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PERSPECTIVE

Nanotechnology-Based Cancer Therapeutics—Promise and Challenge—Lessons Learned Through the NCI Alliance for Nanotechnology in Cancer

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ABSTRACT The new generation of nanotechnology-based drug formulations is challenging the accepted ways of cancer treatment. Multi-functional nanomaterial constructs have the capability to be delivered directly to the tumor site and eradicate cancer cells selectively, while sparing healthy cells. Tailoring of the nano-construct design can result in enhanced drug efficacy at lower doses as compared to free drug treatment, wider therapeutic window, and lower side effects. Nanoparticle carriers can also address several drug delivery problems which could not be effectively solved in the past and include reduction of multi-drug resistance effects, delivery of siRNA, and penetration of the blood-brain-barrier. Although challenges in understanding toxicity, biodistribution, and paving an effective regulatory path must be met, nanoscale devices carry a formidable promise to change ways cancer is diagnosed and treated. This article summarizes current developments in nanotechnology-based drug delivery and discusses path forward in this field. The discussion is done in context of research and development occurring within the NCI Alliance for Nanotechnology in Cancer program.

KEY WORDS drug delivery · multi-functional nanoparticle carriers · nanoparticle · toxicity

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INTRODUCTION

Cancer is arguably the most complex disease known to man and one of the most pressing public health concerns of the 21st century. The statistics are daunting; it was projected that 550,000 people would die of cancer and that another 1.4 million would be diagnosed with the disease in 2009 in the United States alone (1). In contrast to dramatic reversals in death rates from heart disease, stroke and infectious disease over the past 50 years, the death rate from cancer has declined slowly only in the last decade (2), while the number of those living with a diagnosis of cancer has steadily accumulated from 3 million in 1971 to over 10 million today. While highly effective targeted drugs for certain cancers are emerging, treatment strategy has remained mostly unchanged over the past 30 years—surgical resection of the tumor, followed by cytotoxic chemotherapy and/or radiation.

Many medical researchers have turned their attention to nanotechnology to find a more effective approach to drug delivery in cancer. Nanomaterials have the potential to deliver drugs directly to cancerous tissues, eliminating systemic toxicity, and to open up entirely new modalities of cancer therapy, such as photodynamic and hyperthermia treatments. The research in this area is very active; however, the arrival of approved nano-drugs to market is slow. There are only a handful of such drugs approved, with DOXIL® and Abraxane® being the most well known. DOXIL®, a liposomal formulation of doxorubicin, was approved by the FDA in the mid-1990s for treatment of Kaposi's sarcoma and is now also indicated for the treatment of refractory breast and ovarian cancer (3,4). Abraxane®, an albumin-bound formulation of paclitaxel for the treatment of metastatic breast cancer, was approved by the FDA in 2005 (5). The albumin-based formulation

allows for elimination of cremophor and reduces hypersensitivity reactions, which are typical for free paclitaxel treatment (6). It is a simple but very clever idea which demonstrates the power and versatility of nanoparticle drug design. It is disappointing that no approvals of oncology nano-drugs have occurred since 2005. On the other hand, it is encouraging that several clinical trials using nanoparticle delivery platforms are being pursued (a search of www.clinicaltrials.gov reveals over 70 of them).

In hopes of fostering further new ways to approach cancer research and care, the National Cancer Institute (NCI) established the NCI Alliance for Nanotechnology in Cancer (http://nano.cancer.gov) 5 years ago (7). In this paper, we will present an overall perspective of nanotherapeutics development and chart the prospective path forward in this area with specific emphasis of the formulations developed within the Alliance program.

FIRST STEPS—NANOPARTICLE DELIVERY OF CHEMOTHERAPEUTIC DRUGS

There are several immediate benefits of using nanoparticles as drug carriers. Most nanotechnology-based drug formulations under current development aim to increase therapeutic index for established chemotherapeutic drugs via selective delivery to cancerous tissue. Nanoparticles' unique physical properties (size, charge, biocompatibility, solubility) can be manipulated to increase circulation half-life, which in turn can lead to increased accumulation of particles and associated drug cargo at the tumor site. Association with targeting ligands can further enhance drug delivery to tumors. Nanoparticle encapsulation techniques can improve the solubility of hydrophobic drugs, thereby eliminating harmful organic solvents from drug formulations, prevent drug degradation *in vivo* and shield the patient organism from toxic drug properties prior to drug release at the tumor site. Drug payloads can be quite large, due to large surface-to-volume ratios at the nanoscale. Nanoparticles can be further designed into multi-functional delivery systems with a tumor-specific targeting moiety, therapeutic payload, and diagnostic tool (imaging or biochemical sensor) that enables monitoring of therapeutic efficacy (8–11).

