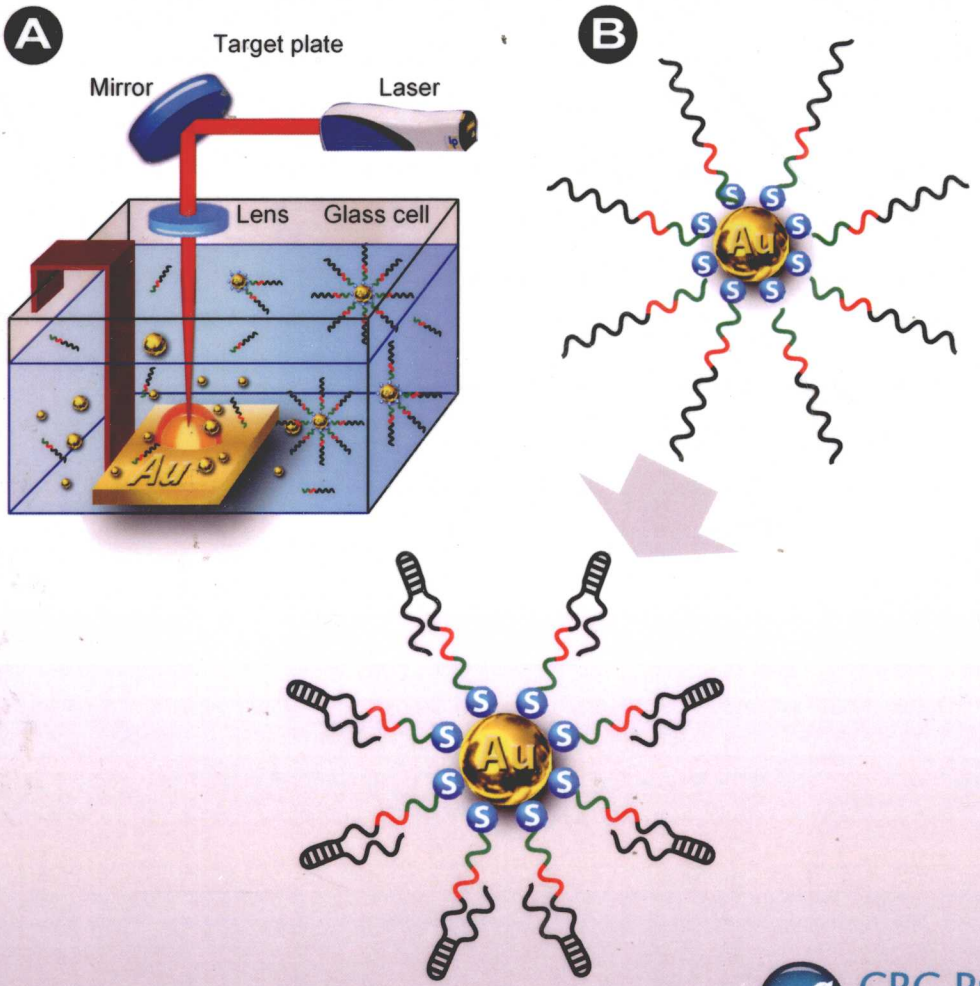
Bioengineered NANOMATERIALS

Edited by **Atul Tiwari • Ashutosh Tiwari**



CRC Press
Taylor & Francis Group

Bioengineered NANOMATERIALS

Edited by **Atul Tiwari • Ashutosh Tiwari**

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed on acid-free paper
Version Date: 20130509

International Standard Book Number-13: 978-1-4665-8595-9 (Hardback)

Library of Congress Cataloging-in-Publication Data

Bioengineered nanomaterials / edited by Atul Tiwari and Ashutosh Tiwari.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-4665-8595-9 (hardcover : alk. paper)
I. Tiwari, Atul, editor of compilation. II. Tiwari, Ashutosh, 1945- editor of compilation.
[DNLM: 1. Nanomedicine--trends. 2. Biocompatible Materials. 3. Bioengineering--trends. 4. Nanostructures. QT 36.5]

R857.M3
610.28--dc23 2013018422

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Bioengineered NANOMATERIALS

Preface

Many varieties of new, complex diseases are constantly being discovered, which leaves scientists with little choice but to embrace innovative methods for controlling the invasion of life-threatening problems. The use of nanotechnology has given scientists an opportunity to create nanomaterials that could help medical professionals in diagnosing and treating problems quickly and effectively. This book focuses on the novel methodologies and strategies adopted in the research and development of bioengineered nanomaterials and technology. It has been written to provide comprehensive and up-to-date information on cutting-edge research in the area of nanomaterials of biotechnological importance.

