

National Cancer Institute



The Nation's Investment in
cancer research

A Plan and
Budget Proposal
for Fiscal Year
2006

Prepared by
the Director
National Cancer
Institute

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

When we as a Nation reach our Challenge Goal to eliminate the suffering and death due to cancer, it will be because we have been able to:

- **Gain a more complete understanding of the causes of cancer and of the biological mechanisms of cancer initiation and progression.**

As we validate the multiple risk factors and improve our understanding of the full range of genetic and biological changes that lead to cancer, we will be able to use that information to develop more effective and tailored strategies for cancer prevention and control, early detection, diagnosis, treatment, and follow-up care across the spectrum of need.

- **Make prevention our first line of defense against cancer.**

Tobacco control programs will help us prevent the 30 percent of U.S. deaths from cancer that are related to smoking. Effective strategies for reducing the incidence of obesity in our Nation could lower cancer death rates by as much as 14 percent in men and 20 percent in women and reduce the risk for several common cancers by up to 30 percent. Cancer prevention medicines, dietary supplements, and vaccines, which have been proven in clinical trials, promise to eliminate or delay the development or progression of cancer.

- **Detect many cancers early enough to make successful treatment possible.**

Universal access to currently available interventions for screening and early detection of cervical, colorectal, and breast cancers will immediately improve patient outcomes. For example, the five-year survival rate for colorectal cancer is nearly 90 percent for early-stage local disease compared with 9 percent for later-stage disease that has spread to distant organs. Diagnostics based on validated biomarkers will someday be used for the early detection of other cancers based on analysis of the protein patterns in a single drop of blood.

- **Effectively eliminate many cancers.**

Improved care has already helped us cure some cancers. As we look to the future, molecularly targeted diagnosis and treatment will help us eliminate other cancers with minimal side effects. Innovative imaging technology will make diagnosis and treatment more accurate and less invasive. Nanotechnology promises to enable better diagnostic platforms and delivery systems for more precise therapies with far fewer adverse side effects.

- **Manage other cancers as chronic diseases.**

New paradigm molecular approaches will enable us to control other cancers so that people can live productive, healthy lives in spite of their cancer. Our ability to monitor and validate healthcare patterns, interventions, and outcomes will inform decision makers and caregivers to ensure quality cancer care for all, including a growing population of patients over 65.

- **Dramatically improve quality of life for cancer survivors.**

More and more people are benefiting from the medical advances that have improved both quality of life and length of survival for cancer patients. Evidence-based and culturally appropriate supportive care, symptom management, and rehabilitation will all help address the medical and psychosocial needs of survivors and their caregivers.

The strategic investments described in this document provide vision and direction for the nationwide community of researchers, public health workers, healthcare providers, patients, advocates, and policymakers working to defeat cancer. To learn more about recent progress in these and other areas of NCI investment, please refer to *The Nation's Progress in Cancer Research: An Annual Report for Year 2004* to be published in early 2005. Go to cancer.gov for regular updates on cancer research and other activities of the National Cancer Institute.

Director's Message

Early in 2003, as the Director of the National Cancer Institute, I announced our Challenge Goal to the Nation – to eliminate the suffering and death due to cancer by 2015. Since that time, we at NCI have worked internally and with the national scientific, medical, and lay community to identify the critical elements required to reach this goal. Our proposed strategic investments for Fiscal Year 2006 reflect our recognition that the only way we will achieve our Challenge Goal is to capitalize on the most promising opportunities, remove any barriers that might be impeding progress, and ensure that laboratory discoveries are validated in clinical trials and reach the patient or the person at risk for cancer.

Exponential advances in cancer research are defining, with ever increasing specificity, the many genetic, molecular, and cellular events that influence the cancer process. We now understand cancer as an ongoing process that can be interrupted at many stages – from susceptibility to initiation to disease progression. We are translating this new knowledge into innovative, evidence-based strategies to prevent cancer from developing, eliminate it early when it does occur, and modulate its devastating effects.

With the cancer Biomedical Informatics Grid (caBIG), we are using the power of information technology to connect all cancer researchers to data and analytical tools that will dramatically improve research efficiency. We are advancing imaging technologies to detect tumors early when they are easier to treat, to guide therapy or surgery, and to monitor in real time the molecular effects of therapeutic interventions. Image-guided interventions are used, not only to aid in the successful treatment of some cancers and precancerous lesions, but also to provide minimally invasive, well tolerated therapies that eliminate or transform cancers into well managed diseases.

Recent advances in proteomics and the technology of mass spectrometry allow for unprecedented analysis of the body's proteins to define the biomarkers of cancer. Identifying the proteins associated with cancers will allow us to employ recent advances in molecularly targeted imaging to locate very small tumors and interrogate their molecular features. Drugs attached to agents that seek out the proteins on cancer cells will direct therapy exactly where it is needed, without damage to surrounding healthy cells.

We are also developing prevention drugs and vaccines. More easily administered strategies like these hold promise for tremendous benefit to people at high risk for certain types of cancer. For example, the cervical cancer vaccines now under development may ultimately save hundreds of thousands of lives around the world every year.

Advances gained through cancer initiatives will translate into progress for other serious diseases as well. The new National Advanced Technologies Initiative for Cancer, for example, will build national scale public-private coordination that will have far reaching benefits for cancer as well as many other diseases.

Our 2015 Challenge Goal is an urgent call to action that will require a concerted, collaborative effort by the entire community. At NCI, we believe that the Goal is within our grasp, and we are prepared to stretch the boundaries of science, imagination, and human will to achieve success.



Andrew C. von Eschenbach
October 2004

Eliminating the Suffering and Death Due to Cancer

The National Cancer Institute, as leader of the National Cancer Program, provides vision and direction to the national community of researchers, public health workers, healthcare providers, patients, advocates, and policymakers working to defeat cancer. Our success will be measured by our ability to leverage resources, remove the major barriers that impede progress, and ensure that all new activities reflect past lessons learned. We must maintain our momentum so that the progress we have made leads us into a better future for those with, or at risk for, cancer. **We will reach our Challenge Goal through investments in scientific research, technology leadership and capacity building, application in public health and patient care, and communication and transfer of results.**

Scientific Research



NCI supports a broad range of scientific research to expand our understanding of cancer at the molecular level and to learn how its development and progression are affected by behavioral and environmental factors. These insights provide the foundation for new interventions and strategies in prevention, control, early detection and diagnosis, treatment, and follow-up care.

Each year, NCI supports nearly 5,000 principal investigators to perform research projects that result in better ways to combat cancer. These dedicated scientists conduct studies at NCI (intramural) and at nearly 650 universities, hospitals, and other sites in almost every State in the Nation and in more than 20 foreign countries. Intramural research activities serve as hubs for new development through cutting edge basic, clinical, and epidemiological research. Extramural program experts provide guidance and oversight for research conducted at universities, teaching hospitals, and other organizations.

Technology Leadership and Capacity Building



NCI leads the Nation in using innovative approaches for harnessing the full potential of advanced technologies for cancer. Recent advances in bioinformatics are dramatically accelerating the rate with which we can process large amounts of information. New molecular imaging and biosensing technologies are opening doors to faster, more accurate detection and diagnosis, facilitating more precise image-guided therapies, and making it easier to monitor treatment outcomes. Nanomedicine offers hope for streamlining cancer care through revolutionary preventive, diagnostic, and therapeutic applications.

We help to build the capacity of the cancer research enterprise through NCI-supported centers, networks, and consortia that allow scientists from around the world to share their expertise and resources. NCI provides incentives for research in special areas of need and for collaborative efforts that promote interdisciplinary team science. Tissue samples, statistics on cancer incidence and mortality, databases of genetic information, imaging databases, mouse models of cancer, full length gene clones, and software for analyzing statistical and genetic data are provided to investigators in all research settings at little or no cost.

Our new paradigm for eliminating the suffering and death due to cancer is to preempt its initiation and progression at every possible point. We must prevent cancer initiation whenever possible, eliminate it in its early stages when it does occur, and help cancer patients live with, rather than die from, the disease. NCI supports basic research and intervention development and works with others to incorporate **evidence-based prevention strategies** into public health programs and medical practice. New molecular diagnostics are on the horizon that will help us make earlier and more individualized assessments and improve the potential for the **successful elimination of some cancers**. And more targeted therapies and new delivery technologies promise to dramatically improve our ability to **control or modulate the effects of other cancers**.

● Application in Public Health and Patient Care



NCI is working with other agencies and organizations to bridge the gap between the promise of research and its application for people. We work to ensure that newly developed interventions move through well designed, well run clinical trials and that those found effective and safe are made available to cancer patients everywhere. Institute leaders have established partnerships with the Food and Drug Administration and the Centers for Medicare and Medicaid Services to speed the development of and improve access to safe and affordable cancer prevention, early detection, and treatment options. Others work with Federal, State, and local agencies and other organizations to develop and support the use of evidence-based tobacco control strategies and promote healthier diets and exercise programs known to be preventive against a number of cancers. In addition, several Patient Navigator Programs are being piloted around the country and will be evaluated for their efficacy and cost effectiveness in helping cancer patients gain access to cancer prevention information, screening, diagnosis, treatment, and follow-up care. NCI is also playing a leadership role in Health and Human Services Department-wide efforts to eliminate health disparities in our country.

● Communication and Transfer of Results



NCI provides Web-based information on cancer and clinical trials, toll-free telephone service in all regions of the country, and printed brochures and educational packages distributed directly to cancer patients and their families as well as to oncology practices and patient advocacy organizations. The NCI Cancer Research Portfolio and the International Cancer Research Portfolio Web sites provide invaluable resources to investigators desiring to locate research information or find collaborators in areas of interest. We foster collaborations for the transfer of research results through liaisons with other organizations. For example, NCI's Cancer Information Service Partnership Program focuses on reaching minority and other medically underserved populations. Partnering with over 450 public and private organizations nationwide, we collaborate on data driven, outcome oriented education and public health projects and provide technical assistance to build capacity in clinical trials, breast and cervical cancer screening, general cancer awareness, and tobacco education.



Our Strategic Investments for Fiscal Year 2006

Integrative Cancer Biology

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Understand the complex networks within cancer cells and between cancer cells and their environment to discover new leads for cancer prevention, detection, diagnosis, and treatment.

- Develop computational models of biological systems.
- Support studies of the tumor microenvironment.
- Conduct tumor macroenvironment research.

Molecular Epidemiology

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Understand the behavioral, genetic, and epigenetic causes of cancer and use this knowledge to generate new means of preventing, detecting, and treating cancers.

- Investigate specific types of cancer through cohort, case-control, and family-based consortial studies.
- Research behavioral and environmental risk factors.
- Integrate population science with genomics and other technologies.
- Build partnerships and interdisciplinary research.

Advanced Technologies

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Accelerate the development and use of advanced technologies to enhance patient care and connect investigators with one another and with healthcare providers and patients.

- Build bioinformatics infrastructure and tools.
- Develop and apply advanced imaging technologies to cancer research and care.
- Support proteomic technology development for overcoming barriers to early detection.
- Continue to foster the use of nanotechnology for cancer research and care.

See also:

When We Reach Our Challenge Goal
INSIDE FRONT COVER

Building Research Teams of the Future
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National Advanced Technologies Initiative
for Cancer

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Cancer Prevention, Early Detection, and Prediction

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Develop new medical approaches and evidence-based public health interventions and policies to substantially reduce the incidence of and improve prognosis for cancer.

- Support development of new technologies and approaches to prevention, through tobacco control, energy balance, vaccines, and new drugs.
- Develop biomarkers and imaging techniques for early detection.
- Develop predictors of cancer risk and treatment success.

An Integrated Clinical Trials System

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Build a highly interactive and optimally coordinated cancer clinical trials system that will prioritize and accelerate the development of new, effective interventions and ensure that they are incorporated into medical practice.

- Strengthen scientific prioritization and coordination.
- Speed novel agent development and marker validation.
- Expand the goals of clinical trials to include health disparities research, symptom management, quality of life, and other areas of focus.

Overcoming Cancer Health Disparities

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Discover the causes of health disparities, develop interventions to reduce them, and facilitate intervention delivery.

- Conduct community-based, multidisciplinary, collaborative studies to understand the causes of health disparities.
- Develop culturally appropriate interventions and assess their efficacy.
- Establish collaborations for research, translation, and application.
- Train minorities in health care and research.

Strategic Development of Cancer Interventions

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Optimize the transfer, development, and delivery of highly effective molecularly targeted drugs and technologies to specifically prevent, detect, diagnose, and treat cancer.

- Expand existing programs to increase the number of new drug candidates and new interventions for understudied malignancies.
- Invest in enterprise initiatives for biospecimen resources and large-scale genome analysis.
- Build capacity for biomarker discovery and development and target validation.
- Support program integration and new technologies for preclinical development.

Delivering the Promise
NCI's Budget Increase Request Emphasizes
Patient Care and Public Health

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Fiscal Year 2006 Budget Request

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Strategic Investments in **Cancer Prevention, Early Detection, and Prediction**

Our Goal Substantially reduce the incidence of cancer and integrate early detection with markers of prognosis, through the development and effective delivery of medical approaches to prevention and early detection and the promotion of effective, evidence-based public health interventions and policies.

Newly aligned goals focused on preventing cancer from occurring and detecting it early when it is most curable are at the heart of our Nation's research and public health agendas. Dramatic developments in technology and a more complete understanding of the causes and mechanisms of cancer will enable us to provide more effective ways to prevent the disease. New evidence-based interventions encourage lifestyle improvements in diet and physical activity, discourage smoking, and promote the use of safe and fully tested chemoprevention approaches for people at risk. Pioneering proteomic and biomarker advances and the promise of nanotechnology give us new hope for the early detection and diagnosis of cancer and prediction of patient response to treatment. Advanced information systems and methods of evaluation will maximize the impact of existing technologies. We are ramping up specimen repositories and widely accessible bioinformatics resources to support the development of these breakthroughs.

Prevention is our first line of defense against cancer.

The prevention of cancer focuses on studying and modifying behaviors that increase risk, mitigating the influence of genetic and environmental risk factors, and interrupting the carcinogenesis process through early medical intervention. We can save many lives, for example, by continuing to advance understanding of the biological and behavioral basis of nicotine addiction and energy balance. The 2004 Surgeon General's Report, *The Health Consequences of Smoking*,¹ estimates that smoking causes 159,600 cancer deaths each year including cancers of the lung, mouth, stomach, bladder, pancreas, esophagus, and larynx. New medications to help smokers quit are under development and current evidence suggests that information and referrals from quit lines, as well as behavioral counseling from healthcare providers, significantly increase abstinence rates. Current evidence also suggests that increasing the price of cigarettes and establishing tobacco-free work places and public areas significantly decrease smoking prevalence.

State and community programs and policies play a critical role in the prevention and control of tobacco use. Because State and local funds have been severely limited in recent years, it is especially important to understand the differential impact of various activities. For example, better insights are needed on how best to implement evidence-based interventions, how to effectively combine clinical- and population-based smoking cessation efforts, and the impact of more widespread clean indoor air laws on smoking prevention and cessation.

Tobacco use and tobacco-related cancers are also a large and increasing threat to health in the developing world. The International Agency for Research on Cancer (IARC), part of the World Health Organization,² coordinates and conducts both epidemiological and laboratory research into the causes of cancer, including tobacco use. As resources permit, NCI will provide funds for IARC research and dissemination efforts. With additional resources for **tobacco control** in Fiscal Year 2006, we will:

- Fund research to increase our knowledge of effective State and community program and policy interventions for tobacco control and prevention.
- Support IARC tobacco control and prevention research and dissemination activities to benefit low- and middle-income nations.
- Fund multidisciplinary research on the interplay of behavior, chemistry, toxicology, and biology to determine the cancer risk potential of reduced-exposure tobacco products.

Stop Smoking Programs Are Pivotal for Preventing Several Types of Cancer

Tobacco use remains the single most preventable cause of death in the United States, accounting for approximately 440,000 deaths in the United States each year. About 46 million people in our country, or 23 percent of the population, currently smoke. Cigarette smoking contributes to nearly one-third of all cancer deaths. Tobacco use is a major risk factor for lung cancer as well as cancers of the esophagus, larynx, kidney, and pancreas.

The health benefits of smoking cessation are immediate and substantial. Within just a few days of quitting, a person's sense of taste and smell return, breathing becomes easier, and blood pressure returns to normal. After 15 to 20 years, a previous tobacco user's risk of premature death approaches that of a person who has never smoked. About 10 years after quitting, an ex-smoker's risk of dying from lung cancer is 30 to 50 percent less than the risk for those who continue to smoke. Research suggests that people who stop smoking before the age of 35 reduce their risk of developing a tobacco-related disease by 90 percent.

The American Stop Smoking Intervention Study (ASSIST),¹ funded by NCI, provides the latest evidence that investing in State tobacco control programs can reduce smoking rates. The goal of ASSIST is to change the social, cultural, economic, and environmental factors that promote smoking by utilizing four policy strategies: promoting smoke-free environments; countering tobacco advertising and promotion; limiting youth access to tobacco products; and raising excise taxes to increase the price of tobacco products. The interventions have been developed and implemented by networks of state and local tobacco control coalitions. ASSIST was evaluated by comparing data regarding changes in adult smoking prevalence, per capita cigarette consumption, and tobacco control policies between the 17 ASSIST states and the 33 non-ASSIST states and the District of Columbia. NCI estimates that if all 50 states and the District of Columbia had implemented ASSIST, approximately 1,213,000 fewer people would smoke.

