Nanostructures in Therapeutic Medicine Series

Nanostructures for Novel Therapy

Synthesis, Characterization and Applications

Edited by

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ELSEVIER

Elsevier
Radarweg 29, PO Box 211, 1000 AE Amsterdam, Netherlands
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States

Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-323-46142-9

For information on all Elsevier publications visit our website at
https://www.elsevier.com/books-and-journals

Publisher: Matthew Deans
Acquisition Editor: Simon Holt
Editorial Project Manager: Sabrina Webber
Production Project Manager: Julie-Ann Stansfield
Designer: Greg Harris

Typeset by Thomson Digital

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Foreword of the Series

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 astounding 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 was 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 in order 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 the 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.

The third volume, *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, 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.

The fourth volume, 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, the fifth volume 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 to prevent widely encountered oral diseases, such as gingivitis, periodontitis, caries, and dental plaque. Moreover, restorative dentistry also 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 nanotechology and nanomedicine. It will appeal to researchers, clinicians, engineers, pharmacologists, pharmacists, oncologists, infectious disease experts, and dentists. More many 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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Preface

ABOUT THE SERIES (VOLUMES I–V)

In our permanently changing world, novel therapeutics are constantly required to manage health and well-being of population. Although numerous diseases are currently considered incurable, impressive progress made in biomedicine and associated fields, such as chemistry, physics, engineering, pharmacology, and materials science, offers a new light 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 a faster healing. Nanotechnology offers great perspectives for personalized medicine, since nanostructured therapeutics proved their efficiency and amazing impact in improving therapy, prophylaxis, and diagnosis. The emerging field of nanosized materials has numerous applications in the biomedical field, especially in therapy. This series of five volumes came out by the need of learning about recent progress of the science of nanostructured materials to improve current therapy and led 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 approach of each chapter contained in these five volumes is clear and easy to understand by most readers and interesting for biomedical specialists, researchers, and engineers. The series is organized in an attractive manner for students and academics on the field, starting with a volume dealing with the synthesis, characterization, and main applications of nanostructures, emphasizing on their impact in therapy. Next volume reveals the most recent progress made on a very investigated field, which is 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 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 about future therapy of severe diseases.

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ABOUT VOLUME I

First volume of the series *Therapeutic nanostructures* introduces the readers in the amazing field of nanostructured size materials, describing types, synthesis and characterization approaches, and emphasizing on their applications. The utility of nanosized materials in the biomedical field is highly influenced by the physicochemical properties of nanostructured materials utilized for therapy. Therefore, knowing their qualities ensure a more successful approach in designing effective agents for the management of a particular disease. This book offers an updated perspective regarding the most interesting advances of nanoarchitectured therapeutics, discusses the wide variety of their synthesis routes, preferential functionalities, and most supported applications for the design of future therapeutics.

Volume I contains 30 chapters, prepared by outstanding international researchers from USA, Brazil, Argentina, Australia, Portugal, Spain, Finland, France, Italy, Germany, Bulgaria, Romania, Turkey, Cyprus, Iran, Pakistan, India, Taiwan, China, and Japan.

In Chapter 1, entitled *Novel Approaches for Preparation of Nanoparticles*, Bolla Govinda Rao et al., give an overview about new developments in various preparation methodologies for the fabrication of nanoparticles. Also, this first chapter offers a great introductory basis in the design of functional nanostructures aimed for particular purposes.

Andreea Aiacoboae et al., in Chapter 2, entitled *Applications of Nanoscale Drugs Carriers in the Treatment of Chronic Diseases*, discuss about smart nanosized drug-delivery systems which made or have the potential to make a great impact in the management of chronic illness. The fact that numerous nanosystems are able to respond to various stimuli, such as pH, temperature, light, ultrasounds, electrical, and magnetical fields, make them special candidates for targeted and efficient therapy. The chapter discusses most investigated examples of nanoparticles which are under consideration for nanotherapy, such as gold nanoparticles (NPs), silver NPs, magnetic NPs, quantum dots, and mesoporous silica NPs, useful in targeting and delivering applications.

Chapter 3, prepared by Giorgia Adamo et al., entitled *Functionalization of Nanoparticles in Specific Targeting and Mechanism Release*, reviews the potential of smart multifunctional nanostructures as customizable, targeted drug-delivery vehicles capable of carrying large doses of therapeutic agents into target cells. Covalent and noncovalent chemical linking using different molecules have been reported for nanoparticles surface functionalization, since this approach confers them specific properties, such as more specific targeting ability.