Chapter 1 introduces the applications of nanoparticles that have clinical utility in cancer treatment. Chapter 2 provides a brief overview of research related to aptamers. The development of aptamer-modified nanoparticles and their use in medical applications are discussed. Chapter 3 describes five immobilization techniques, that is, adsorption, entrapment, encapsulation, covalent coupling, and cross-linking, that are used in the development of biomaterial-based electrodes. Likewise, Chapter 4 reviews research related to the processing of functional nanostructures with a focus on the crucial role of nanofibers and nanoparticle systems. Chapter 5 examines the historical perspective of nanoemulsion vaccine adjuvants, the latest advancements in nanoemulsion adjuvant research, and the direction of future development. Chapter 6 describes the fascinating properties of biocompatible, inorganic nanoparticles of carbonate apatite, including electrostatic interactions with a variety of charged molecules for capturing and subsequent cellular delivery of potential therapeutics. Chapter 7 reviews the synthesis, applications, and biological properties of various ceramic platforms used in medical applications and their potential application as therapeutic nanoparticles in anticancer protein delivery. Chapter 8 discusses the essential aspects in designing the colloidally stable iron oxide nanoparticles. The encapsulation of transplanted cells in nanoporous semipermeable membranes to facilitate adequate diffusion while minimizing immune and foreign cell responses is described in Chapter 9. This chapter also outlines the structural and chemical attributes of various encapsulants. Chapter 10 describes the release of actives from nanoparticles for the application related to topical drug delivery as transdermal patches. A detailed description of toxicity mechanisms, as well as limitations and future prospects of nanotoxicity testing with potential new applications of silver nanocomposites as antibacterial support systems, is provided in Chapter 11. Chapter 12 is devoted to the laser ablation of solid targets to produce a myriad of morphologically distinct nanostructures. This will help readers in understanding the unique one-pot green synthesis method, which gives a precise control over the size, composition, and biofunctionalization, and their results into multifunctional nanoparticles for use in theranostics. The principal applications of nanomedicine in brain tumor treatment, followed by a report on various preclinical and/or clinical studies conducted in brain tumor treatment, are covered in Chapter 13. Chapter 14 provides detailed information on the development of nanomaterials, especially mesoporous silica nanoparticles, that can incorporate high volumes of therapeutic drugs. Such mesoporous nanoparticles can be promising in a wide range of applications, such as information storage systems, magnetic nanodevices, drug delivery, magnetic hyperthermia, medical diagnostics, and ferrofluids. Chapter 15 demonstrates the use of near-infrared-resonant gold nanoshells and carbon nanotubes in tumor imaging and nanodelivery systems for theranostics of carcinomas.

Finally, Chapter 16 has critically upended the requirements for bone regeneration and how biological inspiration is being coupled with the nanoscale engineering of biomaterials in order to create innovative biomimetic scaffolds. The chapter also describes innovative approaches to improve bioactive properties and molecular signaling in cells to stimulate bone repair.

This book contains in-depth information on bioengineered nanomaterials being developed in leading research laboratories around the world. Although the primary focus of attended nanomaterials is on biomedical applications, these technologies would be interesting if explored in multidisciplinary passage. The comprehensively written chapters are targeted to a broad readership, including students and researchers from diverse backgrounds such as chemistry, physics, materials science and engineering, medical science, pharmacy, biotechnology, and biomedical engineering. This book can be used as a textbook by students of bioengineering courses as well as a reference book for researchers.

