtain suitable agents for therapy, prophylaxis, and management of various diseases, highlighting the progress made in antimicrobial therapy.

Chapter 23, entitled "Copper-Based Nanoparticles as Antimicrobials," prepared by Kleoniki Giannousi et al., focuses on the antibacterial activity of CuO, Cu_2O nanoparticles (NPs), and copper composites—Cu/Cu_2O—covered by polymers or embedded into matrices, since the composition of the NPs results in different mechanisms of action. The size- and shape-dependent effects are highlighted as well as the synthetic conditions that have been applied for the preparation of the NPs. Special attention is given to the antifungal activity of Cu-based NPs.

Chapter 24, prepared by Amedea B. Seabra, entitled "Antimicrobial Applications of Superparamagnetic Iron Oxide Nanoparticles: Perspectives and Challenges," presents and discusses what makes SPIONs so unique, showing recent progress, drawbacks, and challenges in the design of SPIONs as nanocarriers for antimicrobial agents. It is intended to be a source of inspiration for new developments in this promising field.

Alexander Lykov et al. in Chapter 25, entitled "Silica Nanoparticles as a Basis for Efficacy of Antimicrobial Drugs," give an up-to-date overview of the screening of the therapeutic efficacy of silica-loaded antibiotics, in comparison with their officinal forms, based on the dynamics of growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli* in vitro and in experimental models of sepsis induced by various strains of microorganisms in mice. The expediency of using this modification of antibiotics to enhance their therapeutic efficacy in experimental sepsis is demonstrated.

Chapter 26, entitled "Silver Nanoparticles as Antimicrobial Agents: Past, Present, and Future," prepared by Luciano Paulino Silva, describes the current state of the art on the use of AgNPs and their derived products for control and prevention of microorganisms and beyond with an emphasis on potential therapeutic and industrial applications related to novel products and processes.

Gennaro A. Dichello et al. in Chapter 27, entitled "Encapsulation of Lethal, Functional, and Therapeutic Medicinal Nanoparticles and Quantum Dots for the Improved Diagnosis and Treatment of Infection," focus on areas where nanoparticle approaches, such as the evolution of heat or light via conjugated metals, have significant potential to treat infections produced by resistant bacteria. These areas might include the targeted delivery of antibiotics, environmentally tunable delivery of antibiotics, and nanoparticle-based bacterial diagnostics for detection, quantification, and identification.

Chapter 28, prepared by Marija Vukomanović, entitled "Advanced Nanocomposites With Noble Metal Antimicrobial Nanoparticles: How to Design a Balance Among Antimicrobial Activity, Bioactivity, and Safe Delivery to the Place of Infection," presents an up-to-date overview of the design of selective antimicrobial nanoparticles capable of making a difference between bacterial and human cells.

Chapter 29, prepared by Gabriel Henrique Hawthorne et al., entitled "Clinical Development in Antimicrobial Nanomedicine: Toward Novel Solutions," reviews the clinical trial concept and the procedures of each step. Trials addressing nanoparticles on catheters, hand gels, therapeutic vaccines, safety, and other issues are presented in this chapter.

Chapter 30, entitled "Recent Citation Classics in Antimicrobial Nanobiomaterials," prepared by Ozcan Konur, gives an overview of the scientometric research in antimicrobials and nanomaterials as well as antimicrobial nanobiomaterials. Major research areas are silver nanoparticles and other antimicrobial nanobiomaterials such as graphene and ZnO. Research into antimicrobial nanobiomaterials has robust public policy implications providing strong incentives for the key stakeholders involved in antimicrobials research.

