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Unraveling the *in vivo* fate and cellular pharmacokinetics of drug nanocarriers

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Research in nanocarrier-based drug delivery systems has exploded over recent years, evidenced by an exponential increase in the number of publications. A casual search of "nano* AND drug delivery" in Web of Science showed that there is a cumulative number of 141,667 papers by 2018, compared with 12,772 by 2008, and just 831 by 1998. While a dozen or so of nanomedicine products have been commercially launched, successful translation from laboratory designs to clinical viable solutions still remains a significant challenge [1–4]. Polymer/carrier toxicity, poor manufacturability, deficiency in stability and difficulties in quality control largely contribute to the translational disappointment of most of nanocarrier systems under research. While the issues are actively addressed, *in vivo* fate and underlying mechanisms of drug delivery designs remain less studied, limiting the advance toward commercial success. Biodistribution, pharmacokinetics, drug release from the carrier, biodegradation and changes in physicochemical properties (particle size, shape, texture, surfac properties, *etc.*) are not routinely investigated of a nanocarrier system. Without thorough comprehension of *in vivo* behaviors of nanomedicines, development will continue to be a hit-or-miss game. Current practice to resort to pharmacological and toxicological evaluations at the end of the development process results in tremendous overhead in time and resources. It is thus of the utmost importance to perform rational nanomedicine studies by knowing where a nanocarrier traverses in the body, how it releases the drug payload, and what pharmacological effects it elicits.

A carrier-based drug delivery system generally comprises of one drug compound (or more) as the payload and at least one polymer or surfactant integrated together in various schemes (Fig. 1). With time in the body, the carrier most likely degrades or dissociates releasing the drug. Study of the *in vivo* fate of a nanocarrier thus requires understanding the spatiotemporal entanglement of respective constituents of the delivery system, including the drug, polymer/surfactant, and other helper chemicals (such as receptor-targeting ligands) (Fig. 1). A major technical hurdle in studying *in vivo* fate stems from the dynamic nature of drug release and carrier disintegration under biological conditions. Because of the complexity of the biological environment, which is dynamically balanced and replenished, drug release kinetics are difficult to estimate from *in vitro* measurement. As a delivery system circulates in the blood, various plasma components actively interact with the surface and constituents of the nanocarrier, interfere with its integrity, and affect drug release. When the delivery system passes endothelial fenestrations and reaches a tissue environment, intact or partially dissociated, it also interacts significantly with extracellular matrix components and immune cells. Such a complicated journey makes the acquisition of actionable pharmacokinetic and pharmacodynamic data difficult. Nevertheless, steps have been made toward developing technologies for monitoring the integrity of a nanocarriers as well as for understanding its treatment mechanisms. The field has arrived at a crucial point where the knowledge build-up of *in vivo* fate of drug delivery system can lift the development of nanocarriers, which seems stalled.

Highlighted in this theme issue are a collection of articles that review various studies of *in vivo* behaviors and performance of carrier-based delivery systems. By guest-editing the issue, we intend to establish a forum in which some of leading efforts in the field are showcased and, more importantly, to foster the enthusiasm in exploration of the biological fate of drug nanocarriers. The themed issue is aimed to provide critical reviews on the state-of-the-art of related studies of nanocarriers and to clarify directions for future endeavors. Several articles touch one of the two aspects and some address both. The physicochemical and surface properties of nanocarriers have long been recognized having tremendous influence on the performance of a delivery system. The subject is well summarized in the article by Zhao and coworkers [5]. The article by Alkilany et al. provides an overview on the impact of ligand density on the targeting efficiency of nanomedicines [6]. Retention, penetration, and internalization of nanoparticles in the tumor microenvironment have been actively studied in cancer therapy. Peng et al. systemically examine studies of the intratumoral fate of functional nanoparticles that response to environmental factors and highlight implications on diagnosis and therapy [7]. The article by Donahue et al. focuses on subcellular behaviors of drug nanocarriers, including cellular uptake, subcellular trafficking, and kinetics [8]. Given the fact that the *in vivo* fate of polymeric materials used in carrier-based delivery systems is less researched, the article by Su et al. is timely as it reviews the most recent advances in studying many functional materials commonly used in nanomedicines, including polyethylene glycols (PEG) and PEG-derived polymers [9]. As it is critical to trace nanoparticles in the body, five papers center around discussing both conventional and emerging tools in bioimaging of drug carriers. Hybridization of drug nanocrystals with fluorophores has proved to be an innovative and practical strategy to illuminate and unravel the dissolution of drug nanocrystals both *in vitro* and *in vivo*, as illustrated in the article by Lu et al. [10]. Man and coworkers offer a critical review on radiolabeling

