

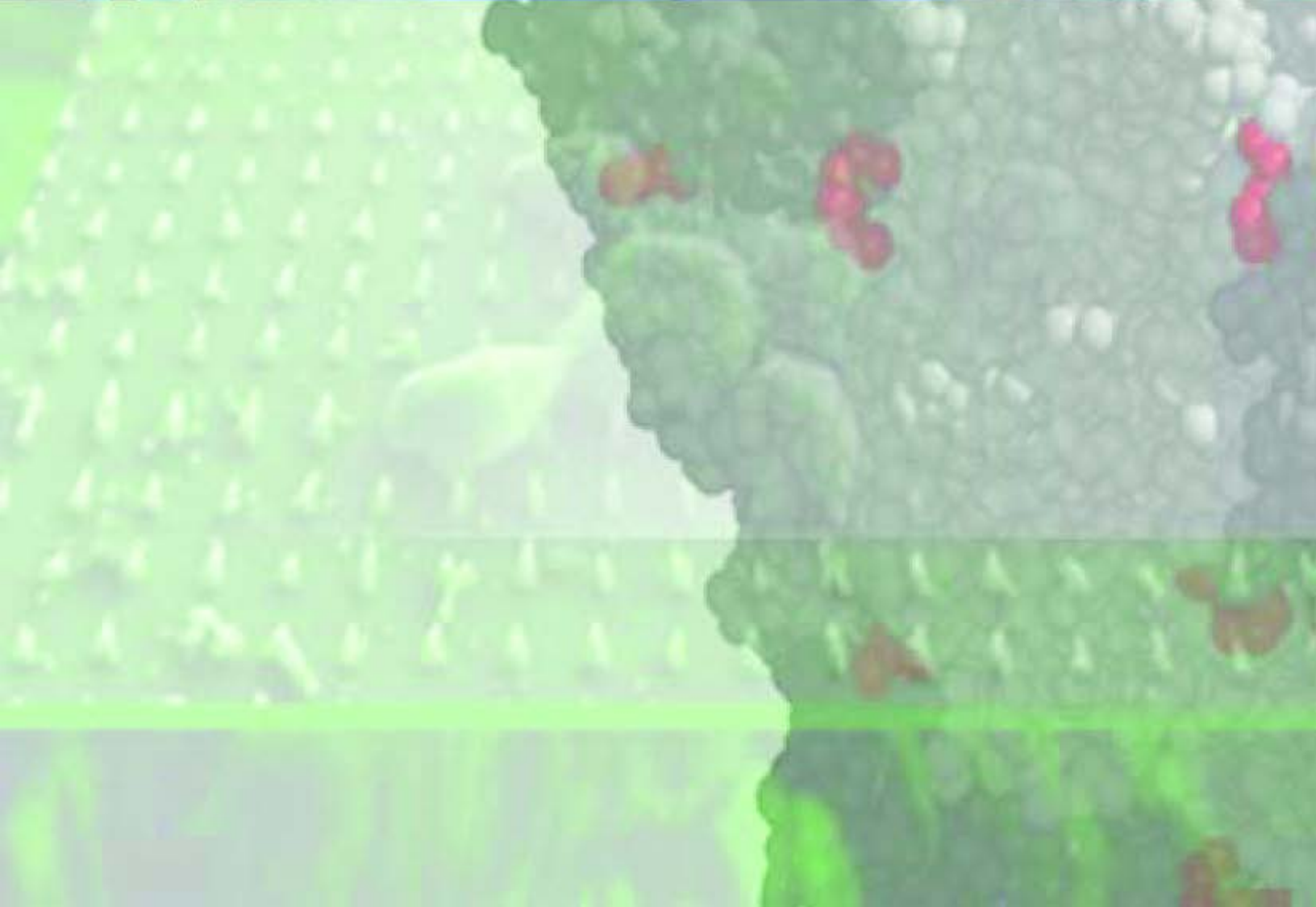
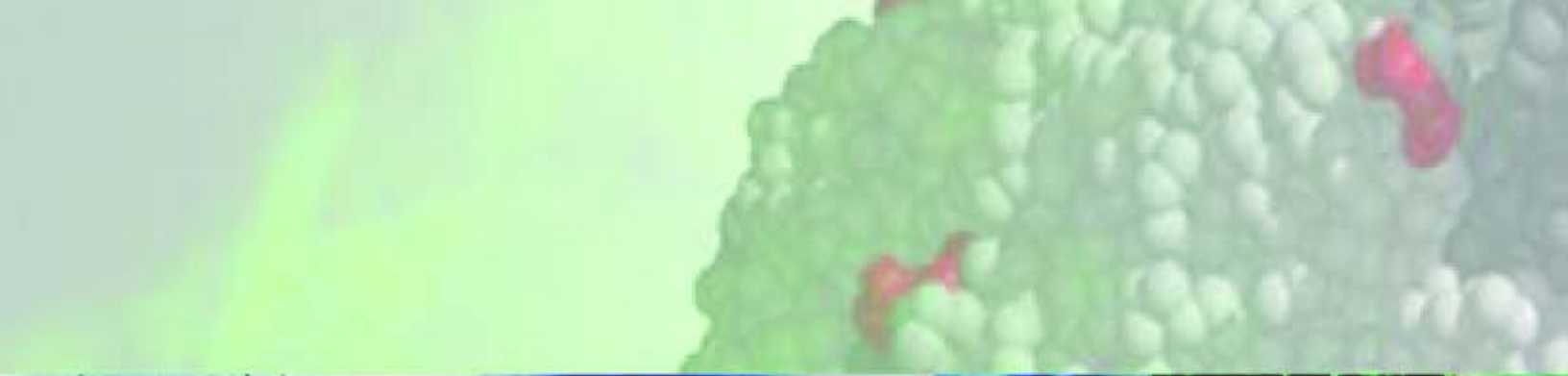


cancer NANOTECHNOLOGY plan

A Strategic Initiative To Transform Clinical Oncology
and Basic Research Through the Directed
Application of Nanotechnology

July 2004

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute



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Message From the Director

To help meet the Challenge Goal of eliminating suffering and death from cancer by 2015, the National Cancer Institute (NCI) is engaged in a concerted effort to harness the power of nanotechnology¹ to radically change the way we diagnose, treat, and prevent cancer. Over the past 5 years, the NCI has taken the lead in *integrating nanotechnology* into biomedical research through a variety of programs. The results of these initial funding efforts have demonstrated clearly that melding nanotechnology and cancer research and development efforts will have a profound, disruptive effect on how we diagnose, treat, and prevent cancer.

The application of nanotechnology to cancer research could not come at a more opportune time given the recent exponential increase in our understanding of the *process of how cancer develops*. It is my belief that nanomaterials and nanodevices will play a critical and unique role in turning that knowledge into clinically useful advances that detect and interact with the cancer cell and its surroundings early in this process. By doing so, we will change for the better the way we diagnose, treat, and ultimately prevent cancer.

Thanks to the scientific expertise and translational development capacity concentrated in our Comprehensive Cancer Centers, SPOREs (Specialized Programs of Research Excellence), research networks, and intramural program, the NCI is well positioned to seize this important opportunity. In particular, I believe it is possible that a concerted, *multidisciplinary* research effort will quickly yield new technologies that will detect and pinpoint the molecular signatures of cancer at its earliest stages and enable physicians to determine early whether an anticancer therapeutic is working. These advances will change the way we care for cancer patients. Such technological advances will have an even greater impact because of their ability to change the way new cancer therapies will be tested and approved, increasing the speed with which new science is turned into new therapies.

Future developments from nanotechnology also include multifunctional nanoscale devices capable of simultaneously detecting and treating cancer. Also in the offing are novel methods for preventing cancer and ameliorating the symptoms that negatively impact a patient's quality of life. Nanotechnology will also create a host of powerful tools that cancer researchers will use to make the next generation of discoveries that will ultimately lead to clinical advances.

To ensure that we capitalize on this opportunity to make dramatic progress today, the NCI has developed this Cancer Nanotechnology Plan (CNPlan). Over the past year, the NCI has held numerous symposia exploring the intersections of nanotechnology and cancer research, and the NCI staff has solicited input from a broad cross-section of the cancer research and clinical oncology communities. Intramural and extramural research working groups have discussed how best to apply the lessons of the NCI's initial explorations into nanotechnology to a focused and coordinated translational research effort that will have near-term benefits for patients.

Created with input from these experts, the CNPlan lays out a pathway and a set of directed mechanisms through which nanotechnology will be the fundamental driver of advances in oncology and cancer research conducted by multidisciplinary teams. The CNPlan will rely heavily on our substantial investments in our Comprehensive Cancer Centers and SPOREs, but it also calls for the development of as many as five Centers of Cancer Nanotechnology Excellence (CCNEs) that will contribute their expertise in nanotechnology to milestone-driven projects. To avoid duplicating efforts conducted through other Federal programs, including the National Nanotechnology Initiative and the NIH Roadmap for Medical Research, the projects initiated

¹Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects.

under the CNPlan will be integrated, milestone driven, and product oriented, with *targeted objectives and goals*, and will use a project-management approach to capitalize in relatively short order on today's opportunities to create the tools that both clinicians and cancer researchers need now to eliminate suffering and death from cancer by 2015. Recognizing the importance of bringing expertise from many areas, *partnership* opportunities with other Federal agencies and the private sector will be critical, particularly in terms of clinical development activities and in our efforts to ensure that nanoscale devices will not themselves be harmful to cancer patients or the environment.

Ultimately, this is not just a plan for the NCI, but a call to action for the cancer research community. It emphasizes the process of building partnerships between the private and public sectors with the goal of creating teams best equipped to translate today's knowledge about cancer biology and nanotechnology into clinically useful products. By joining together, I am confident that we will continue to make substantial scientific and medical progress to achieve the one goal that matters most: the reduction and elimination of the burden of cancer for all who are in need.

Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute

Nanotechnology offers the unprecedented and paradigm-changing opportunity to study and interact with normal and cancer cells in real time, at the molecular and cellular scales, and during the earliest stages of the cancer process. Through the concerted development of nanoscale devices or devices with nanoscale components spearheaded by the NCI, the Comprehensive Cancer Centers, and the SPOREs, and in collaboration with other Federal agencies, nanotechnology will be the enabling technology for:

- Early imaging agents and diagnostics that will allow clinicians to detect cancer in its earliest, most easily treatable, presymptomatic stage
- Systems that will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation
- Multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations, with physiologically appropriate timing, directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer
- Agents capable of monitoring predictive molecular changes and preventing precancerous cells from becoming malignant
- Surveillance systems that will detect mutations that may trigger the cancer process and genetic markers that indicate a predisposition for cancer
- Novel methods for managing the symptoms of cancer that adversely impact quality of life
- Research tools that will enable investigators to quickly identify new targets for clinical development and predict drug resistance

In taking a leadership role, the NCI recognizes that these translational initiatives would benefit greatly from a concerted and coordinated effort to characterize and standardize the wide range of nanoscale devices that are now available for use by the research community and that will undoubtedly be developed in the near future. This role will be filled by the Nanotechnology Characterization Laboratory (NCL), which the NCI will establish at its NCI-Frederick facility. A primary objective of the NCL is to develop data on how nanomaterials and nanodevices interact with biological systems. These research endeavors will chart the common baseline and scientific data that would inform research and development (R&D) as well as future regulatory actions involving nanoscale diagnostics, imaging agents, and therapeutics. Moreover, this information will be linked to the Comprehensive Cancer Centers and related programs through public databases available through the Cancer Biomedical Informatics Grid (CaBIG).

