Editorial

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Promoting the bench-to-bedside translation of nanomedicines

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Since its emergence in the late 1980s, nanotechnology has shown vast potential in biological medicine fields, including drug delivery, diagnostics, and tissue regeneration [1]. Owing to the enhanced permeability and retention (EPR) effect of solid tumors discovered over 30 years ago [2], nanomedicines have mostly been developed for cancer diagnosis and therapy, and few of them have been applied clinically [3]. Despite the long-standing debate on the existence of the EPR effect in human patients [4], clinical outcomes have shown that nanomedicines reduce the systemic toxicity and adverse effects of therapeutic agents by altering their pharmacokinetics and biodistributions [5]. Beyond the applications for cancer, other applications are emerging in nanomedicines for metabolic, cardiovascular, and infectious diseases [6]. With the development and successful application of mRNA-lipid nanoparticle COVID-19 vaccines [7], unprecedented attention has been paid to the bench-to-bedside translation of nanomedicines worldwide. More than 500 ongoing and planned clinical trials in January 2023 were found using the search term "nanoparticle" on the ClinicalTrials.gov website (https://clinicaltrials.gov/). China is also accelerating its pace of nanomedicine translation, and the CFDA has approved seven products for clinical uses in the past 3 years. This special issue compiles eight review articles that discuss recent progress and future directions in nanomedicines to promote their bench-to-bedside translation.

Lipid nanoparticles (LNPs) have provided valuable platforms for various therapeutics, from liposomal drugs applied in clinics to cationic lipid nanoparticles that enable mRNA vaccine delivery; thus, LNPs will continue to be a research hot spot in nanomedicine translation [8]. Liposomes and cationic lipid-nucleic acid complexes have received attention. Solid LNPs (SLNPs) have also attracted attention, owing to their ease of preparation, physicochemical stability, and scalability. These characteristics enable the large-scale production of SLNPs; however, some challenges must be resolved in future industrial manufacturing, such as polymorphism, phase separation, and sterilization resulting from manufacturing processes [9]. Polymeric nanomedicines, including polymeric nanoparticles, micelles, and polymersomes, have many advantages for cancer therapy, such as a solubilizing ability for hydrophobic drugs, significant drug-sustained release, reduced drug toxicity, and enhanced drug accumulation in tumors [10]. To enhance the *in vivo* therapeutic efficacy, various multifunctional nanomedicines have been reported, for example, spontaneous property transitions in response to endogenous and/or exogenous stimuli (e.g., pH, temperature, light, ultrasound, redox, and enzyme) for specific delivery. However, these nanomedicines usually have sophisticated structures, causing difficulties in large-scale production, *in vivo* characterization, and clinical translation. In the review article "'One-for-All' approach: a black technology for nanomedicine development", Youqing Shen et al. provide a promising strategy of "One-for-All", in which the polymeric nanocarrier prepared from phospholipid-affinitive poly (tertiary amine-oxide) has a simple structure but enables all the properties necessary for an *in vivo* delivery process. Because the tumor microenvironment (TME) plays an important role in cancer procession and metastasis, modulating the TME has been an alternate cancer treatment strategy, offering reduced toxicity and enhancing other cancer therapies [11, 12]. Polymeric nanomedicines have substantial potential in remodeling the TME, owing to their controlled synthesis, high modifiability, and tunable responses to various stimuli [13]. The review article "Development of stimuli responsive polymeric nanomedicines modulating tumor microenvironment for improved cancer therapy", by Xuesi Chen et al. provides an overview of the applications of stimuli responsive polymeric nanomedicines for remodeling the TME and contributes valuable insights and strategies for developing the next generation of polymeric nanomedicines in personalized and precise cancer therapy.

Inspired by the natural merits of biocomponents, biomimetic approaches to improve the *in vivo* properties of nanomedicines, such as prolonged blood circulation, reduced immunogenicity, specific delivery, and reduced