¹ cancer.gov/newscenter/pressreleases/ASSISTQandA



Inadequate nutrition and physical activity appear to contribute to a sizable proportion of cancers. A comprehensive review by IARC, conducted in 2002, summarized compelling evidence that prevention of obesity reduces risk for a number of common cancers and that physical activity reduces risk for colon and breast cancers. There are still questions, however, about the specific causative and protective components in a person's diet as well as the carcinogenic mechanisms associated with an overweight and sedentary lifestyle. With additional resources for **energy balance research** in Fiscal Year 2006, we will:

- Expand research at centers for Transdisciplinary Research on Energetics and Cancer (TREC) to enhance our understanding of the mechanisms underlying the association among energetics, energy balance, and cancer and to develop effective innovative approaches for prevention of obesity.
- Conduct studies to identify the molecular mechanisms of bioactive food components as modifiers of cancer risk and tumor behavior.
- Explore the utility of nanotechnologies related to proteomics and metabolomics to evaluate physiological changes influenced by dietary components in normal and cancerous processes.
- Work with bioengineers to develop new technologies for assessing energy intake and balance.

NCI is supporting the development of **prevention vaccines and drugs** for suppressing the carcinogenic process either at its inception or in pre-invasive stages. A new vaccine that targets the infectious agent human papilloma virus (HPV), implicated in cervical cancer, is being tested in clinical trials and is anticipated to be available to women at risk in the near term. Through the use of medicines, vitamins, food compounds, and other substances, we can halt or reverse the progression of disease in people with precancerous conditions and in people at risk for cancer. Preclinical studies will identify prevention agents that impact cellular level targets to intervene in the cancer process, and clinical trials will test the value of these agents in preventing disease. With increased resources in Fiscal Year 2006, we will:

- Promote studies that evaluate second generation HPV vaccines that could most easily be adopted in public health strategies in the United States and elsewhere and that could both protect against initial infection and promote its eradication among those already infected with the family of viruses that causes cervical cancer.
- Conduct preclinical and Phase I and II clinical studies to identify cellular targets and screen potential agents for the prevention of hormonally non-responsive breast cancer and cancers in former smokers.
- Accelerate the discovery and development of agents to help smokers quit and prevent cancers in former smokers.
- Complete Phase II trials for three chemopreventive agents and begin Phase II trials for another three agents each for breast, prostate, colorectal, and lung cancers.

As we make such breakthroughs, we must actively **translate prevention research into improved outcomes and facilitate the role of public policy** to see that all people have knowledge of and access to preventive medicine and approaches. We will use additional resources in Fiscal Year 2006 to:

- Increase adoption of evidence-based prevention approaches in primary care and public health service sectors through existing partnerships with the Centers for Disease Control and Prevention (CDC) and national advocacy organizations.
- Monitor the incorporation of evidence-based preventive interventions into the delivery of clinical care, through provider surveys and partnerships with HMO networks.
- Develop effective strategies for communicating risk prediction and perception to health professionals and patients. Inform these strategies by evaluating public comprehension of health recommendations through the NCI Health Information National Trends Survey³ and by collaborating with other HHS agencies to conduct periodic surveys of healthcare providers to evaluate cancer-related knowledge, attitudes, and practices.

Energy Balance Plays a Major Role in Cancer Prevention and Control

Energy balance is a term used to describe the complex interplay of physical activity, diet, genetics, and body size and its impact on health. Physical inactivity, overweight and obesity increase the risk of numerous cancers including cancers of the breast, colon, endometrium, and kidney. However, the precise mechanisms by which energy balance influences cancer risk are not yet fully understood. NCI, in collaboration with partners throughout NIH, is conducting and funding cutting-edge research to elucidate these mechanisms and better understand how people can modify the risk factors that lead to overweight and obesity.

NCI's investigation of the relationship between energy balance and cancer includes active participation in the NIH Obesity Research Task Force,¹ which recently issued recommendations and goals for research on obesity and how it impacts health outcomes. In line with the task force's goals, we have embarked on several collaborations. One is with the National Institute of Environmental Health Sciences to fund research on how the "built environment" – i.e., how buildings are structured, open spaces are utilized, and people view and use their surroundings – affects diet, physical activity, and weight control practices. A collaboration with the National Heart, Lung, and Blood Institute focuses on a bioengineering initiative to develop objective measures relevant to energy balance. We have also launched a new cutting-edge initiative to establish centers for Transdisciplinary Research on Energetics and Cancer to form transdisciplinary teams of scientists to accelerate progress in reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet. NCI supports innovative research on economic factors impacting energy balance, and the relationship between energy balance and cancer using pre-existing biological specimens from ongoing case control or cohort studies. Finally, we continue to support research on improving the assessment of diet and physical activity, ranging from studies of biological measures of energy intake and expenditure to a conference on the use of e-technologies to assess and modify physical activity, diet, and energy balance in real time.



¹ obesityresearch.nih.gov/about/about.htm#taskforce

Early detection can eliminate a large proportion of deaths due to cancer.

Detecting cancer before metastasis begins can dramatically improve the odds of survival. For example, evidence suggests that 90 percent or more of colorectal cancer deaths could be prevented if precancerous polyps were detected with routine screening and removed at an early stage. Yet, the screening rate for colorectal cancer lags far behind that of other cancers, and the disease remains the second leading cause of cancer death in our Nation. This situation will be reversed only when we develop less invasive screening techniques and overcome psychosocial barriers to screening and follow-up therapy. For still other cancers – e.g., ovarian and pancreatic – there are no reliable early-stage screening tests to offer patients. For others, such as prostate cancer, screening tests are available but have not been proven to reduce mortality. NCI's Early Detection Research Network (EDRN)⁴ and the NCI/FDA Clinical Proteomics Program⁵ are developing non-invasive screening and early detection tests for early stage ovarian, prostate, and other cancers. We will use increased resources for early detection in Fiscal Year 2006 to:

- Expand the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial⁶ biorepository to include collection of tissues from diagnosed cancer patients.
- Build a National Lung Screening Trial Image Library to develop and optimize the use of computer-aided diagnostic programs for early detection of lung cancer and use images to develop a risk stratification algorithm.
- Develop screening approaches that use a combination of body fluid biomarkers and imaging technologies for detection of breast, lung, colorectal, cervical, oral, gastrointestinal, genitourinary, and reproductive cancers.
- Support molecular imaging approaches for the early detection of precancerous lesions.
- Develop minimally invasive treatments for screen-detected tumors.

Research Network Advances Prevention and Early Detection

The Early Detection Research Network (EDRN) promotes collaboration among researchers by creating an environment of cross-fertilization and teamwork among different disciplines and laboratories to achieve common goals. It is comprised of a group of 28 NCI grantees focused on creating validated biomarkers, including those with the potential to be surrogate endpoints for clinical trials, ready for large-scale clinical testing. EDRN is at the forefront of technology-driven research on the early detection of cancer and carcinogenesis and a leader in the disciplined establishment and use of criteria for the validation of markers of risk and precancerous changes. Current validation studies include microsatellite analysis, a promising molecular diagnostic technology for diagnosis of kidney cancer and protein expression profiling of body fluids, a novel approach for the early detection of prostate cancer. The Network is also a leader in the creative use of information technology and the sharing of data. EDRN has pioneered the development of common data elements to speed consistency in data description across institutions and has implemented informatics solutions to enable data sharing among laboratories.

- Evaluate the quality-of-life benefits of prevention and screening.
- Create national standards for performance measures and work with public and private organizations to collect and analyze data for monitoring the success of screening and early detection programs.

Prediction of risk and outcomes optimizes individualized cancer interventions.

More accurate methods for predicting who is at high risk for developing cancer and which treatment option(s) would be most effective on a patient-by-patient basis will contribute significantly to reducing the cancer burden. We know that individual susceptibility based on clinical, epidemiologic, genetic, and biological factors can influence the outcome of a given prevention or treatment strategy. NCI's EDRN develops, evaluates, and validates biomarkers that will be used for prediction of individualized cancer risk and treatment success. High throughput genomic and proteomic prediction techniques are being developed to help guide treatment choice for individual patients with leukemia, lymphoma, and other cancers. With additional support for prediction studies in Fiscal Year 2006, we will:

- Develop risk prediction models for individual cancer risk and success of treatment, incorporating clinical, epidemiologic, genetic, and biologic factors. Develop assays to discover and validate risk and treatment markers for precancers and cancers to inform these risk models. Create annotated specimen repositories to test and compare markers. Develop strategies to swiftly move markers and risk prediction models from discovery through development and into delivery.
- Use NCI's Cancer Intervention and Surveillance Modeling Network (CISNET)⁷ to synthesize knowledge about existing and emerging cancer risk factors, prevention and early detection strategies, current levels of usage, and anticipated future dissemination to project their impact on population trends in cancer incidence and mortality.
- Accelerate the identification of markers of cancer risk and cancer progression in high risk populations.
- Evaluate new and emerging endoscopic imaging technologies for risk and chemopreventive response in Phase I and II intervention trials.

Cancer Prevention, Early Detection, and Prediction Budget Increase Request for Fiscal Year 2006

Strengthening cancer prevention	\$75.00 M
Tobacco control	
Energy balance research	
Prevention vaccines & drugs	
Translation of research into improved outcomes & public policy	
Developing & improving early detection options	16.50 M
Biospecimen repositories	
Lung screening image library	
Biomarkers & molecular imaging for pre-cancerous lesions	
Evaluation and monitoring	
Predicting cancer risk & treatment success	18.75 M
Risk prediction markers & models	
Intervention & surveillance modeling	
Markers of risk in high risk populations	
Endoscopic imaging	
Management & Support	1.87 M
Total	\$112.12 M

¹ surgeongeneral.gov/library/smokingconsequences

² www.iarc.fr

³ cancercontrol.cancer.gov/hints

⁴ cancer.gov/prevention/cbrg/edrn

⁵ cancer.gov/newscenter/proteomicsFDA

⁶ cancer.gov/prevention/plco/index.html

⁷ cisnet.cancer.gov/index.html

New Prevention Strategies Hold Promise for Halting Cancer Before It Develops

The most efficient way to prevent death from cancer is to focus on stopping people from getting it in the first place. NCI is researching promising prevention strategies that use prevention agents and vaccines both separately and in combination. Three examples follow.

Preventing Prostate Cancer with Prevention Agents

Improvements in early detection and treatment have contributed to more than a decade-long decline in prostate cancer mortality. Still, about one-fourth of treated patients ultimately die of their disease – and even at the earliest stages of prostate cancer, treatment can cause significant side effects. Investigators are searching on several fronts for effective chemoprevention agents for prostate cancer.

The Prostate Cancer Prevention Trial (PCPT)¹ was designed to test the drug finasteride (PROSCAR™), which is used to treat benign enlargement of the prostate, as a possible preventive for cancer in men aged 55 and older. In July 2003, PCPT researchers presented findings demonstrating that prostate cancer can be prevented, at least in part, by this intervention. Men in the study who took finasteride for seven years were 25 percent less likely to develop prostate cancer than men taking a placebo. However, those trial participants who did develop prostate cancer while taking finasteride experienced a slightly higher incidence of potentially aggressive tumors. The investigators have developed an ambitious program of laboratory studies to look at the molecular biology of prostate cancer using blood and tissue samples collected during this landmark clinical trial. These studies will help clarify who is at greater risk for developing this disease and who might benefit most from finasteride therapy.



Other agents under study include anti-androgens and anti-estrogen drugs, micronutrients, and anti-inflammatories. The Selenium and Vitamin E Cancer Prevention Trial (SELECT),² which will test the impact of these supplements on prostate cancer risk, has completed recruitment of more than 35,000 men and includes a biorepository to address molecular level research questions.

Preventing Cervical Cancer through Vaccination

Successful interventions in early detection have helped to reduce deaths due to cervical cancer, especially in developed countries such as the United States. However, not all women have ready access to screening tests, and cervical cancer remains the most common cause of cancer death among women worldwide. Estimates suggest that 3,900 women in the United States will die from cervical cancer this year. If healthcare communities around the world had a simple means of preventing cervical cancer, hundreds of thousands of lives could be saved every year. NCI and partners are pursuing a vaccination strategy to do just that. Scientists are designing vaccines to prevent cervical cancer by protecting women against persistent infection with the human papilloma virus (HPV), the cause of virtually all cases of cervical cancer.

Through years of preclinical development and early clinical testing, researchers have designed a vaccine composed of virus-like particles that are produced through recombinant DNA technology. Vaccination causes the immune system to recognize and attack not just the virus-like particles, but also the true HPV virus, which the particles resemble. Two large pharmaceutical companies, Merck and GlaxoSmithKline (GSK), have licensed the vaccine technology from NIH and are developing versions that target the most common cancer-causing strains of HPV. In early clinical trials, these vaccines have conferred 100 percent protection, in fully vaccinated women, against persistent infection by the HPV type(s) targeted. Both companies have begun large, international Phase III clinical trials, a landmark step in development. NCI, together with public health researchers, are conducting a parallel efficacy trial of the GSK vaccine in Costa Rica, where cervical cancer is the most common female tumor.

Combining Prevention Drugs and Vaccine Strategies to Prevent Colorectal Cancer

Researchers are exploring strategies that combine the use of chemoprevention agents with vaccines. One team of NCI researchers recently used a mouse model to study human familial adenomatous polyposis (FAP). This disease genetically predisposes affected individuals to develop numerous colon polyps, followed by early onset colorectal cancer. The mice in this study were designed to develop tumors that mirror the pathology of FAP. There were three treated groups of mice. One was fed a diet containing the drug celecoxib (Celebrex[®]), which is used to reduce FAP polyp formation in people. A second group was given the experimental CEA³ vaccine, designed to prevent colorectal tumors. The third group was given both celecoxib and the vaccine. Although mice in all three groups developed fewer tumors than untreated mice, the group that was both fed celecoxib and vaccinated did the best, with 95 percent less tumor development and significantly improved overall long-term survival compared to the untreated group.

This groundbreaking research removed considerable doubt about the feasibility of effectively combining a potent anti-inflammatory agent like celecoxib with vaccination. Because tissue inflammation is an immune response, usually to injury or infection, it seemed clear that celecoxib must act by at least partially suppressing the immune system. On the other hand, vaccines work by stimulating the immune system to attack tumor cells. Because of the opposing nature of their activity, many suspected that celecoxib and vaccination would need to be used separately. The present study has shown that, despite having some effect on the immune system, celecoxib indeed could work synergistically with vaccination. Clinical trials have shown the safety of the CEA vaccine in colorectal cancer patients. The next step will be to establish the long-term safety of the CEA vaccine in people.

¹ cancer.gov/pcpt

² cancer.gov/clinicaltrials/digestpage/SELECT

³ carcinoembryonic antigen

Strategic Investments for **Overcoming Cancer Health Disparities**

Our Goal Overcome the unequal burden of cancer experienced by various population groups by discovering the fundamental causes of cancer health disparities, developing effective interventions to reduce those disparities, and facilitating intervention delivery.

Some of our greatest opportunities for reducing the burden of cancer reside with our efforts to overcome cancer health disparities. Research studies have provided definitive evidence that equal treatment at the same stage of disease yields equal outcomes across all populations. By providing universal access to the currently tested and available interventions for the prevention, early detection, and treatment with follow-up for breast, cervical, and colorectal cancers, we could see a dramatic reduction in cancer mortality. Similar improvements would occur for other types of cancer within minority and medically underserved populations with consistently applied interventions for tobacco control and energy balance and equal access to clinical trials and state-of-the-art cancer care.

As emphasized by the Trans-HHS Cancer Health Disparities Progress Review Group¹ in their March 2004 report, collaborations among Federal, State, and local decision makers are needed to facilitate the development and adoption of policies to eliminate health care access barriers and to promote quality health education and prevention strategies that lower the risk of cancer. We know that disparities occur at the local level and that the reduction of these disparities depends on community participation. NCI has established the Community Networks Program² to focus on developing strategies to help communities achieve these objectives. Communities, caregivers, and researchers must form strong alliances and explore creative solutions for developing culturally competent venues for service delivery. Community-based participation must be an integral part of the planning, development, and implementation of solutions to bring research advances to all populations. This cross fertilization will build synergism and ensure stronger, more dynamic alliances for overcoming cancer health disparities.

Determining the Underlying Causes and Extent of Cancer Health Disparities

One of our objectives at NCI is to support research to better understand and address the causes of cancer health disparities. Studies in epidemiology and the biology of aging aid in the identification and characterization of the causes of cancer among various population groups. (See pages 44 and 48-49.) Linking this knowledge to the effects of poverty, culture, and social injustice is a critical next step to gain a full understanding of and be able to adequately address cancer health disparities. While health disparities have historically been framed in terms of racial and ethnic categories, recent research has dispelled the biological basis of racial categories. Scientists have provided strong evidence that racial classification is a social and political rather than a biological construct. However, these classifications may act as indicators or surrogates for social injustice, particularly as they relate to factors such as low economic status, cultural generalizations, and perceived genetic similarities. With sufficient resources for these studies in Fiscal Year 2006, we will:

- Continue to examine relationships between genetics and race or ethnicity in order to inform the proper use of these variables in research, through a partnership with the National Human Genome Research Institute.

