国家出版基金项目
NATIONAL PUBLICATION FOUNDATION

纳米科学与技术

生物医药纳米技术
方法与操作

Biomedical Nanotechnology
Methods and Protocols

Sarah J. Hurst

科学出版社

国家出版基金项目

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北 京

图：01-2014-4074

图书在版编目（CIP）数据

生物医药纳米技术：方法与操作＝Biomedical nanotechnology:methods and protocols : 英文/（美）赫斯特（Hurst,S.J.）主编. 一影印本.一北京：科学出版社，2014.7

（纳米科学与技术）

ISBN 978-7-03-041426-7

Ⅰ.①生…　Ⅱ.①赫…　Ⅲ.①纳米技术-应用-生物-工程-医学工程-英文　Ⅳ.①R318

中国版本图书馆 CIP 数据核字（2014）第 165809 号

丛书策划：杨　震 / 责任编辑：王化冰　金　蓉
责任印制：钱玉芬 / 封面设计：陈　敬

科学出版社出版
北京东黄城根北街 16 号
邮政编码：100717
http://www.sciencep.com

中国科学院印刷厂印制
科学出版社发行　各地新华书店经销

*

2014 年 7 月第　一　版　　开本：720×1000 1/16
2014 年 7 月第一次印刷　　印张：28
字数：564 000

定价：188.00 元

（如有印装质量问题，我社负责调换）

《纳米科学与技术》丛书序

在新兴前沿领域的快速发展过程中，及时整理、归纳、出版前沿科学的系统性专著，一直是发达国家在国家层面上推动科学与技术发展的重要手段，是一个国家保持科学技术的领先权和引领作用的重要策略之一。

科学技术的发展和应用，离不开知识的传播：我们从事科学研究，得到了"数据"（论文），这只是"信息"。将相关的大量信息进行整理、分析，使之形成体系并付诸实践，才变成"知识"。信息和知识如果不能交流，就没有用处，所以需要"传播"（出版），这样才能被更多的人"应用"，被更有效地应用，被更准确地应用，知识才能产生更大的社会效益，国家才能在越来越高的水平上发展。所以，数据→信息→知识→传播→应用→效益→发展，这是科学技术推动社会发展的基本流程。其中，知识的传播，无疑具有桥梁的作用。

整个20世纪，我国在及时地编辑、归纳、出版各个领域的科学技术前沿的系列专著方面，已经大大地落后于科技发达国家，其中的原因有许多，我认为更主要的是缘于科学文化的习惯不同：中国科学家不习惯去花时间整理和梳理自己所从事的研究领域的知识，将其变成具有系统性的知识结构。所以，很多学科领域的第一本原创性"教科书"，大都来自欧美国家。当然，真正优秀的著作不仅需要花费时间和精力，更重要的是要有自己的学术思想以及对这个学科领域充分把握和高度概括的学术能力。

纳米科技已经成为21世纪前沿科学技术的代表领域之一，其对经济和社会发展所产生的潜在影响，已经成为全球关注的焦点。国际纯粹与应用化学联合会（IUPAC）会刊在2006年12月评论："现在的发达国家如果不发展纳米科技，今后必将沦为第三世界发展中国家。"因此，世界各国，尤其是科技强国，都将发展纳米科技作为国家战略。

兴起于20世纪后期的纳米科技，给我国提供了与科技发达国家同步发展的良好机遇。目前，各国政府都在加大力度出版纳米科技领域的教材、专著以及科普读物。在我国，纳米科技领域尚没有一套能够系统、科学地展现纳米科学技术各个方面前沿进展的系统性专著。因此，国家纳米科学中心与科学出版社共同发起并组织出版《纳米科学与技术》，力求体现本领域出版读物的科学性、准确性和系统性，全面科学地阐述纳米科学技术前沿、基础和应用。本套丛书的出版以高质量、科学性、准确性、系统性、实用性为目标，将涵盖纳米科学技术的所有领域，全面介绍国内外纳米科学技术发展的前沿知识；并长期组织专家撰写、编辑出版下去，为我国

纳米科技各个相关基础学科和技术领域的科技工作者和研究生、本科生等，提供一套重要的参考资料。

这是我们努力实践“科学发展观”思想的一次创新，也是一件利国利民、对国家科学技术发展具有重要意义的大事。感谢科学出版社给我们提供的这个平台，这不仅有助于我国在科研一线工作的高水平科学家逐渐增强归纳、整理和传播知识的主动性（这也是科学研究回馈和服务社会的重要内涵之一），而且有助于培养我国各个领域的人士对前沿科学技术发展的敏感性和兴趣爱好，从而为提高全民科学素养作出贡献。

