Boosting clinical translation of nanomedicine

“Biomimetic platforms, such as organs-on-a-chip, will provide unprecedented opportunities to accurately evaluate the safety and efficacy of nanomedicine formulations, leading to higher clinical trial success rates.”

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In the past few decades, the field of nanotechnology has significantly progressed, leading to success in the design and synthesis of functional nanoparticles for therapeutic and diagnostic applications. Nanomedicine, which is the application of nanotechnology in medicine, can be utilized to create novel formulations for targeted drug delivery that are potentially safer and thus can lead to better patient outcomes through a reduction in drug side effects. However, the clinical translation of these formulations has been limited due to expensive and lengthy regulatory processes and the inability to comprehensively assess the safety and efficacy of the nanomedicines. Thus, rigorous and innovative preclinical testing models are needed to evaluate these formulations to ensure their successful clinical translation and future commercial availability.

Nanomedicine at play

The unique physiochemical properties of nanomaterials, endowed by their nanometer scale, have enabled new mechanisms to diagnose and treat diseases with enhanced efficacy through maximized target specificity [1]. For example, nanoparticles can be used as therapeutic carriers to encapsulate and release drugs at target sites via systemic delivery and high accessibility to region where large-sized particles cannot reach [2]. Also, nanoparticles containing contrast agents can act as diagnostic sensors for real-time detection and visual-

ization of diseases inside the body [3]. In addition, nanoparticles with optimized shapes and sizes can modulate cellular functions through direct attachment onto the surface of or internalization by the cells [4]. Furthermore, biomimetic nanoparticles have facilitated tissue regeneration through enhanced host integration [5,6]. However, despite the rapid advancement of nanotechnologies in biomedicine, the translation into practice has been relatively slow.

Clinical & regulatory limitations for nanomedicine translation

The main reason for the slow rates of clinical translation lies in the extremely high cost and lengthy time period associated with clinical trials, largely caused by a lack of proper pre-clinical evaluation platforms that can accurately predict the performance of nanomedicine in the human body during the preclinical phases. As a result, although pharmaceutical companies have aimed to bring nanoparticle-based therapeutics into the market due to their high treatment efficacy, the failure and drug attrition rates still remain high during both the clinical trials and after-market entry.

Thus far, only about 175 nanomedicine products have been commercialized, although a significant amount of formulations have been researched [7,8]. In the United States, it usually takes 8–20 years for nanomedicine development and preclinical investigations, including *in vitro* cell studies and

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in vivo animal tests; these results are subsequently submitted to the Food and Drug Administration (FDA) to obtain permission to conduct human clinical trials, which takes another 4–7 years [8,9]. Still, it is estimated that only 1 formulation in 1000–2000 could eventually meet all the stringent requirements and progress into the market [9]. During the three phases of human trials, the safety, effectiveness, and side effects of candidate drugs are evaluated stage by stage [9]: In Phase I, the safety of the drugs and biologics are tested in less than 100 patients, which takes 1–2 years and costs 50–150 million dollars, at ~25% failure rate; in Phase II, the dosage ranges of the drugs and biologics are optimized with hundreds of patients, which takes 1–2 years and 100–200 million dollars at ~25% failure rate; in Phase III, the efficacy and side effects of the compounds are analyzed in up to thousands of patients, which requires 2–3 years and totals 150–250 million dollars, at ~35% of failure rate. Lastly, physicians, statisticians, chemists, pharmacologists and other scientists at the FDA will review the results of the clinical trial, prior to the final approval of the formulation, which takes around 6–10 months. Through this strict verification process, only a few nanomedicine formulations have been made commercially available to patients, despite the enormous amount of research on this subject from academic institutions.

Additionally, there are still significant concerns regarding clinical translation, as the properties and side effects of nanomedicine formulations are not yet fully understood. Since nanoparticles can cross the biological barriers, including cellular membranes as well as air–blood and blood–brain barriers *in vivo*, there are huge opportunities to access local regions where conventional materials cannot reach; however, this may adversely affect patients due to the potential for uncontrolled migration and deposition within tissues [10]. Moreover, the side effects of many new nanomedicine formulations cannot always be comprehensively measured during the clinical trial phase due to the small sample size of patients that does not completely represent the entire disease population.

Thus, it is necessary to rigorously test and assess nanomedicine formulations in preclinical models before proceeding to a clinical trial setting. For instance, in general medicine, serious adverse effects of drug therapies have been increasingly discovered after the clinical trial process was gradually expedited through legislative acts including the Prescription Drug User Fee Acts (PDUFA). Since the 1970s, approximately 35 drugs and biologics that were approved by the FDA have been recalled from the US market due to their fatal side effects that were unknown at the time of approval [11]. Therefore, it is imperative to enact strict and rigor-

ous testing procedures for the premarket approval of nanomedicine in order to ensure patient safety.

Advancing novel preclinical models

Although there are several barriers to the clinical translation of nanomedicine formulations, it is imperative to seek novel and creative mechanisms to overcome these obstacles to allow commercial access to drugs that are more effective than those currently on the market. The implementation of novel preclinical testing models will enable these drugs to be rigorously tested and become available on the market at a faster pace. Animal models, already limited by existing economic and ethical burdens, are not optimal for this aim as they possess different genetic factors and thus do not accurately predict the human response to the drug. Therefore, we need more reliable *in vitro* model platforms, that can precisely mimic the properties and functions of the human organ systems to advance the clinical translation of nanomedicine [12].

Organ-on-a-chip systems are miniaturized human cell culture platforms that can mimic the microarchitecture, functions, and physiology of their *in vivo* counterparts, which can simulate pharmacokinetics/pharmacodynamics of drugs and thus accurately predict their efficacy and toxicity in the human body [12,13]. The human body contains a sophisticated network of blood vessels that interconnect organs; this circulatory system is essential in sustaining the functions of and communications among individual organs. In this integrated environment, neither organs nor their responses are isolated, meaning that the behavior of one organ upon treatment of a nanomedicine formulation will be contingent on that of the other linked organs. Therefore, building realistic *in vitro* human organ models embedded in an interconnected microfluidic platform will allow the observation of the drug's effect on each organ, and accurately predict drug efficacy and any potential side effects [12]. These models can be made across a range of complexity from either individual or multiple organ types, including the lung, kidney, blood vessel, airway, and bone marrow, among others [14], as well as their interconnected forms such as the micro cell culture analog (μ CCA) devices and the microphysiological systems where up to ten organs are integrated in order to represent their interactions [15,16].

Looking forward

The field of nanomedicine is rapidly developing and, consequently, the demand for clinical translation is quickly expanding. Since rationally designed nanomaterials can lead to innovative treatment schemes and better patient outcomes, biomedical scientists and engineers should actively seek the best route to safely develop the field of

nanomedicine. Biomimetic platforms, such as organs-on-a-chip, will provide unprecedented opportunities to accurately evaluate the safety and efficacy of nanomedicine formulations, leading to higher clinical trial success rates. Government organizations have recently allocated a significant amount of funding to help further the development of these innovative biomimetic platforms for drug delivery [17–20]. As interest in this field continues to grow, we envision that the clinical translation of nanomedicine will be significantly facilitated and will lead to groundbreaking revolutions in drug delivery platforms and ultimately, human healthcare.

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