Achieving this vision will also require training a cadre of researchers who are skilled in applying the tools of nanotechnology to critical problems in cancer research and clinical oncology. And given the complex nature of this endeavor, building multidisciplinary teams will be essential to realizing this vision.² Thus, the NCI must take a leadership role by providing the necessary funds and opportunities for the cross-disciplinary training and collaboration that will be needed to maximize the impact that nanotechnology can have on meeting the Challenge Goal of eliminating the suffering and death from cancer by 2015.

The CNPlan lays out the pathway and directed programmatic mechanisms through which nanotechnology will become a fundamental driver of advances in oncology and cancer research. The CNPlan reflects a consensus among the entire cancer community that four significant obstacles impede the revolutionary changes that must occur to meet the 2015 Challenge Goal³:

²National Institutes of Health. *Catalyzing Team Science: Report from the 2003 BECON Symposium*. http://www.becon2.nih.gov/symposia_2003/becon2003_symposium_final.pdf.

³National Cancer Institute. *Leveraging Multi-Sector Technology Development Resources and Capabilities to Accelerate Progress Against Cancer: A National Cancer Institute Roundtable*. 2004.

- The need for cross-disciplinary collaborations
- The widening “gap” between late discovery and early development of diagnostics and therapeutics
- The critical lack of available standards
- The requirement for cross-cutting technology platforms

By taking the pathway and utilizing the mechanisms detailed in the CNPlan, which rely heavily on capacity already developed by the NCI through its national infrastructure, the CNPlan will lower the barriers for developing technology that will become integrated in clinical, basic, and applied research. Nanotechnology will thereby become a core component in the training and translational programs at all leading cancer research institutions and a significant part of comprehensive cancer care. Thus, the focus will be achieving product-driven goals with demanding timelines, realizing that such an approach is necessary to meet the 2015 Challenge Goal.

Key Opportunities for Cancer Nanotechnology

On the basis of discussions with a wide range of clinicians, cancer researchers, and technologists, it is clear that nanotechnology is ready today to solve mission-critical problems in cancer research. Indeed, one of the goals of the CNPlan is to increase the visibility and availability of nanomaterials and nanoscale devices technology within the cancer research and development community to allow investigators the opportunity to do what they do best—discover and invent using new tools, just as they are doing with other disruptive technologies such as DNA microarrays and proteomic analysis.

But the NCI's major goal for the CNPlan is to catalyze targeted discovery and development efforts that offer the greatest opportunity for advances in the near and medium terms and to lower the barriers for those advances to be handed off to the private sector for commercial development. The CNPlan focuses on translational research and development work in the following six major challenge areas, where nanotechnology can have the biggest and fastest impact.

Molecular Imaging and Early Detection

Nanotechnology can have an early, paradigm-changing impact on how clinicians will detect cancer in its earliest stages. Exquisitely sensitive devices constructed of nanoscale components—such as nanocantilevers, nanowires, and nanochannels—offer the potential for detecting even the rarest molecular signals associated with malignancy. Collecting those signals for analysis could fall to nanoscale harvesters, already under development, that selectively isolate cancer-related molecules such as proteins and peptides present in minute amounts from the bloodstream or lymphatic system. Investigators have already demonstrated the feasibility of this approach using the serum protein albumin (a naturally existing nanoparticle), which happens to collect proteins that can signal the presence of malignant ovarian tissue.

Another area with near-term potential is detecting mutations and genome instability *in situ*. Already, investigators have developed novel nanoscale *in vitro* techniques that can analyze genomic variations across different tumor types and distinguish normal from malignant cells. Nanopores are finding use as real-time DNA sequencers, and nanotubes are showing promise in detecting mutations using a scanning electron microscope. Further work could result in a nanoscale system capable of differentiating among different types of tumors accurately and quickly, information that would be invaluable to clinicians and researchers alike. Along similar lines, other investigators have developed nanoscale technologies capable of determining protein expression patterns directly from tissue using mass spectroscopy. This technique has already shown that it can identify different types of cancer and provide data that correlate with clinical prognosis.

In addition, nanoscale devices can enable new approaches for real-time monitoring of exposures to environmental and lifestyle cancer risk factors. Such information would be important not only for identifying individuals who may be at risk for developing cancer, but also for opening the door to complex studies of gene-environment interactions as they relate to the development of or resistance to cancer.

In Vivo Imaging

One of the most pressing needs in clinical oncology is for imaging agents that can identify tumors that are far smaller than those detectable with today's technology, at a scale of 100,000 cells rather than 1,000,000,000 cells. Achieving this level of sensitivity requires better targeting of imaging agents and generation of a bigger imaging signal, both of which nanoscale devices are capable of accomplishing. When attached to a dendrimer, for example, the magnetic resonance imaging (MRI) contrast agent gadolinium generates a 50-fold stronger signal than in its usual form, and given that nanoscale particles can host multiple gadolinium ions, affords an opportunity to create a powerful contrast agent. When linked to one of the increasing number of targeting agents, such a construct would have the potential of meeting the 100,000 cell detection level.

First-generation nanoscale imaging contrast agents are already pointing the way to new methods for spotting tumors and metastatic lesions much earlier in their development, before they are even visible to the eye. In the future, implantable nanoscale biomolecular sensors may enable clinicians to more carefully monitor the disease-free status of patients who have undergone treatment or individuals susceptible to cancer because of various risk factors.

Imaging agents should also be targeted to changes that occur in the environment surrounding a tumor, such as angiogenesis, that are now beyond our capability to detect in the human body. Already, various nanoparticles are being targeted to integrins expressed by growing capillaries. Given that angiogenesis occurs in distinct stages and that antiangiogenic therapies will need to be specific for a given angiogenic state, angiogenesis imaging agents that can distinguish among these stages will be invaluable for obtaining optimal benefit from therapeutics that target angiogenesis.

Reporters of Efficacy

Today, clinicians and patients must often wait months for signs that a given therapy is working. In many instances, this delay means that should the initial therapy fail, subsequent treatments may have a reduced chance of success. This lag also adversely impacts how new therapies undergo clinical testing, since it leaves regulatory agencies reluctant to allow new cancer therapies to be tested on anyone but those patients who have exhausted all other therapeutic possibilities. Unfortunately, this set of patients is far less likely to respond to any therapy, particularly to those molecularly targeted therapies that aim to stop cancer early in its progression, an approach that virtually all of our knowledge says is the best approach for treating cancer.

Nanotechnology offers the potential for developing highly sensitive imaging agents and *ex vivo* diagnostics that can determine whether a therapeutic agent is reaching its intended target and whether that agent is killing malignant or support cells, such as growing blood vessels. Targeted nanoscale devices may also enable surgeons to more readily detect the margins of a tumor before resection or to detect micrometastases in lymph nodes or tissues distant from the primary tumor, information that would inform therapeutic decisions and have a positive impact on patient quality-of-life issues.

The greatest potential for immediate results in this area would focus on detecting apoptosis following cancer therapy. Such systems could be constructed using nanoparticles containing an imaging contrast agent and a targeting molecule that recognizes a biochemical signal seen only when cells undergo apoptosis. Using the molecule annexin V as the targeting ligand attached to nanoscale iron oxide particles, which act as a powerful MRI contrast agent, investigators have shown that they can detect apoptosis in isolated cells and in tumor-bearing mice undergoing successful chemotherapy. Further development of this type of system could provide clinicians with a way of determining therapeutic efficacy in a matter of days after treatment. Other systems could be designed to detect when the p53 system is reactivated or when a therapeutic agent turns on or off the biochemical system that it targets in a cancer cell, such as angiogenesis.

Another approach may be to use targeted nanoparticles that would bind avidly, or perhaps even irreversibly, to a tumor and then be released back into the bloodstream as cells in the tumor undergo apoptosis following therapy. If labeled with a fluorescent probe, these particles could be easily detected in a patient's urine. If also labeled with an imaging contrast agent, such a construct could double as a diagnostic imaging probe.

Multifunctional Therapeutics

Because of their multifunctional capabilities, nanoscale devices can contain both targeting agents and therapeutic payloads at levels that can produce high local levels of a given anticancer drug, particularly in areas of the body that are difficult to access because of a variety of biological barriers, including those developed by tumors. Multifunctional nanoscale devices also offer the opportunity to utilize new approaches to therapy, such as localized heating or reactive oxygen generation, and to combine a diagnostic or imaging agent with a therapeutic and even a reporter of therapeutic efficacy in the same package. "Smart"

nanotherapeutics may provide clinicians with the ability to time the release of an anticancer drug or deliver multiple drugs sequentially in a timed manner or at several locations in the body. Smart nanotherapeutics may also usher in an era of sustained therapy for those cancers that must be treated chronically or to control the quality-of-life symptoms resulting from cancers that cannot be treated successfully. Smart nanotherapeutics could also be used to house engineered cellular “factories” that would make and secrete multiple proteins and other antigrowth factors that would impact both a tumor and its immediate environment.

The list of potential multifunctional nanoscale therapeutics grows with each new targeting ligand discovered through the use of tools such as proteomics. Nanoscale devices containing a given therapeutic agent would be “decorated” with a targeting agent, be it a monoclonal antibody or F_v fragment to a tumor surface molecule, a ligand for a tumor-associated receptor, or other tumor-specific marker. In most cases, such nanotherapeutics could double as imaging agents.

Many nanoparticles will respond to an externally applied field, be it magnetic, focused heat, or light, in ways that might make them ideal therapeutics or therapeutic delivery vehicles. For example, nanoparticulate hydrogels can be targeted to sites of angiogenesis, and, once they have bound to vessels undergoing angiogenesis, it should be possible to apply localized heat to “melt” the hydrogel and release an antiangiogenic drug. Similarly, iron oxide nanoparticles, which can serve as the foundation for targeted MRI contrast agents, can be heated to temperatures lethal to a cancer cell merely by increasing the magnetic field at the very location where these nanoparticles are bound to tumor cells.

In some instances, nanoscale particles will target certain tissue strictly because of their size. Nanoscale dendrimers and iron oxide particles of a specific size will target lymph nodes without any molecular targeting. Nanoscale particles can also be designed to be taken up by cells of the reticuloendothelial system, which raises the possibility of delivering potent chemotherapeutics to the liver, for example.

Nanoscale devices should also find use in creating immunoprotected cellular factories capable of synthesizing and secreting multiple therapeutic compounds. Early-stage research has already demonstrated the value of such cellular factories, and a concerted effort could turn this research into a powerful multivalent therapeutic capable of responding to local conditions in a physiologically relevant manner.

