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Editorial

Guiding Aspects Translating Nanomedicine

Luiza Ianny de Lima and João Paulo Figueiró Longo*

Institute of Biological Science - IB, Genetics and Morphology Department, University of Brasília - UnB, Brazil

***Corresponding Author:** João Paulo Figueiró Longo, Institute of Biological Science - IB, Genetics and Morphology Department, University of Brasília - UnB, Brazil.

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Abstract

As a prospect for the next years, we believe that nanomedicine could be widely translated to clinical practices based on chemotherapy reduction in toxicity provided by the technology. Oncology patients, who are the core point of all this process, can greatly benefit from adopting nanomedicines. In this way, several conventional chemotherapeutical drugs could be used in their nano-based generic form, with lower related toxicity, providing better results for patients. For this approach, doctors could adopt simple and easy production nanocarriers early to reduce the risks. During this process, new innovations with more complex technical structures could be added as confidence in nanomedicine advances.

Keywords: Nanomedicine; Toxicity; Clinical Translation

Nanomedicine is a specific scientific and technological topic that emerged in recent decades from the cooperation between professionals in the field of nanotechnology and medicine [1,2]. Originally, most nanotech researchers were from the institutes of physics and chemistry at universities. However, nowadays we have several institutes, departments, and post-graduate programs worldwide that are exclusively dedicated to Nanomedicine. In this contemporary organization, nanomedicine teams have a much more interdisciplinary profile.

High expectations related to nanomedicine started almost four decades ago, and are strongly related to very promising preclinical investigations conducted in the eighties [3,4]. At that time, reports described that some nano-sized macromolecules, such as nanoparticle drug carriers, could passively accumulate in solid tumors. This was a very important finding at the time, and brought up the possibility of specifically targeting tumor tissues, thus avoiding normal tissues. The hope was that a magic bullet specific for tumor targeting could be designed.

This phenomenon was described as the Enhanced Permeation and Retention (EPR) effect and is related to some pathophysiological patterns in tumor tissues [5,6]. This phenomenon was supported by some information related to the morphophysiological tumor characterization. For these tissues, blood vessels have tortuous, aberrant, and permeable pores that allow the passive flow of certain nano-sized structures [7]. This is the first part of the process, related to the enhanced passive permeability step. In addition, preclinical tumor tissues have a reduced number of lymphatic vessels, a fact that impairs tumor drainage, increasing the tumor's retention of materials that permeate the tumor tissues [8].

Given this context, the EPR effect is considered to be the seminal concept for Nanomedicine [6]. After that, thousands of papers

were published based on this concept, and several clinical trials were conducted with different types of nanoparticles. Despite all this effort, the concept has received significant criticism over the last few years. Among several concerns related to the EPR effect, one is that several nanoparticles that showed excellent pre-clinical results were not able to translate those promising results into clinical studies. Furthermore, in 2016, a meta-analysis paper identified that nanocarriers are delivered to tumor tissues at a rate close to 0.7% [9]. Thus, nanomedicine researchers have since then debated the topic, trying to identify the main points that should be addressed, in order to optimize this clinical translation process.

After several conferences and paper discussions, researchers have identified some points that should be considered on this path to translating nanomedicine. The first point to be highlighted is that this process is far from trivial, and any type of medicinal input will show this lack during innovation and clinical translation. The second is that even for the most studied nanocarriers, we still have some limitations in quality control between each industrial production. The third, and for us, the most important, the drawback is that the interactions between nanocarriers and biological systems are not completely understood at the moment, and several points should be addressed in this specific topic.

The first point that we consider is that the EPR effect which defines nanoparticle tumor accumulation as a passive phenomenon, is not a single argument that supports nanomedicine. However, the effect continues to work very well in pre-clinical studies, and also works in some types of clinical tumors. As an example, we present unpublished data (Figure 1) from our group showing the passive delivery of a fluorescent-labeled liposome to breast tumors in a mouse model. In Figure 1, we present a schematic view of the EPR effect and *in vivo* fluorescent imaging of the fluorescence accumulation close to the tumor regions in a tumor-bearing mouse (4T1). Following this discussion, it is almost a consensus that clinical tumors are highly heterogeneous, some more permeable than others [7,10,11], which contributes to the occurrence or not of the EPR effect. In other words, depending upon tumor type, localization, and individual patient characteristics, the EPR can contribute more or less to tumor targeting.