The benefits described above have been utilized in several early demonstrations of nanoparticle-based drug delivery. In most of these cases, well-established chemotherapeutic drug molecules (paclitaxel, doxorubicin, docetaxel, methotrexate) have been combined with liposomal or polymeric nanoparticle platforms and side-by-side efficacy comparisons performed of free drug versus nanoparticle-delivered drug treatments. Typically, the latter was more efficacious and allowed for the use of significantly lower amounts of drug. For example, Dr. James Baker's group at the University of Michigan, Ann Arbor demonstrated delivery of methotrexate using folic acid targeting and a PAMAM dendrimer delivery system (12). The dendrimer conjugates were evaluated in immunodeficient mice bearing human KB tumors. Targeting methotrexate increased its antitumor activity and markedly decreased its toxicity, allowing therapeutic responses not possible with a free drug. Dr. Omid Farokhzad of Harvard University and Dr. Robert Langer of the Massachusetts Institute of Technology (MIT) have developed aptamer-targeted polymeric particles that bind exclusively to the extra-cellular region of antigens expressed on prostate cancer (PCa) cells (13,14). A proof of concept for this system, using a docetaxel-PLGA nanoparticle-aptamer bioconjugate that targets the PSMA protein on the surface of PCa cells *in vivo*, has been evaluated in animal models (Fig. 1). The technology is being commercialized by BIND Pharmaceuticals in Boston. Dr. Mark Davis of the California Institute of Technology has developed the Cyclosert™ delivery system based on cyclodextrin-containing polymers. Cyclosert™ has been used as a carrier for camptothecin, a potent anticancer agent which is plagued by very poor solubility in water and hydrolysis from its active lactone form to an inactive, yet toxic, form at human blood pH levels (Fig. 2). Cyclosert™ formulation resulted in a 4000-fold increase in camptothecin solubility and provided long circulation half-life of particles, leading to their preferential accumulation in diseased tissues (15,16). Currently, Calando Pharmaceuticals is conducting an open-label, dose-escalation clinical phase I study of camptothecin-conjugated Cyclosert™ in patients with solid tumor malignancies. Dr. Thomas Schluep of Insert Therapeutics and Dr. Davis have shown that the combination of tubulysin A with a cyclodextrin-based polymer delivery platform similar to Cyclosert™ allows for a significant widening of the therapeutic window. Tubulysin A is a naturally occurring tetrapeptide and is highly active against multiple cancer cell lines. However, the maximum tolerable dose (MTD) for free tubulysin is very low, and severe toxicity occurs even at doses as low as 0.1 mg/kg. In contrast, the cyclodextrin formulation of tubulysin allows for MTDs as high as 3 to 10 mg/kg (17). Dr.

David Cheresh's group at the University of California, San Diego (UCSD) has used targeted nanoparticles to deliver doxorubicin to the $\alpha_v\beta_3$-expressing tumor vasculature (18). Experiments showed selective apoptosis in regions of the $\alpha_v\beta_3$-expressing tumor vasculature in pancreatic and renal cell orthotopic animal models. The improved effectiveness of nanoparticle delivery was apparent not only for primary tumors, but it also produced a 15-fold increase in anti-metastatic activity compared to free drug treatment.