We are confident that the most recent and detailed information in this book will be useful for students, researchers, scientists, engineers, and professors.

Atul Tiwari
Ashutosh Tiwari

Editors

Atul Tiwari, PhD, is faculty in the Department of Mechanical Engineering at the University of Hawaii, Honolulu, Hawaii. He earned an MS in chemistry from the University of Kanpur, India, a PhD in polymer science from Macromolecular Research Centre, RD University, Jabalpur, India, and an MS in mechanical engineering from the University of Hawaii at Manoa in the United States. He earned chartered chemist and chartered scientist status from the Royal Society of Chemistry, United Kingdom, and is a member of several professional bodies in the United Kingdom, the United States, and India.

Dr. Tiwari has invented and patented several technologies and has published more than 60 research articles, book chapters, and books in the area of materials science and engineering. He has been actively engaged as a consultant in various fields of materials science and engineering. Dr. Tiwari also serves as a reviewer and coeditor for international publication houses and as a board member in many prestigious institutions worldwide.

Ashutosh Tiwari, PhD, is faculty at the Biosensors and Bioelectronics Centre, IFM-Linkoping University and editor in chief of *Advanced Materials Letters*. He is a materials chemist and a graduate of the University of Allahabad, India. He currently serves as adjunct/visiting professor at many prestigious institutions worldwide. He is also actively engaged as a reviewer, editor, and member of scientific bodies worldwide.

Dr. Tiwari obtained various prestigious fellowships, including JSPS, Japan; SI, Sweden; and Marie Curie, England/Sweden. In his academic career, he has published over 175 articles, acquired several patents, and participated in conference proceedings in the field of materials science and technology. He has also edited or authored ten books on the state of the art of materials science.

Contributors

Nana M. Agyei
Department of Chemistry
University of Limpopo
Medunsa, South Africa

Hossein Abbastabar Ahangar
Department of Materials Science and Engineering
Islamic Azad University
Isfahan, Iran

Eilis Ahern
School of Pharmacy
University College Cork
Cork, Ireland

Toshihiro Akaike
Department of Biomolecular Engineering
Graduate School of Bioscience and Biotechnology
Tokyo Institute of Technology
Yokohama, Japan

Ricard Armengol
Provital Group
Barcelona, Spain

Ana Baptista
Faculdade de Ciências e Tecnologia
(Faculty of Sciences and Technology)
Departamento de Ciência dos Materiais
(Materials Science Department and CENIMAT/I3N)
Universidade Nova de Lisboa
(New University of Lisbon)
Caparica, Portugal

Juana Benavente
Facultad de Ciencias
Departamento de Física Aplicada
Universidad de Málaga
Málaga, Spain

João Paulo Borges
Faculdade de Ciências e Tecnologia
(Faculty of Sciences and Technology)
Departamento de Ciência dos Materiais
(Materials Science Department and CENIMAT/I3N)
Universidade Nova de Lisboa
(New University of Lisbon)
Caparica, Portugal

Levon A. Bostanian
College of Pharmacy
Xavier University of Louisiana
New Orleans, Louisiana

Maria Caffo
Department of Neurosciences Psychiatry and Anesthesiology
Neurosurgical Clinic
School of Medicine
University of Messina
Messina, Italy

Gerardo Caruso
Department of Neurosciences
Neurosurgical Clinic
School of Medicine
University of Messina
Messina, Italy

C.J. Chen
Center of Nanomagnetics and Biotechnology
Florida State University
Tallahassee, Florida

Ezharul Hoque Chowdhury
Jeffrey Cheah School of Medicine and Health Sciences
Monash University
Selangor, Malaysia

Timothy Doody
School of Pharmacy
University College Cork
Cork, Ireland

Gregor P.C. Drummen
Bionanoscience and Bio-Imaging Program
Cellular Stress and Ageing Program
Bio&Nano-Solutions
Düsseldorf, Germany

P.B.A. Fechine
Group of Advanced Chemistry Materials
Department of Analytical Chemistry and Physical-Chemistry
Federal University of Ceará
Ceará, Brazil

