

The Nation's Investment in



Cancer Research

A Plan and
Budget Proposal
for Fiscal Year
2005

Prepared by
the Director
National Cancer
Institute

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

Our Challenge Goal to the Nation

Eliminate the suffering and death
due to cancer by 2015.

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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.

Director's Message

Several months ago, I attended a town hall meeting of the President's Cancer Panel, where I had the good fortune to meet a brave little boy named Dakoda. He had recently been diagnosed with an inoperable brain tumor. Due to start chemotherapy later that night, he came to the meeting with his father, mother, and younger sister. His father, in a voice trembling with emotion, described the challenges of his son's illness and emphasized the progress he was making in his treatment. He also talked about the family's commitment to defeating Dakoda's cancer and encouraged those of us at the meeting that day to rededicate our efforts to develop new and more effective cancer therapies. Dakoda's story embodies universal themes of courage, commitment, and inspiration. Such stories — of the suffering that patients and their families endure on a daily basis because of this disease — remind us of the great value of cancer research and reinforce our determination to achieve our goal of eliminating the suffering and death due to cancer.

In 1971 — with the passage of the National Cancer Act — we committed our national will and resources to eliminating cancer. A cure for this complex set of diseases has proven far more elusive than anticipated thirty-three years ago. Yet our persistence and patience have led to increasingly significant dividends. There are now nearly ten million cancer survivors in the United States compared to three million in 1971. Death rates from the four most common cancers — lung, breast, prostate, and colorectal — continue to decline. Over the past decade, Americans have experienced a 7 percent decline in mortality from cancer and hundreds of thousands of lives have been saved. As this document illustrates, we are making extraordinary progress in cancer research. This progress has opened new avenues to even greater opportunities that will enable us to reach our goal of eliminating the suffering and death due to cancer.

To achieve this goal, we must continue to nurture the investment in infrastructure and intellectual capital that we began over three decades ago. The passage of the National Cancer Act challenged our Nation in 1971 and motivated many of our Nation's best and brightest to devote their professional lives to the study of cancer in all its formidable complexity. Only during the past decade have we amassed sufficient understanding of cancer's genetic, molecular, and cellular puzzle to elucidate the mechanisms responsible for its initiation and progression. We are now engaged in the development of extraordinary interventions directed at the specific processes governed by those mechanisms. We have at last entered into an exponential phase of progress in which scientific research, fueled by previously unimagined technologies, permits us to envision a future when people can live with, and not die from, cancer. While we may not cure cancer in the short term, we will develop the knowledge and tools to preempt its progression and thereby, effectively reduce its burden on our society. Using this strategy, we can and will prevent, detect, eliminate, and control individual cancers, and we must work together to accomplish this by 2015.

In this professional judgment budget, we at the National Cancer Institute highlight our vision for progress on the road ahead. The National Cancer Act of 1971 started us on this journey — and we must build on that momentum to persevere, to rapidly accelerate our pace, and to reach new heights of progress. Dakota and his family, like all the families of America, are depending on the National Cancer Institute — and the entire cancer research community — to eliminate the suffering and death due to cancer by 2015. We will not fail!

A handwritten signature in black ink, reading "Andrew C. von Eschenbach". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

Andrew C. von Eschenbach
Director
National Cancer Institute
October 2003

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Executive Summary

In 2001, the National Cancer Institute (NCI) issued the nationwide cancer community this Challenge Goal: To eliminate the suffering and death due to cancer by 2015. Never before have so many scientific tools and technologies and so much biomedical knowledge been assembled to power our ability to reach our Challenge Goal. We are experiencing exponential growth in our knowledge of cancer, growth fueled by historically high levels of funding, scientific expertise, infrastructure, and enabling technologies. With a sharp focus on our goal and continued budgetary support, we can harness advances in discovery and development research to deliver interventions for preventing cancer; detecting it early; and slowing, stopping, or reversing its progression to a lethal phenotype.

Our success will depend on our ability to integrate our activities, from the discovery of new scientific knowledge, to the development of new interventions, to the delivery of evidence-based interventions for all who need them. We must work to remove the major barriers that impede progress and ensure that all new activities are informed by past lessons learned. Most importantly, we must maintain our momentum so that the progress we have made thus far turns into the promise of a better future for those with, or at risk for, cancer.

As the leader of the National Cancer Program, NCI provides vision and direction to the nationwide community of researchers, public health workers, healthcare providers, patients, advocates, and policymakers working to defeat cancer. Our budget has historically reflected this crucial role. NCI's total proposed Fiscal Year 2005 Budget Request is \$6,211,000,000. This represents an increase of \$1,440,481,000 over the Fiscal Year 2004 President's Budget. Of this increase, \$329,480,000 will allow us to continue our commitments into 2005 (Core Budget). An additional \$471,500,000 will be used for new and expanded work in broad research priority areas, with a focus on optimizing opportunities for intervention development and delivery. An increase of \$555,201,000 will allow for additional support to our major research infrastructures or platforms: investigator-initiated research; centers, networks, and consortia; and clinical trials. And \$84,300,000 will be used to improve and expand cancer bioinformatics and communications tools and approaches to enable precise and accelerated research and ensure the translation of discovery to new intervention development and delivery.

DISEASE-SPECIFIC RESEARCH

“Cancer” is not one but actually more than 100 distinct diseases. We are learning that many disease sites have cancer subtypes with unique molecular characteristics that influence how they develop and progress and how they can be effectively prevented, detected, and treated. NCI continues to work with cancer research and advocacy communities to identify and address needs for work in specific types of cancer. This year, a Sarcoma Progress Review Group is under way, and NCI disease-specific working groups continue their efforts to follow up on recommendations of other Progress Review Groups convened over the past several years. This kind of disease-specific focus is integral to achieving our Challenge Goal.

BROAD RESEARCH PRIORITIES

NCI's action plan for achieving our Challenge Goal includes ongoing research in four core scientific areas and five areas of public health emphasis. Identified with assistance from our advisory boards, the larger research community, and the cancer advocacy community, we believe investment in these areas will allow us to accelerate the pace of discovery and optimize the use of existing and new knowledge for the development and delivery of evidence-based interventions.

Core Scientific Areas

As we more fully understand cancer-related molecular, cellular, microenvironment, behavioral, psychological, and social influences, we can develop more effective and less harmful approaches to cancer prevention, early detection, diagnosis, treatment, and control.

Genes and the Environment. Cancer research has benefited enormously from increasingly sophisticated molecular technologies and the resources generated by the mapping of the human genome. Scientists have a better understanding of the complexity of genetic and environmental interactions that lead to cancer development. To build on this understanding, NCI must continue to develop novel ways to study the complexities of genetic and environmental contributions to cancer. With 2005 funding increases, we will place special emphasis on large-scale interdisciplinary studies to 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 adverse environmental or lifestyle-related exposures.

Signatures of the Cancer Cell and Its Microenvironment. Cancer is not a self-contained collection of malignant cells but rather is integrally associated with its tumor microenvironment, which includes a variety of cell types that are often altered through interaction with cancer cells. Both cancer cells and their surrounding environment need to be fully characterized in order to understand how cancer grows in the body, and both need to be considered when developing new interventions to fight the disease. Scientists are deciphering the “signatures” (signals of the presence of cancer) of cancer cells and cells in the microenvironment. Continued investments will be required in 2005 to sustain progress toward defining the full range of molecular signatures for cancer and understanding how interactions among cancer cells and the microenvironment lead to tumor development and metastasis.

Molecular Targets of Prevention, Diagnosis, and Treatment. As we more fully understand the molecular causes of cancer and its development and progression, we can use that information to discover, develop, and deliver agents that specifically “target” these causes. Such molecularly targeted interventions have the potential to dramatically improve the prevention, diagnosis, and treatment of cancer. In 2005, we must expand our efforts to identify, characterize, and validate the combinations of cellular proteins and pathways that cause cancer. And we must significantly increase the number of highly effective cancer interventions that are directed at validated targets.

Cancer Imaging and Molecular Sensing. Cancer research and care are both critically dependent on imaging technologies. Imaging advances are already permitting

remarkable accuracy in detecting whether a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs; allowing physicians to monitor patient progress without the need for biopsies; and allowing precise delivery of various tumor-destroying approaches. With sufficient resources in 2005, NCI will build on this momentum by expanding the discovery and development of novel imaging agents, devices, and methods; accelerating the integration of advanced imaging methods into therapeutic clinical trials; speeding the development and clinical testing of image-guided interventions (IGI); and stimulating research on components and systems integration of devices for *in vivo* molecular sensing.

Areas of Public Health Emphasis

In each priority area, we need better science to understand the complexities, and there is a pressing need to address the challenges posed to our Nation's health-care system by the rising incidence of cancer in the aging U.S. population.

Research on Tobacco and Tobacco-Related Cancers. Tobacco use is the leading preventable cause of illness and death in the United States and is scientifically linked to an increasing number of cancers. Two obstacles that confront the research community in the fight against tobacco-related disease are particularly complex and drive the research agenda in this area: the addicting nature of tobacco products and the impact of tobacco advertising and marketing, especially on adolescents. In 2005, with sufficient resources, NCI will lead a vigorous research and public health effort consistent with the enormous burden of tobacco-related disease. We will support and develop innovative, integrated studies and interventions to understand, prevent, and treat tobacco use and addiction. And we will work to deliver those interventions to aid in the prevention and treatment of tobacco use and tobacco-related cancers, and to inform public health policy.

Optimizing Energy Balance to Reduce the Cancer Burden. International teams of scientists have assembled compelling evidence that overweight and obesity, as well as low levels of physical activity, increase the risk of developing many cancers. At a time when almost two-thirds of the U.S. population is overweight or obese, NCI plans to invest additional resources into research on energy balance and carcinogenesis and into the development of related interventions for cancer prevention and control. Sufficient resources in 2005 will enable NCI to initiate new research to discover how body weight, physical activity, and diet, along with genetic and environmental factors, interact over a lifetime to influence the cancer process. We will also strive to improve cancer-related health outcomes by accelerating research on energy balance-related behaviors and by developing interventions across diverse populations.

Improving the Quality of Cancer Care. Far too few U.S. cancer patients receive the highest caliber of cancer care. At the same time, experts often differ substantially on what constitutes optimal care, especially from the patient's perspective, and on the best approaches for improvement. NCI plays a vital role in nationwide efforts to improve cancer care quality. With increased funding in 2005, we will further enhance quality-of-care research within and beyond the NCI clinical trials program. We will work to incorporate symptom management and palliative care into the full spectrum of cancer quality improvement research and translation efforts. We will sponsor collaborative projects to identify, develop, and monitor progress on core measures of cancer care quality and to translate research

evidence into better quality care. And we will strengthen the methodological and empirical foundations of cancer care quality assessment as well as the measures that are used in those assessments.

Reducing Cancer-Related Health Disparities. The scientific community has a critical and unique role in addressing the moral and ethical dilemmas posed by the unequal burden of cancer in our society. We know that complex interactions among genetic susceptibilities and the risks imparted by individual and group behaviors, age, and social and environmental circumstances determine health throughout an individual's life span, including who becomes ill, who survives disease, and who maintains good quality of life after diagnosis and treatment. In 2005, NCI will use increased resources to work with other agencies in the Department of Health and Human Services (HHS) to implement recommendations from the Trans-HHS Cancer Health Disparities Progress Review Group, convened in 2003. We will continue discovery efforts to more fully define the magnitude and causes of health disparities in cancer while emphasizing the translation of what we know today into the development and delivery of effective interventions to reduce cancer health disparities in all populations.

Improving Treatment Outcomes and Quality of Life for Cancer Survivors. Although cancer survivors are living longer, more productive lives than ever before, they are not yet free from the adverse effects of cancer diagnosis and treatment. NCI is working collaboratively with other groups to conduct the research that will help cancer survivors enjoy an improved quality of life. We plan to use increased resources in 2005 to discover the biological, physical, psychological, and social mechanisms, and their interactions, that affect a cancer patient's response to disease, treatment, and recovery. We will also accelerate the development of intervention research in these areas and collaborate with others to ensure the delivery of new information, interventions, and best practices to relevant audiences. And we will expand the development and use of tools to assess health-related quality of life and quality of care of post-treatment cancer survivors and their families.

PLATFORMS FOR DISCOVERY, DEVELOPMENT, AND DELIVERY

Bringing the benefits of cancer research to the American people depends on building and sustaining the strong research mechanisms, support structures, and collaborations that make it possible for us to pursue rapidly evolving discoveries.

Enhancing Investigator-Initiated Research

Investigator-initiated research has always been the primary means by which biomedical research is funded and conducted. These investigators ask the critical questions, explore the options, develop and test innovative technologies, and make the discoveries that lead to better cancer science and its application to patient care. With additional resources in 2005, we will be able to increase funding for, and the numbers of, competing research grants and provide incentives for transdisciplinary and collaborative research. We will also apply resources to encourage investigators to commit to careers in cancer research, to propose more innovative and higher-reward projects, and to conduct research in priority areas identified by advisory committees, NCI staff, and Progress Review Groups.

Transforming the Capacity of Centers, Networks, and Consortia. The interdisciplinary nature of today's cancer research requires new infrastructures that support team science and enable the sharing of a multitude of resources. The centers, networks, and consortia created and supported by NCI over the past 10 years comprise a model framework upon which to "grow" this evolving paradigm. In 2005, we will use increased resources to promote the strategic growth of NCI-supported Cancer Centers, incorporating and realigning resources to accelerate discovery, development, and delivery. We will promote collaborations to improve access of minority populations to state-of-the-art clinical and population studies, cancer treatments, technologies, and care. And we will expand the capacity of NCI centers, networks, and consortia to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions.

National Clinical Trials Program. NCI-supported clinical trials provide a crucial infrastructure for moving new cancer interventions from the laboratory to studies in people with, or at risk for, cancer and then to the healthcare setting. We help researchers from public, industrial, and academic settings develop anti-cancer agents for a broader array of tumor types and at a faster pace than would otherwise be possible. While much has been accomplished to streamline cancer clinical trials, NCI must further accelerate movement of promising research discoveries into clinical development and delivery to the public. In 2005, NCI will use increased funding towards identifying and accelerating development of the most promising new agents for cancer treatment and prevention; strengthening scientific planning and leadership for large clinical trials; doubling the rate at which Phase III trials are completed; and ensuring that clinical trials are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for these groups.

NCI's Intramural Research Program. NCI's Intramural Research Program (IRP) provides a unique venue for research innovation, translation, and application. The IRP serves as a proving ground for long-term, high-risk/high-impact projects. It complements our robust Extramural Research Program, which distributes about three-quarters of our research funding to research sites around the country. The opening of the new NIH Clinical Center facility in 2004, the establishment of new consortia linking extramural and intramural investigators, the development of new technologies, and new efforts to foster interdisciplinary approaches to scientific discovery will strengthen the work of NCI's IRP and its unique contributions to helping us meet our Challenge Goal to eliminate suffering and death due to cancer.

ENABLERS OF DISCOVERY, DEVELOPMENT, AND DELIVERY

Making these and other bioinformatics tools available to the research community for analysis and resource sharing is vital for enabling investigators to carry out state-of-the-art studies.

