Pan Stanford Series on
Biomedical Nanotechnology
Volume 5

Handbook of Safety Assessment of Nanomaterials

From Toxicological Testing to Personalized Medicine

edited by
Bengt Fadeel

Handbook of

Safety Assessment of Nanomaterials

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Vladimir Torchilin and Mansoor Amiji

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Preface

". . . for I was never so small as this before, never!"
Lewis Carroll, *Alice's Adventures in Wonderland* (1865)

Nanomedicine is the application of nanobiotechnology in clinical medicine. For instance, nanotechnologies offer exciting opportunities for targeted drug delivery, thus bringing to life the concept of a "magic bullet" imagined by Paul Ehrlich a century ago. Nevertheless, understanding whether such nanoscale objects per se exert adverse effects in a biological system is of critical importance. Nanotoxicology, in turn, may be viewed as the study of the undesirable interference between man-made nanomaterials and cellular nanostructures. In this handbook, included in the Pan Stanford series on *biomedical nanotechnology*, we attempt to bridge nanotoxicology and nanomedicine by applying the lessons learned from toxicological testing of manufactured nanomaterials to the field of nanomedicine.

The present volume opens with a historical perspective on the development of nanomedicine, written by Dr. Duncan, a pioneer in the field. Dr. Duncan points out that a balanced discussion of the risks and benefits of nanotechnologies is critically important to ensure the speedy and safe realization of the promises of nanomedicine. Indeed, this is the underlying motivation for the entire volume. Then, Dr. Stone et al. discuss the basic principles of nanotoxicology, highlighting progress in the field in recent years; the authors also provide recommendations for the proper design of experiments to assess nanomaterial hazards. Drs. Warheit and Sayes touch on the need for robust physicochemical characterization of nanomaterials for toxicity testing, and Drs. Fadeel and Parak discuss the biological "identity" of nanomaterials.

These introductory chapters are followed by a series of chapters on different approaches to nanomaterial testing: Dr. Hartung makes the case for in vitro tests, while Drs. Lai and Warheit argue that short-term in vivo (animal) studies are needed. Dr. Burello adds an important perspective on mathematical modeling of quantitative

structure–activity relationships (QSARs) for nanomaterials, pointing toward a predictive nanotoxicology. Finally, Dr. Riviere explores the use of physiologically based nanomaterial pharmacokinetic models, or PBNPKs, with which to describe nanomaterial distribution and fate in vivo.

Our immune system serves as the first line of defense against foreign intrusion, and it is therefore of key importance to understand nanomaterial interactions with the immune system, not only from a toxicological point of view, but also if we are to develop nanocarriers for targeted drug delivery or imaging. Three chapters are devoted to immune interactions of nanomaterials: Dr. Moghimi et al. discuss factors that regulate nanomaterial interactions with the innate and adaptive immune system, leading to immunostimulation or immunosuppression, while Dr. Szebeni focuses on complement activation by nanomaterials. Dr. Kostarelos et al. discuss a special case of immune cell interactions with nanomaterials, namely, the biodegradation of carbon-based nanomaterials by enzymes expressed in innate immune cells (or in plants).

Next, we find a comprehensive chapter devoted to genotoxicity and carcinogenicity of nanomaterials (Dr. Woei Ng et al.) and a series of chapters on nanomaterial toxicity affecting specific organs, including chapters on pulmonary and cardiovascular toxicity (Drs. Cassee and Castranova), neurotoxicity (Drs. Sharma and Sharma), dermatotoxicity (Drs. Monteiro-Riviere and Riviere), and reproductive toxicity (Dr. Saunders et al.). The chapter on pulmonary and cardiovascular toxicity focuses on two commercially relevant nanomaterials, titanium dioxide and carbon nanotubes, and on the inhalation route of exposure of particular relevance for occupational exposure. These findings may nevertheless inform us on mechanisms of relevance for nanomedicine. Similarly, the chapter on neurotoxicity takes as its starting point accidental exposure to various types of nanoparticles, but the authors add an exciting perspective on the use of nanomaterials for neuroprotection. The chapter on dermal effects of nanoparticles offers an overview of current literature, and the discussion is of equal relevance from pharmacological (i.e., topical application of drugs, vaccines) and toxicological points of view. The potential for nanoparticles to exert adverse effects on the male or female reproductive systems remains poorly understood, but this is of particular importance not only to understand occupational/environmental exposure but also in the

context of the deliberate administration of nanoscale objects in patients.

Finally, a perspective on ethical aspects of nanomedicine is provided. Here, Dr. Kuiken argues that there may be nothing new in terms of the ethical questions that arise as we are confronted with nanomedicines; the question is how much risk we are willing to accept with a new technology before it is proven effective and "safe." This will become even more evident as personalized medicine is enabled, in part, through nanomedicine. This, then, brings us full circle: medicine, and nanomedicine, is essentially the art and science of risk-benefit assessment. Nanotoxicology provides the tools to deal with the "risk."

The book closes with a personal view of the future of (nano) medicine, written by Dr. Hunziker, president of the European Society of Nanomedicine (ESNAM).

I wish to thank the authors who contributed their valuable time and expertise toward the preparation of this book. I hope that the present volume will serve as a useful manual for students and scientists interested in the safe development of nanomedicines.

Bengt Fadeel

Stockholm, July 2014