National Cancer Institute Director John E. Niederhuber, M.D.

Dr. John Niederhuber was appointed the 13th Director of the National Cancer Institute in August 2006. Throughout his distinguished career, he has had ties to both NCI and the National Institutes of Health. In addition to his work as a surgeon, professor, researcher, department chair, senior associate dean, and cancer center director, Dr. Niederhuber has also been the chair of the National Cancer Advisory Board, an external NCI advisor and grant reviewer, and a laboratory investigator supported by NCI and the NIH. He joined NCI in September 2005 as deputy director for translational and clinical sciences, and became NCI's acting director in June 2006.

In addition to his leadership of the NCI, Dr. Niederhuber heads the Laboratory of Tumor and Stem Cell Biology in NCI's Center for Cancer Research, and also holds a clinical appointment on the NIH Clinical Center Medical staff. His lab is studying tissue stem cells as the cell-of-origin for cancer, as well as the complex relationship between tumor cells and their microenvironment.

As a surgeon, Dr. Niederhuber's clinical emphasis is on gastrointestinal cancer, hepatobiliary (liver, bile duct, and gallbladder) cancer, and breast cancer. Recognized for his pioneering work in hepatic artery infusion chemotherapy, he was also the first to demonstrate the feasibility of totally implantable vascular access devices.

Prior to his coming to NCI, Dr. Niederhuber spent his years as Director of the University of Wisconsin School of Medicine Comprehensive Cancer Center, and a professor of surgery and oncology at that same university. Earlier in his career he chaired the Department of Surgery at Stanford University, and held professorships at the Johns Hopkins University School of Medicine and at the University of Michigan.

A native of Steubenville, Ohio, Dr. Niederhuber is a graduate of Bethany College in West Virginia and the Ohio State University School of Medicine.

As NCI supports the full continuum of cancer research, it is crucial that we observe, analyze, understand, and integrate the emerging trends that will determine how *Science Leads the NCI*. Tracking *Advances in 2006* is key to recognizing both the impact of research results and the emergence of new findings and opportunities. Our *Strategic Objectives* allow the Institute to chart a course focused on targeted, collaborative efforts to realize a future free of cancer.

An organization as multi-faceted as the National Cancer Institute requires effective management at a tactical and operational level to implement its research priorities. The following section, *How We Work*, describes NCI's key bioscience infrastructure that enables progress in the National Cancer Program.

NCI is organized into an Office of the Director, two intramural divisions (in-house research) and five extramural divisions (support for research throughout the United States and internationally). This structure serves as the foundation for furthering discovery, development, and delivery, through mechanisms for: investigator initiated research; clinical trials; centers, networks, and consortia; technology development; surveillance and outreach; and career training and development.

The following pages describe how NCI uses its bioscience infrastructure to coordinate and collaborate with the cancer research community, in order to expedite progress against cancer. The proposed NCI budget request reflects this vital, integrated approach.

How We Work

Intramural Research

A portion of NCI's research dollars supports the work of scientists in the two intramural divisions, the Center for Cancer Research (CCR) and the Division of Cancer Epidemiology and Genetics (DCEG), which together comprise the Intramural Research Program (IRP). The IRP is a recognized leader in identifying genetic and environmental determinants of cancer and AIDS. Improved understanding of virology, the study of viruses and the diseases caused by them, will help advance progress against cancer. IRP researchers are able to rapidly translate their discoveries into clinical applications by utilizing the infrastructure provided by the NIH Clinical Center, the largest clinical research hospital in the world. Over the years, NCI's intramural program has produced new drugs and technologies to treat patients with cancer and AIDS as well as improve their quality of life.

A Closer Look — *Collaborative Science at NCI*

Nearly two decades ago, researchers at NCI and other institutions began searching for the underlying causes of cervical cancer. That scientific quest led to Food and Drug Administration (FDA) approval of the vaccine Gardasil® this year. Gardasil® protects against infection from the two types of human papillomavirus (HPV) that cause the majority of cervical cancers worldwide.

Population studies conducted in part by NCI helped to establish the link between HPV infections and the disease. The research revealed that while most HPV infections clear on their own and do not lead to cancer, virtually all cases of cervical cancer are caused by HPV infection. NCI scientists then examined ways to boost the body's immune response to prevent the cancer-causing infection. This work led to development of the technology on which the HPV vaccine is based. The vaccine opens a new era in cancer prevention and has the potential to save women's lives, as well as to reduce health disparities in the United States and around the world.