Isabel Ferreira
Faculdade de Ciências e Tecnologia
(Faculty of Sciences and Technology)
Departamento de Ciência dos Materiais
(Materials Science Department and CENIMAT/I3N)
Universidade Nova de Lisboa
(New University of Lisbon)
Caparica, Portugal

R.M. Freire
Group of Advanced Chemistry Materials
Department of Analytical Chemistry and Physical-Chemistry
Federal University of Ceará
Ceará, Brazil

David H. Gracias
Department of Chemical and Biomolecular Engineering
and
Department of Chemistry
Johns Hopkins University
Baltimore, Maryland

Jesús Hierrezuelo
Facultad de Ciencias
Deptemento de Química Orgánica
Universidad de Málaga
Málaga, Spain

Sharif Hossain
Department of Biomolecular Engineering
Graduate School of Bioscience and Biotechnology
Tokyo Institute of Technology
Yokohama, Japan

Sachin Kadam
Department of Chemical and Biomolecular Engineering
Johns Hopkins University
Baltimore, Maryland

Jagat R. Kanwar
Laboratory of Immunology and Molecular Biomedical Research
Institute for Frontier Materials
Deakin University
Waurn Ponds, Victoria, Australia

Rupinder K. Kanwar
Laboratory of Immunology and Molecular Biomedical Research
Institute for Frontier Materials
Deakin University
Waurn Ponds, Victoria, Australia

S. Kwon
Department of Biological Engineering
Utah State University
Logan, Utah

Giuseppe La Fata
Department of Neurosciences Psychiatry and Anesthesiology
Neurosurgical Clinic
School of Medicine
University of Messina
Messina, Italy

José M. Lanao
Department of Pharmacy and Pharmaceutical Technology
Salamanca Institute for Biomedical Research (IBSAL)
University of Salamanca
Salamanca, Spain

Grace Ledet
College of Pharmacy
Xavier University of Louisiana
New Orleans, Louisiana

E. Longhinotti
Group of Bioinorganic Chemistry
Department of Organic and Inorganic Chemistry
Federal University of Ceará
Ceará, Brazil

Juan Manuel López-Romero
Facultad de Ciencias
Departamento de Química Orgánica
Universidad de Málaga
Málaga, Spain

Cristina Maderuelo
Faculty of Pharmacy
Pharmaceutical R&D Laboratory
Department of Pharmacy and Pharmaceutical Technology
University of Salamanca
Salamanca, Spain

Ganesh Mahidhara
Laboratory of Immunology and Molecular Biomedical Research
Institute for Frontier Materials
Deakin University
Waurn Ponds, Victoria, Australia

Tarun K. Mandal
College of Pharmacy
Xavier University of Louisiana
New Orleans, Louisiana

Laura Martínez-Marcos
Faculty of Pharmacy
Pharmaceutical R&D Laboratory
University of Salamanca
Salamanca, Spain

Lucia Merlo
Pharmaceutical R&D Laboratory
Department of Neurosciences Psychiatry and Anesthesiology
Neurosurgical Clinic
School of Medicine
University of Messina
Messina, Italy

Mambo Moyo
Department of Environmental, Water, and Earth Sciences
Tshwane University of Technology
Pretoria, South Africa

Jonathan O. Okonkwo
Department of Environmental, Water, and Earth Sciences
Tshwane University of Technology
Pretoria, South Africa

Marcello Passalacqua
Department of Neurosciences Psychiatry and Anesthesiology
Neurosurgical Clinic
School of Medicine
University of Messina
Messina, Italy

Laura Peláez
Facultad de Ciencias
Deptmento de Física Aplicada
Universidad de Málaga
Málaga, Spain

Erik Reimhult
Department of Nanobiotechnology
Institute for Biologically Inspired Materials
University of Natural Resources and Life Sciences, Vienna
Vienna, Austria

Christine Reinemann
Centre for Environmental Biotechnology
Helmholtz Centre for Environmental Research—UFZ
Leipzig, Germany

Rodrigo Rico
Facultad de Ciencias
Departamento de Química Orgánica
Universidad de Málaga
Málaga, Spain