我谨代表《纳米科学与技术》编委会，感谢为此付出辛勤劳动的作者、编委会委员和出版社的同仁们。

同时希望您，尊贵的读者，如获此书，开卷有益！

白春礼

中国科学院院长

国家纳米科技指导协调委员会首席科学家

2011 年 3 月于北京

Preface

Nanoscience and technology focuses on synthesizing structures that have at least one dimension on the sub-100 nm length scale. It deals with investigating the fundamental properties of such structures, which usually differ significantly from that of the bulk material, and taking advantage of these qualities in constructing novel materials and devices or developing unique applications. Owing to widespread interest and investment, biomedical nanotechnology, or the use of nanostructures in medicinal applications, is an area of intense research that is growing and progressing at a rapid pace. This rapid development is driven by the fact that nanomaterials often offer superior capabilities when compared with conventionally used materials for the detection, diagnosis, and treatment of disease. Further, they have the potential to enable real-time disease detection and therapy and to advance point-of-care systems.

The goal of this volume is to provide an overview of biomedical nanotechnology, from the conception of novel materials in the laboratory to the application of such structures in the clinic. After a brief introductory chapter, the first section consists of protocol chapters which provide practical information on the synthesis of a variety of solution-phase and surface-bound nanomaterials and their application in sensing, imaging, and/or therapeutics; most chapters provide step-by-step instructions and insight into overcoming possible pitfalls and challenges. The chapters are written by leading researchers in biology, chemistry, physics, engineering, and medicine from academia, industry, and the national laboratories. The second section consists of a series of case study/review chapters that discuss the toxicology of nanomaterials, the regulatory pathways to US Food and Drug Administration (FDA) approval of these materials, their patenting, marketing, and commercialization, and the legal and ethical issues surrounding their use. These are written by experts in the science, social science, business, law, and ethics communities. Nanotechnology looks not only to revolutionize medical care but the fundamental property differences associated with nanomaterials and the potential for their use as multicomponent/multifunctional structures are also transforming the aspects of these fields that take part in mediating their introduction to the public.

This volume is a useful reference for scientists and researchers at all levels who are interested in working in a new area of nanoscience and technology or in expanding their knowledge base in their current field. The case study/review chapters are meant to inform scientists of routes they can take in moving their research beyond the bench, so they can design their systems with real-world considerations in mind. In turn, this volume also will be of interest to the social scientist, lawyer, or businessperson who wants to learn about the salient points of nanotechnology as they are applied to their field.

I would like to thank Prof. John M. Walker, series editor for *Methods in Molecular Biology*, for his guidance and the authors for sharing their expertise and producing such high-quality chapters. It was a pleasure to work with them on this project. I would also like to acknowledge Dr. Haley D. Hill for her support and helpful discussions.

Argonne, IL *Sarah J. Hurst*

Contributors

GHANASHYAM ACHARYA • *Departments of Biomedical Engineering and Pharmaceutics, Purdue University, West Lafayette, IN, USA*
ARCHIE A. ALEXANDER • *Adjunct Instructor of Health Administration (Health Law and Ethics)*
HANENE ALI-BOUCETTA • *Centre for Drug Delivery Research, The School of Pharmacy, University of London, London, UK*
KHULOUD T. AL-JAMAL • *Centre for Drug Delivery Research, The School of Pharmacy, University of London, London, UK*
DARREN J. ANDERSON • *Vive Nano, Inc., Toronto, ON, Canada*
GEORGE P. ANDERSON • *Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC, USA*
ITAI BENHAR • *Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Ramat Aviv, Israel*
DIANA M. BOWMAN • *Melbourne School for Population Health, University of Melbourne, Victoria, Australia; Department of International and European Law, KU Leuven, Leuven, Belgium*
JERRY C. CHANG • *Department of Chemistry, Vanderbilt University, Nashville, TN, USA*
NADA M. DIMITRIJEVIC • *Center of Nanoscale Materials, Argonne National Laboratory, Argonne, IL, USA*
JOSE AMADO DINGLASAN • *Vive Nano, Inc., Toronto, ON, Canada*
AARON C. EIFLER • *Feinberg School of Medicine, Northwestern University, Chicago, IL, USA*
RUTLEDGE G. ELLIS-BEHNKE • *Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA*
ERIK FISHER • *School of Politics and Global Studies, Consortium for Science, Policy & Outcomes, Center for Nanotechnology in Society, Arizona State University, Tempe, AZ, USA*
STEFAN FRANZEN • *Department of Chemistry, North Carolina State University, Raleigh, NC, USA*
DI GAO • *Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburg, PA, USA*
JERED B. HAUN • *Center for Systems Biology, Massachusetts General Hospital, Boston, MA, USA*
SARAH J. HURST • *Center for Nanoscale Materials, Argonne National Laboratory, Argonne, IL, USA*
ROSHAN JAMES • *Department of Orthopaedic Surgery, Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut Health Center, Farmington, CT, USA*

