Perspective

Jiajia Xiang, Shiqun Shao, Zhuxian Zhou* and Youqing Shen*

"One-for-All" approach: a black technology for nanomedicine development?

https://doi.org/10.1515/mr-2023-0003
Received January 10, 2023; accepted March 17, 2023;
published online April 26, 2023

Abstract: Cancer nanomedicines require different, even opposite, properties to voyage the cascade drug delivery process involving a series of biological barriers. Currently-approved nanomedicines can only alleviate adverse effects but cannot improve patient survival because they fail to meet all the requirements. Therefore, nanocarriers with synchronized functions are highly requisite to capacitate efficient drug delivery and enhanced therapeutic efficacies. This perspective article summarizes recent advances in the two main strategies for nanomedicine design, the All-in-One approach (integration of all the functions in one system) and the One-for-All approach (one functional group with proper affinity enables all the functions), and presents our views on future nanomedicine development.

Keywords: cell membrane affinity; clinical translation; nanomedicine; One-for-All; transcytosis.

Successful delivery of therapeutic agents (e.g., chemotherapeutic drugs, nucleic acids, antibodies, etc.) to the target site is the major challenge for any disease treatment, including cancer. Nanoformulation of the therapeutic agents, e.g., nanomedicine, can improve their solubility, pharmacokinetics, disease-targeting capacities, and drug release manners, thus enhancing delivery efficiency [1]. Cancer nanomedicines are designed to passively target tumor tissues by the enhanced pearmeability and retention (EPR) effect, which is the gold standard principle of nanoparticle-based cancer drug delivery. Unfortunately, the current EPR-based cancer nanomedicines have failed to achieve high therapeutic efficacy in patients [2]. Although over twenty nanoformulations have been approved for clinical use, including Doxil (liposomal doxorubicin), Abraxane (albumin-bound paclitaxel), and Onivyde (liposomal irinotecan), they only alleviate some adverse effects but cannot improve patient survival [3]. A meta-analysis study showed that less than 1% of the administrated nanoparticles could be delivered to the tumor tissues [4]. The heterogeneous EPR effect and complex biological barriers have greatly hindered the delivery of cancer nanomedicines into tumors and resulted in limited therapeutic efficiency. Thus, it is highly requisite and urgent to develop innovative nanocarriers with integrated and synchronized functions for efficient cancer drug delivery.

The cancer drug delivery process comprises the following steps, including (1) circulation in the blood compartment, (2) extravasation from the tumor vasculature into the extracellular matrix, (3) penetration into the tumor parenchyma, (4) entry into tumor cells, (5) transport to the subcellular targets, and (6) drug release [5]. To achieve high delivery efficiency, nanomedicines are required to have different or even opposite properties in each step. For instance, nanomedicines should be resistant to protein to avoid the mononuclear phagocyte system (MPS) sequestration for long blood circulation; however, they are also required to be adhesive to cells to facilitate cellular internalization [6]. Moreover, the drug molecules should be retained tightly during blood circulation to prevent unwanted leakage into normal tissues but released efficiently at the site of interest to elicit the therapeutic effects. In addition, the size of nanomedicine also has different impacts on blood circulation and tumor penetration, wherein about 100 nm nanomedicines may favor circulation, but < 30 nm ones may exhibit better tumor penetration [7]. However, none of the approved nanomedicines meet all the requirements, which can explain their low cancer delivery efficiency and limited clinical outcomes.

To enhance the therapeutic efficacy, nanomedicines are designed with sophisticated structures to enable spon-

***Corresponding authors: Zhuxian Zhou and Youqing Shen**, Zhejiang Key Laboratory of Smart Biomaterials and Center for Bionanoengineering, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou 310027, Zhejiang Province, China, E-mail: zhouzx@zju.edu.cn (Z. Zhou), shenyq@zju.edu.cn (Y. Shen). https://orcid.org/0000-0003-1837-7976 (Y. Shen)
Jiajia Xiang and Shiqun Shao, Zhejiang Key Laboratory of Smart Biomaterials and Center for Bionanoengineering, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou, Zhejiang Province, China; and ZJU-Hangzhou Global Scientific and Technological Innovation Center, Zhejiang University, Hangzhou, Zhejiang Province, China

Open Access. © 2023 the author(s), published by De Gruyter. BY-NC-ND This work is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.

