Journal of Controlled Release 298 (2019) 213

Contents lists available at ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Transcending nanomedicine to the next level: Are we there yet?

Nanomedicine has progressed significantly during the last two decades of intensive research. The advances in nanoparticle-based drug delivery systems, mostly to deliver drugs to solid tumors, have been breathtaking. It is common to see several papers on nanomedicine in each issue of the Journal of Controlled Release. In this issue, there are two articles that represent highly innovative drug delivery systems [1,2].

The paper by Professors Luo, Tian, and Battaglia and their coworkers demonstrated intra-tumoral administration of thermosensitive nanocomposite gel for two-photon photodynamic therapy [1]. An efficient pair of probes were applied to adsorb two-photon radiation and up-convert it to excite a photosensitizer that in turn induced localized tumor apoptosis/necrosis. The two hydrophobic molecules were encapsulated in biodegradable mPEG-PDLLA micelles with dual effects of solubilizing the active drugs and keeping them close enough to allow the non-radiative energy transfer between them. This enables up-converting of near-infrared highly penetrant radiation into a localized release of reactive oxygen species. The loaded micelles were further mixed with a thermosensitive PEO-PPO-PEO (Pluronic F127) micellar gel that allows injection as a liquid before forming a gel at body temperature for maximized radiation and reduced phototoxicity. In another article, Professor Yu-Kyoung Oh and her team have investigated a way to overcome the current challenges in thernanostic nanomedicine [2]. Professor Oh's team designed an imaging-combined chemotherapy platform that is selectively and sequentially activated in the tumor microenvironment. To achieve selective activation of the imaging probe, Professor Oh's team took advantage of matrix metalloproteinase (MMP) overexpression in the tumor microenvironment and the imaging-probe–quenching effect of graphene oxide nanosheets. In the environment lacking MMP, the system remained neither fluorescent nor killing cells. However, in the tumor microenvironment with MMP, the system was selectively activated by the MMP-cleaved imaging probe. The cascaded exposure of the shielded anticancer molecule enabled imaging signal-dependent anticancer effect in the tumor microenvironment. The shielding of anticancer effect in blood circulation and imaging-cascaded selective de-shielding of anticancer drugs in tumor microenvironment enable to control the undesirable interaction of anticancer drug with normal tissues.

In the height of the exciting formulations designed to target tumors, we may pause a little while to enjoy the achievement that the field collectively has made. While we all enjoy the vista of the smart drug delivery systems, we may ask ourselves "what's next"? In fact, there are a few questions to ask. First, the majority of nanomedicine research has been focused on tumor-targeted drug delivery. Despite many other important diseases, this unreasonably-biased focus of nanomedicine only on tumor treatment requires our attention. It is necessary to explain why this has been happening and what the future of nanomedicine may be, and whether we can define what the future of nanomedicine should be. What can possibly explain almost exclusive dedication of nanomedicine to tumor-targeted drug delivery? Second, the tumor-targeting research has produced thousands of papers, but why are we still not able to treat tumors or cancers in humans? We all understand that there are hurdles to translate any of the promising drug delivery systems from the mouse studies to the clinic, but, how many more years do we have to wait to see the translation to humans? All too often, we do not give serious consideration to the differences between murine and human tumors. The differences in the blood volumes and tumor sizes between mice and humans are staggering, and yet we are prone to extrapolate the mouse data to clinical applications.

Another important question to ask is "are we critical enough to the progress we have made"? Are we able to separate our emotion from our own research data? We have to keep asking ourselves whether what we think we know is true or not. If we continue our current way of doing nanomedicine research, we will undoubtedly produce tens of thousands of more research papers. But what about cancer patients who are facing dreadful chemotherapy and pain today? The large number of research papers cannot cure them. How long can we say to them that what we are doing has a lot of potential? Are we able to say to our loved ones who happen to have cancer "please wait, new treatments are coming"? We, as scientists, have a big responsibility to spend the research funding in a very responsible way. Research finding is not other people's money. It is our own money and we should use it to really make a difference in human lives, instead of simply making a difference in the number of publications. We need to keep going, and we should never surrender to the difficulties we face. But do we know exactly where we are going and the source of the difficulties? Questioning our own most cherished beliefs is the ultimate form of positive thinking that will lead us to better research.

References

[1] L. Luo, Q. Zhang, Y. Luo, Z. He, X. Tian, G. Battaglia, Thermosensitive nanocomposite gel for intra-tumoral two-photon photodynamic therapy, J. Control. Release 298 (2019) 99–109.

[2] G. Shim, Q.-V. Le, J. Suh, S. Choi, G. Kim, H.-G. Choi, Y.B. Kim, R.B. Macgregor, Y.-K. Oh, Sequential activation of anticancer therapy triggered by tumor microenvironment-selective imaging, J. Control. Release 298 (2019) 110–119.

Kinam Park
Purdue University
Biomedical Engineering and Pharmaceutics
West Lafayette, IN 47907, USA
E-mail address: kpark@purdue.edu

https://doi.org/10.1016/j.jconrel.2019.02.040