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## NCI Image Guided Drug Delivery Summit

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### Abstract

On April 17<sup>th</sup> 2010 scientists from academia, the National Cancer Institute (NCI), and the Food and Drug Administration (FDA) assembled at “The NCI Image Guided Drug Delivery Summit,” in Washington DC, to discuss recent advances, barriers, opportunities and regulatory issues related to the field. The meeting included a scientific session and an NCI/FDA session, followed by a panel discussion of speakers from both sessions. Image guided drug delivery (IGDD) in cancer is a form of individualized therapy where imaging methods are used in guidance and monitoring of localized and targeted delivery of therapeutics to the tumor. So a systematic approach to IGDD requires mechanisms for targeting, delivery, activation and monitoring of the process. While the goal in IGDD is to optimize the therapeutic ratio through personalized image-guided treatments, a major challenge is in overcoming the biological barriers to the delivery of therapeutics into tumors and cells. Speakers discussed potential challenges to clinical translation of nano-based drug delivery systems including in-vivo characterization of nanocarriers, pre-clinical validation of targeting and delivery, studies of biodistribution, pharmacokinetics, pharmacodynamics and toxicity as well as scale-up manufacturing of delivery systems. Physiological and quantitative imaging techniques may serve as enabling tools that could potentially transform many existing challenges into opportunities for advancement of the field.

### Introduction

The NCI Image-Guided Drug Delivery (IGDD) Summit was held in conjunction with the annual meeting of American Association for Cancer Research, on April 17<sup>th</sup>, 2010 at the Embassy Suites Hotel, Washington, D.C. A short version of this program was presented on April 19 as an NCI Session in the annual AACR program. The purpose of this summit was to focus on scientific challenges and opportunities in the field and discuss the roles of government agencies in providing research support and regulatory issues related to IGDD and its translation into the clinic

The meeting was organized by the Cancer Imaging Program (CIP) of NCI and divided into two sessions; Session I - an overview of scientific advances in IGDD, and Session II - federal resources currently available to researchers in the field. Each session was followed by a short panel discussion. The first session was introduced by Keyvan Farahani, PhD, Acting Chief, Image-Guided Interventions Branch (CIP), who provided a brief NCI programmatic overview and a description of the purpose and outline of the meeting. Dr. Farahani described IGDD in cancer as personalized therapy where imaging techniques can

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be utilized in quantitative assessments of tumor-targeted therapeutic delivery, distribution, uptake and response.

The overarching goal in IGDD is to optimize the therapeutic ratio ideally through optimized biodistribution, pharmacokinetic (PK), and pharmacodynamic (PD) of drugs and personalization of oncologic therapies. The full implementation of IGDD requires (a) drugs that can be imaged, localized or targeted and activated at the tumor site and (b) imaging techniques that provide anatomic and quantitative functional measures of the process at various spatial and temporal resolutions for active monitoring. Imaging can play an important role not only in validating drug delivery but also in PK, PD, and biodistribution studies of therapeutic agents. Because imaging is inherent to IGDD, its application post-therapy may provide early indications of response to therapy. Based on this approach, a Program Announcement was developed by NCI entitled “Image-Guided Drug Delivery in Cancer” [PA 09-253] (1).

## Session I: Scientific Opportunities in IGDD

Although there are many challenges toward a full implementation of IGDD, the identification of barriers and ongoing research in various approaches to overcome them are yielding significant progress. These were brought into sharp focus in presentations in this session highlighting a systematic approach to IGDD, including targeting, delivery, activation and monitoring.

In a presentation entitled “Caveolae as Cancer Targets” Jan Schnitzer, MD (Proteomics Research Institute for Systems Medicine, San Diego, CA) identified achieving efficacious *in-vivo* tumor cell targeting as a challenge and a key impediment to effective oncological treatment. He highlighted the use of endothelial caveolae in traversing the endothelial cell barrier to deliver antibody linked imaging and therapeutic agents into solid tumors, and explained that even with numerous “biomarkers” and targets described in the literature, there are few if any that are readily “targetable” *in vivo*. The presence of numerous biological interfaces that the drug must traverse limits targetability to a great extent. Endothelial caveolae provide a means to go beyond standard vascular targeting of endothelial cell surfaces to actually cross these normally restrictive biological barriers, via transcytosis that deliver drugs to specific targets deep inside tissues and into the tumor (2,3). Nanoparticles (NPs) can be targeted to caveolae using antibodies to aminopeptidase P (APP), a protein concentrated within caveolae. These targeted NPs can then be used to transport drug and imaging agents across the endothelial membrane. This targeted transport of NP to the tumor significantly enhances delivered dose, reducing the required systemic dose and the resultant toxicity (4).