taneous property transitions in response to various endogenous and/or exogenous stimuli at specific delivery steps [8], i.e., the All-in-One approach (Figure 1a). Specifically, nanomedicines are synchronized with multiple functions to realize "stealthy" in circulation and "sticky" in tumor tissue by surface transition strategies, including reversible functionalization with polyethylene glycol (PEG) or zwitterionic molecules, hiding/exposing of targeting and functional groups, and surface-charge reversal. Nanomedicines have also been engineered with high PEG densities, changeable sizes or shapes, or tumor-penetrating moieties to promote infiltration in tumor tissues that feature high cell density, dense extracellular matrix, and hyperosmotic pressure. Strategies to remodel the tumor microenvironment, including normalizing tumor vasculatures, degrading dense extracellular matrix, and lowering the interstitial fluid pressure, have been explored to improve nanomedicines' penetration in tumors [9]. However, this All-in-One approach falls into a dilemma that the complicated composition of nanomedicines may enhance therapeutic efficacies but also increase the difficulty of meeting good manufacturing practices (GMP) and cause varied pharmacokinetics between each batch.

For cancer nanomedicine design, how to circumvent the dilemma of reducing structural complexity or enhancing the delivery efficiency? The successful stories of viral vectors in clinical translation may provide many insights. Viral vectors are complex but precise assemblies of multiple viral proteins. Many drugs based on viral vectors have been extensively explored in clinics or even gained regulatory approval for disease treatment, ranging from vector-based cancer therapies to treating monogenic diseases with life-altering outcomes [10]. What we can learn from these stories is that the integrated nanomedicines still hold promise in clinical translation if they can form precise structures made of clinically approved building blocks (Excipientability) and can be large-scale produced in accordance with GMP guidelines (Scale-up ability) as well as provide sufficient therapeutic benefits (Capability), i.e., the CES elements in terms of efficacy, safety, and quality requirements for clinically translated nanomedicines [11]. Alternatively, simplifying the structure but retaining the functions of nanomedicines may make it closer to clinical translation. As opposed to the All-in-One approach, an ideal strategy would be the

