



Theranostic nanomedicine for cancer



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With over 10 million new cases per year worldwide, cancer remains a difficult disease to treat and a significant cause of morbidity and mortality. Over recent decades, there has been explosive development of a variety of nanotechnology platforms to diagnose and treat cancer [1,2]. These nanoplatforms, including polymer–drug conjugates, liposomes, polymeric micelles, dendrimers, polymersomes and Au/Si/polymer shells, have been established with distinctive chemical compositions and physical properties. Compared with traditional molecular-based contrast agents or therapeutic drugs, this new nanomedicine paradigm enables a highly integrated design that incorporates multiple functions, such as cell targeting, ultra-sensitive imaging and therapy, in one system. Multifunctional nanomedicine holds considerable promise as the next generation of medicine that enables the early detection of disease, simultaneous monitoring and treatment and targeted therapy with minimal toxicity. This editorial will focus on the emerging concept of multifunctional theranostic nanomedicine and the opportunities it provides for combating cancer.

Therapeutic challenges of cancer

Clinicians have long realized that cancer represents a heterogeneous population of diverse diseases. More recent advances have shed further light on the molecular heterogeneity found between cancers of the same type, between a primary tumor and its metastatic foci and even between the cells that constitute individual tumors. Because a multitude of cancer phenotypes exist within a given tumor, even before therapy, there is ample opportunity for subpopulations of cancer cells to evade monotherapy. This molecular diversity, combined with the selection of resistant phenotypes of cancer cells

with treatment, is a major challenge in the treatment of this disease. Because cancer cells evolve in response to the selection of therapy, the goal of eradicating all cells within a tumor by targeting a specific pathway unique to cancer cells becomes a Herculean task. When this task is not completed, the cells that do not respond to chemotherapy can then grow and reconstitute the tumor in the body.

Theranostic nanomedicine

Tumor heterogeneity and adaptive resistance remain formidable challenges to therapy. Treatment of cancer requires the ability to address these two intrinsic properties of this complex disease. Theranostics was coined originally as a term to describe a treatment platform that combines a diagnostic test with targeted therapy based on the test results [3]. Here, we define theranostic nanomedicine as an integrated nanotherapeutic system, which can diagnose, deliver targeted therapy and monitor the response to therapy. This integration of diagnostic imaging capability with therapeutic interventions is critical to addressing the challenges of cancer heterogeneity and adaptation. Molecular diagnosis by imaging is used first to characterize the cellular phenotypes present in each tumor to guide target-specific therapy. Both intra- and intertumor heterogeneity make this an essential component of therapy that will take us beyond the era of 'one-size-fits-all' generic medicine to truly personalized medicine. Because cancer is a highly heterogeneous disease, our treatments will probably have to be as diverse. Furthermore, this characterization of tumors cannot simply be analysis of a physical biopsy specimen; the heterogeneity of the cells will make such a sampling prone to error that will fail to give a full description of the phenotypic breadth that exists within a tumor. It will also fail to characterize cells that have metastasized to other locations. All of the tumor cells throughout the body must be subjected to molecular characterization, which can only be performed efficiently through full-body imaging.

After molecular diagnosis, the ability to target the identified molecular markers to eradicate all of the diverse phenotypes of cancer is imperative.

As a platform technology, nanomedicine has the advantage of being able to target multiple tumor markers and deliver multiple agents simultaneously for synergy in addressing the challenges of cancer heterogeneity and adaptive resistance.

Even with a full molecular profiling and multitargeted therapy based on this profile, the task of eradicating all cancer cells within a given patient would not be over. The tumor inevitably evolves in response to even multitargeted therapy, therefore, the molecular analysis of the tumor must be repeated quickly and the results used to intelligently modify the treatment and targeting strategy. This real-time, adaptive targeting is the final essential component of theranostic nanomedicine to address adaptive resistance of cancer cells.

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This is the challenge and the technology to develop platforms that can address these complex properties of cancer is gradually coalescing with input from a range of diverse fields in cancer biology, drug delivery, molecular imaging, materials science and clinical oncology. Here, we provide a brief overview of a few important directions in the development of theranostic nanomedicine.

Zoom in on new cancer targets

Conventional chemotherapy seeks to exploit the differences between cancer cells and normal cells. Typically, these differences are limited to global characteristics of cancer cells, such as rapid proliferation. Cisplatin, for example, is a traditional chemotherapeutic drug that affects rapidly dividing tumor cells preferentially by crosslinking DNA and interfering with its synthesis and repair. Unfortunately, these drugs are also highly toxic and create considerable morbidity in patients. Dosage for these drugs is limited by systemic toxicity and tumors can become resistant to them rapidly by nonspecific processes, such as active transport of the drug out of the cancer cells. New drugs that can provide larger therapeutic indices are greatly needed.

