IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2016; 6(9): 1274-1276. doi: 10.7150/thno.16479

Editorial

Nanostructure-Based Theranostic Systems

Jun Wang[1,2,3*✉] and Honggang Cui[4,5,6*✉]

1. Hefei National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, Hefei Anhui 230027, PR China
2. CAS Center for Excellence in Nanoscience, School of Life Sciences and Medical Center, University of Science and Technology of China, Hefei Anhui 230027, PR China
3. Innovation Center for Cell Signaling Network, University of Science and Technology of China, Hefei, Anhui 230027, PR China
4. Department of Chemical and Biomolecular Engineering, and Institute for NanoBioTechnology, The Johns Hopkins University, 3400 North Charles Street, Baltimore, Maryland 21218, United States
5. Department of Oncology and Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, United States
6. Center for Nanomedicine, The Wilmer Eye Institute, Johns Hopkins University School of Medicine, 400 North Broadway, Baltimore, Maryland 21231, United States.

* **Guest editors**, *Theranostics*

✉ Corresponding authors: jwang699@ustc.edu.cn; hcui6@jhu.edu

Received: 2016.06.14; Accepted: 2016.06.14; Published: 2016.06.18

Abstract

This themed issue continues the focus on the recent developments of nanoscaled theranostic systems for early and accurate disease diagnosis, especially cancer diagnosis, as well as effective cancer treatment and management.

Nanotheranostics, which integrates both therapeutic and diagnostic capabilities into one single nanoplatform, has provided exciting prospects for optimizing treatment outcomes in cancer and other diseases. However, the translation of current nanotheranostic systems into medical practice is still a path strewn with tremendous obstacles. This Themed Issue on **NanoTheranostics** offers a platform for the entire nanomedicine community to exchange their ideas and visions. The first part of this Themed Issue was successfully launched in the July Issue, and has received considerable attention. This is the second part of the special issue, featuring fifteen contributions from leading experts in related fields and comprising six reviews and nine original research articles. In these contributions, the authors either shared their perspective on future directions, or discussed their most recent advancements in associated topics.

To overcome the limitations of conventional nanoplatforms such as uncontrolled cargo release and insufficient tumor drug deposition, various intelligent delivery systems that can respond to external or internal stimuli have been designed in recent decades. Gu and coworkers provided an overview on these intelligent delivery systems for controlled delivery of diagnostic and/or therapeutic agents, and also discussed the obstacles that hinder their clinical translation [1]. Aimed at addressing the same issue, Li and his team introduced a regional delivery strategy using image-guided interventional nanotherapeutics for the management of pancreatic carcinoma (PC). They suggested that interventional procedures may help circumvent the major barriers confronting poor drug delivery to PC [2].

Next, Jo et al. highlighted recent progress in the development of nanotheranostics for cancer diagnosis and therapy. This review showcased the viability of using a single nanoplatform to accommodate cancer therapeutics with various diagnostic modalities such as optical imaging, magnetic resonance imaging (MRI), computed tomography/positron emission tomography (CT/PET) imaging, and ultrasound imaging for potential personalized medicine [3]. Then, Lu and his team specified recent developments in liposomal formulations for disease diagnosis and

therapy. They also summarized the latest understanding towards the fundamental physical interactions between liposomes and biological components, and provided their vision on the future directions of this field [4].

The detection, isolation, and characterization of circulating tumor cells (CTCs) may provide critical information on cancer progression and staging. On this topic, Chen et al. provided a comprehensive review on the development of a series of NanoVelcro Assays for CTC enumeration, phenotyping, genotyping and expression profiling, and highlighted their clinical applications in various cancer types, including prostate cancer, pancreatic cancer, lung cancer, and melanoma [5]. Tan and coworkers focused on cell-based SELEX (systematic evolution of ligands by exponential enrichment) technology for aptamer selection, identification, and validation as well as potential applications in biomarker discovery and cancer diagnosis and therapy. They highlighted the importance of accurate detection and understanding of the molecular events in diseased cells for timely disease diagnosis and therapy [6].

