BIO Integration

Challenges and Opportunities of Nanomedicines in Clinical Translation

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The clinical approval of the first nanoparticle-based drug, liposomal doxorubicin (Doxil®), for cancer therapy in the United States in 1995 has marked the entrance of nanomedicines in the market [1]. With the explosive exploration of nanomedicines, more than 1,500 nanomedicine products have been put into clinical trials [2]. Meanwhile, several types of nanoparticles, such as liposomes, albumin nanoparticles, polymer micelles, and magnetic nanoparticles, have been developed and approved as nanocarriers of therapeutic and diagnostic agents or as medical devices to manage various diseases [3].

Despite the preliminary prosperity of nanomedicine studies and preclinical investigations in the early years of the 21st century (2001–2005), the clinical approval of nanomedicines returns to a steady period during recent years [4]. This declining tendency discourages some scientists, who become pessimistic and frustrated about the prospect of nanomedicines, often saying, "is the wave cresting?" or "why so many papers and so few drugs?" [5]. These concerns are not unreasonable because data have shown that less than 5% of nanoscale therapeutics entering phase I trial successfully obtain the eventual permission for the market due to the low treatment efficacy in clinical trials as well as the technical and cost challenges in product manufacture and scale-up [6, 7]. Meanwhile, a relatively large number of clinical trials are focused on the combinations of marketed nanomedicine products, such as Doxil® and albumin-bound paclitaxel (Abraxane®), with other agents; nevertheless, few nanoparticle-based innovative medicines or therapies are investigated [8]. These bottlenecks illustrate the wide gap between technical revolution and clinical translation. Furthermore, some scientists are concerned that delayed development of clinical nanomedicines may be detrimental to patients. With this in mind, we analyze the current challenges and obstacles confronted in medicinal exploration and regulatory approval and reassess the opportunities to advance next-generation clinical nano-therapeutics with advanced functionalities.

Preclinical–clinical inconsistence

Before permission for phase I clinical investigation is granted, detailed and accurate preclinical results on the efficacy and safety of advanced nanomedicine candidates are required. Unfortunately, despite the promising results obtained in preclinical experiments, most nanomedicine candidates always fail in the clinical trials and result in a low success rate, demonstrating a poor connection of preclinical studies to clinical outcomes. This is because the comprehension of nanoparticle behavior in vivo is based on the data on animal models in preclinical experiments [9]. However, any preclinical efficacy in animal models may not be consistent with the human outcome because of the differences of species-dependent physiological and scaling parameters, including plasma composition, osmotic pressure, blood supply, immune responses, etc., as well as the differentiation in pathological process on experimental animals. Therefore, it is essential to understand the missing relationship between preclinical and clinical models fully. For example, despite the extensive observation of the enhanced permeability and retention (EPR) effect in the xenografted tumor on an animal model, its availability in human solid tumor remains to be unproven, which is widely suspected as the key cause of the failure of tumor-targeting nanomedicines in clinical translation. For this purpose, Ding et al. investigated the EPR effect in the human renal solid tumors using an ex vivo perfusion model via X-ray computed tomography [10]. They confirmed that 87.8% of the human renal tumor possessed a considerable EPR effect, which

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was well correlated with that in rabbit xenografted tumor. Thus, this work closely connects the EPR effect between the human solid tumor and the animal model.

The development of animal-based disease models with more similarities to the human pathological mechanism is another solution to establish the correlation between human trials and preclinical investigations. To date, some preclinical models that more perfectly present cancer features, like a patient-derived orthotopic xenograft using cancer tissues and patient-derived three-dimensional organoids, are reported with more fitness for screening nanomedicine candidates [11]. Moreover, genetic technology is also applied to establish in vivo disease models, such as diabetes mellitus, cancers, and Alzheimer disease, providing a more effective tool for reproducing the characteristics of diseases in animals.

