# Meeting Report: Strategic Workshops on Cancer Nanotechnology

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**Abstract:**
The National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer is a comprehensive, systematized effort encompassing the academic and private sectors in multidisciplinary research and dedicated to the use of nanotechnology in cancer prevention, diagnosis, and therapy. The program is designed to move basic science discoveries into the development pipeline and eventually into clinical use. As the program approaches the midway point of its five-year funding, NCI is once again assessing the field of cancer nanotechnology to determine the current needs and gaps in this area of research. Toward that end, the NCI's Office of Technology and Industry Relations (OTIR) held three strategic workshops on cancer nanotechnology covering the areas of *in-vitro* diagnostics and prevention, *in-vivo* diagnosis and imaging, therapy and post-treatment. To each of these meetings, NCI's program staff invited a wide range of experts from academia, industry, the non-profit sector, and the Federal government, including those from the National Institutes of Health and the U.S. Food and Drug Administration. This meeting report is the summary and compilation of recommendations developed at these strategic workshops.

**Introduction:**

Cancer is one of the main public health problems facing the United States. The statistics for cancer are daunting; the number of Americans who will die of cancer in 2008 is projected to be over 550,000 (nearly one in four of all deaths will be cancer related). (1) The number of people who will be diagnosed with the disease will exceed 1.4 million. With an increasing aging population, the number of people who develop cancer is only going to increase in the years ahead. On the positive side, there are over 12 million cancer survivors today in the United States and their numbers are steadily increasing, mainly due to progress in early screening and treatment. Globally, greater than 70% of all cancer deaths occur in low and middle income countries; hence, the issues surrounding cancer are clearly not a domestic matter.

More than three years ago, the National Cancer Institute (NCI) began the process of developing and funding the NCI Alliance for Nanotechnology (http://nano.cancer.gov) in an attempt to bring the power of nanotechnology to bear on developing new solutions to the major challenges of the disease.(2-6) It has been recognized that nanotechnology carries great potential; if this knowledge is applied to cancer, it could someday revolutionize the way cancer is viewed, diagnosed, and treated as a disease.(7) Moreover, nanotechnology spans all aspects of the Institute's strategic objectives ranging from tools to provide better insight into the fundamentals of cancer biology, through early diagnostics and imaging, to improving cancer treatment and care. In order to organize the discussion topically, three one-day strategic workshops were convened in Spring with the following thrusts:

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| Workshop I: | *In-vitro* Diagnostics and Prevention |
| Workshop II: | Therapy and Post-Treatment |
| Workshop III: | *In-vivo* Diagnosis and Imaging |

These workshops were designed to assess the status of cancer nanotechnology and determine what are the opportunities, the needs of the field and existing knowledge gaps. At each workshop, the attendees listened to few short overview presentations from thought leaders on the technical challenges confronting the use of nanotechnology in cancer and the most promising nanotechnologies that may overcome these challenges. The talks gave the clinician (*e.g.,* oncologist) and technologist (*e.g.,* chemist) perspective and provided impetus for brainstorming and additional discussion. To further guide discussion, NCI staff provided attendees with a list of NCI's thoughts on possible "holy grail" applications for cancer nanotechnology. These included:

- *Personalized diagnostic "nano" kit to screen for 100 cancer-associated agents within the time of a doctor's visit.*
- *Set of nanotechnology tools for "real-time" elucidation of cancer properties for the tumor nano/microenvironment at both the intracellular and extracellular levels.*
- *Tools to monitor and control biodistribution as a function of particle size, shape, and targeting scheme.*
- *Multifunctional particle systems capable of diagnosis and subsequent tailored therapy with controlled release.*

- *Robust efficacy feedback monitoring tools for novel cancer therapeutic drugs in clinical trial settings to reduce the time from months to days or hours.*
- *Nanoparticle platform for effective and controlled delivery of therapeutics to the brain.*
- *Design tools to look beyond tumor size (e.g., microenvironment, follow metastasis).*
- *Tool to identify tumors that are far smaller (100x, 1000x) than those detectable with today's technology.*

After the opening presentations, the invited scientists were divided into three smaller working groups and worked on a list of a common questions and topics. Those included:

*Question 1: Within the theme of each workshop, what are the most important goals in cancer research (not just nano-driven) that might be achieved within the next 5 years? Within the next 10 years?*
*Question 2: How and where do you see (or have seen) nanotechnology contributing to the areas identified in Question 1?*
*Question 3: What are the major barriers (e.g., technical, financial, infrastructure, organizational/managerial) that would be of hindrance in reaching these goals?*

A compilation of responses and recommendations compiled at the workshops are presented here.

