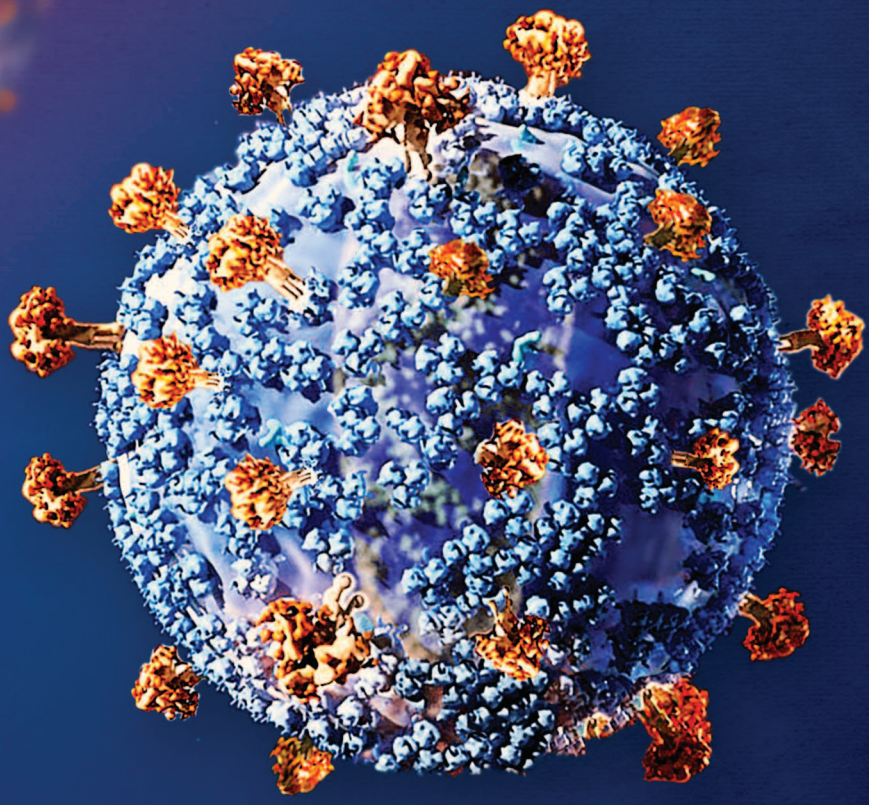
Pan Stanford Series on Nanomedicine Vol. 3

Immune Aspects of Biopharmaceuticals and Nanomedicines

edited by

Raj Bawa | János Szebeni | Thomas J. Webster | Gerald F. Audette



Immune Aspects of Biopharmaceuticals and Nanomedicines

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Series Editor
Raj Bawa

Titles in the Series

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edited by

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Note from the Series Editor and Publisher

It is important to note that knowledge and best practices in the various fields represented in this book (medicine, immunology, biologics, nanomedicine, protein science, patent law, FDA law, regulatory science, toxicology, and pharmaceutical sciences) are constantly evolving. As new research and experience broaden our knowledge base, changes in research methods, legal and business practices, diagnostics, assays, tools and techniques, and/or medical treatments may become necessary. Therefore, the reader is advised to consult the most current information regarding: (i) various products, therapies, assays, diagnostics, technologies, and companies featured; (ii) FDA regulatory guidance documents provided; and (iii) legal, business, or commercial information provided. It is imperative that the reader does not solely rely on the information presented herein and always carefully reviews product labels, warnings, and directions before using or consuming a product. For additional information about a product, please contact the manufacturer, FDA, physician, pharmacist, or other licensed health-care professional, as appropriate. Similarly, careful evaluation of any information, procedures, formulations, legal ideas, medical protocols, regulatory guidances, or assays described herein is warranted. To the fullest extent of the law, neither the publisher nor the editors or the authors make any representations or warranties, express or implied, with respect to the information presented in this book. In this regard, they assume no liability for any injury and/or damage to persons or property as a matter of product liability, negligence or otherwise, or from any use or operation of any medical, therapeutic, immunological, or legal opinions, business methods, medical procedures, therapeutic products, assays, techniques, instructions, or ideas presented or highlighted in this book.

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Immune Aspects of Biopharmaceuticals and Nanomedicines

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This book is dedicated to patients of autoimmune diseases, who endure pain with grace and await new treatments with patience.

—Raj Bawa

I dedicate this book to my sons, hoping that one day they will enjoy science and then understand what kept their dad living enchanted, working at night.

—János Szebeni

I dedicate this book to our next generation (particularly, my daughters, Mia, Zoe, and Ava), who will push the boundaries of science, engineering, and all fields—let this book inspire you to a life with no boundaries.

—Thomas Webster

I dedicate this book to my family, for their unflagging support, and to my students, who continually inspire me with their curiosity.

—Gerald Audette

Dr. Bawa's (above, second from left) personal inspiration for this volume resulted from medical events in the lives of his loved ones. His wife (above left) suffers from rheumatoid arthritis (RA) and Sjögren's syndrome (SjS), both chronic autoimmune diseases. His mother (above, second from right) recently had the "red man syndrome" (a hypersensitivity reaction) while in a hospital emergency room following intravenous administration of vancomycin to treat aspiration pneumonia. She also suffers from Type 1 diabetes (T1D), now considered an autoimmune disease that results from the destruction of the insulin-producing beta cells of the pancreas. His father (above right), a former professor and dean, apart from reviewing numerous chapters of this book, recommended that a volume on the immune aspects of biotherapeutics and nanomedicines was critically needed for regulators, clinicians, and pharma. Note that RA, SjS, and T1D are not caused by immune reactions of biotherapeutics or nanodrugs—autoantibodies are to blame for all. Vancomycin, a glycopeptide antibiotic, is not classified as a biotherapeutic or nanomedicine.

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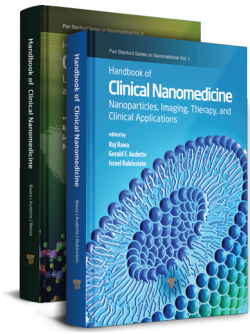

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Handbook of Clinical Nanomedicine. Vol. 1. Nanoparticles, *Imaging, Therapy, and Clinical Applications,* Raj Bawa, PhD, Gerald F. Audette, PhD, and Israel Rubinstein, MD (Editors)

This handbook (55 chapters) provides a comprehensive roadmap of basic research in nanomedicine as well as clinical applications. However, unlike other texts in nanomedicine, it not only highlights current advances in diagnostics and therapeutics but also explores related issues like nomenclature, historical developments, regulatory aspects, nanosimilars and 3D nanofabrication. While bridging the gap between basic biomedical research, engineering, medicine and law, the handbook provides a thorough understanding of nano's potential to address (i) medical problems from both the patient and health provider's perspective, and (ii) current applications and their potential in a healthcare setting.