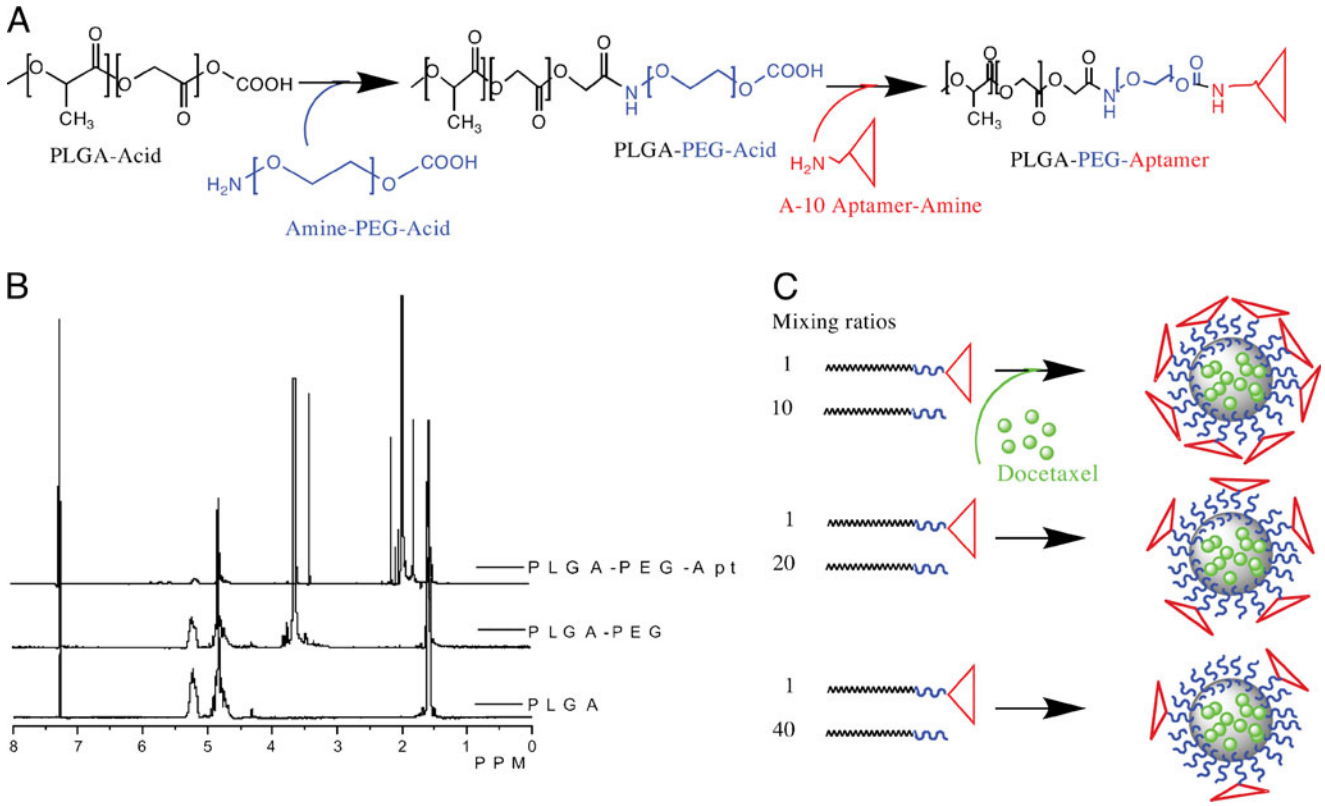

Fig. 1 Development of PSMA-targeted NPs by using PLGA-*b*-PEG-*b*-Apt TCP. **A** The PLGA-*b*-PEG-*b*-Apt-biointegrated TCP was synthesized in two steps: (*i*) synthesis of PLGA-*b*-PEG by conjugating carboxyl-capped PLGA (PLGA-acid) to the amine terminals of heterobifunctional PEG (amine-PEG-acid) and (*ii*) formation of PLGA-*b*-PEG-*b*-Apt by conjugating the carboxyl ends of PLGA-*b*-PEG-acid to the amine ends of A10 PSMA Apt. **B** ^{1}H NMR characterization of PLGA-*b*-PEG and PLGA-*b*-PEG-*b*-Apt. For the synthesis of PLGA-*b*-PEG, the yield of PLGA and PEG conjugation was 73–91%, and the purified PLGA-*b*-PEG DCP was used for the subsequent conjugation to Apt. The presence of Apt on the PLGA-*b*-PEG-*b*-Apt TCP was visualized by the peaks between 1.8 and 2.2 ppm. The Apt conjugation efficiency of the PLGA-*b*-PEG DCP for seven independent reactions was 13–21%. **C** By titration in water, the PLGA-*b*-PEG-aptamer TCPs self-assemble and form PSMA-targeted NP-Apt bioconjugates. By using distinct ratios of PLGA-*b*-PEG-*b*-Apt TCP with PLGA-*b*-PEG DCP lacking the A10 Apt during NP formulation, the Apt surface density can be precisely and reproducibly changed. (Reprinted with permission from Ref (14). Copyright 2008 National Academy of Science USA).