**Overarching Themes in the Recommendations**

Each workshop produced a series of important and specific recommendations that are discussed below. In addition, there were several recommendations that appeared as common themes throughout the three workshops.

*The Technologist and the Clinician*

In spite of organizing the workshops to have overview lectures from a technologist and clinician perspective, overwhelmingly the audience pointed out the continued need for technologists, biomedical researchers, and clinicians to work together in order to make the most out of the opportunities that nanotechnology can generate. Many applauded NCI's efforts in creating multidisciplinary team science environment, and expressed hope that such efforts would continue to be expanded going forward. It was believed that he Alliance program provided a huge boost to the field of cancer nanotechnology and that the Institute should continue providing avenues for both intra-Center for Cancer Nanotechnology Excellence (CCNE)(8) and inter-CCNE partnerships to form. In addition, NCI should consider new mechanisms for creating strategic partnerships with other agencies and other fields to maximize the impact that nanoscience will have on cancer research and clinical oncology. A consensus exists that nanotechnology may be able to drive new advances that will improve cancer diagnosis, imaging, and therapy, in large part because the nature of cancer could be understood better resulting from these disparate research communities working together.

*Multifunctional/Multimodal Nanotechnology Agents*

Prevailing throughout the three workshops was the notion that the real (paradigm shifting) power of cancer nanotechnology will occur when an agent/platform combines two or more of the modalities (associated with workshops thrust areas) namely, diagnosis, imaging, and/or therapy. Clearly, a strong advantage for a nanoparticle system is the potential for a 'plug & play' like approach to integrate multifunctionality and multimodality. However, maintaining a more pragmatic vision, the participants recommended that 'uni-' functionality/modality be established first and subsequently translated to the clinic. The increase in the complexity of the multi-modal solution should then occur gradually. Other recommendations include:

- *Integrate imaging and therapy so that the oncology community can monitor the effects of therapy in real time, both for conventional agents and for nanotechnology-enabled agents.*
- *Multifunctional probes – intracellular identification of markers combined with a subsequent imaging or therapeutic event*
- *Develop multimodal therapy using a nanoplatform that can deliver a novel form of therapy, such as heat, in combination with a standard therapy.*
- *Probes that can localize intracellular concentrations of an analyte and then be addressed and triggered to release a therapeutic payload.*
- *The high payload-carrying capacity of nanoparticles can improve sensitivity and resolution by dramatically increasing the local concentration of an imaging agent at a tumor.*

**_In-vitro_ Diagnostics and Prevention Workshop**

One of the keys to the growing number of cancer survivors is emergence of early diagnostics of the disease. The participants at this workshop believed that further advances to develop and adopt new nanotechnology methodologies that enable cancer to be discovered earlier in its development and ultimately to prevent it from occurring in the first place was paramount. A positive feedback loop mechanism (diagnosis, treatment, and monitoring of treatment results) will be important for pushing this field forward. Early detection methods will be enabled by improved early-stage biomarkers and followed by more effective therapies designed to target early stage disease. As a result, developing new early detection methodologies becomes even more important in the quest to reduce the incidence and mortality from cancer. The long term vision for developing new *in-vitro* diagnostics is to be able to take a body fluid, a blood sample for example, and determine the presence of low-abundance biomarkers, characteristic to cancer that would ideally identify the type of tumor present, specify the appropriate therapy, and predict the outcome of that therapy.

Specific recommendations for future development include:

*Early Detection*

- *The development of modular diagnostics based on bodily fluids, such as blood, serum, cerebrospinal, urine, stools, or saliva. In certain cases, breathe as a*

*collection source. Elucidating the variables that are needed to optimize the modules for a particular bodily fluid.*

- *Multifunctional capabilities – one platform capable of detecting nucleic acid and protein.*
- *Develop new in-vivo diagnostics that would pinpoint tumors and their metastatic lesions (e.g., Detecting rare cancer cells as on cancer-associated molecules).*
- *Nanotechnology should lead to new assays with lower cosst and higher sensitivity markers.*
- *Nanotechnology-based detection and analytical technologies could be incorporated into a multiplexed nano-probe that could be inserted (or targeted) into a tumor, act as sensors of the local environment, and that are then removed when the probe is excised.*

**Therapy and Post-Treatment Workshop**

Targeted cancer therapies represent a glimpse into the future of oncology with ERBB and VEGF based therapies being the first successful examples of using targeted approaches. Similarly, it has been demonstrated that 'nano-carriers' delivery can improve the efficacy of anticancer drugs and reduce the associated toxicities. The participants at this workshop shared a common vision that that nanoparticles will be able to improve the therapeutic index for a wide variety of anticancer drugs, and that this improvement alone will be of great potential benefit. Moreover, multifunctional aspects and the monitoring therapeutic response using "smart" nanoparticles will also represent a paradigm-changing event in oncology.

