Editorial

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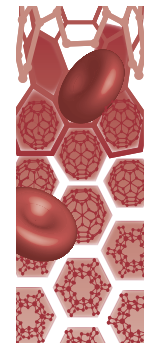

Towards rational design of multifunctional theranostic nanoparticles: what barriers do we need to overcome?

"With diagnosis and therapy combined onto a single platform, theranostics enables real-time monitoring of the status of disease treatment and allows for timely adjustment of type and dose of drugs, paving the way towards personalized medicine."

Keywords: barriers • clinical trial • nanoparticles • theranostics

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The quest for early detection and treatment of diseases has led to intense research on theranostics [1]. With diagnosis and therapy combined onto a single platform, theranostics enables real-time monitoring of the status of disease treatment and allows for timely adjustment of type and dose of drugs, paving the way towards personalized medicine. The unique physiochemical properties of nanoparticles (NPs) make them outstanding platforms for the fusion of diagnostic and therapeutic agents [2].

In general, theranostic NPs feature the following characteristics. NPs serve as carriers and sometimes also as imaging and therapeutic agents. Extrinsic imaging and therapeutic agents are attached to surfaces of NPs or encapsulated within NPs. Numerous moieties that enhance targeting are attached to NP surfaces. Lastly, active control of drug release is realized by the use of responsive NPs or molecular valves and propellers attached to the nanoporous NPs [3]. The availability of a broad range of NPs, imaging agents, drugs and moieties has provided immense scope for multifunctional theranostic NPs to enhance the therapeutic efficacy.

However, the addition of new functions is also associated with new challenges, including an increased complexity in synthesis and behavioral control of NPs in the body [4]. Despite tremendous progress in theranostic NPs, barriers must be overcome for their success in the clinic to be realized. This editorial will identify major barriers in three basic aspects of applying theranostic NPs: circulation of NPs, targeting of NPs and targeted drug delivery. A discussion of the opportunities for optimization and clinical translation of theranostic NPs will then follow.

Circulation of theranostic NPs

A major barrier for theranostic NPs is to control their fate in the body. The human body has developed highly efficient defenses against unfamiliar objects. These include cellular and physiological barriers, which limit the penetration abilities of foreign materials [5]. As a result, NPs must be circulated in the body for long periods of time to enhance their accumulation at the target sites. Modifying NPs to include 'stealth' polymers at their surfaces can reduce clearance of the NPs by the immune system. However, some of the stealth polymers can induce immune recognition and accelerate the clearance of NPs after multiple injections [6].

An alternative approach towards prolonging circulation is to camouflage NPs with surface chemistry that mimics cell membranes. Polymeric NPs encapsulated by red blood cell membranes have exhibited prolonged circulation [7]. However, this biomimic stealth has its own limitations since the immune suppression is effective only when the red blood cell membranes match the blood group of the patient.

The conflict between strategies for prolonging circulation and strategies for targeting of NPs adds another dimension to the circulation barrier. Specifically, approaches that rely on minimal cell–NP interactions

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in an attempt to avoid immune clearance contradict targeting strategies that require enhanced cellular interactions [8]. Therefore, finding the balance between circulation and targeting poses unique challenges and opportunities for the rational design of NPs.

Targeting of theranostic nanoparticles

Effective targeting of theranostic NPs is essential to assessing disease status and administering proper drug dosage. In the context of cancer theranostics, NPs can accumulate in tumors with both passive and active approaches. The passive way, known as the enhanced permeation and retention (EPR) effect, depends on the size and shape of NPs [9]. It remains challenging to precisely determine the optimal geometric parameters of NPs for the EPR effect to occur since a wide range of sizes (from 10 to 100 nm to microscale) has been reported being successful depending on the shape of the NPs [10]. Alternatively, NPs can be designed to actively target tumor cells through modification of their surfaces with ligands such as antibodies, peptides and aptamers that specifically bind to target receptors on the cell membranes [11].

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Despite its tremendous progress, targeting of NPs faces multiple barriers. Intravascularly injected NPs still accumulate primarily in the liver and spleen even if one applies the most advanced targeting strategies. Moreover, protein corona, which is protein adsorbed onto the NP surfaces, can screen the specific interactions between the NPs and the target receptors, causing the NPs to lose their specificity of targeting [12]. It becomes more challenging for the targeting of NPs when many therapeutic targets are actually biologically heterogeneous.