- Conduct think tanks to synthesize the anthropological, historical, social, biological, and medical literature regarding race, ethnicity, and genetics and expand our understanding of how health disparities develop. These think tanks will be conducted collaboratively with experts from the extramural community and the National Human Genome Research Institute.
- Conduct multidisciplinary intervention studies on disparities and the economics of cancer, access to cancer treatment and prevention trials, and other cancer control issues such as diet and physical activity, in collaboration with the NIH Office of Behavioral and Social Sciences Research and the Agency for Healthcare Research and Quality.
- Expand epidemiologic studies exploring racial and ethnic cancer disparities and establish new approaches for data collection and sharing to ensure cross-cultural equivalence and the use of variables such as race, ethnicity, and socioeconomic status in the study of cancer.

Charting the Course for Overcoming Cancer Health Disparities

Cancer health disparities occur within the broad context of human circumstances, including substandard housing, poor educational opportunities, adverse environmental exposures, and limited access to quality health care. Viewing health disparities through the historic and present-day lens of inequity and social injustice reveals a complex problem.

MAKING CANCER HEALTH DISPARITIES History

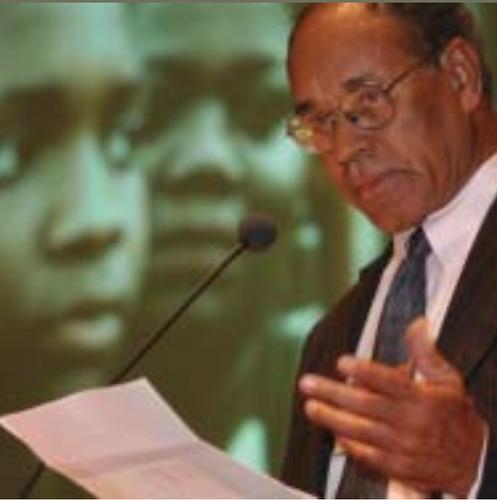
Overcoming cancer health disparities is more than a priority goal of the NCI. It is the will of the Nation. In 2002, the President of the United States and the Department of Health and Human Services charged a group of experts with reviewing the status of health disparities and charting a course toward closing the gap using cancer as the model. In its landmark report, *Making Cancer Health Disparities History*,¹ the Trans-HHS Cancer Health Disparities Progress Review Group (CHD PRG) enthusiastically endorsed a "Call to Action" consisting of an integrated set of forward thinking recommendations to be implemented by the Department and its agencies.

Several of the CHD PRG recommendations are addressed in NCI's planned investments for Fiscal Year 2006. "New approaches for data collection and sharing," as recommended by the PRG, will be developed via NCI-supported epidemiologic studies to ensure cross-cultural equivalence and the appropriate use of variables such as race, ethnicity, and socioeconomic status in the study of cancer. Community Networks to Reduce Cancer Health Disparities will "support the development of sustainable community-based networks for participatory research." The Tobacco and Health Disparities Research Network will research, develop, and "implement evidence-based tobacco control strategies" on a large scale. Training programs co-sponsored by minority institutions and the Community Networks to Reduce Cancer Health Disparities will support the creation of a "diverse and culturally competent cancer care workforce."

The Progress Review Group has charted a course for overcoming cancer health disparities throughout our Nation. With sustained resources and careful planning, NCI will continue to lead the way toward achieving this goal to make cancer health disparities history.

¹ www.hhs.gov/chdprg

Preventable Cancer Incidence and Mortality Plague Specific Population Groups



Dr. Harold P. Freeman, Director of the NCI Center to Reduce Cancer Health Disparities, is leading an effort to publicize "A Lion in the House," a documentary to be aired on PBS in 2006. The series will follow five families whose experiences across six years of fighting cancer reveal issues related to health disparities and the unequal burden of disease in American society.

Distinguished by race/ethnicity, gender, age, socioeconomic status, geographic location, occupation, and education, underserved population groups across the United States suffer disproportionately high cancer incidence and mortality rates for a variety of reasons. These individuals are significantly more likely than the overall U. S. population to:

- Be diagnosed with and die from preventable cancers.
- Be diagnosed with late stage disease for cancers detectable at an early stage through screening.
- Receive either no treatment or treatment that does not meet currently accepted standards of care.
- Die of cancers that are generally curable.
- Suffer from terminal cancers in the absence of adequate pain control and other palliative care.

Across all racial and ethnic groups, the five-year survival rate is more than 10 percent higher for affluent populations than for persons who live in poorer areas. Screening for colorectal, female breast, cervical, and prostate cancers is widely recommended and practiced. Yet, in high poverty areas, the proportion of cancers diagnosed in early, more treatable stages versus those at more advanced, less treatable stages is lower than in low poverty areas. For example, white men in Kentucky, a largely rural state with high poverty levels, are more likely to die from cancer than white men in any other U.S. state. A recent comprehensive review of treatment response for people in poorer economic groups documented substantial differences in receipt of optimal treatment, including definitive primary therapy, adjuvant therapy, conservative surgery, and follow-up after potentially curative treatment.

Recent information on cancer incidence and death rates may reflect socioeconomic characteristics of large populations within racial and ethnic minority groups. African Americans have the highest death rate from all types of cancers combined and from malignancies of the lung and bronchus, colon and rectum, female breast, prostate, and uterine cervix of all racial or ethnic groups in the United States. Vietnamese women experience invasive cervical cancer, largely preventable by screening, at a rate four times as high as all Asian American and Pacific Islander populations combined. Some Asian populations have nasopharyngeal and stomach cancer rates that are unusually high. And Hispanics have had incidence rates of liver and intrahepatic bile duct cancer that were more than 50 percent higher than in the overall population.

Close to 60 percent of all new cancers and 70 percent of deaths from cancer are in persons older than 65, another underserved population. The economic burden of cancer is also taking its toll. As our Nation's population ages, more people will get cancer. Meanwhile, the costs of cancer diagnosis and treatment are on the rise. The combination of these trends will accelerate a rise in the costs of cancer treatment and exacerbate the impact of cancer on people with limited resources.

Individuals affected by cancer bear other burdens as well. Those who have cancer or who must care for someone with cancer are often unable to maintain employment or devote time to other family members. Cancer is clearly much more than a medical problem. It is a serious socioeconomic dilemma.

- Fund and conduct basic, clinical, and epidemiologic studies jointly designed with community groups, including the Community Networks Program and existing Federal clinics and pilot programs to understand reasons for disparities in cancer risk, including racial/ethnic, socioeconomic, cultural, environmental, and geographic factors.
- Foster community studies on individual behaviors and environmental factors to advance knowledge about specific local populations.
- Translate national health survey questions so that they can be administered among speakers of Spanish, Chinese, Vietnamese, Korean, and other languages.
- Continue support for the newly created Cancer Council of the Pacific Islands, a community-based team comprised of health care leaders who can articulate the cancer health needs of indigenous people in each of the six U.S. associated jurisdictions of the Pacific Rim.
- Establish a Federal Task Force with representatives from the Cancer Council of the Pacific Islands, NCI, NIH, and other Federal agencies with programs and resources dedicated to the Pacific Rim, to collaborate in strengthening and sustaining community capacity for addressing cancer health disparities.

Evaluating Promising New Interventions

Our investments in new strategies for cancer interventions must be tested and applied across various populations in a culturally appropriate and community-specific manner. To do this, we first need to draw on science-based knowledge about the causes and variables contributing to health disparities while developing interventions. Once developed, it is critical to assess the efficacy of these interventions across all relevant population groups in terms of reduced prevalence of risk factors, incidence, and mortality and improved survival and quality of life. With additional resources in Fiscal Year 2006, we will:

- Support innovative scientific research to assess risk and other aspects of behaviors associated with the specific sociocultural environments of cancer patient populations and develop interventions tailored to cultural and geographic influences.
- Support tobacco use prevention and cessation research and intervention development for underserved and understudied youth and young adults.
- Support observational and intervention research that focuses on cancer survivorship in medically underserved, low income, ethnic, and minority populations. This research will cover access to and quality of care; the incidence of side effects and management of long-term health; quality of life; health behaviors such as diet, exercise, and tobacco use; and the socioeconomic, physical, and emotional burdens experienced by survivors, family members, and care givers.
- Test community-based interventions in new settings to determine their efficacy and potential to be replicated across populations in a culturally appropriate manner.

Patient Navigator Programs Provide Encouragement and Hope to Cancer Patients



There are too many people who receive a cancer diagnosis either too late for effective early treatment or with limited personal resources to take advantage of the quality cancer care that is available today. The diagnosis itself can be overwhelming, but when coupled with seemingly insurmountable infrastructure barriers, it can destroy motivation to regain health. NCI is piloting an innovative program for placing patients in contact with “patient navigators” who help individuals and their families work with an often complex healthcare system.

Patient navigators are experienced advocates from local communities – e.g., lay people, social workers, and nurses – who are able to communicate credibly with the patients. They work with vulnerable or disadvantaged people to help them obtain accurate information on diagnosis and treatment procedures, access to hospitals and clinics, guidance on financial assistance, and help with tracking their records and obtaining prescriptions. In some cases they also arrange for language translation, travel, social support, or religious counseling.

In support of these programs, NCI is initiating an educational program for patient navigators to enhance their knowledge of the clinical trial process, how trials are designed, and the clinical trial as an option in health care. The goal is to more effectively provide this treatment choice to underserved and minority communities. In addition, information will be provided about how to learn about the clinical trials that are available, both at NCI and at NCI-supported sites, and how to access them.

Newly piloted Patient Navigator Programs in Rapid City, South Dakota, and Laredo, Texas, are supplemented with funds from NCI to serve large Native American and Hispanic communities, respectively, each with high poverty rates.¹ Evaluations of these programs will help to identify successful elements, attract collaborators, and model other services and programs to reduce the devastation of cancer among older, minority, and other medically underserved populations.

¹ crchd.nci.nih.gov/initiatives/#Navigator

Collaborating for Action

NCI also continues to support collaborations among investigators to facilitate research, translation, and application of interventions such as screening, early detection, and treatment services and access to timely and accurate cancer information through community-based programs. These efforts build on partnerships with existing NCI-supported centers, networks, and consortia and pilot programs such as the Patient Navigator Program.³ With new resources in Fiscal Year 2006, we will strengthen and expand these relationships to provide valuable tools for reducing cancer health disparities. We will:

- Fund a minimum of two additional Community Networks to Reduce Cancer Health Disparities and support research to expand the use of proven cancer interventions in minority and other underserved populations not yet reached by the program.

- Support partnerships and international collaborative studies on the social determinants of cancer and cancer disparities through supplements to the NCI-supported Centers for Population Health and Health Disparities.⁴
- Support the development and implementation of a tobacco and health disparities research network for advancing the understanding of tobacco-related disparities and translating that knowledge into practical use by communities.
- Continue to support, in collaboration with the National Institute on Aging, research partnerships with NCI-designated Cancer Centers to improve early detection, diagnosis, prognosis, treatment, and survivorship in persons older than 65.⁵

Training Minorities for Cancer Care and Research

Training programs for minority healthcare providers and scientists, such as the Comprehensive Minority Biomedical Program,⁶ will increase the number of people prepared to address cancer health disparities in their programs and communities. With increased resources in Fiscal Year 2006, we will:

- Develop, implement, and evaluate education and training programs designed to create a diverse and culturally competent research and cancer care workforce.
- Support the development of training and workshops designed to diversify the cadre of mid-career level cancer investigators, expand their understanding of the characteristics of different cultures, and apply that knowledge to research for improving the health of specific populations.
- Create collaborations between the Minority Institution/Cancer Center Partnership program and the Community Networks to Reduce Cancer Disparities for the creation of joint health disparities training programs.⁷

Overcoming Cancer Health Disparities Budget Increase Request for Fiscal Year 2006

Determining the causes & extent of cancer health disparities	\$19.00 M
<ul style="list-style-type: none"> Studies/think tanks on genetics & race/ethnicity Multidisciplinary intervention studies New approaches for data collection & sharing Community-based research & partnerships Studies of & support to specific population groups 	
Evaluating promising new interventions	10.50 M
<ul style="list-style-type: none"> Tobacco cessation Survivorship Culturally appropriate interventions 	
Collaborating for research, translation, & application	6.00 M
<ul style="list-style-type: none"> Social determinants of disparities Tobacco-related disparities Interface of aging & cancer 	
Training minorities for cancer care & research	3.00 M
<ul style="list-style-type: none"> Diversity in workforce Cultural competence 	
Management and support	.65 M
Total	\$39.15 M

¹ www.hhs.gov/chdprg

² crchd.nci.nih.gov/initiatives/#Special

³ crchd.nci.nih.gov/initiatives/#Navigator

⁴ cancercontrol.cancer.gov/populationhealthcenters

⁵ cancer.gov/newscenter/pressreleases/AgingGrants

⁶ minorityopportunities.nci.nih.gov/index.html

⁷ minorityopportunities.nci.nih.gov/institutions/miccp.html

Investments in the **Strategic Development of Cancer Interventions**

Our Goal Optimize the transfer, development, and delivery of highly effective molecularly targeted drugs and technologies to specifically prevent, detect, diagnose, and treat cancer.

One of NCI's key strategies to accelerate progress against cancer in the next decade is to optimize the development and speed the delivery of new targeted cancer diagnostics, therapies, and preventives to patients. Accomplishing our aggressive but achievable objectives in this area will require a truly seamless national system for taking new cancer drugs and diagnostics from preclinical development through commercialization.

While numerous academic laboratories are focused on cancer drug and biomarker discovery, the lack of a robust system and infrastructure for developing these new technologies means that many will never reach patients. Developing and obtaining regulatory approval for a single new therapeutic drug is estimated to take 10 to 15 years at a cost of over \$800 million. These barriers have prompted the Nation's pharmaceutical industries to focus their efforts primarily on markets of a billion dollars or more and, given the many types of cancer and the potential for large numbers of molecular targets for each, cancer does not represent a major market for most large pharmaceutical companies. Conversely, the biotechnology industry has embraced the cancer market and currently there are over 1,500 biotechnology companies, many of which are focused on the development of innovative interventions for cancer. Unfortunately, many of these companies do not succeed due to a lack of funding from the capital markets.

Strategically Expanding Ongoing Activities

NCI has critically examined the strategies and actions required to optimize the transfer of potentially paradigm shifting laboratory discoveries into and through development for targeted cancer drugs and technologies, and we have already undertaken specific activities to address some of the barriers. Current NCI investments such as the Cancer Genome Anatomy Project (CGAP), Academic Public-Private Partnership Programs (AP4s), the Specialized Programs of Research Excellence (SPOREs), Rapid Access to Intervention Development (RAID), Rapid Access to Preventive Intervention Development (RAPID), and the cancer Biomedical Informatics Grid (caBIG)¹ are part of an overarching strategy to lower the risks associated with developing new cancer interventions. This strategy will be optimized by continued investments in advanced bioinformatics platforms, cancer imaging, and nanotechnology. (See pages 32-39.) All of these initiatives will drive an ever increasing need for a new, more responsive clinical trials system that is focused on the evaluation of targeted, safe agents and devices. (See pages 28-31.) We will use new resources in Fiscal Year 2006 for strategic expansion of selected ongoing activities. We will:

- Expand the number of new drug candidates arising from the National Cooperative Drug Discovery Groups (NCDDG) and the Drug Development Group (DDG).²
- Expand the RAID and RAPID programs through NCI's scale-up capabilities and increased use of existing resources in cancer and academic medical centers.
- Fund up to six AP4s to discover new interventions for understudied malignancies and rapidly translate these discoveries to human clinical trials.

Speeding Development of Molecularly-Based Interventions

To further facilitate the creation of new molecularly-based diagnostics, therapeutics, and preventives and provide critical scientific support for areas such as combination therapies and target discovery and validation, NCI must also make investments in new enterprise initiatives.

Biospecimen Initiative. In an era of exciting discovery about the genomic basis of cancer, researchers have identified lack of access to high quality biospecimens as rate limiting to progress in molecular medicine. To use sophisticated assay methods such as genomic sequencing and protein detection and measurement, a highly reliable source of biospecimens that are linked to validated clinical information is essential. With sufficient funding in Fiscal Year 2006, NCI will develop a pilot resource for an integrated system to collect biospecimen and clinical information and make it easily available to the scientific community. We will:

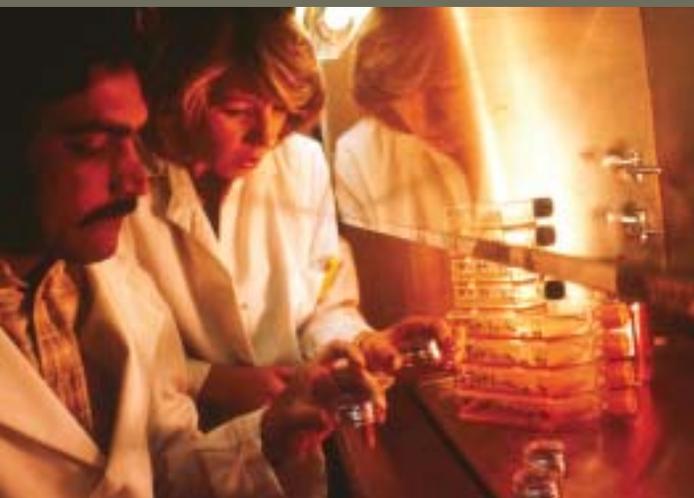
- Provide a standardized system for specimen acquisition, annotation, processing, and storage to support genetic and proteomic research and biomarker discovery and validation.
- Establish a state-of-the-art information system to link investigators to specimens and foster exchange of data across the research enterprise via the cancer Biomedical Informatics Grid (caBIG).
- Provide a test-bed for broader applications of a new era system for biospecimen banking and clinical information management.