Prevention and Control

Many of the advances that nanotechnology will enable in each of the four preceding challenge areas will also find widespread applicability in efforts to prevent and control cancer. Advances driven by the NCI’s initiatives in proteomics and bioinformatics will enable researchers to identify markers of cancer susceptibility and precancerous lesions, and nanotechnology will then be used to develop devices capable of signaling when those markers appear in the body and deliver agents that would reverse premalignant changes or kill those cells that have the potential for becoming malignant. Nanoscale devices may also prove valuable for delivering polypeptide cancer vaccines that would engage the body’s immune system or for delivering cancer-preventing nutraceuticals or other chemopreventive agents in a sustained, time-release and targeted manner.

One intriguing idea for preventing breast cancer comes from work suggesting that breast malignancies may derive from a limited population of pluripotent stem cells in breast tissue. Should this prove true, it may be possible to develop a nanoscale device that could be injected into the ductal system of the breast, bind only to those stem cells, and deliver an agent capable of killing those cells. Such an agent could then be administered to women who are at an increased risk of breast cancer as a preventive therapy.

Research Enablers

Nanotechnology offers a wide range of tools, from chip-based nanolabs capable of monitoring and manipulating individual cells to nanoscale probes that can track the movements of cells, and even individual

molecules, as they move about in their environment. Using such tools will enable cancer biologists to study, monitor, and alter the multiple systems that go awry in the cancer process and identify key biochemical and genetic “choke points” at which the coming wave of molecular therapies might best be directed. As such, nanotechnology can serve as the perfect complement to other technology platforms, such as proteomics and bioinformatics, that the NCI is emphasizing in its research initiatives as critical components of the discovery and development engine that will power both near-term and long-term advances in cancer diagnosis, treatment, and prevention.

The discussion above has already highlighted the potential for nanoscale devices to act as molecular harvesting agents. Such a tool would be invaluable to proteomics efforts aimed at identifying tumor-specific indicators. Similarly, nanoscale devices that can detect the biological changes associated with therapeutic efficacy should also find widespread use as a tool for understanding how cells respond to a variety of perturbations. One of the most powerful near-term uses of nanotechnology to accelerate basic research will come from using molecular-size nanoparticles with a wide range of optical properties, such as quantum dots, to track individual molecules as they move through a cell or individual cells as they move through the body. In combination with the new generation of mouse models that more accurately reproduce the genetic, biochemical, and physiological properties of human cancers, these nanolabels will prove invaluable for systems-scale research. Increased focus on the development of nanoscale devices for making simultaneous biochemical measurements on multiple cells, particularly those grown in such a way as to mimic tissue development *in vivo*, will also have a significant impact on basic cancer research.

Nanoscale devices should also enable direct analysis of single nucleotide polymorphisms (SNPs) and large-scale mutational screening for cancer susceptibility genes. Real-time methylation analysis should also benefit from various nanoscale tools and devices. Indeed, nanotechnology should prove to be a valuable technology platform for the burgeoning field of cancer molecular epidemiology.

New Strategies for Cancer Nanotechnology

Funding activities conducted within the framework of the CNPlan will occur in four areas as detailed below. The first will be to develop three to five CCNEs that will provide engineering and physical science expertise to leverage the cancer biology expertise and access to cancer patients at the Nation's Comprehensive Cancer Centers, SPOREs, and large population infrastructures, such as the Breast and Colon Cancer Family Registries. Second, the CNPlan will fund cross-disciplinary training programs as a means of fostering the creation of the multidisciplinary teams needed to integrate nanotechnology and cancer biology. Third, the CNPlan will fund focused nanotechnology development initiatives that will be milestone driven and product oriented, with an emphasis on commercialization through small-business and larger private-sector project team members. Fourth, the CNPlan will fund projects that apply nanotechnology in cancer biology and translational research, through basic research project grants and other mechanisms. Since the R01 mechanism has historically not been the best mechanism to fund individual investigator-initiated technology development and application projects, the NCI will also make use of program announcements, requests for applications, and request for proposals, as well as a variety of program management and funding mechanisms that have been shown to be successful in prior technology development programs. The NCI will also examine opportunities through the Small Business Innovation Research/Small Business Technology Transfer (SBIR/STTR) programs as well as administrative supplements to existing awards to accelerate the integration of nanotechnology into the NCI research program.

In addition to the largely extramural focus of the CNPlan, a variety of demonstration projects in the NCI intramural program will add to this overall effort by acting as developmental catalysts. For example, the NCI has contracted with a nanotechnology foundry to fabricate materials and provide engineering expertise to aid *in vivo* projects using nanoscale devices. The NCI's intramural expertise, when used in this type of synergistic manner, will accelerate the development of new nanotechnology-driven advances in oncology.

Helping guide these programmatic activities will be the Cancer Nanotechnology Working Group (CNWG), which was recently formed from the Cancer Nanotechnology Intramural Working Group and the Cancer Nanotechnology Extramural Intramural Working Group. The CNWG will have a tracking function and will continue (as the two subgroups have for the past year) to act in an advisory capacity as the CNPlan moves forward. The CNWG is playing a key role in planning an NCI-sponsored intramural nanotechnology seminar series scheduled for fall 2004 and coordinating symposia held at regional cancer and advanced technology centers.

The CNPlan will also include development of program evaluation tools related to the programmatic milestones proposed in this plan as well as mechanisms for conducting annual evaluations. The evaluation processes will involve independent, outside review teams and will assess how program activities conducted as part of the CNPlan meet the goals and milestones set forth in this plan. Feedback from these evaluations will facilitate appropriate milestone adjustment course corrections in the implementation of the plan.

Centers of Cancer Nanotechnology Excellence (CCNEs)

The primary goal of the CCNEs is to integrate nanotechnology development into basic and applied cancer research that is necessary to rapidly facilitate the application of this science to clinical research. The critical requirements for each CCNE will be:

- Integration with a Comprehensive Cancer Center/SPORE program
- Affiliation with university or research centers of engineering and physical sciences (e.g., mathematics, chemistry, physics, and material sciences)
- Advanced biocomputing capabilities
- Required existing not-for-profit/private technology development partnerships

Outcome objectives (performance measures) represent technologies that are developed and effectively utilized to overcome cancer processes. A steering committee will coordinate efforts across all the CCNEs, to facilitate data and technology transfer across centers, interconnecting and leveraging the strengths and advances of each.

Nanotechnology Characterization Laboratory (NCL)

Nanoscale particles and devices are similar in size to biomolecules and can easily enter most cells. Our ability to manipulate the physical, chemical, and biological properties of these particles affords researchers the ability to engineer and use nanoparticles for drug delivery, as image contrast agents, and for diagnostic purposes. NCI is establishing the Nanotechnology Characterization Laboratory (NCL) at its NCI-Frederick facility to provide critical infrastructure support to this rapidly developing field. The intent of the NCL is to accelerate the transition of basic nano-biotech research into clinical applications. (See page 23 for more information on the NCL.)

Building Research Teams

The NCI will create the incentives necessary to integrate nanotechnology into the mainstream of basic and applied cancer research. The CNPlan's approach is centered on supporting training and career development initiatives to establish integrated teams of cancer researchers, including epidemiologists, and engineers with the cancer biology and physical science skills and knowledge base of nanotechnology to approach the fundamental challenges of cancer. One policy consideration is to investigate opportunities for naming multiple principal investigators per project as an incentive for conducting team science.

Under the CNPlan, the NCI will initially use existing training and career development mechanisms to direct talent to this area as quickly as possible. The NCI recognizes, however, that new mechanisms for developing multidisciplinary teams may be needed. The NCI will also encourage programs to be developed with interfaces to the training programs of other Federal agencies as components of the National Nanotechnology Initiative (NNI). The advantages are to rapidly translate knowledge from fundamental nanotechnology sciences to directed application in cancer biology.

Other possible mechanisms for fostering team-building include the Bioengineering Research Partnerships (BRPs) and Bioengineering Research Grants (BRGs). The BRPs are designed to fund basic, applied, and translational multidisciplinary research that addresses important biological or medical research problems. In the context of this program, a partnership is a multidisciplinary research team that applies an integrative, systems approach to developing knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. The partnership must include appropriate bioengineering or allied quantitative sciences in combination with biomedical and/or clinical components. The smaller BRG awards support multidisciplinary research performed in a single laboratory or by a small number of investigators that applies an integrative, systems approach to developing knowledge and/or methods to prevent, detect, diagnose, or treat disease or to understand health and behavior. A BRG application may propose hypothesis-driven, discovery-driven, developmental, or design-directed research at universities, national laboratories, medical schools, large or small businesses, or other public and private entities.

Outcome objectives (performance measures) represent institutions with training programs and scientists and engineers who are trained in cancer nanotechnology. A 3- to 5-year benchmark is to support the entry of 30 scientists with formal training experiences in nanotechnology applied to cancer biology. Recommended mechanisms include the following:

- **F33 NIH National Research Service Awards for Senior Fellows.** This approach would enable experienced cancer researchers and engineers/physical scientists with directed programs of training to be independent researchers and to provide the future building of training programs.

- **F32 NIH National Research Service Awards for Individual Postdoctoral Fellows.** This approach would provide cross-disciplinary research training opportunities for postdoctoral fellows with training in either cancer or technology to gain experience in the other discipline.
- **K08 and K25 Mentored Clinical Scientist Development Awards.** This approach begins to develop research teams with clinical applications of nanotechnology to allow integration of nanotechnology into the clinical assessment phase. At present, there are no programs that support technology development and applications training for clinical researchers. This gap will be an important one to facilitate the clinical testing of nanotechnologies. In these programs, clinical researchers will be offered opportunities in developing clinical assessment paradigms for diagnosis, treatment, and prevention using nanotechnologies.
- **T32 Institutional Training Grant Program.** This approach enables eligible institutions to develop or enhance research training opportunities for predoctoral or postdoctoral trainees, who are training for careers in specified areas of biomedical and clinical research.
- **R25 Cancer Education Grant Program.** This mechanism will be used to develop critical educational programs for cancer biologists, engineers/physical scientists, and trainees. The focus will be on developing programmatic activities at CCNEs to develop curricula, educational programs/seminars, and national forums focused on cancer nanotechnology.

Planning for future training and career development needs will be developed on the basis of the initial success of the above strategies and the assessment of program needs. The NCI recognizes, for example, that there will likely be a need to foster curriculum development for undergraduate and graduate programs that would cross-fertilize training in the biological sciences with engineering, chemistry, and other physical sciences and vice versa.

Creating Cancer Nanotechnology Platforms Through Directed Research Programs

Using Broad Agency Announcements (BAAs), NCI will identify to the R&D community three to five critical technology platform needs for cancer, such as *in vivo* nanotechnology imaging systems and nanotechnology-enabled systems for rapidly assessing therapeutic efficacy and addressing cancer biology processes. The program will fund 3-year technology projects through a contract mechanism that is overseen by project specialists. The project will target cancer centers, small businesses, and Federal laboratories that prepare and submit concepts and project objectives. Upon review of initial submissions, full solicitations will be sought from those of highest value. Technology programs will create platforms that are aimed at deployment for clinical application in cancer research. Applicants will be required to team with the Comprehensive Cancer Centers or SPOREs with a plan for dissemination of the technology.

