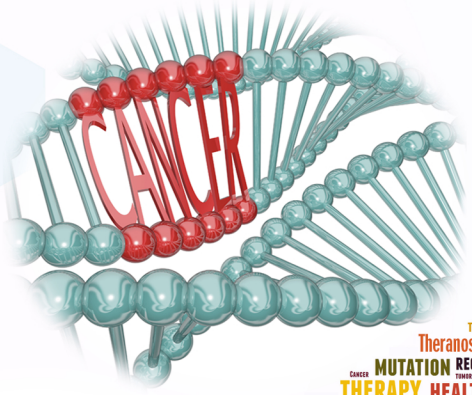
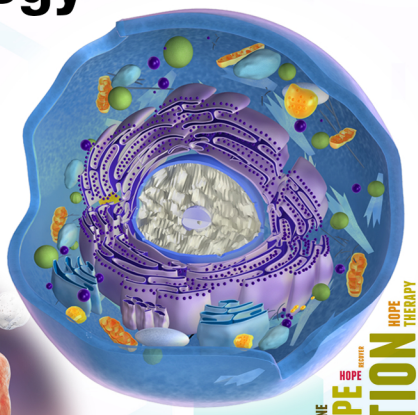
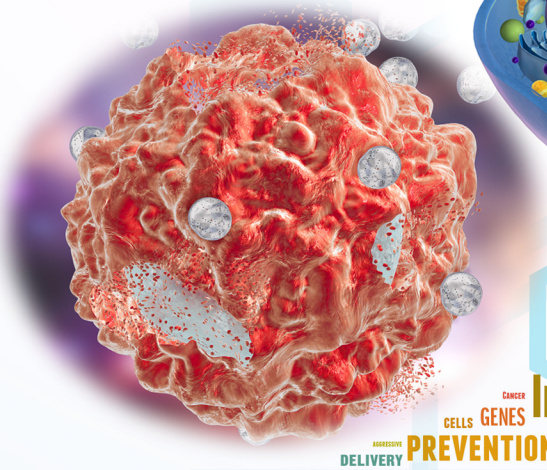
Molecular Medicines for Cancer

Concepts and Applications of Nanotechnology







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I dedicate this book to my little daughters, Samaira (four years) and Aarohi (two years), whose smiles eradicate all the stresses; to my late mother for devoting her life to my upbringing; and to my teachers who always mentored me to grow into a better person.

Deepak Chitkara

I would like to dedicate this book to my parents Ved Prakash Mittal and Urmil Mittal for their unconditional love and support; to my family and to my teachers for showing the right path to achieve a better me.

Anupama Mittal

I dedicate this book to my wife Subhashini, my children Kalika and Vivek for their love and support; my mother Sarswati for believing in me; and to my students and mentors who have always helped me in my quest for learning and in achieving higher goals.

Ram I. Mahato

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Foreword

In today's era of information and communication technology, getting information about a particular subject has become increasingly fast and easy, but the readers are often seen struggling to precisely identify the best source from the plethora of information available. Here arises the need of expert opinion on the subject matter to guide the readers and that is what the editors have successfully accomplished in this book. Talking particularly about the "*molecular medicines*," although summed up in two words, the field is very broad, covering the mechanistic aspects of how a disease could be targeted at the molecular level either by using a novel molecule or employing novel tools for delivering established therapeutics. Further, applications of nanotechnology have generated enormous interest in the medical field in the recent past with many of these new technologies heading towards the clinic. To harness the translational potential of nanotechnology, it is essential to understand how these systems interact with biological targets, ultimately shaping the outcome of the therapy. As rightly said by physicist Richard Feynman, "*there is plenty of room at the bottom.*" The idea of nanotechnology discussed in his famous lecture has now seen the light of the day with its application not being limited to a particular domain of physics but also extending its arms into almost all areas of current research. The field of molecular medicines has witnessed many of its major advancements due to nanotechnology, which is hence rightly covered in this book, while the research is still continuing to unleash the mysteries lying very deep at the bottom. The concept of *"magic bullets"* proposed by German Nobel laureate Paul Ehrlich in the 1900s has always been the driving force in research, particularly cancer research, to resolve the challenges associated with the conventional strategies and provide personalized therapy to patients; these endeavors are rendered fruitful by applying concepts of nanotechnology for precise delivery of newer therapies. In spite of significant achievements in the field, delivery science still needs a precise spacio-temporal control over the molecular medicines to hit the target accurately at the right concentration and at the right time; a nanotechnology-based approach would certainly enable this quantum leap.