Cancer Genome Analysis Program. Now armed with the genomic code developed through the Human Genome Project, researchers are developing technologies that can rapidly and inexpensively sequence regions of genomic information as they seek to identify the genetic basis of each patient's cancer. For the patient and healthcare provider, this sets the stage for a revolutionary approach to cancer care in the next decade. Identifying the genomic code of patients at risk for cancer or aiding in the classification of cancer by the patterns of genes present in a tumor will bring an era of molecular medicine not yet explored.

The Cancer Genome Anatomy Project (CGAP) has provided the cancer research community with an invaluable source of state-of-the-art technologies, tools, and databases that has contributed significantly to our understanding of key genetic changes in cancerous versus normal cells. This information has provided cancer researchers with early direction in their search for molecularly-based targets for new cancer interventions. NCI will further extend the scale and scope of CGAP through a collaborative program that will systematically investigate and catalogue genetic abnormalities across several tumor types using a variety of approaches including gene re-sequencing and array technologies.

In Fiscal Year 2006, NCI will support the first patient oriented research project aimed at systematically developing genomic data from cancer cells, to set the stage for a large scale program. Specimens will be collected from patients along with highly accurate and protected patient information. The tumor specimens will be carefully prepared for genomic sequencing using the most advanced genomic technology platforms available. In the pilot phase, researchers will search for abnormalities in the genetic code of a limited number of human tumor types. Several types of sequencing technologies will be applied to the same specimens to determine which methods are most efficient and yield the highest quality information. Researchers will also identify patterns of abnormal genes in the tumor specimens and investigate the basis of cancer and the stages of cancer development. With initial success, this project will be expanded to additional types of solid and hematologic tumors.

Readily Available Biospecimen Resources Are a Must for Cancer Research



Scientists depend on the availability of high quality biospecimens collected in a standard manner – e.g., blood and tissue samples – from cancer patients, as well as from healthy volunteers, to enable their research. Access to these high quality biospecimens is especially critical in areas such as genomics and proteomics investigations and for:

- Investigating normal and malignant tissue microenvironments. (See pages 43-45.)
- Clarifying the underlying biological relationships between anti-tumor immune responses and autoimmune responses to immunotherapy. (See page 45.)
- Identifying and validating biomarkers of precancers for use in cancer screening and early detection. (See page 10.)
- Developing and validating surrogate molecular endpoints for clinical trials. (See page 30.)

NCI has historically supported a large number of “bio-banks,” ranging from a few biospecimens in the hands of individual investigators to large collections that are available for broad use by the research community. We must act now to better standardize and coordinate the collection and storage of human biospecimens to allow more widespread and productive use of these precious resources. The collection of fresh tissue samples will be pivotal to genomics/proteomics research. These critical samples must be collected in full compliance with genetic privacy protection and annotated to include as much data as possible about the biospecimen and the case and be broadly available to researchers.

NCI has collaborated with others to develop a model for a national biospecimen network and accompanying database to begin to address the problem of standardization for biospecimens, access, data availability, and privacy protection. The network will be pre-competitive, regulatory-compliant, genetic privacy-protected, standardized, and inclusive. As we move ahead with this initiative, we will work to ensure that the common standards of collection and storage and peer-reviewed availability of specimens, specified by the national concept, are fully integrated into NCI’s biospecimen resource banks. This model is in keeping with similar strategies being pursued in other countries such as the United Kingdom and Japan.

Sufficient resources in Fiscal Year 2006 will allow NCI to:

- Develop a comprehensive database of genomic sequence data from a defined set of human tumor types.
- Provide data analysis tools to help researchers begin to efficiently sift through millions of genomic codes to find relevant signals of cancer development.
- Develop improved approaches to sequencing technology that will streamline its application into clinical medicine.
- Provide new databases that will inform and drive the discovery of new targeted agents for cancer.

Building Capacity for Early Detection and Targeted Treatment

NCI will also apply new resources in Fiscal Year 2006 to strategic initiatives that build capacity for targeted intervention development, to help ensure that the numbers of new targeted drugs and devices, developed and ultimately approved for marketing through the FDA, increase exponentially in the next few years.

Biomarkers for Drug Discovery and Early Detection. Biomarkers include a number of biological molecules such as DNA and proteins, but one of the most promising areas for drug and device discovery and development is the field of proteomics. Recent breakthroughs are enabling scientists to identify patterns of protein markers associated with cancer initiation and progression and with particular cancers. Biomarkers in cancer research hold promise for making “personalized” medicine a reality. They have many potential applications including early diagnostic testing, monitoring response to treatment, detecting metastatic disease, and building “designer” therapies. When sufficiently validated, they will enable scientists to more rationally discover and develop drugs and quickly identify patients that will respond to specific therapeutic interventions. Biomarkers are also integral to new cancer detection strategies. In fact, proteomics may well hold the key to diagnosing cancer early and finding recurrence well before it becomes a threat. With increased resources in Fiscal Year 2006, NCI will develop a new Clinical Proteomics and Biomarker Discovery Program to:

- Assess technologies central to biomarker discovery and integrate the best performers into an optimized platform against which new technologies can be tested.
- Develop an open source suite of tools to facilitate the standardization of analysis across laboratories and allow meaningful comparison of results.
- Establish and make publicly available a comprehensive database for storing the data from various biomarker projects.
- Provide a central, virtual source for reagents with quality control and timely access to data on reagent performance and quality.

An NCI-FDA Partnership Is Paying Big Dividends in Targeted Cancer Drug and Device Development

Despite increased spending on biomedical research and development, there are fewer new medical products reaching consumers than at any time in more than a decade. Our Nation is also facing unprecedented challenges involving affordability and access to currently available treatments for all patients. To address these issues, the U. S. Food and Drug Administration (FDA) and NCI announced, in November 2003, the development of a system for submitting investigational new drug applications (INDs) electronically under NCI's cancer Biomedical Informatics Grid (caBIG) project. This will allow the FDA to review applications faster and get new treatments to patients more quickly and at lower cost. The eventual goal of the caBIG project is to have an entirely electronic system for the submission and evaluation of clinical information for cancer trials. As a first step, NCI and the FDA will work together to build tools that facilitate electronic interaction, focusing in particular on IND applications.

In July of 2004, the FDA created the Office on Oncology Drug Products, which will focus on a strong approach to the drug and therapeutic biologics review process. NCI will work with FDA through this and other mechanisms to develop processes to ensure that positive results are more quickly translated into new diagnostic or treatment options for patients. The formation of the FDA/NCI Interagency Oncology Task Force (IOTF) is one such initiative. This joint agreement will enhance the efficiency of clinical research and scientific evaluation of new cancer medications and allow researchers to share knowledge and resources. The IOTF is currently working to speed progress along the pipeline of targeted cancer interventions by:

- Building a cadre of experts in the science of regulatory review of oncology technologies.
- Establishing a senior leadership group to triage issues from NCI-supported investigators and consult on regulatory submissions.
- Integrating common bioinformatics tools, including platforms for reporting clinical trials and electronic filing of INDs.
- Identifying potential clinical endpoints, from areas such as functional imaging and biomarkers, for use in assessing the effectiveness of new agents in clinical trials.
- Developing roadmaps for the future regulation of advanced technologies.

Another joint initiative is the Cancer Fellowship Training Program, which will develop a corps of physicians and scientists who are expert in clinical research, the regulatory process, and translation of research breakthroughs to clinical practice. New programs will make various training opportunities available for NCI researchers at the FDA, including training as product reviewers.

National Molecular Target Validation and Credentialing Program. Our increasing ability to “interrogate” the human genome to determine both the sequence and functions of genes and gene products is providing the foundation for new screening technologies designed to identify targeted drug candidates. These new technologies range from the use of small chemical probes (chemical genomics) to systems that detect specific pathway effects following perturbation with a candidate agent. These new systems will significantly enhance the amount of information that can be derived in early discovery concerning significant parameters such as toxicity. Another key barrier to capitalizing on the discovery and development of targeted cancer agents is the validation of molecular targets. We know that cancer may offer literally thousands of potential molecular targets, but it is critical that each molecular entity be validated in terms of its potential to become a robust target for the discovery and development of highly effective cancer drugs. With new resources in 2006, NCI will:

- Make available to the community enhanced screening systems to better identify targeted agents for cancer.
- Establish a pilot program to evaluate target validation strategies such as RNA interference (RNAi) and systems biology.

Streamlining Preclinical Development

Preclinical development of prospective drugs and diagnostic technologies will require enhanced infrastructure including more accurate, predictive, efficacy models; rational processes for selection of lead candidates; and new NCI capabilities for process scale-up, as described above. Often the most difficult phase of the development of cancer therapeutics and diagnostics is the preparation and presentation of the preclinical information required by the FDA to file an investigational new drug application (IND). The preclinical phase can be daunting and expensive, especially for academic investigators with limited resources. NCI will use new resources in Fiscal Year 2006 to provide support for preclinical development. We will:

- Establish an integrated preclinical development program that places significant emphasis on new approaches to define the pharmacology, toxicology, distribution, and other significant parameters associated with the administration of small molecules and biologics.
- Make available to the community new technologies such as pharmacogenomics and metabolomics as part of a new approach to preclinical development.

Strategic Development of Cancer Interventions Budget Increase Request for Fiscal Year 2006

Expanding ongoing activities	\$20.00 M
Increased number of new drug candidates	
New interventions for understudied malignancies	
Sped up development of molecularly-based interventions	40.00 M
National biospecimen resource	
Large scale cancer genome analysis program	
Building capacity for early detection & targeted treatment	35.00 M
Clinical biomarkers discovery & development program	
National molecular target validation/credentialing program	
Streamlining preclinical development	22.00 M
Infrastructure for preclinical development	
Molecular screening technology platforms	
Management & Support	2.00 M
Total	\$119.00 M

¹ cgap.nci.nih.gov, spores.nci.nih.gov, dtp.nci.nih.gov/docs/raid/raid_index.html, cancer.gov/prevention/rapid, cabig.nci.nih.gov

² dtp.nci.nih.gov/docs/ddg/ddg_descript.html

Building Research Teams of the Future

NIH and NCI Find New Ways to Support Interdisciplinary Team Science



Increasingly, scientists must be able to work in interdisciplinary teams to understand and fully explore the interplay among environmental, lifestyle, genetic, and molecular variables contributing to cancer and take advantage of the technological resources available to help them do this.

NIH Roadmap initiatives for building *Research Teams of the Future* are designed to foster team science by making it easier for scientists to work across disciplines and organizations. NIH will redirect resources to train scientists in interdisciplinary strategies, create specialized centers to help forge innovative and more advanced disciplines from existing ones, and plan forward looking conferences to catalyze collaboration among the life and physical sciences. New funding mechanisms will grant principal investigator status to all key members of a research team, provide research funding to multiple institutions, require integrated reviews of grant applications that take into account the melding of the various disciplines, and encourage interdisciplinary teams to evolve in both directed and serendipitous ways. NCI is aligning funding mechanisms, organizational culture, and strategic investments to accelerate, interdisciplinary and multidisciplinary research.

Within our NCI 2006 Strategic Investments, interdisciplinary training will play a critical role. For example:

- Education and training programs in health disparities will help create a research and cancer care workforce sensitive to the needs of diverse populations and cultures.
- Training opportunities for clinical researchers, oncology research nurses, and basic, clinical, and public health teams will foster the development of a cadre of investigators who can work between bench and bedside.
- Joint training programs with medical and public health schools, new training awards, and new curricula will enhance the ability of teams to collaborate effectively in research relevant to molecular epidemiology.
- Cancer biology training programs will prepare interdisciplinary scientists to build, characterize, and validate computational models and to use organotypic culture systems.

Research partnerships will focus interdisciplinary efforts on such topics as:

- The interplay of behavior, chemistry, toxicology, and biology to determine the cancer risk potential of reduced-exposure tobacco products.
- The mechanisms of energetics, energy balance, and cancer and how they inform approaches for the prevention of obesity.
- The social and genetic determinants of and community-based interventions for overcoming cancer health disparities.

- Interventions to improve early detection, diagnosis, prognosis, treatment, and survivorship in persons older than 65.
- Normal and malignant tissue microenvironments, their molecular signatures, and the origin of the cells and factors that comprise the tumor stem cell and the tumor microenvironment.
- The associations of known cancer viruses with cancers not previously linked to these viruses and the role of microbial agents in the etiology of human cancers.
- The causes of and risks for highly lethal cancers such as pancreatic, liver, and esophageal.

Numerous established and new NCI initiatives and programs support interdisciplinary teams.

These include NCI-supported Cancer Centers, the Specialized Programs for Research Excellence, the Academic Public-Private Partnership Programs, a new Biospecimen Initiative, the cancer Biomedical Informatics Grid and consortium, the Cancer Genetics Network, the Cancer Genome Anatomy Project, a new Cancer Genome Analysis Program, new Centers for Cancer Nanotechnology Excellence, Centers for Population Health and Health Disparities, Centers of Excellence in Cancer Communications Research, a new Clinical Proteomics and Biomarker Discovery Program, the Clinical Trials Cooperative Group Program, the Community Clinical Oncology Program, new Community Networks to Reduce Cancer Disparities, various consortia for interdisciplinary epidemiological studies, the Drug Development Group, the Early Detection Research Network, a network of high-throughput genotyping laboratories, *In Vivo* Cellular and Molecular Imaging Centers, Integrative Cancer Biology Programs, the intramural Molecular Targets Development Program, National Cooperative Drug Discovery Groups, the Network for Translational Research in Optical Imaging, the Minority Institution/Cancer Center Partnership Program, a new integrated preclinical development program, new centers for Transdisciplinary Research on Energetics and Cancer, Interdisciplinary Research Teams for Molecular Target Assessment, and Transdisciplinary Tobacco Use Research Centers.

NCI Plays a Role in the NIH Roadmap for Medical Research

The NIH Roadmap for Medical Research, launched in September 2003, consists of far reaching initiatives intended to accelerate the pace of life science discovery and translation from the bench into practice. The Roadmap is focused on efforts that are beyond the scope of any single NIH Institute and that integrate the full spectrum of Institute missions. NIH Director Elias A. Zerhouni has spearheaded the Roadmap – with input from over 300 nationally recognized leaders in academia, industry, government, and the public – to address major opportunities and gaps in biomedical research.

NCI is involved in several aspects of the NIH Roadmap for Medical Research, contributing expertise to the theme areas that align most closely with the Institute's strategic priorities and overall mission. In addition to participating in building *Research Teams of the Future*, NCI is providing infrastructure, expertise, and other resources toward the development of imaging and molecular libraries, centralized resources and services for translational research, and Regional Translational Research Centers to accelerate the development of new drugs, biomarkers, and treatment strategies.

For more information, visit the NIH Roadmap Web site at nihroadmap.nih.gov.

Strategic Investments in **An Integrated Clinical Trials System**

Our Goal Build a highly interactive and optimally coordinated cancer clinical trials system that will prioritize and accelerate the development of new interventions and ensure that those interventions found to be effective are efficiently and seamlessly incorporated into medical practice.

The 2004 *Annual Report to the Nation on the Status of Cancer*¹ reports that observed overall cancer incidence rates dropped 0.5 percent annually while overall death rates from cancer dropped 1.1 percent each year from 1993 to 2001. Contributing to these encouraging trends are new clinical approaches to cancer prevention, early detection, diagnosis, treatment, and quality of life after treatment. The vast majority of these interventions have one feature in common: they were rigorously tested in clinical trials. Similarly, the majority of interventions arising from research proposed in this document will be tested in clinical trials.

Each year, NCI provides leadership, resources, and expertise for a clinical trials program that spans the entire spectrum of activity – from the discovery of novel molecules to the evaluation and application of new agents and interventions. We support trials at the NIH Clinical Center and at close to 3,000 other sites across the United States. Over 1,500 NCI-supported cancer trials are conducted annually, involving more than 12,000 investigators. With expansion over the past five years, our clinical research base has grown and become increasingly productive, providing hope for untold numbers of current and future cancer patients.

As we look to the future, we recognize the need to make our clinical trials system even more robust, to anticipate scientific and technological advancements and enhance partnerships and collaborations with an interdisciplinary and translational focus. Imaging will play a role not only in monitoring treatment but also in identifying patients who are most likely to respond to a particular drug or combination therapy. In addition, imaging will play a critical part in the pre-clinical screening and validation of new targeted compounds. The clinical trials system of the future will facilitate the effective conduct of Phase I clinical trials, better prioritize and coordinate large Phase II and III trials,² and directly address regulatory and other issues that affect the timeliness with which clinical trials can be completed and their findings translated into practice.

To make clinical trials more efficient and to accelerate the approval of new interventions through the regulatory process, NCI will enhance its working relationship with the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) to develop more streamlined policies and procedures for the conduct of clinical trials. We will build partnerships among disparate NCI clinical trial entities and with industry and promote communication among regulatory agencies and clinical trials groups. We must promote ongoing and forge new communication networks among clinical researchers and the broad community of oncologists. Finally, we need to ensure that the diagnostic and therapeutic interventions emerging from clinical trials are used to benefit all populations and contribute to reducing health disparities.