Basic and Applied Initiatives for Nanotechnology in Cancer

Requests for Application (RFAs) and Program Announcements (PAs) will be issued to solicit applications for projects that apply nanotechnology for specific opportunities in cancer biology and translational research. These may focus on investigator-initiated proposals that address specific biology processes, diagnostic technologies, or drug development methods. Research projects that address the fundamental biology questions identified in the CNPlan will be considered.

Mechanisms for funding would consider R21/R33 approaches for phased innovation with programmatic review of attainment of project milestones. The small-business community would be targeted for use of R41 and R43 mechanisms in this area.

Timeline and Programmatic Milestones

A defining element of the CNPlan is that it calls for the NCI to mark progress in six key areas (see Key Opportunities for Cancer Nanotechnology) over two time periods. During the initial 1 to 3 years, the CNPlan will accelerate selected projects that are already under way and catalyze the development of products that are primed for near-term clinical application. The second period, 3 to 5 years, will see projects come to fruition that reflect solving more difficult technological and biological problems or that require the integration of multiple technological components but have the potential for making paradigm-changing impacts on the detection, treatment, and prevention of cancer. Milestones reached during this latter period will also reflect the growth of the investigator pool that will be catalyzed by the CNPlan. By the end of 5 years, we expect that most of these efforts will generate products in clinical trials or even in clinical use.

The CNPlan represents an integrated program of activities to use a disruptive technology—nanotechnology—as an enabler of rapid clinical and research advances and as a means of lowering the barriers to technology development and commercialization by the private sector, particularly among small businesses. Over the next 5 years, a timeframe merited by the urgency of meeting the NCI’s 2015 Challenge Goal and supported by the solid foundation of promising advances from the NCI’s basic research portfolio, the CNPlan calls for the use of targeted contract funding with project management oversight to meet the following milestones:

| Key Opportunity | 1-3 Years | 3-5 Years |
|--|---|--|
| Molecular Imaging and Early Detection | <ul style="list-style-type: none"> • Begin clinical trials of nanotechnology-assisted automated assay for rapid detection of genetic abnormalities. • Refine <i>in vitro</i> nanotechnology systems (cantilevers, nanowires, nanochannels) for rapid, sensitive analysis of cancer biomarkers. Such systems will be easily expanded as new markers are identified. | <ul style="list-style-type: none"> • Disseminate nanoscale devices for routine validation of cancer biomarkers. • Develop rapid multifactorial genomic and proteomic diagnostic system for tumor identification and staging. • Begin clinical trials with multicomponent nanotechnology platform early diagnosis and therapeutic monitoring. |
| <i>In Vivo</i> Imaging | <ul style="list-style-type: none"> • File Investigational New Drug (IND) application to begin clinical trials of nanoscale MRI contrast agents capable of identifying fewer than 100,000 actively aggressive cancer cells. • Conduct clinical trials for three targeted nanoscale imaging agents using a variety of imaging modalities, including MRI, ultrasound, and near-infrared optical imaging. | <ul style="list-style-type: none"> • Complete clinical trials and file New Drug Application (NDA) for first nanoscale imaging agent capable of detecting <100,000 actively aggressive tumor cells. • Begin clinical trials with multiple nanoscale imaging agents. • Develop capabilities for monitoring active cellular processes as they change over time. |

| Key Opportunity | 1-3 Years | 3-5 Years |
|-------------------------------------|---|--|
| Reporters of Efficacy | <ul style="list-style-type: none"> • Begin clinical trials for nanoscale device (imaging-based or <i>ex vivo</i>) that can rapidly assess apoptosis in clinical trials. • Develop capabilities for monitoring disruption of vascular networks associated with primary solid tumors and metastatic lesions. • Develop nanoscale devices to identify and quantify biological and chemical changes (other than apoptosis) resulting from therapeutic treatment. • Demonstrate proof of concept for nanoscale devices (imaging-based or <i>ex vivo</i>) that can be used with a variety of therapeutics to determine biodistribution <i>in vivo</i>. • Begin clinical trials with one optical imaging device capable of showing surgical margins using nanoscale agents. | <ul style="list-style-type: none"> • Demonstrate multiple systems (imaging-based or <i>ex vivo</i>) that can rapidly assess therapeutic efficacy in terms of apoptosis, angiogenesis regression, and other markers. • Demonstrate multiple systems for monitoring real-time drug distribution. • Promote routine use of nanoscale efficacy reporters for surrogate end point measurements in clinical trials. |
| Multifunctional Therapeutics | <ul style="list-style-type: none"> • File IND to begin clinical trials of one targeted sensitizer (radiation, light, magnetic field). • File IND to begin clinical trials of one multifunctional therapeutic complete with accompanying therapeutic assessment tool. • Develop nanoscale devices capable of multivariate targeting and intervention. • File IND application to begin clinical trials of one nanoscale therapeutic targeting reticuloendothelial system. | <ul style="list-style-type: none"> • Conduct multiple clinical trials with targeted sensitizers (radiation, light, magnetic field). • File INDs to begin clinical trials of multiple targeted therapeutics, complete with accompanying therapeutic assessment tool. • File IND to begin clinical trials of one multifactorial targeted therapeutic agent at IND stage. • Demonstrate five "failed" drugs reconstituted in targeted, "smart" nanoscale devices for retesting in new generation of preclinical models. |
| Prevention and Control | <ul style="list-style-type: none"> • Demonstrate proof of concept for nanoscale device capable of monitoring genetic changes associated with early cancer processes and hyperplasia with the aim of preventing subsequent development of cancer. | <ul style="list-style-type: none"> • File IND to begin clinical trials of a nanoscale device capable of identifying markers of early cancer processes. • Demonstrate proof of concept for nanoscale device capable of metastasis detection. |

| Key Opportunity | 1-3 Years | 3-5 Years |
|-------------------|--|--|
| Research Enablers | <ul style="list-style-type: none"> • Develop nanoscale harvesting devices for proteomics analysis and biomarker identification. • Create prototype for real-time, <i>in situ</i> genome sequencing of malignant and pre-malignant cells. • Develop instrumented cell coculture systems biology research. • Refine cell and cell-component labeling with nanoparticulates such as quantum dots for application to studies of integrated pathways and processes in cancer. • Develop toxicology database for nanoscale devices and nanoparticulates. • Create a scientific framework for regulatory approval of nanoscale diagnostics, therapies, and preventive agents. | <ul style="list-style-type: none"> • Develop nanoscale analytical devices to study DNA methylation and protein phosphorylation. • Promote routine use of nanoscale technology to characterize tumor heterogeneity. • Demonstrate nanoscale technology for detecting multiple mutations <i>in vivo</i>. • Promote routine use of nanoscale analytical tools for studying cellular signaling pathways. |

To rapidly harness the potential of nanotechnology to meet our 2015 Challenge Goal of eliminating suffering and death from cancer, the NCI has crafted the CNPlan. Over the past year, the NCI has held several workshops and symposia exploring the intersections of nanotechnology and various areas of cancer research, and the NCI staff has solicited input from a broad cross-section of the cancer research and clinical oncology communities. Intramural and extramural research working groups have discussed how best to apply the lessons of the NCI's initial forays into nanotechnology to a concerted translational research effort that will have near-term benefits for patients. During this time, the NCI also convened a roundtable of leaders from the private sector, foundations, patient advocacy groups, the Comprehensive Cancer Centers, academia, and other government agencies to identify new ways of leveraging technology to aid in our battle against cancer.³

During the course of these fact-finding discussions, it became clear that nanotechnology offers tremendous opportunities, the most promising of which are presented in this report and represent the major focus of the CNPlan. However, these discussions also increased the NCI's awareness that there are a number of nonscientific barriers that could impede the rapid translation of cancer nanotechnology research into clinically useful, paradigm-changing advances in diagnosing, treating, and preventing cancer. Though numerous in detail, these potential barriers followed several themes:

- **Cross-Disciplinary Collaborations.** For cancer nanotechnology to have its biggest impact, barriers to multidisciplinary and multiple partner collaborations must fall. Though there are many institutional barriers to such research collaborations over which the NCI has no direct control, the NCI can use alternative funding mechanisms to encourage and facilitate such collaborations. In particular, the NCI can use these funding mechanisms to promote increased collaborations among the public, private, and nonprofit sectors that reduce overall development risk.
- **“Gap” Between Late Discovery and Early Development of Diagnostics and Therapeutics.** Too many potential products that reach clinical development fail as they move forward because of a lack of solid science to back up regulatory filings. Moreover, to conduct clinical trials, there is insufficient financial and intellectual support for smaller companies to move novel products through the testing and regulatory approval process and, ultimately, failure to match development goals with clinical and patient needs.
- **Regulatory Uncertainty.** There is no clear regulatory pathway for approval of nanoscale devices, increasing the risk for private-sector development of promising new diagnostics, therapies, and preventive agents. In particular, there is a concern that each new use of a given nanoscale device, such as a particular type of particle, will require full-scale preclinical and clinical testing, a requirement that would dramatically drive up development costs. There is also concern about the difficulty of gaining regulatory approval for nanoscale devices that combine diagnostic and therapeutic modalities or multiple therapeutic agents in the same construct.
- **Standardization and Characterization.** Because nanotechnology is such a new field, there are few standards and little reference physical and biological characterization data that researchers can use to choose which nanodevices might be most suitable for a given clinical or research application. A lack of standard assay and characterization methods also makes it difficult to compare results from different laboratories.
- **In Vivo Behavior.** There is good reason to expect that critical *in vivo* properties of nanoscale devices, such as pharmacokinetics, pharmacodynamics, and biodistribution, will differ markedly from that of current imaging and therapeutic agents; yet there is a marked lack of data on these base characteristics. There is also, however, little ongoing research that will generate these essential data.
- **Technology Transfer and Knowledge Exchange.** Cancer nanotechnology is inherently a discipline that will succeed because of its combinatorial nature—Any given nanoscale technology or device may be combined with any number of diagnostic, imaging, therapeutic, or preventive agents. As a result, there is a need for new mechanisms for sharing and cross-licensing intellectual property to facilitate technology

transfer and knowledge exchange. Though the NCI cannot by itself create such a system, it can work with other Federal agencies to act as a facilitator among the multiple interest groups by convening roundtable events for discussion and problem-solving.

Awareness of these overarching concerns had a great impact on the development of the CNPlan. A major role of the NCL, for example, will be to eliminate barriers resulting from the current lack of standards and characterization data. The CNPlan addresses potential barriers by making the U.S. Food and Drug Administration (FDA) an important partner in this endeavor. The CNPlan's emphasis on contract-based funding will place a premium on collaborations, particularly between the public and private sectors.

