Published OnlineFirst January 10, 2014; DOI: 10.1158/0008-5472.CAN-13-2787

Meeting Report

Cancer Research

Future Opportunities in Cancer Nanotechnology—NCI Strategic Workshop Report

Piotr Grodzinski and Dorothy Farrell

Abstract

There has been significant progress in utilizing nanotechnology in several areas of cancer care, including *in vitro* diagnostics, imaging, and therapy. The National Cancer Institute, which currently supports an array of research activities in cancer nanotechnology, convened a strategic workshop to explore the most promising directions and areas for future resource investment. The major discussion points as well as the opportunities identified are presented herein. *Cancer Res; 1–4. ©2014 AACR.*

Introduction

The National Cancer Institute (NCI) launched the Alliance for Nanotechnology in Cancer in 2004 in response to emerging innovation in the areas of nanomaterials and nanodevices and their potential for applications in cancer research and care. The program has a translational focus and supports discovery research, which has potential to produce clinically useful outcomes. The Alliance engages a multidisciplinary community of biologists and clinicians, chemists, and engineers to leverage innovation and experience originating from different research backgrounds. To monitor the development of the field and chart its strategies for the future, NCI holds strategic workshops on Cancer Nanotechnology every 5 years. The last workshop was convened in June 2013.

Nanotechnologies for Delivery of Therapies

Nanoparticles are capable of facilitating site-selective drug delivery, enabling increased drug accumulation in the tumor and reduced side effects (1). Many approaches currently under development are evolutionary and provide for delivery of established chemotherapeutics with modified delivery profiles. This strategy of pursuing incremental improvements in pharmacologic and/or toxicologic design may be primarily related to the ease of obtaining active pharmaceutical agents (API) that are already approved by the U.S. Food and Drug Administration (FDA) and the body of regulatory data available for them. A handful of such nanoparticle-based formulations have been approved by the FDA (2). Other compounds could also benefit from the improved solubility and reduced side effects of nanoparticle-based drug delivery. The workshop participants emphasized the importance of taking advantage of the opportunity to "recover" drugs that have failed in early-stage clinical trials or even preclinical studies due to unfavorable toxicity or pharmacokinetic profiles. Nanoparticle formulations may facilitate biodistribution and pharmacologic properties that enable safe delivery of therapeutically effective doses of these compounds. The workshop participants pointed out that although pharmaceutical companies are typically reluctant to work on reformulating their failed candidates, they are often willing to share the compounds with academic researchers. A role for NCI was seen in increasing awareness of such opportunities and access to these compounds.

Other drug candidates to be delivered using nanoparticles, in addition to small molecules include siRNAs and biologics. Systemic delivery of siRNA is greatly improved by nanoparticle packaging through reduction of siRNA degradation in blood and increase in its circulation time. The effective delivery of siRNA may enable discovery of new therapeutics that inhibit previously "undruggable" therapeutic targets. Nanoparticle delivery also assures cellular internalization, which is a precondition for activity of some drugs, although subsequent escape from the endosomal compartment that mediates internalization is a standing design challenge for nanoparticle delivery (3).

Many workshop participants felt there are also emerging opportunities for nanotechnology in the renaissance of interest in immunotherapies for cancer, although some participants were not enthusiastic about this. An effective adoptive cell transfer cancer immunotherapy depends on a successful antigen presentation through the use of dendritic cells. However, obtaining large numbers of dendritic cells from the patient and their *ex vivo* culture is not trivial. An alternate strategy relying on nanoparticles explores designs of artificial antigen-presenting cells. The modular nature of nanoparticle designs provides the opportunity for delivery of combinations of ligands with well controlled per particle densities and thus eliminates the variability observed with cell-based systems (4).

Future Drug Design in Nanomedicine

Nanomedicine constructs are multicomponent systems, involving a carrier, therapeutic component, and often targeting moiety. Optimization of physicochemical properties of such

Authors' Affiliation: Office of Cancer Nanotechnology Research, National Cancer Institute, Bethesda, Maryland