Strengthening Scientific Prioritization and Coordination

One of our objectives is to develop a more effective infrastructure for cancer clinical trials that will strengthen scientific prioritization and coordination, thereby improving the timeliness with which clinical trials are completed and making the process more integrated, open, and inclusive of cross-disciplinary and patient advocate input. With increased resources in Fiscal Year 2006, we will:

- Strengthen flexible collaborations with industry, FDA, the Centers for Medicare and Medicaid Services (CMS), OHRP, and other public, private, academic, and patient advocacy organizations to oversee the conduct of cancer clinical trials.
- Expand state-of-the-science meetings in disease and multimodality settings not currently covered and extend the frequency of meetings of established clinical and scientific thought leaders, to identify critical research questions to be addressed by clinical trials and develop strategic plans for prioritizing and implementing those studies.
- Develop new infrastructure and procedures to standardize, coordinate, and track clinical trials development and accrual across all NCI-supported clinical trials venues.
- Expand access to centralized Institutional Review Board (IRB) resources and clinical research administrative support for all NCI-coordinated multi-institutional clinical trials.
- Increase funding for imaging in clinical trials in order to utilize the appropriate imaging tools in screening and therapy trials, evaluate new imaging probes and methodologies, enable access to the imaging data from trials in an electronic format, and facilitate evaluation of image-guided interventions.
- Increase funding for data managers, research nurses, biostatisticians, and clinicians, as well as other functions associated with NCI clinical trials, to both expand access and improve the timeliness for completion of the highest priority clinical studies.
- Increase funding for training pathways for clinical investigators, oncology research nurses, and basic, clinical, and public health teams to foster the development of a cadre of established clinical investigators who can work between bench and bedside.
- Pilot new approaches and develop prototypes for clinical trials networks that will improve the efficiency, coordination, and integration of our national efforts.

Importantly, NCI will integrate clinical trials based on a common clinical trials informatics platform that will be overseen by, and made available to, the full range of investigators working within the cancer clinical trials system. This includes NCI clinical faculty, staff, academicians, community physicians, representatives of regulatory agencies and the pharmaceutical industry, research nurses, and patient advocates. In addition, electronic repositories of currently obtained imaging data in clinical trials will serve as databases for development of future software tools and computer aided design methodologies. (See pages 10 and 35.)

Speeding Agent Development and Biomarker Validation through Clinical Trials

With adequate resources in Fiscal Year 2006, we will also take critical steps to speed the early development of novel preventive and therapeutic agents and to validate biological markers for early detection and diagnosis and for determining the effectiveness of treatment. We will use these new resources to increase the number of promising agents evaluated in NCI-supported clinical trials and to develop new molecular diagnostic and imaging techniques capable of predicting therapeutic outcome during those studies. We will:

- Establish a program of pilot clinical trials employing novel pharmacologic, imaging, and molecular target validation principles that will facilitate new intramural-extramural partnerships and speed the early development of cancer therapeutics.
- Create broadly based working groups to identify clinically relevant surrogate molecular endpoints for clinical trials, develop core facilities to standardize and perform high throughput molecular pathologic evaluations of potential biomarkers for prediction from tumor and normal tissues collected during NCI-supported randomized clinical trials, and develop resources and clinical trial designs to validate these endpoints.
- Expand translational research capacity to use a broad range of laboratory-based correlative studies more extensively in NCI-supported clinical trials.

NCI Partners with CMS to Streamline Patient Access to Cancer Drugs



NCI is partnering with the Centers for Medicare and Medicaid Services (CMS) to improve patient access to life saving anti-cancer drugs. Because new prevention and treatment therapies and diagnostic procedures must first be approved by the FDA, this NCI-CMS partnership will build on an NCI-FDA collaboration to better align the efforts of all three agencies.* NCI and CMS are developing a Memorandum of Understanding for working together in five areas of technology, science, and patient care. The two agencies will work together to:

- Identify high priority clinical questions about the optimal use of new technologies and a process for conducting post-approval studies.
- Define a systematic process for consultation between CMS and NCI for evaluating new diagnostics and therapeutics for payment and coverage decisions.
- Develop more efficient methods for collecting clinical evidence on new technologies and make this information more widely available to physicians, patients, and researchers.
- Identify and evaluate emerging technologies so that reimbursement policies will better anticipate their promise and expedite their adoption in the marketplace.
- Identify opportunities for data and resource sharing aimed at improving quality of care, overcoming health disparities, reducing variations in treatment, and improving symptom management and end-of-life care.

*See page 24 for information on the NCI-FDA collaboration.

Expanding the Goals of Clinical Trials

With adequate resources in Fiscal Year 2006, we will also expand the goals of our clinical trials. We will:

- Provide incentives to include innovative programs in more clinical trials structures, such as patient navigation to increase access to cancer clinical trials for minority and underserved populations.
- Support efforts to improve recruitment and retention of women and minorities in NCI-supported clinical trials programs.
- Increase minority participation in clinical trials through an NCI fellowship training program for healthcare providers and through other forums.
- Provide incentives for the enhancement of symptom management studies within the NCI-supported clinical trials system.
- Support the use of informatics systems to track and record participant information needed by healthcare providers for long-term follow-up and care after the completion of clinical trials.
- Stimulate investigations of the long-term effects of cancer treatment and related survivorship issues.
- Stimulate the use of health related quality-of-life and economic endpoints in NCI-supported Phase III trials.

Integrated Clinical Trials System Budget Increase Request for Fiscal Year 2006

Strengthening scientific prioritization & coordination	\$116.00 M
Flexible collaborations	
State-of-the-science & other planning meetings	
Standardization, coordination, & tracking of trials	
Centralized IRB & administrative support	
Increased use of imaging	
Staffing & training	
New approaches & prototypes for networks	
Speeding novel agent development & biomarker validation	28.00 M
Trials employing novel validation principles	
Identification of surrogate endpoints & biomarkers	
Laboratory-based correlative studies	
Expanding the goals of clinical trials	24.00 M
Increased access for minority & underserved populations	
Symptom management studies	
Patient tracking & record keeping	
Studies of long-term effects of treatment	
Use of quality-of-life & economic endpoints	
Management & Support	2.85 M
Total	\$170.85 M

¹ A collaborative effort of the American Cancer Society, the Centers for Disease Control and Prevention, NCI, and the North American Association of Central Cancer Registries. seer.cancer.gov/report_to_nation/1975_2001

² **Phase I trials** are studies involving small numbers of patients to evaluate how new drugs should be given (by mouth, injected into the blood, or injected into the

muscle), how often, and at what dose level. **Phase II trials** continue to test the safety and efficacy of drugs, usually focusing on how effective they are for specific types of cancer. **Phase III trials** test new drugs, new combinations of drugs, or new surgical procedures in comparison to the current standard. Phase III trials generally enroll larger numbers of people and are frequently conducted at multiple sites – e.g., doctors' offices, clinics, and cancer centers.

Strategic Investments in **Advanced Technologies***

Our Goal Accelerate the development of highly effective advanced technologies and maximize their use to power and streamline research, enhance the options for patient care, and connect investigators with one another and with the healthcare provider and patient communities.

Research over the past three decades has led to unimagined progress in our understanding of the cancer process at the genetic, molecular, and cellular levels. As we search for the most effective ways to apply these insights to the prevention, early detection, and management of cancer as a disease process, we know that our most direct path will be through the optimal integration of science and technology. Our Nation's past successes in creating technologies to enhance discovery – from the space program to the Human Genome Project – have produced dramatic scientific breakthroughs and advances. Now we have an opportunity to achieve an equally unimagined goal: to eliminate the suffering and death due to cancer.

Today's technologies and tools are replacing Einstein's chalk and blackboard with powerful computers, sophisticated software, and networking that enables collaboration on a global scale. Identifying many of the complex mechanisms responsible for cancer through genetic and protein microarrays, molecular imaging, and high throughput screening are proving to be pivotal in accelerating our ability to intervene against these processes. Similarly, technology-dependent, molecularly targeted therapies based on a patient's disease-specific profile of markers provide hope that the cancer burden will be lightened and patients will enjoy a higher quality of life. We are able to make rapid gains against cancer because of the development and availability of advanced technologies that enable accelerated research and create effective interventions.

Bioinformatics

Hastening Progress against Cancer Using A 21st Century Integrated, Electronic Network

By using the power of modern information technology, NCI is leading the way in developing a bioinformatics platform that promises to revolutionize the biomedical research enterprise. Scientists in various disciplines will have access to a common infrastructure for collaboration and integration of findings, and new "plug and play" tools developed by the researcher community will make it possible for investigators to greatly accelerate their research. For example, researchers at Cancer Centers across the country will be able to access data on the molecular characteristics of patients with a particular type of cancer who are being treated with a specific drug. Diverse data mounted on common platforms will permit researchers to use innovative analytic tools to mine the information in ways inconceivable a few years ago. And researchers can take advantage of "in silico" experiments that facilitate rapid, cost-efficient hypothesis generation and evaluation.

* To further the development of the advanced technologies described here, NCI is proposing a national initiative for coordinating and channeling these efforts across public and private organizations to expedite the delivery of cancer diagnostics and therapeutics to patients and their caregivers. See pages 40-41.

Up to the present, bioinformatics resources have been developed in organizational isolation, with tremendous variability in rules, processes, vocabularies, data content, and analytical tools. NCI will address these concerns and strengthen the potential for bioinformatics integration with the cancer Biomedical Informatics Grid (caBIG).¹ The caBIG will provide a unifying architecture to transparently connect information and tools much like a home entertainment system in which components are made by different manufacturers but built to common standards that allow users to combine them in various ways. Our long-term goal for bioinformatics is to improve the sophistication of information technology use and surmount the barriers that limit interaction across research institutions. NCI is currently piloting a core infrastructure with the participation of 50 Cancer Centers.

We are also fostering the development and use of new informatics technology to accelerate, better coordinate, and facilitate participation in NCI-supported clinical research. Currently, volumes of valuable raw data are not tapped, effective best practices are not widely distributed, and resources are wasted because of duplication of effort. With new bioinformatics tools and infrastructure, trials will be completed more quickly in multi-institutional settings with uniform electronic case report forms and data reporting systems. Databases and analytical tools will make information from all clinical trials available to NCI-supported researchers for efficient patient accrual, information retrieval, and data analysis. Informatics systems will assist the cancer community with priority setting and allow for fuller participation and a more transparent decision making process. Advocacy groups and individual patients will be empowered to participate in clinical research and to authorize use of materials for basic science investigations. Confidential clinical and proprietary information will be protected by controlled, secure access. Just as e-business models have transformed the American market place, the caBIG platform will overcome traditional institutional limitations. Community practitioners, clinical research organizations, and academic centers will be linked through this new model of clinical research. Healthcare providers will become full partners in the research enterprise and educated consumers of research findings.

We will use funding increases for bioinformatics in Fiscal Year 2006 to:

- Evaluate the prototype caBIG at the pilot centers and expand the data, software, and infrastructure available through the Grid.
- Expand the development process and extend participation in the caBIG consortium to other cancer research institutions around the country.
- Develop and evaluate a World Wide Web-based, clinical research outcomes reporting system with voluntary participants from Specialized Programs of Research Excellence (SPOREs), Cancer Centers, and the intramural Center for Cancer Research (CCR).²
- Expand World Wide Web-based, clinical trials support infrastructure through a pilot study in conjunction with the CCR trials group, selected inter-SPORE collaborations, and Cancer Centers.
- Develop infrastructure and tools, including an Internet resource, that facilitate community-wide clinical research participation and support.

caBIG Aligns with REMBRANDT to Power Translational Research



Primary brain tumors are a leading cause of cancer mortality in children and young adults and the incidence of brain tumors (gliomas) in older people is increasing. Effective therapeutic options are limited with many patients dying of their disease within a year of diagnosis. Patients, who survive, face devastating effects of the tumor and treatments that impact cognition, function, and quality of life for themselves and their caregivers. Novel therapeutic approaches are desperately needed. REMBRANDT,¹ a partnership between NCI and the National Institute of Neurological Disorders and Stroke (NINDS), is an initiative to create a publicly available database that will house biologically and clinically oriented data regarding primary brain tumors. By using this data to develop novel molecular classification systems, this partnership can move us toward an era of individualized cancer treatment based on the molecular genetics of each patient's tumor.

To accomplish this goal, REMBRANDT will be designed to house two sets of valuable data. The first set of data will come from the NCI-sponsored Glioma Molecular Diagnostic Initiative (GMDI), a prospective clinical trial and the largest genetic/clinical corollary study ever conducted. Hundreds of brain tumor patients throughout the country undergoing surgery will have samples of their tumors sent to NCI for exhaustive genetic and molecular analysis and the findings will ultimately be correlated with the clinical course of the individual patient. The second type of data housed by REMBRANDT will be a wide array of molecular and genetic data regarding all types of primary brain tumors. REMBRANDT will be the vital link that will not only allow disparate types of data to be housed in a single place, but will also supply the bioinformatics tools critically necessary for the useful analyses of such data.

NCI's Cancer Biomedical Informatics Grid, (caBIG), offers a library of tools and resources to initiatives such as REMBRANDT to facilitate integrative analysis from bench to bedside and back. The new molecular glioma classification system that will result from GMDI and REMBRANDT will be biologically based, giving insight into pathology and helping physicians to predict responsiveness to specific therapies. Crosstalk between REMBRANDT and caBIG will serve all initiatives. caBIG and NCI will contribute tools to REMBRANDT and the research community will be able to access REMBRANDT resources through an NCI developed WWW portal.

How does caBIG work? In Cancer Centers, developers and adopters collaborate in "workspaces" to develop and apply tools, systems, and data elements that enable integration and sharing of information. In the REMBRANDT initiative, clinical data to be acquired includes progression of the tumor and survival of the patient, treatment and response, toxicity, imaging parameters, and pharmacology. Populating the database with molecular and genetic data will help identify and analyze patient genetic profiles, molecular pathways of cancer progression, novel molecular targets, and patient-specific tailored therapy. Researchers can explore how genetic changes correlate with the patient's response to therapy and overall survival within given age groups, geographical locations, and ethnicities. The database is planned for development over a three-year timeline and will be fully open and accessible to all investigators, both intramural and extramural.

¹ REMBRANDT, REpository of Molecular BRAin Neoplasia DaTa

Cancer Imaging

Improving Our Understanding of Cancer Biology and Facilitating Cancer Preemption and Clinical Management of Cancer and Cancer Risk

Clinicians are increasingly relying on imaging methods as biomarkers for cancer risk and treatment efficacy. 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 therapies. Imaging informatics optimizes the availability and effectiveness of cancer imaging data in research as well as clinical environments. Imaging methods are used hand-in-hand with emerging technologies such as nanotechnology, proteomics, and high throughput screening to identify cancers earlier and help assess the effectiveness of therapy. Imaging of small animals used in research, particularly genetically engineered mice, is increasingly recognized as a powerful discovery tool in cancer research. As our knowledge of the molecular basis of cancer increases, molecular imaging methods are providing clinicians with telling details about the environs of patients' tissues. With increased resources for cancer imaging in Fiscal Year 2006, we will:

- Establish publicly available image archives, linked to outcome and other clinical data, and partner with industry to support image archives.
- Integrate image-guided intervention research into Cancer Centers, Specialized Programs of Research Excellence (SPOREs), and NCI's Center for Cancer Research (CCR).
- Use nanotechnology to design "smart" injectable, targeted contrast agents that improve the resolution of cancer to the single cell level.
- Engineer nanoscale devices capable of addressing the biological and evolutionary diversity of the multiple cancer cells that make up a tumor within an individual.
- Expand the Small Animal Imaging Resource Program, the Network for Translational Research in Optical Imaging, and the Development of Clinical Imaging Drugs and Enhancers program.³
- Develop a program for imaging validation in animal models.

We will also use new resources in Fiscal Year 2006 to integrate correlative imaging studies, such as monitoring response to therapy, into NCI-supported clinical therapy trials (See page 29.)

Proteomic Technologies Initiative

Overcoming the Barriers to Early Detection of Cancer

Scientists are taking new steps to identify profiles, or signatures, of proteins and peptides (fragments of proteins) that are found in tumors and often in the circulating blood that signal early phases of cancer development. Proteins serve complex and diverse functions in the body, from giving structure to our cells to regulating processes such as digestion, respiration, and the growth rate of cells. When proteins do not function properly, normal body processes can go awry. For example, cancer is caused by errors in proteins that regulate when and how fast cells replicate themselves, as well as the timing of cell death. One of the goals in cancer research is to develop technologies that measure these abnormal proteins and can eventually be used as simple diagnostic blood tests. However, there are some sizeable technical challenges that stand in the way of achieving that goal. These abnormal proteins are found in minute quantities and the blood contains hundreds of thousands of these proteins. The net effect is that we need to refine the technology so that it can find “a needle in the haystack” with unprecedented reliability.

In 2006, NCI will support development of advanced technology platforms for overcoming these barriers and preparing diagnostic methods ready for clinical testing. Mass spectroscopy, a favored approach involving high energy lasers, high powered electronic sensing, and computing, is used to identify specific proteins and their fragments based on their size and electrical charge. Another avenue is to use DNA and antibodies to capture proteins and measure their quantity on electronic chips. Patients in the near future may well have small samples of their blood analyzed using mass spectroscopy and protein chips that will, within minutes, identify abnormal proteins that indicate early, very treatable cancers.