FURTHER POTENTIAL—UNIQUE APPLICATIONS WHERE NANOTECHNOLOGY CAN OFFER ONLY AVAILABLE SOLUTION

The early formulations described above offered improvements in therapeutic index for existing drugs and hopefully will find their way into clinical applications as sole or combination therapies. However, the greatest value of nanotechnology in drug delivery will be fully realized only when treatments which currently are not available can be successfully developed leveraging nanoparticle-based delivery. There are several areas which fall into this category. Multi-drug resistance (MDR) mechanisms associated with cell-surface protein pumps can be overcome using endocytosis-mediated nanoparticle drug delivery. Access to the interior of solid tumors can be enhanced using nanoparticles coated with novel tissue penetrating peptides. Nanoparticle-mediated engineering of the tumor microenvironment, through heat or mechanical disruption, can also enhance drug delivery and efficacy. Nanoparticle constructs that probe and recognize the tumor microenvironment via enzymatic, pH or other biochemical signaling could enable in situ triggered drug release. Careful particle design may even enable penetration of the blood-brain barrier and effective treatment of highly lethal brain tumors. siRNA therapies that are currently hampered by the poor stability of siRNA *in vivo* could significantly advance through nanoparticle delivery, as in the example of siRNA-conjugated Cyclosert™ (19,20) (Fig. 2). On a more fundamental level, nanotechnology-enabled investigation of basic cancer biology, such as cell migration and cell motility studies, may lead to the development of anti-metastatic drugs. Theranostic (therapy + diagnostic) nanoparticle systems may enable personalized medicine by screening and tailoring drugs to particular patients.

Several early works have proven that indeed these more sophisticated applications can be realized. For example, Dr. Mansoor Amiji's group at Northeastern University has

demonstrated that co-administration of ceramide with paclitaxel using polymeric particles can overcome multi-drug resistance (MDR) in human ovarian cancer cell lines through restoration of apoptotic signaling (21,22). The nanoparticle formulation also allowed for resensitization of cells to a dose of paclitaxel indicating a 100-fold increase in chemosensitization. Dr. Davis and colleagues have used the cyclodextrin-based system described above for gene therapy, using a construct consisting of siRNA, a short cyclodextrin-containing polymer, a polythethylene glycol steric stabilization agent, and human transferrin (hTf) as a targeting ligand. hTf binds to transferrin receptors that are typically upregulated on cancer cells (23). The construct was used to treat the first patient in a phase I clinical trial in May of 2008 conducted by Calando Pharmaceuticals. Dr. Sangeeta Bhatia of MIT, Dr. Erkki Ruoslahti of the Burnham Institute for Medical Research and Dr. Michael Sailor of UCSD collaborated to develop a clever nanoparticle aggregation system allowing for recognition of the tumor microenvironment. Aggregation of superparamagnetic iron oxide nanoparticles is inhibited by surface functionalization chemistry (PEG chains anchored by MMP-2-cleavable peptide substrates). Upon proteolytic removal of PEG through cleavage of the peptides upon contact with MMP-2 enzyme in close proximity to the tumor, the particles self-assemble into aggregates with an enhanced magnetic susceptibility sufficient to be detected by MRI (24,25). A similar strategy can be used for triggered drug delivery upon detection of enzymatic environment. Dr. Miqin Zhang of the University of Washington, Seattle has developed a multi-functional nanoparticle system with iron oxide as a core, capable of dual-modality (MR/optical) imaging. This construct will be used for pediatric cancer applications and was demonstrated to cross the blood brain barrier (BBB) in animals after tail-vein injection (26–28). Nanotechnology tools are also being used to study cell migration and cell motility on engineered surfaces (29,30). Selective patterning and surface modifications may lead to further understanding how cells migrate and how their migration can be arrested. These fundamental studies may lead to the development of a new class of cancer therapeutics—anti-metastatic drugs.