Introducing targeting capability to nanotherapeutics is believed to be able to improve their delivery performance. Jiang and coworkers described a strategy of attaching phenylboronic acid (PBA) groups onto chitosan (CS) nanoparticles to mediate active tumor targeting for improved tumor treatment. They demonstrated that the incorporation of PBA moieties not only bestowed the nanoparticles with a zwitterionic surface that increased particle penetration in the tumor matrix, but also endowed the particles with an active targeting capability, which enabled prolonged drug retention at tumor sites. These two factors contributed to the improved antitumor activities of PBA-CS nanoparticles in both *in vitro* and *in vivo* studies [7]. In parallel with active targeting, imparting nanoparticle with stimuli-responsiveness is another targeting strategy. Gu and his colleagues reported a supramolecular PEGylated dendritic system as a pH/redox dual-responsive theranostic nanoplatform for efficient platinum-based drug delivery and near-infrared (NIR) tracking. The *in vivo* study demonstrated that the dual-responsive theranostic system had comparable antitumor effect to clinical cisplatin, but with reduced adverse effects [8].

Recently, nanoparticles-based combination therapy through simultaneous delivery of more than one agents to the same location has received great attention due to the potential for synergistic effects. Shi and his group reported the construction of a crosslinked polyion complex (PIC) micelle to co-deliver doxorubicin (DOX) and (-)-epigallocatechin-3-O-gallate (EGCG) for overcoming cardiotoxicity and multidrug resistance. In their design, EGCG could function synergistically with DOX to simultaneously improve the antitumor effect and reduce drug-associated cardiotoxicity [9]. Along the same lines, Lin et al. developed a novel multifunctional nano-platform for targeted delivery of heat, reactive oxygen species (ROS) and a heat shock protein 90 (Hsp90) inhibitor for combination therapy against prostate cancer. Their nanoporphyrin-based delivery system could generate efficient heat and ROS simultaneously with light activation at the tumor sites for photothermal and photodynamic therapy, meanwhile the encapsulated Hsp90 inhibitors could decrease the levels of pro-survival and angiogenic signaling molecules induced by phototherapy, which further sensitized cancer cells to phototherapy [10].

Cancer screening and early detection is undoubtedly a vital step towards effective cancer treatment. However, the accurate and specific diagnosis of cancer in its early stage remains a formidable challenge. Towards this end, Trau and his colleagues presented a novel, rapid and cost-efficient assay called "FusBLU" to detect a TMPRSS2 (Exon 1)-ERG (Exon 4) gene fusion event that occurred specifically in prostate cancer. Their assay allowed direct detection from a urine sample and possessed a low detection limit. More importantly, the colorimetric readout was detectable by the naked eye, allowing for a quick yes/no evaluation of gene fusion presence [11]. Differing from the direct marker detection in urine, Bao and coworkers described an iron oxide nanoparticle (IONP)-linked immunosorbent assay (ILISA) for detecting disease biomarkers such as IgA, IgG, IgM, and C-reactive protein (CRP) in human serum. According to their results, ILISA can achieve sub-picomolar detection sensitivity, and all four markers can be accurately quantified over a large dynamic range, demonstrating that ILISA is a versatile nano-platform for sensitive and reliable detection of biomarkers in biomedical research and clinical applications [12].

Real-time *in vivo* visualization of tumor cells and their adjacent tumor microenvironment could provide useful information on cancer progression or suppression processes. Fluorescence imaging offers a powerful tool to label tumor cells or other components to make them visible. In this regard, Cheng and coworkers proposed a versatile dibenzocyclooctyne (DBCO)-azido mediated copper-free click chemistry approach to metabolically labeling cancer cells. In contrast to conventional labeling tactics, the authors first labeled cancer cells with DBCO-bearing unnatural sugars, and then

introduced multifunctional azido-modified silica nanoconjugates for subsequent conjugation. Their strategy could significantly improve the tumor targeted accumulation of nanoparticles for effective cell labeling and potential delivery of therapeutic agents [13]. In another study, Zhang and his team constructed a fluorescent model antigen named tfRFP to visualize the performance of immunocytes as they attack and selectively eliminate tfRFP-expressing tumors *in vivo* [14].

Pun and coworkers optimized the structure and improved serum stability of a M2 macrophage-targeting peptide (M2pep), which could target and deliver a pro-apoptotic KLA peptide to M2-like tumor associated macrophages (TAMs). Their studies demonstrated that the cyclic M2pep (RY) outperformed M2pep in tumor localization and selective accumulation in M2-like TAMs in both the CT-26 and 4T1 breast carcinoma models [15].