NCI is developing infrastructure to help researchers speed development of these technologies and bring them to the clinic. Through a new Mouse Models of Human Cancers Consortium (MMHCC)⁴ initiative, researchers will create new resources including antibodies, data that provide standards for future measurement comparison, serum specimens, and histologic data. These resources will enable investigators to develop the technology platforms needed to detect proteins at very low levels and serve as a model for testing this approach for clinical medicine. With sufficient resources in FY 2006, this program will:

- Support two consortia of more than 10 laboratories, each focused on improving protein detection platforms important for early cancer detection research.
- Provide a publicly available database of protein measurements from more than 20 different mouse models of cancer to give researchers a starting point to begin clinical studies.

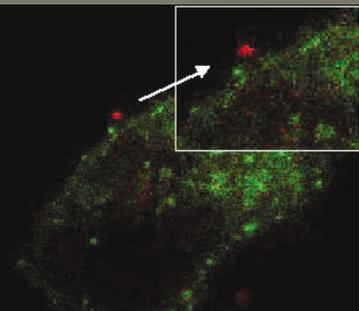
- Develop advanced computer software and use it to analyze the immense amount of data generated by the project.
- Make available a repository of mouse protein antibodies, peptides, and serum as a research resource.
- Improve the accuracy and precision of mass spectroscopy and antibody detection methods.

A Treasure Trove of Diagnostic Information

Late in 2003, NCI scientists and partners reported a breakthrough in proteomic analysis that may make early detection by protein profiling even more practical. These scientists developed a method that enhances detection of the smallest proteins found in the blood. According to this team of scientists, these small proteins represent a “treasure trove of diagnostic information that has largely been ignored until now.” The trouble is that these small proteins are normally carried through the body attached to larger “carrier” proteins. Hidden from detection when attached to a carrier protein, these small proteins are quickly excreted from the body when not bound to a carrier. As a result, these small proteins are notoriously difficult to detect in blood samples. However, this team of scientists has found a way to release small proteins from their carriers after blood has been drawn from the patient and prior to analysis of the blood sample. This simple, but ingenious technique is opening the door for vastly improved proteomic profiling techniques that can include small, as well as large, proteins in signature analysis.

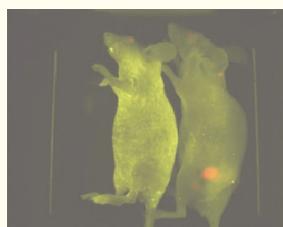


Nanotechnology Will Enhance Future Cancer Imaging



Nanotechnology has emerged as a key strategy for imaging telltale molecular features of cancer that are notoriously difficult to detect. One team of NCI-supported scientists is crafting a nano-sized construct to identify areas of new blood vessel growth, or angiogenesis, which is characteristic of growing tumors. The surface of this construct is designed to interact with specific molecular features indicative of angiogenesis, while the core contains thousands of atoms of a paramagnetic element. The paramagnetic properties allow the probes to be imaged by Magnetic Resonance Imaging (MRI). In addition, this core may contain other signal enhancing agents for improved *in vivo* detection. The use of such multi-modal probes permits highly sensitive imaging of specific molecular features of cancer, with excellent spatial resolution.

In vitro studies have shown that the same nanoprobe can be used for targeted drug delivery. This image shows a targeted nanoprobe in contact with a melanoma cell. The nanoprobe appears red against the green background of the cellular fluid. Evidence is mounting that such nanosystems can achieve a marked improvement in therapeutic effectiveness, as high concentrations of a drug are delivered to targeted cancer cells, while non-targeted cells are spared exposure to toxic concentrations.¹



Another NCI-supported team is investigating *in vivo* cancer imaging using nano-sized “quantum dots” – tiny crystals that glow when they are stimulated by ultraviolet light. This team has achieved sensitive, multicolor fluorescence imaging of cancer cells in mice using a quantum dots probe that preferentially binds to prostate cancer cells. In this *in vivo* image, the mouse on the left is tumor free. A human prostate tumor growing in the mouse on the right shows in fluorescent orange-red.

The structure of this imaging probe makes it well suited to carry diagnostic and therapeutic agents. However, researchers must carefully examine toxicity issues before testing this quantum dots application in people.

With focused investment in these and other nanotechnologies, NCI anticipates a future when nanodevices will be used to detect cancer at its earliest stages, pinpoint its location within the body, deliver anti-cancer drugs specifically to malignant cells, and monitor drug effectiveness.

¹ Image provided by Gregory M. Lanza of Washington University.

² Image published in *Nature Biotechnology*, August 2004, page 972. A special thanks to authors Xiaohu Gao and Shuming Nie of Emory University and Georgia Institute of Technology, Yuanyuan Cui and Leland W. K. Chung of Emory University, and Richard M. Levenson of Cambridge Research & Instrumentation, Inc.

Alliance for Nanotechnology in Cancer

Targeting and Modifying Biological Responses at the Subcellular Level

Nanotechnology offers an unprecedented and paradigm changing opportunity to study and interact with normal and cancer cells at molecular and cellular scales, in real time and during the earliest stages of the cancer process. Nanotechnology will enhance cancer diagnosis and treatment in numerous ways. Imaging agents and diagnostics will allow clinicians to detect cancer in its earliest, most treatable, pre-symptomatic stage. Nanosystems will provide real-time assessments of therapeutic and surgical efficacy for accelerating clinical translation. Multifunctional, targeted devices capable of bypassing biological barriers will deliver multiple therapeutic agents at high local concentrations – and 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. Nanoscale agents will be capable of monitoring predictive molecular changes and preventing precancerous cells from becoming malignant. Novel methods will aid in the management of symptoms of cancer that adversely impact quality of life. And research tools will enable investigators to quickly identify new targets for clinical development and predict drug resistance.

To support and coordinate the cancer nanotechnology programs, NCI has established the Alliance for Nanotechnology in Cancer⁵ to unite a broad array of programs to maximize the technology outputs. Our nanotechnology plans place a premium on supporting cross-disciplinary teams that partner with existing NCI-supported efforts and with the private sector. With adequate resources in Fiscal Year 2006, we will continue to build the programs of the Alliance. We will:

- Support 3-5 Centers of Cancer Nanotechnology Excellence (CCNEs) to serve as hubs for the development and application of nanotechnology and nanoscience solutions to the diagnosis and treatment of cancer.
- Encourage development of multidisciplinary nanotechnology research teams and support the career development of individual investigators who will become future team leaders.
- Support individual projects in cancer nanotechnology platforms for diagnosis, treatment, and prevention.

¹ cabig.nci.nih.gov

² spores.nci.nih.gov, cancer.gov/cancercenters, ccr.cancer.gov

³ cancer.gov/bip/sairp.htm, cancer.gov/bip/ntroi.htm, cancer.gov/dip/DCID_des.htm

⁴ emice.nci.nih.gov

⁵ nano.cancer.gov

Advanced Technologies Budget Increase Request for Fiscal Year 2006

Building bioinformatics infrastructure and tools	\$12.75 M
The cancer Biomedical Informatics Grid (caBIG) Support to NCI clinical trials & community participation	
Developing & applying advanced imaging technologies	18.00 M
Publicly available image archives Image-guided intervention research Correlative imaging studies in NCI clinical trials Nanotechnology for contrast agents Nanoscale devices to address cancer cell diversity	
Supporting a proteomic technologies initiative	50.00 M
Consortia for improving protein detection platforms Protein measurements database Advanced computer software for project data analysis Improvement of mass spectroscopy & antibody detection methods	
Building the Alliance for Nanotechnology in Cancer	40.00 M
Centers for Cancer Nanotechnology Excellence Multidisciplinary nanotechnology research teams Individual projects for diagnosis, treatment, and prevention	
Management & Support	2.05 M
Total	\$122.80 M

The National Advanced Technologies Initiative for Cancer

Harnessing the Power of Advanced Technologies to Eliminate the Suffering and Death Due to Cancer



Although cancer is being unraveled rapidly at the gene, protein, and even the “nano” levels by the largest group of researchers ever to investigate a specific disease, we have not concomitantly created the technology development resources and the seamless system needed to capitalize on their discoveries.

Urgent Need – Unique Opportunity

We need to assemble interdisciplinary teams and create innovative mechanisms that enable the exchange of ideas and materials in ways that maintain incentives for the commercialization and delivery of these new cancer technologies. **On a national scale, we need public-private coordination aimed at delivering advanced technologies through an integrated pipeline of cancer diagnostics and therapeutics development.**

When the National Cancer Act was signed in 1971, our Nation began a journey to defeat cancer. Unfortunately, one person in this country still dies from cancer each minute of every hour of every day.

NCI’s current Cancer Center infrastructure is well established and already plays a central role in the development, transfer, and commercialization of advanced technologies. The discovery and early development of drugs such as Gleevec™, a molecularly targeted drug for chronic myelogenous leukemia, have taken place in these Centers. Cancer Centers have also been pivotal in establishing relationships with state and regional biotechnology programs and are logical connection points for leveraging resources with private companies and other collaborating entities to accelerate the development of advanced cancer technologies. NCI has already taken steps to achieve paradigm shifting advances through the launch of the cancer Bioinformatics Grid (caBIG), an unprecedented platform to be available to the entire cancer research community. We have also undertaken early efforts in areas such as biomarkers and nanotechnology. (See pages 32-39.) **However, without an initiative such as the one described below, it will likely take decades for these technologies to reach patients.**

Proposed Initiative

The National Advanced Technology Initiative for Cancer (NATIC) will provide the research and development community with the necessary infrastructure to harness the Nation’s biomedical technology resources and capabilities and speed product development. This effort will capitalize on discoveries from basic research and leverage existing technology development capabilities nationwide. Through a virtual network of regional “hubs,” the most innovative biomedical scientists, clinicians, physical scientists, mathematicians, engineers, and others will be linked in cutting-edge collaborations for technology development. Partnerships among academic and research institutes, the biotechnology and pharmaceutical industries, and government agencies will integrate and coordinate translational application and commercialization and help bridge the gap between discovery and delivery.

A central coordinating unit will be established to provide core services and integrative technologies to the regional hubs. Specialized technology “nodes” will focus on specific areas of research and development at cancer and academic medical centers, state and regional innovation and biotechnology centers, and start-up and other private sector companies. Examples of specialty areas that will benefit from integration and coordination are bioinformatics and advanced computing; advanced imaging; drug discovery and high-throughput screening; proteomics, biomarkers, and diagnostic platforms; computational and systems biology; nanotechnology; high-throughput genomics sequencing; biopharmaceutical development and scale-up; biosensors and model systems engineering; and bioengineering and advanced prototype facilities.

Anticipated Outcomes

The advanced healthcare technologies that derive from this initiative will provide the Nation with a unique resource to not only help NCI achieve its goal but also support research advances in other diseases and ultimately accelerate the realization of personalized medicine. With the launch of this integrative approach, we anticipate dramatic acceleration in several of the strategic investment areas described in this document.

- Biomarker studies will be completed more quickly, revealing protein patterns and other molecular changes in saliva, sera, urine, or biopsy tissue that indicate the presence of precancerous lesions or malignant tumors.
- New nanotechnology platforms will more quickly allow for the earlier use of biomarker information in diagnosing cancer through a single drop of blood.
- Innovations in cancer imaging will move the field more rapidly beyond anatomical imaging to methods that detect and monitor the molecular features of cancer. Technological advances will speed the availability of new devices and agents for the real-time monitoring of genetic and other cancer-associated changes.
- Novel approaches built through NATIc collaborations will enable clinicians to optimize the use of targeted diagnostics, therapies, and preventives to preempt cancer at its earliest stages and deliver the right treatment to each patient.
- Common bioinformatics platforms and tools provided through a virtual network will support data sharing and allow cross-disciplinary teams to work synergistically to develop and deliver advanced cancer technologies. A “smartcard” for storing electronic medical records and making them available to clinical trial participants and their caregivers for follow-up care is one of the many innovations envisioned by this initiative.

Required Resources

The NCI Fiscal Year 2006 budget increase request for Advanced Technologies is summarized on page 39. We propose to support the NATIc separately, at a total cost of \$2.5 billion over five years, through three funding sources: (1) special appropriations from Congress totaling \$1.5 billion over the five-year period, (2) redeployment of \$500 million of NCI's annual appropriations over five years, and (3) \$500 million in philanthropic contributions.

Strategic Investments in **Integrative Cancer Biology**

Our Goal Understand the complex networks within cancer cells and between cancer cells and their environment to discover new leads for cancer prevention, detection, diagnosis, and treatment.

Integrative cancer biology is the study of cancer as a complex biological system. Researchers in this field seek to understand the dynamic and spatial interactions that exist among molecules in a cell, among cells, between cells and their “microenvironment,” and between the organism and its “macroenvironment.” These interactions are potential targets for new and more rationally designed interventions to prevent, detect, diagnose, and treat cancer. Our integrative cancer biology initiatives focus on creating computational models of the complex networks within and among cancer cells, building our understanding of the tumor microenvironment, and studying the role of the tumor macroenvironment in cancer development. To carry out these initiatives, cancer biologists will depend heavily on a multidisciplinary approach. Expertise in the computational sciences and collaborations with scientists in other fields that study complex systems will be essential. Researchers will also need animal models that mimic the development of cancer in humans and powerful new tools for imaging molecular interactions, integrating large datasets, and validating computational models.

Developing Computational Models of Cancer

With increased resources in Fiscal Year 2006, NCI will expand efforts to build models of the complex networks within and among cancer cells. Scientists know that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell and its surrounding microenvironment also change. Genetic mutations in an evolving cancer cell result in proteins that do not function correctly. These dysfunctional proteins disrupt the intricately balanced molecular communication networks of the cell. Using data derived from research on the tumor micro- and macroenvironments, scientists will create computational models of these complex networks to help develop new ways to preempt the development and progression of cancer. New NCI-supported Integrative Cancer Biology Programs (ICBPs)¹ have already begun the development of reliably predictive computational models of cancer initiation, promotion, and progression; the integration of experimental and computational approaches for understanding cancer biology; and the support of integrative cancer biology as a distinct field. To further the development of computational models, we hope to:

- Increase the number of ICBPs.
- Fund collaborations with the ICBPs to enable the research community to apply the approaches of integrative biology.
- Establish programs in integrative cancer biology to train interdisciplinary scientists to build, characterize, and validate computational models.
- Provide additional funding for the Mouse Models of Human Cancers Consortium² to (a) accelerate the pace at which accurate, reproducible mouse models of human cancers are made available, and (b) define the process for using these mouse models to validate computational models of complex cellular networks and to evaluate targeted therapeutics.

- Expand the imaging acquisition and integration capabilities of the Integrative Cancer Biology Programs and the Mouse Models of Human Cancers Consortium to develop (a) novel cancer imaging agents, nanoparticles, and technologies for use in cells and small animal cancer models, and (b) methods for effectively integrating imaging data with genetic, molecular, and cellular data.
- Expand the intramural Molecular Targets Development Program³ to accelerate discovery of compounds that can serve as bioprobes for functional genomics, proteomics, and molecular target validation research as well as leads or candidates for drug development.

Understanding the Tumor Microenvironment

In Fiscal Year 2006, NCI will also extend efforts to understand the tumor microenvironment, which is the local and systemic architecture surrounding a cancer cell. The microenvironment includes other cells; growth factors; enzymes; and parts of the blood, lymphatic, and immune systems. Dynamic interactions between the cancer cell and its microenvironment can contribute to some of the most destructive characteristics of cancer, including metastasis. The microenvironment can also influence the access of therapeutic agents to cancer cells, the body's processing of treatment agents, and the development of resistance to cancer treatments. Therefore, research to understand the tumor microenvironment more fully may provide additional targets for preempting cancer and better methods for treating it. This research will characterize molecular signatures of cells in the tumor microenvironment as well as the dynamic communication among these cells; interactions between cells and factors in the macroenvironment that predispose individuals to cancer; and interaction between the immune system and the cancer cell during cancer initiation, promotion, and progression. The latter interaction will establish the roles of both the innate inflammatory responses and adaptive immune responses in promoting and controlling tumor formation.

Computational Modeling Has Multiple Applications for Cancer

Computational modeling is a central feature of integrative cancer biology studies aimed at generating predictive and testable models of cancer. Computational biologists are developing computer programs that use complex, interactive calculations to analyze massive amounts of data about cancer cells and their micro- and macroenvironments. These modeling programs use combinations of simple statistical tests, data mining applications, and higher-order mathematical equations. They are similar to those used by meteorologists to help predict the weather, by economists to predict future trends, and by engineers to design complex modern aircraft. Molecular scale models are being designed, for example, to describe the folding patterns¹ of critical cancer proteins. Computational models also might be used to study the response of a cancer patient's immune system to a developing tumor. Researchers anticipate that computational models for cancer, once refined and validated, will not only yield insights and knowledge about cancer, but will also be used to help diagnose cancer patients and to plan and monitor treatment strategies.

¹ In protein synthesis, a series of amino acids are sequentially attached to one another to form a long chain. This linear chain then folds upon itself to form a protein with the correct shape to perform its particular function in the cell.

