Cancer Nanotechnology Symposium
Overcoming Barriers to Collaboration

National Cancer Institute Symposium jointly sponsored by:
CASE Comprehensive Cancer Center
Case Western Reserve University
University Hospitals of Cleveland Ireland Cancer Center
Cleveland Clinic Taussig Cancer Center

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Introduction

If the Nation is to meet the 2015 goal of eliminating death and suffering from cancer, clinicians will need new ways to detect, treat and prevent cancer and metastases. One expectation of the field is that this era of post-genomic science, with its emphasis on genomic and proteomic analysis and systems biology, will generate unprecedented advances in knowledge, fostering paradigm-changing diagnostics, therapeutics and preventatives. At the same time, nanotechnology is rapidly making a mark among a small but growing group of cancer researchers funded by the National Cancer Institute (NCI) as a disruptive set of tools capable of leveraging scientific advances into a new generation of targeted clinical agents.

As a key component of Alliance for Nanotechnology in Cancer, which is guided by the recently approved Cancer Nanotechnology Plan, the NCI desires to boost the number of multidisciplinary teams of cancer and nanotechnology researchers who are interested in working together to develop new methods for diagnosing, treating and preventing cancer. To help catalyze the formation of such multidisciplinary teams, the NCI is holding a series of symposia aimed at bringing together experts in nanotechnology and cancer research, both basic and clinical, for roundtable discussions among one another regarding possible common ground for applying nanotechnology to cancer-related research and development projects.

On October 27, 2004 the NCI convened the second of these symposia, since the Alliance started, in close collaboration with the CASE Comprehensive Cancer Center, Case Western Reserve University, the University Hospitals of Cleveland Ireland Cancer Center and the Cleveland Clinic Taussig Cancer Center. This symposium, held in Cleveland, OH, brought together scientists and clinicians with a wide range of expertise from multiple research institutions and cancer clinics across northern and central Ohio and the Midwest, for a series of technical presentations on the intersection between cancer and nanotechnology. These presentations were designed with two ideas in mind: to give

nanotechnologists and cancer researchers an idea of the state of the art in each other's disciplines, and to generate ideas for collaborations between the two groups.

PLENARY SESSION

The meeting opened with welcoming remarks by Dr. Shuvo Roy, co-director of the BioMEMS Laboratory at the Cleveland Clinic; Dr. Mauro Ferrari, special advisor to the NCI on cancer nanotechnology; Dr. Stanton Gerson, director of both the CASE Comprehensive Cancer Center at Case Western Reserve University and the University Hospitals of Cleveland Ireland Cancer Center, and Dr. Derek Raghavan, director of the Cleveland Clinic Taussig Cancer Center. Dr. Ferrari alerted the audience, as a backdrop for the meeting, to the newly launched Alliance for Nanotechnology in Cancer, $144 million program designed to integrate nanotechnology into many areas of cancer therapeutics and diagnostics, while Dr. Gerson reminded the attendees of the wide-ranging effort in biomedical nanotechnology that is already ongoing in the Cleveland area. Dr. Raghavan commented on the linkage between this meeting and an event on bionanomedicine held in Cleveland over the past two days.

Cancer overview

Following these introductions, Dr. Harold L. Moses, director of the Vanderbilt-Ingram Comprehensive Cancer, gave an overview of cancer as a disease characterized by changes in multiple signals and pathways. Understanding these pathways, he said, will change the way we treat cancer, as evidenced by a new generation of drugs such as Gleevac. He predicted that ongoing efforts in translational and clinical research will revamp the current "search and destroy" paradigm into a "target and control" approach to cancer detection and treatment. After commenting on some of the oft-heard criticisms of what some perceive as the field's limited success at reducing mortality from cancer, particularly when compared to heart disease, Dr. Moses noted that ongoing advances in molecular diagnostics will provide that dramatic decline in cancer mortality because it will enable physicians to treat cancer at its earliest, most treatable stage, and perhaps even prevent cancer from developing in the first place.