This book discusses how nanotechnology based approaches precisely deliver small molecules as well as oligonucleotides and gene-based therapies for cancer treatment presenting all the essential aspects of molecular medicines. The editors have convened the leading experts and researchers to put forth their views on this perpetually advancing field in an easy to understand text for academicians, researchers, undergraduate, and graduate students. I wish them all the best for this book and look forward for further compilations in the future as well.

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Preface

The term "nano" has paved its way into all the fields of science and technology and has shown promising improvements over the conventionally used methodologies. Talking about the field of medicine, it has emerged as a game-changing option by providing new ways of reaching out at the target disease and modifying the therapeutic outcome. With the merger of nanotechnology and medicine, a new term, "nanomedicine," has gained prominence and is applied to applications of nanotechnology in medicine encompassing both therapeutics as well as diagnostics. The reason behind the enormous interest in the field is not only due to the new properties that materials start exhibiting at "nano" scale but also the ability to deliver these therapeutics/diagnostics at the subcellular/molecular level. On the other hand, simultaneous advancements in the field of molecular medicines that deal with the medical interventions targeting molecular structures and mechanisms involved in disease progression require novel technologies to make their therapeutic targets achievable. Particularly in cancer, several molecular mechanisms have been shown to impact its progression, aggressiveness, and chemoresistance. Our growing understanding of the mechanistic association of aberrant cell signaling as well as genetic and epigenetic modifications with cancer has enabled the design of molecular therapeutics. Small targeted molecules, antibodies, and oligonucleotides have been shown to selectively target the molecular structures in the cell thereby influencing the signal transduction process. Also, RNA interference (RNAi), including siRNA and miRNA, has exhibited a marked progress over the past decade with several RNAi technologies in clinical trials including CALLA 01 and ALN-VSP02. The challenges of delivering these molecular medicines to the desired site at therapeutic concentrations have rationalized the use of nanotechnology approaches for achieving the therapeutic goal. There is an increasing body of evidence that demonstrates the role of nanotechnology in influencing the outcome of molecular therapy. Keeping this in mind, we have gathered an array of interrelated topics to apprise the readers with the fundamentals of nanotechnology vis-à-vis the recent advancements in delivering the molecular medicines.

The book has been divided into three sections with a total of 19 chapters that reflect the recent literature as well as the experience of the authors. Section 1 consists of seven chapters covering recent approaches for targeting cancer. Chapter 1 provides an introduction to nanomedicines used for cancer particularly focusing on the nano-based products that have reached the clinic or are under clinical trials. A brief account of different aspects of nanomedicines such as targeting mechanisms, *in vivo* transport as well as clinically relevant animal models required to assess these nanomedicines is also provided. Chapter 2 focuses on the intricate relationship between the physico-chemical properties of the nanoparticles and their *in vivo* journey through various intravascular and transvascular transport routes and biological processes. The significance of nanoparticle size, shape, and surface characteristics with respect to their biological properties such as particle transportation, pharmacokinetics, biodistribution, tumor penetration, cellular uptake, and particle clearance

