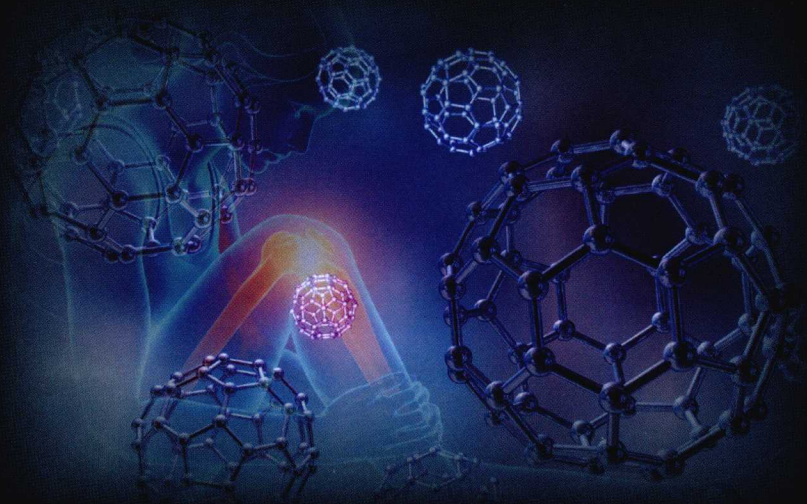


NANOMEDICINE FOR INFLAMMATORY DISEASES



EDITED BY
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Nanomedicine for Inflammatory Diseases

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Nanomedicine for Inflammatory Diseases

I dedicate this work to my family—my lovely wife and our three wonderful daughters.

I also dedicate this work to past and present postdoctoral associates and graduate students who have contributed so much to the research success of my group.

MANSOOR M. AMIJI

I dedicate this work in loving memory to my twin sister, Samantha Tari Jabr; thank you for being my soulmate and for your unwavering love that keeps me going. I also dedicate this work to my daughter, Mirabella; you are the light of my life and I thank you for your eternal brilliance.

LARA SCHEHERAZADE MILANE

PREFACE

Nanomedicine for Inflammatory Diseases is a critical resource for clinicians seeking advancements in the standard of care for inflammatory disease, for educators seeking a textbook for graduate-level courses in nanomedicine, and for both clinicians and scientists working at the intersection of inflammatory disease, nanomedicine, and translational science. *Nanomedicine for Inflammatory Diseases* unites the expertise of remarkable clinicians treating patients with inflammatory disease and high-caliber nanomedicine scientists working to develop new therapies for treating these diseases with the insight of translational medicine specialists, bridging the gap between the laboratory benchtop and the clinical bedside.

The effective treatment of inflammatory disease is a persistent clinical challenge, and managing inflammatory disease impacts the quality of life of many patients; asthma and multiple sclerosis are illustrative of these challenges. The inflammatory response and chronic inflammation is widespread in common disease. Prevalent diseases such as neurodegenerative disease, cancer, and diabetes are now being evaluated and understood in the context of inflammatory disease. Recent advances in immunology and immunotherapies have provided new insight into the molecular biology of the inflammatory response and inflammatory disease. New nanomedicine therapies have been developed to address the deficit of effective treatments for inflammatory disease and exploit the biology of these diseases. Nanomedicine offers

many unique advantages for treating inflammatory disease, such as improved pharmacokinetics and decreased toxicity. Yet, the majority of these nanomedicine therapies have not transitioned into clinical application. The objective of this book is to promote the understanding and action of translation of nanomedicine for inflammatory disease by offering well-needed discussions of the challenges and details. The book is divided into three sections to address the fundamentals, primary inflammatory disease, and secondary inflammatory disease.

