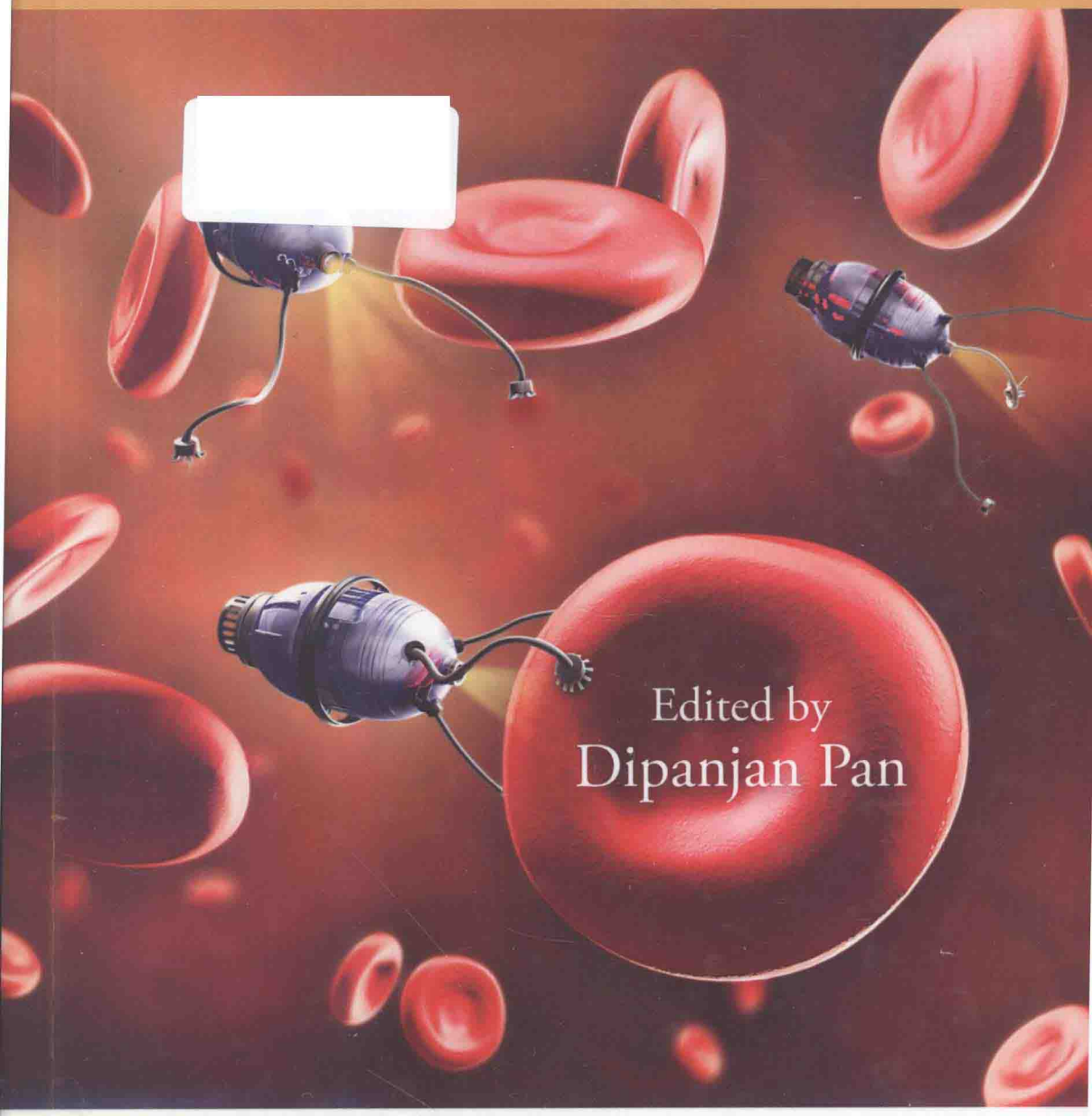

Edited by
Dipanjan Pan

Nanomedicine

A Soft Matter Perspective

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A Soft Matter Perspective

Dedicated to my beloved wife, Angana

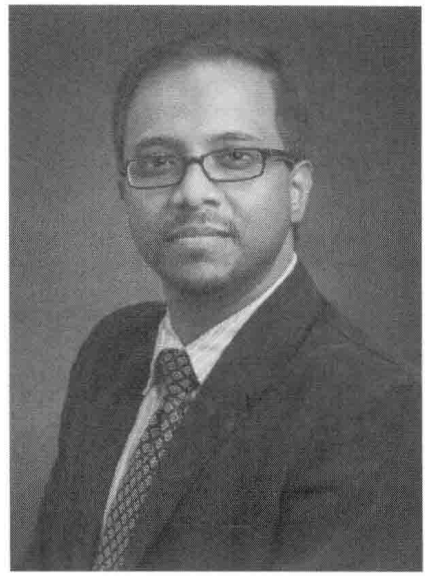
Preface

The capability to monitor disease biosignatures for early and noninvasive detection in combination with targeted therapy is a pressing clinical need and the basis for nanomedicine. This multidisciplinary field is evolving fast and presenting new clinically relevant promises as the science of molecular biology, genomics, chemistry, and nanotechnology contribute greatly. In this book we discuss the unique opportunities presented by biomaterials at the nanoscale. Nanoparticle-based theranostic approaches have emerged as an interdisciplinary area, which shows promise to understand the components, processes, dynamics, and therapies of a disease at a molecular level. The unprecedented potential of nanotechnology for early detection, diagnosis, and personalized treatment of diseases has found application in every biomedical imaging modality. However, with the increasing concern about the ethical and toxicity issues associated with some "nanoplatforms," the biomedical researchers are in pursuit of safer, more precise, and effective ways to practice nanomedicine.

This book provides a broad introduction to matters for nanomedicinal application. It covers comprehensive information regarding "soft" nanoscopic objects with prerequisite features for different imaging modalities. The book also offers a general introduction to the various drug delivery systems and their opportunities from chemistry, materials, biology, and nanomedical standpoints. The book provides a broad introduction to the field and the subfield, with a deeper discussion on the individual modalities for molecular imaging, expanded in four chapters. The theranostic approach is introduced to the readers in the first chapter with discussion about the potential of drug delivery in conjunction with molecular imaging. In Chapter 2, Dr. Ali Azhdarinia and Dr. Sukhen C. Ghosh, from the University of Texas Health Science Center, discuss the potential of nuclear medicine and describe relevant chemical strategies for the design and syntheses of agents suitable for these techniques. In Chapter 3, Dr. Patrick M. Winter, from the Cincinnati