Dr. Moses then briefly discussed why the majority of current cancer therapies are limited in their effectiveness. Cancer cells, he said, are genetically and epigenetically different from normal cells. He told the audience that the emergence of a cancer cell likely involves of 4-6 rate-limiting steps or mutations, though that number may be as high as 10. It is clear, though, that several mutations are needed before a cell appears abnormal structurally. Yet despite the overwhelming evidence that cancer involves aberrations in multiple processes, drugs to treat cancer must be effective in isolation to be approved. Moreover, he added, many pathways are redundant and must be knocked out in combination to be effective. In addition, most of the preclinical models in which cancer drugs have been tested have had little predictive value. New mouse models, based on genetic manipulation and using small interfering RNA (siRNA) hold promise because they more accurately model human cancer.

Also needed are better human clinical trials, particularly for newer generation drugs that are molecularly targeted. As an example, he cited the failed initial clinical trials for

EGFR inhibitors. Though the results were as negative as could be, the physicians who had enrolled patients could see that there were subsets of patients who were absolutely benefiting from this drug. Why the bad data? There was unrecognized genetic heterogeneity among the patients in that mutations in the EGFR gene had occurred in all responders and in none of the non-responders. But with no means of monitoring this as the trial went on, there was no way to adjust the clinical trials process to address this issue.

In an attempt to improve the clinical trials, Dr. Moses is spearheading a joint effort involving the AACI, AACR and ASCO to develop new clinical trials procedures that would incorporate molecular detection and analysis in the clinical trials process. A recent workshop, which brought together industry representatives, cancer center representatives, advocacy group leaders, officials from the NCI and FDA, and the cancer-related scientific societies, came up with a multi-tiered approach that would start with a small, detailed tier-one trial, involving selected academic centers, industry and the NCI, at a cost of $40,000-$50,000 per patient, but that would include molecular profiling as part of the trial. Though expensive, all of the stakeholders accepted that this type of trial represents a better and economically justifiable way to conduct clinical trials for cancer drugs, explained Dr. Moses. As an example of the type of data that might be collected in such a trial, Dr. Moses presented an overview of MALDI-based proteomics assays that have been able to discriminate between normal and lung tumor patients, as well as subclasses of lung cancer. This data also revealed two proteins, as yet unidentified, that could reliably identify nodal involvement. Some 15 peaks were also identified that identified patients who would die within the next 12 months. Conducting such data as part of an ongoing clinical trial would provide immediate benefits in terms of diagnosis, disease classification, prediction of treatment response, and prognosis. Longer-term potential benefits from such studies include target identification and treatment selection.

Dr. Moses then returned to the critical value of early detection, stating that we can reliably cure early stage disease, as shown by the success that early diagnosis in the form of colonoscopy, PAP smears, and skin examinations. He then discussed how proteomics has the potential to provide a far greater number of easily administered and less expensive early detection assays. He closed his talk with his vision for clinical cancer evaluation in 2010. A patient with cancer X comes in to his or her physician and receives a multidisciplinary cancer consult that includes a biopsy of cancer using proteomics on the tumor, stroma, and blood, and nanoscale imaging. Based on the results of these assays, the physician will be able to select a multi-agent, targeted therapy that achieves a 95% durable response. By 2015, he continued, his hope is that physicians will be able to order proteomic and genomic analyses on their patients with risk factors for cancer to identify those who need to receive targeted, preventive agents. By 2020, he added, such assays should be inexpensive enough to perform on all individuals.

Nanotechnology overview

Dr. Chad Mirkin, director of the Northwestern University Institute for Nanotechnology, then gave an overview of some of the tools and techniques that are fueling the nanotechnology revolution in science and engineering. In general, the development of

such tools and techniques has received the most attention from nanotechnologists, with applications in biomedicine still in the early stages of development. He added that this multidisciplinary field is likely to have its first impact in the delivery of therapeutics, with diagnostic applications coming afterwards.

Reviewing his group's work on developing methods to control architecture at the 1-100 nanometer length scale, Dr. Mirkin noted how architectures below 100 nm fall between the expertise of microelectronics fabricators and chemists, yet this is also the scale of biology. He then discussed a technique known as dip-pen nanolithography, which evolved from atomic force microscopy into a writing tool that has allowed his group to build at decent speeds structures that are one molecule high. His group has also modified this technique to print many types of materials and to create arrays with as many as 1.2 million element on a 3-inch piece of silicon. Using dip-pen nanolithography should make it possible to create biological nanoarrays with patterns that reproduce those of biology. Such arrays could be used to study receptor distribution, protein-protein interactions, cell-cell adhesion, multi-valent interactions and even cancer cell migration on multi-valent surfaces that mimic "normal" or altered stroma.