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toxicity, have been reported in the literature. Abraxane (albumin-bound paclitaxel) is an example of a biomimetic nanomedicine approved by the FDA for first-line cancer therapy. Utilizing the innate ability of albumin to bind hydrophobic molecules, Abraxane was shown to enhance the therapeutic efficacy and reduce the unwanted side effects of paclitaxel [14]. Low-density lipoprotein (LDL), endogenous lipid nanoparticles responsible for cholesterol transport, is an ideal biomimetic nanocarrier for drug delivery owing to its excellent biological features, super-high drug loading capacity, and intrinsic targeting ability [15]. Because of the elevated expression of the low-density lipoprotein receptor in several forms of cancer, biomimetic nanomedicines based on LDL have a substantial advantage in cancer-targeted therapy. More importantly, LDL has potential in the clinical treatment of brain cancer and neurological diseases because of its ability to cross the blood–brain barrier [16]. LDL can be isolated from biological fluids or synthesized in a controlled manner; thus, the clinical translation of LDL-based nanomedicines seems inevitable. Ferritin, an endogenous protein for iron storage, is another excellent nanocarrier for developing biomimetic nanomedicines. It has a highly uniform nanocage structure that encapsulates various therapeutic drugs by manipulating disassembly and reassembly [17]. In the article review "Ferritin-based nanomedicine for disease treatment", Jiancheng Wang et al. comprehensively review the research status of ferritin-based nanomedicines and analyze the challenges in their clinical translation. Biomimetic nanomedicines derived from cell primitives, for example, cells, microbes, cell membranes, and exosomes, can combine the innate biofunctions of cell primitives and the advantages of nanotechnology; thus, they are becoming one of the most cutting-edge research directions [18, 19]. The review article "Versatile biomimetic nanomedicine for treating cancer and inflammation disease", by Yaping Li et al. provides a comprehensive overview of this type of biomimetic nanomedicine for cancer and inflammation therapy and offers useful strategies for their further functionalization. I am optimistic regarding the clinical application of exosomes, cell-originated vesicles existing in almost all biological fluids, although challenges such as large-scale production, efficient drug encapsulation, and in-depth characterization remain.

Immunotherapy is becoming a powerful tool for clinical treatments of inflammation, autoimmune diseases, and cancer. An increasing number of immunotherapeutic agents is being approved for clinical use or are ongoing clinical and preclinical studies. However, after administering these immunotherapies, serious adverse effects from autoimmunity and non-specific inflammation have been observed (e.g., cytokine storm, a deadly overaction of the body's immune system) [20]. Nanomedicines show a substantial advantage in the specific and controlled regulation of immune cells, initiating a new era of immunotherapy. The preclinical and clinical data have demonstrated that nanomedicines significantly improve the safety, efficacy, and specificity of immunotherapies [21].

In this special issue, two review articles elucidate the nanomedicine-based regulation of immune cells. One article is "Progress in nanoparticle-based regulation of immune cells", by Jun Wang et al. The authors summarize the current progress of nanomedicines regarding regulating the biofunctions of various immune cells and discuss strategies for developing the next generation of nanomedicine-based immunotherapies. The other article is "Regulation of macrophage polarization by iron-based nanoparticles", by Ning Gu et al., which focuses on the regulation of macrophage polarization by iron-based nanoparticles. Ferumoxytol, iron oxide nanoparticles approved by the FDA as an iron supplement, can strongly induce the M1 polarization of macrophages to suppress the growth and metastasis of *in vivo* tumors [22]. Because iron-based nanoparticles have been extensively investigated in magnetic resonance imaging and drug targeting delivery, the discovery of their functions on specific macrophage modulation will promote their clinical translation.

Although many investigations have shown the distinct advantages of nanomedicines over traditional medicines, the clinical translation of the former has been challenging. The unique features of nanomedicines, such as their ultrasmall size, surface activity, and adjustable components, are a double-edged sword, which may impact human health. With the rapid development of nanomedicines, increasing attention is being paid to nanotoxicity. Different from traditional medicines, in many cases conventional methods are not suitable for characterizing and evaluating nanomedicines. Exploring the pharmacokinetic characteristics of nanomedicines has always been a challenging task. Despite the availability of various animal models, few of them fully mimic all aspects of the human body. Advanced approaches, such as organ-on-chip, multi-omic profiling, and artificial intelligence (AI), have been applied to nanomedicine studies. Daxiang Cui et al. report in their review article "Artificial intelligence in theranostics of gastric cancer, a system review" that AI has considerable potential in the early screening, diagnosis, therapy, and prognosis of stomach carcinoma, and can also serve as an innovative tool for evaluating nanomedicines [23]. Large-scale, controlled production is

a major challenge in the transition of nanomedicines from preclinical to clinical development and subsequent commercialization. Using synthetic biology technologies to obtain nanomaterials with special functions is a promising strategy; Zhifei Dai et al. provide an example in their review article "Ultrasound contrast agents from microbubbles to biogenic gas vesicles". Intelligent manufacturing and online detection are also promising in the industrial production of nanomedicines.

In conclusion, nanomedicines have entered the golden age of rapid development. In 2021, the Center for Drug Evaluation of the CFDA issued guiding principles for the quality control and nonclinical research of nanomedicines (for trial implementation), promoting the further research and application of nanomedicines in China. The ongoing clinical trials indicate that nanomedicines might soon be available in the pharmaceutical market.

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