In Chapter 4, entitled *Fabrication and Characterization of Natural/Synthesized, Micro-, and Nanostructured Materials for Biomedical Applications*, prepared by Hiromichi Takebe et al., is presented an up-to-date overview about the preparation of modified micro/nanoparticles such as, magnetic oxide nanoparticles for thermal coagulation therapy, iron oxide nanocubes and their shape-induced self-assembly and micro/submicrosized, imprinted inorganic glasses for nanointegration. This chapter is a great opportunity to review the properties of most investigated nanosystems for biomedical applications.

In chapter 5, entitled *Multifunctional Nanostructured Biopolymeric Materials for Therapeutic Applications*, prepared by Armentano et al., is revealed the current state and future prospects of the new generation of multifunctional bionanomaterials, based on different natural or synthetic biopolymers, together with their role in development of personalized therapy.

Chapter 6, entitled *Polymeric Pharmaceutical Nanoparticles Developed by Electrospray*, prepared by Faramarzi et al., gives an overview about advantages and disadvantages, basic principles and production methods of electrospray based approaches.

Debjyoti Paul et al., in Chapter 7, entitled *Nanoformulation and Administration of PUFA-Rich Systems for Applications in Modern Healthcare*, explore the realms of nanotechnology that deals with the fabrication methods of polyunsaturated fatty acids (PUFA) rich nanoformulations, the holistic changes in stability, bioavailability, and bioactivity as a consequence of different administration routes (oral, topical, and parenteral) of such nanosystems.

Naruki Kurokawa et al., in Chapter 8, entitled *Electrospinning and Surface Modification Methods for Functionalized Cell Scaffolds*, present an extensive overview of effective techniques for making optimal scaffolds, including electrospinning and surface modification methods.

Daniel Iglesias, et al., in Chapter 9, entitled *Short Peptide Self-Assembled Nanostructures for Therapeutics Innovative Delivery*, described the high innovation potential offered by self-assembling short peptides in the field of drug delivery. Several options for such use are possible, ranging from physical drug entrapment in the hydrogel matrix, through drug noncovalent binding to the supramolecular structure by the covalent binding of the drug to the self-assembling building block.

Avneet Saini et al., in Chapter 10, entitled *Peptoids: Tomorrow's Therapeutics*, summarize the recent research efforts in the field of peptoid biopolymers from synthesis to folded structural motifs. Also, the authors present their major biological applications discovered in the last two decades.

Chapter 11, prepared by N.S. Sampath Kumar, *Electrospinning of Collagen Nanofiber Scaffolds for Tissue Repair and Regeneration*, provide information about tissue repair and regeneration using biomimetic scaffolds and a brief overview of state-of-the-art methods for fabricating nanofibrous scaffolds, including phase-separation, freeze-drying, self-assembly, and electrospinning.

Chapter 12, entitled *Nanostructured Therapeutic Systems With Bioadhesive and Thermoresponsive Properties*, prepared by Marcos Luciano Bruschi et al., discussed the importance, applications, and perspectives of Mucoadhesive Thermoresponsive Systems as potentially useful therapeutic approach.

Chapter 13, entitled *Design Considerations in the Development of Wound Healing Bionanomaterials*, prepared by Parvez Alam et al., provide a comprehensive overview about fundamental considerations in the design of bionanomaterials with a focus on skin properties, material types, surface structures and methods for nanofabrication.

In the Chapter 14, *Role of Nanostructure Molecules in Enhancing the Bioavailability of Oral Drugs*, prepared by Muhammad Ahmed Azmi et al., the main focus is on the role of nanostructured molecules in the enhancement of the bioavailability of drugs. The authors show recent results for different compounds, which are promising candidates for anti-inflammatory, immunosuppressive, antifertility, anticytogenesis, and anticancer responses.

Chapter 15, prepared by Ulvan Ozad, entitled *Improvement Steps of Plastic Surgery to Tissue Engineering by Nanotechnology*, give an overview about the application of nanotechnology in plastic and reconstructive surgery field. The effects of nanotechnology are observed in numerous such procedures; ranging from the nanomaterials used in implantable materials to wound closure, wound healing, and wound dressing, emphasizing on tissue engineering and regeneration.