"Dr. Bawa and his team have meticulously gathered the distilled experience of world-class researchers, clinicians and business leaders addressing the most salient issues confronted in product concept development and translation."

Gregory Lanza, MD, PhD
Professor of Medicine and Oliver M. Langenberg Distinguished Professor
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"This is an outstanding, comprehensive volume that crosscuts disciplines and topics fitting individuals from a variety of fields looking to become knowledgeable in medical nanotech research and its translation from the bench to the bedside."

Shaker A. Mousa, PhD, MBA
Vice Provost and Professor of Pharmacology
Albany College of Pharmacy and Health Sciences, USA

"Masterful! This handbook will have a welcome place in the hands of students, educators, clinicians and experienced scientists alike. In a rapidly evolving arena, the authors have harnessed the field and its future by highlighting both current and future needs in diagnosis and therapies. Bravo!"

Howard E. Gendelman, MD
Margaret R. Larson Professor and Chair
University of Nebraska Medical Center, USA

"It is refreshing to see a handbook that does not merely focus on preclinical aspects or exaggerated projections of nanomedicine. Unlike other books, this handbook not only highlights current advances in diagnostics and therapies but also addresses critical issues like terminology, regulatory aspects and personalized medicine."

Gert Storm, PhD
Professor of Pharmaceutics
Utrecht University, The Netherlands

Handbook of Clinical Nanomedicine. Vol. 2. *Law, Business, Regulation, Safety, and Risk,* Raj Bawa, PhD (Editor), Gerald F. Audette, PhD, and Brian E. Reese, PhD, MBA, JD (Assistant Editors)

This unique handbook (60 chapters) examines the entire "product life cycle," from the creation of nanomedical products to their final market introduction. While focusing on critical issues relevant to nanoproduct development and translational activities, it tackles topics such as regulatory science, patent law, FDA law, ethics, personalized medicine, risk analysis, toxicology, nano-characterization and commercialization activities. A separate section provides fascinating perspectives and editorials from leading experts in this complex interdisciplinary field.

"The distinguished editors have secured contributions from the leading experts in nanomedicine law, business, regulation and policy. This handbook represents possibly the most comprehensive and advanced collections of materials on these critical topics. An invaluable standard resource."

Gregory N. Mandel, JD
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Temple University Beasley School of Law, USA

"This is an outstanding volume for those looking to become familiar with nanotechnology research and its translation from the bench to market. Way ahead of the competition, a standard reference on any shelf."

Shaker A. Mousa, PhD, MBA
Vice Provost and Professor of Pharmacology
Albany College of Pharmacy, USA

"The editors have gathered the distilled experience of leaders addressing the most salient issues confronted in R&D and translation. Knowledge is power, particularly in nanotechnology translation, and this handbook is an essential guide that illustrates and clarifies our way to commercial success."

Gregory Lanza, MD, PhD
Professor of Medicine and Oliver M. Langenberg Distinguished Professor
Washington University Medical School, USA

"The title of the handbook reflects its broad-ranging contents. The intellectual property chapters alone are worthy of their own handbook. Dr. Bawa and his coeditors should be congratulated for gathering the important writings on nanotech law, business and commercialization."

Richard J. Apley, JD
Chief Patent Officer
Litman Law Offices/Becker & Poliakoff, USA

"It is clear that this handbook will serve the interdisciplinary community involved in nanomedicine, pharma and biotech in a highly comprehensive way. It not only covers basic and clinical aspects but the often missing, yet critically important, topics of safety, risk, regulation, IP and licensing. The section titled 'Perspectives and Editorials' is superb."

Yechezkel (Chezy) Barenholz, PhD
Professor Emeritus of Biochemistry and Daniel Miller Professor of Cancer Research
Hebrew University-Hadassah Medical School, Israel

About the Editors

Raj Bawa, MS, PhD, is president of Bawa Biotech LLC, a biotech/pharma consultancy and patent law firm based in Ashburn, Virginia, that he founded in 2002. He is an inventor, entrepreneur, professor and registered patent agent licensed to practice before the U.S. Patent & Trademark Office. Trained as a biochemist and microbiologist, he has extensive expertise in pharmaceutical sciences, biotechnology, nanomedicine, drug delivery, microbial biodefense, FDA regulatory issues, and patent law. Since 1999, he has held various positions at Rensselaer Polytechnic Institute in Troy, NY, where he is an adjunct professor and where he received his doctoral degree in three years (biophysics/biochemistry). Currently, he serves as a scientific advisor to Teva Pharma, Israel, is a visiting research scholar at the Pharmaceutical Research Institute of Albany College of Pharmacy in Albany, NY, and is vice president of Guanine, Inc., based in Rensselaer, NY. He has served as a principal investigator of SBIRs and reviewer for both the NIH and NSF. Currently, he is principal investigator of a CDC SBIR Phase 1 grant to develop an assay for carbapenemase-resistant bacteria. In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office, including primary examiner from 1996–2002. He is a life member of Sigma Xi, co-chair of the nanotech and personalized medicine committees of the American Bar Association and founding director of the American Society for Nanomedicine. He has authored over 100 publications, co-edited four texts and serves on the editorial boards of 14 peer-reviewed journals, including serving as an associate editor of *Nanomedicine* (Elsevier). Some of Dr. Bawa's awards include the Innovations Prize from the Institution of Mechanical Engineers, London, UK (2008); Appreciation Award from the Undersecretary of Commerce, Washington, DC (2001); the

Key Award from Rensselaer's Office of Alumni Relations (2005); and Lifetime Achievement Award from the American Society for Nanomedicine (2014).