Children's Hospital, emphasizes nanomedicine strategies with magnetic resonance imaging. In Chapter 4, Dr. Walter J. Akers, from the Washington University School of Medicine, illustrates various possibilities with optical-based techniques. In Chapter 5, Dr. Dipanjan Pan, Dr. Santosh Misra, and Sumin Kim, from the University of Illinois at Urbana–Champaign, discuss the unique potential for imaging molecular signatures with computed tomography. In Chapter 6, Dr. Dipanjan Pan critically reviews the status of various nanomedicine platforms in clinical trials. This concluding chapter also tries to capture potential pitfalls and challenges faced by the field.

It is anticipated that the book will garner interest across disciplines—within the related areas of chemistry, biochemistry, molecular biology, physiology, and experimental and pharmaceutical sciences. For advanced readers, we expect that it may stimulate experimentation to progress and tune the existing nanomedicine technologies for translational and clinical applications.

The Editor



Prof. Dipanjan Pan joined the University of Illinois in 2013. Previously, he was an assistant professor of medicine, research at the Division of Cardiology, Washington University in St. Louis. He also served as a full faculty member of Siteman Cancer Center at Washington University. After receiving his PhD in chemistry, he pursued a postdoctoral career in polymer science and nanotechnology at the Department of Chemistry, Washington University, in St. Louis. Soon, after a brief stint in the industry (General Electric biosciences/ healthcare), Dr. Pan joined the Washington University faculty in 2007.

Prof. Pan's research is broadly aimed at developing clinically translatable defined nanoparticle platforms for molecular imaging, drug delivery, and nonviral gene delivery applications. His research is highly multidisciplinary, which brings skills from synthetic chemistry, nanoengineering, molecular biology, and preclinical animal models. Prof. Pan is a co-inventor of several engineered nanoplatforms for molecular imaging and therapeutic application. His research covers several imaging modalities, including MRI, CT, optical, PET/SPECT, and photoacoustic imaging. His work has been commercialized for preclinical application and externally supported by federal agencies such as NIH, AHA, as well as the Children's Discovery Institute.