Kislay Roy
Laboratory of Immunology and Molecular Biomedical Research
Institute for Frontier Materials
Deakin University
Waurn Ponds, Victoria, Australia

Katie B. Ryan
School of Pharmacy
University College Cork
Cork, Ireland

Daniela Schmid
Molecular Therapeutics
School of Pharmacy
Queen's University Belfast
Belfast, United Kingdom

Christopher J. Scott
Molecular Therapeutics
School of Pharmacy
Queen's University Belfast
Belfast, United Kingdom

R. Sharma
Center of Nanomagnetics and Biotechnology
Florida State University
Tallahassee, Florida

Paula Soares
Faculdade de Ciências e Tecnologia
(Faculty of Sciences and Technology)
Departamento de Ciência dos Materiais
(Materials Science Department and CENIMAT/I3N)
Universidade Nova de Lisboa
(New University of Lisbon)
Caparica, Portugal

E.H.S. Sousa
Group of Bioinorganic Chemistry
Department of Organic and Inorganic Chemistry
Federal University of Ceará
Ceará, Brazil

Beate Strehlitz
Department of Environmental and Biotechnology Centre
Helmholtz Centre for Environmental Research—UFZ
Leipzig, Germany

Francesco Tomasello
Department of Neurosciences Psychiatry and Anesthesiology
Neurosurgical Clinic
School of Medicine
University of Messina
Messina, Italy

Reza Zamiri
Department of Materials Engineering and Ceramics
University of Aveiro
Aveiro, Portugal

Contents

1

Emerging Potential of Nanoparticles for the Treatment of Solid Tumors and Metastasis

Daniela Schmid and Christopher J. Scott

CONTENTS

1.1 Introduction

Cancer is the third leading cause of death worldwide, and mortality rates are continuously rising due to a growing population, longer life expectancy, and changing lifestyle. Although radiation therapy, surgery, and the development of a range of new chemotherapeutic drugs have proven to be effective control for certain primary tumors, efficient treatment for other cancer types and in particular metastatic cancer is still lacking [1]. Since Paul Ehrlich, inspired by an opera, postulated the theory of *Zauberkugeln*—"magic bullets"—over 100 years ago, generations of researchers have been inspired to pursue the

development of molecular therapeutics that target cancer cells directly and exclusively [2]. The application of nanotechnology holds promise in the realization of this goal, and in this chapter, advances in nanomedicine for the treatment of cancer will be reviewed.

1.2 Cancer Therapy and Drug Development

The first reports to the application of chemotherapeutic drugs date back to the early 1940s when the use of folic acid analogues resulted in remission of acute lymphocytic leukemia. Several years later, methotrexate was discovered and approved, which is still in use for several types of cancer today [3]. Other advances at this time included the development of plant-derived anticancer drugs such as vinca alkaloids, taxanes, and camptothecins [4] or DNA-interfering agents like cisplatin and doxorubicin [5,6]. Due to poor stability, solubility, and half-life issues, new derivatives of these first-generation drugs were developed with improved pharmacokinetic properties. Despite these advances, side effects like nausea, diarrhea, and neutropenia or more severe toxicity issues such as myocardiotoxicity remain [7–9].

Increasing scientific understanding of the molecular basis for cancer, including the identification of oncogenes and tumor suppressors, in tandem with phenomenal advances in associated technologies has enabled researchers to further develop molecularly targeted therapeutics. The rationale behind this approach is that if the tumor can be targeted specifically, more potent drugs with less off-target side effects may be realized. Therapeutics that has been developed by this approach includes both small molecules and biologics (Figure 1.1).

