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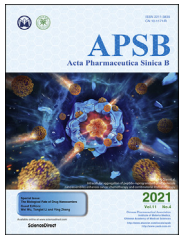

Editorial of Special Issue "The Biological Fate of Drug Nanocarriers"

According to the Merriam-Webster dictionary, the word "fate" refers to "final outcome", among various definitions, and has such synonyms as "destiny", "consequence", and "ending". With regard to the biological or *in vivo* fate of an exogenous ingredient, the wording may refer to the eventual destiny—for example, the end products—of the entity that enters the biological system or the body. However, the term has been used more broadly in the drug delivery field to imply the pharmacokinetic process and structural evolution of drug delivery systems. Although the word "process" sometimes works interchangeably, "fate" puts more emphasis on the dissemination of a delivery system.

As a result of tremendous research activities in nanocarrier-based drug delivery over the last decade, exploration of the biological fate of drug nanocarriers has gained momentum. Despite a relatively limited number of publications, this topic has drawn close attention from prominent scientists worldwide[1,2], owing to its importance in overcoming various challenges to facilitate the clinical translation of nanomedicines. The development of a nanomedicine would be a hit-or-miss game, if the biological fate of its nanocarrier remains un-studied. The metaphor of blind men patting an elephant echoes the impasse of current biological or *in vivo* investigations. Fully unraveling the biological fate will accelerate the clinical translation of a nanocarrier-based delivery system and, more importantly, help develop workable tools to track and discriminate both active ingredients and nanocarriers *in vivo*[3,4]. While radioactive or fluorescent labeling of a delivery system is conventionally employed to track the drug nanocarrier, the approach is indiscriminate in unveiling nanocarrier-bound signals from released label signals, causing uncertainties[3,5]. Encouragingly, the recent application of environment-responsive probes in this field sheds light on the biological fate of drug nanocarriers[6–8].

The scope of "biological fate" is huge, considering the vast approaches in designing and delivering nanocarrier-based systems. It encompasses all relevant bio-nano interactions including adsorption of proteins and formation of the protein corona, biodistribution, cellular uptake and subcellular trafficking, drug release, pharmacokinetics, particokinetics, dissociation of the vehicles, and degradation of the constituting materials. The essence of unraveling the biological fate of drug nanocarriers lies in untangling the spatiotemporal correlation between constructing elements of a drug delivery system—drug, carrier and materials, as well as other helper chemicals including ligands, surfactants, and stabilizers[4]. Because of the widely and rapidly expanded research interests in this topic, we intend to set up a forum by launching a series of special issues for active scientists in the pertinent disciplines to share their most recent findings. The first edition (*Advanced Drug Delivery Reviews* Vol. 143, published on Mar 15, 2019) includes ten review articles that elaborate on various subtopics of *in vivo* fate—utility of different environment-responsive fluorophores, fate of liposomes as revealed by radioactive labeling, cellular uptake and subcellular trafficking, effect of physicochemical properties, and fate of carrier materials. This current edition continues the format to include seven review and nine research articles from some leading scientists in the field that further the discussion on subtopics of *in vivo* fate. Liang et al.[9] review the effect of physicochemical properties on the *in vivo* fate of nanoparticles within the frame of immunotherapy, Mazumdar et al.[10] review the internalization pathways and intracellular fate of polymeric nanoparticles, while other articles review relevant topics on the recent advances in nanocarrier-based delivery systems—that is, immunity responses toward nanomedicines[11], lipid-based nanomedicines[12], biologics and delivery system-based immunotherapy[13], intranasal delivery of lipid nanoparticles[14], and the role of caveolin-1 in tumor targeting[15]. In the research work by Peng et al.[16], a cisplatin prodrug was utilized to induce the formation of cisplatin prodrug/IR820/docetaxel nanoaggregates, thus enabling intracellular immobilization of the nanoparticles, as evidenced by fluorescence images that revealed the intracellular fate of the nanoassemblies. Martínez-López et al.[17] studied the gastrointestinal fate of zein nanoparticles with the potential for enhancement of oral absorption of insulin. Lin et al.[18] investigated the biological fate of 50 and 226 nm PLGA nanoparticles following intradermal delivery in an imiquimod-induced psoriasis-like mice model by employing FRET-based fluorescence probes (DiO/DiI). In another study by Zhang et al.[19], the intracellular uptake, exocytosis, and kinetics of a model nanocrystal of tetrakis (4-hydroxyphenyl) ethylene (THPE) with aggregation-induced emission (AIE) properties, as well as

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dissolved THPE molecules, were systemically investigated. Four studies by different groups utilized fluorescent probes with aggregation-caused quenching (ACQ) properties. Xia et al.[20] investigated the gastrointestinal transit, uptake by enteric epithelia, lymphatic transport, and ultimate distribution after absorption of integral particles following oral administration of a self-nanoemulsifying delivery system. Yang et al.[21] labeled common drug crystals with ACQ probes by the hybrid crystallization strategy and quantified residue crystal particles after oral administration, based on which *in vivo* dissolution profiles were depicted for the first time. Shen et al.[22] explored the oral absorption process of quercetin nanocrystals and managed to conclude the contribution of integral nanocrystals to overall systemic exposure of quercetin. In a proof-of-concept study, Wang et al.[23] investigated the effect of particle size and pH on the formation of protein corona around solid lipid nanoparticles by labeling the vehicles using similar ACQ probes. Moreover, Gu et al.[24] demonstrated a full metabolism profile of a well-documented and marketed diblock copolymer mPEG-PLA.

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