Dr. Mirkin then discussed why nanotechnology will be a critical enabling technology for diagnostics. To begin with, new materials with new properties offer higher sensitivity and higher selectivity at lower cost. Nanotechnology also requires lower amounts of expensive reagents and tissue samples, and may enable the development of miniaturized, hand-held point of care systems that do not require enzymatic amplification to achieve useful results. Indeed, his group has been developing a wide variety of nanoscale bioassays using a wide range of detection technologies, including silver-staining, light absorbance, electrical amplification, Raman spectroscopy, and laser and diffraction grating. He also noted that a commercial version of this system has been developed by Nanosphere.

He then went on to discuss the unique properties of oligonucleotides-functionalized nanoparticle probes. Among the superior attributes of such probes, he listed their high stability, resistance to photobleaching, chemical tailorability, and their ability to support multiple types of functionality. He predicted that the next generation of nanoparticles will come with biobarcodes that will lead to a new generation of highly sensitive, specific, and inexpensive diagnostics for trace constituents. His group has already demonstrated one such system that can detect prostate specific antigen (PSA) at attomolar level, corresponding to about 20 copies of PSA. In contrast, today's clinical assay for PSA has a sensitivity limit of approximately 3 picomolar. Such sensitivity could make PSA a useful marker for breast cancer and as a marker for following relapse of prostate cancer after therapy. Dr. Mirkin then added that a similar system for detecting DNA can identify as few as 10 copies of a given DNA segment, a sensitivity in the zeptomolar range without amplification.

In closing, Dr. Mirkin highlighted the prime attributes of these nanotechnological tools. First, he said, is the unprecedented sensitivity for protein markers, which will provide researchers the ability to search for trace quantities of a given protein and use newly

discovered trace proteins as markers for disease. Second, these nanoscale tools are adaptable for multiplexing and simultaneous detection of multiple protein targets in one solution. Taken together, there properties will result in new ways of studying proteins and DNA from single cells.

In the subsequent question and answer session, one attendee asked what the major limiting factor was for moving nanoparticles into mainstream cancer research. Dr. Mirkin responded that there is a lack of suitable infrastructure to make and characterize nanoscale particles. He has approached this problem by creating companies to make and disseminate materials. The Nanotechnology Characterization Laboratory will serve an important role in eliminating the characterization bottleneck.

Another researcher in the audience asked if nanoscale assays will ever be reduced to something that the average citizen could run in their home. Dr. Mirkin responded that he would have said no to that question four years ago. Today, however, he believes there is a real possibility, but that more work is needed to identify suitable diagnostic targets. Dr. Moses added that as such tests become available, the field will have to answer the question of how to prevent discrimination based on perceived molecular risk for cancer.

BRIDGING COMMUNICATIONS

This session, jointly moderated by Dr. Nancy Olenick of Case Western Reserve University, and Dr. Aaron Fleischman, co-director of the BioMEMS Laboratory at the Lerner Research Institute, started with a presentation by Dr. Andrei Gudkov of the Lerner Research Institute on p53 and NF-κB, two molecules that play a key role in triggering apoptosis in tumor cells and that may form the basis of therapy that can make tumors more susceptible for treatment. As an example, he discussed renal cell carcinoma, a difficult to treat tumor that affects 25,000 new patients yearly and causes 17,000 deaths a year. Screening a series of compound, Dr. Gudkov and his colleagues found that quinacrine, a 9-aminoacridine drug used as an antiseptic since 1943, is able to reactivate p53 in both *in vitro* and *in vivo* assays. Coincidentally, this drug also is an inhibitor of NF-κB.