Janos Szebeni, MD, PhD, DSc, is director of the Nanomedicine Research and Education Center at Semmelweis University in Budapest, Hungary. He is also the founder and CEO of a contract research SME, SeroScience, Ltd., and a full professor of immunology and biology at the University of Miskolc in Hungary. He has held various academic positions in Hungary and abroad, including at the National Institute of Hematology and Blood Transfusion and at the First Clinics of Internal Medicine, Semmelweis University in Budapest, the University of Arizona in Tucson, AZ, the National Institute of Health in Bethesda, Maryland, Massachusetts General Hospital, Harvard University in Boston, MA, the Walter Reed Army Institute of Research in Silver Spring, Maryland. After residing in the United States for over two decades, Dr. Szebeni returned to Hungary in 2006. His research on various themes in hematology, membrane biology, nanotechnology, and immunology has produced 160+ peer-reviewed papers, book chapters, patents, etc. (citations: ≈6000, H index: 39), and a book titled *The Complement System: Novel Roles in Health and Disease* (Kluwer, 2004). He has made significant contributions to three fields: artificial blood, liposomes, and the complement system. His original works led to the "CARPA" concept, i.e., that complement activation underlies numerous drug-induced (pseudo) allergic (infusion) reactions.

Thomas J. Webster, MS, PhD (H index: 77), has degrees in chemical engineering from the University of Pittsburgh (BS, 1995) and in biomedical engineering from Rensselaer Polytechnic Institute (MS, 1997; PhD, 2000). He was appointed department chair of Chemical Engineering at Northeastern University, Boston, in 2012. He is the current director of the Nanomedicine Laboratories (currently at 25 members) and has completed extensive studies on the use of nanophase materials in medicine. In his 17+ years in academics, Dr. Webster has graduated or

supervised over 109 visiting faculty, clinical fellows, post-doctoral students, and thesis completing BS, MS, and PhD students. To date, his lab group has generated over 9 textbooks, 48 book chapters, 306 invited presentations, at least 403 peer-reviewed literature articles (222) and/or conference proceedings (181), at least 567 conference presentations, and 32 provisional or full patents. He is the founding editor-in-chief of the *International Journal of Nanomedicine* (the first international journal in nanomedicine that has a 5-year impact factor of 5.034). Dr. Webster has received numerous honors including: 2012, Fellow, American Institute for Medical and Biological Engineering (AIMBE, representing the top 2% of all medical and biological engineers); 2013, Fellow, Biomedical Engineering Society; 2015, Wenzhou 580 Award; 2015, Zheijang 1000 Talent Program; 2016, International Materials Research Chinese Academy of Science Lee-Hsun Lecture Award; and 2016, International College of Fellows, Biomaterials Science and Engineering. He was recently elected president of the U.S. Society For Biomaterials. He has appeared on BBC, NBC, ABC, Fox News, National Geographic, the Weather Channel, and many other news outlets talking about science and medicine.

Gerald F. Audette, PhD, has been a faculty member at York University in Toronto, Canada, in the Department of Chemistry since 2006. Currently he is associate professor in the department and a member of the Centre for Research on Biomolecular Interactions at York University. He received his doctorate in 2002 from the Department of Biochemistry at the University of Saskatchewan, Canada. Working with Drs. Louis T. J. Delbaere and J. Wilson Quail (1995–2001), Dr. Audette's research focused on the elucidation of the protein-carbohydrate interactions that occur during blood group recognition, in particular, during the recognition of the O-blood type, using high-resolution X-ray crystallography. Dr. Audette conducted his postdoctoral research at the University of Alberta, Canada (2001–2006). Working with Drs. Bart Hazes and Laura Frost, his research again utilized high-resolution protein crystallography to examine the correlation between protein structure and biological activity of type IV pilins from *P. aeruginosa* and the type 4 secretion system from the conjugative F-plasmid

of *Escherichia coli*. His current research interests include structure/function studies of proteins involved in bacterial conjugation systems, as well as the type IV pilins and assembly systems from several bacterial pathogens, and exploring the adaptation of these protein systems for applications in bionanotechnology and nanomedicine. Dr. Audette is the co-editor of volumes 1–4 of the *Pan Stanford Series on Nanomedicine* and is a subject editor of structural chemistry and crystallography for the journal *FACETS*.

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Foreword

It is a pleasure to write the foreword for the third volume of the Series on Nanomedicine, titled *Immune Aspects of Biopharmaceuticals and Nanomedicines*. I have had the pleasure of knowing Dr. Raj Bawa, as a friend and colleague, for more than a decade and have seen firsthand his leadership in the legal, business, translational, and regulatory matters of nanomedicine. These are at the forefront of a global effort to see nanoformulations deployed in the diagnosis and therapy of human disease for the betterment of humankind and the focus of the current volume.

The chapters herein and my own research are congruent as both focus on how the immune system may be harnessed to influence nanomedicine treatment outcomes. My journey in the field centers on harnessing immunity to improve the delivery of biopharmaceuticals. While innate "nonspecific" immunity provides a first line of defense against foreign microbes, cancer, and a spectrum of particulates, nanoparticles potentiate such activities by inciting inflammatory responses. These affect the function and control of neutrophils and macrophages in their fight against a spectrum of diseases. However, it is the size, shape, and charge of the nanoparticles that affect their positive control over immune responses. Thus, as is highlighted in this book, preclinical safety tests for therapeutic nanoparticles need to include the assessment of immune control. A principal part of this control revolves around complement activation, which affects dynamic interactions between the nanoparticle surface composition and the clearance and safety of the formulations themselves. Nanoparticles stimulate immunity and can mimic what is seen by the bacterial lipopolysaccharide. These all can affect the delivery and depot formations of the nanoparticle containing drug, protein, or nucleic acid as well as alter the adverse outcomes of immune-based toxicological assessments. For example, nanoparticles themselves, in severe cases, can induce adverse cardiopulmonary distress. In this instance, the complement system and reactive macrophages become the common effectors. Rapid macrophage

clearance of nanoparticles is the known mediator of these adverse cardiopulmonary reactions and as such delays particle macrophage recognition and attenuates adverse reactions. Indeed, the immune system facilitates the controlled release of drugs to the site of disease or injury and is helped by specific nanocarriers that enable drug efficiency in disease or injury.