"NCI's immunology and vaccine research regarding HPV infection is far from finished. We continue to work on improved vaccines and immunization technology, to make these prevention strategies even more effective and accessible to women worldwide." Dr. John Niederhuber, Director, National Cancer Institute

Extramural Research

Funding and conducting innovative research are the highest priorities at NCI. The largest allocation of NCI's budget is dedicated to building the capacity of the cancer research enterprise by providing infrastructure, resources, and other support. An essential component of this infrastructure is the NCI Extramural Research Program that supports basic and clinical cancer research in institutions outside of the NIH. The program reaches nearly 650 universities, hospitals, Cancer Centers, and other sites throughout the United States and in more than 20 other countries. Approximately 85 percent of NCI's budget funds extramural research activities.

A Closer Look—*Support for Extramural Research*

The majority of NCI's extramural funding supports investigator-initiated Research Project Grants (RPGs); in Fiscal Year (FY) 2007, NCI anticipates investing more than $2.1 billion in support of about 5,000 RPGs. NCI also invests in a significant portfolio of extramural projects solicited through various initiatives. For instance, in FY07 NCI expects to invest more than $440 million in Specialized Programs of Research Excellence (SPOREs), Cancer Centers, and specialized centers. NCI's extramural budget also supports cancer control, investigator training, health disparities, research collaborations with the private sector, and other types of research and development activities.

Program experts in NCI's Divisions of Extramural Activities (DEA), Cancer Biology (DCB), Cancer Treatment and Diagnosis (DCTD), Cancer Prevention (DCP), and Cancer Control and Population Sciences (DCCPS) guide and administer the NCI investment in extramural biomedical research. Central responsibilities of the DEA involve establishing and disseminating extramural policy, coordinating scientific and merit review, and all aspects of grant development and tracking. DCB and DCTD manage a portfolio of grants, cooperative agreements, and contracts in areas relevant to cancer biology (DCB) and diagnostic/therapeutic cancer interventions (DCTD). DCP supports extramural research focused on cancer prevention, early intervention, symptom management, and supportive care, while DCCPS conducts an integrated program of genetic, epidemiologic, behavioral, social, and surveillance cancer research.

Clinical Trials

NCI supports over 1,300 clinical trials a year, assisting more than 200,000 patients. NCI convened the Clinical Trials Working Group (CTWG) to identify ways that NCI's national clinical trial enterprise could be restructured in order to realize the promise of molecular medicine. The goal is to markedly advance clinical practice for cancer in the 21st century. Ultimately, the true value of the CTWG's restructuring plan will be demonstrated by measures of whether clinical trial initiatives better promote the development of new therapies, diagnostic procedures, and biomarkers that enhance the specificity with which cancer treatments are delivered.

A Closer Look — *Personalized Treatment Trial for Breast Cancer*

A new NCI clinical trial, the Trial Assigning IndividuaLized Options for Treatment (Rx), dubbed TAILORx, is being hailed by leading breast cancer researchers as an important step toward more individualized treatment of cancer based on factors such as the expression (activity) of specific genes within a patient's tumor cells. TAILORx is designed to determine whether adjuvant hormonal therapy alone is as effective as adjuvant hormonal therapy in combination with chemotherapy for certain women with early-stage breast cancer. Trial results will help individualize treatment for each breast cancer patient in order to achieve improved clinical outcomes.

The trial will use the results of a new test that measures the expression of 21 genes in tumor samples from women with early-stage invasive breast cancer to assign participants to their treatment regimen. The genomic test used in this trial can more precisely estimate a woman's risk of cancer recurrence than standard characteristics that doctors normally use to assess

recurrence risk (such as tumor size and grade). The test result is expressed as a "Recurrence Score." The higher the score, the greater the chance of breast cancer recurrence if a woman is treated with hormone therapy alone. The treatment that patients receive in this trial will depend upon the results of the Recurrence Score.

Although about 90 percent of women with early-stage breast cancer are advised to undergo adjuvant chemotherapy, studies have shown that it decreases recurrence risk in only a small percentage of them. TAILORx could change the way breast cancer is treated, helping to more accurately identify women who are likely to benefit from chemotherapy and those who are not.