Bioinformatics. The exponential expansion of biomedical knowledge is generating a tidal wave of data. Contemporary bioinformatics tools must be harnessed to support cancer research and care, as well as effective dissemination of information to patients. NCI is positioned to provide the kind of informatics system and analytic tools needed to integrate diverse data types, capture and share research outcome data, and provide user-friendly tools that permit patients and their

Larger investments in cancer communications will enable the translation of successful intervention research into practice.

advocates to interact more directly with the cancer research community. With sufficient resources in 2005, we will establish a network of information technology partners and support the development of a shared infrastructure and tools that facilitate data mining and data integration.

Cancer Communications. Significant barriers impede the flow of effective cancer communications to patients and their caregivers, underserved populations, advocacy groups, health professionals, and the public health community. NCI strives to understand, apply, and disseminate effective communication approaches that maximize access to and appropriate use of cancer information by all who need it. In 2005, we will use funding in this area to increase knowledge about cancer information needs, beliefs, decisionmaking processes, and behaviors; develop and evaluate communication resources and interventions for reducing the cancer burden, particularly among underserved populations; and engage with partners and the media to deliver evidence-based cancer interventions in clinical and public health programs.

NCI's Budget Request for Fiscal Year 2005

(dollars in thousands)

Fiscal Year 2004 President's Budget	\$4,770,519
Increase to Core Budget	329,480
Broad Research Priorities	
Core Scientific Areas	
Genes and the Environment	73,150
Signatures of the Cancer Cell and Its Microenvironment	35,300
Molecular Targets of Prevention, Diagnosis, and Treatment	47,650
Cancer Imaging and Molecular Sensing	44,750
Areas of Public Health Emphasis	
Research on Tobacco and Tobacco-Related Cancers	75,000
Optimizing Energy Balance to Reduce the Cancer Burden	57,800
Improving the Quality of Cancer Care	36,300
Reducing Cancer-Related Health Disparities	71,300
Cancer Survivorship: Optimizing Health and Quality of Life after Cancer	30,250
Subtotal Broad Research Priorities	471,500
Platforms for Discovery, Development, and Delivery	
Enhancing Investigator-Initiated Research	123,501
Transforming the Capacity of Centers, Networks, and Consortia	96,800
National Clinical Trials Program in Treatment and Prevention	334,900
Subtotal Platforms for Discovery, Development, and Delivery	555,201
Enablers of Discovery, Development, and Delivery	
Bioinformatics	40,800
Cancer Communications	43,500
Subtotal Enablers of Discovery, Development, and Delivery	84,300
Total FY 2005 Budget Request	\$6,211,000

Highlights of Progress

One in four deaths in the United States is attributable to cancer, and one in three Americans will eventually develop some form of cancer. Each day, 3,400 people in America are diagnosed with cancer and another 1,500 die from the disease. But the burden of cancer is too often greater for the poor, ethnic minorities, and the uninsured than for the general population.



“As a nurse, I see a lot of the cost of cancer in the faces of my patients and their loved ones. That’s enough for me to want to see our Nation support cancer research. I want to see the suffering erased from every face, no matter who they are, what they look like, or where they come from.”

Mortality from Four Leading Cancers Continues to Decline, but Some Cancer Disparities Are Increasing

The Annual Report to the Nation on the Status of Cancer 1975-2000, Featuring the Uses of Surveillance Data for Cancer Prevention and Control¹ was released in September 2003. The report shows that overall, cancer death rates neither increased nor decreased from 1998 to 2000, and cancer incidence rates were stable from 1995 to 2000. However, mortality rates of the four most common cancers (lung, colorectal, breast, and prostate) continued to decline. Researchers believe the drop in lung cancer mortality reflects similar declines in tobacco smoking. Improvements in breast cancer incidence and mortality rates appear to result from increased use of mammography and the availability of improved therapies. Yet, the report also calls attention to some worsening cancer health disparities. For example, a growing difference in death rates between White and Black populations for colorectal and breast cancers suggests that Black men and women may not have experienced the same benefits from screening and treatment services as their White counterparts. In addition, higher rates of late-stage breast cancer in some population groups and geographic areas may reflect delayed access to care, often among women who lack health insurance and among recent immigrants. The report concludes that further reductions in cancer incidence and death rates will require strong Federal, state, local, and private partnerships to apply evidence-based control measures, improve the delivery of quality cancer care, and develop more effective screening strategies that reach all segments of the population.

Discovery

Protective Effect of Beta Carotene on Colorectal Cancer Risk May Be Reversed by Smoking or Drinking

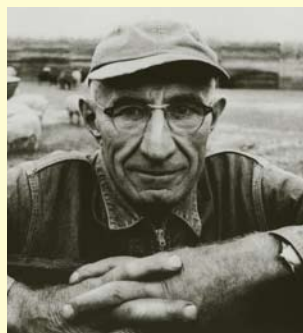
While exploring possible anti-cancer effects of beta carotene as a dietary supplement, NCI-supported researchers discovered that people taking the supplements who also smoke cigarettes and/or regularly consume alcohol tended to have an increased risk of developing lung cancer. They reported recent findings from a large clinical trial exploring the relationship among beta carotene supplementation, smoking and drinking behaviors, and the recurrence of colon polyps, a precursor condition to colorectal cancer. Beta carotene supplementation substantially decreased the recurrence of polyps in the study population among patients who neither smoke nor consume alcohol. In contrast, beta carotene supplementation slightly increased the risk of polyp recurrence in people who smoke or consume one or more alcoholic beverages a day, with the greatest risk elevation seen in people who both smoke and drink regularly. These findings are similar to those of a previous study which showed that beta carotene increased the risk of melanoma in smokers but not in nonsmokers. This varying effect of beta carotene supplementation on cancer risk,

depending on patient behaviors, suggests the need for caution in choosing cancer prevention interventions for general use, especially when mechanisms of action and interactions with other lifestyle factors have not been clearly defined.

Genetic Polymorphism Provides Clues to Adult Brain Tumor Risk

While researchers increasingly discover genetic and environmental risk factors for many types of cancers, the causes of brain tumors in adults remain poorly understood. Well established risk factors, such as high doses of radiation and certain rare genetic disorders, account for only a small number of brain tumors. In a recent study, investigators hypothesized that differences in the make-up of some genes — those that code for proteins that help break down harmful chemicals such as solvents, pesticides, and ethanol — may affect brain tumor risk. These researchers tested the blood of nearly 800 adult brain tumor patients, and a similar number of control patients, for genetic polymorphisms in two such genes, *GST* and *CYP2*, that have been implicated in brain tumor risk. A number of the polymorphisms were indeed associated with the development of brain tumors. If these findings are validated in other studies of a similar scale, the next step would be to pool samples from multiple epidemiological studies and examine interactions of genotypes with specific occupational exposures. Defining the risk of brain tumor development by specific gene/environment interactions will help the cancer community to identify appropriate interventions and precautions for people at high risk.

Prostate cancer is the second leading cause of cancer death among men in the United States. Although many of the almost 221,000 U.S. men diagnosed with prostate cancer in 2003 will be cured, almost 29,000 will die from this disease in the same year.



“My wife worries about all the chemicals I have to work with. She talks about cancer. I tell her not to worry. But sometimes I wonder myself.”

Researchers Uncover Possible Occupational Risk Factors of Prostate Cancer in Farmers

Prostate cancer is the most common malignancy, and the second leading cause of cancer death, among men in the United States and in most Western countries.² A number of risk factors are implicated in the development of prostate cancer, including age, family history, ethnicity, hormonal factors, smoking, high consumption of animal fat and red meat, and low consumption of fruits and vegetables. Even so, the etiology of prostate cancer remains largely unknown. Since farming is the most consistent occupational risk factor for this disease, scientists have been seeking to clarify the potential risks associated with pesticide use. Investigators of the Agricultural Health Study, a cohort study of over 55,000 male pesticide applicators with no prior history of prostate cancer, discovered two unexpected relationships between the use of certain pesticides and prostate cancer risks. First, men who reported occupational use of the fumigant methyl bromide (one of 45 common agricultural pesticides examined in the study) had a slightly higher risk of developing prostate cancer than the cohort overall. Second, exposure to several widely used insecticides seemed to increase the risk of prostate cancer, but only in men with a family history of the disease. In addition to these novel findings, evidence suggests that the use of chlorinated pesticides may have been related to

increased prostate cancer risk, especially in men over 50 years of age. If further validated, this new knowledge about the hereditary and environmental etiology of prostate cancer risk may help scientists develop interventions to prevent, detect, and treat this disease in the farming community and in other populations.

Scientists Explore Effects of Biobehavioral Factors on Ovarian Cancer

Biobehavioral factors such as stress, depression, and social support are known to influence how well the immune system responds to disease, including cancers. Scientists have documented the effects of biobehavioral factors on the function of immune cells (such as white blood cells), cytokines (proteins that heighten immune activity), and hormones that help regulate immune activity. For the first time, a team of investigators has extended this research to vascular endothelial growth factor (VEGF), a stress-related cytokine that stimulates new blood vessel growth (angiogenesis) in growing tumors. In this study, women with ovarian cancer who were found to have a greater sense of social well being³ had markedly lower blood levels of VEGF. This research suggests that biobehavioral effects on VEGF levels, and consequent stimulation of angiogenesis, may be one way in which biobehavioral factors affect the progression of ovarian cancer. Further research is needed to validate this mechanism and to explore ways to target it through prevention and treatment interventions.

Breast cancer is the second leading cause of cancer death among women in the United States. Approximately 40,000 women are expected to die from this disease in 2003.



"When my doctor told me I had cancer – Hodgkin's disease – that was pretty scary. Thankfully, the treatment worked. But I'm told I may have a greater risk of developing other cancers, like breast cancer, later in life. Scary again."

Investigators Study Risk Factors for Future Breast Cancers in Female Survivors of Hodgkin's Disease

Hodgkin's disease, a once deadly cancer of the lymphatic system, is now highly curable, with 85 percent of patients surviving at least 5 years after diagnosis. However, with some treatments comes an increased risk of second cancers, including leukemia, sarcoma, and breast, lung, and thyroid cancers. Among female survivors, breast cancer is the most likely tumor to develop, especially in women who are age 30 or younger when treated with radiotherapy. An international team of scientists recently analyzed data from over 3,800 Hodgkin's survivors in this subgroup to identify specific risk factors. They discovered that the higher the radiation dose to the breast, the more likely the women were to develop breast cancer. Conversely, higher concentrations of alkylating agents given in chemotherapy and higher radiation doses to the ovaries were associated with lower future breast cancer risk. Researchers suspect that premature menopause induced by damage to the ovaries is at the root of this risk reduction, since premature menopause by surgery is also known to reduce breast cancer risk. Because of improvements to Hodgkin's disease treatments over time, women treated more recently may be at lower risk for breast cancer development than the women included in this study. However, current female survivors of Hodgkin's disease will require lifetime surveillance and breast cancer prevention strategies. Despite the risks of future breast cancers highlighted by these investigators, the

benefits of radiotherapy and chemotherapy for Hodgkin's disease patients far outweigh the treatment-related risks.

Effects of Stress Can Linger for Family Members of Pediatric Cancer Survivors

Few would argue that cancer is a major stressor for anyone diagnosed. Recent research reveals that family members of cancer patients also are subject to trauma. Investigators applied the posttraumatic stress (PTS) model to siblings of childhood cancer survivors. Adolescent siblings of pediatric cancer survivors reported more PTS symptoms than did a reference group of unaffected teens with similar levels of general anxiety. Among the survivors' siblings, about half (47 percent) reported mild PTS, 32 percent indicated moderate to severe levels, and 25 percent said they thought their brother/sister would die during treatment. These data remind us that cancer is often a family disease. Consequences to siblings can include uncertainty about the future, distress over witnessing physical and emotional pain, sudden and extended separation from parents, and changes in family members' roles and responsibilities. Identifying those at risk and intervening early to reduce emotional distress may be critical for the subsequent health and well being of both the cancer patient and his or her siblings and other family members.

Development

Some cancers can be treated successfully if detected early. Unfortunately, for many, like esophageal cancer, we do not have good early detection tests. Researchers are using genomics and proteomics to develop tests to screen for hard-to-detect cancers.



"Okay, I knew I had GERD⁴, and now I have Barrett's esophagus. No big deal right? Most people with Barrett's esophagus don't get cancer, right? So it won't be me, right? No problem. Still, I wonder if there's a good way to screen for this cancer, just to be safe."

Researchers Use Artificial Neural Networks to Study Esophageal Cancer

Esophageal cancer incidence has been rising at a rate faster than that of any other malignancy. With no good test for early detection, patients are usually diagnosed in the advanced stages of disease, and mortality is high. Investigators recently discovered that an artificial intelligence technique called "artificial neural networks" (ANNs) can accurately analyze microarray data to detect esophageal cancer. In this study, investigators identified ANNs as the best of several artificial intelligence techniques for distinguishing between esophageal cancer and a precancerous condition, Barrett's esophagus (BE). Investigators first "trained" the ANNs to recognize the difference between biopsy samples from patients with BE or esophageal cancer. To train the ANNs, researchers had it analyze eight tissue samples from BE patients and four from patients with esophageal cancer. The ANNs thus "learned" the difference in what the microarray data of cancer and precancer "looks" like. Once fully trained, the ANNs correctly classified 10 new samples as BE or esophageal cancer. This research shows ANNs as a promising technique that can extract and analyze microarray data. With further development, this technology may have a far-ranging impact on cancer detection, diagnosis, and management. Furthermore, the ANN-identified differences in gene expression

discovered in this study may provide biomarkers that can be used to develop early detection techniques for esophageal cancer.

Screening for Genetic Mutation May Improve Detection and Treatment of Thyroid Cancer

Papillary thyroid cancer is the most common and most curable type of thyroid cancer, with approximately 95 percent of patients cured if treated appropriately. However, scientists believe survival rates could be further improved if clinicians had better tools for early detection. Tumors are usually detected after a patient or family member notices a lump in the neck, and a physician recommends a clinical needle biopsy. However, these needle biopsies are often not definitive, and patients undergo unnecessary surgery or delayed diagnosis. Scientists have now discovered a genetic mutation that may assist physicians in identifying tumors earlier. In a recent study, investigators screened tumor tissue from six different disease sites for a cancer-related genetic mutation prevalent in melanoma cancers. This mutation of the *BRAF* gene was detected in 24 of 35 tumors of the papillary thyroid (69 percent). In addition to providing a potential aid for early detection, this discovery provides clues about the molecular pathways that may be involved in the development and progression of this cancer. Further research into these molecular mechanisms may lead to new treatments for people who do not respond to current therapies.