NCI Program Development in Nanotechnology

Although the NCI is a strong supporter of investigator-initiated, R01-supported research, the Institute also recognizes that this funding mechanism is not universally applicable to all its research initiatives. In particular, the NCI believes that to be effective, the CNPlan must utilize funding mechanisms that place a premium on meeting project goals on a timely basis, produce a desired deliverable at the end of the project's lifetime, and integrate with other planning initiatives within the NCI. Through its experience with existing technology development programs and with input from the research community and from other government agencies—specifically the Defense Advanced Research Projects Agency (DARPA) and the Homeland Security Advanced Research Projects Agency (HSARPA)—the NCI recognizes that project-management style contracts with specified goals, timelines, and deliverables must be the central funding mechanism used in conjunction with the CNPlan if this initiative is to achieve its admittedly aggressive vision and associated goals and milestones.

Utilizing contract-based, project-management style funding will require that NCI program officers work closely with potential contracting groups, with an emphasis on helping prospective participants put together the multidisciplinary teams that the NCI envisions will be needed to accomplish the aggressive goals of the CNPlan. Such teams, which will preferentially include private-sector partners and small-business participation, will form the core element of CNPlan-related contracts.

Coordination with other NCI initiatives will be monitored by both the program officers and the planning coordinator in the Office of the NCI Director. Though the NCI has been funding nanotechnology research for a number of years now, nanotechnology, as part of the new NIH Roadmap initiative, has emerged as an area of interest across the entire NIH. The current goals of the NIH nanomedicine initiative are much more basic and obviously less focused than those laid out in the CNPlan. The nanomedicine roadmap group has just released a solicitation that will lead by the end of 2005 to the funding of planning awards for nanomedicine center development. The goal of this initiative is to fund centers using and developing nanotechnology to examine biological processes compatible with the missions of the various NIH institutes. This supports a long-term goal of the NIH to support infrastructure development in nanomedicine. In contrast, the CNPlan is a focused plan to capitalize on past NCI investment in nanotechnology and focus those and new efforts on the immediate mission of the NCI. The plan carries a shorter timeline and specific milestones to achieve the NCI goals. The NCI plans on continued support and participation with the NIH nanomedicine as well as all of the roadmap working groups where appropriate.

Discussions with leaders in academia, at the NCI Comprehensive Cancer Centers and SPOREs, and in the private sector indicate that this type of managed, targeted, milestone-driven, team-based funding mechanism, though admittedly novel for most researchers in the public sector, will be embraced by those members of the cancer research community who want to see their work turned rapidly into advances that help cancer patients. Furthermore, the consensus among the entire cancer community is that this type of project-management structure is critically needed at this very moment in order to most efficiently and rapidly translate 21st century science and technology into the tools and products that will revolutionize the detection, treatment, and prevention of cancer.

Reflecting the recommendations of the NIH Bioengineering Consortium report on promoting team science, the CNPlan places a premium on supporting cross-disciplinary teams that partner with the Comprehensive Cancer Centers, SPOREs, CCNEs, large existing population infrastructures such as the Breast and Colon Cancer Family Registries, and the private sector. Such partnerships, operating in a project-management environment, present an opportunity to leverage existing skills in a way that enables such teams to meet the milestones and deliverables that will be called for under CNPlan contracts and grants. By placing a premium on building cross-disciplinary teams, the CNPlan will also bring in expertise, such as in population genetics and epidemiology, that is often overlooked in terms of potential contributions to research and development efforts.

In addition, the CNPlan will initially utilize existing F33, K08, and K25 training grant programs to incentivize cross-disciplinary research through training. F33 awards go to experienced scientists who wish to make major changes in the direction of their research careers or wish to broaden their scientific background by acquiring new research capabilities. These awards will enable current established cancer investigators to train in the labs of leading nanotechnologists to facilitate bringing the technology back to their own labs to be applied toward future research activities. Alternatively, nanotechnologists could be funded to spend a year gaining insight into cancer research so that these problems could be addressed when returning to the nanotechnologist's lab. In both cases, the spillover of ideas from the trainee to the mentor's lab will continue to cross-pollinate the cancer and nanotechnology fields. The K08 and K25 mechanisms provide for specialized postdoctoral study for individuals with a health professional doctoral degree committed to a career in laboratory or field-based research. These awards will bring clinicians into nanotechnology-focused laboratories as a means of providing clinical expertise to nanotechnology-driven development programs. After 3 years, the NCI will evaluate the success of these programs to increase cross-disciplinary activities and determine whether new programs are necessary. For now, however, these existing mechanisms will provide a needed boost to such efforts. (For additional recommendations on how training can be used to incentivize cross-disciplinary activities, see Appendix A.)

Today, thanks in part to the growing acceptance of the 2015 Challenge Goal by the cancer community, the NCI believes that the majority of cancer researchers now appreciate the need to pick the most promising areas of research and focus on conducting the translational work needed to turn promise into clinical benefit. Indeed, there is a realization within the broad cancer community that while R01-style research efforts are key to generating the stream of discoveries upon which the CNPlan will capitalize, the time is ripe to select the most promising projects for focused development. The CNPlan represents the NCI's effort to capitalize on the gathering momentum within the field to do something different.

Interagency collaborations will also play a critical role in realizing the CNPlan's vision, achieving its goals, and meeting its milestones, and the NCI is already in discussions with multiple Federal agencies and other NIH Institutes to develop such cooperative efforts. In particular, a potential joint collaboration with the National Institute of Standards and Technology (NIST) and the FDA is a high priority. This collaboration will focus on developing standards for nanoscale devices and both *in vitro* and *in vivo* characterization assays that could serve as a starting point for regulatory filings. The NCI-FDA Interagency Oncology Task Force, which facilitates dialogue between the two agencies on research and policy issues, will also be addressing nanotechnology programs. The U.S. Department of Defense, which has its own cancer research programs and appreciates the growing burden that cancer represents for current and former members of the Armed Forces, is also a potential collaborator. Both the DARPA and the HSARPA, which have extensive, successful experience using project-management, product-focused research contracts, are providing guidance to the NCI as it develops new funding mechanisms. The NCI and the U.S. Department of Energy, which has a significant biomedical research initiative, are also discussing areas of joint interest in the nanotechnology field. The NCI recognizes the importance of science that supports safe use of nanomaterials in humans and will work with other institutes and centers as well as other programs, such as the National Institute of Environmental Health Sciences and the National Toxicology Program, to characterize any potential health and environmental issues with biomedical nanoscale devices.

Nanotechnology Characterization Laboratory for Cancer Research

During the course of the NCI's activities to develop the CNPlan, it became clear that the lack of standards and characterization data for the many nanoscale devices being developed could become a significant obstacle on the development and regulatory approval pathways. On the basis of input from the academic and private sectors, the NCI believes that the most effective manner for removing this potential obstacle is to establish and fund a national Nanotechnology Characterization Laboratory (NCL), which would work in concert with the NIST and the FDA to perform and standardize the preclinical characterization of nanoscale devices in a way that will facilitate the accelerated regulatory review and translation of these devices into the clinical realm.

The NCL, which will be operated under a contract with SAIC-Frederick, will have the following goals:

- Standardize the preclinical testing and characterization of nanoscale devices to speed the regulatory review of novel diagnostics, therapeutics, and prevention strategies that use nanoscale devices.
- Perform preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices created by both NCI intramural and extramural efforts as well as the private sector.
- Facilitate collaborations between the NCI, academia, and the private sector to accelerate the translation of basic nanotechnology research into clinical advances.
- Serve as a nexus for multidisciplinary research, development, and clinical applications of nanotechnology; provide resources, knowledge, tools, and methods for intramural and extramural cancer researchers.
- Collaborate with other government agencies to leverage resources and expertise in pursuit of common goals in the acceleration of the use of nanotechnology for critical national applications, and team with industry to bring those applications to market.

A key activity of the NCL will be to work together with FDA scientists to develop an assay cascade that can serve as the standard protocol for preclinical toxicology, pharmacology, and efficacy testing of nanoscale devices. This assay cascade will characterize a nanoscale device's physical attributes, its *in vitro* biological properties, and its *in vivo* compatibility.

In carrying out these functions, the NCL will provide a comprehensive set of baseline characterization parameters that will enable cancer biologists, drug and diagnostic developers, and clinical oncologists to concentrate on what they do best—applying these tools to solving problems that most affect cancer patients. This work will also lay a scientific foundation that will enable the FDA to make sound decisions concerning testing and approval of nanoscale cancer diagnostics, imaging agents, and therapeutics.

From its discussions with experts in academia and the private sector, the NCI believes that the NCL's activities will markedly speed the development of nanotechnology-based products for cancer patients, reduce the risk of doing so, and encourage private-sector investment in this promising area of technology development. By taking on this role, the NCL will greatly accelerate the development of the paradigm-changing advances needed to meet the goal of eliminating suffering and death from cancer by 2015.

Interfacing With the Cancer Research Community

A central goal of the NCL is to leverage the existing resources in science and technology which are needed to accelerate the translation of basic research into clinical advances, whether in the public or the private sector. Substantial investments have been made and continue to be made in nanoscience and nanotechnology:

- Through funding from the National Nanotechnology Initiative to support fundamental and applied research, the establishment of multidisciplinary centers of excellence, and the development of infrastructure,
- Through NCI-funded intramural and extramural projects, such as those funded by the Unconventional Innovations Programs (UIP), to support development of novel technologies for noninvasive detection, diagnosis, and treatment of cancer,

- Through other government agency investment, such as the Nanomedicine Roadmap Initiative at NIH to understand molecular pathways and networks and to use that knowledge to design and develop new technologies and devices to improve human health, and
- Through private investment across industry, but primarily through the increasing investment in small businesses to bring new nanomaterials and nanotechnology products to market.

There has also been large investment in technology areas that are critical to the rapid development and application of nanotechnology, such as:

- Investments in microfluidics, MEMS, biotechnology, and bioinformatics, and
- Development of new and advanced measurement technologies and devices, such as the atomic force microscope and MALDI-TOF spectroscopy, which are capable of providing measurements with unprecedented detail and precision.

The new Advanced Measurement Laboratory at NIST, created to respond to the need for advanced measurement methods and standardization in research and development, is another example of the type of facilities that can be leveraged to achieve the NCI's 2015 Challenge Goal.

In order to accelerate the transition of nanotechnology to clinical applications, the NCL must also work closely with regulatory bodies, primarily the FDA, in providing a much closer relationship with industry throughout the pre-clinical tests and clinical trials. The mechanism for this enhanced relationship is already in place in the NCI/FDA Oncology Task Force, an interagency agreement between NCI and FDA to share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. The NCL can play a significant role in accelerating the transition of nanomaterials and nanodevices to aid in delivering and targeting new cancer drugs as well as contrast agents and reporters to aid in cancer detection and diagnosis.

This relationship with the FDA is crucial in the NCL's interaction with industry. Industry presently assumes significant risk in nanoparticles R&D for clinical applications; the regulatory guidelines are presently undefined. A standardized assay cascade, developed in collaboration with the FDA, will "incentivize" industry to submit nanomaterials to the NCL for characterization, thereby reducing the high risks associated with regulatory approval.