Eliana D. Farías et al., in Chapter 16, entitled *Dendrimers and Dendronized Materials as Nanocarriers*, describe general characteristics of dendrimers and dendronized materials, synthetic methodologies and their properties. Successful applications of dendrimers and novel dendritic structures to obtain efficient nanocarriers are also discussed.

Petar A. Atanasov, in Chapter 17, entitled *Gold Nanostructures: Preparation, Properties, Application in SERS, and Biophotonics*, present an up to date overview about the development of several advanced methods for fabrication of nanoparticles and nanosized arrays and examples of their application in SERS and biophotonics. Also, advanced laser systems which are used for controlling and manipulating the properties of the structures are presented and dissected.

Chapter 18, entitled *Quantum Dots for Bioimaging and Therapeutic Applications*, prepared by George Vlasceanu et al., presents an up to date review about Quantum Dots synthesis methods and bioimaging techniques, with the focus on the latter. Bioimaging emerged as a relatively recent field, as the integration of chemistry, physics, and biology in an intricate overlapping. This intriguing field proved a great impact in modern therapeutics and the potential for future therapy seems endless.

Nily Dan et al., in Chapter 19, entitled *Lipid-Based Synthetic Gene Carriers*, review the equilibrium properties of lipoplexes and the kinetics pathways for their formation. Better understanding of lipoplex formation can not only lead to the design of effective nucleic acid lipoplex-based gene delivery or silencing agents, but is also of interest as a fundamental multicomponent, multilength scale, and multitime scale process.

Chapter 20 prepared by Corinne Dejous et al., *Using Microsensors to Promote Development of Innovative Therapeutic Nanostructures*, gives an overview of the existing micro- and nanosensors, and their principles and describe microsensors that can be developed for fast evaluation of efficiency and toxicity of innovative therapeutic nanostructures. The authors also describe their key applications and analytical techniques employed.

D. Schipper et al., in Chapter 21, entitled *The effect of Nanostructured Surfaces on Stem Cell Fate*, present details about the chemical structure of various nanomaterials used as scaffolds for stem cell differentiation including bulk and surface properties and corresponding analytical methods for surface characterization. Furthermore, the authors present recently developed methods for the design of tailored nanomaterials used in stem cell differentiation.

Chapter 22, prepared by Sepideh Khoee, entitled *Applications of Aptamers for the Diagnosis and Therapy of Different Diseases*, gives an up to date overview about aptamers and their application as biotechnological tools in biosensor development and therapeutic agents for drug delivery and diagnosis of diseases.

Chapter 23, entitled *Recent Progress in Therapeutic Diagnosis Using Photonic Crystal Nanostructures*, prepared by Saeed Olyaee, discusses about photonic crystals and their properties, as well as the fabrication procedure. The chapter presents several demonstrations using photonic crystals and their laser biosensors module, as lab on chip devices.

Chapter 24, prepared by Surbhi Dubey, entitled *Novel Carriers and Approaches: Insight for Psoriasis Management*, presents recent progress in the field of psoriasis in terms of pathogenesis, role of cytokines, currently available treatment options pertaining to mode of action, pharmacokinetics, major hindrances in psoriasis treatment, side effects of individual antipsoriatic drugs, and recent developments in the delivery of various antipsoriatic drugs through lipid-based novel colloidal drug carriers. Recent nano-based approaches bring a new light in the management of this disease.

Jalpa Soni et al., in Chapter 25, entitled *Use of Nanostructures Based on Noble Metals in Nanobiomedicine*, present new developments in the nanobiotechnology with a general overview on the impact of various types of nanostructures based on noble metals for various biomedical applications.

Chapter 26, entitled *Innovative Nonviral Vectors for Small-Interfering RNA Delivery and Therapy*, prepared by Danielle Campiol Arruda, introduces the biological barriers to siRNA delivery *in vivo* and discusses recent advances in material sciences, nanotechnology, and nucleic acid chemistry that have yielded promising nonviral delivery systems, some of which are currently undergoing testing in clinical trials. The diversity of these systems highlights the recent progress of siRNA-based therapy using nonviral approaches.

Ali Rastegari et al., in Chapter 27, entitled *siRNA-Based Nucleoceuticals for Tissue Regeneration*, provide an in-depth discussion of the development of siRNA-based nucleoceuticals for tissue engineering applications.

Paula V. Messina et al., in Chapter 28, entitled *Bone Tissue Regenerative Medicine Via Bioactive Nanomaterials*, summarize the most recent developments related to the application of nanomaterials to the bone regenerative medicine and discusses their commercialization projection in consideration to their toxicological risks.

