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Nanomedicine and thermal therapies: where are we going?

I am very pleased to serve as Editor for this special issue of the International Journal of Hyperthermia entitled *Nanomedicine and thermal therapies: where are we going?* [1] I expect that readers with different interests (biological, physical or technological) and distinct backgrounds, spanning from scientists, clinicians and engineers, will benefit from the contributions of this issue that discuss new directions on nanomedicine and nanoparticle-mediated thermal therapies.

Nanomedicine deals with medical applications using nanotechnology, with interest on prevention, monitoring, diagnosis and/or therapy of diseases. Several nanostructures, organic (liposomes, nanocapsules, micelles, etc) or inorganic (gold, iron oxide, silica, etc), with distinct shapes (spheres, cubes, rods, etc) and dimensions, can be used to achieve this goal. On the other hand, thermal nanomedicine deals with nanoparticle-mediated heat therapies, where two modalities play a significant role, named magnetic nanoparticle hyperthermia (MNH) and photothermal therapy (PTT). MNH arises from the interaction of nanoparticles with ac magnetic fields (in the radio frequency region), while PTT occurs through the interaction with non-ionizing electromagnetic radiation (near-infrared region). There is a lot of expectation on these medical nanotechnologies, but clinical translation has been limited up to now.

Perhaps the most popular clinical nanomedicine applications are related to drug delivery, where Doxil® (pegylated liposome containing doxorubicin – approved in 1995) and Abraxane® (protein aggregates containing paclitaxel – approved in 2005), among others, play a role. The nanodrugs enhanced drug delivery (although not as much as expected [2]) and drug tolerability, while in some cases, successfully improved the quality of life of patients (e.g. reduction of cardiomyopathy by Doxil®). Thermosensitive nanoparticles have also been designed for heat-triggered drug release, for example ThermoDox® (combined with radiofrequency ablation). However, so far, no significant impact on the overall survival of patients has been observed [3], but hopefully this might change in the near future due to progress in the field.

The mechanism of nanoparticle transport inside the body is under intense debate, where active transport, not expected by the Enhanced Permeability and Retention (EPR) effect, has been reported [4]. Also, the differences between humans and animal model tumors are better understood today, and tumor microenvironment knowledge has grown. So, it is becoming clear that there is a complex interaction between the nanostructures, the host (patient/animal model) environment and the immune system [5]. So, can we take advantage of this to treat diseases? On the other hand, are there advantages on nanoparticle-mediated heat therapies? What are the challenges for more efficient clinical translation of PTT and/or MNH? Can thermal nanotherapies impact on patient survival?

In this special issue we are particularly interested on therapeutic applications using nanostructures, and will discuss the possible therapeutic benefits of using nanoparticles, with or without nanoparticle-mediated heat generation. The contributions of the special issue deliberate some future directions for nanomedicine (clinical) research and development, and present some challenges and technologies that might have impact on clinical translation.

Inspired by the important role of nanoparticle-immune interactions, some articles focus on nano-immunotherapy, mediated or not by heat delivery. One of the goals of the contributions was to close the gap between materials-like and biological/immunological scientists/clinicians. Mao et al. introduce some immunological concepts while discussing the role of *in situ* vaccination (ISV) with nanoparticles (NPs) for cancer immunotherapy [6]. The authors detail how a tumor's microenvironment inhibits immune cells through immunosuppression, explain how ISV can modulate tumor microenvironment to induce anti-tumor immune responses, and consider mechanisms of immunogenic cell death. Gorbet et al. focus on reviewing the types of nanoparticles used for ISV against cancer [7]. The authors describe several synthesized nanoparticles (liposomes, inorganic NPs, polymeric NPs, etc), biologically derived NPs (virus, bacteria-based NPs), as well as heat-mediated (PTT and MNH) NPs for ISV.

On the other hand, another important contribution arises from Balakrishnan et al. that indicates the potential of nanoparticle-based PTT to enhance the effect of immune checkpoint blockade (ICB) therapy [8]. The review presents information about the mechanisms of action of ICB therapy, as well as the importance of a combination therapy (ICB + PTT). Three classes of nanoparticles for PTT combined with ICB in preclinical models are reviewed, namely metallic inorganic NPs, carbon-based Nps and organic dyes, which illustrate the potential to improve cancer immunotherapy.

PTT clinical studies have just started [9], and one expects that emerging biomedical approaches would result in a wider clinical application for PTT or other light-activated therapies, as for example photodynamic therapy (PDT) [10]. Indeed, Vendette et al. present a clinical study for the treatment of intraepithelial cervical neoplasia with PDT using chitosan nanocapsules containing a phthalocyanine-based photoactive agent [11]. The trial demonstrates that treatment is feasible and safe, although a large randomized clinical study is necessary to establish efficacy. So far, most PDT studies have not yet considered heat-mediated effects that could be explored by researchers on thermal medicine in order to improve clinical impact.