The lack of knowledge concerning the health and safety of nanomaterials may also become an obstacle to the rapid implementation of nanotechnology. Although industry has long manufactured fine and ultra-fine particles for use in a variety of applications, the effects of those particles on human health has been studied only for a small number of materials and applications. In addition, the waste streams generated by the manufacturing and assembly processes for nanomaterials and by their disposal have generally not been subjected to detailed examination and analysis. The assay cascades developed by the NCL to characterize the effect of nanomaterials and platforms in *in vitro* and *in vivo* tests can also provide standardized measures of the effect of these materials, devices, and waste products on human safety—especially the carcinogenic properties of nanomaterials. This additional NCL service will require close collaboration with nanotechnology research institutions and product developers and manufacturers to develop the appropriate standard assays and protocols in response to this public need.

It is precisely this sharp focus on the many facets of cancer research that enables the NCL to serve as a nexus for trans-disciplinary research, development, and clinical applications of nanotechnology. The NCL seeks to provide resources, knowledge, tools, and methods for cancer researchers. It does not seek to duplicate the efforts of established and emerging programs by academia, industry, or government in nanotechnology or to intrude on the domain of other programs. Rather it seeks to partner with these programs. To this end the NCL will collaborate wherever possible with other government agencies, academia, and industry to leverage their resources and expertise in pursuit of common goals and to accelerate the use of nanotechnology in critical national applications to cancer.

Scientific Foundations for the Cancer Nanotechnology Plan

What Is Nanotechnology?

Nanotechnology refers to the interactions of cellular and molecular components and engineered materials—typically clusters of atoms, molecules, and molecular fragments—at the most elemental level of biology. Such nanoscale objects—typically, though not exclusively, with dimensions smaller than 100 nanometers—can be useful by themselves or as part of larger devices containing multiple nanoscale objects. At the nanoscale, the physical, chemical, and biological properties of materials differ fundamentally and often unexpectedly from those of the corresponding bulk material because the quantum mechanical properties of atomic interactions are influenced by material variations on the nanometer scale.

Nanoscale devices and nanoscale components of larger devices are of the same size as biological entities. They are smaller than human cells (10,000 to 20,000 nanometers in diameter) and organelles and similar in size to large biological macromolecules such as enzymes and receptors—hemoglobin, for example, is approximately 5 nanometers in diameter, while the lipid bilayer surrounding cells is on the order of 6 nanometers thick. Nanoscale devices smaller than 50 nanometers can easily enter most cells, while those smaller than 20 nanometers can transit out of blood vessels, offering the possibility that nanoscale devices will be able to penetrate biological barriers such as the blood-brain barrier or the stomach epithelium that can make it difficult for therapeutic and imaging agents to reach certain tumors. And because of their size, nanoscale devices can readily interact with biomolecules on both the cell surface and within the cell, often in ways that do not alter the behavior and biochemical properties of those molecules.

Such ready, noninvasive access to the interior of a living cell affords the opportunity for unprecedented gains on both the clinical and basic research frontiers. The ability to simultaneously interact with multiple critical proteins and nucleic acids at their own molecular scales should provide the data needed to better understand the complex regulatory and signaling networks that govern the behavior of cells in their normal state and as they undergo the changes that transform them into malignant cells. In particular, nanotechnology will provide an important platform for integrating efforts in proteomics with other scientific investigations into the molecular nature of cancer. Similarly, nanoscale devices are already proving that they can deliver therapeutic agents that can act where they are likely to be most effective, that is, within the cell or even within specific organelles. Yet despite their small size, nanoscale devices can also hold tens of thousands of small molecules, such as an MRI contrast agent or a multicomponent diagnostic system capable of assaying a cell's metabolic state, creating the opportunity for unmatched detection sensitivity of cancer in its earliest stages.

In some instances, nanotechnology will take advantage of years of clinically relevant technological developments at larger scales. A good example of this approach will capitalize on existing “lab-on-a-chip” and microarray technologies developed at the micron scale. Widely used in biomedical research and clinical diagnostic applications today, these technologies will find new uses when shrunk to the nanoscale. There, they will be able to interact with an individual cell in real time and in that cell's native environment. The CNPlan, with its targeted approach to development, will take advantage of such synergies through several projects directed toward developing real-time diagnostics, reporter systems, and new tools for studying cancer cell and molecular biology.

Current Progress in Cancer Nanotechnology

Today, clinical, cancer-related nanotechnology research is proceeding on two main fronts: laboratory-based diagnostics and *in vivo* diagnostics imaging and therapeutics. Here are just a few of the illustrative highlights of progress in these areas, as well as with the use of nanotechnology to extend our understanding of cancer cellular and molecular biology.

Nanotechnology and Molecular Imaging

- 1-2 nanometer-wide wires built on a micron-scale silicon grid can be coated with monoclonal antibodies directed against various tumor markers, leading to a hundredfold increase in sensitivity over current diagnostic techniques with minimal sample preparation.
- Nanoscale “lab-on-a-chip” applications are now capable of conducting real-time analysis of single biochemical markers.
- Quantum dots have been used to tag and follow multiple individual molecules within cells, providing an opportunity to study the biochemical and genetic systems that go awry in cancer.
- Nanoscale “harvesting” devices have collected proteins capable of distinguishing cancerous tissue from normal tissue.

Nanotechnology and *In Vivo* Imaging

- Nanoscale MRI contrast agents, containing paramagnetic iron nanoparticles, dramatically improve the ability to detect metastatic lesions in lymph nodes associated with breast and prostate cancer.
- Gold nanoparticles demonstrate usefulness contrast agents for *in vivo* endoscopic optical imaging of specific molecular cancer markers.
- Gas-filled lipid nanoparticles have shown promise for use as acoustically activated imaging agents, and perhaps targeted drug delivery systems, for tumors with a spatial resolution of 0.5 to 1.0 millimeters and a temporal timeframe of several images per second.
- Her-2 conjugated, gold-coated nanoparticles with a dielectric silicon core can identify breast carcinoma cells *in vivo*. Once bound to their target cells, these nanoparticles were subjected to increased optical power, turning them into nanoscale thermal scalpels that attain cell-killing temperatures.

Nanotechnology and Cancer Therapy

- A wide variety of synthetic nanoscale particles are shown to target tumor cells, enter cancer cells, and release therapeutic agents.
- Engineered virus particles can serve as multifunctional, targeted non-immunogenic nanoscale devices with potential for a broad range of *in vivo* uses.
- Photosensitizers used in photodynamic therapy, in which light is used to generate reactive oxygen locally within tumors, have also been entrapped in targeted nanoscale devices. The next step in this work is to also entrap a light-generating system, such as the luciferin-luciferase pair, in such a way as to trigger light production only after the nanoparticles have been taken up by a targeted cell. If successful, such an approach would greatly extend the usefulness of photodynamic therapy to include treatment of tumors deep within the body.

Nanotechnology as a Research Enabler

- Construction and testing of nanoplatfroms can consolidate cell biology lab tests on a chip. These nanoplatfroms can be constructed to accurately mimic the microenvironment in which a particular cell normally grows, producing a system capable of both perturbing cells and recording their responses in a manner more representative of how those cells would behave in the body than is observed in cells grown in standard tissue culture systems.
- A nanoscale device analyzes genome complexity and shows that early-stage tumors expressing similar phenotypes can be distinguished on the basis of how each tumor selects a slightly different approach to derange its genome.

Opportunities From the Fundamental Understanding of Cancer Processes

Nanotechnology offers a wide range of tools, from chip-based nanolabs capable of monitoring and manipulating individual cells to nanoscale probes that can track the movements of cells, and even individual molecules, as they move about in their environment. Using such tools will enable cancer biologists to study, monitor, and alter the multiple systems that go awry in the cancer process and identify key biochemical and genetic “choke points” at which the coming wave of molecular therapies might best be directed. As such,

nanotechnology can serve as the perfect complement to other technology platforms, such as proteomics and bioinformatics, that the NCI is emphasizing in its research initiatives as critical components of the discovery and development engine that will power both near-term and long-term advances in cancer diagnosis, treatment, and prevention. More importantly, however, nanotechnology will serve as a versatile development platform that will be able to quickly turn biological insights into clinically useful products.

Thirty years ago, cancer was a poorly understood and usually deadly disease. This is no longer the case. Today, we know that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell also change over a progression of steps that can take years to reach the stage at which a cell becomes malignant and develops into a tumor. These changes are unique molecular “signatures” and serve as signals of the presence of cancer and of the cellular states that precede cancer. This more robust understanding of the genetic alterations that occur within a cancer cell has changed the course of cancer research and has fueled new approaches to prevention, detection, diagnosis, and treatment. One goal of the CNPlan is to foster the development of nanoscale devices that can identify the early molecular signatures of cancer and deliver therapeutic or preventive agents that can intervene in the cancer process at this early stage.

However, the cancer cell is only part of the story in cancer development. As a cancer cell grows within the elaborate architecture of the body’s tissues and organs, it interacts with its surrounding environment. Mounting evidence now suggests that a dynamic interaction occurs between the cancer cell and its local and systemic microenvironment, with each profoundly influencing the behavior of the other. This “tumor microenvironment” is populated with a variety of different cell types, is rich in growth factors and enzymes, and includes parts of the blood and lymphatic systems. It promotes some of the most destructive characteristics of cancer cells and permits the tumor to grow and spread. Nanoscale devices, because of their designed multifunctionality, offer the opportunity to manage this complex interaction in ways that could stop the growth and spread of cancer.

The microenvironment can also influence the access of therapeutic agents to tumor cells, the body’s processing of treatment agents, and the development of resistance to cancer treatments. Again, these are problems that nanoscale devices should be able to address. Although the cells in the microenvironment may not be genetically altered, their behavior can be changed through interactions with tumor cells. Physicians now realize that they confront a tumor entity that consists of malignant cells combined with their host tumor environment when treating a cancer patient. The tumor cells and their surrounding environment both need to be fully characterized to understand how cancer grows in the body, and both need to be considered when developing new interventions to fight it.

We now understand that cancer is the culmination of many biochemical and genetic processes going awry in the malignant cell and its microenvironment and that no one change will cause a cell to become cancerous. Thus, we now view cancer as a “systems” disease, one that involves the interactions of many cellular processes. The changes that affect these processes fall into seven broad categories, which can be characterized as follows:

Cancer Cells Attain Self-Sufficiency in Growth Signals

Cells grow and multiply in response to a wide variety of growth signals that trigger a series of orchestrated biochemical and genetic events. The production of these growth signals is tightly controlled in a normal cellular environment, but malignant cells have developed numerous ways of either producing their own growth signals or short-circuiting the control mechanisms associated with these growth signals. Many of the oncogenes discovered to date give cancer cells the ability to mimic normal growth signaling processes. Because of the multifactor nature of growth factor activity, it may be necessary to deliver several molecularly targeted agents to a tumor to control its growth, a task for which multifunctional nanoscale devices are ideally suited.

Cancer Cells Become Insensitive to Antigrowth Signals

The normal cellular environment also provides multiple antigrowth signals that act as a check to unregulated cellular reproduction. These growth-controlling signals come mainly from neighboring cells and the extracellular matrix, and they too trigger a series of orchestrated biochemical and genetic events that regulate the cell cycle. Our current understanding of these systems suggests that these signals come through three closely related receptors on the cell surface and that cancer cells are able to disrupt these receptors or the systems that these receptors control. Again, the multifunctional nature of nanoscale devices offers the potential for interacting with more than one of these receptors simultaneously.