With the identification of possible therapeutic targets, chemists have used a variety of approaches including structure–activity relationship (SAR) and high-throughput screening to identify potent inhibitors with high specificity [10]. Small molecules have been developed toward a range of new targets revealed by molecular medicine including cytoplasmic tyrosine kinases, which play fundamental roles in cellular processes such as cell proliferation and survival. Highly specific molecules have been rationally designed toward these enzymes to inhibit cell signaling upon binding [11]. The first small-molecule inhibitor of this class, the tyrosine kinase inhibitor imatinib (Glivec®), was approved in 2001 for the treatment of chronic myelogenous leukemia (CML) and inhibits the transfer

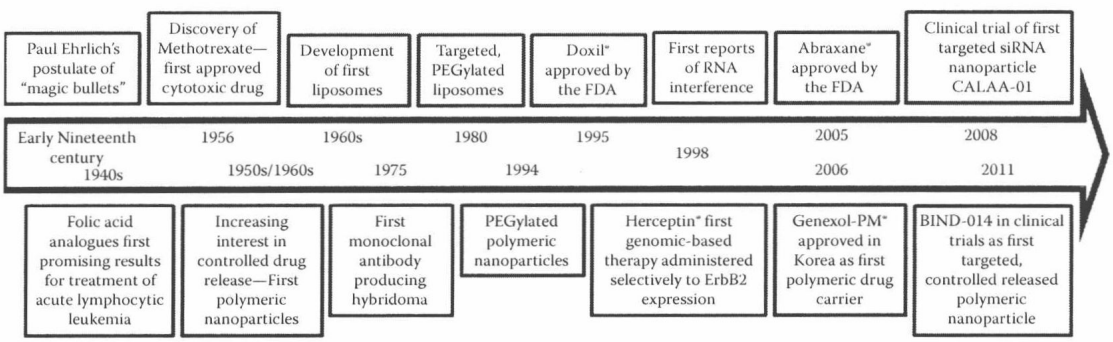


FIGURE 1.1
Milestones in cancer drug development—from the theory of magic bullets to the clinical evaluation of long-circulating therapeutic nanoparticles targeted to cancer cells.

of phosphate from adenosine triphosphate (ATP) to a tyrosine residue of target proteins [12,13]. Remarkably, the response rate to imatinib is over 90%, reducing the white blood cell count in patients to normal. However, resistance in patients has been observed due to gene mutations in the target kinase domain [14]. Several other small-molecule kinase inhibitors have been approved since imatinib became available on the market. Thus, inhibitors like sunitinib (Sutent®) or pazopanib (Votrient®) have broadened the scope of treatment options for renal cell carcinoma where other treatment options are limited [15]. Despite the success that has been realized with small-molecule drugs, many fail to reach the clinic due to issues such as poor bioavailability and lack of specificity.

Another new technology that holds much promise for developing synthetic drug molecules with excellent specificity is RNA interference (RNAi). Fire and Mello first showed the potential of RNAi using double-stranded RNA in *Caenorhabditis elegans* [16]. This principle turned out to be transferrable to mammalian cells and potential RNAi-based therapeutics have been rapidly developed. The main disadvantage of RNAi is its *in vivo* bioavailability, as they do not easily penetrate cell membranes and have very short serum half-lives due to plasma degradation. Thus, efficient delivery remains a challenge for the clinical translation of RNAi-based therapy [17–19].

The major group of molecularly targeted drugs now entering clinical evaluation is biologics, dominated by antibodies. The publication on monoclonal antibody hybridoma generation by Köhler and Milstein in 1975 set a milestone in personalized medicine for targeting specific antigens, in providing a methodology to scalable produce homogenous antibodies [20]. Since then, atleast 12 therapeutic antibodies, targeting proteins overexpressed in tumors, have been approved by the Food and Drug Administration (FDA). These antibodies can either block receptor activation by blocking ligand binding or induce antiproliferative effects [21]. Trastuzumab (Herceptin®) received FDA approval in 1998 for the treatment of patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancers and remains one of the most successful monoclonal antibodies in clinical use. The ErbB2 gene coding for HER2 plays an important role in the development of breast cancer and is expressed in 20%–30% of patients with invasive breast carcinoma [22]. In 2010, the FDA granted the clinical use of trastuzumab for the treatment of HER2-overexpressing metastatic gastric or gastroesophageal (GE) junction adenocarcinoma in combination with chemotherapy [23]. Another leading therapeutic antibody is bevacizumab (Avastin®), which was approved in 2004 for the treatment of metastatic colorectal cancer. Today, this inhibitor of the pro-angiogenic vascular endothelial growth factor (VEGF) is approved for a range of solid tumors [24].