NANOTHERAPEUTICS SO FAR

Nanoformulation is an important and active area of research in cancer nanotechnology, and dendrimers and diverse polymers have been used for formulations. The first generation of passively targeted nanocarriers that localize to and infiltrate tumors by virtue of their leaky vasculature, i.e., the enhanced permeability and retention effect (EPR),

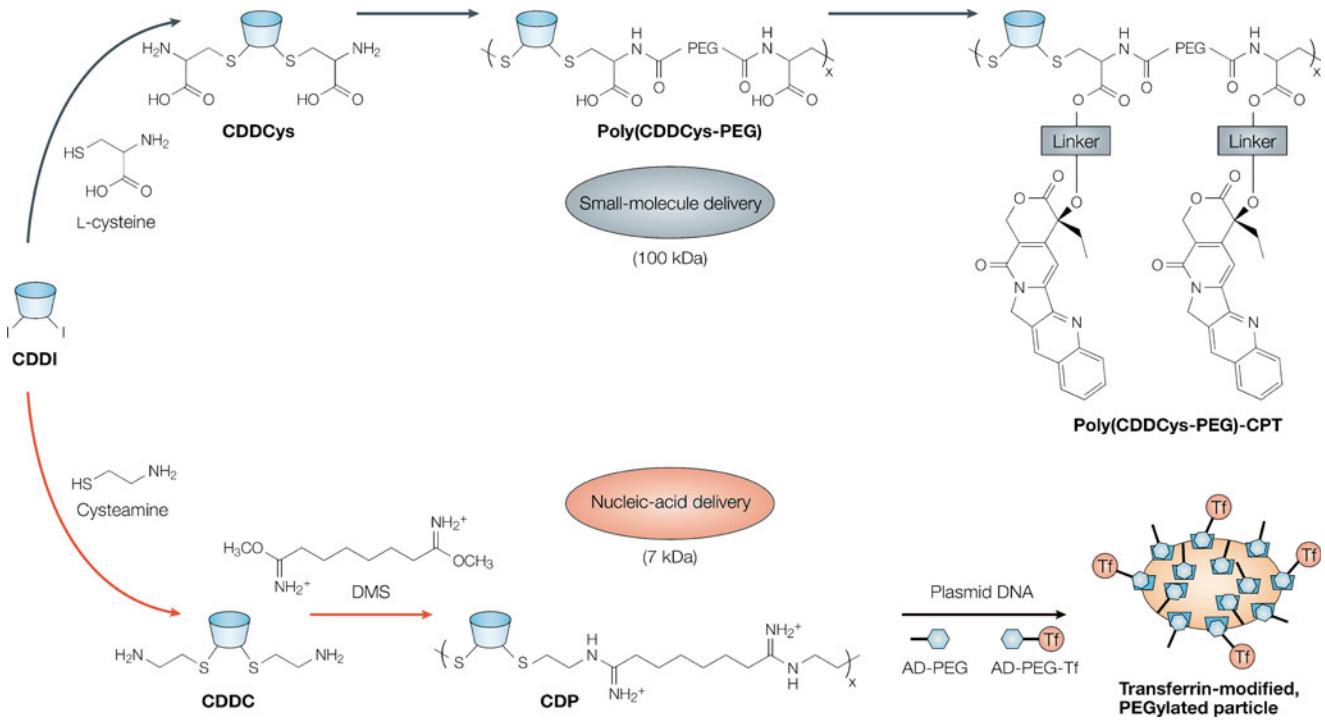

Fig. 2 Examples of linear β-cyclodextrin-containing polymers and their use in compositions with small-molecule (*top pathway*) and nucleic-acid (*bottom pathway*) therapeutics. AD-PEG and AD-PEG-Tf denote adamantane conjugated to polyethylene glycol (PEG) and adamantane and transferrin conjugated to PEG, respectively. (Reprinted with permission from Davis and Brewster, Nat Rev Drug Disc 2004:3:1023-1035). Copyright 2004 Nature Publishing Group).

is now being joined by a new generation of targeted nanocarriers that use ligands directed towards cancer cell surface receptors to localize at the cancer site and internalize their cargo drugs in cancer cells. A growing number of chemotherapeutics are being delivered with enhanced therapeutic indices using these formulations, including paclitaxel, doxorubicin, methotrexate, docetaxel, camptothecin.