Chapter 29, prepared by Stefana Iosub et al., entitled *Toxicity of Nanostructures—A General Approach*, provides a general picture of the toxicological responses that nanomaterials can generate. Beside the size and the concentration of nanoparticles, there are several factors that influence their cytotoxicity, such as: aggregation state, shape, chemistry, biodistribution, etc. However, the toxic effects could be diminished by capping or coating the nanoparticles with various molecules to enhance their biocompatibility, which also may increase their specificity.

Chapter 30, entitled *Role of Excipients in Formulation Development and Biocompatibility of Lipid Nanoparticles*, prepared by Slavomira Doktorovova, discusses the role of excipients in the production of lipid nanoparticles. An overview of commonly used and upcoming promising excipients, which can facilitate the development of lipid nanoparticles and lipid-based formulations, is presented. A review of new research outcomes and market status of lipid nanoparticles is also addressed in this chapter.

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CHAPTER

1 NOVEL APPROACHES FOR PREPARATION OF NANOPARTICLES

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CHAPTER OUTLINE

1 INTRODUCTION

Since the beginning of the 21st century, with the rising concern of multidrug resistance and scarcity of new antibiotics, the use of metal nanoparticles (NPs) in medicine is undergoing renaissance. In contrast to bulk, nanomaterials exhibit huge surface area per unit volume and tunable optical, electronic, magnetic, and biological properties. Metal NPs can be engineered to have different sizes, shapes, and surface characteristics. The size and shape tunable properties of metal nanoparticles and their wide scope of applicability in pharmacy and biotechnology have drawn global attention toward their size and shape-controlled synthesis. However, while dealing with metal nanoparticle synthesis, few things should be considered seriously. First, the chosen method must be simple, less expensive, ecofriendly, and commercially viable. Second, the simultaneous control of particle size and shape along with their uniformity is another key objective (Kwon and Hyeon, 2008). Moreover, the NPs are kinetically unstable, they should be stabilized against aggregation into larger particles (Richter et al., 2010). Micelles, polymers, and coordinative ligands are frequently used as stabilizers to control the growth of NPs (Kim et al., 2004). Solution-based nanofabrication methods usually offer more control and reproducibility over the metal NPs. A wide range of nanofabrication methods, including precipitation, deposition-precipitation, sol–gel, liquid–liquid interface technique, hydrothermal and solvothermal syntheses, microwave-assisted processes, polyol method, template-directed synthesis, ionic-liquid assisted methods, and so on are reported in the literature. In this chapter, the frequently used fabrication techniques are addressed in detail with appropriate literature references. A careful study of their usefulness and drawbacks with special importance on the laboratory scale synthesis has also been discussed with appropriate illustrations.

1.1 EVOLUTION OF METAL NANOPARTICLES IN PHARMACY AND BIOTECHNOLOGY

Medicinal application of metals is already known from the ancient time. The Ebers Papyrus from 1500 BC is the earliest written account of the use of metals for treatment and describes more than 800 recipes. It has mentioned the use of copper to reduce inflammation and the use of iron to treat anemia. Sushruta Samhita, the ancient book on Indian Ayurvedic treatment methodology written around 7th century BC, mentioned the use of some primary metals like gold, silver, copper, lead, tin, zinc, and iron in medicines (Prakash, 1997). Sodium vanadate has also been used since the early 20th century to treat rheumatoid arthritis. Antimicrobial properties of metals are also known, and have been in use for thousands of years. For example, copper and silver vessels have been used for water disinfection and food preservation since the time of the Persian kings. This practice was later adopted by the Phoenicians, Greeks, Romans, and Egyptians (Alexander, 2009). Settlers of North America used to drop Ag coins into transport containers to preserve water, wine, milk, and vinegar, and a similar strategy was used by Japanese soldiers during the Second World War to prevent the spread of dysentery (Borkow and Gabbay, 2009). The medicinal use of metals was prevalent until the discovery of antibiotics by Nobel laureate Sir Alexander Fleming in the 1920s.