The method of administration of antibodies, e.g. systemic delivery for ICB, or NPs for PTT and/or MNH is very important to the success of the therapy. In an original research contribution, Yang et al. demonstrate that systemically delivered antibody-coated magnetic nanoparticles (MNPs) have a different biodistribution from that found in their counterpart plain MNPs, which leads to a less toxic formulation after whole-body MNH therapy due to distinct off-target effects [12]. The authors present evidence that IgG-coated MNPs interact more strongly with cells in the spleen than plain NPs, which corroborates with the importance of better understanding of the nanoparticle-immune cell interactions.

MNH therapy had been proposed by Gilchrist et al. in 1957 [13], but clinical translation was only achieved 10 years ago. The nanomedicine NanoTherm® therapy holds the European CE certificate to treat brain tumors when combined with radiotherapy [14]. But the use in the clinic has been limited, although some other tumor type (prostate) clinical studies are in progress. Possible reasons for this are discussed by Rodrigues et al., although the review focus on preclinical studies with MNH [15]. The authors mention the necessity of better low-field magnetic nano-heaters (that could avoid undesirable nonspecific heating arising from free-current loss), review computer simulations studies for treatment planning, and emphasize the importance and challenges of developing noninvasive thermometry for MNH, factors that could result in clinical impact.

On the other hand, the role of data selection on the determination of heating efficiency during MNH, also known as SAR (specific absorption rate), is discussed by Ring et al. [16]. Data from two distinct Labs are analyzed, where the authors compare SAR calculation using two methods, Time-Rise and Box-Lucas fitting. At the end of the article, the researchers provide recommendations to improve experimental accuracy and precision. This discussion is under intense debate in the community, since this is an important issue for standardization of protocols for MNH.

In another original research study, Attaluri et al. discuss the advantage of MNH to treat large tumors after nanoparticle intratumoral injection [17]. The authors present MNH preclinical studies in a pancreatic xenograft tumor model, and include computer simulations analysis. They solve the bioheat equation for a human-scale multilayer model, and demonstrate that pulsed alternating magnetic fields can minimize nonspecific eddy current heating. This is an interesting idea that explores higher field regimes and might impact MNH clinical translation.

Further, Capistrano et al. examine how to determine noninvasively the intratumoral thermal dose during MNH [18]. Preliminary preclinical data in a murine tumor model is presented. The authors combine surface temperature measurements using infrared thermometry, develop a multifunctional magnetic nanocarrier to obtain the nanoheaters intratumor localization using the near-infrared image technique named fluorescence molecular tomography (FMT), and perform computer simulations in order to establish a method for determining noninvasively intratumoral thermal dose during MNH. This is probably the first time this information is obtained in MNH therapy. The method is able to explain the long-term preclinical outcome of the animals, and implies that the intratumor thermal dose can be very heterogeneous in MNH, which suggests that the clinical approach that uses few fiber-optic thermometers might be limited and can impact patient outcome.

Image-guided strategies are very important for the success of nanomedicine therapies. The previous work used FMT for magnetic particle localization, which determines the fluorescent dye position (attached to the particle's surface) and not exactly the magnetic nanoheaters position. In 2005, Gleich and Weizenecker propose a new imaging method that uses the nonlinear magnetic response of nanoparticles for imaging [19]. The new image modality is known as magnetic particle imaging (MPI), and is able to determine the magnetic tracers position. Recently, in 2018, one of the pioneers in the field of MPI, demonstrated in a preclinical model that one can also combine MPI with MNH for cancer therapy [20]. The authors make an interesting contribution to this special issue. In this review, Lu et al. discuss how combining MPI with MNH can be used for millimeter-precision localized heating, avoiding undesirable heating of off-target tissues, and also briefly discuss how this new technology can be scaled up to human-sized MPI-MNH scanners [21]. The advance of this new technique might have a great impact in clinical translation of MNH. Not only because of localized heating control, but may be also because information for noninvasive thermometry might be achievable in the future by applying this technology.

In the final contribution, Fuentes et al. discuss how to use computed tomography (CT) perfusion imaging data, through the monitoring of nanoparticle transport within porous tissue, to calibrate a mathematical model that is able to predict tissue properties, for example perfusion [22]. The approach is compared to an extended Tofts model (control) and is applicable to typical flow rates of nanoparticle systemic delivery. This is an example of an imaging-guided strategy that might be useful in treatment planning for the convection enhanced delivery of nanomedicine, at least for passive nanoparticle transport. The authors also include a brief discussion about how to extend the model to active nanoparticle transport.

Finally, I would like to thank all the researchers that accepted our invitation to make these valuable contributions to this special issue on nanomedicine. I should also thank the reviewers of those articles that through their reports gave directions to the authors on enhancing the clarity and the quality of the scientific reports. It is my hope that readers will also be challenged by those contributions and inspired to develop new ideas of research that potentially can impact clinical translation of nanomedicine.

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