Centers, Networks, and Consortia

The new research paradigm hinges on interdisciplinary science, strategic partnerships, immediate application of new technologies, optimal information sharing, and close links to health care delivery systems. The centers, networks, and consortia created and supported by NCI over the last 12 years

comprise a model framework to support team science. They also provide a means of fostering coalitions with other cancer research funding organizations, professional societies, business and industry, and local and state governments. Examples of NCI centers, networks, and consortia include:

- **NCI-designated Cancer Centers integrate multidisciplinary research across single or multiple institutions and reach out to the local community with education and other services.**
- **Specialized Programs of Research Excellence (SPOREs) focus entirely on discovery-to-delivery research dedicated to specific cancers.**
- **Clinical Trial Cooperative Groups and the Community Clinical Oncology Program extend the opportunity for participation in clinical trials to patients treated in the community rather than at Cancer Centers.**
- **The SEER (Surveillance, Epidemiology and End Results) network tracks incidence, mortality, and survival.**
- **The NCI Community Cancer Centers Program (NCCCP) is a concept designed to work through partnerships with NCI-designated Cancer Centers to improve quality of care.**
- **NCI Centers of Excellence connect specialized groups of scientists.**

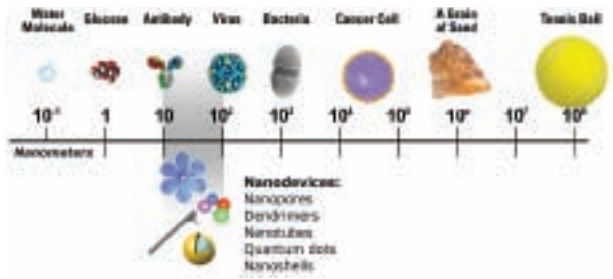
A Closer Look—*The Cohort Consortium*

Networks and consortia are geographically dispersed groups that focus on developing or validating new interventions or research in specialty areas. The NCI Cohort Consortium demonstrates the power of pooling biologic samples and resources in a collaborative effort to enhance our understanding of genetic susceptibility to cancer. The consortium combines the long-term investment in biobanks from large cohorts of individuals followed for many years. It applies the power of genome-wide scans on samples from roughly 800,000 individuals to assess 500,000 genetic markers in order to uncover those that determine cancer risk. Groups of toxicologists, developmental biologists, and epidemiologists studied the effects of specific environmental agents and the subsequent risk of hormone-related cancers. These and similar studies have begun to identify genes previously unrecognized as important to cancer susceptibility. Laboratory, clinical, and population researchers are rapidly following-up on these discoveries to elucidate the underlying responsible mechanisms.

Technology Development

Research over the past three decades has led to significant progress in our understanding of cancer at the genetic, molecular, and cellular levels. As we work to apply these discoveries to cancer prevention, early detection, and management, it is increasingly important to integrate research, science, and technology as effectively as possible. NCI supports a range of studies and projects to pursue the benefits of these combined approaches. Some of these activities are described below.

Bioinformatics: Using powerful information technology, NCI is leading the development of a bioinformatics platform that will enable researchers and clinicians to access and integrate cancer research results across scientific disciplines, populations, and geography. Under the cancer



As an additional example, the width of a human hair is approximately 80,000 nanometers.

Biomedical Informatics Grid™ (caBIG™) umbrella, NCI and a large group of private and public collaborators are building a voluntary network or grid, including common terminology and tools, to connect scientists and institutions into a virtual World Wide Web of cancer research. The overall goal is to speed the delivery of innovative approaches for preventing and treating cancer, including increased mutually beneficial flow of bench-to-bedside interactions.

Cancer Imaging: Imaging methods are being combined with emerging technologies such as nanotechnology, proteomics, and high throughput screening to identify cancers earlier and help assess the effectiveness of therapy. Imaging informatics brings cancer imaging data to research and clinical environments more efficiently and effectively. Image-guided cancer intervention is a rapidly evolving area that may be used to cure some cancers and precancerous lesions, and also to provide minimally invasive, well-tolerated palliative treatments. As our knowledge of the molecular basis of cancer increases, molecular imaging methods are providing researchers with powerful discovery tools and clinicians with telling biomarkers for cancer risk and treatment efficacy.

Proteomics: Evidence suggests that measurements of proteins and peptides circulating in the blood may represent reliable indicators of early-stage cancer. Proteins serve complex and diverse functions in the body, from giving structure to our cells to regulating processes such as digestion, breathing, and the growth rate of cells. When proteins fail to function properly, normal body processes can go awry. For example, errors in proteins that regulate when and how fast cells reproduce, as well as the timing of cell death, can result in cancer. One of the goals in cancer research is to develop technologies that measure and evaluate these abnormal proteins with enough accuracy to be used as cancer diagnostic blood tests.

