Book Review

Handbook of Immunological Properties of Engineered Nanoparticles

The *Handbook of Immunological Properties of Engineered Nanoparticles* is a one-volume compendium of almost every conceivable aspect of immunotoxicity elicited by exposure to engineered nanomaterials. This book casts an all-encompassing net, resulting in the inclusion of topics ranging from analytical methods for nanomaterial characterization to the possibility of drug delivery. This book is comprehensive, having nearly 680 pages and 21 chapters. The text is organized in a very straightforward manner, with general introductory material being set forth in the first few chapters, followed by an outline of nanomaterials responsible for immunological regulation/modulation and therapeutic aspects. Most chapters generally consist of an abstract/overview, introduction, a section on the role of nanomaterials in the area discussed, conclusive remarks and future perspectives, in relatively easily understood terms that are supported by clear line drawings. However, one criticism of the book is that it is unclear who it is written for. Is it for industrial workers/managers, college students on medical courses, engineering departments, life sciences departments, toxicologists, epidemiologists, physicians or immunologists? While it is difficult to cover enough to allow a good understanding for readers in every field, writing for a narrower, but precisely targeted field of readers (e.g., toxicologists and immunologists) would have tightened the contents (e.g., a chapter could describe the precise correlation between chemical components on nanomaterials and immunological status and/or more detailed mechanistic pathways such as the responsible intracellular signaling pathways).

HANDBOOK OF IMMUNOLOGICAL PROPERTIES OF ENGINEERED NANOMATERIALS

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Reading impressions

The book is well organized, with an overview of the subject matter relating to nano-immunotoxicity and its utility in diagnostics and medicine discussed in the first few chapters. How nanomaterials influence immune cells, the immune system and the pathophysiology associated with immunological abnormalities and several related cascades are then described. Thereafter, a range of both *in vitro* and *in vivo* examinations to detect immunotoxicity caused by nanomaterials is introduced. Finally, the toxicological implications of nanomaterials are considered, as well as the ethical and regulatory aspects and future perspectives. Overall, this layout works well to introduce nanoimmunotoxicity to an audience who may not have expert knowledge on this subject matter. However, considering the vastness of the field, this book could be readily expanded into a multivolume set. Various nanomaterials were introduced and reintroduced throughout the text as examples that should be used with careful attention because of their particular toxicity.

In Chapter 1, Dobrovolskaia and McNeil, the chief editors of the book, outline the purpose of this publication. Figure 1 in this chapter clearly demonstrates the balance between nanolevel materials and the immune system. The authors first provide an outline of the book and the importance of the immunological properties of nanomaterials in health (e.g., interaction with blood components, uptake and phagocytizing, immunogenicity and inflammation, antigenicity and adjuvanticity), immunosuppression and future directions. Chapters 2–5 describe how the biological/immunological properties of nanomaterials depend on physiochemical characteristics, such as size, ζ -potential, targeting/drug/imaging quantitation, purity, stability, sterilization, endotoxin contamination and surface adsorbates, all of which toxicologists and physicians vaguely consider in studies using nanomaterials. Furthermore, these chapters describe the importance of instrumentation and methodology when analyzing these materials. Figures in Chapter 2

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that relate to methodological protocols and examples of factors such as size distribution and ζ -potential, and Figure 1 in Chapter 4, which relates to the adverse effects of endotoxins on health, are useful. Interactions between nanomaterials and plasma proteins and peripheral blood differentials and the consequent impact on the coagulatory system are mainly discussed in Chapters 6–10. As I have experienced, exposed nanomaterials are able to enter the circulatory system (encounters between nanomaterials and epithelial cells should also be important for the immunotoxicity of these materials) due to their tiny sizes and shapes; therefore, the impact of nanomaterials on the circulatory system is worth discussing, because this system not only plays a role in the immune response, but is also related to cardiovascular adverse events such as angina pectoris, myocardial ischemia and cerebral infarction. These chapters document the impact of nanomaterials on these cells/systems, and refer to a vast numbers of previous articles. These systems are also an important biochemical cascade for the recognition and eradication of foreign materials. In Chapter 11, the authors mainly focus on the activating effect of nanoparticles on the complement system, which is important for the elimination of exogenous microbes. In Chapters 12–14, the authors refer to the effects of exposed nanomaterials on cells responsible for recognition, phagocytizing and signaling to other cells, such as mononuclear phagocytic cells and dendritic cells. In particular, activation of dendritic cells, a representative player for antigen presentation, may modulate consequent immunological interactions with T cells and other leukocytes, such as B cells and mast cells/basophils. In Chapters 15 and 16, the possibility of using nanomaterials/nanoparticles as therapeutic tools, such as for vaccination and drug delivery, is also discussed. Regarding their potential, many researchers, including physicians, have hopes for their use. Chapters 17 and 18 focus on important issues of immunotoxicity and effects on/interactions with allergic reactions. The role of nanomaterials in enhancing allergic pathophysiology and provoking allergy should be differently estimated. Of note, the authors introduce allergic pathophysiology ranging from type I to IV, and the effects of

