

HANDBOOK OF IMMUNOLOGICAL PROPERTIES OF ENGINEERED NANOMATERIALS

SECTION I

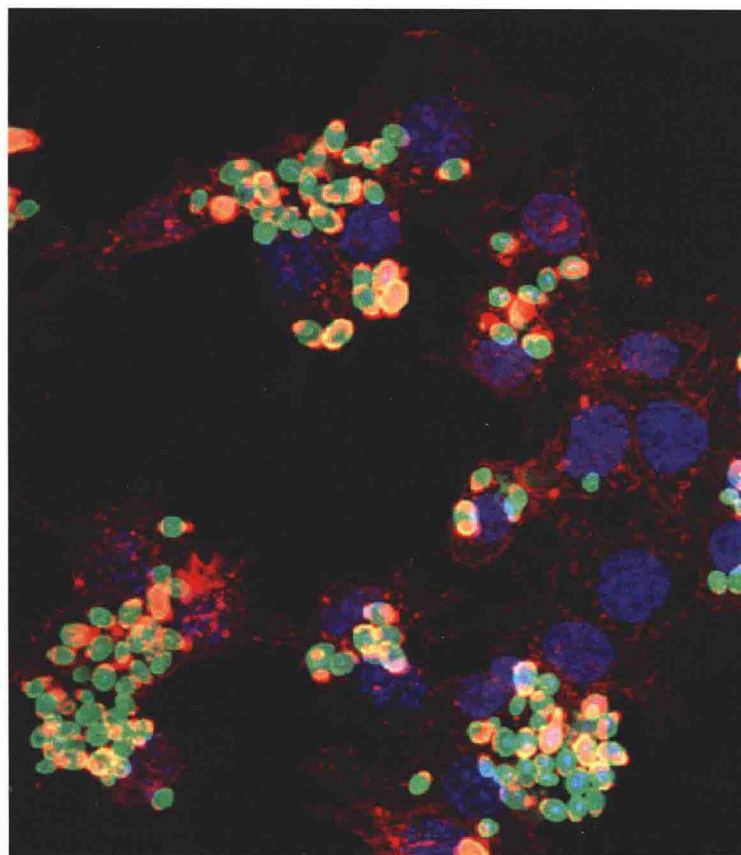
③ Engineered Nanomaterials and the Immune Cell Function

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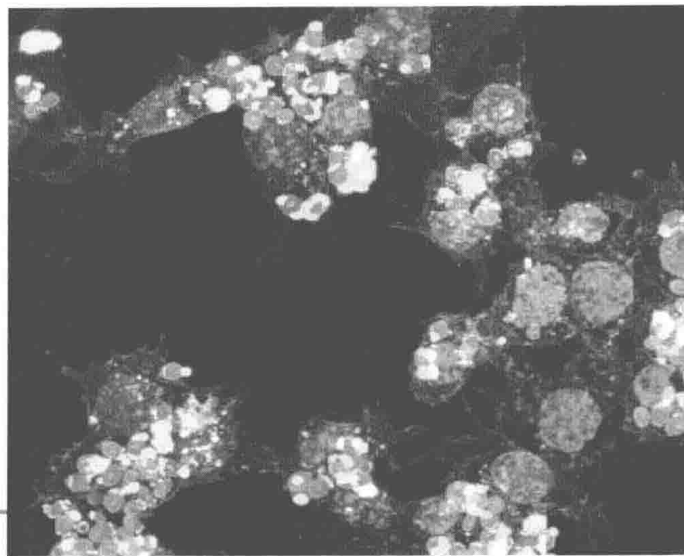
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Frontiers in
Nanobiomedical
Research