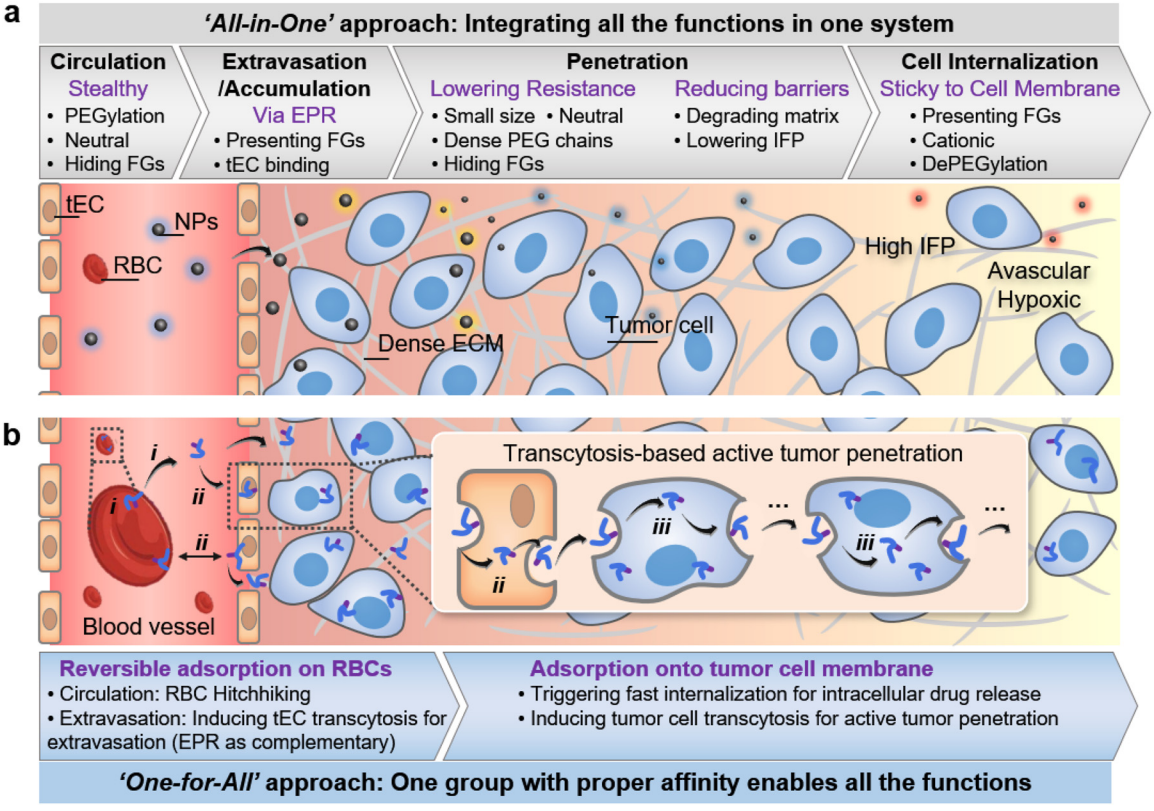

Figure 1: Comparisons of the current "All-in-One" approach (a) for nanomedicine design with the herein proposed "One-for-All" strategy (b). ECM, extracellular matrix; NPs, nanoparticles; FGs, functional groups; RBC, red blood cell; IFP, interstitial fluid pressure; tEC, tumor capillary endothelial cell.

One-for-All strategy, where the nanocarrier contains only one functional moiety but enables all the properties needed for the delivery process (Figure 1b). The structural simplicity would facilitate robust reproducibility of the corresponding nanomedicines and ease the *in vivo* characterizations, promising a high potential for clinical translation.

We have recently demonstrated a phospholipid-affinitive poly (tertiary amine-oxide) (PTAO) carrier as the first proof of this concept [12–14]. PTAO had a zwitterionic surface that was resistant towards protein binding, while it could reversibly bind to cell membranes by forming weak hydrogen bonds with the hydrophilic heads of phosphatidylcholine and phosphatidylethanolamine. After intravenous administration, PTAO could hitchhike on red blood cells (RBCs), thus escaping from the MPS recognition and circulating long in the blood. After reaching the tumor capillary, where the blood flow is much slower than that in normal tissues, PTAO could detach from the RBCs and translocate to tumor capillary endothelial cells (tECs) with enhanced endocytic activity relative to normal ECs. Subsequently, PTAO extravasated from the blood vessels into tumor tissues mainly via adsorption-mediated transcytosis (AMT) — its adhesion to tECs’ membrane triggered efficient endocytosis of nanomedicines from the endovascular side via micropinocytosis followed by exocytosis to the other side through the endoplasmic reticulum/Golgi apparatus pathway, acquiring dramatic tumor accumulation. In the tumor interstitium, PTAO penetrated throughout the tumors via transcytosis-based successive transcellular transport processes among tumor cells rather than paracellular diffusion, enabling the homogeneous intratumoral distribution of the nanomedicines. The PTAO-based nanomedicine showed highly potent antitumor activity, which could eradicate exponentially growing large tumors (about 500 mm^3) in rodents and clinically relevant patient-derived xenograft tumors [12, 13]. Similar properties were also observed in tertiary amine oxide (TAO)-containing zwitterionic liposomal nanocarriers screened from a library of TAO liposomes with different chemical structures and particle sizes [15].

The PTAO/TAO-based nanomedicine with a simple TAO group achieved high drug delivery efficiency due to the proper affinity gradient of nanocarriers towards proteins, RBCs, tECs, and tumor cells, mainly including three processes (*i*) Non-stickiness to proteins but reversible binding to RBCs enabled nanomedicines to circulate in plasma by RBC hitchhiking, favoring a long lifetime in blood and thus providing more opportunities to bind to tECs; (*ii*) Translocation of the nanocarrier from RBCs to tECs triggered tECs to undergo fast transcytosis and thus facilitating extravasation from tumor blood vessels and enhancing tumor accumulation independent of the EPR effect; (*iii*) Adsorption on tumor cells facilitated fast cellular uptake for intracellular drug release and boosted transcytosis-mediated active tumor penetration [16]. The transcellular transport route circumvented the inherent physiological barriers in the tumor microenvironment and size restriction to paracellular diffusion and enabled extensive distribution throughout the tumor tissues, even the avascular areas.

Another typical example of the One-for-All nanomedicine is the γ-glutamyl transpeptidase (GGT)-responsive zwitterionic polymer-camptothecin conjugate (PBEAGA-CPT) [17]. PBEAGA-CPT circulated long in the blood due to the zwitterionic nature of pendant γ-glutamylamides. Once arriving at the tumor region, this zwitterionic conjugate was cationized quickly by the overexpressed membrane GGT on tECs and tumor cells, thus inducing efficient transcytosis to extravasate and infiltrate into tumor tissues rapidly. This enzyme-activated transcytosis enabled uniform distribution of PBEAGA-CPT, significantly augmenting the anticancer activities in clinically relevant tumor models. Most recently, polyzwitterionic micelles of the aminopeptidase N-responsive charge-reversal polymer-drug conjugate BP-iBu were also demonstrated to achieve optimal overall drug delivery efficiency [18]. In these two examples, the key structures, zwitterionic but enzyme-cleavable charge-reversal α-or γ-glutamylamides, conferred the nanomedicines with non-fouling and transcytosis-inducing abilities for completing the whole drug delivery process.