FABRICE JOTTERAND • *Division of Ethics and Health Policy, Department of Clinical Sciences and Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA*
RAOUL KOPELMAN • *Department of Chemistry, University of Michigan, Ann Arbor, MI, USA*
KOSTAS KOSTARELOS • *Centre for Drug Delivery Research, The School of Pharmacy, University of London, London, UK*
QIN KUANG • *School of Materials Science and Engineering, Georgia Institute of Technology, Altanta, GA, USA*
SANGAMESH G. KUMBAR • *Department of Orthopaedic Surgery, Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut Health Center, Farmington, CT, USA*
CATO T. LAURENCIN • *Department of Orthopaedic Surgery, Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut Health Center, Farmington, CT, USA*
HAKHO LEE • *Center for Systems Biology, Massachusetts General Hospital, Boston, MA, USA*
JAE-SEUNG LEE • *Department of Materials Science and Engineering, Korea University, Seoul, Republic of Korea*
ONE-SUN LEE • *Department of Chemistry, Northwestern University, Evanston, IL, USA*
YONG-EUN KOO LEE • *Department of Chemistry, University of Michigan, Ann Arbor, MI, USA*
HONGWEI LIAO • *Department of Chemistry and Biochemistry, University of Maryland, College Park, MD, USA*
FRANCES S. LIGLER • *Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC, USA*
DUSTIN LOCKNEY • *Department of Chemistry, North Carolina State University, Raleigh, NC, USA*
STEVEN LOMMEL • *Department of Plant Pathology, North Carolina State University, Raleigh, NC, USA*
MATTHEW MCDERMOTT • *Akina Inc., West Lafayette, IN, USA*
IGOR L. MEDINTZ • *Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC, USA*
GWEN E. OWENS • *Department of Molecular and Medical Pharmacology, Crump Institute for Molecular Imaging, Institute for Molecular Medicine, University of California, Los Angeles, Los Angeles, CA, USA*
BHAVNA PARATALA • *Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, NY, USA*
HAESUN PARK • *Departments of Biomedical Engineering and Pharmaceutics, Purdue University, West Lafayette, IN, USA*
KINAM PARK • *Departments of Biomedical Engineering and Pharmaceutics, Purdue University, West Lafayette, IN, USA; Akina Inc., West Lafayette, IN, USA*
ROBIN PHELPS • *School of Public Affairs, University of Colorado, Denver, Denver, CO, USA*
DUANE E. PRASUHN • *Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC, USA*

