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Nanoparticles in medicine: Current challenges facing inorganic nanoparticle toxicity assessments and standardizations

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Abstract

Although nanoparticles research is ongoing since more than 30 years, the development of methods and standard protocols required for their safety and efficacy testing for human use is still in development. The review covers questions on toxicity, safety, risk and legal issues over the lifecycle of inorganic nanoparticles for medical applications. The following topics were covered: (i) In vitro tests may give only a very first indication of possible toxicity as in the actual methods interactions at systemic level are mainly neglected; (ii) the science-driven and the regulation-driven approaches do not really fit for decisive strategies whether or not a nanoparticle should be further developed and may receive a kind of "safety label". (iii) Cost and time of development are the limiting factors for the drug pipeline. Knowing which property of a nanoparticle makes it toxic it may be feasible to re-engineer the particle for higher safety (safety by design).

From the Clinical Editor: Testing the safety and efficacy of nanoparticles for human use is still in need of standardization. In this concise review, the author described and discussed the current unresolved issues over the application of inorganic nanoparticles for medical applications.

Key words: Nanoparticles; Nanomedicine; Regulation; Toxicity; Standardization

Key issues in nanomedicine

Although scientists and clinicians have been engaged in nanomaterials and, more specifically, inorganic nanoparticles research for more than 30 years, the development of methods and standard protocols required for their safety and efficacy testing for possible human use is still work in progress. Inorganic nanoparticle use, especially magnetic iron oxide materials for imaging, over this period has been a particular focus, and their impact on human cell and tissue functions a compelling safety and toxicity concern. Assessments of the influences of particle size, morphology, surface charge and resulting interfacial protein adsorption on their interactions with tissues, uptake by lymphatic or blood components, and correlations with toxicity or safety risks certainly provide no consensus to date. In vitro methods and preclinical models to produce such correlations to human use currently lack validation and standards. Hence, without accepted approaches for assessing safety, translation of nanomaterials and nanoparticles may prove challenging as marketable biomedical products.

Under the auspices of the European Research Project NanoDiaRA (Development of Novel Nanotechnology Based Diagnostic Systems for Rheumatoid Arthritis and Osteoarthritis), funded by European Commission Framework 7, two workshops were organized on "Nanoparticles in Medicine: Toxicity Methods and Standards" in May, 2012 and September, 2013. Experts representing the following expertise were assembled: (i) nanoparticle synthesis processes and characterization from pure compositional and physical testing to investigations with the human components in vitro, (ii) regulatory issues surrounding nanotechnology and nanomedicine, and (iii) commercialization aspects required to take certified nanomaterials from laboratory-scale to GMP-certified biomedical product. Workshop discussions focused on the current plethora of diverse and invalidated research methods commonly

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employed in both academic and industrial nanoparticle in vitro and in vivo characterization. Lack of assay standards, comparisons and consistency frequently produce confounding results. Several critical issues involve the ability to translate inorganic nanoparticle from the many academic reports and studies to industrial scaling processes that comply with commercial quality systems, governmental standards, and regulatory contexts for human use. A more detailed report of the workshops is given on the Web page "Meeting summaries" of the journal, *Nanomedicine: Nanotechnology, Biology, and Medicine*.[1]

The many variations in reported investigations, often with vague descriptions of materials and preparation, storage, and analytical certification methods, prevent robust scientific comparisons of the diverse published results on seemingly related inorganic particle chemistries. Additionally, industrial standards are lacking for these systems: relevant legal guidelines and important definitions remain vague. Therefore, it is important to address the compelling need for improved, standardized assessments of inorganic nanoparticles and their toxicity in various biomedical uses, for coherence between scientific developments and corresponding health and safety regulations, and for defining prerequisites necessary for implementing and enforcing such regulations. These concerns lead to the following key issues:

(i) "Nanoparticle Properties and Characterization Methods": Inorganic nanoparticle size and shape, their physicochemical properties and, most importantly, surface and interfacial properties in biological milieu[2] that result in formation of the ubiquitous adsorbed protein corona on particle surfaces are proposed as critical parameters to measure. Importantly, these properties should be verified and followed to correlate and control their interactions with living systems throughout the entire product life cycle. This is the basis for the second key issue.

(ii) "Toxicity Assessment": Despite global proliferation of engineered nanoparticle research and production, reliable, validated high-throughput standardized methods are still needed for rapid assessment of their toxicity under various environmental conditionings, human routes of exposure, dosing to cell cultures and in vivo biological conditions. Correlations of in vitro cell and protein exposure results to in vivo host responses that are often uncertain and non-predictable to use for risk–benefit analysis. Furthermore, pre-clinical in vivo experiments and models necessary to best mimic a given dose–exposure situation for these nanoparticles in formulations appropriate for human uses have no current consensus, validation or standardization to date. These key issues represented in (i) and (ii) are again prerequisites of (iii) — the regulatory aspects for translating nanoparticle formulations to clinical use.

(iii) "Regulation": Government policies governing nanomaterials production and occupational exposures, environmental release, commercial product stewardship, and human exposure remain a critical part of the entire product life cycle for nano-enabled products.[3] Policy formulation and implementation must enable clear guidelines that govern interactions between nanomaterials researchers, developers, and regulatory bodies to together facilitate the responsible transfer of research results assessing toxicity (if any) to ensure product safety for industrial and medical users. This should be a living, dynamic engagement: research and development in nanotechnologies/nanoparticles for biomedical products are continuously evolving. New details about nanoparticle properties and toxicity with their associated implications for benefits and risks are continuously reported in scientific reports as well as consumer digests in the public media. Associated, evolving legal aspects surrounding these issues must also be considered and appropriate measures taken to provide both stability via responsibility to industrial developers for their future markets and also safety to the consumer in both proper use and exposure.

Considering the various discussions at workshops, conferences and recent publications, a general picture of the current situation and future needs can be constructed[4]:

(i) improved methodology and test tools for characterizing nanomaterials from research toward marketable versions and the throughout the product life cycles are necessary, covering the diverse manifestations and impacts of these materials on both human health and on the environment;

(ii) the assessment of possible risk should be harmonized between the main stakeholders in Europe, USA and if possible, other countries, regarding the spectra of current materials R&D and marketing for nanomaterials-based products;

(iii) nanomaterial-based products for industry and medicine should seek a common approach to safety and toxicology testing distinct in certain aspects from traditional new, soluble drug testing. This is especially important for those nanomedicinal products based on inorganic nanoparticles and for which conventional toxicology knowledge is often insufficient in routine pharmaceutical toxicology testing. Nanoparticle assays and their outcomes are not comparable with soluble molecule-based product assessments and must be treated differently;

(iv) improvements in regulating nanomaterials, especially nanoparticles, are necessary to address current ambiguities for industries that avoid the use of "nano-branding" in their nanomaterials-containing products if it is not specified as a marketing instrument;

(v) several current nanomedicinal products are based on re-invention or adaptation of formulating strategies for existing poorly soluble or insoluble drugs showing improved performance when encapsulated within lipid vehicles (i.e., liposomes) or as protein complexes, or in nanocapsules and organic (polymer) nanoparticles. Because of their complex synthetic preparation and composition, inorganic particles processed with various analogous organic or inorganic coatings and other possible conjugated biological moieties encounter greater difficulties in their translation toward clinical applications, depending on application and specific use.