Targeted drug delivery

Timely, on-demand drug delivery from NPs to the target sites is highly desired for enhanced therapeutic efficacy with minimal side effects. However, challenges such as premature release and enzymatic degradation of drugs must be overcome to translate theranostic NPs to clinical applications.

The instability of NPs (especially those made of polymers) and drugs in various physiological and pathological conditions can cause undesired effects. For example, variations in temperature, pH and mechanical stress during administration causes polymorphic transitions in lipid NPs, resulting in premature release of drugs [13]. As a result, one must design polymeric NPs that strike a balance between the stability during circulation and at targeting sites. Enzymatic degradation can occur to drugs on the surfaces of NPs during the circulation. A protection layer such as an outer lipid shell can avoid the enzymatic degradation, but adds complexity to the synthesis.

Nanoporous inorganic NPs have been recognized as appealing carriers to solve the problems of premature release and enzymatic degradation. The stable, rigid frame of these NPs allows for resistance to pH, degradation, and mechanical stress. They encapsulate a payload of drugs in the nanopores to avoid interactions with enzymes. Molecular valves and propellers have been employed at the openings and sidewalls of the pores of NPs to enable timely, on-demand release of drugs [3]. However, the precision and versatility of drug release profiles have to be improved for the optimal therapeutic performances of these NPs.

Prospects & opportunities

The aforementioned barriers provide opportunities for innovations in multifunctional theranostic NPs by allowing progress in chemical synthesis, surface chemistry, nanoscience, and nanobiotechnology to be made. Herein, the future research directions to overcome those barriers and to translate multifunctional theranostic NPs into the clinic will be discussed.

Circulation of NPs

To prolong the circulation of NPs requires a paradigm shift in the approach towards the design of NPs. A few different techniques for achieving longer circulation times are emerging. Rather than using polymers at the surfaces of NPs to avoid immune clearance, one emerging method is to trick the immune system to consider a foreign NP as its own [14]. Other promising approaches include NPs with mechanical flexibility and NPs on red blood cells [15].

The long circulation time in natural systems indicates the potential for further improvement of the circulation of NPs. For instance, red blood cells circulate throughout the body for several months. Superior and generic methodologies need to be developed to increase the circulation of NPs in the blood stream from a few days to a few months.

Targeting of NPs

Better targeting strategies should be pursued intensely to increase the targeting. For targeting based on the EPR effect, systematic *in vivo* experiments are needed to identify the optimal parameters for NPs with regard to shape, size, composition and mechanical property. Future targeting strategies also need to take into account

the heterogeneity of therapeutic targets. Along this line, one of the most promising approaches is the use of multi-targeting NPs, which can increase the specificity of targeting based on the simultaneous binding of multiple ligands to multiple receptors. Multi-targeting NPs can be made by incorporating multiple ligands on the surfaces of individual NPs. Considering the effects of the protein corona on the interactions of NPs and cells, it is strongly recommended that future studies of the targeting of NPs be carried out under physiological conditions.

Targeted drug delivery

Personalized medicine requires the precise control of drug release using an appropriate trigger that is based on a unique characteristic within the environments of tumor cells. Ideally, there would be smart drug delivery systems that can circulate within the body and get activated when a disease arises. A better understanding of the tumor microenvironments and the nano–bio interactions must be gained in order for this type of drug delivery to be feasible.

One of the most promising systems for smart drug delivery is based on inorganic NPs functionalized with molecular switches that work as molecular valves and propellers [3]. One needs better control over the orientation, arrangements and switching properties of these functional molecules on the surfaces of NPs to enhance the precision and versatility of drug release profiles. Advanced molecular assembly and measurements need to be developed to achieve the single-molecule control of molecular switches on the curved or faceted surfaces associated with the NPs [16].

Clinical trials

The development of multifunctional theranostic NPs makes the regulatory clinical trials complex. One needs to understand various aspects that impact behaviors of NPs in a biological system along with the toxicity profiles [17]. Rather than focus on single aspects like targeting or side effects, a holistic approach that tests an overall outcome of the NPs has to be devised for the clinical trial. Alternatively, 'organs on a chip' can be employed to make the clinical trials more efficient and cost effective [18].

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