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Chapter 1

Antimicrobials: Meeting the Challenges of Antibiotic Resistance Through Nanotechnology

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Chapter Outline

1. INTRODUCTION

Antimicrobials are probably one of the most successful forms of chemotherapy in medical history and have contributed significantly to controlling infectious diseases that threaten the existence of human civilization (Aminov, 2010). The word antimicrobial is derived from the Greek words *anti* (against), *mikros* (little), and *bios* (life) and refers to agents that kill microorganisms or cause growth inhibition. Antibiotics are substances that are produced by microorganisms that inhibit or kill other microorganisms. On the contrary, an antimicrobial is a natural (plant or animal), semisynthetic, or synthetic substance that kills or inhibits microbial growth with no or minimal damage to the host. Antimicrobials act against all microbial varieties and thus are classified according to the microbial group they act against. Antibacterials act against bacteria, antivirals act against viruses, antifungals act against fungi, and antiprotozoals act against protozoa (www.amrls.cvm.msu.edu). Antimicrobials that kill microbes are known as microbicidal, while those that inhibit microbial growth are referred to as biostatic. Use of antibiotics is not only restricted to the modern "antibiotic era" but dates back to ancient civilizations. Traces of tetracycline have been determined in human skeletal remains from the ancient Sudanese Nubia

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dating back to 350−550 CE, and Roman period skeletons from Egypt indicated exposure to tetracycline-containing material in their diet (Nelson et al., 2010; Basset et al., 1980). In India, Ayurveda, the oldest healthcare system in the world (about 5000 years old), has references to various types of microorganisms that cause diseases and stresses the need to destroy them to preserve human health. Many Ayurvedic drugs were known to be effective against common microbial infections such as *Mycobacterium tuberculosis* (treated by *Suvarna Bhasma* or gold calyx), malaria (treated using *Mahasudarshan Kwath*), and surgical prophylaxis (treated using *Triphala Guggulu*) (Sharma et al., 2014). With the advent of the germ theory of disease, the vital role of microbes in causing infectious diseases has been established, setting the stage for the beginning of the "modern antibiotic era." The major breakthrough in field of antibiotics came in 1928 when Alexander Fleming discovered the antibiotic penicillin from *Penicillium rubens*. Penicillin has found clinical applications to successfully treat many fatal infectious diseases such as *Streptococcus* infection, gonorrhea, strep throat, and pneumonia. In 1935, Gerhard Domagk developed the first synthetic antibacterial sulfonamide with tremendous clinical success in treating diseases such as meningitis, child bed fever, and pneumonia. The discovery and clinical application of such antibiotics set the paradigm for the search for new antimicrobials by other researchers. The clinical value of an antimicrobial would be compromised by development of microbial resistance against it. Even before the clinical use of antibiotics, Alexander Fleming's research group discovered a bacterial penicillinase that can inactivate penicillin. Uncontrolled widespread use of penicillin resulted in the emergence of penicillin-resistant strains, mostly *Staphylococci*, and most countries restricted penicillin use "by prescription" only. To counteract this, a semisynthetic penicillin variety, methicillin, which is insensitive to penicillinase, was developed and used successfully for antibacterial chemotherapy. However, after few years of clinical use, methicillin-resistant strains of *Staphylococcus aureus* (MRSA) emerged, which has become a current challenge faced by antimicrobial therapy worldwide. The pattern of emergence of antibiotic resistance is the same for other antibiotics that were commercially available in the latter half of the 20th century (www.amrls.cvm.msu.edu). Mortality rates caused by multidrug-resistant bacterial infection have been reported to be quite high in the European Union and the Unites States, being 25,000 and 63,000 patients per year, respectively. Scientists have warned that the world will return to a preantibiotic era plagued by life-threatening microbial infections on the basis of a recent antibiotic resistance gene database that lists the existence of more than 20,000 antibiotic-resistant genes of 400 types predicted from available genome sequences (Liu and Pop, 2009). Thus discovery of novel antimicrobial agents to which microbes cannot develop resistance easily is one of the major medical concerns of the 21st century. The development of new antimicrobials alone will not be effective for antimicrobial therapy unless efficient drug delivery strategies are developed. Inefficient drug delivery would result in decreased therapeutic index of the antimicrobials along with local and systemic side effects. The current clinical application of nanotechnology has the potential to revolutionize antimicrobial therapy by overcoming the problems associated with conventional therapy. Nanoparticles (NPs) could serve as novel antimicrobial agents with less chances of development of microbial resistance (Huh and Kwon, 2011). Also the therapeutic index of antimicrobials can be improved by loading drugs on NP-based carriers, in contrast to its free drug counterparts. Use of NPs for antimicrobial delivery will significantly increase the drugs' serum solubility, prolong the lifetime of systemic circulation of the drug, sustain drug release in target tissues, and make use of combination therapy by delivering multiple drugs to the same target cell (Zhang et al., 2010). Because of the seriousness of these issues in antimicrobial therapy, we need to review the current scientific advancements related to understanding the mechanisms of microbial antibiotic resistance, the counter strategy against antibiotic-resistant pathogenic strains, and antimicrobial drug delivery. In this chapter, we will comprehensively review the current advances underlying the emergence of antibiotic-resistant pathogens, the strategies employed to counteract antimicrobial resistance, and the delivery of antimicrobials using nanostructured biomaterials.