Interestingly, it is the macrophage that acts as the conductor of immune repair. It has been my lifelong quest to understand and apply the role of the immune system, specifically the macrophage, in combating disease. Many believe that the macrophage leads the orchestra that makes up various components of innate and adaptive immunity. The macrophage is a versatile cell. This versatility is realized by its abilities to sense its environment, engulf toxic tissue products and microbes, and rid the body of all of them. The elimination of harmful factors occurs in tandem with a cell's abilities to maintain the tissue microenvironment. This is made possible through the secretion of bioactive products enabling the continuance of general homeostatic functions. Macrophages perform specific adaptive activities and serve also as the major body armor protecting it against infectious, cancerous, and chemical insults. The past decade has seen a realization that macrophage function could be harnessed for biopharmaceuticals and nanomedicines to promote drug delivery and to sustain drug depots. Moreover, the cell's mobility function enables it to carry payloads of active biopharmaceuticals to action sites to curb microbial growth or sustain tissue and neighboring cell function. Receptor-based targeting facilitates drug-carried nanoparticles resulting in improved outcome measures. All are made possible through high loading capacity, reduced toxicity, and nanoparticle drug stability when comparisons are made against native medicines. Macrophages serve as therapeutic carriers, facilitate tissue repair, and rid the body of cancer, toxic cells, debris, and proteins. All are anchored to nanotherapeutics and create a footprint for pharmaceutical developments. Indeed, state-of-the-art "instruments," including functionalizing ligands and targeting modalities, serve to facilitate cell-based delivery. Nanotechnology promotes cell-to-cell interactions improving a diseased microenvironment, an especially important outcome for cancer treatment.

This volume, forged by experts in the field, demonstrates that whether it is cell-based delivery or direct targeting of cells by

biomaterials, harnessing immune control for nanomedicines is promising for diagnostic and therapeutic gain. This, at the end of the day, is a singular goal of all nanoscientists engaged in health care. However, the immune system may prove to be *friend or foe* in such an effort. As a friend, it serves to facilitate the actual formulations and their development, is used as a drug carrier, enables probes for imaging, improves targets for chemotherapy, serves as a means to modulate immune responses after vaccines to prevent infections, or repairs disease-associated tissue injuries. Nanocarriers serve as the enablers of improved drug distribution that occurs by slow effective release of bioactive agents at specific disease sites either by altering the hydrolysis of drug or by serving as particle-drug depots. Drugs or bioagents most amenable for drug action are by definition poorly soluble and evolve through improved bioavailability and lipophilicity. The cells' membranes are penetrated by nanoparticles and as such can overcome a lack of drug specificity. Drug specificity can be improved by nanoparticle decoration, by extending drug circulation time, by altering dissolution rates, or by encasing prodrugs into particles and affecting hydrolysis. All this can result in improved outcomes for the immune clearance of infectious agents and tumor cells. The foe, of course, are the harmful effects that occur as a result of immune engagement of the particles themselves. Particles will nearly always engage the innate immune system and stimulate this function resulting in tissue injuries. This can also lead to the blockade of functionalized particles to specific parts of the immune system that would otherwise metabolize and destroy them. Allergic reactions may also occur as a result of the particles. Thus, to act as immune stimulators or to facilitate adaptive immune responses, a balance is struck between the clearance of infectious and tumor agents and the generalized immune dysfunction. This could preclude therapeutic outcomes if the balance between help and harm is not achieved.

The process of simulating an infectious agent to aid in the clearance of infectious agents and for cancer and other diseases typifies the positive aspects of nanotechnology and medicine. Without question, nanoparticles can provide successful vaccination outcomes with virus-like particles mimicking natural infection and are able to elicit effective immune responses. The events linked to immune control not only improve drug biodistribution and drug action but can affect their rapid polymer degradation.

Such polymers can also enable such active proteins to assemble at appropriate times and under specified biological conditions by using the nanocarrier as a delivery vehicle and shield of the protein of interest. Proteins may serve as adjuvants for vaccines, maintain tissue homeostasis, and stimulate the conversion of somatic cells to inducible pluripotential stem cells (iPSCs). The iPSC technology has been aided greatly by nanomedicines and currently is undergoing a renaissance strongly dependent on the use of recombinant proteins for cell growth, differentiation, and replacement. The enablers are proteins that provide the required growth factors, and as such nanomaterials hold numerous prospective applications and therapeutic opportunities, including a plethora of anti-infective and anti-cancerous medicines.

On balance, vaccine approaches have had considerably less success for latent microbial infections. Organisms that are latent or that can change their molecular coat are singled out as they are much less effectively eliminated by the immune system. These include, but are not limited to, the human immunodeficiency virus, protozoal infections, and tuberculosis. Underlying the lack of pathogen clearance is the capability of the innate and adaptive immune systems. For example, macrophages often become reservoirs of such infections, and replication can continue unabated or the organisms can be stored with subcellular organelles. Alternatively, B and T cells, while producing large amounts of antibodies and cytotoxic T cells, become ineffective in their responses to antigens. Neutralizing antibodies and cytotoxic effector cells mounted against the invading pathogens fall short of eliminating them. While neutralizing antibodies elicit protective immunity, later microbial exposures fail to curtail disease symptoms. Moreover, during these types of chronic infections and notably in cancer, the host fails to be protected, as the spectrum of antigens changes and antibody affinity is not adequate to clear the organism or the cancerous cells. There is simply no protective immunity against individual pathogen strains, and any re-exposure leads to disease and, in the more severe cases, death. There are numerous explanations for the lack of protective immunity, and many of them could be overcome through the use of novel nanoparticle strategies for antigen delivery. Apart from the traditional and conjugate vaccines, recombinants were developed where genetically engineered

nucleic acid encodes a specific antigen. This antigen is used to elicit specific immunological responses. DNA-induced immunity results from dendritic cell induction of cytotoxic lymphocytes through MHC and enhances specific adaptive immunity. Nanoparticles have proved to be helpful in vaccine development based on improved delivery and in the generation of potent immune responses. Increased antigen stability and immunogenicity with improved delivery to dendritic cells can be accomplished through nanoformulations. Once the nanocarrier is delivered in polymeric, liposomal, virus-like nanoparticles it can deliver the antigen in conjunction with the MHC II complex and facilitates effector T cell activation. This leads to humoral and cell-mediated immunity responses. Therapeutic nanoparticle vaccines are also being developed to target tumor cells as well as to suppress those elements of the immune system (innate or adaptive) that affect potent immune activities against cancer cells.