In “Nanotechnologies in Image-Guided Drug Delivery,” Gregory Lanza, MD, PhD (Washington University, St. Louis, MO) presented an overview of the state of nanotechnology-enabled IGDD in cancer along with barriers to translation and possible solutions. Nanomedicine-based IGDD focuses on the use of imaging agents not only for drug delivery but also for early detection, characterization and treatment monitoring. The last decade has seen an exponential growth of research in nanomedicine. Iron oxide NPs are being used for detection of gliomas using MRI and molecular probes (5), and for characterization, treatment and serial follow up of nascent solid tumors (6). Dendrimer platforms can deliver iron oxide, gold or gadolinium to tumor cells with high specificity and uptake while new asymmetric polymers offer improved targeting and intracellular concentration of payloads (7). The inherent ability of HDL to transfer cholesterol esters from its core to cytosol within cells is being utilized for cytosolic delivery of imaging probes and drugs (8), and photodynamic therapy using polyacrylamide nanoparticles is showing

potential (9). Early clinical success has recently been seen by Chang, et al. (10) in targeting of cationic liposomes to transferrin receptor (TfR), a biosignature frequently elevated in aggressive or proliferative cancer cells.

Although nanotechnology is ideal for IGDD its translation into the clinic has been slow. Development of NP-based IGDD faces unique challenges. Pharmaceutical nanocarriers are three dimensional entities that may contain two or more functional moieties and present unique regulatory approval issues. Achieving fully validated NP products requires rigorous in-vivo toxicity assessments. Interaction and active dialogue between chemist and engineers designing NPs with input from physicians and cancer biologists providing clinical insight is essential for moving the field forward. These issues may be overcome with better product development and industrial collaboration with pharmaceutical and medical imaging partners.

Chrit Moonen, PhD (Bordeaux University, Bordeaux, France) described magnetic resonance imaging (MRI)-guided focused ultrasound (FUS) as a means for localized drug delivery, activation and monitoring. He described recent developments in the application of MR-guided FUS to selectively disrupt the blood-brain-barrier (BBB) in a mouse model for the delivery of trastuzumab (Herceptin™) to brain tissue (11). This approach in IGDD may play a significant role in treatment of a variety of brain ailments, including primary and metastatic tumors. Focused ultrasound can also be used for drug release from temperature sensitive liposomes (12) and can promote temperature dependent drug or gene activation (13,14). These temperature changes can be monitored by MRI, with the added advantage of imaging the pharmacodistribution of co-released MRI contrast agents.

Esther Chang, PhD (Georgetown University, Washington, D.C.) presented her work on multifunctional tumor targeting platform technology involving targeted liposome encapsulation of chemotherapeutic agents or tumor suppressor genes. A part of this work is completing a Phase I clinical trial in which the targeted nanoparticle, encapsulating a tumor suppressor gene (wild-type p53), for treatment of solid tumors including head and neck cancer, is demonstrating safety and efficacy. The intravenously delivered NP can be seen in the metastatic tumors bypassing the normal tissue. A combination trial is already planned and awaiting the conclusion of the Phase I study. According to Chang imaging brings immense capability for studying PK/PD and biodistribution. It allows these parameters to be studied along with the determination of therapeutic duration and response, which can lead to change in therapeutic ratio and dose adjustment, thereby reducing systemic toxicity.

## Panel I

The panel discussion was led by Gary Kelloff, MD (CIP/NCI) from an oncology perspective related to the key IGDD objective of improving the therapeutic ratio by direct delivery to the tumor environment. Even with advent of molecular targeted therapy, the maximum tolerated drug dose is still used to define cytotoxicity and efficacy, driving Phase II studies. The concept of optimal biological dose was introduced with the hope that dosing could be defined in biological terms. This has not happened as yet, although imaging is changing this paradigm. There is a need to engage clinicians, especially in the neoadjuvant setting where a patient is diagnosed with life threatening disease, to understand that opportunities exist to test these new technologies discussed during the summit. Most of these therapies fall into the category of companion diagnostics. The capability to evaluate therapeutic effects by imaging can provide enormous savings in treatment time, cost, and morbidity, as well as the ability to screen patients for specific therapies. In the nanotechnology arena, the complexity of nanoconstructs makes it difficult to acquire the data needed to obtain IND (Investigational New Drug) exemption from the Food and Drug Administration (FDA). The resources needed are usually larger than academia and public sector can provide alone, making public-

private partnerships very important. Another caveat for the field is the limited number of companies interested in translational challenge for nanomedicine.

