Guest Editorial

Bengt Fadeel*

Sizing up the safety of nanomaterials

DOI 10.1515/ejnm-2015-0031

Nanosafety assessment is an essential and integral part of nanotechnology development. We have witnessed an exponential increase in the number of publications on environmental and health effects of nanomaterials in the past decade, and it is indeed appropriate to ask whether we are on the right track in terms of understanding engineered nanomaterials from a toxicological and regulatory perspective (1). In his recent survey of the literature, Krug emphasized that an international agreement is needed on the characterization of the physico-chemical properties of nanomaterials in all studies on health hazards, in order to make the data meaningful and comparable (1).

Further to this point, Duncan recently provided a perspective on safety assessment of nanomaterials based on lessons learned from decades of clinical experience of nanomedicines, stressing that it is essential to use well-characterized materials at all stages of preclinical and clinical testing if the results obtained are to be meaningful (2). Therefore, careful material characterization (and characterization of the biological "identity" of nanomaterials; see below) is a common requirement in nanotoxicology and in nanomedicine. However, Duncan also pointed out that the notion that nanotoxicology and nanomedicine are "two sides of the same coin" is an oversimplification because nanomedicines are made up of many components and the nanomaterials therefore should not be studied in isolation; the bioactive payload (such as a drug) may be a primary determinant of the toxicity or behavior of the nanomedical pharmaceutical formulation ultimately administered to a patient (2).

This special issue of the *European Journal of Nanomedicine* includes a collection of reviews and other contributions on the topic of nanosafety assessment and the development of nanomedicines. In the opening essay, the authors argue that engineered nanomaterials are, by definition, materials that have the propensity to interact with biological systems at the nanoscale, and that this very fact underlies both the potentially very promising applications of nanomaterials in nanomedicine as well as their toxicity (3). One portion of the essay is devoted to the question of the biological "identity" of nanomaterials resulting from the acquisition of a so-called corona of adsorbed biomolecules on the surface of nanomaterials in living systems. Examples of molecular (nanoscale) interactions between various engineered nanomaterials such as carbon nanotubes and extracellular as well as intracellular biological structures are discussed, along with examples of the exploitation of nanomaterials as drugs per se – by virtue of their intrinsic nanoscale properties – focusing on metallofullerenols and dendrimers.

This essay is followed by a review specifically on the bio-corona and its role in toxicity of nanomaterials. Here, Westmeier et al. (4) highlight the importance of describing and understanding the behavior of nanomaterials in biological systems and point out that by coating the nanoparticle, the proteins adsorbed to the nanoparticle define the surface of the nanoparticle and mediate further interactions between the nanoparticle and the biological environment. The composition and evolution of the protein corona depends on the physico-chemical properties of the nanoparticle, underscoring the interplay between the synthetic (intrinsic) and the biological "identity" of nanomaterials. The authors propose that a tiered approach should be applied when studying the corona in order to reduce the biological complexity, with the final aim to understand (and predict) the impact of the bio-corona on living systems. The authors thus suggest cell-based, high-throughput screening, complemented by more advanced 3-D cell culture and/or co-culture model systems and, finally, animal models to verify the importance of the identified corona-dependent activities or toxicities.

In the third review in this special issue, Wick et al. (5) discuss recent developments of in vitro and ex vivo models for nanosafety assessment. This review, which nicely complements the discussion on advanced in vitro systems for efficacy and toxicity assessment of nanomedicines published recently in this journal (6), explores the notion that a paradigm shift is needed in regulatory toxicology with an emphasis on mechanism-based understanding supported by in vitro and ex vivo models – including advanced, biomimetic "organ-on-a-chip" systems – with which to replace, reduce or refine animal testing.

These reviews are followed by a short meeting report on the recent Nanosafety Forum for Young Scientists, a conference organized with the aim to allow young scientists engaged in EU-funded nanosafety projects to present and discuss their research (7), and a short communication on the nanomedicines that are currently in the translational process from product design to market, with a view to EU-funded projects and European clinical trials, as well as nanomedicinal products authorized in Europe (8). The authors highlight, amongst other things, the importance of having a European "nanocharacterization laboratory" to support the quality and safety assessment of nanomedicines in preclinical development and conclude optimistically that nanomedicines may offer solutions to public health needs.

References

1. Krug HF. Nanosafety research – are we on the right track? Angew Chem Int Ed Engl 2014;53:12304–19.
2. Duncan R. Nanomedicine(s) and their regulation. In: Fadeel B, editor. Handbook of Safety Assessment of Nanomaterials: From Toxicological Testing to Personalized Medicine. Singapore: Pan Stanford Publishing, 2014.
3. Gallud A, Fadeel B. Keeping it small: Towards a molecular definition of nanotoxicology. Eur J Nanomed 2015.
4. Westmeier D, Stauber RH, Docter D. The bio-corona and its impact on nanomaterial toxicity. Eur J Nanomed 2015.
5. Wick P, Chortarea S, Guenat OT, Roesslein M, Stucki JD, Hirn S, et al. In vitro-ex vivo model systems for nanosafety assessment. Eur J Nanomed. 2015.
6. Fabbrizi MR, Duff T, Oliver J, Wilde C. Advanced in vitro systems for efficacy and toxicity testing in nanomedicine. Eur J Nanomed 2014;6:171–83.
7. Pietroiusti A, Tran L, Campagnolo L. Nanosafety forum for young scientists: a meeting report. Eur J Nanomed 2015.
8. Bremer-Hoffmann S, Amenta V, Rossi F. Nanomedicines in the European translational process. Eur J Nanomed 2015.

Bengt Fadeel
Nanosafety and Nanomedicine Laboratory,
Institute of Environmental Medicine,
Division of Molecular Toxicology,
Karolinska Institutet,
Stockholm,
Sweden,
Phone: +46 8 524 877 37, Fax: +46 8 34 38 49,
E-mail: bengt.fadeel@ki.se