Nanotechnology: Nanotechnology offers researchers a paradigm-changing opportunity to study and interact with both normal and cancer cells at molecular and cellular scales. For reference, 8 to 10 atoms span one nanometer; the human hair is approximately 70,000 to 80,000 nanometers thick. Increasing abilities to perform research at this nano level will enhance cancer diagnosis and treatment. For example, imaging agents and diagnostics designed with nanoscale precision will optimize their usefulness and function and allow clinicians to detect cancer in its earliest, most treatable stage. Multifunctional, targeted devices capable of bypassing biological barriers will

enhance our ability to effectively and efficiently treat cancer by delivering multiple therapeutic agents at high concentrations — and with physiologically appropriate timing — directly to cancer cells. In preclinical studies, nanotech-based cancer treatments are demonstrating increased efficacy and significant decreases in life-threatening side effects.

A Closer Look — *Nanotechnology Characterization Laboratory*

NCI is engaged in efforts to harness the power of nanotechnology to radically change the way we detect, diagnose, treat, and prevent cancer. NCI has established the Nanotechnology Characterization Laboratory (NCL) at its NCI-Frederick facility to provide critical infrastructure support to this rapidly developing field.

The NCL is an effective scientific collaboration between three Federal agencies: NCI, Food and Drug Administration (FDA), and the National Institute of Standards and Technology (NIST) of the U.S. Department of Commerce. Scientists from each agency bring critical knowledge, experience, and skills to the new laboratory setting. NCI brings expertise in the biomedical research arenas necessary for the biological and chemical characterization of the nanoparticles and devices. FDA brings a strong and standardized model for evaluating diagnostics, a new integrated program for regulating diagnostic devices, and initial exploratory methods for evaluating multiple complex technologies for their possible use in drug development. NIST provides expertise in determining the best measurement tools, protocols, and analysis algorithms for physically characterizing nanoparticles.

The NCL enables researchers to develop their nanotechnology concepts into clinical applications by characterizing the material's properties as they relate to biological systems. Tests developed by the NCL and its partners will be codified and then distributed as a "gold standard" for academic, industry, and government laboratories. The NCL will serve as a national resource and knowledge base for cancer researchers to aid the regulatory review of nanotechnologies intended for cancer therapies and diagnostics. By providing the critical infrastructure and characterization services to nanomaterial providers, the NCL can accelerate the translation of basic nanoscale particles and devices into clinical applications.

Surveillance and Outreach

Cancer surveillance provides quantitative measures of the burden of cancer and the impact of cancer control in the general population. Moreover, the national cancer registry system in the United States provides a powerful tool for cancer research. The system is comprised of interdependent Federal, state, and private sector programs and provides surveillance data on all cancers. NCI and other Federal agencies help support cancer registries in all 50 states, the District of Columbia, and several United States territories. NCI is working with multiple partners to better integrate surveillance data into cancer control planning. This use of cancer surveillance to help guide resource allocation is essential to reducing the cancer burden in all populations.

Outreach through cancer communication empowers people: it can raise their awareness of health problems and help them make informed cancer-related decisions. Effective cancer communications are targeted to users' needs across the cancer continuum — prevention, detection and diagnosis, treatment, survivorship, and end-of-life issues. Changes in the role and accessibility of this information are continually altering health care practices, patient-physician relationships, and the way patients acquire and use information. Besides consulting their physicians, many consumers now seek health information from Internet and other media sources, which can vary in quality and reliability. NCI is working to ensure that everyone has ready access to timely, reliable, understandable information that is also culturally appropriate.

A Closer Look — *NCI Outreach*

NCI launched the Centers of Excellence in Cancer Communications Research (CECCR) initiative in 2003. CECCR provides the infrastructure for interdisciplinary teams at four centers to promote advances in cancer communications, develop interventions, translate theory into practice, and train health communicators. Their recent work includes:

- The University of Michigan's "Guide to Decide" project is exploring ways of communicating risk about using tamoxifen for breast cancer prevention to women at high risk for the disease across all sociodemographic groups.
- The University of Pennsylvania is studying cancer-related information searching and scanning behavior in the general population, assessing associations with post-diagnosis treatment choices or cancer screening and prevention behavior.
- The Saint Louis University Ozioma News Service project is developing and testing a computer-based news service that will contribute community-specific stories and cancer data to local Black newspapers.
- The University of Wisconsin-Madison is examining whether Comprehensive Health Enhancement Support Systems that create "healing relationships" for patients over time improve cancer outcomes and survivorship experiences. This project supports the Institute of Medicine goal to improve health outcomes for patients with chronic conditions.