2. CURRENT STATUS OF THE MENACE OF ANTIMICROBIAL RESISTANCE

Each time an antibiotic is used for treatment of microbial infections in humans or animals the probability of spread of antibiotic resistance looms large (Austin et al., 1999). Inappropriate antibiotic use has led to the evolution of pathogenic epidemic-causing organisms into multidrug-resistant forms (Davies and Davies, 2010). In spite of the high global risks associated with antimicrobial resistance it has been given low priority in both developing and developed nations. Each nation must adopt a strategy to fight antimicrobial resistance tailored to its conditions. The problem is graver in developing nations where easy availability, use of antibiotics in inappropriate high doses, and cost constraints to replace older antibiotics with new expensive antibiotics increase the probability of increased production of antimicrobial-resistant strains (Kumar et al., 2013). A widely known form of antibiotic resistance is New Delhi metallo-β-lactamase-1 (NDM-1) produced by the gene $bla_{\text{NDM-1}}$, which is plasmid borne and could be transferred between the bacterial species *Klebsiella pneumoniae* and *Escherichia coli*. This has resulted in strains with broad antibiotic resistance including carbapenems. Multidrug-resistant *M. tuberculosis*, a 20th century version of an old pathogen, infects one-third of the world's population

in both developed and developing countries. The effectiveness of antituberculosis drugs has been compromised by the rapid emergence and spread of strains resistant to four or more frontline tuberculosis treatments, i.e., extremely drug-resistant strains and totally drug-resistant strains (Davies and Davies, 2010). The causative organisms of hospital-acquired infections (HAIs) have become a matter of concern worldwide. MRSA has the reputation of being the most notorious multidrug-resistant superbug causing nosocomial infections. From being a causative organism in HAIs, MRSA has now become a major community-acquired pathogen combined with the characteristics of enhanced virulence caused by acquired pathogenic genes encoding cytotoxic Panton−Valentine leukocidin (Davies and Davies, 2010; DeLeo and Chambers, 2009). *Pseudomonas aeruginosa* originally caused burn wound infection and developed into a major nosocomial infection. Metallo-β-lactamase-producing *P. aeruginosa* has shown resistance to carbapenems. The rapid emergence of multidrug-resistant Enterobacteriaceae-producing extended spectrum β-lactamases (ESBLs), ESBL-producing *K. pneumoniae*, ciprofloxacin-resistant *Salmonella enterica* serovar Typhi, the emergence of vancomycin-intermediate *Staphylococci*, fluoroquinolone-resistant *Salmonella*, and *P. aeruginosa* and *Acinetobacter baumannii* resistant to ceftazidime, cefepime, and ciprofloxacin is a matter of concern to antimicrobial therapy (Kumar et al., 2013). Genome studies on *A. baumanni* showed the presence of at least 28 genomic islands encoding determinants for antibiotic resistance, explaining the serious concerns raised because of the rapid emergence of drug-resistant strains of *A. baumanni* (Davies and Davies, 2010; Gomez and Neyfakh, 2006). A hypervirulent and toxic HAI strain of *Clostridium difficile* has emerged because of the extensive use of antibiotics as expanded spectrum cephalosporin, newer penicillins, and fluoroquinolones (Davies and Davies, 2010). The influenza A (H1N1) virus responsible for the recent outbreak of avian influenza worldwide was found to be susceptible to neuraminidase inhibitors oseltamivir and zanamivir. However, resistance to oseltamivir was reported in June 2009 and since then 570 oseltamivir-resistant cases have been reported worldwide (Potdar et al., 2013). Because of the pressing nature of the problem of antibiotic resistance, it is high time to raise awareness about this problem and develop efficient strategies to tackle it.

