



## Challenges and opportunities in developing nanoparticles for detoxification

“While the proof-of-concept of detoxifying blood has been provided using retrievable nanoparticles, the development of an integrated system containing retrievable nanoparticles for detoxifying blood is still of great interest.”

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Owing to their inherent small size and flexibility in design and preparation, nanoparticles have shown great potential in clinical applications [1]. Detoxification is a pivotal treatment procedure for patients suffering from intoxication. However, the existing antidotes are limited to a small number of toxic agents. The clinically used detoxification procedures mainly focus on intoxication support, such as gastric emptying, correction of electrolyte disturbances and removal of toxins through extracorporeal procedures. Recently, rationally designed nanoparticles have gained profound attention in detoxification [2,3].

Nanoparticles provide a platform for delivering cargos *in vivo*, enduing nanoparticles with promising applications, such as detoxification [4]. First, nanoparticles can be used to deliver therapeutic drugs to reduce the systemic toxicity. Most current anticancer drugs can not effectively differentiate between cancerous and normal cells, leading to systemic toxicity and adverse effects. Some anticancer drugs are also hydrophobic, such as paclitaxel, whose clinical formulation (Taxol®; Bristol-Myers Squibb, NJ, USA) containing Cremophor EL® (BASF, Ludwigshafen, Germany) has a high risk of hypersensitivity reactions. The encapsulation of drugs in nanoparticles can render hydrophobic drugs completely dispersible in Cremophor EL-free aqueous media, target drugs to cancer cells, release drugs selectively in cancer cells and reduce the extravasation of drugs in normal tissue, which can enhance the therapeutic activity and mitigate the systemic toxicity [5,6]. Second, antidotes, which are commonly used treatments in clinical practice, can be delivered by nanoparticles to facilitate detoxification. Previous work has demon-

strated that nanoparticle-delivered antidotes with improved pharmacokinetics or capacity to target the intoxicated tissues have an enhanced detoxification efficiency [7]. Meanwhile, nanoparticles can also be harnessed to codeliver antidotes for synergistic detoxification. Normally, alcohol can be decomposed *in vivo* by enzymes that function in tandem. Inspired by this, Liu and colleagues assembled and encapsulated alcohol oxidase and catalase with complementary functions within a thin polymer shell, forming enzyme nanocomplexes, which could then effectively reduce blood alcohol levels in intoxicated mice. This approach offers a novel alternative antidote and prophylactic for alcohol intoxication [8].

In addition to their function as drug carriers, nanoparticles can also be designed to capture and neutralize toxins, strengthening the detoxification power of nanoparticles [9]. Fat emulsions are composed of nanosized (200–400 nm) droplets of soy bean oil stabilized with phospholipids. These fat emulsions can uptake toxin *in situ* to reduce the effective toxic concentration at different target sites. However, this uptake depends on the toxin's lipophilicity and is limited by relatively fast clearance of the droplets from the bloodstream [10]. Poly(ethylene glycol)-stabilized liposomes with a transmembrane pH gradient can act as an alternative system for detoxification. While poly(ethylene glycol)-stabilized liposomes of less than 200 nm are known to provide a long circulation time *in vivo*, nanovesicles with a transmembrane pH gradient possess ion-trapping properties for toxins [11]. Recently, a novel concept of ‘plastic antidotes’ was introduced by utilizing synthetic polymer nanoparticles to bind toxins and neutralize their function *in vivo*. By

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optimizing the composition of the functional monomers incorporated in the nanoparticles, the binding affinity and capacity can be maximized toward a target toxin. The particle size, surface charge and hydrophobicity are also important parameters that can correlate to the binding affinity and capacity to target venomous biomolecules. These parameters can also affect the cytotoxicity and the performance of the nanoparticles. It is critical to minimize toxicity of nanoparticles by optimizing the surface charge and hydrophobicity and to reduce aggregation mediated by nonspecific interactions with plasma proteins [12,13].