Training and Career Development

Rapid developments on the frontiers of science and technology, including molecular biology and translational medicine, have broadened the scope of cancer research and have presented new challenges for training future cancer researchers in diverse disciplines. NCI devotes approximately four percent of its annual budget and multiple strategies to preparing the next generation of cancer researchers for challenges that increasingly are multidisciplinary and span basic, clinical, behavioral, and applied research. Each year, we provide cancer research training and career development opportunities to more than 2,000 graduate students, postdoctoral fellows, and oncologists. Some of this training takes place on the NIH campus, but most occurs in universities and teaching hospitals across the United States.

All sponsored traineeships are intended to increase the number of scientists who specialize in the basic or clinical biomedical research fields. We invest in training to support the use of advanced technologies and provide career opportunities to equip scientists to address cancer in underserved populations. We foster development of interdisciplinary teams of scientists to carry out critical translational research. These investments will ensure a steady flow of well-trained investigators to focus on the challenges of fighting cancer.

A Closer Look — *A Researcher's Story*

NCI training and career development experiences provided a young investigator with the background and resources that facilitated a notable cancer scientific advance. The Principal Investigator and his team were able to generate mice that develop pancreatic cancer that mimics the human disease. They then isolated a molecular signature in the blood serum of these mice that reliably predicts the presence of early pancreatic cancer. This new mouse model has helped to advance the work of other researchers studying the development, detection, and treatment of pancreatic cancer.

NCI mechanisms of support for the investigator included funding through the Medical Scientist Training Program for his sub-specialization in medical oncology. He was able to advance his mouse model research through an NCI fellowship training grant, and as a result of his success he has received additional funding to continue his investigation in this promising area.

"I have always been attracted to illnesses that had few efficacious treatments, and pancreatic cancer is at the top of my short list. Finding the right environment to start your career is the most important thing. Sufficient funding is required from the beginning." NCI-funded investigator

Cancer in America — *What the Statistics Tell Us*

Although the nation's investment in cancer research is making a difference in the lives of Americans every day, cancer remains one of our most urgent health concerns and the disease many fear most. The lifetime risk for developing cancer is one in two for men, and one in three for women. Nearly 1.4 million new cancer cases will be diagnosed this year and more than a half million people will die of the disease. In 2005, the economic burden of cancer to the nation was estimated to be over $200 billion.

Progress has been made toward our goal of reducing the many types of cancer burden in the United States. Overall cancer mortality continues the gradual decline that began in the early 1990s. The number of deaths from some of the most common cancers — colorectal, breast, and prostate continues to decrease. These trends reflect effective prevention and risk reduction interventions, better screening and early detection methods, and improved treatment and medical management.

Today, approximately 10 million people are alive with a history of cancer, and with a better quality of life than was possible years ago. More than two-thirds of people diagnosed with cancer can expect to live for five years or longer. For children diagnosed with cancer, five-year overall survival exceeds 75 percent. Increasingly, with new imaging techniques and the identification of novel biomarkers, we are finding cancers at earlier, more curable stages, and are able to predict clinical outcomes. Improved diagnostic tools are advancing individualized, tailored therapy, while newly discovered molecular targets are transforming the way we develop interventions.

NCI Tracks Cancer Trends and Progress:

Annual Report to the Nation on the Status of Cancer
First issued in 1998, this publication is a collaborative effort of the American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), NCI, and the North American Association of Central Cancer Registries (NAACCR). The publication provides updated information on cancer rates and trends in the United States. NCI's SEER databases are a major source of information.

Cancer Trends Progress Report
This is a biannual NCI electronic publication about our nation's progress against cancer, including prevention, early detection, diagnosis, treatment, life after cancer, and end of life. The information is gathered through a collaborative effort with other key agencies and groups, such as CDC and the ACS. The report was first issued in 2001 and will be updated again in 2007.

Surveillance, Epidemiology, and End Results (SEER) Program
The NCI SEER program currently collects and publishes cancer incidence and survival data from 14 population-based cancer registries and three supplemental registries covering approximately 26 percent of the U.S. population.

NCI Cancer Bulletin
The NCI Cancer Bulletin is a weekly online publication that provides updates on NCI activities, the research and clinical trials funded by the Institute, and other activities of both the U.S. and international cancer communities.