Micro- and nanoparticles have also been developed to improve diagnostic endpoints. For example, paramagnetic microparticles, when coated with specific antigens, can enhance magnetic resonance imaging and can be used for precise cancerous or microbial diagnoses. Rapid detection methods are being developed with antibody-immobilized fluorescent nanoparticles for point-of-care diagnostics. Positron emission tomography and single-photon emission computed tomography imaging have led to the development of new nanoparticle drug delivery systems, and at the same time, afford new diagnostic and therapeutic radiopharmaceuticals. These particles offer diagnostic and therapeutic (theranostic pharmaceuticals) approaches for delivering drugs, ferrite, and radionuclides and can be completed using the identical biological and pharmacological mechanisms. The discovery and development of innovative nanomedicines will certainly improve the delivery of therapeutic and diagnostic agents. The “next generation” therapies will deliver drugs, therapeutic proteins, and recombinant DNA to focal areas of disease or to tumors to maximize clinical benefits while limiting untoward side effects. The use of nanoscale technologies to design novel drug delivery systems and devices in biomedical research promises breakthrough advances in immunology and cell biology. All are facilitated by the engagement of the innate immune system.

In summary, the scholarly chapters presented in this book represent a rich undertaking of the roles by which nanoparticles can engage the immune system to improve health as well as cautionary notes for notable untoward reactions. The work is both comprehensive and well written and surely will occupy a place for experts and students alike seeking to better understand the consequences of the immune control of nanotechnologies. Hearty congratulations to the editors and the contributors for a job well done.

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Howard E. Gendelman is Margaret R. Larson Professor of Internal Medicine and Infectious Diseases, and Chairman of the Department of Pharmacology and Experimental Neuroscience at the University of Nebraska Medical Center. He is credited for unraveling how functional alterations in brain immunity induce metabolic changes and ultimately lead to neural cell damage for a broad range of infectious, metabolic, and neurodegenerative disorders. These discoveries have had broad implications in developmental therapeutics aimed at preventing, slowing, or reversing neural maladies. He is also the first to demonstrate that AIDS dementia is a reversible metabolic encephalopathy. His work has led to novel immunotherapy and nanomedicine strategies for Parkinson's and viral diseases recently tested in early clinical trials. Dr. Gendelman obtained his bachelor's degree in natural sciences and Russian studies with honors from Muhlenberg College and his MD from the Pennsylvania State University-Hershey Medical Center, where he

was the 1999 Distinguished Alumnus. He completed a residency in internal medicine at Montefiore Hospital, Albert Einstein College of Medicine, and was a clinical and research fellow in Neurology and Infectious Diseases at the Johns Hopkins University Medical Center. He occupied senior faculty and research positions at the Johns Hopkins Medical Institutions, the National Institute of Allergy and Infectious Diseases, the Uniformed Services University of the Health Sciences Center, the Walter Reed Army Institute of Research, and the Henry Jackson Foundation for the Advancement in Military Medicine before joining the University of Nebraska Medical Center faculty in March 1993. He retired from the US Army as a lieutenant colonel. Dr. Gendelman has authored over 450 peer-reviewed publications, edited 11 books and monographs, holds 12 patents, is the founding editor-in-chief of the *Journal of Neuroimmune Pharmacology*, and serves on many editorial boards international scientific review and federal and state committees. He has been an invited lecturer to more than 250 scientific seminars and symposia and is a recipient of numerous honors, including the Henry L. Moses Award in Basic Science, the Carter-Wallace Fellow for Distinction in AIDS Research, the David T. Purtilo Distinguished Chair of Pathology and Microbiology, the UNMC Scientist Laureate, NU Outstanding Research and Creativity, the 2013 UNMC Innovator of the Year, the 2014 Outstanding Faculty Mentor of Graduate Students, the 2016 Pioneer in Neurovirology, the 2017 Humanitarian of the Year from the Jewish Federation of Omaha, and the Joseph Wybran Distinguished Scientist. Dr. Gendelman was named a J. William Fulbright Research Scholar at the Weizmann Institute of Science in Israel. In 2001, he received the prestigious Jacob Javits Neuroscience Research Award from the National Institute of Neurological Disorders and Stroke and the Career Research Award in Medicine from the Department of Internal Medicine, UNMC. He is included among a selective scientific group listed on http://hcr.stateofinnovation.com/ as one of the top cited scientists in his field. He has trained more than 50 scientists and his leadership is credited with the growth of the department to be among the top-like ranked and federally funded departments (top seven) nationwide—a particularly noted feat as its position was 89 when he assumed its leadership.

My Life with Biologicals and Nanodrugs: A Twenty-Year Affair

Twenty years now
Where'd they go?
Twenty years
I don't know
Sit and I wonder sometimes
Where they've gone[1]

Twenty years ago, as Primary Examiner at the US Patent Office, I reviewed and granted many US patents on biotechnology-based drug products and nanoparticulate drug formulations, a small fraction of which were approved by drug regulatory agencies[2] and eventually commercialized. Most of these first-generation, early drug products are still on the market. Since then, I have been involved in all aspects of biotherapeutics and nanomedicines—research, patent practitioner, professor, journal editor, FDA regulatory filings, conference organizer, keynote speaker, and advisor to the drug industry. I have seen the evolution of anything and everything "biotherapeutic" and "nanomedicine." I have marveled at the cutting-edge discoveries and inventions in these emerging fields. I have also stood up to criticize inept governmental regulatory policies, spotty patent examination at patent offices, hyped-up press releases from eminent university professors taunting translation potential of their basic research and development (R&D), inadequate safety policies, and inaccurate

[1]This is an excerpt from the classic song titled *Like A Rock* by music legend Bob Seger, in which the aging songwriter laments the loss of his youth once filled with vim and vigor and wonders where time went.

[2]The primary drug agencies are the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), Health Canada (HC), and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).

depiction of these drug products by scientists, media, government agencies, and politicians.

Twenty years later, there is a wave of "newer" therapeutics sweeping the world of medicines. Specifically, there is a rapid introduction of two somewhat distinct but overlapping categories of drugs into the pharmaceutical landscape: (1) biotherapeutics ("biologics," "biologicals," "biological products," "biopharmaceuticals," "biomolecular drugs," or "protein products")[3] and (2) nanomedicines ("nanodrugs," "nanoparticulate drug formulations," or "nanopharmaceuticals").[4] For example, biotherapeutics alone have grown from 11% of the total global drug market in 2002 to around 20% in 2017.[5] I estimate that there are over 225 approved biotherapeutics and around 75 approved nanomedicines for various clinical applications. Similarly, by my estimate, hundreds of companies globally are engaged in nanomedicine R&D; the majority of these have continued to be startups or small- to medium-sized enterprises rather than big pharma.