Osteopontin Gene May Aid Detection and Treatment of Metastatic Liver Cancer

Hepatocellular carcinoma (HCC or liver cancer) is an extremely aggressive disease of high mortality that is common in Asia and Africa, with incidence rising in Europe and North America. Metastasis within the liver causes most of the mortality from this disease. Researchers used gene expression microarrays to identify genes that affect both tumor metastasis and patient survival for HCC. These investigators identified, for the first time, a molecular signature to distinguish between metastatic and nonmetastatic hepatocellular cancers. Of special note, the gene *osteopontin* was overexpressed in metastatic HCC compared to nonmetastatic tumors. Correlative laboratory experiments were encouraging. Investigators were able to block the metastatic behavior of HCC cells *in vitro* with an antibody that inhibits the action of the osteopontin protein. The same antibody prevented HCC metastasis to the lungs in a mouse model. Further research is needed to refine and validate the clinical usefulness of this promising biomarker. If developed for early detection of metastatic HCC and for therapy to prevent metastasis, this discovery could improve long-term survival of patients who ordinarily succumb to this disease.

New Type of Nanoparticle Improves Imaging of Lymph Nodes in Prostate Cancer Patients

Testing for the presence or absence of lymph node metastasis is an important element in the care of men diagnosed with prostate cancer. Men with local prostate cancer are usually given the choice of treatment by radical prostatectomy, radiotherapy, or watchful waiting. However, the standard of care for men with lymph node metastasis is a more aggressive treatment with adjuvant androgen-deprivation therapy with radiation. Currently, lymph nodes near the prostate gland must be surgically removed and examined in the laboratory for metastasis. No imaging technique has proven sufficiently sensitive to replace this invasive biopsy procedure. But recently, researchers tested a type of nanoparticle called lymphotropic superparamagnetic nanoparticles (LSNs) to enhance imaging of lymph nodes in prostate cancer patients. LSNs, small enough to enter individual cells, actively accumulate in lymph nodes once injected into the body and are sufficiently magnetic to be detected by magnetic resonance imaging (MRI). Animal studies have shown that MRI using LSNs can distinguish between normal and metastatic lymph nodes. Investigators have used LSNs in conjunction with MRI to correctly identify lymph node metastasis in 100 percent of 33 patients known to have metastatic prostate cancer. This test also correctly classified 96 percent of patients with nonmetastatic cancer. Large prospective clinical trials are needed to determine the clinical utility of this promising new procedure.

Lung cancer is the leading cause of cancer death in both men and women in the United States. Close to 92,000 men and 80,000 women will be diagnosed with lung cancer in 2003. In the same year, the disease will kill over 88,000 men and close to 69,000 women. Non-small cell lung cancer is the most common form of lung cancer.



"How am I going to tell my family about my lung cancer diagnosis? The doctor says standard treatments don't cure many patients with this type of lung cancer, although it might buy me some extra time. Time is precious. The doctor did tell me about a clinical trial. But I don't know. Is there really hope?"

Cancer Vaccine Shows Promise for Non-Small Cell Lung Cancer

Investigators studying non-small cell lung cancer (NSCLC) recently built on findings that a vaccine containing genetically modified irradiated tumor cells is highly active against tumors in a number of mouse models as well as in some melanoma patients. In a Phase I clinical trial, researchers produced patient-specific vaccines by isolating, genetically modifying, and irradiating tumor cells taken from patients with metastatic NSCLC. The genetic modification caused the cells to produce granulocyte macrophage colony-stimulating factor (GM-CSF), a protein known to activate the immune system to attack tumor cells. The radiation rendered the tumor cells unable to replicate. The vaccine caused only low-level toxicities, and 18 out of 25 vaccinated patients showed at least some immune response. The disease of five patients was stabilized for up to 3 years after treatment. Of patients whose tumors were surgically removed before vaccination, two were still cancer free 3½ years later. While the response was not uniform across all patients, this study adds to accumulating evidence that GM-CSF-based vaccines activate the immune system to attack tumors in many cancers and could perhaps be combined effectively with other treatment strategies. The prolonged response of some patients suggests promise for this vaccine strategy in early-stage NSCLC patients.

Researchers Identify Prognostic Factors for Survival in Pancreatic Surgery Patients

Pancreatic cancer is a high-mortality disease with an overall 5-year survival rate for patients with adenocarcinoma, the most common form of this disease, at less than 5 percent. Only about 10 percent of adenocarcinoma patients are diagnosed while the cancer is confined to the pancreas. These patients are eligible for surgical resection, and their 5-year survival rate increases to about 20 percent. Recently, a team of investigators accessed data from NCI's Medicare-linked Surveillance, Epidemiology, and End Results (SEER) registries to examine the prognostic factors that influence survival in this group of patients. This retrospective cohort analysis of 396 adenocarcinoma surgical patients revealed that the strongest predictor of improved survival was postoperative adjuvant chemoradiation therapy. The investigators also found that a trend toward more patients being treated in teaching hospitals was leading to a gradual improvement in survival over time. Other predictors of improved survival included tumor size of less than 2 centimeters in diameter, no detection of cancer in nearby lymph nodes, well-differentiated histology, and high socioeconomic status. African Americans tended to have lower overall survival rates than other racial/ethnic groups. Of special note, socioeconomic status was shown to affect the likelihood of receiving adjuvant treatment, the most powerful predictor of survival.

Delivery

The Steroid Dexamethasone Improves Survival of Children with Acute Lymphoblastic Leukemia

Survival outcomes for children with acute lymphoblastic leukemia (ALL) have improved dramatically over the years. The number of young patients who survive 5 or more years has risen from less than 5 percent in the early 1960s to more recent rates of about 85 percent. This improvement is a testament to the success of sequential clinical trials that have progressively identified more effective treatment regimens. Recent conventional therapy for childhood ALL has included chemotherapy with mercaptopurine, accompanied by treatment with the steroid prednisone to help kill the cancer cells. Researchers have now discovered that replacing prednisone with a different steroid, dexamethasone, further improves survival. In a clinical trial of more than 1,000 standard-risk ALL patients younger than 10 years of age, 85 percent of those given dexamethasone survived at least 6 years without evidence of relapse, versus 77 percent of patients treated with prednisone. Fewer children treated with dexamethasone experienced central nervous system relapses, an important cause of treatment failure for children with ALL. There was also a trend toward fewer ALL relapses in bone marrow. These findings change the standard of treatment for ALL patients younger than 10 years of age by making dexamethasone, rather than prednisone, the steroid of choice. Additional research is needed to evaluate the use of dexamethasone in the treatment of older children and adolescents with ALL.

Gleevec™ May Be Used to Treat Rare Cancer Idiopathic Hypereosinophilic Syndrome

Idiopathic hypereosinophilic syndrome (IHS) is a condition in which the body produces an overabundance of eosinophils, a type of white blood cell involved in ridding the body of foreign substances. The cause of this anomaly is unknown. Current treatments focus on controlling deadly damage to vital organs that become infiltrated by eosinophils, but mortality nevertheless is extremely high. Researchers recently treated 11 IHS patients with an experimental trial of Gleevec, a molecularly targeted drug used to treat chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GIST). In 9 of 11 patients, eosinophil levels returned to normal, in treatment responses lasting three or more months. Based on knowledge of Gleevec's mechanism of action, investigators searched for and identified the genetic mutation causing IHS in the majority of these patients. In addition to survival benefits for IHS patients, this work sheds light on the molecular origins of IHS, which may lead to a better understanding of this disease and still better ways to treat it. This study also points to a perhaps even greater number of cancers that may respond to Gleevec and encourages continued searching for molecular targets for this drug in a variety of disease sites.

Improved Therapy Boosts Survival of AIDS-Related Lymphoma Patients

Survival of HIV-positive patients with AIDS-related lymphoma (ARL) has improved since treatment with highly active antiretroviral therapy (HAART) for AIDS patients has become standard practice. However, prognosis remains poor with the standard treatment for ARL, the CHOP⁵ regimen — ARL still causes death in up to 20 percent of HIV-positive patients. Researchers recently developed a treatment regimen known as dose-adjusted EPOCH⁶ (DA-EPOCH) that substantially improves survival for ARL patients. Three factors make DA-EPOCH effective in these patients. First, given in low concentrations over long periods, this drug combination can overcome the drug resistance encountered with CHOP therapy. Second, the patients receive individualized dosages to minimize certain toxicities. And third, antiretroviral therapy can safely be suspended during chemotherapy to boost the effectiveness of the treatment. Out of 39 patients treated with DA-EPOCH, 29 experienced complete remission, and 5 achieved partial remission. Over the long term, 60 percent of the patients survived at least 53 months; 92 percent of these were disease free. These survival rates are dramatically better than for patients given standard CHOP therapy. Researchers expect DA-EPOCH therapy to greatly boost survival of ARL patients, with the exception of those with central nervous system involvement who did not respond well to DA-EPOCH therapy.

Participation of Older Patients in Cancer Clinical Trials Could Be Improved by As Much As 60 Percent

Although close to 61 percent of new cancer cases occur among persons 65 years of age and older, and approximately 71 percent of all cancer deaths are in this population, only 25 percent of the patients enrolled in cancer clinical trials are from this age group. NCI-supported researchers examined the reasons behind this disparity by conducting a retrospective analysis of patient and trial characteristics for 59,300 patients enrolled in 495 NCI-supported trials. Of all the criteria used for excluding participation in a trial, exclusions based on organ system abnormalities and functional status limitations were found to be most significant for low participation by older patients. Overall, older patients do have more disqualifying medical conditions than younger patients. Investigators noted that while insurance coverage for clinical trials for the aging has improved access to trials for this population group, changes in study design and in protocol exclusions are needed to improve overall enrollment opportunities. Results from this study suggest that if protocol exclusions were relaxed, participation by this age group in cancer trials could be as high as 60 percent. The investigators emphasized that clinical trials must have exclusion criteria. For example, normal renal function may be required in trials that use agents that can cause kidney toxicity. However, these investigators suggest that, when designing a clinical trial, researchers must examine each exclusion criterion to ensure it is scientifically justified.

Incidence and mortality rates for cancers of the colon and rectum are the third highest in the United States for both men and women. Statisticians predict that in 2003, more than 144,000 people will be diagnosed with, and more than 57,000 will die from, colorectal cancer.



“As a doctor, it isn’t easy when I have to tell my patients they have cancer. This was one of the easier cases. With quality surgical care and adjuvant therapy for his rectal cancer, he has a good chance of full recovery.”

Rectal Cancer Patients Fare Better at Hospitals with High Surgical Volume

For many cancers requiring surgery, patient survival and quality-of-life outcomes are better when patients are treated at hospitals that perform a large number of the surgeries (“high-volume” hospitals). A recent study of over 7,000 rectal cancer patients has revealed that rates for permanent colostomy and postoperative mortality were lower and overall survival higher for rectal cancer patients undergoing surgery at high- compared to low-volume hospitals. It is particularly important to understand the relationship between hospital volume and patient outcomes for rectal cancer, because scientists have found surgical management of this disease to markedly affect tumor control and quality of life. This research suggests that the morbidity and mortality of rectal cancer could be substantially reduced if all patients were to receive the same quality of care found at high-volume hospitals. Researchers recommend additional investigation to identify processes of care that contribute to these differences in patient outcomes. Many factors, including but not limited to quality of imaging, anesthesia support, surgical technique, and nursing care could be examined. Such information would help scientists to design clinically meaningful approaches to assessing and improving quality of care for all patients with rectal cancer.

Abundant evidence now links diet, physical activity, and weight to cancer risk, development, and progression. NCI and partners support programs such as 5 A Day for Better Health and Men: Shoot for 9 for Better Health to deliver the message of cancer prevention through more healthful lifestyle choices. With increasing evidence of the role that lifestyle factors can play in reducing the cancer burden, NCI has begun placing even greater emphasis on this area of research. (See pages 45-50.)



"I eat my fruits and vegetables, but I've never exercised much. It's so hard to get started, and there always seemed to be something else that needed doing. I just never got to it. I figured I was too old for it to make a difference now, but my doctor says walking just a half hour a day would help."

Recreational Activity Reduces Breast Cancer Risk in Postmenopausal Women

Data from the Women's Health Initiative (WHI) Observational Study, a large prospective cohort study of postmenopausal U.S. women age 50 to 79, demonstrate a protective role for physical activity on breast cancer risk. Risk reductions were higher in healthy weight than overweight women, with decreasing benefit with increasing obesity. Women who reported engaging in strenuous activity at earlier ages had the greatest reductions in risk with current physical activity also protective. Investigators noted the lowest risk levels in women who were the most physically active, although even moderate activity was protective. This finding may be especially encouraging to older women who may be able to achieve moderate, but not strenuous, exercise levels. For example, breast cancer risks were 18 percent lower in women who walked briskly for a total of 1-1/2 to 2-1/2 hours weekly than in inactive women. The walking did not have to be done all at once, but could be spaced throughout the week. Another promising finding is that physical activity reduced risk among women on hormone replacement therapy (HRT). Since HRT is known to slightly increase breast cancer risk, physical activity may provide a countermeasure for women who wish to continue HRT for menopausal symptoms.

The quotes in this chapter are representative of many people's experiences with cancer.

¹ Prepared by the National Cancer Institute, the Centers for Disease Control and Prevention, the National Center for Health Statistics, the American Cancer Society, and the North American Association of Cancer Registries. seer.cancer.gov/reportcard

² Other than nonmelanoma skin cancer.

³ According to two measures: the Functional Assessment of Cancer Therapy, which measures quality of life in patients with malignant disease, and the Profile of Mood States.

⁴ GERD, gastroesophageal reflux disease, is a risk factor for Barrett's esophagus, where cells lining the lower part of the esophagus are replaced by cells resembling the lining of the stomach. Barrett's esophagus is a risk factor for esophageal cancer.

⁵ Cyclophosphamide, doxorubicin, vincristine, and prednisone.

⁶ Etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin.

Other Highlights in This Document

Discovery

Genetics of programmed cell death, page 17
Genetic subtypes of breast cancer, page 18
Imaging molecular interactions in cells, page 32
Genetics of smoking cessation, page 39
Imaging nicotine receptors in the brain, page 39
ADHD and tobacco marketing, page 39
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Assessing quality of cancer care, page 52
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Development

Ovarian cancer screening test, page 17
Genetic prognosis of ovarian cancer tumors, page 18
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Prostate cancer and diet, page 27
Improving cervical cancer screening, page 74
Classifying diffuse large B-cell lymphoma subtypes, page 84
Chemoprevention of prostate cancer, page 92

Delivery

Improved survival for Ewing's sarcoma patients, page 8
Celecoxib and cancer prevention, pages 23 and 87
Nicotine, dopamine metabolism, and tobacco cessation, page 39
Assessing dietary intake measures for clinical trials, page 45
Recent patterns of care studies, page 53
Recent childhood survivorship research, page 69
Avastin™ and renal cell and colorectal cancer treatment, pages 84 and 87
Velcade™, proteasomes, and multiple myeloma treatment, pages 85 and 89
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Tamoxifen and benign breast disease prevention, page 92

The Challenge Is Before Us and the Opportunity Is Now.

Our Action Plan for Fiscal Year 2005

In 2001, the National Cancer Institute (NCI) issued to the nationwide cancer community a Challenge Goal: Eliminate the suffering and death due to cancer by 2015.



Never before have so many scientific tools and technologies and so much biomedical knowledge been assembled to power our ability to reach our Challenge Goal. The cancer community is currently experiencing exponential growth in its knowledge of cancer as a disease process, growth that has been fueled by historically high levels of funding, scientific expertise, infrastructure, and enabling technologies. With a sharp focus on our goal and continued budgetary support, we will be able to assemble the necessary pieces and achieve the type of progress needed to remove the ring of fear from the word “cancer” for future generations.