Another way in which these proteins may be useful in cancer therapy is to turn off p53 in healthy tissue to avoid the side effects of chemotherapy. Toward that end, Dr. Gudkov and his group looked for small molecules that would protect against radiation damage, which they were able to find but which triggered an unanticipated problem involving gastrointestinal sensitivity. The group decided to look at NF-κB inhibitors, instead, finding that flagellin, a protein secreted by intestinal organisms, showed promise. A version modified to render it non-toxic and stable was able to protect normal mice against the normal ravages of radiotherapy.

Lance Liotta, of the National Cancer Institute, then spoke about an ongoing joint NCI/FDA initiative using microtechnologies aimed at realizing Dr. Moses's vision of using biomarkers to choose the optimal therapy tailored to an individual patient, to monitor success of therapy, provide early diagnosis of disease and early warning of therapy-associated toxicity. The current program is developing two approaches: blood

profiling using proteomics chips and laser-capture microdissection. Both show promise, but both have serious technical challenges that must be overcome before they become widely applicable. For serum proteomics, the primary issues are ones of specificity – distinguishing cancer from normal cells and those affected by other diseases – and sensitivity having to do with the trace amounts of the key marker proteins.

Dr. Liotta noted that the first applications will not be for general population screening, but as a follow up screening method to improve the specificity of other diagnostic modes, such as spiral CT. Already, he added, he and his team have been able to identify serum proteomic patterns that correlate well with the presence of premalignant pancreatic cancer. One new avenue of research is to examine the proteins carried by other proteins in blood, which act as concentrators of these trace proteins. His group has found over 2000 new proteins this way, and is now attempting to see if there is any useful diagnostic information contained in these proteins. He believes that nanoscale harvesting devices should be able to improve the sensitivity and collection of these trace proteins in blood.

Since cancer is a product of the tissue microenvironment, core needle biopsies and robotic automated microdissection, combined with proteomic arrays and labeled quantum dots, offer a new approach to profile entire tumor region. Using off the shelf technology, Dr. Liotta's group has been able to detect proteins at a two-cell level, enabling them to spot proteomic profiles that revealed a novel biochemical pathway leading to treatment resistance. His group has already developed a drug that can circumvent this pathway, and he hopes to test this drug's ability to turn resistant patients into responders.

Dr. Cheryl Willman, director of the University of New Mexico Cancer Research and Treatment Center, then spoke on the use of molecular profiling to classify cancer. She noted that leukemia is a great model disease for cancer "stem cell" biology, since even solid tumors are clonal outgrowths of very few stem cells. She explained that human leukemias are derived from clonal expansion of hematopoietic stem cells in the bone marrow. She added that acute leukemias are hundreds of different cancers characterized by distinct genetic mutations, most of which affect intracellular proteins, and that leukemia cells have an adhesion dependence on marrow stroma and vasculature for survival, making them similar to solid tumor cells. This ability to adhere to surrounding cells makes these malignant cells more difficult to kill. Indeed, even when leukemia patients achieve remission, they still have leukemia cells that are significant in number.

Using data mining and visualization software developed at Sandia National Laboratories, and available at http://hsc.unm.edu/crtc/willmanresearch, Dr. Willman and her colleagues were able to analyze data taken from three large cohorts of leukemia patients: infant leukemia, pediatric ALL and adult AML. This effort, developed under the auspices of an NCI Director's Challenge, showed clearly that the three groups of leukemia did not correlate well with the pathological diagnosis. Instead, these diseases seemed to be better classified according to three different biochemical pathways identified in the course of this project. In addition, the visualization software, named VxInsight, revealed distinct clusters of gene expression that were clearly associated with remission and fatal disease.

The next step in this research, she concluded, is to move from gene expression profiling to protein-based profiling.

Dr. Fleishman then discussed a multidisciplinary project, involving nanomagnetic tags, fluid dynamics, magnetics, microfluidics, and electrical engineering, aimed at developing a cell identification chip with a sensitivity exceeding 1 in 25 million cells. This chip, which will use magnetic fields to separate cells, labeled with magnetic nanoparticles, is in the design stage of development, with work ongoing to create fabrication methods that will produce shaped magnetic fields. Dr. Fleishman's group is also using MEMS techniques to create microscale ultrasonic transducers that can be used to achieve high resolution, minimally invasive ultrasonic imaging.