Even more transformative research is currently being done on leveraging the properties of nanomaterials for therapeutic effect. These nanotherapeutics exploit the unique properties of nanomaterials for therapeutic gain, such as endocytosis-mediated uptake of nanoparticles to bypass efflux pump mechanisms of multidrug resistance or the ability of iron oxide nanoparticles to act as high sensitivity MRI contrast agents capable of recognizing the tumor microenvironment for site-specific drug delivery. Peptides, aptamers, and other ligands on both first and next generation materials allow for microenvironment targeting, sensing and manipulating, enabling greater therapeutic functionality and versatility. They can target new cancer targets, e.g., cell surface proteins, as well as well-established clinical targets.

SAFETY AND REGULATION OF NANOTHERAPIES

Before nanomaterials can be used in cancer treatments, however, issues of biodistribution and toxicity must be addressed. Biodistribution and cellular uptake of nanoparticles depend on the nanoparticle size, shape, deformability and surface chemistry, for reasons that are poorly understood. Efforts to target drugs to intracellular compartments are complicated by insufficient data and understanding on cellular uptake. The role and importance of targeting agents, e.g., peptides, oligonucleotides and antibodies, in delivering nanoparticles to cells and tissue must also be understood and compared to the EPR effect, to further increase the therapeutic index of existing anticancer drugs (31,32).

New systematic protocols for product safety regulation need to be devised based on a clear set of nanoparticle classification schemes. In this area, NCI's Nanotechnology Characterization Laboratory (NCL) has joined forces with the National Institute of Standards and Technology (NIST) and the U.S. Food and Drug Administration (FDA) to develop standard preclinical toxicology, pharmacology and efficacy assay cascades (30,31). This collaboration is intended to facilitate the clinical development and regulatory review of nanomaterials for future filings with the FDA for Investigational New Drug (IND) or Investigational Device Exemption (IDE) approvals. Complex, multi-functional nanoparticle therapies present special challenges to the current system of regulation and market approval. As composite products, they may fall under the purview of all three branches of the U.S. Food and Drug Administration: drugs, devices, and biological agents, depending on the mode of action. For example, polymeric particle-carrying paclitaxel will be considered as a drug, while nanoshells, which eradicate cancer cells through thermal ablation, will be classified as a device. The FDA formed an Office of Combination Products to make final determinations how such complex constructs should be moved through the agency's regulatory process.

FDA policy is that combination products are assigned to a regulatory review by an individual center within FDA based on the "primary mode of action" (PMOA) of the product, defined as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product." If neither the FDA nor sponsor can determine a PMOA, or if no one of the product's modes is subordinate to another, the product will be classed with similar combination products raising similar safety and effectiveness questions or assigned to the FDA center with the most expertise in the most serious safety and effectiveness questions raised by the product. The FDA allows sponsors to request designation as a combination product and assignment to a particular FDA center for regulatory review.

FUTURE OPPORTUNITIES

The development of nanoparticle-based oncology drugs is at an interesting and promising stage. FDA approval of Abraxane and several on-going clinical trials give confidence that several of these formulations will successfully enter the clinic. It is possible that initially these drug formulations may have limited use and acceptance in the medical community due to the incremental efficacy improvement, high cost, and public concerns about safety of nanotechnology. There is strong evidence, however, that nanoparticle delivery can address several otherwise unsolvable problems in cancer treatment. Thus, future developments need to be clearly focused on specific applications where demonstration of paradigm shifting improvement due to the use of nanotechnology will be apparent. Several of these opportunities are discussed in section III of this paper, such as effective delivery of siRNA therapies and reduction of multi-drug resistance mechanisms. The effective development of these techniques will benefit from strong multi-disciplinary research environments where nanotechnology developers work side-by-side with oncologists and cancer biologists.

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