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Journal of Nanomedicine Research

Calling for Improved Translation in Nanomedical Research

Abstract

Nanomedicines have emerged as alternative tools for targeted delivery of therapeutics, promising safer and more efficacious treatments most particularly in the cancer field. Indeed, several formulations from the first-generation nanomedicines have reached the clinics, which are followed by many more in the pipeline. However, nano-based strategies reveal unprecedented hurdles requiring critical assessment of the efficacy of nanomedical approaches and calling for improved translational strategies and guidelines to improve drug development of novel treatment strategies. Here, we summarize some of the commonly overlooked aspects of translational nanomedicine approaches and emphasize the need for a rigorous preclinical characterization of nanomedical applicability.

Keywords: Drug delivery; Nanomedicine; Translation; Preclinical models

Opinion

Volume 5 Issue 5 - 2017

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Received: June 09, 2017 | **Published:** June 22, 2017

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The use of nanoparticles as novel diagnostic and therapeutic tools has gained immense attention in the field of cancer management. Nano-based therapies offer numerous possibilities such as enhanced drug solubility and stability, extended circulation times, tissue, cell, organelle-specific targeting, early detection and monitoring of diseases, stimuli-controlled drug release and co-delivery of multiple agents, all contributing to a safer drug delivery with minimized dose-limiting side-effects [1]. Several nanomedicines bearing these features are already on the market with many others following in the pipeline.

Yet inevitably along with their rise, nano-based strategies also reveal unprecedented hurdles requiring critical assessment of the efficacy of nanomedical approaches and calling for improved translational strategies and guidelines to improve drug development of novel treatment strategies. Indeed, while the literature is stocked with ever-expanding articles, implementation of nanomedicines in the clinics has been disappointing so far; a PubMed search for the term "nanomedicine" hits over 15,000 articles for the last decade against only a handful of treatments available on the market [2]. Here, we summarize some of the commonly overlooked aspects of translational nanomedicine approaches and emphasize the need for a rigorous preclinical characterization of nanomedical applicability.

First, in-depth characterization of nanoparticle stability from different synthesis batches in biological fluids should be established. Physicochemical characteristics such as size distribution, surface charge, loading capacity, and stability over time must be validated. Synthesis of the nanoparticles should follow Good Manufacturing Practices (GMP) guidelines, hence support for mass production and marketing of the agents for future demand. The development of prostate-specific membrane antigen (PSMA)-targeted docetaxel nanoparticles which are currently being assessed in phase II clinical trials is a prominent example [3]. Hrkach et al. [3] followed a strategy to generate these novel nanomedicines strictly comprised of clinically validated set of biomaterials using a multi-kilogram manufacturing process capable of clinical and commercial scale production.

Second, preclinical models must be chosen with caution in order to use representative and clinically-oriented cell, disease and delivery models rather than artificial experimental designs. *In vitro*, the ideal systems should mimic the physiological conditions and environment as much as possibly allowing for high-throughput analysis. Likewise, *in vivo* models should be chosen according to their resemblance to the disease conditions found in humans. Additionally, immune responses should be taken into account. Animal experiments conducted on immune compromised models may lack the information on the systemic effects of the administered nanoparticles due to mitigated immune cell populations. Hence, transgenic or externally-induced disease models should be preferred where applicable over the most commonly used xenograft models. For instance, the mouse model generated by Johnson et al. [4] with spontaneous *in vivo* activation of the common oncogene Kras, strongly correlates with the pathophysiology of lung cancer [4], and thus can be a proper model to validate nanomedicine efficacy. Essentially, for proof-of-concept studies, several animal models should be used in parallel for reproducibility of the findings. It was reported that different species have alternating tolerances against the same nanomaterial and this can lead to variations in pharmacokinetics as well as induce serious adverse effects such as anaphylaxis in certain species [5]. Therefore, immunotoxicity of nano-agents needs to be characterized in depth, presumably in more immuno-sensitive species such as rabbits before reaching clinical trials. Route of delivery in *in vivo* models must be wisely selected keeping the translational aspects in mind. In nanomedical experimental models, administration of nanomedicines are mostly done via intravenous, intraperitoneal, intratumoral, or intratracheal

routes. While intratumoral injection of nanomaterials in flank tumor models seems rather convenient, data achieved from such models can hardly be regarded translational with regard to the treatment of internal tumors in patients [6]. Recently emerging *ex vivo* models of disease can also stand as alternative tools to bridge the gap between *in vitro* and *in vivo* studies. Our own published data represent examples of exploiting 3-dimensional lung tissue cultures from humans and mice for a high-throughput analysis of controlled release from mesoporous silica nanoparticles and subsequent apoptosis of tumor cells [7]. Such *ex vivo* models allow for a reproducible real-time analysis of nanomedicines on patients' samples providing the natural tumor microenvironment.

Third, utmost attention must be drawn to *in situ* stability and biodistribution of nanomedicines. It was shown that in biological environments, nanoparticles are prone to formation of protein corona by attachment of abundant proteins onto their surface which often leads to loss of target specificity and redirection of the particles to the mononuclear phagocyte system [8]. This eventually results in clearance or deposition of the nanoparticles in major organs such as the liver and spleen. It has been shown that the nature of the corona is dependent on various factors including nanoparticle size, shape, charge and solubility [9]. Furthermore, while protein corona is influenced by the complexity of biological fluids, its composition significantly evolves from *in vitro* to *in vivo* environments, having a direct impact on trafficking of the particles. Nanoparticles designed for selective localization should be thoroughly analyzed with regard to their pharmacokinetics [10]. Targeted regions (e.g. tumors) as well as off-target organs should be investigated at the cellular level to validate cell-specific deposition of the particles and controlled release of their cargo. Non-invasive imaging techniques are often used to track *in vivo* biodistribution and localization of nanoparticles in organs. They obviously shed light on the pharmacokinetics of the particles; however, without cellular resolution of nanomedical applications, these data might lead to misinterpretation of the findings regarding cell-specific targeting. For future attempts, emerging techniques such as multistage delivery of nanomedicines may hold promise where each delivery step is dissected. For instance, Xu et al. [11] recently demonstrated cellular uptake of polymeric nanoformulations derived from micrometer-sized injectable nanoparticle generators and reported enhanced therapeutic efficacy. This example highlights the assets of a better-segmented approach in tackling multiple biological hurdles in efficient drug delivery *in vivo* [11].

Conclusion

Nanoparticle-based therapies have already shown remarkable therapeutic potential in life-threatening diseases such as cancer where they increase drug circulation times and lessen the side-effects of the conventional toxic agents. As the nanomedicine market grows, novel approaches are ever emerging. However, as nano-theranostic systems get more sophisticated, there are obvious challenges for nano-agents to move on from bench-to-bedside. Some of these pitfalls can be addressed and resolved by better designed preclinical approaches and more thorough characterization of nanomedical efficacy in preclinical *in vitro*, *in vivo* and *ex vivo* models. Setting up defined guidelines for preclinical testing of nanomedicines may contribute to increase the bench-to-bedside translation efficacy of innovative nanomedical approaches.

Conflict of interest

There is no conflict of interest for the article.

Acknowledgment

We would like to acknowledge **Nanosystems Initiative Munich (NIM)** for the funding.

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