Reducing the metal particle size to nanorange (<100 nm), however, has been demonstrated as an efficient and reliable tool for improving biocompatibility (Taton et al., 2000). Earlier studies have shown that antimicrobial formulations in the form of NPs could be used as effective bactericidal materials (Fresta et al., 1995). Later on, it was revealed that highly reactive metal oxide NPs exhibit excellent biocidal action against Gram-positive and Gram-negative bacteria (Stoimenov et al., 2002). Zero-valent metal nanoparticles like, Au, Ag, and FeNPs, as well as, metal oxide NPs like, zinc oxide (ZnO), titanium dioxide (TiO_2), magnesium oxide (MgO), etc., exhibit bactericidal activity and have been found to be stable and safe for human beings (Lemire et al., 2013). The intrinsic properties and related possible applications of different metal NPs are mainly dependent on their size, shape, composition, crystallinity, and morphology (Dickson and Lyon, 2000). NP toxicity may arise from several attributes, which include the traits that are specific to the properties of the NPs, such as size, shape, or surface charge, and traits that control the release of metal ions (El Badawy et al., 2011; Morones et al., 2005; Pal et al., 2007). The toxic mode of action of NPs has also been connected with the generation of reactive oxygen species (ROS) and membrane disruption (Fig. 1.1) (Bandyopadhyay et al., 2012; Gunawan et al., 2011). A striking capability that has been reported for many NPs is their