Breakthrough of traditional functionalities of nanoparticles

A nanoscale drug aims to shift the balance from a potentially harmful therapy to a beneficial one. The traditional nanomedicines approved for disease management are only serving as delivery vehicles, which are principally dependent on optimizing the pharmacokinetics and biodistribution of loaded compounds by regulating their physical and chemical properties to overcome some obstacles during the in vivo application, such as solubility, stability, biodegradation, and so forth [9, 12]. However, these strategies cannot fully exert the therapeutic efficacy of drugs [7]. Therefore, developing next-generation nanomedicines with advanced functionalities, which are not limited to delivery strategies, is warranted to benefit their therapeutic efficacy further.

To date, some second-generation nanomedicines, which are formulated with active-targeting vehicles or smart vectors with stimuli-responsive properties, have shown advanced targeting and upregulated efficacy [13, 14]. These nanomedicines can overcome one or more critical barriers in vivo, including immune clearance in the liver and spleen, permeation across the endothelium into target tissues, penetration through the tissue interstitium, endocytosis in target cells, and diffusion through the cytoplasm to reach the lesion site with high concentrations while minimizing the accumulation at undesired sites for an optimized efficacy. Several nanomedicines have been tested in preclinical investigation and are already in early clinical trials [7]. For example, an innovative irinotecan-loaded micelle developed by Liang and colleagues has entered phase I clinical trial in 2021 for colorectal cancer treatment [15]. Meanwhile, nano–bio interface interactions have also attracted the intention of researchers, which is related to the maximization of the effect of nano-dimensional therapeutics and the creation of new-concept nanomedicines for disease management [2]. For example, Zhao et al. proposed an advanced strategy to use functional nanointerfaces to intervene in biological processes to control disease development [16, 17]. They designed a nanocomposite containing a peptide KLVFF-containing polymer layer on its surface, which could formulate amorphous nanocluster with amyloid β (Aβ) aggregate to significantly change their morphology to replace Aβ oligomer, thereby reducing Aβ-induced neurotoxicity and facilitating Aβ aggregate removal for treatment of Alzheimer disease [16]. Moreover, some nanomaterials possessing inherent immunogenic properties, such as antigenicity, adjuvant properties, and inflammatory properties, also gain increasing considerations for the design and engineering of nano-vaccines or nano-adjuvants for disease management [18]. These works break the limitation of nanoparticles as delivery vehicles and pioneer the advanced functionalities of nanomedicines, providing a unique idea for the design of nanoparticle-based drugs for disease treatments. Therefore, we expect that the advanced nanomedicines based on unique functionalities will be emerging in clinical trials.

Controllable, reproducible, and scalable production

The determination of optimal physicochemical parameters, which are firmly responsible for effective immune escape, tumor penetration, and cell targeting and uptake as well as controllable drug release, is crucial for successfully developing therapeutic nanoparticles [19]. However, due to the difficulty of rapid, accurate, and reproducible synthesis of nanoparticles with varying properties, it remains challenging to systematically screen plenty of nanoparticle parameters in parallel. Microfluidic technology is probably a solution to address this challenge, which can achieve fast self-assembly of nanoparticles with a narrow size distribution, adjustable physicochemical properties, and good batch-to-batch reproducibility [20, 21]. Moreover, particle replication in non-wetting template (PRINT) technology can also facilitate the production of monodisperse nanoparticles with accurate control of chemical constituents, sizes, shapes, surface features, and drug loading efficiencies [22]. Thus, this advanced technology, similar to the high-throughput screening method for small molecule drugs, can accelerate nanoparticle exploration.

Moreover, the contradiction between the escalating complexity of nanoparticle synthetic process with Chemistry, Manufacturing and Controls (CMC) and Good Manufacturing Practice (GMP) requirements is also an obstacle for the translation from preclinical to clinical application and succeeding commercialization or market [2]. So far, the large-scale production of simple nanoparticles, such as liposomes and polymer nanoparticles containing small-molecule, active pharmaceutical ingredients with outstanding physical and chemical features, is readily and extensively achievable in the pharmaceutical industry by manufacturing unit operations [2]. However, the large-scale production of nanomedicines with more complexity to meet the standards of CMC and GMP remains challenging and requires the adjustment of currently used unit operations or the exploration of innovative manufacturing procedures [7]. These complex nanomedicines may be equipped with targeting ligands or biological components, convey multiple active pharmaceutical ingredients, be produced via elaborate layer-by-layer assembly, or be incorporated with two or

more functional modalities, like theranostics or multistage systems.