In the morning's penultimate talk, Dr. Miquin Zhang, of the Center for Nanotechnology at the University of Washington, discussed her group's work on using nanotechnology to solve problems related to brain cancer diagnosis and therapy. She noted that there are many obstacles to this type of research, including the fact that the blood-brain barrier is difficult to cross unless particle size is kept below 20 nm, about half the size of most commercially available nanoparticles. As a result, Dr. Zhang's group has devoted a significant amount of time to developing 10 nm nanoparticles that have the additional property of not aggregating with one another. Specifically, her group has developed a nanoparticulate construct that includes polyethylene glycol (PEG), and infrared dye, and chlorotoxin, which appears to target glioma cells. These particles do cross the blood-brain barrier and were able to reach and bind to glioma cells in an animal model.

Dr. Zhang then discussed her group's effort to couple a nanoparticle to an agent that might reveal that treated tumor cells are undergoing apoptosis *in vivo*. As a probe, her group used Annexin V, a well-established indicator of apoptosis. Using these nanoparticles did, indeed, reveal apoptosis underway following chemotherapy. She closed her talk by showing how conjugating methotrexate to a tumor-targeted nanoparticle allowed this drug to be delivered specifically into cells, where a pH change caused it to be released from the nanoparticle. Such an approach should minimize toxicity to normal cells.

Gregory Lanza, of the Washington University School of Medicine in St. Louis, closed the morning session with a review of the work that his group has done using fluorocarbon-based nanoparticles to deliver MRI contrast agents, as part of NCI's Unconventional Innovations Program (UIP). His group has been using $\alpha_v\beta_3$-targeted nanoparticles loaded with tens of thousands of gadolinium ions, which they have shown can detect 2 mm tumors in mice and 3 mm tumors in rabbits. He noted that these particles are detecting angiogenesis surrounding tumors that are so small he would be unable to find them on a conventional MRI scan.

He then discussed using these same nanoparticles to deliver therapeutic payloads specifically to tumors. Because these nanoparticles are lipid coated, they will fuse with a targeted cell. Placing the drug in the lipid monolayer, rather than in the particle core, allows the drug to enter a cell via a lipid exchange process that occurs when two cells

make contact with one another. Because the drug remains trapped in the particle's lipid layer unless there is contact with a targeted cell, there will be little if any drug released into the general circulation. He noted that adding gadolinium to the core would allow imaging and dosing using the same nanoparticle.

In closing the session, all the speakers noted that there is a great opportunity for collaboration in these developing areas. Indeed, without collaboration, particularly with industry, these efforts are far less likely to succeed in a useful timeframe.

TOWARD PARTNERSHIPS

Following an after-lunch talk by Dr. Jeffery Schloss, technology development coordinator for the National Human Genome Research Institute, on the NIH's perspective on nanotechnology, the afternoon session began with a few brief introductory remarks by moderator Bryan Williams, chair of the department of cancer biology at the Lerner Research Institute. Then, Dr. Jinming Gao, director of the Center of Biomolecular and Nanoscale Engineering for Targeted Therapeutics at Case Western Reserve University, spoke about the barriers for collaboration between nanotechnology and cancer researchers. He noted that there are differences in motivation, pitting a desire to improve patient care against advancing science and technology for the sake of gaining new knowledge. Temporal barriers – translating scientific advances into clinical advances takes longer than physician's expect – and spatial barriers – the two groups of researchers usually reside in different institutions – also make it hard to establish collaborations, as does a lack of communication and common understanding of current medical problems and available technologies.

To create effective partnerships, it is necessary, explained Dr. Gao, to establish a common vision and create synergy among efforts in different fields. Communicating differences, he added, creates a trusting team atmosphere, particularly when the focus is on translational research that crosses from the bench to the bedside. He noted that small pilot grants, on the order of $20,000, can do wonders toward spurring collaboration, as will joint seminars. Student ambassadors, who either have internships in collaborator's laboratories or joint advising from multiple departments, can play a big role in making collaboration proceed smoothly and fruitfully. He explained that a local consortium of researchers from the cancer center and Case Western Reserve University, the Biomolecular and Nanoscale Engineering for Targeted Therapeutics (BioNETT), had made use of these mechanisms to develop nanoscale micelles that target tumors, image them, and deliver therapeutics in a controlled manner.