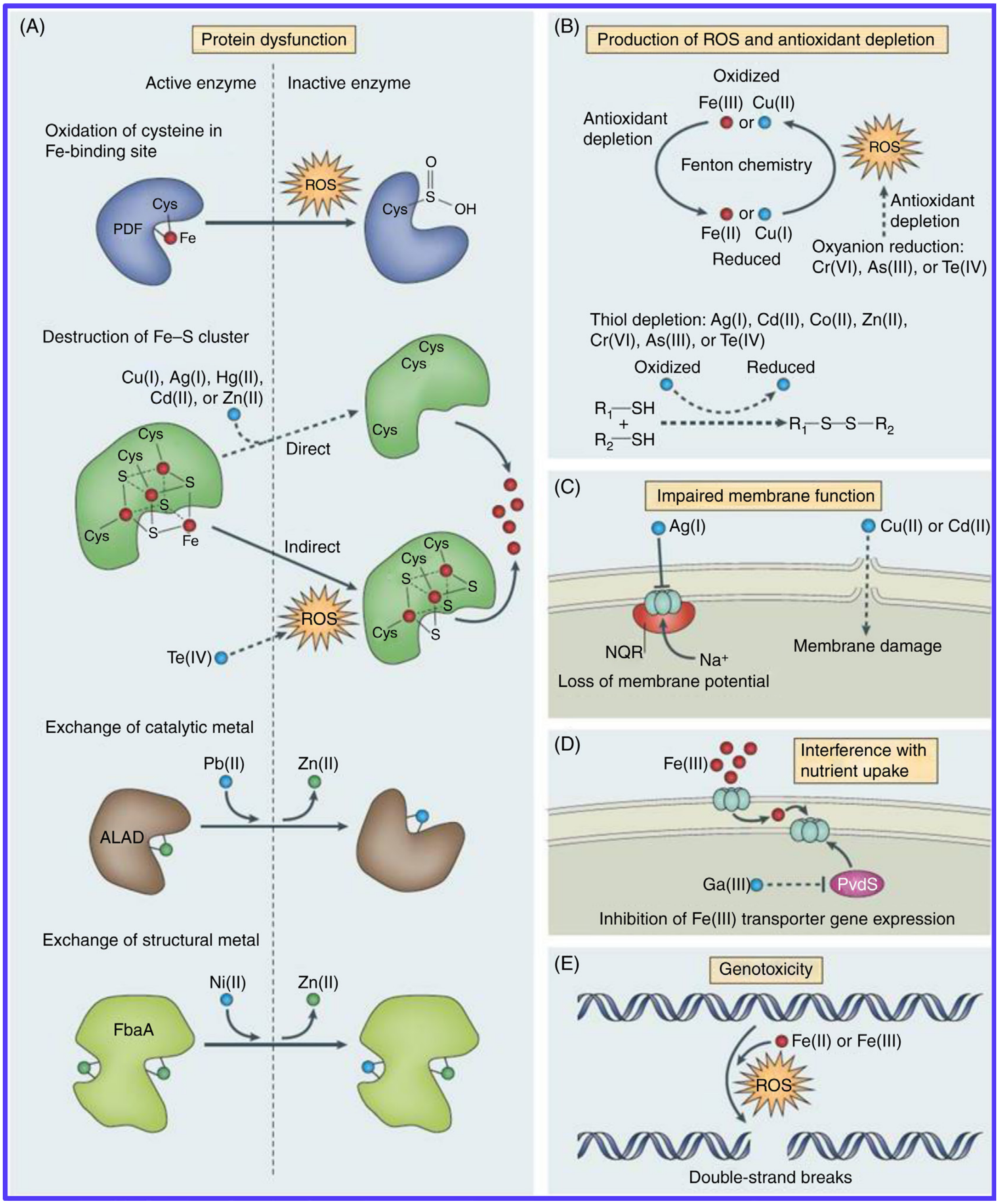

FIGURE 1.1 Antibacterial Mechanisms of Metal Toxicity

(A) Metals can lead to protein dysfunction. (B) Production of reactive oxygen species (ROS) and depletion of antioxidants. (C) Certain metals have been shown to impair membrane function. (D) Interference with nutrient assimilation. (E) They can also be genotoxic. *Solid arrows* represent elucidated biochemical mechanism, whereas, *dashed arrows* represent a route of toxicity for which the underlying biochemical mechanism is unclear. *ALAD*, δ-Aminolevulinic acid dehydratase; *FbaA*, fructose-1,6-bisphosphate aldolase; *NQR, NADH*; quinone oxidoreductase; *PDF*, peptide deformylase; *PvdS*, a σ-factor (σ24) from *Pseudomonas aeruginosa*.

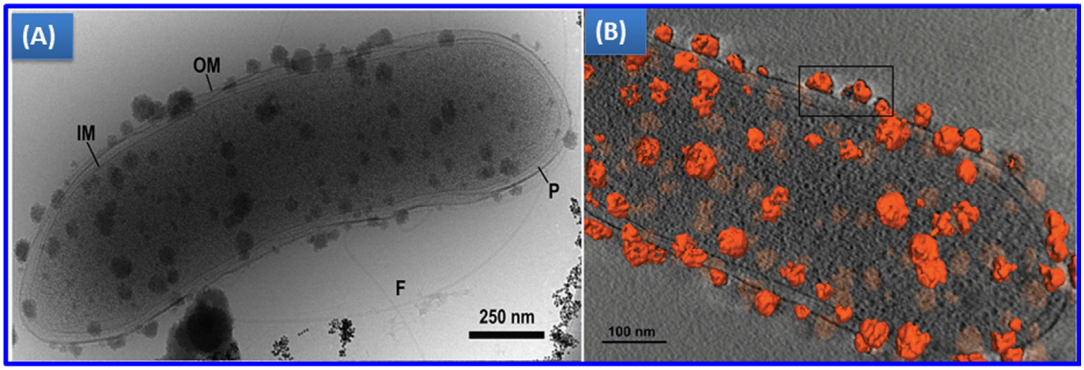

FIGURE 1.2

(A) The figure shows cryo-TEM image of a single cell planktonic Fe-reducing bacterium isolated from groundwater at a site in Rifle, Colorado, USA. (B) A 3-D construction of nanoaggregates *[orange (mid-gray in print version)]* attached to the groundwater bacterium cell wall (Luef et al., 2013).

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ability to physically interact with the cell surfaces of some bacteria. For example, Fe-reducing bacteria that naturally accumulate NPs of ferric oxyhydroxide at their cell surface (Fig. 1.2) can be exploited in targeting a specific bacterial cell (Luef et al., 2013). However, a large number of reports in the literature indicate that the driving force behind the antimicrobial properties of antibacterial NPs is the release of ions (Xiu et al., 2012). Tactically designed NPs, which release ions in a controlled manner or can be targeted to specific bacterial cells, have numerous antimicrobial applications and bagged a business of US$17.5 billion in the year 2011 in global market (Lemire et al., 2013).

Metal and metal oxide NPs have also found applications in advanced techniques of therapeutics, diagnosis, and drug delivery. For example, there are a wide range of paramagnetic metal NPs, mostly but not exclusively based on iron; when an external magnetic field is applied, these NPs become magnetic themselves, and align themselves with the direction of the external field, showing up as a hypoexposed region on an MRI scan (Edmundson et al., 2003). Iron-based magnetic NPs, such as Feridex, have mostly been used in in vitro or in vivo experiments, for example, in tracking the movement of stem cells implanted into a wound site (Okada et al., 2005). In recent times, nanometer-sized crystals made of metallic or semiconductor materials, known as quantum dots have gained much popularity in synthetic biology (Nath and Banerjee, 2013).