Following questions from the audience, the panel continued the discussion of barriers and provided suggestions for taking a multifunctional NP through an IND application. As these NPs contain multiple components it is important to consider PK/PD of individual components (i.e., targeting moiety, therapeutic and imaging agents, etc.) as well as the overall system. It was also emphasized that incorporating an “in use” (or approved) drug or an imaging probe into a multifunctional NP for testing an IGDD system would be advantageous and increase the probability of success when applying for an IND. The importance of ideal targeting *in vivo*, considering heterogeneity of the tumor milieu and allowing for better penetration across biological barriers to increase efficacy of drugs and imaging probes was also emphasized. The lack of such targets was considered to be a barrier in developing effective therapies for cancer.

## Session II: Federal Resources

In addition to grant opportunities in IGDD, NCI provides centralized resources to support investigations of NP-based IGDD. Anil Patri, PhD, Deputy Director, NCI Nanotechnology-Characterization Laboratory (NCL) presented the resources that NCL provides to investigators of nanotechnology in cancer. Joining resources with National Institute of Standards and Technology (NIST) and the FDA, NCI established the NCL to perform preclinical NP efficacy and toxicity testing and to serve as a national resource for all researchers to facilitate regulatory review of nanotechnologies intended for cancer therapies. The NCL also provides critical infrastructure and characterization services to NP developers from academia, industry and other government laboratories. Multi modality *in vivo* imaging is a major resource of NCL that is of particular importance in the development of nanotechnology-based IGDD approaches. Data acquired in NCL studies are linked to the network of NCI Cancer Centers and related programs through the Cancer Nanotechnology Laboratory (caNanoLab) web portal (15). This portal is designed to facilitate data sharing in the research community, allowing the submission and retrieval of information on NPs, including the protocols and data on experimental characterization from physical and *in vitro* assays and related publications.

Nakissa Sadrieh, PhD from the FDA Center for Drug Evaluation and Research presented regulatory consideration and FDA’s approach to the review of applications involving nanotechnologies with relevance to IGDD. She explained that after development and characterization of nanocarriers and drug delivery devices the next step in translation is the submission to FDA for an IND application for clinical testing. Nanoparticles are well suited for drug delivery because they can serve as vectors and multicomponent constructs containing imaging, sensing, targeting and therapeutic entities. These nano-constructs can be regulated as “devices” or “combination products”, multicomponent constructs that deliver imaging agents and/or drugs, especially for IGDD systems. Pharmaceutical nanoparticles currently on the market are mostly reformulations of existing conventional pharmaceuticals with few approved entities for use as oncological or imaging agents. As for any pharmaceutical, NPs have important regulatory considerations including product quality and safety. The existing regulatory framework can accommodate the types of NP therapeutics that are currently under development. The FDA does not have specific guidance documents that pertain to nanomaterials and until unique issues regarding NP-containing therapies are fully identified, FDA maintains that all existing guidance documents are applicable and should be used by investigators when submitting applications for approval of clinical testing of NP-based drug delivery systems. The sponsor must show appropriate characterization, evaluation and quality control measures for manufacture of these NP-based drug or delivery

device before clinical testing can proceed. With the use of resources like NCL and developing a dialogue with FDA early in the process, the FDA approval is a hurdle that can be overcome.

## Panel II

The panel discussion opened with remarks by Piotr Grodzinski, PhD (NCI), describing the NCI Nanotechnology Alliance in Cancer. The alliance is engaged in efforts to harness the power of nanotechnology to improve the way we diagnose, treat and prevent cancer. There has been tremendous activity in moving technologies from academic laboratories to small businesses, which for the most part have been spinoffs from academic institutions. Some of these industrial partners have moved the technologies to clinical investigation; eight trials related to the program are now underway. Another significant outcome has been the leveraging of NCI funds to obtain further funding from multiple additional sources. NCI is now starting initiatives such as the IGDD initiative, focusing on specific applications as an extension of the NCI Nanotechnology Alliance in Cancer program. The panelist saw this as maturing of the nanotechnology field and anticipated that in five years this initiative will also be successful in moving IGDD systems into the clinic.

There were extensive discussions in both panels on the importance of quality control and validation of IGDD systems along with the need for development of consensus documents, protocols and procedures for characterization of nano-based systems that could be used by the FDA to develop guidance documents. There was consensus that higher prioritization and collective research efforts are needed to overcome barriers to realization of drug delivery.

Image-guided drug delivery can help us understand and define factors preventing tumor therapies from being effective. Technology development for non-invasive and dynamic imaging at high resolution is essential to study drug or probe transport *in vivo*. These can only be achieved by bringing academics and industry together into the process at an early stage. IGDD can play an important role in providing personalized targeted therapies and lowering the overall costs by reducing morbidity and mortality associated with cancer.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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