Cancer Cells Escape Apoptosis

A third mechanism for regulating improper cell growth involves apoptosis, a set of programmed cellular processes that result in cell death. It is clear from a variety of studies that cancer cells acquire the ability to avoid apoptosis and that effective cancer therapies are able to trigger reactive apoptosis in malignant cells. A cell's apoptotic machinery consists of sensors that monitor the internal and external state of a cell and its environment and effectors that trigger apoptosis when the sensors detect abnormal conditions. The loss of the p53 protein, characteristic of over half of all cancers, allows cells to avoid apoptosis. It appears, however, that cancer cells with damaged apoptotic systems may possess redundant, though inactive, mechanisms for triggering apoptosis. Nanoscale devices will be critical to detecting the reappearance of apoptosis as a sign that cancer therapy is working.

Cancer Cells Gain Limitless Potential for Replication

Telomeres, a stretch of repeat sequences located at the ends of chromosomes, represent a fourth mechanism for controlling the unlimited cellular growth that characterizes cancer. Each time a cell reproduces normally, its chromosomes fail to fully replicate the telomeres, and when the telomeres reach a defined, shortened length, the chromosomes begin to fuse, triggering apoptosis. Thus, telomeres act as a "reproduction counter" that limits a cell's potential for immortality. Some 85 to 90 percent of all cancer cells develop the ability to turn on expression of telomerase, an enzyme that can maintain normal telomere length and that is strongly suppressed in almost all normal cells. The remaining 10 to 15 percent develop a mechanism that maintains telomere length through chromosome-to-chromosome sequence exchange. Nanoparticles, because of their ability to deliver substances to specific cells, and perhaps compartments within a cell, may be the technological platform needed for therapeutic and preventive agents that would intervene in this process.

Cancer Cells Trigger Sustained Angiogenesis

All solid tumors develop the ability to trigger angiogenesis in order to provide oxygen and nutrients. Incipient tumors do not immediately trigger angiogenesis, but at some point tumors are able to alter the balance between angiogenic and antiangiogenic factors in favor of capillary growth in a multi-step process that can be reversed. Recent work with mouse models has shown that different antiangiogenic factors are effective at turning off angiogenesis and starving tumors at specific stages of the angiogenesis and tumor growth. It is also clear that different types of tumor cells use distinct molecular strategies to trigger angiogenesis. Nanoscale devices capable of imaging angiogenesis could provide a new early detection technology; multifunctional nanoscale devices will be able to deliver multiple angiogenesis inhibitors simultaneously.

Cancer Cells Metastasize and Invade Other Tissues

Approximately 90 percent of all cancer deaths result from metastatic spread of the primary tumor. At some point in their development, some number of malignant cells develop an ability to dissociate themselves from the primary tumor mass, invade adjacent tissues, and spread to sites throughout the body. It is clear that invasion and metastatic spread result from a complex series of biochemical and genetic events that affect numerous systems, both in the metastatic cell and in the tissues that it invades. Though most of these events are still poorly characterized, recent work has established that the molecular systems involved in maintaining the normal contact between neighboring cells become altered prior to metastasis. In addition, metastatic cells turn on the expression of proteases capable of degrading the extracellular matrix. Nanoscale analytical devices may be able to detect the early molecular signatures of metastasis before secondary tumors are detectable by other means.

Cancer Cell Genomes Become Unstable

There is little doubt that most of the six molecular characteristics of cancer cells listed above result from genetic changes in a cancer cell, but acquiring multiple mutations through random processes is unlikely given the enormous effort that cells put into maintaining the integrity of their genomes. Yet, cancer cells do accumulate the necessary mutations needed to change from normal to pre-malignant to malignant, suggesting that cancer cells must also have genomes that are unnaturally unstable; indeed, recent research has shown that malignant cells do have grossly rearranged genomes, including multiple copies of specific chromosomes. Furthermore, this research has shown that cells can acquire one or more of the above traits, but they will not become cancerous until their genomes exhibit such instability. Already, nanoscale devices are being developed that can detect genetic mutation and genome instability.

Some of the unanswered questions concerning nanoscale devices relate to their potential toxicity or their fate in the environment, neither of which has yet to be studied in any concerted manner. To date, the few published studies in these areas have concentrated on the potential toxicity of inhaled nanoscale particles, specifically various forms of C₆₀, including “buckyballs” and single-walled carbon nanotubes. That such nanoparticles, when inhaled, might have the potential to damage lung tissue is no surprise given the well-documented hazardous nature of nanoscale diesel exhaust particles. However, such particles are not currently envisioned as having use in the clinical setting. Nevertheless, these studies reinforce the recognized need to conduct thorough toxicology studies on nanoscale devices. Of course, given that any material envisioned for use in humans must undergo rigorous toxicology studies as part of the regulatory approval process, this requirement is neither unexpected nor onerous.

To help address such safety issues, the NCI plans several approaches to supplement the standard complement of toxicology studies that the private sector or any public-private partnerships will conduct as part of the preclinical development process. Under the aegis of the CNPlan, the NCL, in close collaboration with the FDA, will develop a battery of toxicology and safety tests as part of its assay cascade. The NCL will then make these assays available to the field at large as well as use them to develop baseline toxicology data for a wide range of nanoscale particles and devices. The NCI will be evaluating future collaborations and partnerships with the National Toxicology Program and the National Institute of Environmental Health Sciences for these important areas of science.

The NCI's CNPlan dovetails perfectly with the Institute's Action Plan for 2005 and various initiatives aimed at meeting the Challenge Goal of eliminating suffering and death due to cancer by 2015. In particular, the CNPlan stresses work that strengthens the Institute's core multidisciplinary scientific areas of emphasis, including:

- Elucidating the *Signatures of the Cancer Cell and Its Microenvironment*
- Validating and developing effective agents aimed at *Molecular Targets of Prevention, Diagnosis, and Treatment*
- Optimizing *Cancer Imaging and Molecular Sensing* technologies

The CNPlan's heavy emphasis on development and delivery are consistent with goals that the NCI has laid out in its Plan and Budget Proposal for FY 2005. In addition, the CNPlan's activities fit with the Institute's high-profile initiatives in developing new platforms for and enablers of discovery, development, and delivery.

The CNPlan's use of novel, team-oriented funding mechanisms will continue the NCI's work on building capacity through large-scale collaborations. These funding mechanisms also build on efforts to increase translational research involving public-private partnerships.

Appendix A: Training and Cross-Disciplinary Collaboration

One important challenge to reaching the goals of the CNPlan involves bridging the gulf between those who are experts in nanotechnology and those who possess the vision and knowledge to apply this technology to the task of eliminating suffering and death due to cancer. To develop a well-trained cadre of cancer researchers who can bring nanotechnology to the fight against cancer, the NCI anticipates taking a multi-pronged approach. Current, technologically nonspecific funding mechanisms exist that would facilitate building a cancer nanotechnology research program. These can be viewed in terms of immediate impact and future impact. The mechanisms are broken down into categories based on their anticipated effect on the field of cancer nanotechnology.

Immediate Impact Mechanisms

In the short term, the NCI must bring together nanotechnology specialists and cancer specialists for the exchange of ideas, focused educational opportunities, and short-term training and mentoring. Possible mechanisms for accomplishing this goal include:

F33 Awards

- *F33 NIH National Research Service Awards for Senior Fellows.* “(T)he National Institutes of Health (NIH) awards NRSA senior fellowships (F33) to experienced scientists who wish to make major changes in the direction of their research careers or who wish to broaden their scientific background by acquiring new research capabilities. These awards will enable individuals with at least seven years of research experience beyond the doctorate, and who have progressed to the stage of independent investigator, to take time from regular professional responsibilities for the purpose of receiving training to increase their scientific capabilities. In most cases, this award is used to support sabbatical experiences for established independent scientists.”

This mechanism would allow current established cancer investigators to train in the labs of leading nanotechnologists to facilitate bringing the technology back to their own labs to be applied toward future research activities. Alternatively, nanotechnologists could be funded to spend a year gaining insight into cancer research so that these problems could be addressed when returning to the nanotechnologist’s lab. In both cases, the spillover of ideas from the trainee to the mentor’s lab will continue to cross-pollinate the cancer and nanotechnology fields.

K05 Awards

- *K05 Established Investigator Award in Cancer Prevention, Control, Behavioral, and Population Sciences.* “The purpose of the NCI Established Investigator Award in Cancer Prevention, Control, Behavioral and Population Research (K05) is to provide established investigators protected time to devote to research and to act as mentors for new investigators and junior faculty members. The target candidates are outstanding established scientists who have demonstrated a sustained, high level of research productivity and significant contributions to cancer prevention, control, behavioral and/or population cancer research. They must demonstrate the need to develop and enhance their own research and a commitment to serve as mentors to new scientists.”

This mechanism can be used by established scientists to free themselves of some administrative responsibilities so that they may mentor recipients of training and career awards in cancer nanotechnology.

R25 Awards

- *R25E Cancer Education Grant Program.* “The Cancer Education Grant Program (CEGP) of the National Cancer Institute is a flexible, curriculum-driven program aimed at developing and sustaining innovative educational approaches that ultimately will have an impact on reducing cancer incidence,

mortality and morbidity, as well as on improving the quality of life of cancer patients. The CEGP invites investigator-initiated R25 Grant applications that pursue a wide range of objectives from short courses, national forums, seminars, and/or hands-on workshops designed to educate scientists, health care professionals and the lay community; to the design, development and evaluation of new curricula of special significance to cancer in educational institutions; to structured short-term didactic and research experiences designed to motivate high school; college; and medical, dental and other health professional students to pursue careers in cancer research; to the development and evaluation of new educational methods and tools directed at different audiences with the intent of having an impact on reducing cancer incidence and mortality. The R25 can also be used to fund symposia and support rapidly evolving areas (e.g., courses in innovative screening).

Education Grants such as the R25 can focus on education activities before, during and after the completion of a doctoral level degree (e.g., Ph.D., M.D., D.P.H., D.D.S., and D.N.S.) as long as they address a need that is not fulfilled adequately by any other grant mechanism available at the National Institutes of Health and are dedicated to areas of particular concern to the National Cancer Institute. The CEGP encourages innovative uses of the R25 grant to explore educational approaches that will help promote progress in preventing and curing cancer.”

This mechanism can be an integral part of the ability to rapidly adjust to changes in science technology. Nanotechnology workshops, short-term courses, training seminars, and so forth can be developed and funded through this mechanism to quickly bridge the gap and bring nanotechnology to cancer research.

Future Impact Mechanisms

The core of the future cancer nanotechnology cadre will be based not on current established investigators who have adopted a new technology or a new application for their technology but on those who have extensive training in both nanotechnology and cancer research. This core will come from those postdoctoral fellows and junior investigators who, over a 3- to 5-year period, train extensively outside their discipline. Ultimately, the field of cancer nanotechnology will be populated by scientists who have received training that has integrated nanotechnology into the research curriculum. The development of these curricula and the implementation and evaluation of these programs will take time but result in cancer researchers who are as versant in nanotechnology as they are in molecular biology, imaging, or any other technology.