TIJANA RAJH • *Center for Nanoscale Materials, Argonne National Laboratory, Argonne, IL, USA*
KENNETH L. REED • *DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, DE, USA*
SANDRA J. ROSENTHAL • *Department of Chemistry, Department of Pharmacology, Department of Chemical and Biomolecular Engineering, Department of Physics and Astronomy, Vanderbilt University, Nashville, TN, USA*
ELENA A. ROZHKOVA • *Center for Nanoscale Materials, Argonne National Laboratory, Argonne, IL, USA*
CHRISTIE M. SAYES • *Department of Veterinary Physiology & Pharmacology, Texas A&M University, College Station, TX, USA*
GEORGE C. SCHATZ • *Department of Chemistry, Northwestern University, Evanston, IL, USA*
GERALD E. SCHNEIDER • *Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA*
SOO JUNG SHIN • *Akina Inc., West Lafayette, IN, USA*
LISA C. SHRIVER-LAKE • *Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC, USA*
BALAJI SITHARAMAN • *Department of Biomedical Engineering, State University of New York at Stony Brook, Stony Brook, NY, USA*
KIMIHIRO SUSUMU • *Division of Optical Sciences, U.S. Naval Research Laboratory, Washington, DC, USA*
DOUGLAS J. SYLVESTER • *Sandra Day O'Connor College of Law, Center for the Study of Law, Science and Technology, Arizona State University, Tempe, AZ, USA*
CHRIS R. TAITT • *Center for Bio/Molecular Science and Engineering, U.S. Naval Research Laboratory, Washington, DC, USA*
C. SHAD THAXTON • *Department of Urology, Feinberg School of Medicine, Institute for BioNanotechnology and Medicine, and the International Institute for Nanotechnology, Northwestern University, Chicago, IL, USA*
KEITH THOMAS • *Vive Nano, Inc., Toronto, ON, Canada*
MICHAEL S. TOMCZYK • *The Wharton School, The University of Pennsylvania, Philadelphia, PA, USA*
UDAYA S. TOTI • *Department of Orthopaedic Surgery, Department of Chemical, Materials and Biomolecular Engineering, University of Connecticut Health Center, Farmington, CT, USA*
HSIAN-RONG TSENG • *Department of Molecular and Medical Pharmacology, Crump Institute for Molecular Imaging, Institute for Molecular Medicine, University of California, Los Angeles, Los Angeles, CA, USA*
LILACH VAKS • *Department of Molecular Microbiology and Biotechnology, Tel Aviv University, Ramat Aviv, Israel*
SHUTAO WANG • *Department of Molecular and Medical Pharmacology, Crump Institute for Molecular Imaging, Institute for Molecular Medicine, University of California, Los Angeles, Los Angeles, CA, USA*
YUHUANG WANG • *Department of Chemistry and Biochemistry, University of Maryland, College Park, MD, USA*
ZHONG LIN WANG • *School of Materials Science and Engineering, Georgia Institute of Technology, Altanta, GA, USA*

DAVID B. WARHEIT • *DuPont Haskell Global Centers for Health and Environmental Sciences, Newark, DE, USA*
YAGUANG WEI • *School of Materials Science and Engineering, Georgia Institute of Technology, Altanta, GA, USA*
RALPH WEISSLEDER • *Center for Systems Biology, Department of Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
ASHISH YERI • *Department of Chemical and Petroleum Engineering, University of Pittsburgh, Pittsburg, PA, USA*
TAE-JONG YOON • *Center for Systems Biology, Massachusetts General Hospital, Boston, MA, USA*
JUN ZHOU • *School of Materials Science and Engineering, Georgia Institute of Technology, Altanta, GA, USA*

Contents

Chapter 1

Biomedical Nanotechnology

Sarah J. Hurst

Abstract

This chapter summarizes the roles of nanomaterials in biomedical applications, focusing on those highlighted in this volume. A brief history of nanoscience and technology and a general introduction to the field are presented. Then, the chemical and physical properties of nanostructures that make them ideal for use in biomedical applications are highlighted. Examples of common applications, including sensing, imaging, and therapeutics, are given. Finally, the challenges associated with translating this field from the research laboratory to the clinic setting, in terms of the larger societal implications, are discussed.

Key words: Nanoparticles, Nanodevices, Biomedical nanotechnology, Biodetection, Nanotherapeutics, Implant materials

1. Introduction

Nanoscience and technology is a field that focuses on developing new synthetic and analytical tools for building and studying structures with submicrometer, and more typically sub-100 nm dimensions ($1\ \text{nm} = 1 \times 10^{-9}$ m) (see Fig. 1) (1, 2). Moreover, it is concerned with the study of the chemical and physical properties of such structures and how these properties change as the size of a material is scaled down from the bulk to a collection of several atoms. Finally, nanoscience and technology centers on utilizing the capabilities and the fundamental property differences associated with such highly miniaturized structures to construct novel functional materials and devices and to develop ground-breaking applications. The nanoscale is a length scale that falls between that of traditional chemistry and physics, which deals with the manipulation of atomic bonds ($\sim 10^{-10}$ m) and that of biology, where most structures are on the order of $\sim 10^{-6}$ to 10^{-7} m in

Sarah J. Hurst (ed.), *Biomedical Nanotechnology: Methods and Protocols*, Methods in Molecular Biology, vol. 726, DOI 10.1007/978-1-61779-052-2_1, © Springer Science+Business Media, LLC 2011

