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CCR 20th Anniversary Commentary: Prospects and Challenges of Therapeutic Nanoparticles in Cancer

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Summary

The review article by Cho and colleagues, published in the March 1, 2008, issue of *Clinical Cancer Research*, presented the strong potential of nanotechnology in cancer. This commentary discusses the latest advances in nanotechnology, which provide novel approaches for cancer diagnosis, imaging, drug delivery, and personalized therapy; highlights the perspectives for therapeutic nanoparticles; and describes the advantages and challenges of their multifunctionalities.

Nanotechnology is a multidisciplinary science and technology that encompasses engineering, chemistry, physics, biology, imaging science and applied clinical science and has recently emerged as one of the most rapidly growing fields in the development of novel cancer therapy. The heterogeneity of cancer makes the disease particularly complicated to diagnose and treat, with therapy options largely restricted to molecularly targeted therapy, chemotherapy, radiation, and surgery (1). Our previously published article (2) contributed valuable discussion of different types of nanomaterials that can provide sophisticated multifunctional strategies for cancer therapy. We stated our support for a multifunctional approach, and indeed in recent years we have observed the development of such nanotechnologies with significant advantages for clinical translation.

Conventional anti-cancer drugs encounter several challenges to their therapeutic efficacy, including short half-life, drug resistance, non-specific distribution with toxicity, delivery to desired location, internalization and control of intracellular drug concentration, co-delivery of multiple drugs to target multiple signaling pathways, physiologic barriers, and the combination of therapeutics with imaging modalities. Although molecularly targeted therapies have shifted the paradigm of cancer treatment, their success is also limited by toxicities, suboptimal tumor distribution, and drug resistance. In recent years, we have identified complex signaling networks, cross-talk between oncogenes, and specific genetic mutations in patients that together reduce drug efficacy and often result in resistance to the targeted agent. A promising approach to overcome these challenges is to target multiple

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signaling pathways using multiple drugs while precisely controlling drug release, tuning of distribution, timing, and sufficient dosing (3). We discussed in our earlier article (2) how nanotechnology could be a powerful tool to circumvent these hurdles and result in improved efficacy. Since then, many important bench-to-bedside and bedside-to-bench milestones have been achieved. For example, a targeted nanoparticle (NP) platform able to control blood circulation, tissue distribution and drug release by targeting the tumor tissue was discussed by Nicolas Bertrand (4). Drug encapsulation by NPs overcomes drug solubility issues and protects therapeutic molecules (5). More than 100,000 articles are currently reported in PubMed using the search term “nanoparticles”. This suggests that nanotechnologies will remain a substantial component of anti-cancer research over the decades to come. In the following, we discuss recent developments in nanotherapeutics and opportunities to develop multifunctional NPs to address challenges encountered during drug development.

Our previous article highlighted the types of NPs derived from biological, organic and inorganic origins and the engineering of their properties for cancer therapy. NPs are usually composed of non-toxic, biodegradable lipid-based and polymeric materials that allow the addition of tumor targeting molecules and the capacity to carry large loads and undergo degradation under certain conditions. Recent developments have improved the stability and anti-cancer properties of NPs, although only a small number of nanomedicines have been approved for human use so far. A variety of new materials are advancing as tumor-targeted multifunctional constituents, including micelles, liposomes, dendrimers, gold nanomaterials, magnetic NPs, functionalized carbon nanotubes, macrophage-specific NPs, DNA origami cages, worm-like filomicelles, silica particles, modified plant viruses, nanodiamonds, and others (6).

NPs can be categorized into three generations. First generation nanodrugs are non–tumor-targeted but tend to accumulate preferentially in tumor tissues through the enhanced permeability and retention (EPR) effect. Consequently, most of these NPs prolong the drug half-life and favor an improved toxicity profile. As we discussed previously, several first generation drugs are FDA-approved, including NP-bound paclitaxel (Abraxane; Abraxis Bioscience) and other lipid-based nanodrugs: non-pegylated liposomal doxorubicin (Myocet®), non-pegylated liposomal daunorubicin (DaunoXome®), non-pegylated liposomal cytarabine (DepoCyt®), vincristine sulfate liposomes (Marqibo®), and liposomal mifamurtide (Mepact®) (7). The Nab-paclitaxel formulation improved the response rate in breast cancer and increased the survival rate in pancreatic cancer when given with gemcitabine and in non-small-cell lung cancer with carboplatin (7).

Second generation NPs are actively targeted to tumor cells. We previously demonstrated the promise of this complementary strategy to EPR to improve drug delivery. Overexpressed cell surface receptors such as transferin receptor (Tf-R), epidermal growth factor receptor (EGFR), prostate specific membrane antigen (PSMA), and folic acid receptor (FA-R) are among the most appealing targets for nanoformulated drugs. Several liposomal and polymeric NPs that carry ligands for specific cell surface receptors have been developed and moved into clinical studies. The results of phase I/II clinical trials for several agents, including MBP-426, MCC-465, SGT53, MM-302, BIND-014, CALAA-01, cetuximab,

Doxil®/Caelyx® liposomes and a retroviral vector have been discussed elsewhere (4). While further evaluation of these drugs in clinical settings brings hope for cancer treatment, the debate is still ongoing as to whether targeting has any meaningful advantages. In recent years, many studies have shown that targeting of NPs leads to greater internalization, albeit via an unknown mechanism.