**“In contrast to conventional vaccination approaches, which have an inherent trade-off between efficacy and safety owing to the challenge of retaining faithful antigenic presentation while removing toxin virulence, this nanoparticle-based toxin-detainment strategy shows great promise in presenting nondisrupted pore-forming toxins for vaccination.”**

Besides molecular structure-targeted detoxification, nanoparticles can also be used as an action mechanism-targeted detoxification platform. Pore-forming toxins (PFTs) that can damage the cellular membrane are key virulence factors of pathologies. More than 80 PFTs have been identified, displaying diverse molecular structures and distinctive epitopic targets. The commonly used antidotes target the specific molecular structures of PFTs, making customized treatments necessary for different toxins. However, the functional similarity among these toxins in perforating cellular membranes provides a target for an action mechanism-targeted detoxification platform with broad applicability. Recently, Zhang and colleagues described a biomimetic nanosponge that functions as a toxin decoy for detoxification. They fabricated the nanosponge with a polymeric core covered by red blood cell membranes. It was demonstrated that the toxins could be absorbed by the polymeric core-stabilized cell membrane and, eventually, diverted away from the vulnerable cellular targets [14]. Owing to the stabilization effect from the polymeric core, this nanosponge can be used to deliver toxins as antigens to safely generate an effective immune response against the toxins. In contrast to conventional vaccination approaches, which have an inherent trade-off between efficacy and safety owing to the challenge of retaining faithful antigenic presentation while removing toxin virulence, this nanoparticle-based toxin-detainment strategy shows great promise in presenting nondisrupted PFTs for vaccination [15]. To better fulfill the requirement of clinical practice, *in vitro* devices functionalized with immobilized

nanoparticles have also been studied and developed to neutralize and remove toxins. Recently, a liver-inspired 3D detoxification device was reported. This device is created by 3D printing of designer hydrogels with functional polydiacetylene nanoparticles installed in the hydrogel matrix. The fully synthetic polydiacetylene nanoparticles can capture and sense toxins, while the 3D matrix with a modified liver lobule microstructure allows toxins to be trapped efficiently, providing an alternative platform for detoxification [16].

Despite tremendous effort and impressive progress in the development of novel detoxification strategies based on nanoparticles, there are still significant challenges in this field. There is almost no way to overemphasize the safety issues of nanotechnology [17]. Before any nanoparticle is used for detoxification *in vivo*, the potential toxicity of nanoparticles should be well assessed. The degradability, biocompatibility and metabolism of nanoparticles should be systematically considered while designing nanoparticles for detoxification *in vivo*. Meanwhile, there is still significant work needed to improve the specificity and capacity of nanoparticles to capture toxins, which in turn can enhance the detoxification efficiency and reduce the nanoparticle-associated toxicity. Moreover, intravenous administration of nanoparticles for detoxification often leads to nanoparticle accumulation in the liver, posing a risk of secondary poisoning, especially in liver-failure patients. Thus, optimized tissue distribution *in vivo* is an important feature for nanoparticle-based antidotes. While the proof-of-concept of detoxifying blood has been provided using retrievable nanoparticles, the development of an integrated system containing retrievable nanoparticles for detoxifying blood is still of great interest. In addition to the safety issues, the efficiency of nanoparticle-based antidotes should be addressed. While the existing nanoparticles can neutralize one kind of toxin, it is difficult to design nanoparticles that detoxify every kind of toxin. Therefore, nanoparticles with broad applications are desired for safe and effective detoxification. Despite a great deal of effort in the preclinical stage, more clinical research is necessary to reveal the challenges and opportunities in developing nanoparticles for detoxification. Close collaboration among clinicians, engineers and scientists of diverse expertise (i.e., materials science, nanotechnology, chemistry, physics, pharmacology/pharmaceutics and medicine) will facilitate the development and clinical use of these intelligent nanoparticles for detoxification.

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