3. ANTIMICROBIAL CLASSES AND THEIR CURRENT EFFECTIVENESS WITH RESPECT TO EMERGING DRUG RESISTANCE

Antimicrobials are classified based on a variety of methods such as spectrum of activity, effect on microbes, and mode of action.

3.1 Classification on the Basis of Spectrum of Activity

If an antibacterial is active against both Gram-positive and Gram-negative bacteria it is referred to as a broad spectrum antibacterial, e.g., tertracyclines, phenicols, third and fourth generation cephalosporins, and fluoroquinolones. On the other hand, an antibacterial that is effective against a particular species of microbe, e.g., glycopeptides and bacitracin are effective only against Gram-positive bacteria, polymyxins are effective only against Gram-negative bacteria, aminoglycosides and sulfonamides are effective only against aerobic organisms, and nitoimidazoles are effective against anaerobes (www.amrls.cvm.msu.edu).

3.2 Classification on the Basis of Nature of Effect

Based on the nature of effect on bacteria, antibiotics are classified as bactericidal (which kill the target bacteria) and bacteriostatic (which inhibit bacterial growth and replication), e.g., antibiotics such as aminoglycosides, cephalosporins, penicillins, and quinolones are bactericidal, while tetracyclines, sulfonamides, and macrolides exert bacteriostatic effects on target bacteria. The effect of bactericidal agents is faster as compared to bacteriostatic agents. Bacteriostatic agents require an effective immune system in the host for elimination of pathogenic bacteria and hence are not applicable to immunosuppressed host conditions or acute infections. However, some antibiotics may behave as both bacteriostatic and bactericidal based on dosage concentration and duration of exposure, e.g., aminoglycosides, fluoroquinolones, and metronidazole exert concentration-dependent bactericidal characteristics (www.amrls.cvm.msu.edu).

3.3 Classification on the Basis of Mode of Action

The mode of action of antimicrobials varies on the basis of the nature of their structure and degree of affinity to target sites within bacterial cells.

3.3.1 Cell Wall Synthesis Inhibitors

Since the cell wall is critical for the survival of bacterial species, an antibacterial that affects the cell wall would behave as a bacteriostatic or bacteriocidal agent. The β-lactam group of antibiotics contains a four-membered nitrogen-containing β-lactam ring responsible for its antibacterial action. β-Lactam antibiotics bind to penicillin-binding proteins (PBPs) present on the cell membrane rendering them incapable of performing cell wall synthesis (Elander, 2003). This kills the target bacteria by osmotic instability or autolysis, e.g., natural penicillin, penicillinase-resistant penicillin such as methicillin, nafcillin, and oxalin, extended spectrum penicillin such as ampicillin, carbenicillin, and amoxicillin, cephalosporins, carbapenems, and monobactams. Carbapenems and second, third, and fourth generation cephalosporins have broad spectrum activity, while penicillin, first generation cephalosporins, and monobactams have a narrow spectrum of activity. The activity of β-lactams varies among bacterial species on account of species-specific variation of PBP content and nature. Gram-negative bacteria with an outer membrane layer hinder the interaction of PBP and β-lactam antibiotics, thus rendering the antibacterial ineffective. The glycopeptide group of antibiotics inhibits bacterial cell wall synthesis by binding to precursors of cell wall synthesis, which leads to the inhibition of cell wall synthesis activity by PBPs. Actinomycetes species such as *Streptomyces orientalis* and *Nocardia actinoides* produce the glycopeptides vancomycin and actinoidin, respectively. These drugs have a narrow spectrum of bactericidal activity affecting only Gram-positive bacteria. Vancomycin is considered a last resort drug for the treatment of skin and bone infection, bloodstream infection, endocarditis, and meningitis caused by MRSA (www.amrls.cvm.msu.edu).

