HHS Public Access

Author manuscript

Nanomedicine (Lond). Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:

Nanomedicine (Lond). 2014 November ; 9(16): 2437–2439. doi:10.2217/nnm.14.168.

Challenges and opportunities in developing nanoparticles for detoxification

Xin Qu[#],
Department of NanoEngineering, University of California, San Diego, La Jolla, CA 92093, USA

Maling Gou[#],
State Key Laboratory of Biotherapy/Collaborative Innovation Center for Biotherapy, West China Hospital, Sichuan University, Chengdu, 610041, China

Jana Zaidan,
Department of NanoEngineering, University of California, San Diego, La Jolla, CA 92093, USA

Kang Zhang, and
Shiley Eye Center, University of California, San Diego, La Jolla, CA 92093, USA and Biomaterials & Tissue Engineering Center, University of California, San Diego, La Jolla, CA 92093, USA

Shaochen Chen
Department of NanoEngineering, University of California, San Diego, La Jolla, CA 92093, USA and Biomaterials & Tissue Engineering Center, University of California, San Diego, La Jolla, CA 92093, USA

[#] These authors contributed equally to this work.

Keywords

3D printing; detoxification; nanomedicine; nanoparticles; polymer

---

> "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."

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].

Author for correspondence: chen168@eng.ucsd.edu.

Financial & competing interests disclosure
The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
No writing assistance was utilized in the production of this manuscript.

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 demonstrated 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 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 canenhance 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 nano particle-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 nano

particles 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.

Acknowledgments

This work was supported in part by grants (EB012597 and EB017876) from the National Institute of Biomedical Imaging and Bioengineering and a grant (CMMI-1120795) from the US National Science Foundation to S Chen and 863 program (2014AA020509), National Science and Technology Major Project (2013ZX09301304-008) and National Natural Science Foundation (81201785) to M Gou.

References

1. Hubbell JA, Langer R. Translating materials design to the clinic. Nat. Mater. 2013; 12(11):963–966. [PubMed: 24150414]
2. Graham LM, Nguyen TM, Lee SB. Nanodetoxification: emerging role of nanomaterials in drug intoxication treatment. Nanomedicine. 2011; 6(5):921–928. [PubMed: 21793680]
3. Leroux JC. Injectable nanocarriers for biodetoxification. Nat. Nanotechnol. 2007; 2(11):679–684. [PubMed: 18654405]
4. Hubbell JA, Chilkoti A. Nanomaterials for drug delivery. Science. 2012; 337(6092):303–307. [PubMed: 22822138]
5. Gou ML, Shi HS, Guo G, et al. Improving anticancer activity and reducing systemic toxicity of doxorubicin by self-assembled polymeric micelles. Nanotechnology. 2011; 22(9):095102. [PubMed: 21270494]
6. Feng SS, Mu L, Win KY, Huang G. Nanoparticles of biodegradable polymers for clinical administration of paclitaxel. Curr. Med. Chem. 2004; 11(4):413–424. [PubMed: 14965222]
7. Hu X, Tulsieram KL, Zhou Q, Mu L, Wen J. Polymeric nanoparticle–aptamer bioconjugates can diminish the toxicity of mercury *in vivo*. Toxic. Lett. 2012; 208(1):69–74.
8. Liu Y, Du J, Yan M, et al. Biomimetic enzyme nanocomplexes and their use as antidotes and preventive measures for alcohol intoxication. Nat. Nanotechnol. 2013; 8(3):187–192. [PubMed: 23416793]
9. Bertrand N, Gauthier MA, Bouvet C, et al. New pharmaceutical applications for macromolecular binders. J. Control. Release. 2011; 155(2):200–210. [PubMed: 21571017]
10. Jamaty C, Bailey B, Larocque A, Notebaert E, Sanogo K, Chauny JM. Lipid emulsions in the treatment of acute poisoning: a systematic review of human and animal studies. Clin. Toxicol. 2010; 48(1):1–27.
11. Bertrand N, Bouvet C, Moreau P, Leroux JC. Transmembrane pH-gradient liposomes to treat cardiovascular drug intoxication. ACS Nano. 2010; 4(12):7552–7558. [PubMed: 21067150]
12. Hoshino Y, Urakami T, Kodama T, et al. Design of synthetic polymer nanoparticles that capture and neutralize a toxic peptide. Small. 2009; 5(13):1562–1568. [PubMed: 19296557]
13. Hoshino Y, Koide H, Furuya F, et al. The rational design of a synthetic polymer nanoparticle that neutralizes a toxic peptide *in vivo*. Proc. Natl Acad. Sci. USA. 2012; 109(1):33–38. [PubMed: 22198772]
14. Hu CMJ, Fang RH, Copp J, Luk BT, Zhang L. A biomimetic nanosponge that absorbs pore-forming toxins. Nat. Nanotechnol. 2013; 8(5):336–340. [PubMed: 23584215]
15. Hu CMJ, Fang RH, Luk BT, Zhang L. Nanoparticle-detained toxins for safe and effective vaccination. Nat. Nanotechnol. 2013; 8(12):933–938. [PubMed: 24292514]

16. Gou M, Qu X, Zhu W, et al. Bio-inspired detoxification using 3D-printed hydrogel nanocomposites. Nat. Commun. 2014; 4:3774. [PubMed: 24805923]

17. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. Science. 2006; 311(5761):622–627. [PubMed: 16456071]