Despite the successful drugs that have been brought to the clinic, many are far from ideal in terms of their efficacy and side effects that are still evident in healthy tissue. Indeed the inability to reach a therapeutic concentration of a drug at the disease site is often a reason that many exciting novel compounds do not progress to the clinic. Targeted delivery strategies aim to address these limitations, by reducing off-target effects, improving drug half-life, and therefore increasing drug efficiency at the disease site. The most advanced targeting strategies being examined currently use antibodies. As well as their proven efficacy in their own right as therapeutic agents, antibodies can be exploited to carry cytotoxins or imaging reagents to disease sites, targeting disease-specific biomarkers. Recently, an increasing number of antibody-drug conjugates (ADCs) have been developed that deliver cytotoxic drugs specifically to target cells [25–27]. Gemtuzumab ozogamicin (Mylotarg®) was the first ADC approved by the FDA in 2000 for the treatment of acute myeloid leukemia. The drug cargo in this ADC, calicheamicin, is a cytotoxic DNA-binding agent, conjugated to an antibody targeted to the CD33 receptor, an antigen that is presented on

leukemic cells in most patients [28,29]. However, Mylotarg was recently withdrawn from the market due to safety issues and lack of clinical benefit [30]. Nonetheless, interest in this field continues and this is exemplified by brentuximab vedotin, a CD30-targeted antibody conjugated to the potent antimicrotubule agent monomethyl auristatin E. It showed antitumor activity in 85% of the patients inducing mainly mild or moderate side effects. This ADC has just received FDA approval for the treatment of Hodgkin's lymphoma and systemic anaplastic large cell lymphoma [31,32]. Trastuzumab emtansine (T-DM1) uses the highly successful breast cancer treatment trastuzumab as targeting antibody and delivers an antimicrotubule agent mertansine selectively to HER2-positive cells. This ADC is currently in phase 3 clinical studies after it has proven to be well-tolerated and effective with a clinical benefit rate of 48% in phase 2 studies on patients with HER2-positive metastatic breast cancer who were extensively pretreated (median of seven therapeutic agents). T-DM1 has the potential to replace trastuzumab and increase therapeutic efficacy of refractory metastatic breast cancer [33,34].

In addition to these current targeting strategies, nanoscale devices represent an exciting emerging platform that have enormous diversity and could revolutionize cancer therapy through the following key parameters [35]:

- Improved drug pharmacokinetics especially of hydrophobic drugs
- Drug targeting to defined tissue and cellular components
- Drug delivery beyond biological barriers
- Co-delivery of drugs
- Therapy and imaging in a combined system

Strategies for this new era of cancer therapy and diagnosis using nanoparticles reflecting 35 years of research including applications of nanoparticles for drug delivery, photothermal therapy, and imaging for early diagnosis and imaging of disease progression are now discussed.

1.3 Therapeutic Nanoparticles for Tumor Treatment

The advances in pharmaceutics in the 1950s and 1960s initiated interest in the concept of controlled drug release. Peter Paul Speiser and his group, pioneers in the field of nanotechnology, developed polyacrylic beads for oral administration and sustained release of chloramphenicol [36]. Subsequently, his group also generated the first nanoparticles for vaccination purposes using micelles with promising immune responses [37]. Since then, an explosion of interest in nanomedicine has occurred ranging from albumin-based to biodegradable nanoparticles and liposomes for a plethora of disease conditions, particularly cancer [38]. Encapsulation in a nanocarrier can protect the cargo drug from premature clearance, and moreover, exposure of normal healthy tissue to the drug can be reduced or even avoided. Thus, the increased bioavailability along with passive and active targeting (discussed later) can increase the levels of a therapeutic at the tumor site. The fact that nanoparticles can be internalized by cancer cells to reach certain cell compartments or bypass biological barriers by appropriate functionalization has the potential to further increase the efficacy of the cargo molecule if its site of action is intracellular [39,40].