K25 Awards

- *K25 Mentored Quantitative Research Career Development Award.* “The K25 mechanism is meant to attract to NIH-relevant research those investigators whose quantitative science and engineering research has thus far not been focused primarily on questions of health and disease. Examples of quantitative scientific and technical backgrounds considered appropriate for this award include, but are not limited to: mathematics, statistics, economics, computer science, imaging science, informatics, physics, chemistry, and engineering. This award provides support for a period of supervised study and research for productive professionals with quantitative backgrounds who have the potential to integrate their expertise with NIH-relevant research and develop into productive investigators. It is intended for research-oriented investigators from the postdoctoral level to the level of senior faculty.”

This mechanism is already bringing in scientists with quantitative and engineering backgrounds to apply different technologies and backgrounds to cancer research. Although certain areas were specifically mentioned, nanotechnology was not. We have begun to specifically mention nanotechnology in these announcements to attract this group to cancer research. This mechanism, in conjunction with mechanisms facilitating mentoring opportunities can, within 5 years, bring about a small cadre of nanotechnology-based, independent cancer researchers.

K01 Awards

- ***K01 Howard Temin Award.*** “The goal of the National Cancer Institute’s (NCI) Howard Temin Award is to bridge the transition from a mentored research environment to an independent basic cancer research career for scientists who have demonstrated unusually high potential during their initial stages of training and development. This special award is aimed at fostering the research careers of outstanding junior scientists in basic research who are committed to developing research programs directly relevant to the understanding of human biology and human disease as it relates to the etiology, pathogenesis, prevention, diagnosis, and treatment of human cancer. The major objective of the award is to sustain and advance the early research careers of the most promising M.D.s and Ph.D.s while they consolidate and focus their independent research programs and obtain their own research grant support. To achieve this objective, the Howard Temin Award offers candidates up to five years to gain additional skills and knowledge in human cancer research during a period of one to three years in a mentored environment, followed by transition to the equivalent of a junior faculty position to develop an independent research program.”

The Temin Award offers the opportunity for junior scientists, on the cusp of independence, to receive 1 to 3 years of mentoring before setting out as independent investigators. The 1- to 3-year mentoring period is well suited to applying a new technology to a cancer project. These grants, along with the K25, have the ability to build a cadre of young cancer nanotechnologists who can become the nuclei of cancer nanotechnology programs.

K07 Awards

- ***K07 Cancer Prevention, Control, Behavioral and Population Sciences Career Development Award.*** “The purpose of the Cancer Prevention, Control, Behavioral and Population Sciences Career Development Award (K07) is to support the career development of investigators who have made a commitment to focus their research endeavors on cancer prevention, control, behavioral and the population sciences. This is achieved by providing protected time through salary and research support for up to 5 years to individuals with a health professional or science doctoral degree who are 1) already proficient in general epidemiology, behavioral sciences, or other relevant disciplines, and now want to make use of these proficiencies in cancer-focused research careers in prevention, control, population and/or the behavioral sciences, or 2) already trained in cancer epidemiology, etiology, prevention, control and the behavioral and population sciences but are not yet fully independent investigators. Examples of relevant disciplines for this Program Announcement (PA) include any aspect of human cancer prevention (modifiable risk factors, new animal models and extrapolation of these models to human cancer, genetic predisposition to cancer and detection of precursor lesions, patient-oriented research focused on cancer prevention, and behavioral research and behavioral intervention trials in cancer prevention), epidemiology (biochemical, genetic, molecular), biostatistics, human cancer genetics, clinical oncology, human nutrition, behavioral and social sciences, health promotion, health services and health policy research; and medical decision analysis, survivorship and quality of life as they relate to cancer.”

The K07 is a mentored award designed for researchers in the area of prevention, control, behavioral, and population sciences. K07 recipients often progress to the K22 Transition Career Development Award as they begin their independent research career.

K08 Awards

- ***K08 Mentored Clinical Scientist Development Award.*** “The purpose of the Mentored Clinical Scientist Development Award (K08) is to support the development of outstanding clinician research scientists. This mechanism provides specialized study for individuals with a health professional doctoral degree committed to a career in laboratory or field-based research. Candidates must have the potential to develop into independent investigators. The K08 supports a three, four, or five year period of supervised research experience that may integrate didactic studies with laboratory or clinically based research. The proposed research must have intrinsic research importance as well as serving as a suitable vehicle for learning the methodology, theories, and conceptualizations necessary for a well trained independent researcher.”

The K08 mechanism provides a postdoctoral experience for clinically degreed individuals. It is anticipated that this mechanism will be used in a similar manner as the F32 with the added possibility that research produced under the K08 mechanism may have an increased capacity to be translated into the clinic due to the clinical degrees of the applicants. Many K08 recipients progress to the K22 mechanism as they transition to independence.

K22 Awards

- ***K22 NCI Transition Career Development Award.*** “This K22 award is intended to facilitate the transition of investigators from the mentored to the independent stage of their careers in cancer research, by providing ‘protected time’ for newly independent investigators to develop and receive support for their initial cancer research programs. The award applies to clinicians who are pursuing basic science careers; clinicians who are pursuing careers in patient-oriented research; and to individuals pursuing careers in the prevention, control and population sciences. To apply, a candidate must have completed two years of postdoctoral, mentored research or have been in an independent position for less than two years at the time the application is submitted. The unique feature of this award is that individuals may apply without a sponsoring institution while they are still in a ‘mentored’ position. Successful postdoctoral applicants will be given up to 12 months to identify an independent, preferably tenure-track, position at a sponsoring institution before an award can be activated. For postdoctoral applicants, the sponsoring institution for a K22 award can be their current institution or a new institution.”

As our career awardees develop and are ready to achieve independence, it will be critical to provide them with the protected time to establish their own labs and with the preliminary data required to successfully compete for research grants. The K22 award is designed to bridge the time between mentored status and independently funded investigator.

R25T, K12, and T32 Awards

- ***R25T Cancer Education and Career Development Program.*** “The purpose of NCI Cancer Education and Career Development Program (R25) is to train predoctoral and postdoctoral candidates in cancer research settings that are highly interdisciplinary and collaborative. This Program requires sustained leadership, dedicated faculty time, specialized curriculum development and implementation, interdisciplinary research environments, and more than one mentor per trainee to achieve career development research and education objectives. Areas of research particularly applicable but not all inclusive to interdisciplinary training are cancer prevention and control, nutrition, population sciences, behavioral sciences, imaging and molecular diagnostics.”
- ***K12 Institutional Clinical Oncology Research Career Development Program.*** “The purpose of the National Cancer Institute (NCI) Institutional Clinical Oncology Career Development Program is to increase the number of medical doctors and doctorally degreed Oncology Registered Nurses who are motivated and properly trained to: (1) communicate and collaborate with basic/behavioral research scientists in order to expedite the translation of basic/behavioral research information into patient-oriented cancer research; (2) perform independent clinical oncology research that develops and tests rational scientific hypotheses based on fundamental and clinical research findings with the potential for improving the medical care of cancer patients; and (3) design and test innovative clinical protocols and manage all phases (i.e., pilot/Phase I, Phase II, and Phase III) of clinical trials research. To achieve this purpose, awards are made to institutions for up to five years for the development and implementation of training programs providing clinicians with all of the necessary information and training that will enable them to design, implement and manage all phases of cancer clinical trials research. The distinguishing features of this career development Program are that a Program Leader in the institution together with an Advisory Committee selects the candidates and oversees the course of their training, and that candidates are likely to have more than one mentor as they are exposed to the basic sciences and to the many disciplines critical to the clinical sciences.”

- *T32 NIH National Research Service Award Institutional Research Training Grants.* “The National Institutes of Health (NIH) will award National Research Service Award (NRSA) Institutional Training Grants (T32) to eligible institutions to develop or enhance research training opportunities for individuals, selected by the institution, who are training for careers in specified areas of biomedical, behavioral, and clinical research. The purpose of the NRSA program is to help ensure that a diverse and highly trained workforce is available to assume leadership roles related to the Nation’s biomedical and behavioral research agenda. Accordingly, the NRSA program supports predoctoral, postdoctoral, and short-term research training experiences.”

All three mechanisms are designed to create a training environment within the institutions. Through these mechanisms, cancer nanotechnology training programs can be created in basic research (T32), prevention, control, behavioral, and population sciences (including screening, diagnostic, and imaging) (R25T) and, as the field matures and products are ready to enter the clinic, clinical oncology (K12).

F32 Awards

- *F32 Ruth L. Kirschstein National Research Service Awards for Individual Postdoctoral Fellows.* “The Congress of the United States enacted the National Research Service Award (NRSA) Program in 1974 to help ensure that highly trained scientists will be available in adequate numbers and in appropriate research areas to carry out the Nation’s biomedical and behavioral research agenda. Under this congressional authority, the National Institutes of Health (NIH) awards NRSA individual postdoctoral fellowships (F32) to promising applicants with the potential to become productive, independent investigators in fields related to the mission of the NIH constituent institutes and centers.”

This is the basic postdoctoral funding mechanism and will undoubtedly provide the bulk of the future nanotechnology-focused cancer researchers. In the short term, it is anticipated that Ph.D.s with training in either cancer or technology will use the F32 to gain postdoctoral experience in the other discipline. Eventually, once a cadre of cancer nanotechnology researchers has been established, graduates will be able to obtain research experience specifically in cancer nanotechnology.

K23 and K24 Awards

- *K23 Mentored Patient-Oriented Research Career Development Award.* “The purpose of the Mentored Patient-oriented Research Career Development Award (K23) is to support the career development of investigators who have made a commitment to focus their research endeavors on patient-oriented research. This mechanism provides support for three to five years of supervised study and research for clinically trained professionals who have the potential to develop into productive, clinical investigators focusing on patient-oriented research.”
- *K24 Midcareer Investigator Award in Patient-Oriented Research.* “The purpose of the Midcareer Investigator Award in Patient-Oriented Research (K24) is to provide support for clinicians to allow them protected time to devote to patient-oriented research and to act as mentors for beginning clinical investigators. The target candidates are outstanding clinical scientists who are actively engaged in patient-oriented research. Candidates are generally within 15 years of their specialty training. Candidates must be able to demonstrate the need for a period of intensive research focus as a means of enhancing their clinical research careers and must be committed to mentoring the next generation of patient-oriented researchers. The award is intended to further both the research and mentoring endeavors of outstanding patient-oriented investigators, to enable them to expand their potential for significant contributions to their field, and to act as mentors for beginning clinician researchers.”

As the cancer nanotechnology field matures and products begin to make their way to the clinics, it will be important to develop cancer nanotechnology researchers who are involved in patient-oriented research. The K23 mechanism provides a mentored experience for patient-oriented researchers and the K24 provides the mentors with the protected time to do patient-oriented research and act as mentors for K23 fellows.



Cowpea mosaic virus. From Marianne Manchester and M. G. Finn, Scripps Research Institute



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Printed July 2004