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NEWS AND OPINIONS

Biotransformations of magnetic nanoparticles in the body

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Summary Current research overflows with instant proof of concept studies proposing nanoparticles for biomedical applications. The biological environment — more or less hurriedly — interacts with nanoparticles, reshapes their structure and changes their properties; thus modifies particles distribution, biotransformations and potential toxicity. As the understanding of nanoparticles processing, persistence, degradation and recycling will help predicting potential exposure risks, it is necessary to associate the concept of nanoparticles lifecycle to biological effects and employ (specific) methodologies to detect, quantify and follow the bioprocessing of nanoparticles *in vivo* over time, from the whole body level to the nanoscopic scale. Besides the composition, nanoparticles persistence/degradability is governed by their architecture and the nature/quality of the surface coating; therefore strategies can be adopted to control the long-term fate of nanoparticles in the organism. In this Opinion we focus on the lifecycle of magnetic iron oxide nanoparticles, a versatile and biocompatible class of nanoparticles, which found their way to clinical trials.

Exposures to nanoparticles (NPs) and developments of nanomedicines justify an exhaustive assessment of the fate and potential toxicity of nanomaterials *in vivo*. While acute effects of NPs, evaluated by exposure/response assays, are sometimes described, the transformations of nanomaterials, inflicted by the biological environment, are much less investigated. Decreasing the size to nanoscale endows

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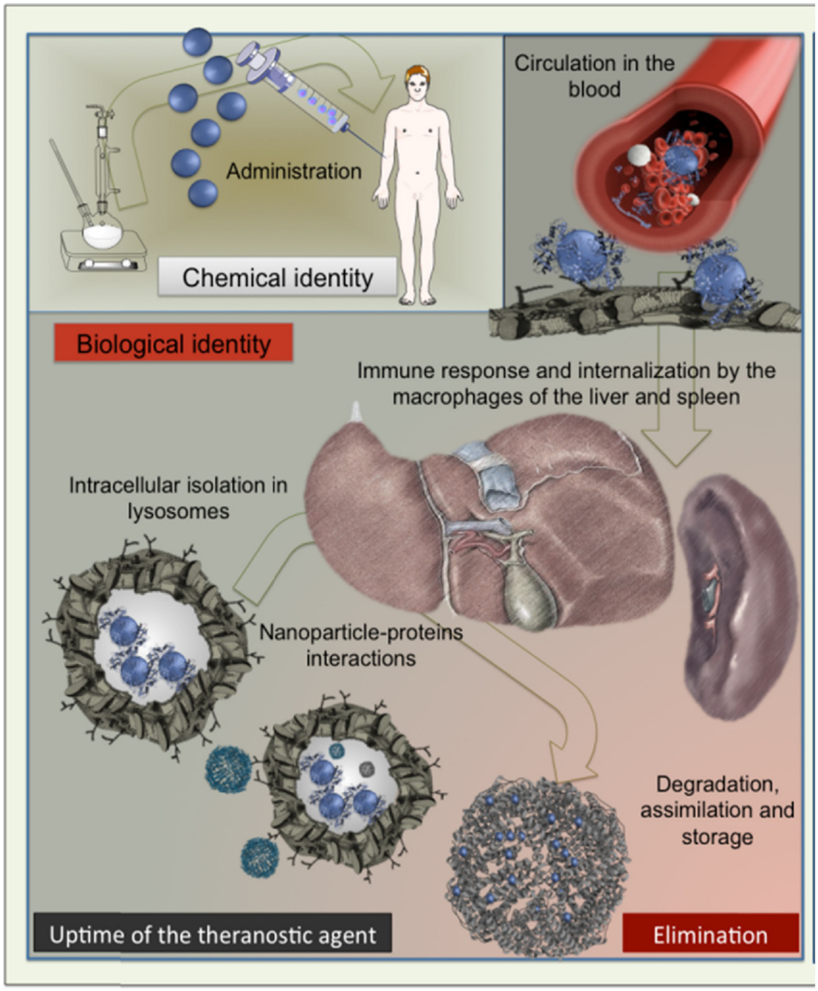

Figure 1 Schematic view of nanoparticles lifecycle after intravenous administration.

materials with new properties while enhancing particles reactivity. NP processing *in vivo* includes biotransformation, degradation, bio-assimilation, elimination or simply persistence — processes orchestrated by complex and dynamic interactions with various components of biological media, crossed by NPs during their odyssey throughout the organism (Fig. 1). Recent studies evidenced that biological interactions continuously remodel NPs identity and properties [1]. The molecules within biological fluids severely reshape NPs surface [2,3] and initiate particle aggregation, opsonization or enzymatic attack and degradation [4]. Such remodeling may regulate nanoparticles transport in physiological media, cellular internalization and potential toxicity [5]. The main difficulty is thus to characterize and follow complex interactions between nanoparticles and the biological milieu *in situ*.

Another crucial factor influencing nanoparticles fate is obviously the time passed within the organism. NPs are transported and transformed through kinetic processes that are eventually slow. One of the main fears concerning NPs is related to a potential long-time persistence within the body, which could elicit chronic inflammatory reactions to foreign materials. Such apprehension is likely inherited from asbestos-related diseases, emerging decades after asbestos exposure. Henceforth the central issue becomes the lifecycle of NPs in the body from initial exposure to complete elimination or assimilation. Indeed at times we should prefer reactive, rapidly degradable NPs, while in others long-term, inert and persistent NPs will be required to reside ''inactive'' in the organism. On one hand, degradation processes of NPs and their by-products may cause unexpected biological reactions, and on the other hand, accumulation of non-degradable NPs might saturate lysosomal compartments and perturb degradative and autophagic pathways that are essential for cells to degrade proteins [6].

Surprisingly, while chemists can easily handle NPs synthesis and tune sizes, shapes, organization and properties of NPs, the exploration of nanoparticles lifecycle *in vivo* is still in its infancy. Undeniably, majorities of studies investigate the behavior of NPs in the first hours or days after exposure, but rarely focus on periods of months or years after administration, which can be necessary for the body to eliminate or degrade the particles. The lack of time for comprehensive investigations (publish or perish) partly explains this fact, but methodological difficulties to trace rare NPs *in vivo*, over long periods of time, are also involved. Accordingly, specific methodologies should be developed to detect and quantify nanomaterials, their speciation and their residues in biological tissues, and characterize their morphological modifications at relevant scales over time.