James Baker, Jr., co-director of the Center for Biomedical Engineering at the University of Michigan, spoke next on another effort funded by NCI's UIP program, this one aimed at developing polymeric dendrimers as multifunctional imaging, detection and therapeutic devices. He began his talk by noting that nanotechnology must offer unique capabilities in order to succeed in the clinical realm. Materials must be biocompatible for *in vivo* applications, and products must offer improved outcomes, reduce utilization of health care services, and save money. These are big, but not impossible, hurdles to overcome.

He then described the dendrimers that he and his colleagues have been developing. These are small (10-12 nm) particles, of very well-defined size, that can escape circulation and enter cells. As an example of the multidisciplinary effort involved in creating these particles, and some of the twists that can accompany this research, he recounted how his group tried using folate as the targeting agent only to have the particles fail miserably in various *in vitro* and *in vivo* tests. But with the help of researchers with expertise in molecular modeling at the Pittsburgh superconducting center, the reason for this failure was uncovered and Baker's group redesigned the dendrimers based on this finding. The resulting nanoparticles target tumors very well, and several imaging and therapeutic applications are now under development. So far, he said, data generated in mice look promising.

Speaking next, William Carson III, from The Ohio State University, talked about a nanochannels delivery system for treating malignant melanoma. The trend in surgery today is to conduct fewer, shorter surgeries coupled with more aggressive therapy. The nanochannels delivery device that he and his colleagues are developing is designed to give constant, steady release of drug. The main challenges to this work, said Dr. Carson, are team communications, device limitations, device construction, and understanding clinical parameters.

Reza Ghodssi, of the University of Maryland in College Park, then discussed the interdisciplinary team that is working with MEMS sensors and actuators lab to develop multi-step biochemical process sequences in biomicrosystem environments (bioMEMS). The idea is to take a top down approach, which is capable of creating a minimum feature size of 50 nm, to build devices that can probe systems using a broad range of stimuli with high spatial localization. In contrast, biotechnology, he noted, operates in a bottom-up manner up to about 5 nm. To date, this group of researchers has been exploring the use of the natural polymer chitosan, which will deposit in a pH dependent mechanism on a cathode surface in defined patterns. This enables the assembly of labile biological components within a MEMS device with good spatial control.

Bridget Wilson, co-director of the Cancer Center Microscopy Facility at the University of New Mexico Cancer Research and Treatment Center, discussed her work on exploring problems in signaling through spatio-temporal organization of molecules during the signaling process. She noted that abnormal signaling is a characteristic of cancer cells, explaining that signals are initiated and propagated at the membrane, which is organized into nanoscale subdomains. Also, membrane reorganization occurs during signaling process in a dynamic process.

Her group's approach to the problem of studying the membrane during signaling is to isolate the plasma membrane away from the cell without using detergents. She explained that the technique her group uses involves sandwiching a cell between a microscope cover slip and an electron microscopy grid. If you do this just right and pull the sandwich apart, various subdomains of the membrane stick to the grid. Using this technique, Dr. Wilson's group was able to show that there are pools of EGFR receptors along with

clustered bunches of the receptor. One limitation of such studies is that there are no good probes for lipids, so Dr. Wilson and her colleagues decided to develop new probes for electron microscopy studies based on shapes and metals and using a ceramic core. So far, her group has created a probe for phosphatidyl serine, which is normally found on the insides of cells. She and her team are currently working with investigators at Sandia National Laboratories to explore the usefulness of these probes.

At the end of her talk, Dr. Wilson noted that one way to build interdisciplinary teams is to start with an interesting problem, and then meet regularly with team members in order to learn all the languages used by the disciplines in the team. Recruiting students is key to such an effort, as is providing learning forums and interdisciplinary courses. She also noted that welcoming students from disparate departments can really spur such team-oriented research. She added that the State of New Mexico holds regular scientific meeting designed to foster partnerships among researchers at the State's various institutions.