Corresponding Author: Piotr Grodzinski, National Cancer Institute, 31 Center Drive, MSC 2580, Building. 31, Room 10A52, Bethesda, MD 20892. Phone: 301-594-4177; Fax: 301-496-7807; E-mail: grodzinp@mail.nih.gov

doi: 10.1158/0008-5472.CAN-13-2787

Published OnlineFirst January 10, 2014; DOI: 10.1158/0008-5472.CAN-13-2787

constructs is challenging due to the interdependence of characteristics of individual components. The workshop participants acknowledged these difficulties and proposed to move the development of therapeutic constructs beyond the current model in which carrier and therapeutic cargo are independently developed and then combined to form a nanotherapeutic. Optimizing a construct (carrier + drug molecule) as one unit and making this optimization part of an entire drug discovery process will allow nanotherapeutics to become a new class of drugs rather than being delivery vehicles for existing drugs. This approach will bring greater flexibility to the design of APIs because drug properties (solubility, metabolism, biodistribution, and target tissue accumulation) will reflect the combined properties of the drug molecule and nanoparticle. This will relax constraints on API chemical composition, as unfavorable physicochemical properties such as low plasma solubility, can be modified by association with the nanoparticle. This streamlined nanomedicine development approach combined with preparation of high-throughput screening of large combinatorial libraries of nanoparticles with different properties is expected to produce a better path to nanotherapeutic optimization and should result in higher success rate of nanotherapeutics translation to clinical environment.

Recent works (5) demonstrated nanotherapeutic design optimization using screens of libraries containing up to 100 nanoparticle constructs with systematically varied physical and chemical properties, such as particle size, surface polyethylene glycol and ligand density, and drug release profile. This library undergoes an iterative *in vitro* and *in vivo* screening process to optimize drug release, cell surface binding, pharmacokinetic/pharmacodynamic characteristics, biodistribution, and efficacy for a given indication. The broader use of such screening processes to include candidate APIs will lead to new classes of drugs along with well defined and possibly standardized processes of nanotherapeutic optimization.

Next-Generation Nanoparticles and Systems

Materials science will continue to produce new and more functional nanosystems that are responsive to changes in pH, temperature, and enzymatic environment and can recognize changes in physiology or in the state of the disease. Similarly, external triggers such as light or applied electromagnetic fields can also be used to activate nanoparticles. Exploitation of external or physiologic triggers will allow for more sophisticated nanoparticle designs and programmed drug release. Rational and personalized design of nanoparticles, including optimization of pharmacokinetics and tumor accumulation in coordination with drug release kinetics and matching targeting ligand type and density to tumor antigen profile, was also discussed as a path to improving nanoparticle drug delivery performance.

The value of nanoparticles capable of penetrating biologic barriers was acknowledged in discussions about nanoparticle vehicle design. Greater focus should be placed on overcoming biologic barriers such as tumor stroma, the blood–brain barrier, and vascular endothelium, which inhibit effective delivery of drugs to tumor tissue. Nanoparticle designs effectively facilitating alternate routes of oral or nasal delivery in addition to predominantly used systemic delivery were also of interest to the workshop participants.

One new and exciting area discussed at the workshop was biomimetic nanoparticle design. This has already proved helpful in the development of new families of therapeutic nanoparticles: "leukolike" and "plateloids," which have properties that reproduce features of biologic cells to delay uptake by the mononuclear phagocyte system and penetrate across vascular endothelia (leukolike) or adhere firmly to the target vascular surface (plateloids). Another bioinspired approach is the development of cooperative systems of nanoparticles that exploit host signaling networks to generate superior functionalities. A system relying on the coagulation signaling cascade resulting from deliberately inflicted tissue damage to recruit "clot-targeted" nanomedicines to the tumor was recently demonstrated (6). These systems demonstrate communication and bioresponsive capabilities that go well beyond the traditional design of contemporary nanoparticles for drug delivery.

Nanotechnology-Based Diagnostics

There was consensus that *in vitro* nanotechnology-based devices and systems can be instrumental to early and precise diagnosis and therapy monitoring, but that further development of reliable cancer biomarkers is urgently needed. Nanotechnology-enabled devices capable of simultaneous measurement of multiple protein biomarkers with high sensitivity and specificity have been demonstrated (7). The information collected using these devices can be analyzed to establish correlations among biomarker levels and optimize panels containing a minimum number of biomarkers needed to identify the disease (8). These platforms should be able to identify signatures of disease, progression, and therapeutic responsiveness. Ideally, direct probing of the tumor environment, rather than performing analysis on bodily fluids, can provide more clinically relevant information. There was an interest in implantable devices that could monitor parameters associated with tumor growth and its response to treatment over extended period of time.