[3]Biologicals, including those made by biotechnology, are a special category of "drugs" or medicines. They differ from conventional small-molecule drugs derived by chemical means in that they are derived biologically from microorganisms (generally engineered) or cells (often mammalian, including human cells). In other words, these are human health products generated or produced by modern molecular biological methods, and differ from traditional biological products that are directly extracted from natural biological sources such as proteins obtained from plasma or plants. Most biologicals are large, complex molecules as compared to small-molecule pharmaceuticals. Slight variations between manufactured lots of the same biological product are normal and expected within the manufacturing process. As part of its review, the FDA assesses this and the manufacturer's strategy to control within-product variations. See: Walsh, G. (2002). Biopharmaceuticals and biotechnology medicines: an issue of nomenclature. *Eur. J. Pharm. Sci.,* **15**, 135–138: *"A biopharmaceutical is a protein or nucleic acid-based pharmaceutical substance used for therapeutic or in vivo diagnostic purposes, which is produced by means other than direct extraction from a native (non-engineered) biological source."*

[4]There is no formal or internationally accepted definition for a nanodrug. The following is my definition (see: Bawa, R. (2016). What's in a name? Defining "nano" in the context of drug delivery. In: Bawa, R., Audette, G., Rubinstein, I., eds. *Handbook of Clinical Nanomedicine: Nanoparticles, Imaging, Therapy, and Clinical Applications*, Pan Stanford Publishing, Singapore, chapter 6, pp. 127–169): "*A nanomedicine is (1) a formulation, often colloidal, containing therapeutic particles (nanoparticles) ranging in size from 1–1,000 nm; and (2) either (a) the carrier(s) is/are the therapeutic (i.e., a conventional therapeutic agent is absent), or (b) the therapeutic is directly coupled (functionalized, solubilized, entrapped, coated, etc.) to a carrier.*"

[5]Data from the IMS Institute for Healthcare Informatics.

This book will focus on those biologics, biotechnology products, nanomedicines, nanodrug products, and nanomaterials that are employed for medicinal purposes for humans. Many terms used in this book are definitions that come from specific regulations or compendia, but others are being defined as they are used here. The terms "product," "drug formulation," "therapeutic product," or "medicinal product" will be used in the manner the FDA defines a "drug," encompassing both small-molecule pharmaceutical drugs, biologicals, and nanomedicines in the context of describing the final "drug product."[6] Some of the terms will be used synonymously. For example, biotherapeutics, biologicals, biological products, and biologics are equivalent terms. Similarly, nanomedicines, nanodrugs, nanopharmaceuticals, nanoparticulate drug formulations, and nanotherapeutics are the same.

Although there are major benefits touted for these "newer" therapeutics, including a reduction in unwanted side effects, their use does not guarantee the absence of side effects. For example, studies have shown that these therapeutic agents can interact with various components of the immune system to various immunological endpoints, interactions that are fast, complex, and poorly understood. These interactions with the immune system play a leading role in the intensity and extent of side effects occurring simultaneously with their therapeutic efficacy. In fact, when compared to conventional small-molecule pharmaceutical drugs, both biologics and nanomedicines have biological and synthetic entities of a size, shape, reactivity, and structure that are *often* recognized by the human immune system, *sometimes* in an adverse manner. This obviously can negatively affect their effectiveness and safety, and thereby limit their therapeutic application.[7] Some of the undesired immune responses

[6]Branded drugs are referred to as "pioneer," "branded" or "reference" drugs. Small molecule drugs approved by the FDA are known as New Chemical Entities (NCEs) while approved biologics are referred to as New Biological Entities (NBEs). As a result, a new drug application for an NCE is known as a New Drug Application (NDA), whereas a new drug application for an NBE is called a Biologic License Application (BLA). Note that prior to the 1980s there were very few marketed biologics, so the very term "pharmaceutical" or "drug" implied a small molecule drug.

[7]10–20% of the medicinal products removed from clinical practice between 1969 and 2005 were withdrawn due to immunotoxic effects. See: Wysowski, D. K., Swartz, L. (2005). Adverse drug event surveillance and drug withdrawals in the United States, 1969–2002: The importance of reporting suspected reactions. *Archiv. Intern. Med.*, **165**(12), 1363–1369.

include complement activation, tissue inflammation, leucocyte hypersensitivity and formation of antibodies associated with clinical conditions. This has highlighted the critical need to evaluate, assay, and devise strategies to overcome adverse immunogenicity of both biotherapeutics[8] and nanotherapeutics[9].

[8]Early developers of biologics assumed that as many of these drugs were based on human genes and proteins, the human immune system would not treat them as foreign and not produce antidrug antibodies (ADAs). However, this optimistic view has turned into alarm as some biologics elicit a vigorous immune response that *may sometimes* neutralize, block, or destroy them. Also, most biotherapeutics are engineered to enable dual or multiple binding sites (e.g., conjugated proteins, functionalized antibodies)—all of which could lead to them being recognized as foreign and therefore immunogenic. Specifically, ADAs may (i) neutralize the activity of the biotherapeutic, (ii) reduce half-life by enhancing clearance, (iii) result in allergic reactions, and/or (iv) cross-react with endogenous counterparts to result in "autoimmune-like" reactions. Such effects are rarely observed with conventional small-molecule drug products. For example, some studies have shown that AbbVie's HUMIRA® (adalimumab) does not work in ~20% of patients. Similarly, in 2016, Pfizer had to withdraw a promising anticholesterol biologic (bococizumab) after testing it in more than 25,000 persons. In 2016, the Netherlands Cancer Institute reported that >50% of the anticancer biologics in 81 clinical trials worldwide were generating ADAs, although they could not confirm that this always negatively affected the drug candidate being tested.

Another issue with some biologics is that they show a concentration-dependent propensity for self-association. This can induce adverse immune responses in patients that may affect drug safety and efficacy. See: Ratanji, K. D., Derrick, J. P., Dearman, R. J., Kimber, I. (2014). Immunogenicity of therapeutic proteins: influence of aggregation. *J. Immunotoxicol*., **11**(2), 99–109.