NCI will concentrate its research investments on preempting the process of cancer by preventing its initiation; detecting it early; and slowing, stopping, or reversing the cancer process so that it cannot progress to a lethal phenotype. We will also work to ensure that emerging knowledge is used immediately to develop, test, and deliver new interventions for public health programs, medical practice, and policy making. Our success will depend on our ability to seamlessly integrate activities both within NCI and with our partners, remove major barriers to progress, and ensure that all new activities are informed by lessons learned along the way.

DISCOVERY, DEVELOPMENT, AND DELIVERY AS A SEAMLESS PROCESS

As the leader of the National Cancer Program, NCI provides vision and leadership to the nationwide community of researchers, public health workers, healthcare providers, patients, advocates, and policy makers working to defeat cancer. We strive to facilitate a seamless process for integrating discovery activities, accelerating the development of new interventions, and ensuring the delivery of new evidence-based interventions for all cancers and all people in need. We must ensure that results of research are continuously evaluated for their potential for practical application and quickly moved into arenas of developmental research. Throughout all of our efforts in discovery and development, we must have an eye toward the delivery of validated interventions to clinical practice and public health settings. Likewise, as interventions are taken to the people, we must continue to study their impact on individual and public health to inform future research and development. Movement in each of our priority areas along the discovery-development-delivery research continuum must be smooth and unencumbered by traditional infrastructure boundaries and linear ways of thinking.

NCI's **Action Plan for Fiscal Year 2005** outlines our next steps in achieving our Challenge Goal to eliminate the suffering and death due to cancer. It includes continued work in broad research areas and optimal use of existing and new knowledge for the development and application of evidence-based interventions, all of which will have implications for many types of cancer.

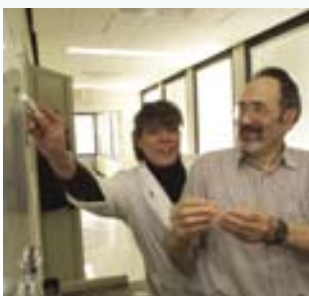
Discovery Objectives



To advance toward our goal to eliminate the suffering and death due to cancer, we must continue to improve our understanding of:

- The genetic, environmental, and lifestyle factors and their interactions that define cancer risk.
- The interaction between cancer cells and their microenvironment.
- How body weight, physical activity, and diet interact with genetic and environmental factors to influence the cancer process.
- The causes of tobacco use, addiction, and tobacco-related cancers.
- The biological, physical, psychological, and social mechanisms, and their interactions that affect a cancer patient's response to disease, treatment, and recovery.
- The scientific basis for quality cancer care.
- The fundamental causes of cancer health disparities.
- Imaging methods, molecular biosensors, and imaging-guided interventions.
- Molecular targets for treatment and prevention.

Development Objectives

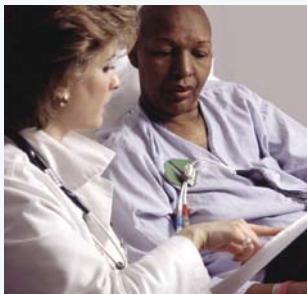


. . . then use that information to develop highly effective evidence-based interventions including:

- Strategies to address the clinical, behavioral, and societal issues associated with cancer susceptibility.
- Validated molecularly targeted drugs for treatment and prevention.
- New drugs and reagents that target cells in the microenvironment.
- Novel combinations of drugs and modalities that can preempt or arrest malignancy.
- Imaging and molecular biosensors for use in early detection, diagnosis, treatment, and prediction.
- New approaches to the prevention and treatment of tobacco use, nicotine addiction, and tobacco-related cancers.
- Tools to improve physical fitness, diet, and weight control.
- Process and outcome measures for assessing the quality of cancer care.
- Incorporation of symptom management and palliative care into quality care improvement.
- Specific approaches to reducing cancer-related health disparities.
- Strategies for reducing cancer-related chronic or late morbidity and mortality.

oment Delivery

Delivery Objectives



... and ensure that these new interventions are used to:

- Make novel and effective prevention, early detection, and prediction measures available to all who need them.
- Deliver targeted and effective therapeutic interventions to all cancer patients.
- Eliminate cancer-causing behaviors such as tobacco use, unhealthy diet, and sedentary lifestyle.
- Eliminate disparities in cancer incidence, mortality, and access to quality cancer care.
- Eliminate the adverse effects of cancer diagnosis and treatment on cancer survivors.
- Capture the experience and knowledge gained from application to inform future discovery in cancer biology, molecular epidemiology, and the behavioral sciences.

To meet these objectives for research discovery, development, and delivery, we must optimize our research platforms and enable investigators to work at peak efficiency. Our success in achieving these objectives will depend on our ability to:

Platforms for Discovery, Development, and Delivery

- Accelerate innovation in investigator-initiated research by expanding access to resources and new technologies.
- Integrate infrastructures and collaborations through Cancer Centers, networks, and consortia to address large problems in human cancer.
- Ensure that our national clinical trials program addresses the most important research questions quickly and effectively.
- Promote networks, partnerships, and coalitions to translate results of research into clinical practice and public health benefit.

Enablers of Discovery, Development, and Delivery

- Create and use bioinformatics and analytical tools to redefine how cancer research is conducted; care is provided; and patients, physicians, and researchers interact.
- Understand, apply, and disseminate communication approaches that maximize access to and appropriate use of cancer information by all who need it.

Toward Our Challenge Goal: Budget Increase Request for Fiscal Year 2005

Broad Research Priorities

(dollars in thousands)

Core Scientific Areas

We will be able to accelerate our understanding of the causes of cancer through large-scale studies in *Genes and the Environment*. \$73,150

We will further explain the biological mechanisms that influence the development and progression of cancer through studies on the *Signatures of the Cancer Cell and Its Microenvironment*. \$35,300

As we more fully understand the causes, development, and progression of cancer, we will be able to accelerate the validation of *Molecular Targets of Prevention, Diagnosis, and Treatment*. \$47,650

And we will continue to expand the discovery and development of *Imaging* tools, accelerate the development of image-guided interventions, and stimulate research on *in vivo Molecular Sensing*. \$44,750

Areas of Public Health Emphasis

We will continue to investigate the pervasiveness and causes of *Tobacco Use and Tobacco-Related Cancers* and apply this knowledge to prevention and treatment. \$75,000

Studies in *Optimizing Energy Balance* will help us better understand the interactions among weight, physical activity, diet, and cancer and apply this knowledge to cancer prevention and control. \$57,800

We will strengthen the scientific basis for public and private decision making to *Improve the Quality of Cancer Care* on behalf of millions of people who do not receive adequate cancer care. \$36,300

We will work to *Reduce Cancer-Related Health Disparities* for the untold numbers of people who suffer because of social or economic status, cultural or language barriers, or geographic location. \$71,300

We will work to better understand *Cancer Survivorship* and develop interventions that will optimize health and quality of life after cancer. \$30,250

Platforms for Discovery, Development, and Delivery

Investigator-Initiated Research builds on the synergism at institutions across the country to ask the critical questions, explore research options, and develop and test innovative technologies. \$123,501

Centers, Networks, and Consortia allow investigators to work in teams, collaborate for progress, and ensure that results advance from discovery to intervention development and delivery. \$96,800

NCI's *National Clinical Trials Program* provides the infrastructure to move new cancer interventions from the laboratory to studies in people and then to the healthcare setting. \$334,900

Enablers of Discovery, Development, and Delivery

We will harness *Bioinformatics* tools to integrate data, capture and share research outcomes, and provide tools for patients to interact more directly with cancer researchers. \$40,800

As we better understand, apply, and disseminate effective *Communication* approaches, we will be able to maximize access to and appropriate use of cancer information by all who need it. \$43,500

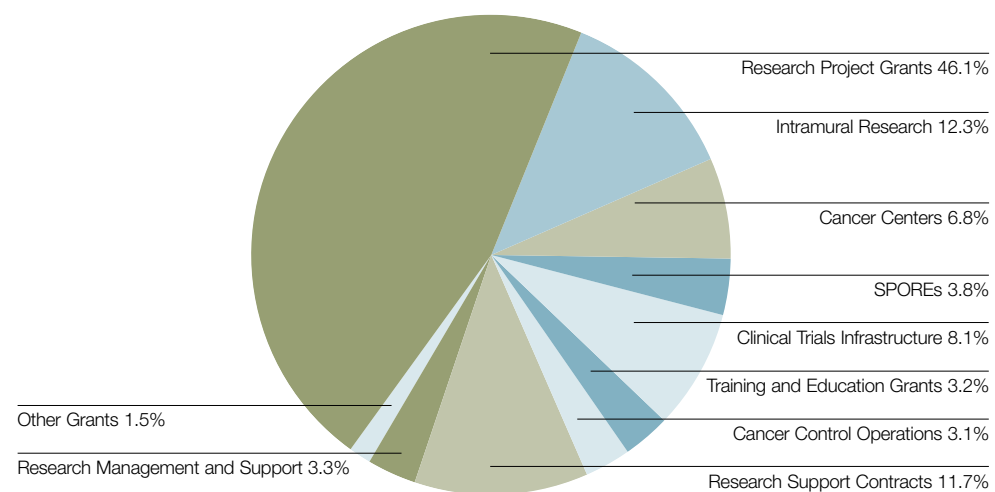
Total Increase Request for Fiscal Year 2005 Priority Areas \$1,111,001



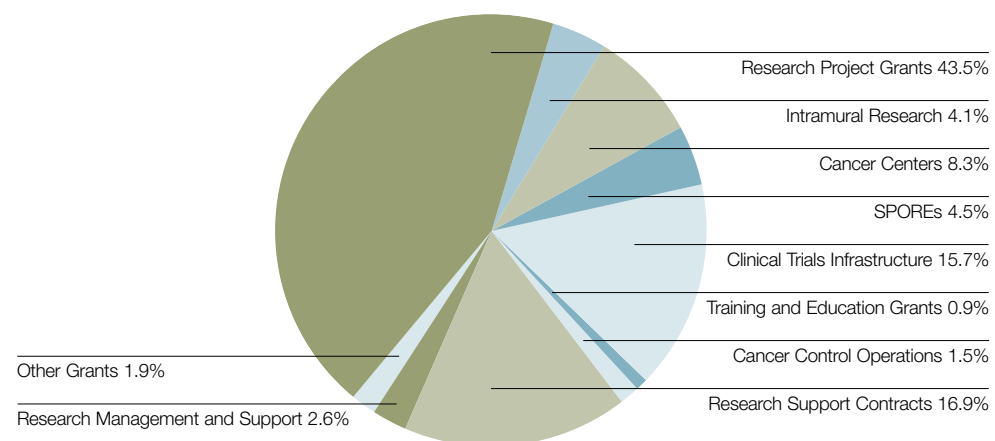
The Nation's Investment in Cancer Research

National Cancer Institute Budget Request for Fiscal Year 2005

Distribution of 2005 Budget Request (\$6,211,000,000)



Distribution of 2005 Requested Increases (\$1,440,481,000)



(dollars in thousands)

	2003 Operating Budget	2004 President's Budget	2005 Budget Request Increases	Total
Research Project Grants (RPGs)				
Ongoing	\$1,588,852	\$1,614,169	\$122,985	\$1,737,154
New and Renewal	491,556	523,295	471,429	994,724
Subtotal RPGs	2,080,408	2,137,464	594,414	2,731,878
Small Business Innovation Research (SBIR)	90,554	101,210	32,566	133,776
Total RPGs	2,170,962	2,238,674	626,980	2,865,654
Intramural Research	648,227	704,551	59,000	763,551
Cancer Centers	267,430	302,281	120,225	422,506
Specialized Programs of Research Excellence (SPOREs)	163,403	170,700	65,383	236,083
Clinical Trials Infrastructure				
Cooperative Clinical Research	156,582	180,330	149,851	330,181
Community Clinical Oncology Program (CCOPs)	95,905	95,458	76,200	171,658
Subtotal Clinical Trials Infrastructure	252,487	275,788	226,051	501,839
Training and Education Grants				
National Research Service Awards	66,570	75,048	3,477	78,525
Research Career Program	69,063	66,827	4,205	71,032
Cancer Education Program	30,849	32,206	4,563	36,769
Minority Biomedical Research Support	8,385	11,372	375	11,747
Subtotal Training and Education Grants	174,867	185,453	12,620	198,073
Cancer Control Operations	172,021	174,355	21,204	195,559
Research Support Contracts	515,190	485,790	243,131	728,921
Research Management and Support	166,483	170,208	37,817	208,025
Other Grants	61,278	62,719	28,070	90,789
Total Budget Request	\$4,592,348	\$4,770,519	\$1,440,481	\$6,211,000
<i>Cancer Control included above**</i>	555,863	554,290	285,087	839,377

Research Project Grants

Funding for extramural research, primarily through investigator-initiated Research Project Grants (RPGs), comprises the largest part of the NCI core budget. Increases through the NCI Challenge and Extraordinary Opportunity initiatives contribute to the expansion of research supported through RPGs. NCI funds about 4,800 RPGs each year to nearly 600 institutions across the United States at an average cost of approximately \$400,000 per grant. If fully supported, our budget request for Fiscal Year 2005 would add \$594 million to the funds available to support investigator-initiated research.

Intramural Research

NCI intramural research focuses on projects conducted by some 400 researchers located on the NIH campus. These researchers build upon the proximity between their research laboratories and the NIH Clinical Center and the synergism among NIH Institutes to support the rapid translation of basic laboratory research to the clinic and to maintain a special focus on long-term epidemiologic and genetics studies.

Cancer Centers and Special Programs of Research Excellence (SPOREs)

Sixty 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. Funding increases will allow NCI to broaden the number and range of activities at Cancer Centers and SPOREs.

Clinical Trials Infrastructure

NCI supports clinical trials at the NIH clinical center and close to 3,000 other sites across the U.S. each year. 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. About three-quarters of this funding is for treatment trials and the other quarter supports prevention and screening trials.

Training and Education Grants

NCI funds approximately 200 institutions and 2,200 individuals each year through extramural cancer research training programs to prepare the next generation of scientists and clinicians to use new technologies and work effectively in interdisciplinary, collaborative research environments. Increased funding will be used to enhance these programs and to support the participation and growth of scientists within 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 other information dissemination activities.