Understanding the Biology of Aging and Cancer



Courtesy of the National Institute on Aging

Older patients differ from younger cancer patients in susceptibility to disease progression and response to treatment. The underlying mechanisms of cancer and aging overlap in the study of tumor initiation, progression, and maintenance. NCI and the National Institute on Aging (NIA) have partnered to invigorate the research community's interest on the intersection of aging and cancer. Studies on the biology of aging and cancer are fundamental to this endeavor. Researchers supported by the NCI/NIA partnership will broaden studies of genetics, molecular signatures, age-related changes that contribute to mortality, and vulnerability versus resilience in older patients. The work will include studies in human biology that reveal which aspects of tumor biology and tumor growth vary by age. Teams of researchers will investigate:

- Genetic change, environmental influences, and host factors such as oxidant stress and cell death that may alter tumor progression in the aging patient
- The interaction of normal aging cells and cancer cells within the tumor microenvironment
- Differences in manifestation of cancer types in older and younger patients
- Cellular and molecular characteristics that distinguish between those patients who could benefit from aggressive therapy and those who could be spared further therapy
- Molecular alterations in carcinogenesis that are related to aging cells
- The potential short- and long-term medical effects induced by treatment, such as susceptibility of the older patient to multiple primary tumors, anti-tumor drug alterations, and cancer recurrence
- The human biology of cancer and aging that reveal which aspects of tumor biology and tumor growth vary by age

This research will also provide necessary data for development of the computational models of interactions between the tumor and its microenvironment. To extend our understanding of the tumor microenvironment, we will:

- Establish a multidisciplinary alliance of researchers, engineers, and bioinformatics experts to:
 - Create technical resources that will facilitate the visualization of stromal components at the molecular and cellular levels and the establishment of a repository of normal stromal cells and matrix molecules.
 - Investigate the normal and malignant tissue microenvironments, identify their molecular signatures, and identify the origin of the cells and factors that comprise the tumor stem cell and the tumor microenvironment.

- Fund grant supplements to train investigators to use organotypic culture systems that accurately model the interaction between the cancer cell and the microenvironment and make these systems readily accessible to the research community.
- Support the development of strategies for investigating, manipulating, and monitoring/imaging *in vivo* human immune responses to cancer.
- Support studies to clarify the underlying biological relationship between anti-tumor immune responses and autoimmune responses to normal cells/tissues in humans undergoing cancer immunotherapy.
- Expand the availability of resources to academic laboratories for small molecule and biologics development through the Rapid Access to NCI Discovery Resources (R*A*N*D) program.⁴

Defining the Role of the Tumor Macroenvironment

In addition to seeking to understand the interactions among molecules in a cell, among cells, and between cells and their microenvironment, integrative cancer biology also addresses the role of the tumor macroenvironment. This includes the poorly understood effects of an individual's exposure to various elements in the environment such as unhealthy air and water and the influence of lifestyle factors such as diet, obesity, physical activity, and tobacco use. Research on the tumor macroenvironment also includes studies of certain microbial agents that are known to be closely associated with the etiology of some cancers (e.g., HPV with cervical cancer; HBV and HCV with liver cancer; EBV with breast cancer; helicobacter with stomach cancer). The mechanism by which these agents increase risks for cancer is not firmly established, and scientists continue to explore the extent to which other known or unknown viruses or microbes may impact cancer development and progression. Research on these topics will be critical to developing new interventions and tools for preventing, detecting, diagnosing, and treating cancer. With sufficient resources in Fiscal Year 2006, we will:

- Establish collaborative research groups to explore, characterize, and validate associations of known cancer viruses with cancers not previously linked to these viruses (e.g., study the role of human papillomaviruses in squamous cell esophageal and non-melanoma skin cancers). Characterize the role of microbial agents in the etiology of human cancers such as leukemia, lung cancer, and non-Hodgkin's lymphoma.
- Support studies of the role of microbial agents in tumor development by investigating (a) viral latency and reactivation, (b) the microbial flora of stromal cells, and (c) the anti-microbial inflammatory response. Included will be studies on immunosuppressed individuals with cancer and studies on the immune response to HPV.

- Support investigations into the role of co-carcinogenic agents (biological and chemical) in cancer initiation, promotion, and progression. Include investigations of the contribution of inflammation, injury, and specific mutations to lung carcinogenesis.
- Support investigations of the relationship between autoimmune diseases and the risk of cancer.
- Support studies to assess the effects of anti-inflammatory agents on cancers associated with microbial etiology.
- Continue to develop the vaccine program at NCI to target infectious agents that initiate and promote cancer.
- Support studies to identify and evaluate agents that will prevent or ameliorate cancer-causing radiological injury.

Integrative Cancer Biology Budget Increase Request for Fiscal Year 2006

Developing computational models	\$24.00 M
Integrative Cancer Biology Programs	
Training	
Mouse models for validation	
Innovative technologies for use in cells & animal models	
Bioprobes and candidates for drug development	
Understanding the tumor microenvironment	16.50 M
Cross-disciplinary research alliance	
Training in using organotypic culture systems	
Studies on immune responses to cancer	
Resources for the development of small molecules & biologics	
Studying the tumor macroenvironment	24.00 M
Collaborative research groups studying cancer viruses & microbial agents	
Studies of biological and chemical co-carcinogenic agents	
Studies of autoimmune diseases & cancer risk	
Effects of anti-inflammatory agents on cancer	
Vaccine development	
Studies to prevent/ameliorate radiological injury	
Management & Support	1.10 M
Total	\$65.60 M

¹ dcb.nci.nih.gov/branchdetail.cfm?branch=1

² emice.nci.nih.gov

³ home.ncifcrf.gov/mtdp

⁴ dtp.nci.nih.gov/docs/rand/rand_index.html

Highly Lethal Cancers – Changing the Statistics

In 2004, about 31,860 people in the United States will be diagnosed with pancreatic cancer. There will be about 14,250 new cases of esophageal cancer, and an expected 18,920 people will be told they have liver cancer. These are highly lethal diseases. About 15 percent of Whites and 8 percent of African Americans diagnosed with esophageal cancer are expected to survive five years. The five-year survival rate for patients newly diagnosed with pancreatic cancer is estimated at just 4 percent. For liver cancer, it is 7 percent. If we are to reach our challenge goal to eliminate the suffering and death due to cancer, we must invest in research and development that will change these statistics.

Epidemiologists have already identified several risk factors in common for these three cancers. For example, people who develop these cancers often have a history of chronic inflammation. Tobacco use, alcohol use, and obesity are also prevalent among people with these cancers. Large population studies are needed to draw valid statistical conclusions about the roles of genetic, environmental, and lifestyle factors in the initiation and progression of these diseases.

One challenge is that the relative rarity and high lethality of pancreatic, esophageal, and liver cancers make it difficult to conduct these large studies. It is not unusual, for example, for population studies of breast or prostate cancer to enroll tens of thousands of participants. In contrast, the relatively low numbers of patients with highly lethal cancers demand significant cooperation and coordination to assemble enough patients to conduct even one study. NCI is proposing to address this obstacle by developing a consortium of investigators to conduct epidemiological studies of highly lethal cancers.

This consortium approach will pool the resources of multiple institutions. Through the collection, storage, management, and sharing of data for a large numbers of cases, investigators will be able to amass enough knowledge to evaluate the possible combinations of genetic, environmental, and lifestyle factors – from molecular to behavioral – that are causing these cancers. This unparalleled collection of data will provide an ideal resource for exploring new hypotheses emerging from basic and clinical research, and provide hope for those individuals who suffer from highly lethal cancer.



Strategic Investments in **Molecular Epidemiology**

Our Goal Understand the behavioral, environmental, genetic, and epigenetic causes of the vast majority of cancers in the human population in order to generate new means of prevention, detection, and treatment.

Cancer is a complex disease that develops when the genes that regulate such functions as cell growth, cell death, and signal response are impaired. This impairment can occur through either genetic or epigenetic pathways. Genetic errors are caused by structural changes in the DNA of a person's genes, whereas epigenetic transformation refers to those processes which cause normal cells to become tumor cells without the occurrence of any mutations affecting DNA or other genetic machinery. Some of these genetic and/or epigenetic errors are inherited. Others result from certain environmental exposures or individual behaviors such as energy balance status; tobacco and alcohol use; exposure to ionizing, solar, and other radiation; viruses and other infectious agents; imbalances in hormones and metabolic processes; and exposure to chemicals in the occupational and general environment. It is important to understand the roles of both inherited susceptibility and lifestyle or environmental risk factors for cancer. Furthermore, we need to uncover the interactions among genetic and environmental risk factors, harnessing the statistical power of bioinformatics and taking advantage of the emerging insights from integrative biology.

NCI is developing novel ways to unravel the complexities of inherited and environmental contributions to cancer. We are supporting individual efforts as well as large collaborative programs to maximize the sharing of population data, biospecimens, laboratory models, and *in vitro* observations. In particular, large-scale studies with heightened levels of interdisciplinary cooperation and innovation are encouraged. Future investments will help scientists uncover environmental risk factors, identify genetically susceptible individuals, develop appropriate interventions and precautions for people at high risk, and generate new individual and public health strategies to avoid or mitigate adverse exposures. This expanded information will enable NCI to develop more effective approaches for the prediction, prevention, early detection, and treatment of cancer in all population groups.

Expanding Our Understanding of Specific Cancers

With increased resources in Fiscal Year 2006, we will expand efforts to understand specific types of cancer through consortia of cohort and case-control studies and consortia of cancer-prone families that integrate genomics, epigenomics, proteomics, and other emerging technologies into epidemiologic studies. We will:

- Initiate large-scale studies of highly lethal cancers (e.g., cancers of the pancreas, liver, and esophagus).
- Continue to conduct and analyze consortial studies of breast and prostate cancer and non-Hodgkin's lymphoma and initiate consortial studies of ovarian and brain cancers.
- Expand existing international consortia for family-based studies (e.g., melanoma, leukemia, lymphoma, and testicular, colon, breast, prostate, and pancreatic cancers) and initiate family-based consortia for other cancers, in order to identify genetic determinants.

- Expand the number of participants, population diversity, and types of biospecimens (including tumor specimens) in these consortia.
- Develop innovative review and reward processes that foster large-scale consortial research.

Expanding Studies of Behavioral and Environmental Risk Factors

We will also use new resources to expand studies on the influence of behavioral and environmental factors on the risk of cancer induction and progression, utilizing genetic and molecular probes, including studies in populations with exceptional or changing cancer rates or unusual environmental exposures. International studies and investigations of populations in transition, including migrant populations, provide particular opportunities for identifying biomarkers of carcinogenic exposure, genetic susceptibility, precursor states, and mechanisms of cancer causation. Special emphasis will be given to studies of specific behavioral factors (e.g., tobacco and alcohol use, energy balance) and their relation to cancer risk. In Fiscal Year 2006, we will:

- Fund and conduct etiologic studies targeted to U.S. minority groups, including Hispanic and African American populations.
- Initiate and fund studies of populations in transition, such as populations in Asia and migrant populations in the United States.
- Incorporate instruments to collect enhanced behavioral information on dietary and environmental exposures in case-control and cohort studies.
- Conduct population-based studies of cancer risk associated with tobacco and other products, including studies that explore molecular damage in former smokers.

Integrating Population Science with Genomics and Other Technologies

We are now in a position to greatly expand the knowledge base of cancer risk factors and biologic mechanisms through the convergence of epidemiologic and molecular approaches and the integration of population science with genomics and other emerging technologies. Research in this area has begun to yield important insights into a fundamental understanding of cancer causation, including the role of environmental and genetic determinants and their interactions. With sufficient resources in Fiscal Year 2006, we will establish a much needed, regional network of high-throughput laboratories for existing and emerging biomarkers of cancer risk. The network will provide the support for the genomic, molecular, and biochemical components of the molecular epidemiology consortia. We will:

- Build a network of high-throughput genotyping laboratories that incorporate advances in genomic technology into large-scale population studies.
- Initiate programs to implement public health measures and educational activities based on emerging genomic, epigenomic, and proteomic technologies.

Partnering to Leverage Resources

Partnerships with clinical oncology groups will allow us to leverage research resources and integrate clinical, laboratory, and population sciences. We will:

- Expand the program of surveillance and research into second primary cancers and recurrence to determine risk factors, such as the role of therapy and genetic susceptibility mechanisms, including DNA repair.
- Conduct collaborative studies of etiology and natural history with the Gynecologic Oncology and Children's Oncology Groups conducting clinical trials.
- Provide supplemental funds to Cancer Centers to develop molecular epidemiology capabilities, especially for hospital-based case-control studies of highly lethal cancers.

Molecular Epidemiology

Budget Increase Request for Fiscal Year 2006

Expanding understanding of specific cancers	\$35.25 M
<ul style="list-style-type: none"> Large-scale studies of highly lethal cancers Disease-specific consortial studies International consortia for family studies Expansion and incentives for consortial research 	
Expanding studies of risk factors	9.50 M
<ul style="list-style-type: none"> U.S. minority groups Populations in transition Lifestyle & environmental exposures 	
Integrating population science with emerging technologies	6.00 M
<ul style="list-style-type: none"> Network of high-throughput genotyping laboratories Public health & education programs 	
Partnering to leverage research resources	7.50 M
<ul style="list-style-type: none"> Research on second primary cancers & recurrence Collaborative studies with the Gynecologic & Children's Oncology Groups Supplemental funds to Cancer Centers 	
Stimulating training & interdisciplinary research	1.40 M
<ul style="list-style-type: none"> Joint training programs with medical & public health schools Interdisciplinary training & research awards 	
Management & Support	\$1.02 M
Total	\$60.67 M

- Develop population studies to identify genetic factors that affect tumor progression, prognosis, therapeutic outcomes, and side effects (e.g., pharmacogenomics).

Stimulating Cross Training and Interdisciplinary Science

Finally, initiatives to stimulate cross training and interdisciplinary and multidisciplinary research opportunities will provide a pool of investigators poised to advance the new and integrated objectives in molecular epidemiology. We will use new resources to:

- Work with medical and public health schools to develop joint training programs and new curricula in genetic and molecular epidemiology.
- Initiate new training awards for predoctoral students in interdisciplinary and multidisciplinary research relevant to molecular epidemiology.
- Initiate new interdisciplinary and multidisciplinary research awards in molecular epidemiology.

Strategic Partnerships Advance Studies in Molecular Epidemiology

Epidemiology has been depicted as a scientific approach that moves slowly but with great force. By incorporating powerful new tools generated by recent advances in genomics and molecular sciences, however, we have an unparalleled opportunity to move more quickly and with greater impact than ever before. Poised to accelerate knowledge about the genetic and environmental components of cancer initiation and progression, our investments in Molecular Epidemiology will help identify new preventive, diagnostic, and therapeutic interventions.

Cultivating strategic partnerships that link epidemiologists with one another and with genomicists and other investigators from the clinical, basic, and population sciences is integral to these investments. This transdisciplinary team-based approach responds to a growing consensus in the scientific community that the full potential of genomic and other emerging technologies will require large-scale epidemiologic studies. Study designs must have the efficiency and power to identify, from questionnaires and biospecimen collections, common low-penetrant susceptibility genes and their interactions with exogenous or endogenous exposures. This can be accomplished through consortia that combine the resources of several cohort and/or case-control studies in a coordinated approach that enables rapid replication of positive findings using independent datasets. This strategy avoids the cumbersome and expensive trial-and-error process that often occurs when false-positive findings from individual studies appear in the literature. When reproducible findings emerge in the consortia, pooling of datasets provides the statistical power to quantify the risks associated with specific gene variants and exposures and to enable subset analyses that uncover gene-gene and gene-environment interactions.

One such partnership is the *Consortium of Cohorts*, an international collaboration of investigators responsible for 23 independently funded population cohorts involving 1.2 million individuals. Each cohort will characterize thousands of individuals who have developed cancer with extensive information on known or suspected risk factors and biospecimens (including germline DNA) collected prior to diagnosis. This consortium provides an integrative framework for nested case-control studies of specific cancers arising within the cohorts and opportunities to systematically evaluate molecular and biochemical biomarkers of susceptibility and early-stage disease.

Other types of strategic partnerships are under development, including international *case-control consortia* of investigators responsible for population- or hospital-based studies of less common cancers that cannot be easily evaluated in cohort studies. In addition, several scientists interested in familial cancer have formed international *family-based consortia*. Current emphasis is on familial syndromes in which high penetrant genes have eluded discovery and on opportunities to identify genetic and environmental modifiers of inherited risk.

Many complex scientific, administrative, and cultural challenges are involved in developing these team-based transdisciplinary partnerships, which seemingly run counter to the traditional model of individual investigators or groups that work independently. The two strategies are really complementary and synergistic, however, and they are speeding the discovery of causal agents and pathways, early detection markers, and interventions designed to prevent and control cancer.

Delivering the Promise

NCI's Budget Increase Request Emphasizes Patient Care and Public Health

With a sizable portion of our increase request devoted to quality of care, survivorship, tobacco control, and energy balance issues, the seven strategic investment areas outlined in this document point to improved patient care and public health as our ultimate destination.

Improving the Quality of Cancer Care

Quality cancer care means evidence-based, patient centered care that is timely, technically competent, and administered with sound communication, shared decision making, and cultural sensitivity. NCI investments in Fiscal Year 2006 will support:

- Community-based interventions that address disparities in care and their potential to be replicated in a culturally appropriate manner.
- Training programs for creating a diverse and culturally sensitive research and care workforce.
- Collaborations to improve early detection, diagnosis, prognosis, treatment, and survivorship for people over 65.
- Collaborations for communicating risk, delivering evidence-based preventions, and evaluating prevention practices for improved patient outcomes.