Molecular imaging is also benefiting from nanotechnology developments. Bioactivatable imaging probes can detect biomarkers *in vivo* and can serve as monitoring systems of disease. For example, it is known that many types of enzymes are constitutively active or inactivated during the process of oncogenesis, but there is no clinically relevant way to assess enzyme activity *in vivo*. Researchers are developing probes based on readouts of optical imaging, MRI, photoacoustics, and radionucleotides as well as their combinations to measure proteases, kinases, hydrolases, and peroxidases. In general, dynamic imaging probes can be activated by changes associated with tumor microenvironment *in vivo* and serve as monitoring systems of disease.

Understanding Nanoparticle Delivery Mechanisms

The majority of experimental evidence for the enhanced permeability and retention (EPR) effect, believed to be

Published OnlineFirst January 10, 2014; DOI: 10.1158/0008-5472.CAN-13-2787

responsible for accumulation of nanoparticles at the tumor site, originates from animal testing. EPR and its variation among different tumor types needs to be further and better understood in humans, and parameters associated with high versus low EPR need to be identified (9). Answering these questions will be fundamental to establishing a process for selecting patients who have high probability of responding to nanotherapies.

Better understanding of interactions between nanoparticles and cells is also critical. Construct design parameters leading to effective intracellular uptake and trafficking of nanoparticles and efficient release of cargo are still not entirely clear. For example, the debate on the advantages of "active targeting" using specific targeting agents such as peptides, aptamers, or antibodies over "passive targeting" (relying solely on the EPR effect) is still not settled (1). Whether active targeting increases tissue localization or just cellular internalization remains a somewhat open question, although a body of evidence for tumor-specific delivery seems to support increased cellular internalization as the dominant mechanism for enhanced therapeutic efficacy. Nanoparticles enter the cell using endocytosis, so designing effective strategies for endosomal escape to prevent the degradation of cargo in lysosome and instead enabling its effective intracellular trafficking into the cytoplasm is critical to effective delivery and utilization of particle-bound drug molecule (3). The workshop participants expected that the use of modeling tools that incorporate the dynamic interactions of nanoparticles with the complex physiologic environment into which they are delivered will aid the design and improve effectiveness of future nanoparticle delivery vehicles.

Preclinical and Clinical Considerations

Although nanotechnology researchers can readily develop nanotherapeutics that are efficacious in cell culture and animal models, translating them into the clinical setting is a much more complicated matter. The difficulty of translation from both the technologic and funding standpoints was broadly discussed at the meeting. There were concerns that despite very active research in the area of nanotherapeutics, the number of nanodrugs that reach FDA approval stage is still limited (10). The ability of animal models to predict efficacy and adverse reactions in humans is an issue of critical importance and selecting an animal model that is representative of conditions in human tumors is a challenging task. For example, stromal tissue is believed to be a major barrier to effective delivery into pancreatic tumors, yet availability of animal models that possess stroma is quite limited. Clinical translation will require use of appropriate systems that recapitulate the tumor microenvironment and conditions to accurately model the interactions that will occur when the nanoparticle is applied in the intended clinical situation.

Several stages of the nanoparticle drug development pipeline require sophisticated laboratory and manufacturing services, which can consume significant funds to be accomplished. The areas of lead drug selection, scale up using good manufacturing practices (GMP), investigational new drug (IND) enabling good laboratory practices (GLP) toxicology studies in small and large animals, supply chain considerations, and regulatory planning all go beyond the typical responsibilities and expertise of an academic researcher, yet need to be addressed in the translational process. NCI formed the Nanotechnology Characterization Laboratory (NCL) to assist academic and industrial researchers in preclinical characterization of nanomaterials. NCL has carried out studies on a very large number of nanoparticle delivery vehicles carrying various cargo and has collected initial data on toxicology and biodistribution in small animals. These efforts need to be further supported and advanced.

Regulatory pathways for nanotherapeutics are relatively well established and the FDA does not have special review criteria for nanotechnology-based products. These submissions follow the same process as other drugs or devices and their regulatory path is determined on the basis of the final mode of action of a particular construct. However, the complexity and multiple components constituting a nanoconstruct can increase the amount of required data for review and make gaining IND or investigational device exemption approval more challenging as compared with less complex drug molecules.

Overall, meeting participants observed that the majority of translational efforts in nanomedicine are carried out by small companies, most of them spun out from academic laboratories. These companies have extremely limited resources and struggle not necessarily because of an innate weakness in their science or products, but because they are not able to handle the complexities associated with scale-up and manufacturing of large quantities of stable product.

