CCR 20th Anniversary Commentary: Prospects and Challenges of Therapeutic Nanoparticles in Cancer
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In their review article published in the March 1, 2008, issue of Clinical Cancer Research, Cho and colleagues 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. Clin Cancer Res; 21(20); 4499–501. ©2015 AACR.

See related article by Cho et al., Clin Cancer Res 2008;14(5) March 1, 2008;1310–6

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, radiotherapy, 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 anticancer drugs encounter several challenges to their therapeutic efficacy, including short half-life, drug resistance, nonspecific distribution with toxicity, delivery to desired location, internalization and control of intracellular drug concentration, codelivery 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 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 Bertrand and colleagues (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 anticancer research over the decades to come. Herein 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 biologic, organic, and inorganic origins, and the engineering of their properties for cancer therapy. NPs are usually composed of nontoxic, 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 anticancer 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: nonpegylated liposomal doxorubicin (Myocet; Teva), nonpegylated liposomal daunorubicin (DaunoXome; Galen), nonpegylated liposomal cytarabine (DepoCyt; Sigma-Tau), vincristine sulfate liposomes (Marqibo; Talon Therapeutics/Spectrum), and liposomal mifamurtide (Mepact; Takeda UK; ref. 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 nonsmall 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), EGFR, prostate-specific membrane antigen, and folate acid receptor (FA-R), are among the most appealing targets for nanoformulated drugs. Several liposomal and polymeric NPs that carry ligands for specific 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 (Azaya Therapeutics), and a retroviral vector, have been discussed elsewhere (4). Although 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 multistaging advances in early detection, diagnostics, prognosticstics, 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 its 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). In the time following our previously published article, many exciting developments have been achieved in nanotechnology-based gene therapy, photodynamic therapy, and cancer theranostics. Multiple 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 therapy, and cancer theranostics. Multiple 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).

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NPs, are approaching clinical trials more rapidly. Although surgery, radiotherapy, chemotherapy, and targeted therapy are the mainstay of cancer treatment, NPs provide enormous opportunities to be added to mainstream cancer treatment.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
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