



## Preface

## Current and forthcoming approaches for systemic detoxification



Our body must constantly deal with the threat that comes from potentially harmful and poisonous compounds both endogenous and exogenous in nature. Swiss physician Paracelsus (1493–1541) perhaps put it best when he stated that any compound is potentially toxic, as the “dose makes the poison.” These can be drugs, radiochemicals, or peptides/proteins that are introduced into the body either inadvertently (*i.e.* accidental exposure, infections, or venomous injuries) or deliberately (*i.e.* suicide attempts or weaponry). Toxic burden can also arise from malfunctioning detoxification mechanisms that result from liver or kidney failure and genetic metabolic disorders. In total, these harmful substances represent a significant global health issue, and thus technologies for effective detoxification are in high demand.

In the majority of cases, the treatments for intoxications remain suboptimal and present significant hurdles that need to be overcome. In the case of pharmaceutical abuse, antidotes only exist for a select few such as acetaminophen, fentanyl, methadone, and alprazolam [1]. Treatments for overdoses are most often supportive (*i.e.* gastrointestinal decontamination or breathing assistance) and do not directly eliminate or neutralize the causative agents. In the case of animal or insect bites, antivenins can be readily made, but the need to identify the offending species is a challenge that is further compounded by the poor economics of treating rare afflictions [2]. For enzymatic therapies, some have demonstrated great promise in a laboratory setting, but the fragile nature or suboptimal pharmacokinetic and biodistribution properties of enzymes can significantly hamper their clinical efficacy [3].

It is apparent that there is an unmet medical need for new, more efficient, and versatile detoxification procedures. The number of intoxications has dramatically risen over time—a 2011 data brief from the United States Centers for Disease Control and Prevention indicated that deaths from poisoning had overtaken those from motor vehicle traffic [4]. This is true not only for chemicals and drugs but also for bacterial toxins, as the number of antibiotic-resistant pathogens continues to rise and outpace the development of new treatments. The dire nature of the problem led the President of the United States to issue an executive order in September 2014 for implementing the *National Strategy on Combating Antibiotic-Resistant Bacteria*. These troubling trends are not likely to abate in the near future, necessitating the need for accelerated research and development.

At first sight, it may appear a bit contradictory to dedicate a special issue of *Advanced Drug Delivery Reviews* to technologies aimed at removing, rather than delivering, compounds from the body. Upon closer inspection, the commonalities between these two opposing fields become more apparent, as many new approaches in the field of detoxification rely on established drug delivery systems, including different forms of nanoparticle technology. The challenges facing the two fields are also oftentimes the same, including the need to improve bioavailability, enhance stability, and modulate localization within the body.

The issue starts with a review by Patel et al. that covers extracorporeal therapies, including hemodialysis hemoperfusion and plasmapheresis [5]. Such technologies have had a long history of being applied towards detoxification, and efforts are ongoing to develop guidelines that will enable their widespread use to treat poisoning and drug overdoses. This is followed by several reviews on injectable systems for the detoxification of harmful compounds and elements. Damitz et al. focus on emulsion-based and liposomal systems for the sequestration of toxic agents in the treatment of drug overdose [6]. Liu et al. cover enzyme therapeutics and how such systems can benefit from increased stability and lowered immunogenicity when packaged into nanocarriers [7]. Lastly, Fattal et al. describe the development of smart delivery systems to help modulate the localization of chelating agents for the decontamination of harmful radionuclides such as plutonium and uranium [8]. Other than exogenously introduced substances, the buildup of endogenous compounds within the body can also lead toxicity. Such is the case with hyperammonemia, which results from either inherited or acquired defects in liver function. Matoori et al. give a comprehensive review on the different treatments for this potentially life-threatening condition [9]. The subsequent set of reviews centers largely on methods for addressing toxins of biological origin. Fang et al. describe novel nanosystems mimicking the cell membrane, a barrier that all toxins must interact with in order to take effect [10]. By taking design cues from nature, it is possible to design treatments that target the working mechanisms shared by broad classes of toxins. Weisman et al. follow this with a discussion on synthetic antidotes, including molecularly imprinted polymers, which can be used as alternatives to those derived from natural sources [11]. The final review in this issue brings things around full circle. Instead of trying to eliminate toxic materials from the body, Zhan et al. discuss how researchers have taken advantage of the natural biological interactions that toxins and their derivatives are capable of in order to precisely engineer targeted therapies [12].

It is our great hope that this special issue of *Advanced Drug Delivery Reviews* will help to foster more research in the exciting, re-emerging field of detoxification. We foresee that an increased understanding of the problems at hand, combined with the application of emerging technologies, will bring about novel strategies for addressing toxins and poisons that will help to alleviate a great deal of human suffering in the future.

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