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1 Introduction

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1.1 INTRODUCTION

Nanotechnology is the science of manipulating matter on an atomic and molecular scale. Over the past decade, this field has seen enormous growth in terms of precisely manipulating matter at the "nano" scale. At scales on the order of hundreds of nanometers, novel materials properties emerge, enabling the development of new classes of materials. The unique properties experienced at that scale have been utilized to create many new materials with a vast range of applications, such as in electronics, energy production, and, very recently, human health. It can create opportunities for paradigm shifting results, creating preventive, diagnostic, and therapeutic approaches to human diseases such as cancer, neurological, and cardiovascular [1–7] diseases. The strategy for uniting diagnostics and/or therapeutics on the nanoscale is defined popularly as nanomedicine, which offers benefits due to the high degree of equivalent transport and distribution of the active agents within the biological systems for the diagnosis and treatment of diseases.

The biological transport routes, functionally and at the cellular and subcellular levels, are heavily influenced by the physical attributes of the nanoagents. These physical attributes include their size (extra- or intravascular), shape/morphology (e.g., spherical vs. rod), and flexibility ("soft" vs. "hard"), as well as their chemical identities, including surfaces presenting homing agents for specific recognition by and triggering of biological receptors, cell penetrating peptides (CPPs), etc. It is of critical significance to gain understanding of these parameters in details that govern their uniformity with control over their physical and chemical characters.

A subtopic of nanomedicine research is molecular imaging. Emerging trends in molecular imaging (MI) bring promises to recognize the components, progressions, dynamics, and therapies of a disease at a molecular level. MI unites new agents with biomedical imaging tools to identify cellular events visually and depict specific molecular trails in vivo that are key targets in disease progression. The recognition of the existing prospect to detect preclinical pathology has seen myriad progress in this area to synchronous development of sensitive, high-resolution imaging modalities and specific molecular probes.

The most commonly used noninvasive cellular and molecular imaging techniques include clinical modalities—that is, ultrasound (US), positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI) and experimental imaging techniques (e.g., optical, photoacoustic imaging [PAI], etc.). Nanoarchitectures for medicinal application can be designed from various precursor materials (e.g., lipids, polymers, metals, etc.). They can act as a reservoir material to encapsulate a wide range of active constituents, including contrast agents, therapeutics, and homing moieties. Soft nanomaterials (e.g., well-defined polymers, lipids, etc.) are excellent examples for their versatility in terms of modifying their structures for high payload and delivery to the disease site. Some of the materials are also known to respond to environmental factors (e.g., physiological or external stimuli). The physiological factors include pH, enzymatic, oxidative, and reductive conditions. The external stimuli can be exemplified as temperature, ultraviolet (UV)-visible (vis) light, near-IR (infrared), stimulation with magnetic fields or ultrasonic vibrations, etc.

The physicochemical properties of these nanoparticles influence their shelf-life and in vivo stability, biodegradability, biocompatibility, biodistribution, and bioelimination. Therefore, the strategy for generating particles for nanomedicine application depends on the target disease, intended site of delivery (organs, tissues, cellular or subcellular organelles), route of administration, and the technique used for imaging. In most cases, intravenous injection is the primary route of administration, but there are other, nonconventional ways of administration (e.g., intradermal/transdermal, oral, and mucosal delivery).

1.2 BIOLOGICAL BARRIERS

For cell- or tissue-specific delivery, drugs are encapsulated into nanoparticles and are modified in a defined way so that they reach their destinations (i.e., sites of action), typically on the cellular or molecular levels. The hurdles of the delivery of these drugs (also their carrier nanoparticles) can be classified into pathway barriers and cellular barriers (the limited cellular uptake, endosomal or lysosomal degradation, and the inefficient translocation to the targeted subcellular organelles). Pathway barriers ("en route" barriers) can be exemplified as the obstacles that nanoparticles experience once they are in blood and extracellular matrix. The behavior of the nanoparticles following intravenous administration is complex. Once in the blood, they are exposed to renal and hepatic clearance, disruption, clumping, opsonization, and clearance by the reticuloendothelial system (RES). RES is now referred to as the mononuclear phagocytic system (MPS). Nanoparticles can extravasate or allocate