Optimizing Health and Quality of Life after Cancer

For the nearly ten million Americans now living with a history of cancer, life after cancer means finding a new balance – one that celebrates the triumph and relief of completing treatment, recognizes changes or losses the disease has wrought, and assimilates revised perspectives, newfound strengths, and lingering uncertainties. NCI's Fiscal Year 2006 investments will include research and development to:

- Better understand and address survivorship issues in underserved populations.
- Reduce the long-term side effects of cancer treatment and improve symptom management.
- Include more quality-of-life endpoints within NCI-supported clinical trials.
- Track, store, and retrieve patient information needed by healthcare providers for follow-up care.
- Identify genetic factors that affect prognosis, tumor progression, therapeutic outcomes, and side effects.

Overcoming Cancer Health Disparities

While Overcoming Cancer Health Disparities is one of our strategic investment areas for 2006, it is also emphasized in conjunction with other priorities.

- Prevention, Early Detection, and Prediction investments include tobacco research and dissemination in low- and middle-income nations, studies to project the impact of cancer interventions in specific populations, and identification of markers of cancer risk and cancer progression in high risk populations.
- Proposed Clinical Trials Integration efforts include increasing access to and participation of minority and underserved people in cancer clinical trials.
- Molecular Epidemiology efforts investments will expand the diversity of participants in consortia studies and support etiologic studies of minority groups and populations in transition.

Understanding Tobacco Use and Tobacco-Related Cancers

Tobacco use is the leading preventable cause of illness and death in the United States. Cancers of the lung, oral cavity, pharynx, larynx, esophagus, pancreas, urinary bladder and renal pelvis have all been scientifically linked to tobacco use. Dramatically reducing and treating tobacco use and tobacco-related cancers across all ages and populations is critical to eliminating the suffering and death due to cancer. NCI investments in Fiscal 2006 will support:

- Tobacco use prevention and smoking cessation research that addresses underserved and understudied youth and young adults.
- Health behaviors research, including tobacco use, among medically underserved people who have survived cancer.
- A tobacco and health disparities research network.
- Research on effective State and community programmatic and policy interventions for tobacco control.
- International research on tobacco control, prevention, and dissemination to benefit low- and middle-income nations.
- Determination of the cancer risk potential of reduced-exposure tobacco products.
- Studies to identify cellular targets and screen and develop agents to help smokers quit and prevent cancers in former smokers.
- Population-based studies of cancer risk associated with tobacco, including molecular damage in former smokers.
- Large-scale studies of highly lethal cancers, several of which are tobacco related.
- A National Lung Screening Trial Image Library to optimize diagnostic programs.

Understanding and Promoting Energy Balance to Prevent Cancer

Compelling evidence suggests that excess body weight is a risk factor for many cancers. Body weight is determined by each individual's "energy balance," the complex interaction among diet, physical activity, and genetics over his or her lifetime. NCI's research goals include understanding the causes of adverse patterns of weight, physical activity, and diet; defining how these causes contribute to cancer; and applying this knowledge to prevent and control cancer. NCI investments in Fiscal Year 2006 will support:

- Multidisciplinary research on patterns of diet and exercise among cancer survivors and in underserved populations.
- Development of innovative approaches for prevention of obesity.
- Studies to identify the molecular mechanisms of bioactive food components as modifiers of cancer risk and tumor behavior.
- Studies to evaluate physiological changes influenced by dietary components in normal and cancerous processes.
- Development of new technologies for assessing energy intake and balance.
- Collection of behavioral information on dietary and environmental exposures in case-control and cohort population studies.

Our Strategic Investments Will Help Preempt Cancer at Every Stage

What we learn through continued studies in **Molecular Epidemiology** and **Integrative Cancer Biology** coupled with **Advanced Technologies** in bioinformatics, imaging, proteomics, and nanotechnology will provide the knowledge and tools to link research progress across all areas of strategic investment.

Metastatic Progression

An Integrated Clinical Trials System will streamline processes and speed delivery of new preventive agents, diagnostic approaches, and cancer treatments to all who need them.

Malignant Transformation

Strategic Development of Cancer Interventions will increase our capacity for delivering molecularly based diagnostics and treatment.

Cancer Initiation

Overcoming Cancer Health Disparities is essential at every juncture from basic discovery to intervention development to the collaborative delivery of public health programs and patient care.

Susceptibility & Pre-Cancerous Changes

Prevention, Early Detection, and Prediction initiatives will provide needed resources for making prevention our first line of defense against cancer and improving our ability to detect, diagnose, and treat cancer at its earliest stages.

At a Glance

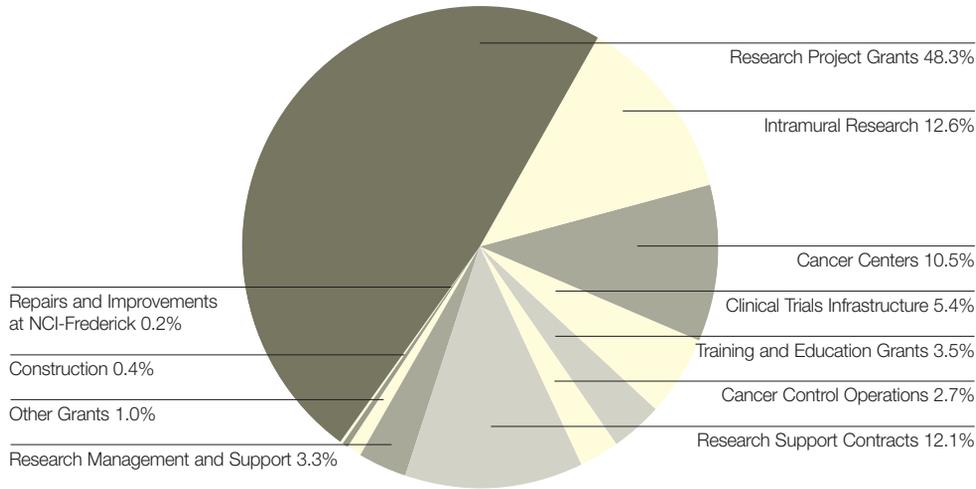
NCI's Budget Request for Fiscal Year 2006 (dollars in thousands)

Fiscal Year 2005 Congressional Justification Budget	\$4,870,025
Core Budget Increases (includes funding of RPGs, limited expansion of Cancer Centers and SPOREs, construction, maintenance, and personnel)	609,785
Strategic Investment Increases	
Cancer Prevention, Early Detection, and Prediction	112,120
Overcoming Cancer Health Disparities	39,150
Strategic Development of Cancer Interventions	119,000
An Integrated Clinical Trials System	170,850
Advanced Technologies	122,800
Integrative Cancer Biology	65,600
Molecular Epidemiology	60,670
Subtotal Strategic Investment Increases	690,190
Total Fiscal Year 2006 Budget Request*	\$6,170,000

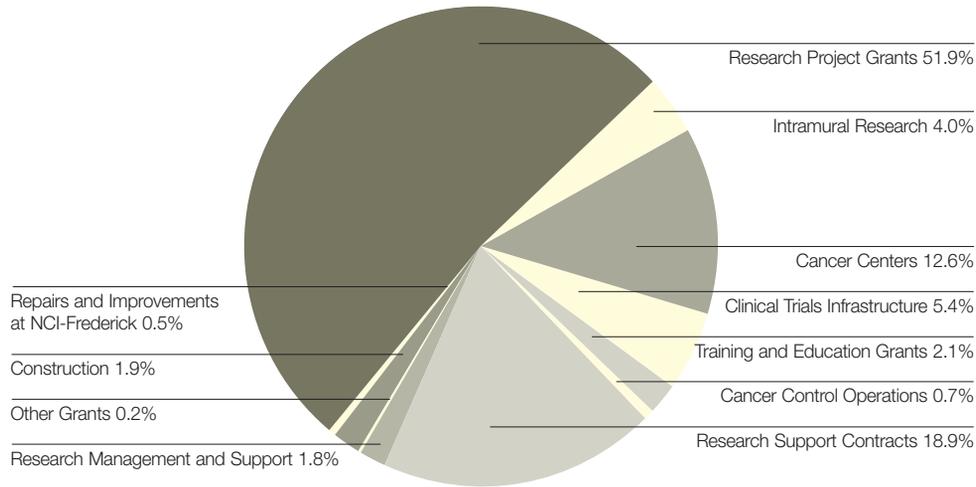
* In addition, a National Advanced Technology Initiative for cancer (NATIC) is described on pages 40-41, including the initiative's resource requirements.

The Nation's Investment in Cancer Research

Distribution of Fiscal Year 2006 Budget Request (\$6,170,000,000)



Distribution of Fiscal Year 2006 Requested Increases (\$1,299,975,000)



Research Project Grants

Funding for extramural research, primarily through Research Project Grants (RPGs), comprises the largest part of the NCI core budget. We fund about 4,500 RPGs each year to nearly 600 institutions across the United States at an average cost of approximately \$400,000 per grant.

Intramural Research

NCI intramural research focuses on projects conducted by some 400 researchers located on the NIH campus. Some of these investigators conduct long-term epidemiologic and genetics studies requiring the continuity of an intramural program. Others work synergistically with other NIH Institutes and with the NIH Clinical Center to quickly transfer laboratory research to the clinic.

Cancer Centers and Specialized Programs of Research Excellence (SPOREs)

Some 60 NCI-supported Cancer Centers serve as hubs for cutting-edge research, high quality cancer care, and outreach and education for healthcare providers and patients. Centers of Excellence like the SPOREs use flexible funding to pursue questions related to specific forms of cancer and to move disease-specific research quickly from the laboratory to the patient.

National Cancer Institute Budget Request for Fiscal Year 2006

(dollars in thousands)	2004 Operating Budget	2005 Congressional Justification	2006 Budget Request	
			2006 Increases	2006 Budget Request
Research Project Grants (RPGs)				
Ongoing	\$1,663,656	\$1,701,664	\$93,818	\$1,795,482
New and Renewal	492,369	501,682	554,163	1,055,845
Subtotal RPGs	2,156,025	2,203,346	647,981	2,851,327
Small Business Innovation Research (SBIR)	99,979	103,773	26,632	130,405
Total RPGs	2,256,004	2,307,119	674,613	2,981,732
Intramural Research	687,193	725,344	51,462	776,806
Cancer Centers				
Comprehensive/Clinical/Basic (P30)	250,022	244,710	69,564	314,274
Planning Grants	0	10,815	379	11,194
Specialized Center (U54)	26,088	46,272	40,120	86,392
Specialized Programs of Research Excellence (SPOREs)	185,387	178,902	54,262	233,164
Subtotal Cancer Centers	461,497	480,699	164,325	645,024
Clinical Trials Infrastructure				
Cooperative Clinical Research	153,882	167,330	36,957	204,287
Community Clinical Oncology Program (CCOPs)	95,424	98,118	32,934	131,052
Subtotal Clinical Trials Infrastructure	249,306	265,448	69,891	335,339
Training and Education Grants				
National Research Service Awards	66,480	70,860	8,480	79,340
Research Career Program	75,346	76,812	12,888	89,700
Cancer Education Program	31,769	32,006	5,120	37,126
Minority Biomedical Research Support	4,012	7,890	477	8,367
Subtotal Training and Education Grants	177,607	187,568	26,965	214,533
Cancer Control Operations	143,930	157,596	9,390	166,986
Research Support Contracts	538,607	504,335	245,152	749,487
Research Management and Support	165,581	177,224	23,993	201,217
Other Research Grants	52,473	56,692	2,184	58,876
Construction			25,000	25,000
Repairs and Improvements at NCI-Frederick		8,000	7,000	15,000
Total Budget Request	4,732,198	4,870,025	1,299,975	6,170,000
<i>Cancer Control included above*</i>	<i>521,487</i>	<i>544,890</i>	<i>135,776</i>	<i>680,666</i>

Clinical Trials Infrastructure

NCI supports clinical trials at the NIH clinical center and at close to 3,000 other sites across the U.S. Over 1,500 trials are conducted annually, involving more than 12,000 investigators assisting thousands of patients. These trials make possible the testing of targeted agents that hold promise for more effective, less invasive, cancer prevention and treatment and technologies that can be used for better detection and diagnosis.

Training and Education Grants

NCI funds training and education programs involving approximately 170 institutions and 2,000 individuals each year to prepare the next generation of scientists and clinicians to use new technologies and to work effectively in interdisciplinary, collaborative research environments. Increased funding will be used to support the development of interdisciplinary team science and to increase the number of scientists working with underserved populations.

Cancer Control*

NCI's cancer control operational funds along with numerous grants and contracts included throughout the budget are used to support research, communication, and other activities focused on ways to reduce cancer risk, incidence, morbidity, and mortality and improve the quality of life for all cancer patients. Increases will be used to support research on tobacco and tobacco-related cancers, reducing cancer-related health disparities, improving the quality of cancer care, cancer survivorship, cancer communications, and a host of information dissemination activities.

Requested Increases for Fiscal Year 2006

(dollars in thousands)	Core**	Strategic Investments	Total
Research Project Grants (RPGs)			
Ongoing	\$90,318	\$3,500	\$93,818
New and Renewal	263,013	291,150	554,163
	<hr/>		
Subtotal RPGs	353,331	294,650	647,981
Small Business Innovation Research (SBIR)	26,632		26,632
	<hr/>		
Total RPGs	379,963	294,650	674,613
Intramural Research	35,387	16,075	51,462
Cancer Centers			
Basic/Clinical/Comprehensive (P30)	63,564	6,000	69,564
Planning Grants	379		379
Specialized Center (U54)	1,620	38,500	40,120
Specialized Programs of Research Excellence (SPOREs)	38,262	16,000	54,262
	<hr/>		
Subtotal Cancer Centers	103,825	60,500	164,325
Clinical Trials Infrastructure			
Cooperative Clinical Research	5,857	31,100	36,957
Community Clinical Oncology Program (CCOPs)	3,434	29,500	32,934
	<hr/>		
Subtotal Clinical Trials Infrastructure	9,291	60,600	69,891
Training and Education Grants			
National Research Service Awards	2,480	6,000	8,480
Research Career Program	7,688	5,200	12,888
Cancer Education Program	1,120	4,000	5,120
Minority Biomedical Research Support	477		477
	<hr/>		
Subtotal Training and Education Grants	11,765	15,200	26,965
Cancer Control Operations	5,515	3,875	9,390
Research Support Contracts	17,652	227,500	245,152
Research Management and Support	12,203	11,790	23,993
Other Research Grants	2,184		2,184
Construction	25,000		25,000
Repairs and Improvements at NCI-Frederick	7,000		7,000
	<hr/>		
Total Increase Request	609,785	690,190	1,299,975

Research Support Contracts

Research support contracts are used for diverse programs across the Institute. These include drug development, cancer control research, information dissemination, and support to epidemiological research.

Research Management and Support

Research management and support funds are used for the critical technical and administrative services required for NCI to carry out its work. They cover the cost of central administrative functions, overall program direction, grant and contract review and administration, personnel, program coordination, and financial management.

Other Grants

Other grants support partnerships; shared resources; and scientific evaluation, workshops, and conferences.

** Core funds will be used for maintaining the FY 2005 program level of effort; funding 35% of competing RPGs at recommended levels and funding non-competing RPGs at committed levels; limited expansion for Cancer Centers, SPOREs, the Research Career Program, Construction, and Repairs and Improvements at NCI-Frederick; and funds for an additional 100 full-time-equivalent staff members.

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For Cancer Information

National Cancer Institute cancer.gov
NCI Cancer Information Service cis.nci.nih.gov
Cancer News newscenter.cancer.gov
Cancer Science newscenter.cancer.gov/sciencebehind
Progress Report progressreport.cancer.gov
Mortality Maps and Graphs www.cancer.gov/atlasplus
Surveillance, Epidemiology, and End Results seer.cancer.gov
NCI Annual Report cancer.gov/aboutnci/annualreport
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ccr.cancer.gov/tci/imaging.asp
Developmental Therapeutics Program dtp.nci.nih.gov
Intramural Resources ccr.cancer.gov/initiatives
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Cancer Research Funding
Funding Opportunities cancer.gov/researchfunding
Initiatives by Type of Research cri.cancer.gov

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Specialized Programs of Research Excellence spores.nci.nih.gov
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cancer.gov/prevention/cbrg/edrn
Cancer Family Registries epi.grants.cancer.gov/CFR
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Mouse Models of Human Cancers Consortium emice.nci.nih.gov
Training Opportunities
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Cancer and Public Health
Health Disparities crchd.nci.nih.gov
Survivorship Research dccps.cancer.gov/ocs
Tobacco Research dccps.cancer.gov/tcrb
Quality of Care appliedresearch.cancer.gov
Health Communications dccps.cancer.gov/hcirb

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Each year, as mandated by the National Cancer Act of 1971 (P.L. 92-218), the National Cancer Institute (NCI) prepares a plan for building on research successes, supporting the cancer research workforce with the technologies and resources it needs, and ensuring that research discoveries are applied to improve human health. This annual plan and budget proposal is provided directly to the President of the United States for formulating the budget request to Congress. This document is also used by NCI staff; the researcher community; professional organizations; advisory groups; cancer information, education, and advocacy organizations; and public and private policy makers. It is our hope that this document will inspire all who read it to join the fight against cancer.



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