[9]Clinical application of nanomedicines and nanocarriers is also dogged by safety and nanotoxicity concerns (undesirable adverse effects), especially about their long-term use. In the case of nanomedicines, therapeutic particles are engineered to break tissue physiological barriers for entry and to escape immune surveillance, thereby persisting in body fluids and delivering their active pharmaceutical ingredients (APIs) to the right tissue site. However, this persistence in the body may trigger immune responses. Novel "immune-toxicity" from nanomedicines may result from the unique combinations of shape, size, surface charge, porosity, reactivity, and chemical composition—all aspects to which the immune system may not have adapted to. Often, intravenously administered nanomedicines prime the immune system, leading to adverse reactions and/or loss of efficacy of the drug product. For example, it is now well established that intravenous administration of nanomedicines and nanocarriers *may* provoke "hypersensitivity reactions" (HSR) or "anaphylactoid reactions" that are referred to as complement (C) activation-related pseudoallergy (CARPA). See: Szebeni, J. (2005). Complement activation-related pseudoallergy: A new class of drug-induced acute immune toxicity. *Toxicology*, **216**, 106–121 and Szebeni, J. (2018). Mechanism of nanoparticle-induced hypersensitivity in pigs: complement or not complement? *Drug Discov.*

Not all biotherapeutics, nanoformulations, and nanomaterials are created equal. Given this scientific fact, the risks for immunogenicity should be assessed on a case-by-case basis. In fact, while some biologics, particularly glycoproteins, cause the body to produce antidrug antibodies (ADAs),[8] few elicit immunogenicity in a manner that induces any clinically relevant reaction. Similarly, the diversity of nanomedicines makes it impossible to extrapolate or generalize the immunologic findings from one class of nanomedicines (e.g., nanoliposomes, solid nanoparticles, carbon nanotubes) to another. Nevertheless, the degree of risk for eliciting immune responses from biotherapeutics, nanoformulations, or nanomaterials is considered a major issue during drug R&D and administration to patients. It is now well established that any biotherapeutic, nanoformulation, or nanomaterial can *potentially* exert an immunogenic effect ("immunogenicity risks") depending on a patient's immunologic status, prior history, route/dose/frequency of delivery and unique characteristics of the administered therapeutic product. Therefore, regulatory agencies, particularly the FDA and the EMA, recommend that drug developers employ a risk-based approach to evaluate and reduce adverse immune events related to the administration of these therapeutics that could affect safety and efficacy. These must be carefully evaluated at the earliest stages of drug formulation/development as well as throughout the product lifecycle, including during phase IV. Biotherapeutic drug products containing a non-biologic nanomaterial component are on the rise and may have different immunogenic properties compared with those that contain the biologic alone. Consequently, it is also important that immunogenicity aspects and risks of biotherapeutic drug products

Today, **23**(3), 487–492. These hypersensitivity reactions typically occur directly at first exposure to the nanocarriers without prior sensitization, and the symptoms usually lessen and/or disappear on later treatment. That is why these reactions are labelled as "pseudoallergic" or "nonspecific hypersensitivity." Nanomedicines causing CARPA include radio-contrast media, liposomal drugs (Doxil®, Ambisome® and DaunoXome®, Abelcet®, Visudyne®), micellar solvents (e.g., Cremophor EL, the vehicle of Taxol®), PEGylated proteins and monoclonal antibodies. Drug products other than biologics and nanomedicines such as nonsteroidal anti-inflammatory medicinal products, analgesics and morphine can also trigger CARPA. Also, see: Szebeni, J, Bawa, R. (2018). Immunological issues with medicines of nano size: The price of dimension paradox. In: Bawa, R., et al., eds. *Immune Aspects of Biopharmaceuticals and Nanomedicines,* Pan Stanford Publishing, Singapore, chapter 2, pp. 83–122.

containing non-biologic nanomaterial components be assessed with a focus on whether the nanomaterial components possess adjuvant properties. Similarly, carriers may exhibit inherent immunologic activity that is not related to the loaded active pharmaceutical ingredient (API); this could also affect the safety and effectiveness of the drug product. Another important issue involves the approval of follow-on versions of both biologics and nanomedicines.[10] I wonder how often cost considerations drive the approval process. I suspect that there are enormous pressures on drug regulatory agencies (e.g., the Trump administration's FDA) to grant these drug products. It is no secret that in certain countries these follow-on versions are the preferred drug products and driven by government-controlled healthcare programs. However, it is critical that immune aspects of these so-called "biosimilars" and "nanosimilars" be transparently evaluated and reported during the drug approval process: *Lower drug prices should not supplant patient safety and efficacy*. The recent FDA approval of follow-on versions of Copaxone® is an example that highlights this troubling trend. I believe that accelerating the approval of follow-on versions of biologics and nanomedicines should be science-based and undertaken on a case-by-case basis.[11]

[10]Since the replication of biologics is complex and less precise as compared to small molecule drug products, the term generic has been deemed inappropriate.

[11]See: Conner, J. B., Bawa, R., Nicholas, J. M., Weinstein, V. (2016). Copaxone® in the era of biosimilars and nanosimilars. In: Bawa, R., Audette, G., Rubinstein, I., eds. *Handbook of Clinical Nanomedicine: Nanoparticles, Imaging, Therapy, and Clinical Applications,* Pan Stanford Publishing, Singapore, chapter 28, pp. 783–826; Bawa, R. (2018). Immunogenicity of biologics and nanodrugs: An overview. In: Bawa, R., Szebeni, J., Webster, T. J. and Audette, G. F. eds. *Immune Aspects of Biopharmaceuticals and Nanomedicines*, Pan Stanford Publishing, Singapore, chapter 1, pp. 1–82.

Copaxone® is a non-biologic (synthetic) complex drug ("NBCD") and can be considered a first-generation nanomedicine. It is composed of an uncharacterized mixture of immunogenic polypeptides in a colloidal solution. The complexity of glatiramer acetate is amplified by several aspects: (1) the active moieties in glatiramer acetate are unknown; (2) the mechanisms of action are not completely elucidated; (3) pharmacokinetic testing is not indicative of glatiramer acetate bioavailability; (4) pharmacodynamic testing is not indicative of therapeutic activity and there are no biomarkers available as surrogate measures of efficacy; and (5) small changes in the glatiramer acetate mixture can change its immunogenicity profile. There is one aspect of Copaxone® that raises special safety and effectiveness

In our rapidly changing yet interconnected and globalized world, biologics and nanomedicines will continue to surprise and expand. There are numerous second- and third-generation biologics and nanomedicines at the basic research stage. Hopefully, despite enormous bottlenecks, we will find a greater number of these translated into practical patient applications. In the meantime, we need to temper our expectations yet continue to hope for paradigm-shifting advances in the bio-nano world.