Thanks to advances in cancer biology, a plethora of novel cancer-specific targets are being characterized, including cancer-specific enzymes and receptors, changes in signal transduction pathways, angiogenesis-related receptor expression, as

well as alterations in replication, repair, translation, transcription, post-synthetic modification and chromosome-regulatory processes. Screening of compound and phage libraries has also led to the discovery of many new therapeutic agents and targeting ligands with high binding affinity and specificity. Recently, agents that target molecular markers unique to cancer cells, such as monoclonal antibodies, have been approved to reduce systemic toxicity by achieving targeted therapy. However, targeted agents can, by their very precision, enable cancer cells to bypass targeted pathways and can develop stronger resistance than older chemotherapeutic agents. A good example of this is found in breast tumors with Her2/neu expression, where treatment with Herceptin[®] causes resistance over time by using pathways that bypass the Her2/neu receptor. Administration of a combination of monoclonal antibodies to multiple receptors, however, effectively reduced the tumor recurrence rates [4]. This synergistic effect can be achieved with a single nanomedicine formulation, by attaching differentially targeted peptides or antibodies to the same nano-platform. This would reduce the complexity of multidrug administration. The nano-platform can also be further engineered to provide controlled release of cytotoxic drugs on delivery to cancer cells. The multifunctional nanomedicine would therefore achieve synergistic targeted therapy by blocking multiple receptors, reduce systemic toxicity by minimizing chemotherapeutic drugs in systemic circulation and achieve further synergy by combining these drugs with molecular targeting, and deliver the targeted chemotherapeutic agent specifically to tumors, thus improving the therapeutic index.

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Cancer molecular imaging

Drug development and imaging have become increasingly intertwined in recent years owing to the advantages of using noninvasive, high-throughput imaging studies. Almost all imaging modalities can be used in drug studies to provide anatomic, pharmacokinetic and pharmacodynamic information. Current nuclear-imaging

methods (e.g., PET and single photon emission computed tomography) offer superior sensitivity compared with other modalities, such as computed tomography (CT), MRI and ultrasound. However, CT and particularly MRI can provide high-resolution images with great anatomical resolution and soft-tissue contrast. Consequently, multimodality imaging is emerging as a powerful combination to provide complementary information for pharmaceutical applications.

‘Successful development of theranostic nanomedicine requires significant advances in materials science and nanocomposite materials.’

Imaging studies are also used increasingly to provide molecular information in cancer applications [5]. Like therapeutics, targeted delivery of contrast agents with a nano-platform can be achieved by functionalization of the nano-platform to cancer markers. By sequential functionalization of the nano-platform against different cancer targets, the surface target expression of the whole tumor can be mapped molecularly through imaging. The combination of targets that would enable delivery of the nano-platform to the entire tumor can then be used to functionalize the therapeutic version of the nanoparticle. In addition, codelivery of imaging contrast agent and chemotherapeutic drugs can provide real-time validation of the targeting strategy. If molecular targets become unavailable owing to down-regulation or saturation, imaging can be used to map out alternate targets. Finally, molecular markers of cellular death can also be imaged to confirm tumor response. These markers can be downstream effector molecules of the drug or molecular or cellular markers for processes, such as apoptosis and angiogenesis. The advantage of this approach is that it can provide early feedback of therapeutic efficacy before detection of traditional end points, such as tumor shrinkage. In summary, imaging can be used to track nanoparticles systemically, pre-validate appropriate targeting and track the expression pattern of surface markers for adaptive targeting, as well as provide real-time information on tumor response.

Nanocomposite materials

Successful development of theranostic nanomedicine requires significant advances in materials science and nanocomposite materials. Ideal nanomedicine platforms should be small in size,

provide high drug-loading densities, be efficient in targeting to the tumor tissues with minimal nonspecific uptake, provide responsive release mechanisms to improve drug bioavailability and also imaging ultrasensitivity to pre-validate and monitor therapy. Extensive studies have shown an ideal size range of 10–200 nm for spherical nanoparticles. Achieving multifunctional design confined within such a small size range is a challenging task in the development of theranostic nanomedicine.

Recent progress has brought these goals within reach. For example, a perfluorocarbon-based nanoparticle system (~200nm) has been established as a tumor vascular targeting system that can simultaneously deliver drug molecules as well as ultrasound and MRI contrast agents [6]. Mixtures of nanoparticles with different perfluorocarbon cores also provide a quantitative, multispectral signal, which can be used to distinguish the relative concentrations of epitopes within a region of interest. Another recent study has demonstrated the feasibility of developing multifunctional polymeric micelles (<100 nm in diameter) with specific cancer targeting, ultrasensitive MRI detection and pH-sensitive release of drugs for cancer therapy [7]. Clustering of hydrophobic superparamagnetic iron oxide nanoparticles in the hydrophobic micelle core resulted in dramatically increased T2 relaxivity that subsequently lowered the MR detection limit to nanomolar particle concentrations. This permits the detection of as few as 50,000 tumor endothelial cells that overexpress $\alpha v\beta 3$ integrin, an angiogenic tumor marker.

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It should be noted that most current nanotherapeutic systems are developed for a limited number of clinically approved drugs, such as paclitaxel and doxorubicin. For many new therapeutic agents with diverse physico-chemical properties, drug carriers need to be tailored to increase their compatibility with these agents to achieve adequate therapeutic payload and imaging sensitivity. Meanwhile, controlled release of the encapsulated agents in tumors is critical and presents another challenge in the development of these therapeutic nanocomposite materials.

Concluding remarks

Despite tremendous advances in cancer therapy, many scientific, technological and clinical challenges remain that will require a highly interdisciplinary and collaborative approach to overcome. Regulatory challenges also need to be addressed. The current paradigm for regulatory approval of therapeutics might have to be altered in the new era of multicomponent nanomedicine with modular designs that can be personalized to individual patients and altered during therapy for adaptive targeting. With advances in cancer biology and explosive developments in materials science and imaging technology, we have reason to be optimistic that we are at the critical threshold of a major breakthrough in the treatment of cancer. As the

capabilities of multifunctional nanoplatforms continue to increase, the integration of cancer biology, diagnostic imaging and materials science in the future will be essential, not just for theranostic nanomedicine, but for cancer therapy overall.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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