Shape-dependent optical activity of the metal NPs has brought a revolution in the field of bioimaging and diagnosis. Huang and coworkers demonstrated that due to longitudinal absorption band in the near infrared (NIR), Au-nanorods are effective in acoustic imaging and are suitable as photothermal agents for hyperthermia therapy of cancer cells. Small diameter Au-nanorods are being used as photothermal converters of near infrared radiation (NIR) for in vivo applications due to their high absorption cross-sections beyond the tissue absorption spectra (Huang et al., 2006a,b). Gold nanocages and nanoframes developed by Xia and coworkers also exhibit potential biomedical applications due to their desirable optical properties and cargo-holding hollow structures (Skrabalak et al., 2008). Silica-gold core–shell NPs, or gold nanoshells, have attracted much attention due to their interesting optical properties and numerous biomedical applications. Aden and Kerker (1951) predicted that concentric spherical particles could exhibit tunable plasmon resonance which vary as a function of the ratio of shell thickness to core radius. Other gold nanostructures, such as Au-nanoshells, Au-nanocages, and spherical AuNPs have also demonstrated effective photothermal destruction of cancer cells and tissue (Conde et al., 2011). Novel optical properties of other related structures, such as asymmetric "nanoeggs" and quadruply concentric "nanomatryushkas" have also been explored (Wang et al., 2007).

2 SYNTHETIC METHODS FOR PREPARATION OF METAL NANOPARTICLES

2.1 THERMAL DECOMPOSITION METHOD

Thermal decomposition method is an excellent synthetic route to fabricate metal NPs. This method is facile and involves single step process. It is inexpensive, environmentally benign, and provides higher quality of metal NPs in terms of morphology, size, and particle-size distribution (Luo et al., 2009). It is a well-known fact from literature that, nucleation step and particle growth are the crucial factors to achieve monodisperse NPs (Kashchiev and van Rosmalen, 2003). The size and shape of the NP can be tuned in thermal decomposition method by controlling the previously mentioned factors by the use of appropriate surfactants. This method involves thermal decomposition of organometallic precursor, like metal carbonyls and metal surfactant complex in solution resulting in metallic NPs (Kwon and Hyeon, 2008). For example, Bao et al. (2010) have synthesized monodisperse cobalt NPs using $CO_2(CO)_8$ as the precursor and oleic acid (OA), tri-*n*-octylphosphine oxide (TOPO), and di-*n*-octylamine (DOA) as the surfactants. Fig. 1.3 shows the TEM images of CoNPs at different time periods in the presence of OA and TOPO surfactants. The particle size was found to rapidly increase with respect to time period. Growth pathway was also investigated in terms of the influence of the surfactant. Combination of OA and TOPO provides diffusional growth pathway, whereas OA and DOA combination and TOPO alone allowed aggregation and ripening growth pathways, respectively. In a similar way, metallic Cu and PdNPs were prepared using precursors, copper cupferronate $Cu(cupf)_2$ complex, and Pd–trioctylphosphine complex, respectively in the presence of trioctylphosphine (TOP) and DOA surfactant. The concentration of stabilizing or capping agent (TOP) played a vital role in controlling the particle size (Diab et al., 2011; Kim et al., 2003).

Chen et al. (2007) have reported the preparation of monodisperse spherical NiNPs via thermal decomposition of nickel (II) acetylacetonate ($Ni\ (acac)_2$) complex in the presence of various alkyl amines. Reaction temperature and solvent type exhibit profound influence on the crystalline phase of NiNPs, whereas, surfactants played a significant role in controlling the particle size as well as morphology. Kura et al. (2010) successfully synthesized monodisperse FeNPs with high saturation magnetization from Fe(CO)x-OAm precursor, in which CO ligands are partially replaced with OAm. During the course of the reaction the precursor decomposed and yielded monodispersed FeNPs. However, OAm played a significant role as a ligand and surfactant to produce small Fe particles by covering the surface of the metal particle.

Kim et al. (2007) have reported the synthesis of hollow iron nanoframes by thermal decomposition of Fe (II)–oleate complex, yielding uniform size Fe nanocubes in the presence of oleic acid. Fig. 1.4 shows various morphologies of iron and inset shows the HRTEM image of FeNPs. However, the addition of a little amount of sodium oleate to the reaction solution, resulted in a remarkable change in the