from blood and tissues is highlighted in this chapter. Once into the cell, nanomedicine should be able to target a particular subcellular organelle. The particle surface could be suitably modified for this purpose; this is thoroughly dealt with in Chapter 3 wherein, several strategies are outlined to target the sub-cellular structures including mitochondria, nucleus, lysosomes, and endoplasmic reticulum. Chapter 4 focuses on the reversal of chemoresistance wherein, several key mechanisms involved in the emergence of chemoresistance are discussed to provide the reader with a clear understanding of key pathways utilized by cancer cells to evade the drug effects. A brief account of the general concepts of nanomedicines is then provided for better understanding followed by a thorough description of nanomedicines utilized for the reversal of chemoresistance. Chapter 5 provides an in-depth understanding on dendrimers as a powerful multifunctional platform for delivering cancer therapeutics and discusses several biomedical applications of peptide-modified dendrimers. Chapter 6 explores an important component involved in cancer progression i.e. tumor microenvironment (TME) as several therapeutic strategies now aim to manipulate TME and to disrupt the cross-talk between tumor and stroma. A detailed account of TME is given in this chapter followed by nanotherapeutic approaches for TME-specific delivery. The last chapter of this section, Chapter 7 provides an insight into the recent nanotherapeutics containing active ingredients of traditional Chinese medicine (AITCM).

Section 2 comprises three chapters (8, 9, and 10) that deal with imaging technologies for cancer, recent trends in theranostic nanosystems and nanotechnologies for immunodiagnosis and immunotherapy, respectively. Herein, a detailed discussion of the imaging techniques in cancer is first provided to apprise the reader with the current state of the art followed by how nanotechnology could be utilized to improve the diagnostic capability. The emergence of theranostic systems that encompass both the diagnostic and therapeutic modalities together and enable personalized therapy is also focused upon in this section. Further, a thorough account on advancements in the fields of immunodiagnostics and immunotherapies vis-à-vis the emerging nanotechnologies that combine the sensitivity of nanomaterials with the specificity of the immunological interactions is provided.

Section 3 comprises nine chapters and provides a detailed account on the emerging gene-based therapies. Chapter 11 gives a brief introduction on the nucleic acids (DNA and RNA) and their use as cancer therapeutics. Further, various nanotechnology-based approaches utilized to deliver these nucleic acid-based therapeutics are discussed followed by the challenges in their *in-vivo* and intracellular delivery. The reader is then apprised of the non-coding RNAs (long non-coding RNAs [lncRNAs] and microRNAs [miRNAs] in Chapters 12 and 13, respectively). LncRNAs are 200–1,000 nucleotides long, non-coding transcripts involved in numerous essential cellular processes and epigenetic mechanisms including genomic imprinting, transcription, translation, chromatin modification, cell development, and differentiation and apoptosis. On the other hand, miRNAs are small oligonucleotides that regulate the expression of target mRNA by binding to 3'-untranslated regions (UTRs) resulting in translation repression. Molecular pathways involved in cancer including WNT/β-catenin, TGF-β/Smad, PI3K/AKT, and p53 signaling that could be targeted by miRNAs are discussed followed by current strategies and challenges in miRNA-based

therapies. Further, Chapter 14 provides an introduction to siRNA therapeutics and their delivery strategies including chemical modifications, RNA-based nanostructures, and lipid systems. Fine tuning of these systems for on-demand release is then discussed. Chapters 15 and 16 provide a detailed account on the lipidic and polymeric carriers for delivering the RNAi-based therapeutics, respectively. Recently it has been shown that both RNA and DNA could be used as nanoscaffolds for delivering various functionalities for regulating cell function and gene expression. The same is dealt with in detail in Chapter 17. Genetic mutations and genomic instability have long been thought of as drivers of the tumorigenesis process. The damage caused by endogenous or exogenous agents needs to be repaired to avoid these mutations. DNA repair mechanisms involve identification of the alterations in DNA molecules followed by a correction to restore the integrity of the genome. On the other hand, cancers with low mutations have pointed at the role of epigenetics, which is defined as the inheritable changes in gene expression with no alterations in DNA sequences. A connection between disruptions of the epigenome and tumor progression has been demonstrated by several studies. A detailed account of both DNA repair mechanisms and epigenetics in cancer is provided in Chapter 18. Recently, CRISPR/Cas9 has been shown as a potential tool for editing the genome and thereby correcting the detrimental mutations. Chapter 19 provides an account on the CRISPR/Cas9 technology and its application in cancer for generation of tumor models as well as gene- and cell-based therapy.