nanomaterials on these diseases. The figure on antigenicity is easy to understand. In Chapters 19 and 20, several versions of tests for the immunotoxicity of nanomaterials, both *in vitro* and *in vivo* assay systems, are introduced. Of note, the methodology of targeting is described for researchers. I am impressed with the information regarding *in vitro* assays using dendritic cells. The description seems to be an ideal model for the immunotoxic assay. In this section, very good information has been provided on *in vitro* assays with (immature) dendritic cells and (memory/sensitized) T cells for alternative immunotesting. Measuring T-cell proliferation and protein/messenger levels for helper T-cell cytokines such as IL-4, -5, -9, -13, -17, -18 and -33 should be informative for elucidating nanomaterial exposure. These chapters, for general researchers, imply the difficulties, in particular, associated with animal models (*in vivo* studies) for immunological estimations against pollutants, and these have room for improvement in the future. As I have experienced, it is quite difficult to develop testing systems to properly evaluate immunological imbalances; therefore, these chapters may provide toxicologists with a precise method that can be modified for use in their studies. Chapter 21 focuses on the US FDA regulatory requirements for immunotoxicity tests and their applicability to nanomaterial-based drug research, a hot topic in the medical sciences. This chapter emphasizes the importance of regulating immunotoxicological examinations of nanoparticle-related drugs (including conjugates). The readers can understand the structural society (industrial–academic–government cooperation) for the application of nano-based drugs. Therefore, the importance of immunotoxicological evaluations for safer medicine in the future is emphasized.

There are a few places where I feel that the book could have been improved: a chapter on the very important topic ‘tumor immunity’ is missing. Carbon nanotubes, for example, reportedly induce carcinoma *in vivo*, which is often found in asbestosis, implicating their devastating impact on tumor immunity of hosts. The effects of T cells is an important issue for immunological evaluation that was not covered. Even *in vitro* data on nanomaterials’ effects

on cells might have been informative to the readers. As for the chapter on allergy, adjuvanticity of nanomaterials should be emphasized as well as their antigenicity. Particulate matters in the atmosphere, such as those derived from diesel engines have adjuvant potential against Th2-skewed allergic pathophysiology. Some engineered nanoparticles have similar proallergic potential. Their synergistic impact on antigen sensitization and provocation has been reported throughout the world, although their precise mechanisms are not known. Developmental health effects of exposed nanomaterials could have been discussed. For example, maternal exposure to some kinds of nanomaterials may lead to allergic susceptibility in newborn children, as reported for some environmental chemicals such as phthalates and bisphenol A. Although few studies have been published in the context of nanomaterials, investigation of the issue is meaningful for the future, and should be clarified as soon as possible. Alternatively, it may be interesting to introduce the immunotoxicity of materials such as carbon nanotubes, latex and fullerene, since it is difficult to unify their effects due to their heterogeneity.

Due to the extremely broad nature of the field of nanoimmunotoxicology, it would have been exceedingly difficult to include the extensive number of citations necessary to fully reference every aspect of the text. Thus, almost all of the authors selected seminal references to illustrate their intention and direction. Overall, this approach makes sense and is applied properly throughout the text. Nonetheless, there are times when new subjects were introduced with limited background information and appropriate references were not available for further investigation.

Conclusion

The current updated edition of this book is both timely and necessary. In particular, focusing on 'immunotoxicity' elicited by 'engineered (artificial) materials' is innovative and novel. Overall, it is exceedingly difficult to give an overview of the state of the field due to its breadth and multidisciplinary nature. However, Dobrovolskaia and McNeil, the chief editors have done an admirable job in giving the reader the essence of the different facets of nanoimmunotoxicity, supplementing their writing with references selected to give the reader a more detailed insight. The potential problem I pointed out in the introduction (that the target audience has not been defined) might be resolved by indicating that the book is for toxicologists and immunologists in the title and in the introductory chapter, and/or the removal of descriptions that are too simple throughout the book in future editions. In summary, I hope this textbook will aid immunotoxicity researchers and provide significant insights into toxicology, immunology, environmental, occupational and public health, preventive medicine, and therapeutics, as well as engineering.

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