ADVANCING CANCER RESEARCH

The day's final session, designed to inform the attendees about the NCI's new nanotechnology initiates, was moderated by Dr. Maciej Zborowski. The first talk in the session was given by Dr. Mauro Ferrari, the NCI's special expert on nanotechnology and an associate vice president for health science technology and communications at the Ohio State University. Before reviewing the NCI's Cancer Nanotechnology Plan, Dr. Ferrari spoke briefly about many of the nanoscale technologies that are already either in clinical use or are well developed as tools. He included liposomes used to deliver drugs; nanochannels, cantilevers, and other nanoscale technologies that can be used to provide a new realm of sensitivities for detecting molecules important in cancer; nanoparticles for use in molecular imaging of malignant lesions both before and after delivery of therapy; and nanoshells, which are proving useful in imaging and tumor-killing applications.

He then reviewed what the NCI hopes nanotechnology can do for the cancer field, including:

- Identify signs of disease early
- Visualize the development of disease
- Capture early signals of drug efficacy
- Deliver improved cancer therapy with increased therapeutic efficacy, fewer side effects, and enabling personalized medicine
- Accelerated review of therapeutic agents, both nano-based and regular
- Improve quality of life

The key to success, Dr. Ferrari noted, will be the development of vibrant interdisciplinary teams that are driven by clinical translation. The NCI believes, he added, that the Cancer Nanotechnology Plan, and the newly launch Alliance for Nanotechnology in Cancer, offers significant opportunities for integrating targeted development work with the private sector. Such efforts must maintain a constant eye on the regulatory perspective.

Travis Earles, of the NCI's Office of Technology and Industrial Relations, which is overseeing the Alliance and the Cancer Nanotechnology Plan, then presented details about the Alliance. He reviewed the 18-month process for developing the Alliance, emphasizing the input that NCI received from a wide range of researchers. He noted that the Alliance represents the first step in the implementation of the Cancer Nanotechnology Plan and laid out the six key focus areas:

- Molecular imaging and early detection
- *In vivo* imaging
- Reporters of efficacy
- Multifunctional therapeutics
- Prevention and control
- Enablers of research

In contrast to the NIH Nanomedicine Roadmap, with its emphasis on basic research, the activities of the Alliance will be driven by clinical applications. Toward that end, the major programs in the Alliance include the Centers of Cancer Nanotechnology Excellence; multidisciplinary research teams using training grants for postdoctoral and senior research awards; the development of nanotechnology platforms for cancer research using individual projects modeled after the bioengineering research program; and the Nanotechnology Characterization Laboratory (NCL), which will establish a pathway for clinical development and regulatory approval of nanotechnology-driven diagnostics, imaging agents and therapeutics.

Dr. Scott McNeil, director of the NCL, then gave a brief description of the NCL's mission, which is to overcome obstacles that the research and development community identified during the construction of the Cancer Nanotechnology Plan. Those obstacles include a critical lack of available standardized nanomaterials, little in the way of biological characterization, and an uncertain pathway for regulatory approval. In response to these hurdles, the NCL will have four objectives:

- Identify and characterize critical parameters related to the behavior of nanomaterials in the body.
- Establish and standardize an assay cascade for nanomaterials characterization that facilitates rapid regulatory review of nanodevices for cancer clinical trials
- Examine the biological characteristics of the multicomponent/combinatorial aspects of nanoscale therapeutic, diagnostic and detection platforms
- Engage and facilitate academic and industrial-based knowledge sharing of nanomaterials performance data and behavior generated by pre-clinical testing.

He then detailed some of the assays being developed and announced that the NCL was ready to begin accepting materials for testing. In response to a question, Dr. McNeil said it was the NCL's goal to complete the characterization/assay cascade within 18 months of material submission.

The final speaker of the afternoon was Dr. Daniel Gallahan of the NCI, who spoke about the newly launched integrative cancer biology program (ICBP). The goal of the ICBP is to establish consortia of independent centers that will develop and apply computational and mathematical models to the understanding and management of cancer. In addition, the ICBP will develop and implement a training and outreach program for a broader and

longer impact on this emerging field. He noted that the first year of the program will fund six full centers and three planning centers, all of which will be linked with one another and with program officers at NCI in order to facilitate the type of iterative research that will be needed to understand cancer as a disease of biological systems.