This book presents an overview of the entire field of molecular medicines in cancer treatment and the use of nanotechnology as an efficient delivery approach. The content presented here has never before been compiled into a single book. The book brings together the leading experts and researchers to provide an account on the topic, such that the academicians, industrial researchers, higher-level undergraduate and graduate students may easily comprehend the molecular therapy concepts and the applications thereof and could integrate them with the ever-advancing field of nanotechnology. This will further enable the reader to understand and structure the concepts and applications of nanotechnology in a more comprehensive manner.

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Acknowledgments

While editing this book, we have been constantly asking ourselves: What/who is driving this field of work? We recognize the tireless efforts made by leaders in this field that set forth a vision for the future. We take this opportunity to especially acknowledge the contributions of the pioneers in the field, professors Vincent H. L. Lee, Mitsura Hashida, and Sung Wan Kim whose research endeavors have largely shaped our current knowledge.

Editing a book takes an immense effort to put together and interlink the available information and make it a meaningful object. This could not have been achieved without the contribution of leading experts who graciously agreed to put forth their precious time in writing the chapters. We would like to thank them for entrusting us as an appropriate means for spreading their knowledge and views. Further, we would also like to acknowledge the efforts of the reviewers who provided their critical comments and suggestions on the chapters that helped us to improve the book. We also extend our gratitude to our students, mentors, and colleagues for sharing their thoughts in the overall designing of the book.

We especially thank the staff members of CRC Press, Taylor & Francis Group for lending their expertise in the planning, preparation, and production of this book. Particularly we would like to acknowledge Hilary Lafoe and Natasha Hallard for constantly providing the much necessary support in converting a draft into an assembled book.

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Deepak Chitkara is an Assistant Professor at the Department of Pharmacy, Birla Institute of Technology and Science (BITS)-Pilani, Vidya Vihar Campus, India. He obtained his Ph.D. in Pharmaceutical Sciences from the National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, India. He was an exchange research scholar at University of Tennessee Health Science Center, Memphis, TN for one year. After that he did his post-doctoral training at University of Nebraska Medical Center, Omaha, NE in the area of nanomedicines for pancreatic cancer. He is the recipient of Ranbaxy Science Scholar Award-2011. His research interests include the nano-based delivery systems for small molecules, miRNAs, and CRISPR/Cas genome editing tools. He has been working in the area of nanotechnology since 2007.

Dr. Chitkara has developed and taught courses on advanced drug delivery systems and advanced pharmaceutical technology to students of the Department of Pharmacy, BITS-Pilani. The mechanisms, designing, delivery, and therapeutic applications of small molecules, proteins, and peptides and RNAi are extensively discussed in these courses.

Anupama Mittal is an Assistant Professor at the Department of Pharmacy, Birla Institute of Technology and Science (BITS)-Pilani, Vidya Vihar Campus, India. She graduated from the Department of Pharmaceutics at National Institute of Pharmaceutical Education and Research (NIPER), SAS Nagar, India. Thereafter, she worked as a post-doctoral research associate at the University of Tennessee Health Science Center, Memphis, TN and the University of Nebraska Medical Center, Omaha, NE.

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Dr. Mahato has published 140 papers, 17 book chapters, holds two US patents, and has edited/written eight books and ten journal issues (total Google citations=9554 and h-Index=56). He was a feature editor of the Pharmaceutical Research (2006–2013) and an editorial board member of eight journals. He is a CRS and AAPS Fellow, a permanent member of BTSS/NIH study section, and an ASGCT scientific advisor. He applies sound principles in pharmaceutical sciences in the context of the latest advances in life and material sciences to solve challenging drug delivery problems in therapeutics.