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HANDBOOK OF IMMUNOLOGICAL PROPERTIES OF ENGINEERED NANOMATERIALS

SECOND EDITION

③ Engineered Nanomaterials and the Immune Cell Function



editors

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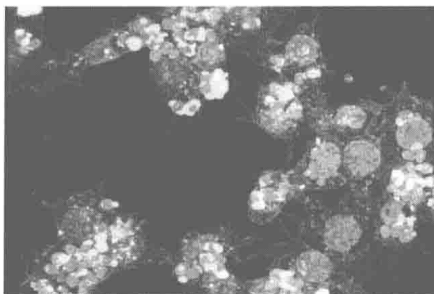
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Preface

The story of this book began in 2007 when we published our first review article “Immunological properties of engineered nanomaterials” in *Nature Nanotechnology*.¹ In 2010 World Scientific Publishing has published a book entitled *Nanoscience and Nanotechnology: A Collection of Reviews from Nature Journals* edited by Dr. Peter Rogers, and our review was included into this book.² Soon after that Dr. Zvi Ruder, senior executive editor of World Scientific Publishing, contacted us with a question about expanding our review into a book.

Instead of simply re-writing the extended version of the review ourselves, we have contacted top experts in various areas of nanoimmunotoxicology and asked them to contribute a chapter related to their unique area of expertise such as nanoparticle interaction with erythrocytes, endothelial cells, various types of antigen-presenting cells, complement, platelets and plasma coagulation system, bone marrow, nanoparticle use for drug delivery and vaccine adjuvants, sterility and sterilization, presence of surface contaminants and regulatory considerations for screening of nanoparticle toxicity to the immune system, as well as the use of animal models to study nanoparticle immunotoxicity. Since we strongly believe that success of immunotoxicological studies of nanoparticles vitally depends on understanding their physico-chemical properties and composition, we have also asked chemists to contribute a chapter to guide immunologists in appropriate material characterization. Their agreement to contribute a chapter within their individual areas of expertise allowed us to establish the international team of experts, whose great work was presented in the first edition of the book.

Since the release of the first edition we received a lot of positive feedback from readers. In the year following the release of the first edition, many more great studies exploring nanoparticle interaction with the immune system were published. They included novel ways of preventing nanoparticle recognition

by the immune cells, nanoparticle targeting to the lymphatic system, application of nanoparticles for delivery of anti-inflammatory drugs, anti-viral and anti-microbial agents, as well as advances of using nanoparticles in tumor immunology. The main challenge we experienced while working on the 1st edition was the breadth and multidisciplinary nature of the field of immunotoxicology as it relates to the engineered nanomaterials. Our primary target audience were scientists working on applying nanoparticles in biology and medicine, yet we felt that the information presented in the book will be of interest to those working in other areas of toxicology including developmental, environmental, food, and ecosystems toxicology. We felt that updated and expanded edition of the book is necessary to address interests of the broader audience. With this idea in mind we have approached the team, established during preparation of the first edition, and asked their opinion about updating the book. We were happy to hear that many contributors felt that the update is timely, and we started working on the second edition. During the initial planning phase, we came across the review of our book by Dr. Ken-Ichiro Inoue in *Nanomedicine*, who stated that “the current updated edition of this book is both timely and necessary”.³ His review and critique further encouraged us to update and expand the content of the book to include additional subjects such as tumor immunology. The second edition is published in three volumes formulated according to the nanoparticle characterization at the NCL: physicochemical characterization, sterility and endotoxin screening, hematology and immune cell function. Volume 1 of the second edition contains comprehensive coverage of nanomaterial characterization, approaches to design *in vitro* and *in vivo* immunological studies and regulatory guideline review. Volume 2 is focused on hematocompatibility of nanomaterials and their interactions with the lymphatic system, while the primary target of Volume 3 is nanoparticle interaction with the immune cells and their effects on the immune cells function.

