

## Editorial

# Biotransformation of Nanomaterial is Pivotal for Nanotoxicology Research

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## Editorial

New material synthesis through manipulation of atoms has spurred interest in nanotechnology development for more than five decades [1]. Materials with at least one dimension sized from 1 to 100 nanometers have been manufactured with enhanced physical strength and greater chemical reactivity than their larger-scale counterparts. At this dimension, some material properties are governed by the laws of atomic physics. Today nanotechnology touches nearly all aspects of our lives and for biomedical researchers nanotechnology holds the promise of new drug formulation and new approaches of molecular targeting therapies [2,3]. Other discoveries in nanotechnology that influence agricultural developments, environmental sciences, and for material science advancement including nanocomposites have been made [4,5].

Nanomaterial for medical applications alone has been projected, with a compound annual growth rate of 13.5%, to surpass \$100 billion in 2014 [6]. However, challenge imposed by technical limitations have allowed the successful emergence of only a few nanotherapeutics that included doxorubicin-loaded liposomes, paclitaxel micelles and albumin-bound paclitaxel nanoparticles as well as few injectable materials. It should be noted that most materials currently used for gene delivery or with good photo-electric properties designs have limited therapeutic applications due to the systemic toxicity concerns. Natural materials with little inherent toxic components could offer superior alternatives in the future. CNS disorders, such as inflammation and psychosis may be ameliorated by brain targeting nanoparticles [2,3,7]. Systemic released microvesicles and exosomes, nanoparticles containing small RNAs, mRNA and proteins may be used to affect cells at distant sites. Through autocrine, paracrine, and endocrine signaling these vesicles may be regarded as a component of a newly identified intercellular communication system [8,9]. Investigations on the edible nanoemulsion-based delivery systems could further enhance the bioavailability of these encapsulated substances [10]. Future studies on the nanoemulsion-induced exosomes release from the gastrointestinal tract could offer valuable clues on the additional functional importance of these nanoparticles.

Despite the plethora of benefits, potential toxicity of biomaterials remains a concern and the bioretention of nanomaterial necessitates

regulatory oversight. Inadvertent exposures to nanomaterials through inhalation, ingestion, penetration of dermal layers, or deliberate parenteral administration may result in subsequent systemic distribution through the circulatory system. Indeed, the increased production of nanomaterial, especially carbon nanotubes has raised concerns over potential risks of adverse human health effects [11]. Titanium dioxide nanoparticles, considered as biologically inert, have been extensively used as additives in sunscreen products, antimicrobial, bio-medical ceramic and implanted biomaterials, plastic packaging, and self-cleaning sanitary ceramics. Their widespread use has raised the question of potential adverse effects and health risks to workers as well as to the general population. As a matter of fact, in vitro and in vivo studies have showed toxic effects such as chronic pulmonary inflammation, changes in gene expression including apoptosis-related genes and inflammatory genes, and promotion of oxidative stress and DNA damage responses [12]. Cerium oxide nanoparticle (CeO<sub>2</sub> NP), another metal oxide, has expanded beyond its traditional role as polishing agents to be found in television tubes components, in precision optics materials and in various consumer products including semiconductors. The use of cerium oxide as a fuel borne catalyst improves fuel burning efficiency; as a result, CeO<sub>2</sub> NP are directly released into the environment with no clear impact on human health [13]. However, a recent study showed combined nanoceria with diesel exhaust nanoparticles from diesel engine induced pulmonary fibrosis and renewed concerns for its safety [14]. In the agricultural arena, untransformed CeO<sub>2</sub> NPs are up taken and stored in a variety of plants including soybean, corn, cucumber, tomato, and cilantro. While majority of the CeO<sub>2</sub> NPs absorbed in hydroponics plants remains in the nascent form, a small percentage is biotransformed to CePO<sub>4</sub> and to cerium carboxylates [15]. Owing to its natural multivalent state, nanoceria has been proposed as a novel therapeutic strategy to cerium neurodegenerative diseases in human including oxidative stress-mediated ocular diseases such as age-related macular degeneration and retinal angiomas proliferation [16]. As a redox mediator ceria can bind reactive oxygen species reversibly. Internalized nanoceria elicits responses with both therapeutic effects and as oxidative stress inducer [17,18]. Experimental exposure of high iv dose of nanoceria quickly saturated elements of the reticuloendothelial system in liver and spleen, together with sustained proliferation of T lymphocytes, resulted in the formation of granuloma in the rat [19]. The behavior of CeO<sub>2</sub> NP in plants may undergo biotransformation with the assistance of PO<sub>4</sub> and other organic acids, to modulate their toxicity potential [15]. Regarding the biotransformation of nanoceria in mammalian system, a recent report examined the fate of nanoceria while being retained in the hepatic phagolysosomes and found the release of a secondary plum of the CeO<sub>2</sub> NPs. These very small 1-3 nm CeO<sub>2</sub> NPs are known to reduce free radical formation [20]. The in situ formation and release of secondary CeO<sub>2</sub>-plum signifies the discharge of cerium ions

from the iv-infused ceria in the liver for systemic distribution. Aside from the obvious implication in the principal of administration, delivery, metabolism and elimination (ADME) for nanomaterial, the observed in situ biotransformation appeared to play a functional role in oxidative stress reversal found in the rat brain [21]. Perhaps due to their miniature dimension, migration pathway from cell cytoplasm interior to extracellular domains remains to be identified for this nanomaterial; nevertheless, biotransformation clearly is a pivotal bioprocessing junction for many of the newly manufactured nanomaterial.

Applying the principal of ADME, a framework can be developed for analyzing and evaluating the biological impact of nanomaterial to safeguard cell, tissue, and organisms. Tiered toxicity testing involving cell-free, cellular and in vivo methodologies have been developed with endpoints relating to induction of oxidative stress, inflammation, geno toxicity and others to determine the safe levels for human exposure. Parallel structural biology analysis using advanced instrumentation for image generation reaching near-atomic resolution should be encouraged in future studies in risk assessment of nanomaterial and for their beneficial applications.

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