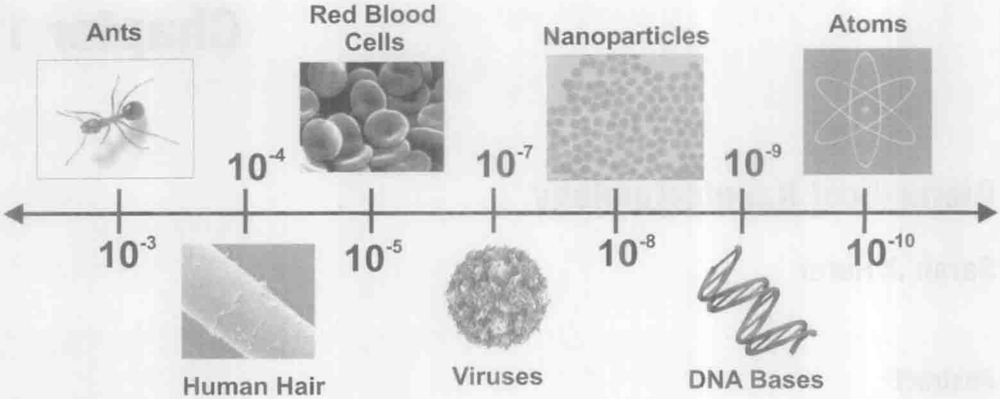

Fig. 1. Length scales.

diameter (e.g., cells, viruses, and bacteria), and as a consequence the field is highly interdisciplinary, encompassing aspects of physics, chemistry, biology, engineering, and medicine.

Although a boom in nanoscience and technology research occurred only recently, nanomaterials, in particular metallic nanoparticles, have been used for centuries in art (i.e., the Lycurgus cup), architecture (i.e., stained glass windows), photography (i.e., the developing process), and medicinal remedies (3, 4). In the late 1800s, Michael Faraday discovered and developed reliable syntheses for pseudo-spherical gold nanoparticles and later (in 1908) a theoretical framework for understanding of their optical properties was put in place by Gustav Mie. In the mid-1900s, enabling technologies for the imaging and manipulation of atoms and nanostructures were pioneered as atomic force, and electron microscopes were designed and put to use. It was also during this time that biologists were unraveling cellular structure and discovering a multitude of biological species (e.g., DNA and proteins) that have nanoscale dimensions. Further, the advent of novel electronic components such as transistors was ushering in the age of high-powered computing. Such findings led prominent scientists such as Richard Feynman and others to speculate that nanoscience and technology would be a revolutionary new research direction for many fields of science (5).

Today, one of the main thrusts of nanoscience research is the synthesis of novel nanoparticle materials and devices. Solution-based syntheses exist for making monodisperse samples of both isotropic and anisotropic metallic, semiconducting, and polymeric nanoparticles of a variety of shapes (6) including spheres (7–10), disks (11–13), prisms (14, 15), cubes (16–18), wires (19), rods

