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HIGHLIGHT

DELIVER: The core principles for the clinic translation of nanomedicines

KEY WORDS

Nanomedicines;
Clinic translation;
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Nanomedicines have revolutionized disease prevention, diagnosis, and treatment. Since the approval of Liposomal doxorubicin (Doxil) in 1995, various nanomedicines have been successfully developed[1]. Specifically, the COVID-19 pandemic highlighted the significance of nanomedicines, as lipid nanoparticles facilitated the mRNA vaccines success, thereby remarkable accelerating the development of RNA-drugs[2,3]. Despite these advancements, only about 1%−5% of all nanomedicines development projects achieve clinical application[4]. Contributing factors include biocompatibility, complexity, and regulatory hurdles, many nanomedicine candidates languish in the preclinical stage[5-7]. Hence, innovating nanomedicines and facilitating their clinical translation is crucial to fully harness their therapeutic potential.

Recently, an article published in Nature Nanotechnology, titled "A Translational Framework to DELIVER Nanomedicines to the Clinic" outlined the potential obstacles that arise during the various stages of nanomedicine development, particularly those posing challenges in later clinical trials[8]. This article encompasses essential considerations and required outcomes related to each stage of nanomedicine development, spanning from design, experimentation, manufacturing, preclinical assessment, clinical trials, regulatory compliance, to commercialization. It also clarifies the relevant stakeholders for each stage (Fig. 1).

Every stage of the process faces with numerous risks that can lead to failure. For example, during design, materials may exhibit poor biocompatibility, toxicity, and low target specificity. *In vitro* and *in vivo* models may lack sufficient representation, making it hard to simulate patient heterogeneity. Inconsistencies in material batches and repeatability during manufacturing pose significant challenges to large-scale production. Moreover, the complex regulatory pattern and inadequate commercialization strategies further obstruct the progression to clinical trials and market launch. This article introduces risk mitigation strategies encapsulated in the **"DELIVER"** framework, which identifies core principles essential for advancing preclinical development and aims to enhance the clinical investigation of nanomedicines.

The core of the "**DELIVER**" framework encompasses seven key points vital for deliver design throughout the clinical phase: 1) Target Product Profile **D**efinition: Integrate drug, deliver system, and target patient population with specific biological targets, to define a clear product profile. 2) **E**ssential Characterization: Conduct comprehensive investigations of chemical composition, physicochemical properties, and compatibility across multiple batches in simulated pathological environments. 3) **L**ead Candidate Optimization: Focus on refining the necessary chemical composition, properties, safety/toxicity profiles, and therapeutic efficacy. 4) **I**ntellectual Property Collaboration: Collaborate with patent attorneys and commercialization teams early to ensure commercial viability and a competitive edge. 5) Preclinical **V**alidated: Repeatedly test and verify biomarkers and therapeutic index across multiple cell-based and/or animal models, considering the heterogeneous of clinical manifestations. 6) **E**conomic and Scalable Production Design: Understand critical product attributes and process parameters to achieve optimal nanomedicine functionality and streamline manufacturing. 7) **R**egulatory and Clinical Pathway Identification: Consult with regulatory agencies in target regions to mitigate approval risks and identify suitable pathways. Each core principle is supported by expert recommendations, formulated by consortia of diverse stakeholders, to overcome the critical challenges impeding the translation of nanomedicines. By conducting comprehensive reviews with the **"DELIVER"** framework during the initial stages of nanomedicine