In closing, with 27 contributions (15 in this Issue and 12 in the July Issue) from leading researchers in the field of nanoscience, molecular imaging, drug delivery, and biomedical engineering, this thematic issue on Nanotheranostics should have provided an overview on the recent progress in the development of nanotheranostic systems. We understand that, given the great diversity of the topic, this collection is representative rather than comprehensive. It is our hope that the perspectives offered by the authors have laid out a foundation for more provocative discussion on, or perhaps inspiration of, the future development of nanotheranostic systems. Once again, we would like to express our sincere gratitude to all the authors that have contributed to this topic.

References

[1] Liu D, Yang F, Xiong F, Gu N. The Smart Drug Delivery System and Its Clinical Potential. Theranostics 2016; 6(9): 1306-1323.

[2] Li JJ, Liu FY, Gupta S, Li C. Interventional Nanotheranostics of Pancreatic Ductal Adenocarcinoma. Theranostics 2016; 6(9): 1393-1402.

[3] Jo SD, Ku SH, Won YY, Kim SH, Kwon IC. Targeted Nanotheranostics for Future Personalized Medicine: Recent Progress in Cancer Therapy. Theranostics 2016; 6(9): 1362-1377.

[4] Xing H, Hwang K, Lu Y. Recent Developments of Liposomes as Nanocarriers for Theranostic Applications. Theranostics 2016; 6(9): 1336-1352.

[5] Chen J-F, Zhu YZ, Lu Y-T, Hodara E, Hou S, Agopian VG, *et al.* Clinical Applications of NanoVelcro Rare-Cell Assays for Detection and Characterization of Circulating Tumor Cells. Theranostics 2016; 6(9): 1425-1439.

[6] Lyu YF, Chen G, Shangguan DH, Zhang LQ, Wan S, Wu Y, *et al*. Generating Cell Targeting Aptamers for Nanotheranostics Using Cell-SELEX. Theranostics 2016; 6(9): 1440-1452.

[7] Wang X, Tang H, Wang CZ, Zhang JL, Wu W, Jiang XQ. Phenylboronic Acid-Mediated Tumor Targeting of Chitosan Nanoparticles. Theranostics 2016; 6(9): 1378-1392.

[8] Li YK, Li YC, Zhang X, Xu XH, Zhang ZJ, Hu C, *et al.* Supramolecular PEGylated Dendritic Systems as pH/Redox Dual-Responsive Theranostic Nanoplatforms for Platinum Drug Delivery and NIR Imaging. Theranostics 2016; 6(9): 1293-1305.

[9] Cheng TJ, Liu JJ, Ren J, Huang F, Ou HL, Ding YX, *et al.* Green Tea Catechin-Based Complex Micelles Combined with Doxorubicin to Overcome Cardiotoxicity and Multidrug Resistance. Theranostics 2016; 6(9): 1277-1292.

[10] Lin T-Y, Guo WC, Long QL, Ma AH, Liu QQ, Zhang HY, *et al.* HSP90 Inhibitor Encapsulated Photo-Theranostic Nanoparticles for Synergistic Combination Cancer Therapy. Theranostics 2016; 6(9): 1324-1335.

[11] Koo KM, Wee EJH, Trau M. Colorimetric TMPRSS2-ERG Gene Fusion Detection in Prostate Cancer Urinary Samples via Recombinase Polymerase Amplification. Theranostics 2016; 6(9): 1415-1424.

[12] Zhang LL, Tong S, Zhou J, Bao G. Accurate Quantification of Disease Markers in Human Serum Using Iron Oxide Nanoparticle-linked Immunosorbent Assay. Theranostics 2016; 6(9): 1353-1361.

[13] Wang H, Tang L, Liu Y, Dobrucka IT, Dobrucki LW, Yin LC, *et al.* In Vivo Targeting of Metabolically Labeled Cancers with Ultra-Small Silica Nanoconjugates. Theranostics 2016; 6(9): 1467-1476.

[14] Yang F, Liu S, Liu XL, Liu L, Luo MJ, Qi SH, *et al.* In Vivo Visualization of Tumor Antigen-containing Microparticles Generated in Fluorescent-protein-elicited Immunity. Theranostics 2016; 6(9): 1453-1466.

[15] Ngambenjawong C, Gustafson HH, Pineda JM, Kacherovsky NA, Cieslewicz M, Pun SH. Serum Stability and Affinity Optimization of an M2 Macrophage-Targeting Peptide (M2pep). Theranostics 2016; 6(9): 1403-1414.