Requested Increases for Fiscal Year 2005

(dollars in thousands)	Core	Broad Research Priorities	Platforms for Discovery, Development, and Delivery	Enablers for Discovery, Development, and Delivery	Total
Research Project Grants (RPGs)					
Ongoing	\$122,985				\$122,985
New and Renewal	62,378	\$260,500	\$131,551	\$17,000	471,429
Subtotal RPGs	185,363	260,500	131,551	17,000	594,414
Small Business Innovation Research (SBIR)	22,566	8,000	-	2,000	32,566
Total RPGs	207,929	268,500	131,551	19,000	626,980
Intramural Research					
Cancer Centers	33,250	15,500	9,500	750	59,000
Specialized Programs of Research Excellence (SPOREs)	9,975	13,250	96,000	1,000	120,225
Clinical Trials Infrastructure					
Cooperative Clinical Research	5,633	40,750	18,000	1,000	65,383
Community Clinical Oncology Program (CCOPs)	5,951	9,000	134,900	-	149,851
Subtotal Clinical Trials Infrastructure	3,150	1,500	71,550	-	76,200
Subtotal Intramural Research	9,101	10,500	206,450	-	226,051
Training and Education Grants					
National Research Service Awards	2,477	1,000	-	-	3,477
Research Career Program	2,205	2,000	-	-	4,205
Cancer Education Program	1,063	3,500	-	-	4,563
Minority Biomedical Research Support	375	-	-	-	375
Subtotal Training and Education Grants	6,120	6,500	-	-	12,620
Cancer Control Operations	13,754	2,450	5,000	-	21,204
Research Support Contracts	16,031	99,800	69,550	57,750	243,131
Research Management and Support	5,617	9,250	18,150	4,800	37,817
Other Grants	22,070	5,000	1,000	-	28,070
Total Increase Request	\$329,480	\$471,500	\$555,201	\$84,300	\$1,440,481

Research Support Contracts

Research support contracts are used to support program efforts across the Institute. Areas that utilize contracts are diverse and include such areas as drug development, cancer control research, information dissemination, and support to epidemiological research.

Research Management and Support

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

Other Grants

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

Unlike the commonly held belief of 30 or 40 years ago, we know today that there are more than 100 distinct types of cancer. We are also learning that several of these have subtypes with unique molecular characteristics that influence how they develop and progress and how they can be effectively prevented, detected, and treated. While the majority of the research supported by NCI has broad application across various types of cancer, we also have in place plans for ensuring coverage of essential research directed toward specific types of cancer. This disease-specific focus is absolutely critical to achieving our Challenge Goal and is bolstered by recent gains in understanding the molecular features both shared by and unique to specific cancers. Ultimately, we look for ways to apply all of our research results to the development and delivery of disease-specific interventions.



NCI's Planning and Evaluation Process for Disease-Specific Research

NCI's planning and evaluation process for disease-specific research involves three distinct phases: (1) developing recommendations through external Progress Review Groups (PRGs), (2) planning for and implementing initiatives that respond to these recommendations with advice from internal implementation working groups, and (3) reporting on progress. This comprehensive and integrated approach to planning and evaluation helps us demonstrate progress toward our Challenge Goal and the wise use of resources to the scientific community and the public. Through these and other crosscutting efforts,

NCI has established a framework for accountability that is consistent with the President's Management Agenda (PMA) and the congressionally mandated Government Performance and Results Act (GPRA).

During the past seven years, NCI has called upon a number of PRGs, each composed of prominent members of the scientific, clinical, industry, and advocacy communities, to assess the state of the science and recommend future research-related priorities for specific types or groups of related cancers. Go to prg.nci.nih.gov for additional information about and reports from each of these PRGs.

Impacts of PRGs on Disease-Specific Research Agendas

PRG recommendations are central to sustaining the best possible science and making the fastest advances against specific cancers and have proven to be a valuable asset to NCI strategic planning. For example:

- **PRGs have helped shape research directions.** PRG reports have had substantial impact. NCI divisions and programs use them in planning and developing new initiatives. Extramural scientists cite them in their grant applications. They are cited regularly in Congressional documents. And they are used by advocates, researchers, and members of professional societies to attract funding from other sources.
- **PRGs have led to an expanded understanding and awareness of opportunities related to cancer research.** PRG members and roundtable participants report that new collaborative research relationships have been formed as a result of their interactions with a diverse, multi-disciplinary group of people involved in all aspects of cancer research.

ment Delivery

- **PRGs have led to the development of new information tools.** Developed in response to needs identified by the groups, new tools are now available to aid both NCI staff and the community in learning about and responding to needs and opportunities for cancer research. For example, the Common Scientific Outline is a classification system that provides a consistent approach to comparing and assessing cancer research supported by different funding organizations. The Cancer Research Initiatives Website provides user friendly access to a database of selected NCI research funding opportunities that can be searched by type of research or type of cancer. And the Cancer Research Portfolio Website provides a structure for searching, organizing, and analyzing NCI-supported research by type of cancer and/or type of research.
- **PRGs have provided new opportunities for interaction between NCI and the extramural community.** Participants have found the PRG venue a very effective way to gain input from the wider community and for individuals to influence both NCI priority setting and overall disease-specific priority setting.

The NCI PRG process has been highly successful as a model for gaining outside input and feedback focused on opportunities, needs, and gaps in research and fostering greater understanding of common issues across diseases. Similar approaches have now been adopted by other research funders including the National Institute of Neurological Disorders and Stroke (Stroke Research), the National Institute of Diabetes and Digestive and Kidney Diseases (Bladder Disease Research), the National Institute on Aging (Exploring the Role of Cancer Centers for Integrating Aging and Cancer Research), the Department of Health and Human Services (Cancer Health Disparities), and the National Cancer Research Institute of the United Kingdom.

Collaborations for Assessing PRG Recommendations

NCI recognizes that research agendas developed by the PRGs are larger than we can address alone. Therefore, NCI works to engage other organizations that fund cancer research in addressing PRG recommendations and collaborating on relevant initiatives in order to leverage and optimize collective research efforts. To this end, NCI is bringing together groups of cancer funders to focus on joint implementation of research agendas. The objectives of these meetings are to:

- Share and discuss information on ongoing and proposed initiatives related to specific cancers in order to identify common areas of emphasis, eliminate duplication, and address gaps in critical research areas.
- Establish consensus on where the most serious gaps are and identify organizations that will be able to fill them.
- Identify opportunities for collaboration or coordination in areas of mutual interest.
- Establish a plan of action that includes mechanisms for continued communication and reporting on progress.
- Optimize deployment of resources among participating groups.

**I'm only 13
years old, and
now they tell me
I have cancer?**



"I knew I was sick, but I thought I would just get better. I never thought about this. Almost nobody gets this disease. Is anybody working on a better treatment?"

Ewing's sarcoma is a rare malignant bone tumor that occurs in children and adolescents, with highest known incidence among Caucasian males. About 150 new cases are reported each year in the United States. Prior to the new treatment regimen highlighted here, 50 to 60 percent of patients without metastases and about 25 percent with metastases have survived at least 5 years.

The Sarcoma Progress Review Group

In 2003, NCI launched a PRG to focus on sarcomas, a general group of less common cancers in which the cancer cells arise from or resemble normal cells in the body collectively known as "connective tissues." Normal connective tissues include fat, blood vessels, nerves, bones, muscles, deep skin tissues, and cartilage.

Sarcomas in general are rare tumors, accounting for less than five percent of adult malignancies and less than 20 percent of pediatric cancers. Nearly half of all sarcoma patients die of the disease. The most common forms of sarcoma include:

- **Soft tissue sarcomas** that originate in connective tissues, fat, blood vessels, nerves, joints, muscles, cartilage, and deep dermal tissue. They occur more often in adults.
- **Osteosarcoma**, which is the most common type of bone cancer. In children, it occurs most commonly in the bones around the knee. Although osteosarcoma occurs most often in adolescents and young adults, about 10 percent of cases develop in people in their 60s and 70s.
- **Kaposi's sarcoma (KS)**, which usually develops in the skin or in the lining of the mouth, nose, or eye. In the last 20 years, the vast majority of KS cases have developed in association with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS).

As with past efforts, the Sarcoma PRG is soliciting extensive input from the research and advocacy communities and is examining the NCI's research portfolio as well as research funded by other institutes and organizations for these cancers, with the goal of identifying scientific priorities and resource needs for making progress against all sarcomas. A written report describing the group's findings and recommendations will be presented to the NCI and disseminated widely within the cancer community. The PRG will then meet with NCI leaders to discuss NCI's plan for addressing the recommendations.

Modified Chemotherapy Regimen Improves Survival for Ewing's Sarcoma Patients

Since the introduction in the 1970s of adjuvant chemotherapy for patients with Ewing's sarcoma, survival rates for patients with this disease increased dramatically but are still considerably low. Recently, scientists have discovered that the addition of the drugs ifosfamide and epirubicin to standard chemotherapy seems to improve treatment outcomes for relapsed patients with either Ewing's sarcoma or the closely related primitive neuroectodermal tumor of the bone. These findings led investigators to test this treatment regimen in newly diagnosed patients. Although outcomes for patients with metastatic disease were not improved, the added drugs significantly improved survival in patients with newly diagnosed nonmetastatic disease. After five years, 69 percent of patients who received the experimental drug regimen were disease free, compared to 54 percent of those treated with standard therapy. Overall five year survival was 72 percent in the experimental therapy group, compared with 61 percent in the group treated with standard therapy. Although patients receiving experimental therapy suffered more infections and spent more time in the hospital, overall toxicity levels were similar between the two groups. These findings hold promise for patients with Ewing's sarcoma and primitive neuroectodermal tumor of the bone.

Broad Research Priorities: Optimizing New Knowledge and Opportunities

NCI's Action Plan for 2005 includes ongoing work in nine broad research priorities for focused efforts in core scientific and public health emphasis areas. Identified with assistance from our advisory boards, the larger research community, and the cancer advocacy community, these investments will allow us to accelerate the pace of discovery and to optimize use of existing and new knowledge for the development and delivery of evidence-based interventions.

Core Scientific Areas

Reaching our Challenge Goal to eliminate the suffering and death due to cancer will require long-term investment in large-scale and interdisciplinary studies to:

- Understand the interactions between *Genes and the Environment* as they relate to cancer.
- Elucidate the *Signatures of the Cancer Cell and Its Microenvironment* through a more integrative approach to cancer biology.
- Validate and develop effective agents aimed at *Molecular Targets of Prevention, Diagnosis, and Treatment*.
- Optimize *Cancer Imaging and Molecular Sensing* to both further research and allow for less invasive and more accurate cancer care.

As we more fully understand cancer-related molecular, cellular, microenvironment, behavioral, psychological, and social influences, we can develop more effective and less harmful approaches to cancer prevention, early detection, diagnosis, treatment, and control.

Areas of Public Health Emphasis

Purposeful investment must also be made for research and development in the public health arena:

- *Tobacco and Tobacco-Related Cancers*. We can no longer ignore the damage done by tobacco use in this country and the lure of smoking to our youth.
- *Energy Balance*. We must face the issues of overweight and obesity and the sedentary lifestyle that is plaguing our country and raising people's risk of developing cancer.
- *Quality of Cancer Care*. We must work on behalf of the millions of people in our country today who do not receive appropriate care for their cancer.
- *Cancer-Related Health Disparities*. Untold numbers of people suffer disproportionately from cancer and receive poorer care because of social position, economic status, cultural or language barriers, or geographic location.
- *Cancer Survivorship*. The numbers of people surviving cancer have increased dramatically over the past several years. Sadly, a large portion of these people suffer post-treatment effects and do not receive the continued care they need.

Investment in each of these areas is at the heart of our ability to reach our Challenge Goal to eliminate suffering and death due to cancer. In each instance, we need better science to understand the complexities. And there is a pressing need to address the challenges posed to our Nation's healthcare system by the rising incidence of cancer in the aging U.S. population. For all Americans, we need evidence-based interventions that will prevent cancer from occurring and improve the health and quality of life for those who are affected by cancer.

Genes and the Environment

Cancer is a complex disease that develops when errors occur in a person's genes. Some of these genetic errors are inherited. Others result from certain environmental exposures or individual behaviors, usually coupled with inherited susceptibility. Through the use of increasingly sophisticated molecular technologies and the tremendous resource generated by the mapping of the human genome, scientists now know that some inherited genetic errors nearly always give rise to cancer, regardless of a patient's environmental or lifestyle history. For example, carriers of mutations in the gene for familial adenomatous polyposis are almost certain to develop colon cancer. Other mutations present at birth only lead to cancer in combination with certain environmental exposures. This relationship is seen in women with *BRACA* mutations, who are at increased risk for hormonally induced breast cancers. Still other cancers are caused by long-term damage to multiple genes caused by environmental factors, with some people inherently at higher risk than others. For instance, people with certain combinations of genetic mutations to the *NAT2* gene are at increased risk for smoking-related bladder cancer.

Scientists have developed technologies to compare complex profiles of genes and proteins from cancer patients to corresponding profiles of cancer-free individuals. This innovation is helping to identify specific molecular profiles associated with cancer risk.

New tools and technologies are helping us to better assess who is at risk for specific cancers based on genetic makeup and environmental exposures. Furthermore, we are increasingly able to identify and assess a variety of carcinogenic exposures encountered outdoors, in the home, and in the workplace. These include pollutants in air, water, and soil; components of food, tobacco, alcohol, and drugs; sunlight and other forms of radiation; and infectious agents. Other new technologies are revealing the intricate biological processes involved in the development of cancer.

To build on this progress, NCI must continue to develop novel ways to study the complexities of genetic and environmental contributions to cancer. We must support both individual efforts and large collaborative programs to maximize the availability of population data, biospecimens, laboratory models, and *in vitro* observations. In particular, large-scale studies with new levels of interdisciplinary cooperation and innovation are needed. These 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 adverse exposures.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

NCI is pursuing research opportunities in several growth areas to better understand cancer-related genes, environmental and lifestyle factors, and their interactions.

Building Capacity through Large-Scale Collaborations

NCI continues to promote collaboration through cohort consortia, bringing together researchers across the United States and Europe who are studying the same disease site to collaborate and pool exposure data and biospecimens. This type of data pooling is essential for detecting patterns. The Cohort Consortium for Breast and Prostate Cancer pioneered the approach and developed the Hormone-Related Gene Variants program to identify genes that may influence a person's susceptibility to hormone-related breast or prostate cancer and to develop methods of data sharing across genome and genotyping centers, removing a major obstacle to consortium research.

NCI and NIEHS collaborations encourage the development and use of innovative methods for assessing difficult to measure environmental exposures.

NCI also supports development of **case-control consortia** composed of epidemiologic investigators studying less common cancers. For example, the InterLymph Consortium is studying the genetic and environmental basis of non-Hodgkin's lymphoma. Another consortium is focusing on brain tumors. Members of the NCI-supported Health Maintenance Organization Cancer Research Network are pooling their resources to develop the largest ever case-control study of pancreatic cancer. In addition, we are examining the feasibility of a cohort study in India to focus on nutrition and gene-diet interactions in cancer causation.

Assessing and Measuring Environmental Exposures

NCI and the National Institute of Environmental Health Sciences (NIEHS) continue to support interdisciplinary **collaborations for improving research tools** used in etiologic studies of cancer and risk assessment. For example, these institutes are funding centers for the study of breast cancer risk associated with environmental exposures and several projects to support the use of geographic information systems in cancer epidemiology and control studies.

NCI scientists are using innovative **nanotechnologies in molecular profiling** to examine chromosomal alterations and changes in protein levels following exposure to environmental carcinogens. For example, scientists have found that changes in the levels of proteins following alteration of their gene precursors by the biochemical process of methylation are associated with the development of cancer.