We are grateful to all of our colleagues who contributed to the first edition of the book and updated their chapters for the second edition: Drs. Nanda Subbarao of Biological Consulting Group Inc for sharing her expertise with nanoparticle sterility and sterilization; Drs. Clinton Jones and David Grainger of University of Utah for their work on surface contaminants as it related to nanoparticle immunotoxicity; Drs. Ulrich Nienhaus and Lennart Treuel for their expertise in nanoparticle interaction with plasma proteins; Drs. Bridget Wildt, Ronald Brown, and Richard Malinauskas of the US FDA CDRH for their expertise in nanoparticle effects on erythrocytes; Dr. Jan Simak of the US FDA CBER for his heroic effort to write three extensive chapters focusing on nanoparticle interactions with platelets, endothelial cells

and plasma coagulation system; Drs. Carolina Salvador-Morales of the George Mason University and Robert Sim of the University of Oxford for sharing their expertise in nanoparticle interaction with the complement system; Dr. William Zamboni and the team of his graduate students Sara O'Neal, Andrew Lucas, Whitney Caron, Gina Song, and John Layt of the University of North Carolina for contributing their expert opinion on nanoparticle interaction with phagocytes; Dr. Valentina Fesenkova of the National Cancer Institute for sharing her expert opinion on dendritic cells; Dr. Ekaterina Dadachova for sharing her expertise in nanoparticle interaction with bone marrow; Drs. Magdalena Plebanski and Sue Xiang and their colleagues at the Monash University in Australia Martina Fuchsberger, Tanya De Karlson, Charles Hardy and Cordelia Selomulya for contributing extensive chapter and sharing their expert opinion about nanoparticle use in vaccine delivery; Dr. Deepthy Meanon and her colleagues at the Amrita Center for Nanoscience and Molecular Medicine in India, Gopikrishna J, Dhanya Narayanan and Shantikumar Nair, for sharing their work on nanoparticle use for the delivery of anti-inflammatory drugs; Dr. Africa Gonzalez-Fernandez and her colleague Silvia Lorenzo-Abalde of the University of Vigo in Spain for sharing their expertise in nanoparticle allergenicity; Dr. Matthew Smith, Dori Germolec of the NIEHS and their colleagues Coleen McLoughlin and Kimber White Jr for sharing their expertise in investigating nanoparticle immunotoxicity *in vivo*, and Drs. James Weaver, Katherine Tyner and Simona Bancos of the US FDA CDER for their expert opinion of regulatory considerations during nanoparticle testing for immunotoxicity.

We are happy to welcome and very grateful to the new contributors of the second edition: Drs. Ángela França, Beatriz Pelaz, María Moros, Christian Sánchez-Espinel, Andrea Hernández, Cristina Fernández-López, Valeria Grazú, Jesús M. de la Fuente, Isabel Pastoriza-Santos, Luis M. Liz-Marzán, of the University of Vigo in Spain who along with their leader Dr. Africa Gonzalez-Fernandez contributed case study demonstrating effects of various sterilization methods on nanoparticle integrity; to Dr. Tommy Cedervall of the Lund University of Sweden and his colleagues Daniele Dell'Orco, Martin Lundqvist and Sara Linse for sharing their expertise in mathematical modeling of the protein corona and its implications on development of safe nanomedicines; our colleague at the Nanotechnology Characterization Lab. Dr. Anna Ilinskaya for contributing her work on immunocompatibility of nanoparticles; Drs. Janos Szebeni of Semmelweis University in Budapest and members of his international team Dr. Yechezkel Barenholz of the Hebrew University in Jerusalem and Dr. Franco Muggia of the New York University Cancer Institute for sharing their expertise in clinical experience with