Specific recommendations for future development include:

*Therapeutic Development, Delivery, & Monitoring*

- *Develop a monitoring test (ultimately to be designed for home use) for monitoring disease response to therapy and disease progression; the immune system to determine if the immune system is attacking the tumor or supporting it, information that would contribute to clinical decision-making.*
- *Create endpoint measurements in addition to apoptosis to assess therapeutic efficacy.*
- *Develop nanomaterials and targeting strategies aimed specifically at the tumor microenvironment.*
- *Develop tumor cell surface targeting ligands to deliver nanoparticles to the tumor site in humans.*
- *Improve the pharmacokinetics of current nanocarriers in order to decrease the toxicity of their drug payloads.*
- *Understand how nanomaterials affect cell signaling and drug response.*
- *Development of new chemistries that would trigger drug release from a nanoparticle only at the site of a tumor*
- *Develop new biomaterials that would change the biodistribution patterns of nanomaterials and their drug cargos.*
- *Create methods for 'programming' nanoparticles for use in personalized anticancer therapy.*

- *Activation of targeted nanoparticle could enable timed release of imaging agents and drugs, while bidirectional communication with the nanoparticle would provide therapeutic feedback.*

This workshop group also recommended that the NCI continue its efforts to work with FDA and clinicians to address the unique features of nanoparticles and the opportunities to change the approval paradigm as far as modularity and personalized therapies are concerned. The group also recommended that the NCI and its Nanotechnology Characterization Laboratory (NCL; http://ncl.cancer.gov) continue their efforts to develop bioanalytical methods suitable for characterization of nanoparticles and to fund efforts for mathematical modeling that might help drug developers rationalize their choice of a specific nanoparticle for a particular application. To accomplish these goals, the audience identified several critical needs. These included the need for relevant animal models of human cancer; the development of a streamlined approach to evaluate toxicology, pharmacokinetics, and the efficacy of potential nanotherapeutics, essentially expanding the scope of the NCL's mission, and along the lines of the current NCL effort; and the creation of an infrastructure for translational nanotechnology research that would feed promising therapeutics into the nation's clinical trials apparatus.

### *In-vivo* Diagnosis and Imaging Workshop

Perhaps, the most impacting use of nanotechnology which is relatively close to the clinic is *in-vivo* imaging. Improving diagnosis by detecting tumors at ever small stages, via *in-vivo* imaging, opens new opportunities for improving treatment, as well as for understanding of metastasic processes. Currently, imaging provides limited information about the tumor type, with subsequent surgery and then pathology being used to actually identify the tumor and determine therapy. A vision that this workshop participants shared is to develop *in-vivo* imaging techniques which can provide more specific information about tumor type and tumor environment and thus virtually eliminate the need for surgical biopsy prior to determining the therapy. Moreover, the group believed that nanotechnology-enabled imaging methodology would be capable of monitoring the response to therapy in real time. This, in turn, would reduce the time lapse to determine if therapy is effective, would greatly improve the quality of life for patients by getting patients off ineffective drugs that could cause adverse side effects, and would decrease the likelihood that drug resistance might develop before an effective therapy is established for particular patients.

Specific recommendations for future development include:

**Imaging Tools**

- *Develop minimal or non-invasive methods to access to currently inaccessible organs such as brain, pancreas, lungs, and ovaries and to help better understand in vivo tumor biology.*
- *Develop enhanced imaging technologies and contrast agents to help diagnose, stratify, and monitor patient treatment.*

- *Improve spatial and temporal resolution, as well as sensitivity, in order to detect the very low tumor burdens, improve surgical guidance, and monitor the response of those small tumors to therapy.*
- *Achieve a broader distribution of existing imaging agents beyond the major research medical centers.*
- *Develop image-guided biopsies with simultaneous, multiplexed in situ analysis to eliminate the need for diagnoses based on histopathology.*
- *The development of more sensitive and less expensive imaging hardware, such as the development of carbon nanotube-based CT instruments.*
- *Develop entirely new nano-imaging strategies to change limits of detection.*
- *Improve detection systems for optical imaging in humans by optimizing imaging platforms to take advantage of the unique payload carrying characteristics of nanoparticles.*

**Additional Common Themes**

In addition to establishing recommendations specific to each workshop thrust, there were several additional comments that appeared as common themes throughout the three workshops as listed below. As the level of detection is lowered and sensitivity increases, the issues associated with 'good' biospecimens and sample preparation practices were clearly viewed as a concern to translating nanotechnology platforms in a timely manner. Improving the specificity of biomarker assays (and reducing non-specific binding) was another common issue.