Discovering and Characterizing Cancer Predisposing Genes in High-Risk Families

NCI's **Interdisciplinary Studies in the Genetic Epidemiology of Cancer** emphasize case-control and familial studies of gene-environment interactions for various forms of cancer. NCI-supported work includes a consortium of investigators searching for pancreatic cancer susceptibility genes, the Colon, Breast, and Ovarian Cancer Family Registries (CFRs), a high-risk families tissue resource, and other family registries and collaborative groups working to identify susceptibility genes for prostate cancer and other familial cancer syndromes including melanoma, renal cancer, testicular cancer, and brain tumors.

The **Cancer Genetics Network (CGN)** is a major NCI-supported infrastructure for studies of persons at high risk for developing cancer and for related translational research. CGN pilot studies combine existing and prospectively collected data to discover potentially important gene-environment interactions. The Network holds epidemiologic data on participants consistent with data collected by other NCI-supported consortia and registries, allowing the information to be used either independently or in combination with other groups. The CGN implemented and improved upon a state-of-the-art clinical trials informatics system (Trial-DB) across all Network sites.

CGF researchers develop and validate assays for gene sequence verification in conjunction with the SNP500 cancer program.

Developing and Improving Resources for Gene Discovery and Characterization

NCI is providing readily available resources to support researchers studying gene-environment interactions in cancer causation, including the following:

- The **Cancer Genome Anatomy Project (CGAP)** continues to provide genomic resources for identifying and studying cancer genes. For example, CGAP's Mammalian Gene Collection establishes reference clones validated by sequence analysis for research use and has importance for both *in vitro* and population-based studies. The SNP500 program provides sequence verification of single nucleotide polymorphisms (SNPs). SNP500 will also develop assays for the Cohort Consortium, making all information immediately available on the Web. (For more information on these and other CGAP programs, see pages 16-17.)
- NCI has developed a high-throughput **Core Genotyping Facility (CGF)** to support case-control and cohort studies in partnerships with the National Human Genome Research Institute, the Centers for Disease Control and Prevention, and academic and commercial organizations. The CGF provides high-throughput genotyping and gene sequencing, including verification of SNPs and other types of genetic variations. The Facility is also a test site for the development of policies, systems, and infrastructure to expedite data analysis of large-scale interdisciplinary studies and to enhance data sharing.
- CGN has substantially increased the number of participating patients and family members in its **biospecimen repository**.
- CFRs are developing a **repository of EBV-transformed cell lines**¹ from patients and selected family members for use by researchers.
- The **Gail Model** is a statistical tool to help estimate a woman's risk of breast cancer based on a number of predisposing factors, including family history. A study examining mammographic density as a risk factor for breast cancer development was completed recently, showing this characteristic reliable enough to be formally included in the model.
- NCI continues to support **workshops to develop collaborative studies** between population scientists and groups developing mouse models of cancer for the localization and characterization of cancer susceptibility genes.

Improving Quality Control Measures to Maximize the Value of Specimens

Biological specimens collected from patients, people at risk for cancer, and their families must be processed and stored according to strict requirements. This level of care is needed to ensure that the specimens are of sufficient quality to be used in a wide variety of assays and test procedures. NCI and partners are helping to develop and disseminate procedures to safeguard the quality of such samples. For example:

- CFRs support academic-commercial **biotechnology partnerships** to establish an integrated and standardized infrastructure for the collection and management of biospecimens from large populations, the production of related microarrays, and the development of novel relational data management software for associated molecular, clinical, and risk factor data.

¹ Cells taken from individuals normally do not live long *in vitro*. Cells "transformed" by *in vitro* infection with Epstein-Barr virus (EBV) will live and replicate indefinitely, providing a ready supply for research.

- CGF activities include sponsorship of **conferences on specimen handling and quality control** for DNA storage and analysis.
- NCI's intramural Epidemiology and Carcinogenesis Faculty has sponsored national **workshops on how to process specimens** to optimize their use in conjunction with current technologies. This faculty also helped found the International Society for Biological and Environmental Repositories, which developed a "**best practices**" document for the collection and storage of specimens.
- A series of NCI-supported studies have established an **optimal protocol for collecting oral epithelial cell samples** for genetic testing from large populations by mail, and pilot work has established acceptably high rates of compliance by study populations. Progress has been made in addressing issues of potential DNA damage by irradiation of samples during transport through the mail.
- The NCI Center for Bioinformatics has recommended a set of **informatics standards, guidelines, and procedures** for handling and storage of biospecimens.

Development

Supporting Intervention Trials and Translational Research on Inherited Susceptibility

NCI scientists and CGN are conducting a collaborative, prospective **study of risk reduction in women at high genetic risk for breast and ovarian cancers**. Researchers are comparing and evaluating two risk reduction strategies: preventive removal of the ovaries and fallopian tubes and a novel screening strategy. Investigators will include the impact of these procedures on quality of life in their evaluation.

NCI is also collaborating with the National Surgical Adjuvant Breast and Bowel Project to **genotype participants in the Breast Cancer Prevention Trial**, which showed that tamoxifen reduced the risk of breast cancer among high-risk women. Collaborators will focus on determining if variants in genes related to estrogen and tamoxifen metabolism can identify subsets of women who might be more or less likely to benefit from tamoxifen.

NCI is researching **alternative screening techniques for early breast cancer detection** in women genetically at risk for the disease. These include magnetic resonance imaging (MRI), positron emission tomography (PET) imaging, and *in vitro* analysis of cells obtained from breast duct lavage.

GOAL

Discover those genetic, environmental, and lifestyle factors and their interactions that define cancer risk and that can inform the development and delivery of new strategies for prevention, early detection, and treatment.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

- 1. Identify susceptibility genes, haplotypes, and epigenetic events, and their interactions with environmental factors in cancer causation. \$32.00 M**

 - Continue to investigate interactions among susceptibility genes, haplotypes, and environmental risk factors through support to the Cohort Consortium:

 - Plan and support studies of additional cancer sites, using the results of the study of hormone-related variants and breast and prostate cancer. \$5.00 M
 - Increase the number of study participants and cancer types, enhance population diversity, and augment the biospecimen repository by continuing to expand the number of participating cohorts. \$3.00 M
 - Continue to investigate gene-environment interactions in lymphoma, brain, melanoma, prostate, and other selected cancers through case-control consortia. Fully support population-based and hospital-based studies to analyze pooled data for genetic and environmental susceptibility factors. \$1.00M
 - Conduct new initiatives in resequence analysis of genes chosen from known biological pathways or identified by microarray expression or comparative genomic hybridization analysis.
 - Study cancers of high lethality by combining data from several studies using a consortial approach. \$15.00 M
 - Study populations at low risk of cancer to identify genes that may confer resistance to tumor development and environmental factors that may modulate the effect of these genes. \$8.00 M
 - Provide a forum for developing innovative new investigations through a consortium of groups capable and willing to conduct site-specific, case-control, and consortial studies.

- 2. Develop new ways to assess and measure environmental exposures for use in population studies. \$6.00 M**

 - Continue to develop new noninvasive techniques for collecting and analyzing genes and gene products in very small biologic samples by expanding the Innovative Molecular Analysis Technologies Program. \$2.00 M
 - Continue to apply and validate measures of the cumulative cellular, genetic, and molecular effects of environmental exposure through funding supplements for ongoing research programs. \$3.00 M
 - Develop improved measures of nutrition and energy balance and of components of tobacco use. \$1.00 M

- 3. Identify cancer predisposing genes in high-risk families and investigate how other genes and environmental factors modify expression of these genes. \$11.00 M**

 - Extend studies and the geographical and population diversity of registries for familial cancers as well as additional heritable cancer sites in the United States, in cooperation with the Surveillance, Epidemiology, and End Results Program (population data) and Cancer Centers/Specialized Programs of Research Excellence (patient data). \$4.00 M
 - Expand the family registries for breast, ovarian, and colon cancers. \$7.00 M

4. Develop and improve tools and infrastructures for the study of gene-environment interactions in human populations. \$11.00 M

- Continue to maximize the quality, efficiency, and cost-effectiveness of specimen collection, processing, storage techniques, and high-throughput assays for human population studies and develop pilot feasibility projects for regional genotyping facilities. \$3.00 M

 - Develop with other NIH institutes a comprehensive informatics system to capture store, analyze, and integrate the expanding amount of information generated by studies of gene-environment interactions. \$4.00 M

 - Accelerate identification, validation, and development technologies for genetic epidemiology studies through the Cancer Genome Anatomy Project. \$1.00 M

 - Facilitate the localization of cancer susceptibility genes in humans and determine their function, by supporting the Mouse Models of Human Cancers Consortium, which has targeted mouse models in breast, colon, prostate, and pancreatic cancer. \$3.00 M
-

Development

5. Support collaborative studies of high-risk individuals to address the clinical, behavioral, and societal issues associated with cancer susceptibility. \$12.00 M

- Facilitate studies of outcomes for early detection, diagnosis, and treatment of genetically high-risk individuals, especially those from minority and underserved populations, through resources provided by the Cancer Genetics Network.

 - Expand development of effective strategies to communicate cancer risk information to high-risk persons, patients, healthcare providers, and the public and maximize the recipients' abilities to make decisions and choices. \$4.00 M

 - Refine cancer risk prediction methods/models to integrate genetic and environmental determinants of cancer among diverse populations. \$1.00 M

 - Study the screening and treatment choices and preventive and other health behaviors of cancer survivors and persons at known genetic risk or in families with a high prevalence of cancer. \$2.00 M

 - Conduct observational studies, and trials where appropriate, of the long-term risks and benefits of currently used cancer risk reduction strategies (e.g., surgical, drug) for genetically high-risk individuals. \$5.00 M
-

Management and Support		\$ 1.15 M
	Total	\$73.15 M

Signatures of the Cancer Cell and Its Microenvironment

Thirty years ago, cancer was a poorly understood, and usually deadly, disease. Today, we have a far better understanding of how cancer develops and progresses within the human body. We know that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell also change. These changes form unique, measurable molecular “signatures” that signal the presence of disease. This more robust understanding of the genetic changes within a cancer cell — and the resulting changes in the production and function of proteins — has altered the course of cancer research and has fueled new approaches to prevention, detection, diagnosis, prognosis, and treatment.

NCI's long-range goal for signatures research is to characterize the interactions between a tumor and its microenvironment and these with the entire body. Defining more fully this range of molecular signatures for cancer will dramatically increase our understanding of cancer development, detection, diagnosis, and prognosis and lead to the identification of new targets for prevention and treatment.

Scientists also realize, however, that they cannot view cancer as a self-contained collection of malignant cells but must consider the integral association of the cancer with its host environment. This “tumor microenvironment” includes a variety of cell types, their behavior often altered through interaction with the cancer cells. The microenvironment is also rich in growth factors and enzymes and includes parts of the blood and lymphatic 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 tumor cells, the body's processing of treatment agents, and the development of resistance to cancer treatments. Both cancer cells and their surrounding environment need to be fully characterized in order to understand how cancer grows in the body, and both need to be considered when developing new interventions to fight the disease.

The interactions between cancer cells and their microenvironment permit, and even encourage, cancer progression. Scientists are deciphering the signatures of cancer cells, those of seemingly normal cells in the tumor microenvironment, and signatures that reflect changes that occur as cancer cells interact with the host environment.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery and Development

Cancer researchers continue to make significant progress in understanding the genetics and biology of precancerous and cancerous cells and cells within the tumor microenvironment. They are defining the molecular signatures of these cells and identifying those that can be used as markers for early detection, diagnosis, or prognosis or be targeted by new interventions for prevention or treatment.

Searching the Genome for Cancer Signatures

All Cancer Genome Anatomy Project (CGAP) data and resources are readily available to the biomedical research community, enabling researchers to find “in silico” answers to biological questions in a fraction of the time it once took in the laboratory. In 2003, CGAP and its private, academic, and industry partners made several new resources available to the research community.

- Through the **SAGE Genie Anatomic Viewer**, a scientist can identify the genes uniquely expressed in specific cancers. One team of researchers has used this tool to identify a gene previously known to be overexpressed in **prostate cancer** that also appears to be a marker for metastatic **breast cancer** (cgap.nci.nih.gov/SAGE/AnatomicViewer).
- Through the **CGAP SNP500 Cancer Project**, scientists are currently examining samples taken from individuals of four ethnic groups to find known or newly discovered single nucleotide polymorphisms (SNPs) of immediate importance to molecular epidemiology studies in cancer (snp500cancer.nci.nih.gov/home.cfm).

CGAP and private-sector Affymetrix scientists are collaborating to develop a new technological approach that will ultimately enable cancer researchers to peer more deeply and broadly into gene expression changes in cancer. These scientists have produced whole chromosome chips for chromosomes 21 and 22, allowing researchers to look at genetic activity in all regions of these chromosomes, and have discovered thousands of previously unknown regions that contain coding for proteins. This approach may also provide a valuable tool for discovering “hidden” RNA activity that may have an important structural or regulatory role in the cell.

- **SAGE Genie** is an informatics system that provides a view of all CGAP data produced through the Serial Analysis of Gene Expression (SAGE) approach. SAGE can be used to distinguish normal cells from tumor cells and to reveal potential markers for detection or diagnosis.
- CGAP scientists have collaborated with scientists from Lynx Pharmaceuticals, the Ludwig Institute, Duke University, and Johns Hopkins University to use a new technique known as **Massively Parallel Signature Sequencing (MPSS)** to study genes that are expressed at relatively low levels, as well as functional relationships among genes, greatly increasing our ability to find all the genes that are important to cancer.

Searching the Proteome for Cancer Signatures

Proteomics, the comprehensive study of proteins and their functions, is an important complement to studies exploring the genetic changes associated with cancer. Scientists at NCI and the Food and Drug Administration (FDA) are working together through the **Clinical Proteomics Program (CPP)** to explore complex protein patterns and define protein profiles that can be used for early detection, diagnosis, prognosis, and treatment monitoring.

- CPP scientists are developing a **screening test for ovarian cancer** that has demonstrated an ability to successfully use complex protein pattern analysis to distinguish with 100 percent accuracy between ovarian cancer patients and unaffected persons. A refined test even promises to accurately detect Stage 1 ovarian cancers, a potentially curable stage for which no reliable screening tool is yet available.
- CPP investigators are examining **serum protein patterns** that may someday help clinicians determine whether men with mildly elevated prostate-specific antigen (PSA) levels have **prostate cancer** or need no further diagnostic analysis and treatment. Such a test could save many men from having to undergo biopsy and help them make more informed decisions about “watchful waiting.” Similar studies are being conducted to identify protein profiles for detecting and diagnosing **pancreatic, breast, and lung cancers**.

Providing Resources for Molecular Profiling

Scientists now have the **tissue microarray tool** as a quick and cost-effective means of performing automated, high-throughput analyses of multiple cancer tissues and can use that information to develop and validate molecular profiles of tumor cells. Microarray slides contain as many as a thousand tissue specimens of a specific cancer and can be used to determine whether specific genes are valuable biomarkers for cancer and whether the protein encoded by the candidate gene affects the tumor’s behavior and holds potential as a molecular target for treatment. Researchers can use microarray technology to perform the equivalent of hundreds of experiments simultaneously. The **Tissue Array Research Program (TARP)**, a collaborative effort with the National Human Genome Research Institute, has allowed one research team to study the ***Akt* oncogene**, which encodes a protein that blocks programmed cell death and its signaling pathway in different types of tumor cells. These investigators found that cellular signaling through this pathway varied among different tumor cells, suggesting tumor type-specific targets for therapy and highlighting the complexity of signaling pathways in human tumors.