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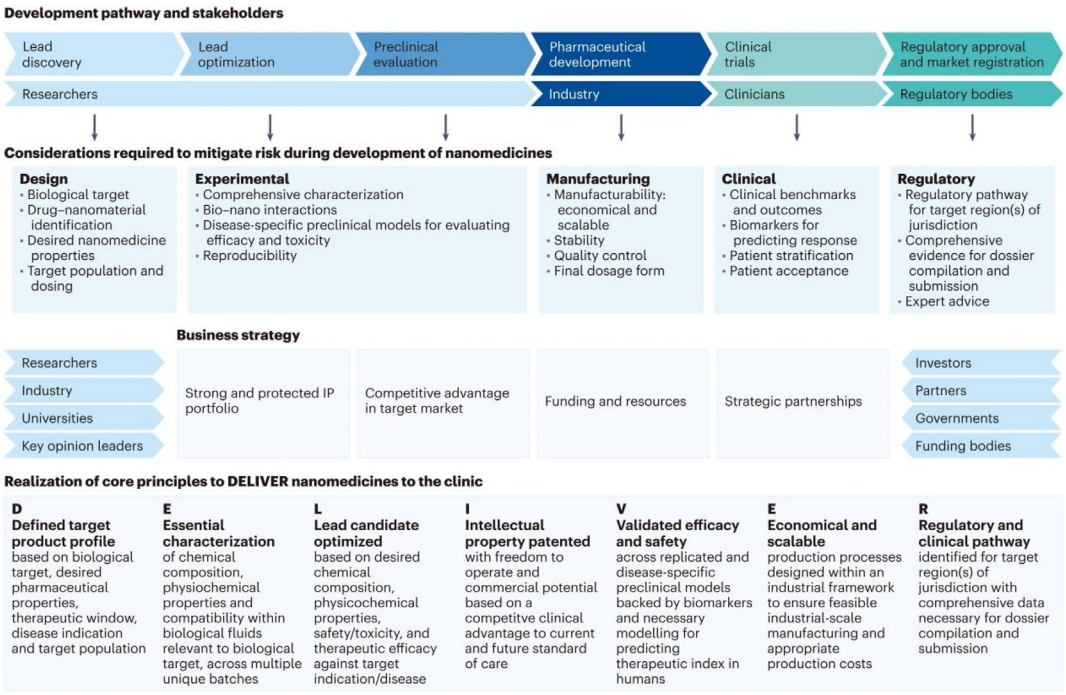

Figure 1 Summary of the development pathway and stakeholders, essential considerations and outcomes required at each development stage, realization of core principles to "DELIVER" nanomedicines to the clinic. Reproduced with permission from Ref. 8. Copyright © 2024 Springer Nature.

design and development, researchers can significantly reduce the risk of failure and increase the likelihood of clinical success.

Looking forward, despite the inherent and complex challenges encountered in the process of nanomedicine clinical translation, and this framework cannot guarantee success for every nanomedicine, we anticipate that the **"DELIVER"** framework will significantly facilitate the progression of nanomedicines through preclinical evaluation, pharmaceutical development, clinical trials, regulatory approval, and market registration. As nanotechnology, disease biology, physiology, machine learning and artificial intelligence continue to evolve, as well as concerted efforts from researchers, universities, industry, regulatory bodies, clinicians and others, the **"DELIVER"** framework will undoubtedly improve, driving more nanomedicines to achieve their ultimate goal: clinical translation and global application. It is noteworthy that the fundamental researches are highly valued as the cornerstone for translation-oriented studies. It reveals the underlying mechanisms of disease pathology, the fate of nanomedicines *in vivo*, the need for patient stratification, and the future strategies that can be employed for optimizing nanomedicines efficacy, which will profoundly influence the future landscape of nanomedicine translation.

We look forward to witness more researchers benefiting from the **"DELIVER"** framework, facilitating a smoother transition into clinical settings, shortening the development duration, minimize the failures in clinical trials, ensuring a successful market introduction, and thereby driving nanomedicine to the next frontier in medicine science.

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Author contributions

Chuan Hu: Writing-original draft, Writing-review & editing. Xinling He: Writing original draft. Huile Gao: Conceptualization, Writing-review & editing. Jinming Zhang: Conceptualization, Writing-review & editing.

Conflicts of interest

The authors declare no conflicts of interest.

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