Third generation NPs possess multifunctional abilities, as described in our previous article, which offer exciting advances in early detection, diagnostics, prognostics and therapeutic strategies for cancer. These include the potential to modulate the pharmacokinetic profile of a drug to increase its half-life and allow for controlled drug release, thereby enhancing therapeutic index. Recent advances in nanotechnology have created the platform for a combinatorial approach to cancer therapy, and synergistic efficacy of NP-based agents has been shown in *in vitro* and *in vivo* studies. Third generation NPs offer great advantages for the delivery of drugs, imaging molecules, and genes to solid tumors (8). Since our previously published article, many exciting developments have been achieved in nanotechnology-based gene therapy, photodynamic therapy, and cancer theragnostics. Multiplex nanocarriers have been formulated to deliver multiple drugs such as doxorubicin and paclitaxel, together with DNA or siRNA (7). Any gene could be druggable if gene-specific siRNA can be successfully delivered to the desired cancer site. The delivery of siRNA is the greatest challenge to this approach, and in 2010 the first evidence of gene silencing in humans was obtained by delivering siRNA nanotherapeutics (9).

Nanotechnology presents new opportunities in the field and also new challenges, particularly with the shift in focus from passive targeting to tumor targeting and combinatorial approaches. Critical factors include the characteristics of the targeting agent and the drug carrier, the NP components, ligand conjugation chemistry, ligand number and orientation on the NP surface. The biological environment is crucial in functionalizing NPs. Optimum effect depends on the route of NP administration; interaction with serum proteins and immune system molecules; expression level, cellular localization and accessibility to bind NPs of the targeted moiety; the biodistribution and retention of NPs inside tumors; and the release of drug. To effectively address these challenges, it is important to employ a multidisciplinary approach from chemist to clinician. Clinical development can be delayed by issues of NP characterization, large scale preparation and reproducibility and knowledge regarding the safety of nanocarriers. The pharmacokinetic behavior of nanocomponents requires detailed investigation, and associated health risk databases should be considered. The regulatory approval of nanomedicine therapeutics remains challenging. Each component of a NP agent must be evaluated for toxicity, making the approval process even more complex for multifunctional nanostructures comprising therapeutic, diagnostic, imaging and targeting agents. Considering the enormous potential benefits of NPs in cancer research, there is an urgent need for the development of safety guidelines and approval processes by the government.

In recent years, several challenges have been successfully addressed by nanotechnology. Multidrug resistance (MDR) is one of the major hurdles in cancer therapy. We discussed previously (2) that multifunctional NP-based approaches might play an important role in carrying, protecting and delivering drugs specifically to tumors to overcome resistance

issues. Recent developments suggest that NPs may also facilitate combinatorial therapy and controlled drug release (3), further contributing to overcoming MDR. Cancer diagnosis is another significant hurdle. Conventional cancer diagnosis mainly depends on a single parameter, and is significantly complicated by health conditions, drug response and immune status. Identifying molecular, DNA, or transcriptome biomarkers that can be detected in small amounts of blood or tissue specimens would facilitate appropriate patient diagnosis. Multiplexed NPs have been developed in recent years for miRNA profiling. Many miRNAs function as oncogenes or tumor suppressors, and are good candidates for profiling in terms of diagnosis. Nanotheranostic agents are multifunctional NPs that can serve both drug delivery and detection roles. We have developed NPs with dual effects in therapy and imaging or detection (10, 11). This is an area of rapid growth and we expect an increasing number of multifunctional NPs to be developed for cancer treatment and diagnosis. Metastasis is the major cause of death in cancer patients, and there is currently no promising treatment for metastatic cancer, which has spread to multiple organs, and is sometimes undetectable. The physiological microenvironment is particularly challenging in this setting. Nanotechnology has shown promising tumor-specific targeting in different organs and may thus be very effective in treating metastatic lesions. Personalized treatment has become a new paradigm of oncology as specific genetic variations and molecular markers have been identified as prognostic markers for certain cancers. Multifunctional NPs may provide valuable opportunities in the personalized treatment of cancer.

Together, the continued efforts of multi-disciplinary teams of investigators and enthusiastic support from grant agencies will promote the rapid growth of nanotechnology. Our knowledge of the interactions between nanocomponents and the cancer microenvironment continues to expand, and it is crucial to increase this understanding and to further optimize NPs to continually improve efficacy and toxicity profiles. The applications of nanotechnology in cancer are blossoming through multidisciplinary approaches in academic centers, pharmaceutical and nanotechnology companies. This is one of the fastest growing research areas in cancer, and nanotechnology-based agents, particularly multifunctional NPs, are approaching clinical trials more rapidly. While surgery, radiation, chemotherapy, and targeted therapy are the mainstay of cancer treatment, NPs provide enormous opportunities to be added to mainstream cancer treatment.

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