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Section I

Nanotechnology-Based Approaches to Target Cancer

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1 Nanomedicines for Cancer

Jiasheng Tu, Birendra Chaurasiya, and Yanan Li

CONTENTS

1.1 INTRODUCTION

Recently, nanotechnologies have been gaining popularity in the medical field for the treatment as well as diagnosis of various diseases. Formulations prepared by nanotechnology are generally engineered below 100 nm size (Farokhzad & Langer, 2006). By definition, nanotechnology works on two principles: (i) nanoscale size of the whole system or its vital components; (ii) man-made nature and unique

characteristics of new materials that arise due to their nanoscopic size (Godin et al., 2010). Nanotechnology is a convergent system of various research areas like chemistry, biology, physics, mathematics, and engineering. This multidisciplinary effort made nanotechnology a unique delivery system to be used in clinical application (Shvedova, Kagan, & Fadeel, 2010). These nanoplatforms have been proven to carry varieties of therapeutic and diagnostic agents such as drugs, genes, and imaging agents at targeted site in a safe and effective manner. Their unique attributes such as ultra-small size, large surface area-to-mass ratio, and high reactivity makes them deliver varieties of theranostics. With these multidisciplinary efforts, these nanocarriers loaded with various therapeutic agents have started to be used in clinical practice as nanomedicines (Liu, Miyoshi, & Nakamura, 2007). Nanocarriers play a major role in the improvement of solubility, bioavailability, and in decreasing the potential toxicity of chemotherapeutic drugs over conventional formulation strategies. This pivotal partnership between nanocarriers and theranostic agents represents a changing paradigm over the last two decades in the drug delivery system to provide nanomedicines for clinical use for many disease conditions like diabetes, asthma, allergies, infections, and so on, most notably in cancer treatment (Brannon-Peppas & Blanchette, 2004; Forrest & Kwon, 2008; Kawasaki & Player, 2005). For therapeutic applications, these nanomedicines precisely deliver the therapeutic agents to the targeted site in a controlled manner without significant systemic side effects. For diagnosis applications, these nanocarriers help to detect abnormalities on a molecular scale such as fragments of viruses, precancerous cells, and diseases markers that are not able to be identified with the traditional diagnosis system.

Nanotechnology, although recently applied to prepare medication for clinical use, was recognized as a drug delivery system long ago. The first nanotechnology based preparation was made of lipid vesicles in 1960s and was later described as liposomes in 1965 (Bangham, Standish, & Watkins, 1965). Similarly, several other nanotechnologies were established over the passage of time, for example, the first controlled-release polymer system of macromolecules was studied in 1976; the first long circulating stealth polymeric nanoparticle was described in 1994; the first quantum dot bioconjugate was described in 1998; and the first nanowire-based nanosensor described in 2001 (Farokhzad & Langer, 2006). History shows that the nanocarrier systems were explored more than 50 years ago but have got popularity in drug delivery date back about 40 years (Marty, Oppenheim, & Speiser, 1977). The first nanomedicine of anthracyclines was prepared in the form of nanosized phospholipid vesicles (liposomes) to reduce cardiotoxicity at the end of 1970s (Forssen & Tökès, 1981). The landmark of nanotechnology-based nanomedicines was harnessed in clinical practice after approval of Doxil®, the first doxorubicin-loaded liposome approved by the Food and Drug Administration (FDA) in 1995 (Barenholz, 2012). Most common nanoplatforms studied today are polymer-based nanoparticles, nanoshells, micelles, liposomes, dendrimers, quantum dots, magnetic nanoparticles, silicone oxide-based nanoparticles, and engineered viral-based nanoparticles (Ferrari, 2005). In this chapter we have focused on nanotechnology-based nanomedicines in clinical uses for various ailments and diagnoses and have included some nanomedicines that are under clinical trial.

1.2 NANOMEDICINES IN CLINICAL USE AND UNDER CLINICAL TRIALS

According to an earlier survey conducted by the European Science and Technology Observatory, in last two decades huge progress has been made in the development of nanotechnology-based therapeutics and diagnostics (Wagner et al., 2006). Based on survey data conducted in recent years, the FDA has approved 20 nanotechnology-based nanomedicines (Table 1.1) for cancer treatment and 67 nanodevices (not listed). A total of 122 therapeutics were under development and more than 795 nanoproducts were in ongoing clinical trials (Hare et al., 2017). Among these products, liposomal and polymer-based drugs are the dominant groups, which account for more than 85% of the total number. Recently ongoing therapeutic clinical trials are listed in Table 1.2. All the products listed in tables were obtained from www.fda.gov and https://clinicaltrials.gov database.