Figure 1: Schematic view of the EPR effect in vivo. (a) marking the liposomal nanocarrier with a fluorescent dye. (b) nanocarriers can be accumulated in the tumor through a passive mechanism known as the EPR effect, because of the increased vascular permeability in the tumor region (c) in vivo fluorescent imaging of the fluorescence nanocarrier liposome accumulation close to the regions near the tumor and in the tumor in a mouse bearing murine breast cancer (4T1).

Just as an example, in a previous article [12], our group followed the EPR effect in the same group of tumor-bearing mice for four consecutive weeks. During this period, several pathophysiological patterns of the tumors evolved over time, and this process significantly influences the EPR effect. In this article, we confirmed that tumor heterogeneity, which changes over time, is an important aspect that affects the absorption of nanocarriers. These results can be explained and supported by the EPR effect. However, recently some interesting reports have shown that the EPR effect should not be the only mechanism involved in the delivery of nanoparticles to tumor tissues [2,9,13].

In this article, it was identified that the tumor vasculature is mainly continuous and the gaps occur with a very low frequency. This observation raises a controversial issue in the initial theory of the EPR effect [13]. Furthermore, the paper also reports that most of the nanoparticle absorbed by tumor tissues were captured by

the active transport process. Following this idea, the authors show that the traffic of nanoparticles to solid tumors is not mediated by passive mechanisms, such as suggested by the EPR effect [13]. In a perspective view for nanomedicine, this initial report will bring up several discussions regarding the mechanisms of tumor targeting by using nanotechnology. In terms of scientific interpretation, we believe that the next few years will be quite fruitful in terms of research in the area.

Furthermore, the real understanding of this targeting and delivery process can help researchers to highlight other nanomedical areas that were marginally explored, especially for clinical applications. For instance, nanomedicine provides other benefits besides the EPR effect [1]. In particular, we can cite nanocarriers as [1] a suitable pharmacotechnical solution that increases hydrophobic drugs' solubility [2]; an important technological tool for increasing drug circulation time, by avoiding kidney circulation and excretion [3]; protective capsules for carried drugs, thus increasing the chances of targeting, preventing enzymatic degradation; and finally [5] in reducing the toxicity of conventional drugs, thus improving the tolerance of chemotherapy [14].

From the patient's point of view, the reduction in side effects provided by nanomedicine is probably one of the most important features of this technology. For sure, chemotherapy's adverse effects are the main problem affecting a patient's quality of life during oncology treatment. In addition to all the suffering related to the cytotoxic drugs, doctors have to change or adapt the drug cocktail depending on the toxic-limiting dosage. In our experience with pre-clinical models, it is possible to significantly improve dose-limiting toxicities of chemotherapy drugs, thus reducing side effects and improving efficacy. In a previous study, using a nanoemulsion formulation containing doxorubicin, we showed that by using the nanocarrier it was possible to use twice the concentration of doxorubicin without observing the adverse effects of doxorubicin in its free form [14].

As a prospect for the next years, we believe that nanomedicine could be translated to clinical practices based on this reduction in toxicity provided by the technology (Figure 2). Oncology patients, who are the core point of all this process, can greatly benefit from adopting nanomedicines. In this way, several conventional chemotherapeutical drugs could be used in their nano-based generic form, with lower related toxicity, providing better results for patients. For this approach, doctors could adopt simple and easy production nanocarriers early to reduce the risks. During this process, new innovations with more complex technical structures could be added as confidence in nanomedicine advances.

Figure 2: Nanomedicine: Tolerance of drugs. Oncologic treatment using nanomedicine could be translated to clinical practice, based on nanocarriers as a suitable pharmacotechnical solution for treatment with autotoxic drugs. The protective capsules for carried drugs increase the chances of targeting specific cells, thus reducing the toxicity of conventional drugs. Oncology patients can greatly benefit from nanomedicines improved in this way.

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Declaration of Conflicting Interests

The authors declares that there is no conflict of interest.

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