Other common categories, which were identified, include:

*Biospecimen & Sample Preparation*

- *Analytical issues: Developing techniques to increase signal to background (chemists and biologists approach these problems differently. Chemists and biologists, for instance, try to increase signal, while physicists look to reduce noise and the medical community works to make sense of poor signals).*
- *Sample preparation issues: Improving faster and facile sample concentration techniques.*
- *Improved biospecimen sampling and validation, which is absolutely critical for retrospective studies and biomarker validation.*
- *Specimen collection issues: Preparing the patient for sample donation (e.g., nanocarriers be administered prior to sample collection to ensure trace biomarkers are recovered; in vivo collection using injected particles).*
- *New nano-capabilities for making metabolic correlations between anoxia response and changes in glycolysis, for example, and the development of cancer or the occurrence of metastasis.*

*Biomarkers*

- *New (and improved) recognition agents – better antibodies or antibody equivalents.*
- *Validation of new cancer specific biomarkers.*
- *Develop faster validation, higher selectivity and higher affinity systems for molecular recognition using nanotechnology*

- *Low-cost panel assays for multiple protein markers, such as those being developed already for ovarian cancer.*

*Biomedical Informatics and Modeling/Simulations*

- *Develop medicine metrics using database information that includes patient profiles with imaging and outcomes. There is no mechanism now for "one-stop shopping" that accumulates all the different types of imaging combined with outcome data. In addition, there is a need for automated analytical tools that can extract information from the images in a way that can be incorporated into these databases and searched.*
- *Develop simulations for nanodevices to predict and validate in-vivo pharmacokinetic and pharmacodynamic measurement as well as to design better nanomaterials.*
- *Develop better models of cancer that are more predictive of response in human cancers.*

*Funding and Training Mechanism*

The groups believed strongly that the NCI needs to continue and expand on the multiple funding mechanisms that it has developed for creating focused, multidisciplinary teams. In particular, funding should include expanded opportunities for individual investigators to work with the CCNEs and the Platform Partnerships (R01s), and for students and postdoctoral fellows to engage in more multidisciplinary training opportunities (e.g., F32/F33) in order to get the next generation of researchers firmly entrenched.

Additionally, participants expressed a desire for a Defense Advanced Research Projects Agency (DARPA)-style funding initiative for more translational projects and exploratory-based for more fundamental research. The workshop participants were in agreement regarding the value of focused research aimed at bringing cancer nanotechnology-enabled platforms into the clinic, but there were some discussions about how NCI can transition this type of applied research to the private sector providing additional funding (which is not in place, currently), while at the same time maintaining future funding for either cutting edge research or fundamental research that will feed into the translational research phase.

**Summary**

The strategic workshops echoed a clear consensus that cancer nanotechnology had made very significant advancements over the past three years, both in fundamental discovery and the development of practical, clinic-worthy solutions. The participants clearly believed that the NCI supported infrastructures, such as the CCNEs and NCL, have aided the cancer nanotechnology community in awareness, nurture of promising science, dissemination of 'best practices', and standardization of characterization methods. The audience viewed many more discoveries to ensue as long as funding is available to maintain and expand number of researchers working in the field.

Cancer nanotechnology field has the potential to better monitor therapeutic efficacy, provide novel methods for detecting and profiling early stage cancers, and for enabling surgeons to delineate tumor margins and sentinel lymph nodes. This field is

well positioned to provide improved methods for imaging and staging cancers and for more effectively delivering therapeutics in a targeted manner to tumors. Ultimately, if the nanotechnology researchers can establish methods to detect tumors at a very early stage, that is, before tumors begin to vascularize and metastasize, cancer will become a disease that will become amenable to complete cure via surgical resection. The impact on the disease survival rates and disease management expenditures could be exceedingly high.

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8. The eight Centers of Cancer Nanotechnology Excellence (CCNEs) listed below for the NCI Alliance for Nanotechnology in Cancer are (in alphabetical order): 1) Carolina Center of Cancer Nanotechnology Excellence (University of North Carolina, Chapel Hill); 2) Center for Cancer Nanotechnology Excellence Focused on Therapy Response (Stanford University); 3) Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer (University of California, San Diego); 4) Emory-Georgia Tech Nanotechnology Center for Personalized and Predictive Oncology (Emory University and Georgia Institute of Technology); 5) MIT-Harvard Center of Cancer Nanotechnology Excellence (MIT and Harvard University, Massachusetts General Hospital); 6) Nanomaterials for Cancer Diagnostics and Therapeutics (Northwestern University); 7) Nanosystems Biology Cancer Center (California Institute of Technology); and 8) The Siteman Center of Cancer Nanotechnology Excellence (Washington University).