Against this backdrop, the editors felt that enormous advances in the past 20 years in immunology of biologics and nanomedicines warranted an authoritative and comprehensive reference resource that can be relied upon by immunologists, biomedical researchers, clinicians, pharmaceutical companies, formulation scientists, regulatory agencies, technology transfer officers, venture capitalists, and policy makers alike. Hence, this volume aims to provide a broad survey of theoretical and experimental knowledge currently available and presents a framework that is readily applicable to develop strategies for clinical applications. Each chapter contains key words, tables and figures in color, future predictions, and an extensive list of references. The focus is on the current, most relevant information, all accomplished in a user-friendly format.

Assorted topics pertain to the immune effects of biologics and nanomedicines, both beneficial and adverse. A thorough understanding of immunology, therapeutic potential, clinical applications, adverse reactions and approaches to overcoming

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concerns that merit heightened vigilance with respect to the approval of any potentially interchangeable follow-on glatiramer acetate product: Glatiramer acetate is an immunomodulator. In other words, Copaxone® is intended to achieve its therapeutic effects by interacting with and modulating a patient's immune system over an extended period. For this reason, Copaxone®'s package insert warns that chronic use has the potential to alter healthy immune function as well as induce pathogenic immune mechanisms, although no such effects have been observed with Copaxone®. Due to the complexity and inexorable link between the manufacturing process and quality, any follow-on product almost certainly will differ from Copaxone®'s structure and composition of active ingredients because it will be made using a different manufacturing process than that developed by the branded product developer (Teva). Although it is not possible to fully characterize and compare these complex mixtures, differences are revealed via sophisticated analytical techniques. Despite these immunological concerns, the FDA in 2017 approved so-called follow-on versions of Copaxone®.

immunotoxicity of biologics and nanomedicines is presented. For instance, chapters are devoted to immune stimulatory and suppressive effects of antibodies, peptides and other biologics, as well as various nanomedicines. The state of the art in therapeutic and preventive vaccines along with their potential molecular mechanisms underlying immunogenicity is also highlighted. Adverse immune effect of certain biologics and nanomedicines, namely, complement (C) activation-related pseudoallergy (CARPA), is discussed in unprecedented detail in terms of occurrence, prediction, prevention, and mechanism. Furthermore, critical, yet often overlooked topics such as immune aspects of nano-bio interactions, current FDA regulatory guidance, immunogenicity testing of therapeutic protein products, and engineering bio/nanotherapeutics to overcome barriers to immunotherapy are also covered.

I express my sincere gratitude to the authors, coeditors, and reviewers for their excellent effort in undertaking this project with great enthusiasm. I thank my father, Dr. S. R. Bawa, for meticulously reviewing various chapters of this book. Finally, I also thank Mr. Stanford Chong and Ms. Jenny Rompas of Pan Stanford Publishing for commissioning me to edit this volume. Mr. Arvind Kanswal of Pan Stanford Publishing and my staff at Bawa Biotech LLC are acknowledged for their valuable assistance with publication coordination.

Raj Bawa, MS, PhD
Series Editor
Ashburn, Virginia, USA
June 7, 2018*

*The day my beloved *Washington Capitals* ice hockey team won the Stanley Cup for the first time in franchise history!

"This outstanding volume represents a review of the various effects of biopharmaceuticals and nanomedicines on the immune system: immunotherapy, vaccines, and drug delivery; challenges and overcoming translational barriers stemming from immunotoxicity; strategies to designing more immunologically friendly formulations."

África González-Fernández, PhD, MD
Professor of Immunology and President of the Spanish Society of Immunology, University of Vigo, Spain

"For those who are specialists, and for those interested in a broader understanding of biologics and nanomedicines, this is a superb book, with internationally accomplished contributors. It serves both as a reference and as a practical guide to the newest advances in these important fields. Highly recommended!"

Carl R. Alving, MD
Emeritus Senior Scientist, Walter Reed Army Institute of Research, Silver Spring, Maryland, USA

"A skillfully produced book that addresses an often-missed topic: immune aspects of biologicals and nanoscale therapeutics, with an emphasis on clinical relevance and applications."

Rajiv R. Mohan, PhD
Professor and Ruth M. Kraeuchi Missouri Endowed Chair Professor, University of Missouri, Columbia, USA

"An indispensable masterpiece! It represents a rich source of information on interactions of biologics and nanodrugs with the immune system—all critical for medical applications. Volume 3, once again, achieves the series' high standards."

László Rosivall, MD, PhD, DSc Med, Med habil.
Széchenyi Prize Laureate and Professor, Faculty of Medicine, Semmelweis University, Budapest, Hungary

"Hats off to Dr. Bawa for producing yet another impressive volume in terms of scope, timeliness, and relevance. With expert contributions from around the globe, this book addresses topics germane to researchers, clinicians, drug and biotherapeutic companies, regulators, policymakers, and patients."

Sara Brenner, MD, MPH
Associate Professor and Assistant Vice President, SUNY Polytechnic Institute, Albany, New York, USA

"Marvelous! This timely book shows clearly that while an immune reaction to "nano-exposure" is usually unwanted, the same response also bears an immense potential."

Silke Krol, PhD
IRCCS Istituto Tumori "Giovanni Paolo II" and Fondazione IRCCS Istituto Neurologico "Carlo Besta," Italy

The enormous advances in the immunologic aspects of biotherapeutics and nanomedicines in the past two decades has necessitated an authoritative and comprehensive reference source that can be relied upon by immunologists, biomedical researchers, clinicians, pharmaceutical companies, regulators, venture capitalists, and policy makers alike. This text provides a thorough understanding of immunology, therapeutic potential, clinical applications, adverse reactions, and approaches to overcoming immunotoxicity of biotherapeutics and nanomedicines. It also tackles critical, yet often overlooked topics such as immune aspects of nano-bio interactions, current FDA regulatory guidances, complement activation-related pseudoallergy (CARPA), advances in nanovaccines, and immunogenicity testing of protein therapeutics.

About the Series Editor

Dr. Raj Bawa is president of Bawa Biotech LLC, a biotech/pharma consultancy and patent law firm based in Ashburn, Virginia, that he founded in 2002. He is an entrepreneur, professor, inventor, and registered patent agent licensed to practice before the US Patent Office. Trained as a biochemist and microbiologist, he is currently an adjunct professor at Rensselaer Polytechnic Institute in Troy, New York, and serves as a scientific advisor to Teva Pharmaceutical Industries, Israel. In 2008, he and Dr. Esther Chang of Georgetown Medical Center founded the American Society for Nanomedicine. He has authored over 100 publications and coedited 4 books and serves on the editorial board of 14 peer-reviewed journals.

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