1.2.1 Liposome-Based Nanomedicines

Liposome is derived from the Greek words: *lipo* ("fat") and *soma* ("body"). It was first described by British hematologist Alec D. Bangham in 1961. It is a spherical vesicle composed of phospholipids especially phosphatidylcholine, but also includes other lipids like egg phosphatidylethanolamine (Sahoo, Parveen, & Panda, 2007). Liposomes are categorized as unilamellar, multilamellar, and cochleate vesicles. Unilamellar vesicles contain one lipid bilayer and generally have a diameter ranging from 50 to 250 nm. They contain a large aqueous core that is preferentially used to encapsulate water-soluble drugs. Multilamellar vesicles comprise several concentric lipid bilayers in an onion-skin arrangement and usually have diameters of 1–5 μm. Their high lipid content allows multilamellar vesicles to passively encapsulate hydrophobic drugs. Compared with the multilamellar vesicles above, cochleate vesicles comprise several lipid bilayers that are not concentric (Figure 1.1). Based on liposome preparation methods, the size distribution of liposomes varies from 25–1000 nm (Weissig, Pettinger, & Murdock, 2014). Liposomes have been widely used as pharmaceutical carriers in the past decades because of their unique abilities to (a) encapsulate both hydrophilic and hydrophobic therapeutic agents with high efficiency, (b) protect the encapsulated drugs from undesired effects of external conditions, (c) be functionalized with specific ligands that can target specific cells, tissues, and organs of interest, (d) be coated with inert and biocompatible polymers such as polyethylene glycol (PEG), in turn prolonging the liposome circulation half-life *in vivo*, and (e) form desired formulations with needed composition, size, surface charge, and other properties (Moghimi & Szebeni, 2003; Torchilin, 2005).

Liposome-based nanomedicines approved by the FDA for the treatment of cancer are listed in Table 1.1. Doxil® was the first liposome-based anticancer nanomedicine approved by the FDA in 1995 for the treatment of AIDS-associated Kaposi's sarcoma, ovarian cancer, and multiple myeloma, as well as for metastatic breast cancer (Zhang et al., 2008). Doxil® was prepared by encapsulating doxorubicin into stealth liposome carriers comprised of hydrogenated soy phosphatidylcholine, cholesterol, and PEGylated phosphoethanolamine (Figure 1.2). Doxil® has shown prolonged

TABLE 1.1
Nanotechnology-Based Nanomedicines Approved by the FDA for Clinical Use

Brand Name	Payloads	Route	Indications	Company	Approval Year
			Liposome Based Nanomedicines		
Doxil®/ Caelyx®	PEG-Liposome doxorubicin	i.m.	HIV-related Kaposi's sarcoma; ovarian cancer; multiple myelomas; breast cancer	Janseen-Cilag Pty, Ltd.	1995 2005
Myocet®	Liposomal doxorubicin	i.v.	HIV-related Kaposi's sarcoma; ovarian cancer; multiple myelomas; breast cancer	Zeneus	2008
DepoCyt®	Liposomal cytarabine	i.t.	Malignant lymphomatous meningitis	SkyePharma	1996
DaunoXome®	Liposomal daunorubicin	i.v.	HIV-related Kaposi's sarcoma	Gilead Sciences	1996
Marqibo®	Liposomal vincristine	i.v.	Acute Lymphoblastic Leukemia	Onco TCS	2012
Onco-TCS®	Liposomal vincristine	i.v.	Non-Hodgkin's lymphoma	Enzon & INEX	2004
Onivyde®	Liposomal Irinotecan	i.v.	Metastatic pancreatic cancer	Merrimack Pharmaceutical, Inc.	2015
Lipusu®	Liposomal paclitaxel	i.v.	NSCLC, breast cancer	Sike Pharmaceutical	2006
PICN®	Liposomal paclitaxel	i.v.	Metastatic breast cancer	Sun Pharmaceutical	2014
LEP-ETU®	Liposomal paclitaxel	i.v.	Ovarian cancer	Insys Therapeutics, Inc.	2015
Mepact®	Liposomal Mifamurtide	i.v.	Mononuclear phagocyte targeting for Osteosarcoma	IDM Pharma	2009