Generally speaking, scale-up and repeatable production is more onerous if nanoparticle formulation processes contain multistep or complex techniques. However, the clinical translation of nanomedicines is always simultaneous with optimizing formulation parameters and methods, which prompts the scientists to put nanomedicine scale-up as the critical aspect during early nanoparticle design and engineering. Recently, a coaxial turbulent jet mixer technology, with the superiorities of uniformity, repeatability, and adjustability, has been applied for bulk production of polymer nanoparticles [23]. Moreover, the PRINT technology can produce nanoparticles repeatably, but scale up to kilograms remains challenging [22]. Thus, the advancement of these robust and versatile technologies in the industrial-scale production of nanoparticles will significantly accelerate the clinical translation of nanomedicines.

Control of cost

Nanomedicine-based therapy is relatively expensive due to the high cost of raw materials and the requirement of a tedious and multistep manufacturing process. For example, the cost of manufacturing nanoscale drugs, such as Doxil® and Abraxane®, is much higher than that of the free parent drugs paclitaxel and doxorubicin [24]. This can hinder the large-scale manufacturing of nanocarriers by pharmaceutical companies. Furthermore, compared with traditional free drugs, the clinical benefits of nanomedicines must be offset significantly by higher prices due to their development and manufacturing costs. Therefore, the development of some advanced synthesis, such as mRNA synthesis technology, and scale-up technologies, e.g., coaxial turbulent jet mixer and PRINT technology, could enable easier procurement of raw materials as well as a simpler and more controllable production process, which eventually leads to the control of nanodrug price within an acceptable range.

Safety concern

The nano-sized drugs share analogous cell signaling pathways to organelles or biomolecules that may induce adverse biological interactions, leading to the emergence of nanotoxicology [8]. Up to now, the toxicity of nanoparticles has been widely explored. However, the currently utilized evaluation methods for nanomaterial toxicity are almost the same as those used for classical drugs, which may be inadequate to reveal the factors causing toxicities in vivo at present entirely. To offset this insufficiency, the factors that influence the behaviors and interactions of nanocarriers at the nano–bio interface to modulate the toxicity of nanomedicines, including size, shape, surface area, surface charge, porosity, hydrophilicity, and hydrophobicity, should be comprehensively characterized firstly [12]. Then in vivo toxicity assessment should be designed and implemented with necessary consideration of toxicokinetics, administration routes, acute toxicity comprising complement activation, hemolysis, inflammation, oxidative stress, or mitochondrial function impairment as well as chronic toxicity, which includes neurotoxicology, immunotoxicology, cardiovascular function, ophthalmological evaluations, genotoxicity, carcinogenesis, and developmental toxicity (embryotoxicity), which may not be fully covered in the in vitro assays. The results of these assays can be incorporated into a rational framework for further data generation and regulatory decision-making with respect to the technical translation. If necessary, a safe-by-design approach could be helpful to improve nanomedicine's safety features.

Conclusion

The above challenges facilitate the interdisciplinary scientists to collaborate to accelerate the clinical translation of nanomedicines [25]. First, the deep exploration of the connections between preclinical and clinical modeling will facilitate the development of unique animal-based disease models remarkably similar to the human pathological mechanism to elevate the accuracy of predicting therapeutic efficacy in human clinical trials. Second, the integration of active-targeting ligands and smart stimuli-responsive materials as well as the bio–nano interface interactions will endow nanomedicines with advanced functionalities to pioneer new-concept nanoparticle-based drugs. Then, by overcoming the obstacles of controllable, reproducible, as well as scalable nanoparticle production, cost, and toxicity, the next generation of nanomedicines that are incorporated with unique molecular modules and therapeutic agents, including cell-based therapeutics, siRNA, mRNA, DNA, protein, and so forth, will be accelerated into clinical development [26, 27]. Overall, we are rapidly gaining a much deeper understanding of the challenges and opportunities of nanomedicines. Thus, we hope that nanomedicines will change the paradigm of disease treatment and improve patient survival shortly.

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