Part 1 covers the fundamentals. Chapter 1, "Fundamentals of Immunology and Inflammation," introduces the details of the inflammatory response, explains how these details can go awry and lead to chronic inflammation, and discusses exciting new discoveries, such as the formation of neutrophil extracellular traps. Neutrophil extracellular traps occur when neutrophils essentially sacrifice themselves to capture pathogens by unraveling their DNA and using DNA as a "net" to trap pathogens. Chapter 2, "Principles of Nanomedicine," answers some important questions, such as, what can nanomedicine really do, and what are the best nanomedicine formulations for particular applications? How are common nanomedicines made, and what is the fate of nanomedicine in the body? Chapter 3 addresses the important topic of nanotoxicity: What are the unique safety concerns that must be considered for the clinical use of nanomedicine? What are the main toxicity concerns, and how are they evaluated? Chapter 4, "Translational

Nanomedicine,” discusses the history and progress in nanomedicine translation and highlights a crowning precedent for nanomedicine translation: the National Cancer Institute’s Nanotechnology Characterization Laboratory (NCL). The NCL is developing and establishing standardized protocols with the National Institute of Standards and Technology and successfully outlining the process for nanomedicine translation for cancer. Although this is just for cancer, this is a powerful step for translational nanomedicine, as there is now a clear path to follow. This chapter also discusses the challenges of nanomedicine translation and the need for deliberate translational design with a schema for this design process.

Part 2 focuses on primary inflammatory disease, disease with established inflammatory etiology. The section foreword discusses rheumatoid arthritis as establishing a precedent for nanomedicine in primary inflammatory disease, as there are current clinical trials evaluating glucocorticoid liposomes for the treatment of rheumatoid arthritis. This section then goes into three disease-focused chapters for which nanomedicine translation is imperative: inflammatory bowel disease, multiple sclerosis, and asthma. Each chapter is divided into three sections:

- Section 1: Focuses on the biology of the disease and the current standard of care for the clinical treatment of the disease. The etiology and epidemiology of the disease are discussed, as are the specific concerns, challenges, and deficits for treatment.
- Section 2: Focuses on the nanomedicine in development for treating the disease. Nanomedicine and formulation design for the disease is contextualized and discussed. The current status of the disease-specific therapeutics that are being researched and evaluated in nanomedicine formulations is portrayed.
- Section 3: Focuses on the issues and challenges of bridging the gap between the bench (the nanomedicine research discussed in Section 2) and the clinic (the standard of care discussed in Section 1). A perspective of the current status of nanomedicine translation for the disease is detailed.

By dividing the chapters in Section 2 into these three parts, three distinct needs are addressed: (1) the need for a current assessment of inflammatory disease biology and the current standard of care of these diseases, (2) the need for a comprehensive analysis of nanotherapeutics that have been developed for these diseases, and (3) the need to understand the pathway for the clinical translation of these nanomedicine therapies as new treatments for inflammatory diseases. Comprehension of these three specific needs is essential for enabling successful nanomedicine translation for inflammatory disease.

Part 3, “The Emerging Role of Inflammation in Common Diseases,” is the last section. In recent years, research into immune function and dysfunction in prominent disease has revealed an inflammatory component to many diseases that were not previously associated with an inflammatory etiology. These diseases are referred to as secondary inflammatory diseases. The disease-focused chapters of this section cover neurodegenerative disease, cancer, and diabetes. Each chapter discusses the disease in the context of inflammation and translational nanomedicine. Treating these secondary inflammatory diseases with nanomedicine is a promising approach, as demonstrated by current nanomedicine therapies for cancer. The pathways of nanomedicine translation for primary and secondary inflammatory disease intersect, and the National Cancer Institute’s NCL offers a model for success.

Nanomedicine for Inflammatory Diseases is a translational medicine book that strives to push the field forward by offering insightful perspectives and interweaving the fundamentals of inflammation, nanomedicine, nanotoxicity, and translation; the biology and clinical treatment of inflammatory bowel disease, multiple sclerosis, and asthma; the nanomedicine therapies in development for these diseases; the pathway for translation of these therapies; the role of inflammation in neurodegenerative disease, cancer, and diabetes; and the current status of nanomedicine translation for these diseases. *Nanomedicine for Inflammatory Diseases* seeks to bridge the gaps between inflammation, nanomedicine, and translation by offering a foundational resource for the present and the future.