Such a “One-for-All” nanocarrier has simple structures and high drug delivery efficiency, which can perfectly solve the dilemma of the traditional “All-in-One” multifunctional nanocarrier, and thus might be a black technology for developing clinically translational nanomedicines.

Research funding: This work was supported by the National Key Research and Development Program (2021YFA1201200), the National Natural Science Foundation of China (51833008 and 52203193), and the Zhejiang Provincial Key Research and Development Program (2020C01123).
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: The local Institutional Review Board deemed the study exempt from review.

References

1. Shi J, Kantoff PW, Wooster R, Farokhzad OC. Cancer nanomedicine: progress, challenges and opportunities. Nat Rev Cancer 2017;17:20–37.
2. Chen H, Zhang W, Zhu G, Xie J, Chen X. Rethinking cancer nanotheranostics. Nat Rev Mater 2017;2:17024.
3. Min Y, Caster JM, Eblan MJ, Wang AZ. Clinical translation of nanomedicine. Chem Rev 2015;115:11147–90.
4. Wilhelm S, Tavares AJ, Dai Q, Ohta S, Audet J, Dvorak HF, et al. Analysis of nanoparticle delivery to tumours. Nat Rev Mater 2016;1: 16014.
5. Sun Q, Zhou Z, Qiu N, Shen Y. Rational design of cancer nanomedicine: nanoproperty integration and synchronization. Adv Mater 2017;29: 1606628.
6. Mailander V, Landfester K. Interaction of nanoparticles with cells. Biomacromolecules 2009;10:2379–400.
7. Wang J, Mao W, Lock LL, Tang J, Sui M, Sun W, et al. The role of micelle size in tumor accumulation, penetration, and treatment. ACS Nano 2015;9:7195–206.
8. Kakkar A, Traverso G, Farokhzad OC, Weissleder R, Langer R. Evolution of macromolecular complexity in drug delivery systems. Nat Rev Chem 2017;1:0063.
9. Li J, Kataoka K. Chemo-physical strategies to advance the in vivo functionality of targeted nanomedicine: the next generation. J Am Chem Soc 2020;143:538–59.
10. Lundstrom K. Self-amplifying RNA virus vectors: clinical applications in cancer drug delivery. Expet Opin Drug Deliv 2019;16:1027–9.
11. Xiang J, Liu X, Yuan G, Zhang R, Quan Z, Xie T, et al. Nanomedicine from amphiphilized prodrugs: concept and clinical translation. Adv Drug Deliv Rev 2021;179:114027.
12. Chen S, Zhong Y, Fan W, Xiang J, Wang G, Zhou Q, et al. Enhanced tumour penetration and prolonged circulation in blood of polyzwitterion-drug conjugates with cell-membrane affinity. Nat Biomed Eng 2021;5:1019–37.
13. Xiang J, Shen Y, Zhang Y, Liu X, Zhou Q, Zhou Z, et al. Multipotent poly (tertiary amine-oxide) micelles for efficient cancer drug delivery. Adv Sci 2022;9:2200173.
14. Fan W, Wei Q, Xiang J, Tang Y, Zhou Q, Geng Y, et al. Mucus penetrating and cell-binding polyzwitterionic micelles as potent oral nanomedicine for cancer drug delivery. Adv Mater 2022;34:2109189.
15. Zhao Z, Feng Y, Xiang J, Liu J, Piao Y, Shao S, et al. Screening of zwitterionic liposomes with red blood cell-hitchhiking and tumor cell-active transporting capability for efficient tumor entrance. Adv Funct Mater 2023;33:2214369.
16. Zhou Q, Li J, Xiang J, Shao S, Zhou Z, Tang J, et al. Transcytosis-enabled active extravasation of tumor nanomedicine. Adv Drug Deliv Rev 2022; 189:114480.
17. Zhou Q, Shao S, Wang J, Xu C, Xiang J, Piao Y, et al. Enzyme-activatable polymer-drug conjugate augments tumour penetration and treatment efficacy. Nat Nanotechnol 2019;14:799–809.
18. Sun R, Zhang YF, Lin XW, Piao Y, Xie T, He Y, et al. Aminopeptidase N-responsive conjugates with tunable charge-reversal properties for highly efficient tumor accumulation and penetration. Angew Chem Int Ed 2023;62:e202217408.