PEGylated liposomal formulations; Drs. Khan and Sistla of the National Institute of Pharmaceutical Education and Research in India for contributing a comprehensive overview of nanoparticle interaction with the lymphatic system; Dr. Ennio Tasciotti of the Huston Methodist Research Institute and his colleagues Naama E. Toledano Furman, Roberto Molinaro, Alessandro Parodi, Michael Evangelopoulos, Jonathan O. Martinez, ClaudiaCorbo, Roberto Palomba, and Iman K. Yazdi for sharing their cutting edge LeukoLike technology preventing nanoparticle from the immune recognition; Dr. Ken-ichiro Inoue of the International University of Health and Welfare in Japan for sharing his expertise in undesirable adjuvanticity of the nanomaterials; Drs. Neil Liptrott, Paul Curley, Lee M. Tatham and Andrew Owen of the University of Liverpool for sharing their expertise in developing nanoparticle for the delivery of anti-retroviral drugs; Dr. Steven Fiering of Geisel School of Medicine at Dartmouth and his colleagues Seiko Toraya-Browna, Mee Rie Sheena, Peisheng Zhanga, Lei Chena, Jason R. Bairda, Eugene Demidenkob, Mary Jo Turka, P. Jack Hoopesd, and Jose R. Conejo-Garciag for sharing their expertise in using nanoparticles for cancer immunotherapy.

Nanotechnology Characterization Laboratory (NCL) has been established in 2004 to promote transition of basic research nanotechnology concepts into clinic. Following the main mission of conducting preclinical characterization of engineered nanomaterials and sharing knowledge about nanoparticles with the research community, NCL has characterized more than 300 different types of engineered nanomaterials. Our experience with nanoparticle physicochemical characterization, dealing with endotoxin contamination in various types of nanoparticles, using *in vitro* methods to screen for nanoparticle immunotoxicity as well as weighting potential concerns regarding nanoparticle antigenicity is shared in this book. We are grateful to Drs. Jeffrey Clogston and Anil Patri for sharing their expertise and performing not trivial task of explaining nuances of nanoparticle physicochemical characterization in a language easily understandable to immunologists. It is hard to overestimate the contribution of the NCL technical staff Barry Neun, Timothy Potter, Christopher McLeland and Sarah Skoczen to chapters discussing *in vitro* assays and endotoxin detection, quantification and role in nanoparticle immunotoxicity. We are grateful to the NCL's toxicologist Dr. Stephan Stern for sharing his expertise and help with establishing *in vitro-in vivo* correlation for immunoassays. We are grateful to Drs. Jennifer Grossman and Rachael Crist for the help with preparation of NCL chapters.

We would also like to express our gratitude to Drs. Larry Tamarkin, President and the CEO of CytImmune Sciences developing PEGylated

colloidal-gold nanoparticles as carriers of therapeutic protein tumor necrosis factor alpha, and Dr. Neil Desai of Cellgene, inventor of the nanoalbumin particle-Paclitaxel formulation Abraxane, for their support and encouragement in the preparation of the first edition. We are also thankful to Dr. Stefanie Vogel of the University of Maryland and Dr. Ai Lin Chun of Nature Nanotechnology for their support of the second edition.

Nanoimmunotoxicology is new and rapidly developing field. In spite of many obstacles significant progress in our understanding of nanoparticle interaction with components of the immune system has been achieved. Many more has yet to be studied and understood. We are certain that this book will be of interest to the broad audience, those who are just starting their work in this new and exciting field, as well as experts representing academia, industry and regulatory agencies. This book provides not only comprehensive overview of the current literature and regulatory guidelines, but also includes protocols, case studies and practical considerations for studying nanoparticle immunoreactivity both *in vitro* and *in vivo*.

One more time we are grateful to everyone who contributed to this book by sharing their expertise and writing chapters, contributing data and expert opinions. We hope that the reader will find it useful and enjoy it as much as we did while working on it.

References

1. Dobrovolskaia MA, McNeil SE. Immunological properties of engineered nanomaterials. *Nat Nanotechnol.* 2007 Aug; 2(8): 469–78
2. *Nanoscience and Nanotechnology: A Collection of Reviews from Nature Journals*, World Scientific Publishing, Singapore, 2010.
3. Inoue K. Book review: Handbook of Immunological Properties of Engineered Nanoparticles. *Nanomedicine*, London, 2013, 8 (10), 1567–1569

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