Several researchers are developing **microarrays and nanotechnologies** such as carbon nanotubes, nanowires, microcantilevers, and quantum dots through NCI's **Innovative Molecular Analysis Technologies (IMAT)** program. These molecular sensing tools can be used to analyze interactions among proteins, perform molecular classification of tumors, conduct high-throughput screening, and predict therapeutic efficacy.

Using Molecular Signatures for Early Detection of Cancer

Scientists in the **Early Detection Research Network (EDRN)** have applied advances in genomics and proteomics to discover a variety of promising biomarkers including two genes unique to **ovarian cancer**, chemical modification (methylation) of specific genes predictive of **lung cancer**, and protein patterns predictive of **prostate cancer**. They are also applying a recently formulated roadmap outlining the five key phases of biomarker development to evaluate microsatellite instability as a marker for **recurrent bladder cancer**. Similar tests may eventually be developed for screening other cancers that shed cells into body fluids, such as tumors of the oral cavity and the gastrointestinal tract.

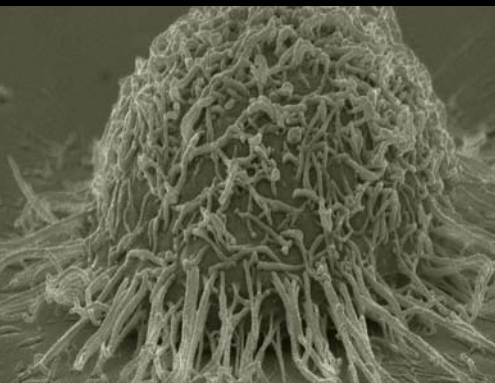
Developing Better Classification Schemes to Improve Diagnostic Tests

Researchers supported through the **NCI Director's Challenge: Toward a Molecular Classification of Tumors** (dc.nci.nih.gov) use comprehensive molecular analysis technologies to help scientists identify better strategies for classifying tumors and in turn allow for more accurate diagnosis and prognosis as well as the opportunity to select therapies tailored to individual patients through the targeting of specific molecular features. Director's Challenge investigators recently studied the gene expression patterns of **ovarian cancer** tumors to develop a molecular classification. Their classification provided insight into why some subtypes have a worse prognosis than others. This type of gene profiling may lead to improved patient diagnosis and prognosis for a broad range of cancers and provide clues for identifying molecularly targeted interventions.

Using Molecular Signatures to Study Models of Human Cancer

In less than 4 years, **Mouse Models of Human Cancers Consortium (MMHCC)** investigators have rapidly evolved a suite of novel approaches for mouse germline engineering and biological analysis. These fundamental advances are furnishing the research community with cancer-prone strains that not only accurately mimic human cancers but also support unprecedented discoveries about these cancers. One research team made an important discovery using a mouse model for human **breast cancers** caused by overexpression of the gene *c-Myc*. They identified a gene expression pattern in these animals that has also been found in human *c-Myc*-related breast cancers. This finding provides valuable clues for distinguishing among human cancer subtypes. Comparable studies on models of **other malignancies** are underway with similar results.

Research on Cancer and Viruses — Attacking the Cancer Burden



Cervical cancer cell.

This large rounded cell has an uneven surface with many cytoplasmic projections, which may enable it to be motile. Typically, cancer cells are large and they divide rapidly in a chaotic manner. Cancer cells may clump to form tumors which may invade and destroy surrounding tissues. Cancer of the cervix (the neck of the uterus or womb) is one of the most common cancers affecting women.

Studies suggest that as many as 15 percent of all cancers worldwide may be caused, at least in part, by viral infections. Clearly, effective prevention and treatment interventions aimed at these cancers are critical to reducing the cancer burden. The drastic reduction in cervical cancer mortality since 1955 is one success story. This disease, found only in women infected with human papillomavirus, was once the most common cancer killer of women. Thanks to detection of virus-related lesions by Pap testing, this disease can now be detected early and is highly curable. However, with the advent of the HIV/AIDS pandemic, certain virus-related cancers are becoming more prevalent, both nationally and worldwide. Immunocompromised HIV/AIDS patients are vulnerable to infections and associated cancers that healthy individuals would easily resist.

To successfully address cancers caused by viral infection, we must learn more about the biological mechanisms of their development and progression and apply this knowledge to develop effective treatment and prevention measures. Highlighted below are a few recent NCI-supported national and international collaborations that are providing greater insights into virus-related cancers.

- Human papillomavirus is the primary cause of cervical cancer. Investigators are developing a vaccine to prevent cervical and other cancers caused by this virus.
- Epstein-Barr virus (EBV) infection, although usually benign, can promote aggressive lymphomas, soft tissue tumors in HIV-infected children, and other tumors. Researchers are studying the epidemiology of EBV-related tumors and are developing novel therapies including strategies that harness the immune system to attack cancer cells. Investigators are also exploring a possible link between EBV and some aggressive breast cancers.
- Infection with hepatitis virus B or C increases a person's risk of developing liver cancer. Scientists are investigating how genetic and environmental factors interact to make some infected individuals more at risk than others.
- Human T-cell lymphotropic virus causes adult T-cell leukemia. Investigators are studying the natural history of this virus, how the virus is transmitted between individuals, and risk factors for cancer progression.
- Human herpesvirus-8 (HHV-8) is associated with Kaposi's sarcoma and aggressive lymphomas, particularly in HIV-positive individuals. Scientists are examining the epidemiology of this virus, identifying routes of transmission, researching strategies to prevent infection and tumor development, and developing novel therapies for Kaposi's sarcoma and other tumors caused by HHV-8.
- Investigators are developing better treatments for AIDS-related lymphomas, making this previously universally fatal disease highly curable in many patients. (See page xix.)

GOAL

Accelerate our progress in understanding the dynamic interaction between cancer cells and their microenvironment and our application of this knowledge to the detection, diagnosis, prevention, treatment, and control of all cancers.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

- 1. Define the molecular signatures of cells in the cancer microenvironment at various points during the initiation and progression of cancer. Compare the molecular signatures of stromal and cancer cells during development and aging. \$9.50 M**

 - Promote the analysis of cancer as a complex biological system by establishing an Integrative Cancer Biology Program, with the ultimate goal of developing reliably predictive models for “in silico” development of cancer interventions. \$2.00 M
 - Provide a focus for research into the dynamic interaction between cancer cells and their microenvironment and a forum for the exchange of information and resources by supporting a series of new initiatives relating to the microenvironment of tumors. \$3.50 M
 - Facilitate the analysis of normal and cancerous cell samples for signature profiling studies by establishing a national core facility. Develop a database of the molecular signature profiles of cells in the microenvironment and make these data readily available to the research community. \$1.00 M
 - Advance the development of nanoparticles, molecular beacons, and high-resolution sensors for cancer signature detection, targeting, and treatment from the development stage into clinical trials and translation into the clinic, through expansion of the Unconventional Innovations Program (UIP). \$1.50 M
 - Expedite the translation of micro- and nanotechnology tools for detecting molecular signatures of cancer and monitoring major signal transduction networks into products that can be used in clinical practice, through expansion of the Innovative Molecular Analysis Technologies Program (IMAT). \$1.50M
- 2. Define the dynamic communications among cancer cells, surrounding cells, and immune cells that control or promote primary and/or secondary tumor growth. Characterize the interaction between the immune system and the cancer cell during cancer initiation and progression. \$8.00 M**

 - Identify the factors used by cancer cells to activate cells in the tumor microenvironment that support tumor growth and progression. Encourage studies that explore the unique role the bone microenvironment plays in metastasis of cancer to bone, focusing in particular on breast cancer, prostate cancer, and myeloma. \$3.50 M
 - Identify the origin of the cells and factors that comprise the tumor microenvironment. \$2.00 M
 - Develop organotypic culture systems that accurately model the interaction between the cancer cell and the tumor microenvironment in living systems. Make these systems readily accessible to the research community. \$1.00 M
 - Identify the molecular composition and physiological or pathological contributions of extracellular matrix components to biological properties such as survival, proliferation, and migration of normal and malignant cells. \$1.50 M

3. Support new approaches to provide the research community with rapid access to validated reagents. \$7.00 M

- Establish a repository for antibodies, cell lines, animal models, and tissues that relate to cells in the microenvironment. \$2.00 M

- Establish a database that includes comparisons of cellular interactions between cancer cells and surrounding cells in animal models and in humans. \$1.00 M

- Identify proteins and proteomic signatures in microdissected tissue samples of human cancers (normal epithelium, premalignant lesions, adjacent tissue, and invasive tumors) through expansion of the Clinical Proteomics Program. \$4.00 M

4. Stimulate progress in understanding the role of stromal cell interactions in cancer development by establishing a spectrum of educational and communication initiatives involving scientists across disciplines and with a broad range of expertise. \$4.00 M

- Encourage multi- and trans-disciplinary investigations by establishing a new funding mechanism to allow co-investigators from different scientific fields to submit a collaborative grant application. \$2.00 M

- Develop training curricula for students and established investigators and facilitate the development of novel studies in understanding the role of cellular interactions in cancer development, by establishing national trans-disciplinary training centers. \$2.00 M

Development

5. Create targeted interventions by applying knowledge of cellular interactions in cancer development derived from profiling studies that explore cell-microenvironment interactions. \$6.00 M

- Efficiently develop new drugs that target cells in the microenvironment, and move them into clinical use by initiating a Rapid Access to Intervention Development-type program. \$1.00 M

- Develop new “targeted” reagents, including small molecules, RNAi, and antibodies through supplemental funding to NCI-funded investigators. \$1.00 M

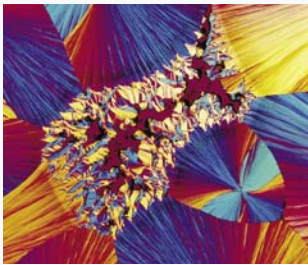
- Visualize the physiologic, cellular, and molecular processes in living tissues through functional and molecular imaging studies. These studies will focus on (1) identifying the subtle and important early changes in the molecular biology of tumors and the microenvironment as tumors become malignant, and (2) monitoring the effects of therapy on tumor cells and the tumor microenvironment. \$4.00 M

Management and Support	\$ 0.80 M
Total	\$ 35.30 M

Story of Discovery

ANTI-INFLAMMATORY THERAPEUTICS MAY PROVIDE SECONDARY BENEFITS FOR CANCER

Nearly 150 years ago, the German physician Rudolph Virchow first proposed a connection between inflammation and cancer. Noting that cancerous tissue also contains the cells and factors that are hallmark features of the body's inflammatory response, Virchow hypothesized that cancer begins at sites of chronic inflammation.¹ At the time — and for many years to follow — the scientific community disavowed this idea because few could envision how the body's first line of defense against tissue injury and infection could also cause harm. Over the past decade, however, scientists have uncovered increasing evidence to support Virchow's claim. They have determined that the very factors recruited by the body to prevent infection and encourage healing at an injured site can misfire and produce damage. And, if the triggering bacteria, virus, or chemical irritant lingers in the body, a state of chronic inflammation can arise.



Polarized light micrograph (PLM) of prostaglandin B1. Prostaglandin is a hormone-like substance that influences metabolism, blood pressure, smooth muscle activity, and modulation of inflammation. Magnification: 10x.

Today, research indicates that chronic inflammation underpins a host of diseases, including cancer. Studies have shown that inflammatory cells promote tumor growth by producing a favorable growth environment, stimulating DNA instability and damage, enabling blood vessel development (angiogenesis), and facilitating the spread of cancer. About 15 percent of cancers throughout the world are linked to infectious agents that provoke chronic inflammation — for example, *Helicobacter pylori* with gastric cancer and hepatitis B and C viruses with liver cancer. In addition, cancer may be associated with chronic inflammation caused by long standing exposure to chemicals such as those found in cigarettes or asbestos. But the most established and elucidated connection between chronic inflammation and cancer is with colorectal cancer.

Drug Therapy Establishes the Link

Evidence supporting a link between chronic inflammation and colon cancer came together from multiple paths of scientific discovery. For years, scientists observed that patients with long-term chronic inflammatory bowel disease, a group of disorders causing chronic and recurring inflammation of the intestines, often develop colorectal cancer. Population studies confirmed this association. At the same time, scientists studying the effects of non-steroidal anti-inflammatory drugs (NSAIDs) were also finding evidence to support this link. NSAIDs, which include aspirin, are among the oldest and most widely used drugs in history. In a 1980 animal study and a 1983 case study in humans, scientists observed that NSAIDs caused the regression of intestinal polyps — non-cancerous growths that often lead to cancer. Several studies reported reduced rates of colorectal cancer in arthritis sufferers who treated their pain with daily doses of aspirin and other NSAIDs. And two large population studies found that regular use of NSAIDs over several years reduced the occurrence and mortality for colorectal cancer in the populations studied. The weight of this collective evidence prompted various research teams throughout the country to explore how NSAIDs act on the body and how this action results in reduced polyp growth and colon cancer risk.

The Search for a Common Thread

With a chemically diverse group of drugs like NSAIDs sharing the same therapeutic qualities and adverse side effects, it was assumed that they also share a common mode of action. The activity of these drugs was determined in 1971 when Dr. John Vane and his colleagues demonstrated that aspirin and all NSAIDs restrict inflammation by inhibiting the body's production of prostaglandins. Vane predicted that NSAIDs accomplish this outcome by

¹ Inflammation is the body's natural response to the tissue injury caused by a wound or bacterial, viral, or parasitic infection. It is characterized by increased blood flow to the injured site, redness, swelling, elevated temperature, and pain.



Colonic polyp. Colonoscope (endoscope) view of a benign (non-cancerous) polyp in a 67-year-old man's colon (large intestine). This is a tubulovillous adenoma, a tumor arising from the epithelial tissue lining an organ. Unlike more common polyps, which are attached on a stalk, this type (tubulovillous) forms in a tube shape. If the polyp causes discomfort, or it is suspected that it may turn cancerous, it is removed surgically. In this case, after removal the polyp was found to contain high-grade dysplasia (HGD), the medical term for cell abnormality, which could indicate that the polyp was becoming cancerous.

blocking the activity of the cyclooxygenase (COX) enzyme, which catalyzes a key step in prostaglandin synthesis. Vane's Nobel Prize winning discovery paved the way for future studies confirming the role of COX enzymes in prostaglandin production, and ultimately for the development of drugs that treat inflammatory diseases by blocking the activity of the enzymes. At first, scientists knew of only one COX enzyme. In 1990, however, three research teams became interested in a protein produced by cells that were becoming cancerous. Through further research, they found the gene responsible for producing this protein, and noted it was related to the COX enzyme. Naming the new protein COX-2, the scientists determined that it is activated only during inflammation, while the "original" COX-1 enzyme is present in cells at all times and functions to protect the lining of the stomach and intestines by stimulating mucous production.