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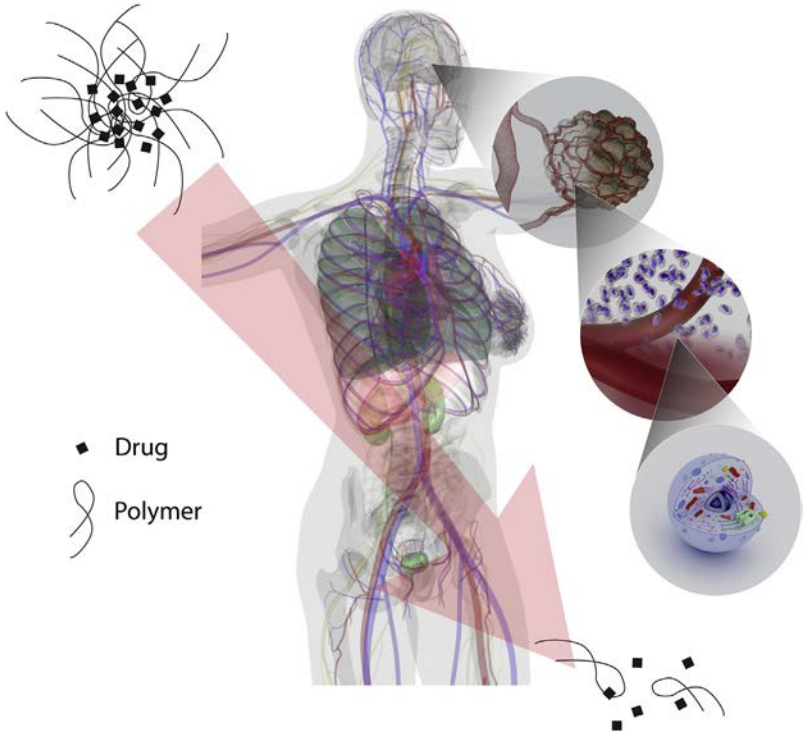

Fig. 1. Schematic illustration of the complex *in vivo* fate of nanocarrier-based drug delivery systems, which interact with the body at various scales from organ to tissue and to cell. Their behavior is marked by numerous spatiotemporal changes, which lead to dissociation of respective constituents and release of the drug.

of drug liposomes with discussion of limitations and demonstration of applications in nuclear bioimaging [11]. Finally, three articles examine using environment-responsive fluorophores for understanding the integrity and biological fate of drug nanocarriers, as the special dyes are capable of indication of physical states of a carrier based on aggregation-induced emission (AIE) [12], Förster resonance energy transfer (FRET) [13], and aggregation-caused quenching (ACQ) [14], respectively.

The scope of the current topic is enormous and cannot be fully reviewed in one special issue. This collection is assembled to illustrate some leading efforts to understand the *in vivo* fate of drug delivery systems, especially nanocarriers where the drug is solubilized and/or encapsulated. To motivate further discussion and studies, our team hopes to continue editing following-up issues. Last but not least, we want to thank the authors for their significant contributions and prompt efforts to turn-around their manuscripts.

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