EDITORS



Lara Scheherazade Milane recently joined Burrell College of Osteopathic Medicine (Las Cruces, New Mexico) as founding faculty in the Biomedical Sciences Department and is the director of online programing. Dr. Milane received her training as a National Cancer Institute/

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Dr. Milane's research interests are in cancer biology, mitochondrial medicine, and translational nanomedicine. She is interested in developing a library of clinically translatable targeted nanomedicine therapies for cancer treatment. She teaches in the medical program and in the post-baccalaureate program. Dr. Milane is an advocate for women in the sciences and is a pioneer for outreach. She has published 18 peer-reviewed journal articles, 3 book chapters, and 3 white papers.



Mansoor M. Amiji is currently the university distinguished professor in the Department of Pharmaceutical Sciences and codirector of the Northeastern University Nanomedicine Education and Research Consortium at Northeastern University in Boston. The consortium

oversees a doctoral training program in nanomedicine science and technology that was co-funded by the National Institutes of Health and the National Science Foundation. Dr. Amiji earned his BS in pharmacy from Northeastern University in 1988 and a PhD in pharmaceutical sciences from Purdue University in 1992.

His research is focused on the development of biocompatible materials from natural and synthetic polymers, target-specific drug and gene delivery systems for cancer and infectious diseases, and nanotechnology applications for medical diagnosis, imaging, and therapy. His research has received more than \$18 million in sustained funding from the National Institutes of Health, the National Science Foundation, private foundations, and the pharmaceutical/biotech industries.

Dr. Amiji teaches in the professional pharmacy program and in the graduate programs of pharmaceutical science, biotechnology, and nanomedicine. He has published six books and more than 200 book chapters, peer-reviewed articles, and conference proceedings. He has received a number of honors and awards, including the Nano Science and Technology

Institute's Award for Outstanding Contributions toward the Advancement of Nanotechnology, Microtechnology, and Biotechnology; the American Association of Pharmaceutical Scientists Meritorious Manuscript Award; the Controlled Release Society's Nagai Award; and American Association of Pharmaceutical Scientists and Controlled Release Society fellowships.

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PART ONE

Introduction

INTRODUCTION TO INFLAMMATORY DISEASE, NANOMEDICINE, AND TRANSLATIONAL NANOMEDICINE

Part 1 covers important foundational concepts in inflammation, nanomedicine, and translation. The inflammatory response is an important protective response; however, it is also central to primary inflammatory disease associated with chronic inflammation and secondary inflammatory disease, such as cancer. Why is inflammation associated with so many diseases? The inflammatory response is a very scripted process; understanding the normal physiology and transduction that occurs is helpful to understanding inflammatory dysfunction associated with disease etiologies and pathologies.

Understanding the benefits of nanomedicine is essential for understanding the need for translation. What does nanomedicine have to offer? How is it superior to traditional formulations? How are the desired properties of a nanomedicine formulation achieved through design? Foundational knowledge of the different nanomedicine platforms aids in understanding this important field of medicine. Being aware of nanotoxicity is also imperative. What are the risks of nanomedicine, and how

are the safety concerns addressed? Are the risks of using nanomedicine worth the benefits? Being able to answer this question for individual therapies is important before translation begins.

Translational medicine has emerged as a distinct area of therapeutics. What is bionanotechnology, and what is the real “nanoappeal” for translational medicine? Translation has progressed from the Critical Path Initiative to the great model of the Nanotechnology Characterization Laboratory. How can this model be used to overcome the challenges of translation? What is the future of translational nanomedicine? These questions are discussed and contextualized to inflammatory disease.

The core concepts in inflammatory disease, nanomedicine, nanotoxicity, and translational nanomedicine are discussed and interconnected to establish foundational knowledge of nanomedicine translation for inflammatory disease. This section even offers a novel schema for translational design workflow. These concepts are the framework for the disease-focused discussions in Part 2 (primary inflammatory disease) and Part 3 (secondary inflammatory disease).