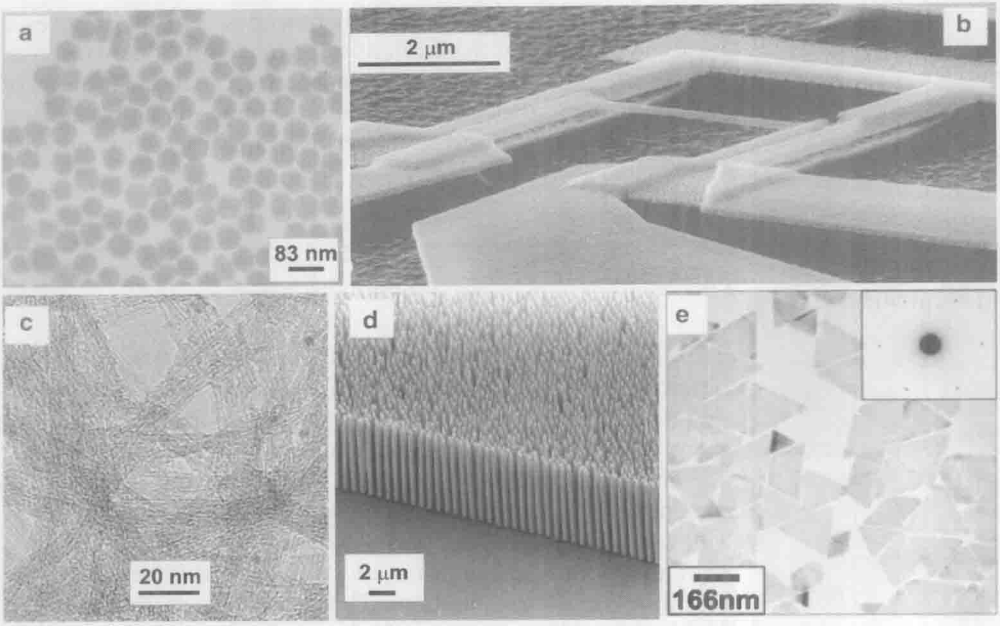

Fig. 2. Electron microscopy images of some common nanostructures. (**b**) Adapted with permission from *Nano Lett.* (2009), **9**, 3116. Copyright 2009 American Chemical Society. (**c**) Adapted with permission from *J. Phys. Chem. B* (2007), **111**, 1249. Copyright 2007 American Chemical Society. (**d**) Adapted with permission from *J. Am. Chem. Soc.* (2008), **130**, 14958. Copyright 2008 American Chemical Society. (**e**) Adapted with permission from *J. Am. Chem. Soc.* (2005), **127**, 5312. Copyright 2005 American Chemical Society.

(20–23), and branched (24–26) structures (see Fig. 2). Techniques such as arc discharge, laser ablation, and chemical vapor deposition (CVD) are being used to create carbon-based nanomaterials (i.e., fullerenes and carbon nanotubes) (27, 28) (see Chapter 15). Surface-based techniques (e.g., electrospinning (29), lithography (30–32), and templation (20)) are being utilized to make surface-bound nanostructures (33) (see Chapters 8 and 10), nanostructured scaffolding materials (see Chapters 15–17) (34–36), nanoelectromechanical devices (NEMS) (see Chapter 9) (37, 38), and nanofluidic devices (39). The nanomaterials produced using these processes are being applied in electronics (40), catalysis (41, 42), energy storage and generation (43, 44), environmental remediation (45, 46), security (47), and especially in biology and medicine (48–50).

In particular, this volume focuses on the application of the above types of nanomaterials in biomedicine. This chapter provides a brief introduction to this field. It highlights the common properties of such structures and the main advantages that they can offer compared to conventionally used materials. It then discusses the key applications in which these structures are used, namely, sensing, imaging, and therapeutics. Finally, it gives a future perspective of this field, not only in terms of new research directions, but also in terms of the larger societal implications of and challenges associated with transitioning nanoscience and technology products and strategies from the research laboratory to the clinical setting.

2. Nanomaterials in Medicine

The types of nanoparticles and nanodevices that are utilized in biomedical applications are chemically and physically diverse, but despite this diversity, they share several commonalities that make them advantageous compared to conventionally used structures.

First, nanomaterials are small in size, having at least one dimension (e.g., particle diameter or feature size) between 1 and 100 nm (1). Due to their small size, these nanostructures have high surface-to-volume ratios and hence are very reactive both during and after their synthesis. This property in part makes them highly tailorable and since their chemical and physical properties depend on their size, shape, and composition, important parameters including their charge, hydrophobicity, solubility, and stability can be easily tuned. For example, a given nanostructure could be designed to be either structurally robust (51) or easily biodegradable (52) over a certain period of time in a biological environment. Also, their small size allows nanostructures to readily interact with biological entities, which have similar dimension. Nanoparticles have been shown to be taken into cells through the pores of their membranes (53) and even localized in particular areas of the cell (54). They also have been known to cross the blood–brain-barrier through tight biological junctions unlike larger macrosized objects (55).

In addition, the nanomaterials employed in biomedical applications usually are multicomponent in nature (20, 49). Often, a nanoparticle or nanostructure is conjugated to one or more types of chemical and/or biological species such as oligonucleotides (short, synthetic DNA strands), proteins, drugs, or lipids through techniques including chemical conjugation, encapsulation, infusion, or adsorption (56, 57) (see Chapters 6 and 7). For instance, the gold nanoparticles discussed in Chapter 2 are functionalized with oligonucleotides of more than one sequence (58) while the bacteriophages discussed in Chapter 13 are modified with antibodies as well as the hydrophobic drug, chloramphenicol (59). Further, the nanomaterial itself is often composed of two or more inorganic components or a combination of inorganic and organic components in an alloy, core-shell, multishell, or dumb-bell arrangement (60, 61). In Chapter 3, for instance, the utilized