(*Continued*)

TABLE 1.1 (CONTINUED)
Nanotechnology-Based Nanomedicines Approved by the FDA for Clinical Use

Brand Name	Payloads	Route	Indications	Company	Approval Year
			Polymer-Based Nanomedicines		
Genexol-PM®	Methoxy-PEG-poly(D,L-lactide) Paclitaxel	i.v.	Metastatic breast cancer	Samyang	2005
Neulasta®	PEG–granulocyte colony-stimulating factor	s.c.	Neutropenia associated with cancer chemotherapy	Amgen	2002
Eligard®	Leuprolide acetate and polymer (PLGH [poly (DL-Lactide-co-glycolide])	i.v.	Prostate cancer	Tolmar	2002
			Protein-Based Nanomedicines		
Abraxane®	Albumin-bound paclitaxel Nanoparticles	i.v.	Breast cancer, NSCLC, pancreatic cancer	Celgene	2005 2012 2013
Ontak®	Engineered Protein combining IL-2 and diphtheria toxin	i.v.	Cutaneous T-Cell Lymphoma	Seragen, Inc	2008
Kadcyla®	ado-trastuzumab emtansine	i.v.	Metastatic breast cancer	Genentech	2013
			Nanotechnology-Based Miscellaneous Nanomedicines		
Nanotherm®	Iron oxide	Intra-dural	Glioblastoma	MagForce	2010
Ryanodex®	Dantrolene sodium	i.v.	Malignant hypothermia	Eagle Pharmaceutical	2014

TABLE 1.2
Nanotechnology-Based Nanomedicines in Clinical Trials

Brand Name	Payloads	Route	Indications	Company	Status Phase
			Liposome-Based Nanomedicines		
L-Annamycin	Liposomal annamycin	i.v.	Acute lymphocytic leukemia, acute myeloid leukemia	Callisto	I
Thermodox®	Liposomal doxorubicin	i.v.	Liver, breast cancers	Celsion	III
Lipolatin®	Liposomal cisplatin	i.v.	NSCLC	Regulon	III
9NC-LP®	Liposomal 9-nitrocamptothecin	aerosol	Hepatocellular carcinoma	ChemWerth	II/III
SPI-077®	Liposomal cisplatin	i.v.	Solid tumors	ALZA Pharmaceutical	I/II/III
Lipoxal®	Liposomal oxaliplatin	i.v.	Advanced cancers	BioCentury	II
EndoTAG-1®	Liposomal paclitaxel	i.v.	Breast, liver, pancreatic cancers	BioCentury	II
LE-DT®	Liposomal docetaxel	i.v.	Pancreatic, prostatic cancers	NeoPharma	I/II
TKM-080301®	Liposomal PLK1 siRNA	i.v.	Neuroendocrine tumors	Arbutus Biopharma	I/II
Atu027®	Liposomal PLK3 siRNA	i.v.	Pancreatic cancer	BioCentury	I/II
2B3-101®	Liposomal doxorubicin	i.v.	Solid tumors	Netherlands Cancer Institute	I/II
SLIT® cisplatin	Liposomal cisplatin	Aerosol	Osteogenic sarcoma metastatic to the lung	Transave	II
Sarcodoxome®	Liposomal doxorubicin	i.v.	Soft tissue sarcoma	GP-Pharm	I/II
OSI-211®	Liposomal lurtotecan	i.v.	Ovarian cancer	OSI Pharmaceuticals	II
OncoTCS®	Liposomal vincristine	i.v.	Non-Hodgkin's lymphoma	Inex, Enzon	II/III
NL CPT-11®	Liposomal Irinotecan	i.v.	Reccurent high grade glioma	Merrimack Pharmaceutical	I
MTL-CEBPA®	Liposomal CEBPA saran	i.v.	Liver cancer	MiNA Theraputics	I
TL1®	Liposomal topotecan	i.v.	Various solid tumors	Sagent Pharmaceutical	I
IHL-305®	Liposomal Irinotecan	i.v.	Advanced solid tumors	Taiwan Liposome Co.	I

(*Continued*)