3.3.2 Cell Membrane Function Inhibitors

Exchange of intra- and extracellular substances takes place through microbial cell membranes. Thus cell survival can be at stake if there is disruption of cell membrane structure because of leakage of important intercellular solutes. Cell membrane is found in both prokaryotic and eukaryotic organisms causing poor selectivity and thus compromising its use in the mammalian host, e.g., polymyxin (www.amrls.cvm.msu.edu). The polymyxin group of antibiotics is characterized by a cyclic peptide with a long hydrophobic tail. Polymyxins bind to lipopolysaccharides (LPS) in the outer membrane of Gram-negative bacteria and disrupt the cell membrane structure. The hydrophobic tail with its detergent-like mode of action is instrumental in damaging the cell membrane. Their specificity to LPS molecules that exist in the outer membrane of Gram-negative bacteria renders them selective to bactericidal activity against Gram-negative bacteria. They are produced by nonribosomal peptide synthetase systems in *Paenibacillus polymyxa* (www.nlm.nih.gov). On account of their neurotoxicity and nephrotoxicity, polymyxins are used as a last resort when other clinical antibiotics prove ineffective (Falagas and Kasiakau, 2006). They have found application in controlling infection caused by multiple drug-resistant *P. aeruginosa* and carbepenemase-producing Enterobactericeae. Colistin is a polymyxin antibiotic that confers its bactericidal activity to its polycationic nature with both hydrophilic and lipophilic moieties. The polycationic regions interact and displace bacterial counter ions from LPS present in the bacterial outer membrane. Hydrophobic and hydrophilic regions interact with the cytoplasmic membrane solubilizing the bacterial membrane leading to bactericidal activity. Colistin is produced by *P. polymyxa* var. *colistinus*. In India, colistin is commercially available as Colymonas and Koolistin. Although it is not favored because of nephrotoxic effects, it is considered a last resort antibiotic against multidrug-resistant *P. aeruginosa*, *K. pneumoniae*, and *Acinetobacter*, etc. (Falagas et al., 2008). Colistin susceptibility is also observed in NDM-1 metallo-β-lactamase multidrug resistant Enterobacteriaceae (Kumarasamy et al., 1999).

3.3.3 Protein Synthesis Inhibitors

One of the vital processes for microbial multiplication and survival is protein synthesis. With an attempt to kill or inhibit the growth of pathogenic microbes, many antimicrobials disrupt the protein synthesis machinery by binding to the 30S or 50S subunit of intracellular ribosomes, e.g., aminoglycosides, macrolides, lincosamides, streptogramins, chloramphenicol, and tetracyclines (www.amrls.cvm.msu.edu).

3.3.3.1 Aminoglycosides

Inhibition of protein synthesis by aminoglycosides is caused by its binding to the 30S ribosomal subunit. This perturbs peptide elongation at the 30S ribosomal subunit resulting in errors during mRNA translation and thus biosynthesis of truncated proteins that bear altered amino acid compositions (Mingeot-Leclercq et al., 1999). Aminoglycosides are derived from bacteria of the genus *Streptomyces* and *Micromonospora* (Kroppenstedt et al., 2005). They are useful to treat infections caused by aerobic, Gram-negative bacteria such as *Pseudomonas*, *Acinetobacter*, *Enterobacter*, and