Summary

The workshop participants were optimistic about future development of nanotechnologies in cancer. Further progress in the field was viewed as moving along two parallel tracks. The first track will be associated with ongoing translation to the clinical environment and the second with the development of new tools and techniques in the research arena. It is expected that small-molecule drugs in nanoparticle-based formulations currently undergoing clinical trials will be joined by other modes of therapy, including siRNAs and biologics. Active targeting, when appropriate, will be used more frequently. To make translational efforts more wide spread, access to reliable GLP characterization and GMP manufacturing facilities will need to become more available. Imaging based on nanotechnology will evolve toward greater use of bioactivatable probes for assessing the tumor microenvironment. Imaging will be also be increasingly used in intraoperative imaging to guide real-time surgery using single and multimodality imaging nanoconstructs. *In vitro* diagnostic devices have matured to a stage in which the development of additional device modalities with new transduction methods does not seem necessary. However, devices need to demonstrate their robustness in tests with complex clinical samples before entering main stream use. These devices could also find greater use in establishing clinically relevant diagnostic, prognostic, and predictive signatures.

Published OnlineFirst January 10, 2014; DOI: 10.1158/0008-5472.CAN-13-2787

The research community pursuing cancer nanotechnology is expected to continue relying on multidisciplinary environments of chemists, physicists, and engineers driving innovation in nanotechnology devices and tools and biologists and clinicians defining compelling areas of applications and clinical needs. It is hoped that involvement of clinicians in the early stage of research and technology development will increase.

The NCI alliance program has promoted the development of cancer nanotechnology community since 2004 and is expected to continue doing so through a dynamic network program. Participants stressed the importance of NCI leveraging the network by encouraging collaboration both within and with outside researchers, particularly in clinical research. In this period of constrained government funding, it is also important to maximize collective support for the further development of the field. Partnerships with external stakeholders, including nonprofit organizations interested in cancer research and patient advocacy groups, and involvement of industrial partners pursuing clinical translation will be an important and ongoing part of the strategy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received September 26, 2013; revised December 3, 2013; accepted December 23, 2013; published OnlineFirst January 10, 2014.

References

1. Kamaly N, Xiao Z, Valencia PM, Radovic-Moreno AF, Farokhzad OC, Targeted polymeric therapeutic nanoparticles: design, development, and clinical translation. Chem Soc Rev 2012;41:2971–3010.
2. Duncan R, Gaspar R. Nanomedicine(s) under the microscope. Mol Pharm 2011;8:2101–41.
3. Sahay G, Querbes W, Alabi C, Eltoukhy A, Langer R, Anderson DG, et al. Efficiency of siRNA delivery by lipid nanoparticles is limited by endocytic recycling. Nat Biotechnol 2013;31:653–8.
4. Steenblock ER, Wrzesinski SH, Flavell RA, Fahmy TM, Antigen presentation on artificial acellular substrates: modular systems for flexible, adaptable immunotherapy. Expert Opin Biol Ther 2009;9:451–64.
5. Hrkach J, Von Hoff D, Mukkaram Ali M, Andrianova E, Auer J, Campbell T, et al. Preclinical development and clinical translation of a PSMA targeted docetaxel nanoparticle with a differentiated pharmacological profile. Sci Transl Med 2012;4:128ra39.
6. von Maltzahn G, Park JH, Lin KY, Ruoslahti E, Sailor MJ, Bhatia SN, et al. Nanoparticles that communicate *in vivo* to amplify tumour targeting. Nature Mater 2011;10:545–52.
7. Shi Q, Qin L, Wei W, Geng F, Hood L, Mischel PS, et al. Single-cell proteomic chip for profiling intracellular signaling pathways in single tumor cells. Proc Natl Acad Sci U S A 2012;109:419–24.
8. Haun JB, Castro CM, Wang R, Peterson VM, Lee H, Weissleder R, et al. Micro-NMR for rapid molecular analysis of human tumor samples. Sci Transl Med 2011;71:71ra16.
9. Prabhakar U, Maeda H, Jain RK, Sevick-Muraca EM, Zamboni W, Farokhzad OC, et al. Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. Cancer Res 2013;73:2412–7.
10. Venditto VJ, Szoka FC Jr, Cancer nanomedicines: so many papers and so few drugs!. Adv Drug Deliv Rev. 2013;65:80–8.

Cancer Research
The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

AACR American Association for Cancer Research

Future Opportunities in Cancer Nanotechnology——NCI Strategic Workshop Report

Piotr Grodzinski and Dorothy Farrell

Cancer Res Published OnlineFirst January 10, 2014.