Scientists recognized that NSAIDs reduce inflammation by blocking the actions of the COX-2 protein, making them potent treatments for inflammation-associated diseases like arthritis. But they still did not have the findings to document why these anti-inflammatory agents reduce colorectal cancer risk. In 1994, a key piece to this puzzle — the link between COX-2 and colorectal tumors — was provided by Charles Eberhart and Raymond DuBois who observed that COX-2 (but not COX-1) levels are elevated in as many as 80 percent of colorectal tumors. This finding, since replicated by animal studies, suggests a role for COX-2 and inflammation in tumor development.

Promising Therapies and Future Paths

The potential of NSAIDs as chemoprevention agents for colon cancer is considerably limited by the fact that these drugs can cause serious adverse effects. Because they block the actions of both COX proteins, dosing can lead to excessive stomach acid production, ulceration, and gastrointestinal bleeding. Scientists thought that a better chemoprevention drug would need to selectively target only the COX-2 enzyme, thereby reducing the most harmful effect of NSAIDs while capitalizing on their benefits. In a milestone NCI-sponsored cancer prevention trial, researchers reported on such a drug, celecoxib, an arthritis medicine that selectively targets the COX-2 enzyme, substantially reducing the number of polyps in patients with an inherited disorder of the colon and rectum which causes polyp growth and almost always progresses to cancer. Recent studies suggest that elevated levels of COX-2 may contribute to the development of tumors originating at other sites in the body, including the breast, skin, lung, esophagus, bladder, cervix, head and neck, stomach, liver and pancreas. Based on this information, through 11 clinical trials, scientists are now working to determine if these tumors may be vulnerable to the effects of COX-2 inhibitors.

More recently, three research teams found that daily intake of low doses of aspirin reduced the recurrence of colon polyps among people with previous colon cancers or polyps. These data suggest that daily aspirin may be an appropriate supplement to regular surveillance procedures in individuals who have an increased risk for colon cancer that is similar to the level of risk among the trial participants. It is important to note that long-term aspirin therapy is not appropriate for everyone: most people do not have the same elevated risk for colon cancer as those observed in these clinical trials. In addition, aspirin, like many drugs, can have side effects. All people age 50 and older should continue to get colorectal cancer screening exams regularly.

Molecular Targets of Prevention, Diagnosis, and Treatment

A new era in biomedical research holds extraordinary potential for new strategies in cancer prevention, diagnosis, and treatment. Proteomics, specific biomarkers, and newer nanotechnology assays will provide the basis for a wide range of technologies for early detection and diagnosis. Physicians will have specific information on the stage of progression of most cancers, and patients will be treated with targeted agents both singly and in combinations uniquely designed to prevent some cancers and control others with minimal or no side effects.

Targeted delivery of new drugs and real-time monitoring of drug levels through biosensors will ensure ongoing treatment efficacy and minimize the possibility of resistance. Cancer patients will more often experience a chronic rather than fatal disease and will be able to enjoy a high quality of life. We will also be able to apply our knowledge of the molecular signatures of cancer to predict the course of the disease, individual responses to cancer/precancer therapies, and the risk of adverse drug reactions for treating the most fatal cancers. Such approaches will allow for the development and selection of more individualized and effective therapies.

PROGRESS IN PURSUIT OF OUR GOAL

An interdisciplinary, collaborative, cooperative approach is needed if we are to realize rapid, efficient translation of basic scientific advances into new tools, reagents, and molecularly targeted lead compounds for use in clinical research. NCI is partnering with various groups as a way to carry out this research agenda. (See page 84.)

Discovery

The process of creating an effective, molecularly targeted cancer drug begins with basic research and the search for chemical compounds with potential anti-cancer properties and molecules within cancer cells and their surroundings that might provide targets for cancer interventions.

Identifying and Validating Molecular Targets for Cancer Intervention

Through the **Molecular Target Drug Discovery (MTDD)** program, investigators are identifying novel molecular targets, validating these as targets for cancer therapy, and developing tests that determine how well potential agents work against these targets. One researcher used a computational model to study the site of interaction between a drug and a protein involved in apoptosis. Another team discovered a breast cancer-relevant gene that is expressed differently in Caucasian and African American patients. This discovery could help scientists to understand differences among races in susceptibility to breast cancer.

In the **NCI Intramural Research Program**, investigators are discovering new hereditary cancer syndromes and identifying genes that contribute to disease, such as the gene associated with clear cell renal carcinoma in von Hippel-Lindau disease. The study of inherited mutations is providing new insight into sporadic disease. In addition, the study of pathways for these inherited diseases may spur new developments in future diagnostics and therapeutics.

The **Chemical Genetics Institute** (formerly the Molecular Targets Laboratory) was first funded in Fiscal Year 2002 to capitalize on the opportunities emerging from advances in genomics, molecular biology, combinatorial chemistry, informatics, and imaging. Scientists are creating a resource of biological assays and chemical probes (compounds used to study molecular targets) to study cancer-related

targets. This work facilitates biological studies of cancer, including physiological and biochemical monitoring, and provides a platform for drug discovery.

The **Mouse Models of Human Cancers Consortium (MMHCC)** is a collaborative program designed to derive and characterize mouse models, and to generate resources, information, and innovative approaches to the application of mouse models in cancer research. Through the MMHCC, groups of academic researchers have created and are making available to other researchers mice with defined genetic alterations that predispose the animals to certain types of cancer. More than 75 strains were available as of 2003. These mouse models could serve as a basis for testing new, molecularly targeted treatment and prevention strategies. The Consortium will develop partnerships with pharmaceutical industry sponsors to facilitate the testing and evaluation of new compounds identified by Consortium members. (emice.nci.nih.gov)

Through several NCI initiatives, chemists and biologists are collaborating to create libraries of compounds to be either evaluated for their overall therapeutic potential, or screened to identify those that modulate the biological activity of validated targets.

Identifying Compounds That Hit the Targets

NCI provides, at no cost, samples of synthetic chemicals, collected natural products, and biological materials to investigators who want to screen them against molecular targets.

- The **National Cooperative Drug Discovery Groups (NCDDG)** program supports innovative, interdisciplinary, multi-project approaches to discover new anti-cancer treatments.
- In **Biology and Chemistry Centers**, multidisciplinary teams of scientists use a combination of chemical and biological techniques to create libraries of chemically-diverse structures with potential anti-cancer effects. Using “smart” assays, scientists screen the compounds to identify those that will interact with cancer-specific molecular targets.
- The **Rapid Access to NCI Discovery Resources (R*A*N*D)** program expedites the development of drug research capabilities in academic institutions. R*A*N*D assists in the development of high-throughput laboratory assays to screen large numbers of promising chemicals. The program supports the development of libraries of chemicals for use by scientists.

Development

Providing Resources for Pre-Clinical Development of Promising Compounds

The **Rapid Access to Intervention Development (RAID)** program provides preclinical drug development resources to academic institutions. One team is developing a steroidal compound that suppresses estrogen-stimulated breast tumor growth through inhibition of a particular enzyme. RAID is providing radiolabeled material as well as additional efficacy, formulation, and toxicology studies for this compound. Another researcher has hypothesized that a treatment regimen involving high-dose chemotherapy, stem cell transplantation, and an Yttrium-labeled antibody will prove effective for relapsed Hodgkin’s lymphoma. RAID is producing clinical-grade antibody that will be radiolabeled by the researchers. (dtp.nci.nih.gov/docs/raid/raid_index.html)

The **National Cancer Drug Development Group (DDG)** supports the development of experimental cancer drugs for which NCI holds the FDA-approved

Translating laboratory discoveries into agents for human use is an exacting task that requires very specific, interrelated activities. For example, investigators must produce sufficient quantities of a drug for formulation, stability, and safety testing. Subsequent studies enable scientists to determine the mode and amount of drug to use in early clinical testing or whether a drug should even be advanced to this stage. NCI is supporting this critical arm of drug development through a variety of initiatives.

Investigational New Drug (IND) application, regardless of whether the drug was discovered by NCI, industry, academia, or another source. A number of promising agents from this program have progressed to clinical trials. One agent developed by DDG-supported researchers is a synthetic improvement on a naturally-occurring anti-tumor antibiotic. This agent binds to DNA and is highly active in animal models against ovarian, melanoma, and breast tumors, while exhibiting less toxicity than the parent compound. Another agent developed through this program is a synthetic compound derived from a marine sponge that has shown anti-cancer activity in animal models representing breast and lung cancers, producing tumor-free animals in both cancers. (dtp.nci.nih.gov/docs/ddg/ddg_descript.html)

The Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA) is a new program that enables interdisciplinary teams of scientists to develop molecular assays, molecular and cellular imaging probes, and other tools to assess the effects of targeted interventions in preclinical models and in early clinical trials. Groups are targeting angiogenesis, survival and proliferation signals for tumors, new ways to measure the effectiveness of tumor vaccines, and the structure of tumor chromosomes.

The Flexible System to Advance Innovative Research (FLAIR) provides funds to small businesses to develop cancer therapeutic and prevention agents. FLAIR supports the development of novel drug delivery systems, imaging technologies, anti-angiogenesis drugs, and anti-metastatic agents; the design of small compounds able to mimic the action of proteins; and agents that sensitize cancer cells to radiation.

Within the Intramural Program, the **Molecular Targets Development Program (MTDP)** facilitates the discovery of compounds that may serve as bioprobes for functional genomics, proteomics, and molecular target validation research. During the past year, the MTDP has focused on biomolecular assay development, drug development, and collaborations with various academic and private pharmaceutical partners.

Developing New Strategies for Cancer Intervention

Intramural laboratories are currently developing treatment and prevention therapies for a variety of cancers. Integration of molecular imaging, molecular signatures, and molecular therapeutics with radiation therapy is a high priority of NCI's Intramural Program because new anti-cancer agents may ultimately be used in combination with radiation therapy. The **Radiation Modifier Evaluation Module (RAMEM)** program will serve individual investigators and industry in the design and development of treatment programs for the use of novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. Intramural investigators have also shown that "adoptive transfer" is a promising approach to treating patients with refractory metastatic melanoma and has potential applications to other tumor types. Cells of the immune system are harvested from the patient, activated against the tumor antigen, and re-introduced into the patient, where they attack the tumor.

Delivery

Once preclinical testing has been completed, agents that are deemed suitable for human testing enter early-stage clinical trials for safety and efficacy. Compounds that survive early clinical testing proceed to broader clinical testing to determine whether cancer patients or those at risk for cancer will actually benefit from the agents.

Moving Developed Agents into Clinical Testing for Safety and Efficacy

The RAID and DDG programs have delivered more than 30 new therapies for clinical testing in the past 10 years.

- One therapy that uses a virus modified to deliver a pair of therapeutic suicide genes to prostate tumors entered clinical trials in January 2002. NCI produced the virus, conducted *in vivo* studies, and assessed initial safety studies.
- Clinical trials have been initiated in the United States and England on a derivative of geldanamycin, a potent growth inhibitor of several pediatric neural tumor cell lines. NCI contractors produced a large quantity of geldanamycin and developed a viable formulation of the derivatives for clinical use.
- An immunotoxin (BL-22) developed intramurally and manufactured by NCI is being tested in patients with hairy cell leukemia (HCL) and investigators are modifying it for testing in patients with chronic lymphocytic leukemia.
- Another compound, a histone deacetylase (HDAC) inhibitor, is being used for cytotoxic T-cell lymphoma therapy.

The Rapid Access to Prevention Intervention Development Program (RAPID) supports the movement of agents for cancer prevention into clinical testing. RAPID helps academic investigators expedite preclinical and early clinical drug development of investigational agents with the potential to prevent, reverse, or delay carcinogenesis. Current projects include a second-generation human papillomavirus (HPV) vaccine that is both economical and stable; mycochemicals with specific efficacy in lung and colon cancer prevention models; and modified components of dietary crucifers developed in preclinical prevention models of breast and prostate cancer, as well as HPV replication models. (www3.cancer.gov/prevention/rapid)

Supporting Clinical Trials of Molecularly Targeted Agents for Cancer Prevention

NCI supports clinical trials for chemoprevention that measure or identify molecular targets involved in the cancer process.

- The **Selenium and Vitamin E Cancer Prevention Trial (SELECT)** will assess the molecular genetics of cancer risk and associations between diet and prostate cancer.
- Investigators are studying the estrogen receptor as a key to breast cancer risk in the **Breast Cancer Prevention Trial (BCPT)** and the **Study of Tamoxifen and Raloxifene (STAR)**. NCI has also begun an initiative that funds investigator-initiated research focused on two key aspects of this problem: validating surrogate biomarkers and identifying potential molecular targets for chemoprevention of human ER-negative breast cancer.
- Epidemiologic studies have suggested that prostate cancer risk may be higher in men who consume only small amounts of fruits and vegetables or high amounts of milk, dairy products, and meat. NCI is fostering investigator-initiated research to identify and characterize **molecular targets affected by nutrients**, and further, to determine how these targets can affect outcomes in prostate cancer prevention.

GOAL

Facilitate the expanded exploration of the causes of cancer and the discovery, development, and delivery of agents that specifically “target” these causes to prevent, diagnose, treat, and provide follow-up surveillance of cancer.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

1. **Identify, characterize, and validate the combinations of deregulated cellular proteins and pathways that cause cancer, in order to find targets for treatment and prevention.** **\$18.75 M**
 - Expand research to identify cellular targets, discover related anti-cancer agents, and quickly translate these new discoveries for use in clinical trials through the Academic Public Private Partnership Program (AP4) and other grant mechanisms. Provide late drug development assistance. \$4.75 M
 - Identify cellular targets and screen potential cancer preventive agents using human cells from individuals with autosomal dominant cancer syndromes through genomic, proteomic, and bioinformatics approaches. \$5.00 M
 - Expand the availability of NCI discovery resources to academic laboratories for small molecule and biologics through the Rapid Access to NCI Discovery Resources (R*A*N*D) program. \$1.00 M
 - Accelerate the pace at which accurate, reproducible mouse models of human cancers are made available, and define the process of using mouse models to evaluate targeted therapeutics, through support of the Mouse Models of Human Cancers Consortium. \$2.00 M
 - Identify and evaluate agents to prevent or ameliorate cancer-causing radiological injury due to terrorist acts. \$5.00 M
 - Support an intramural Molecular Targets Discovery Program. \$1.00 M

Development

2. **Provide the infrastructure for researchers to find effective interventions directed at validated targets (e.g., assays, proteomics, imaging).** **\$16.00 M**
 - Expand the number of new drug candidates arising from the National Cooperative Drug Discovery Groups (NCDDG), through the Drug Development Group (DDG), and Rapid Access to Intervention Development (RAID) programs. \$1.00 M
 - Develop a translational research program to closely link molecular imaging, cancer signatures, and molecular targets. The ability to conduct multiple studies will provide a robust data set to understand the biology behind the image needed to credential new molecular targets. \$3.00 M

Supporting Clinical Trials of Anti-Cancer Vaccines

NCI has initiated a **consortium to develop a new generation of anti-cancer vaccines**. This consortium consists of translational research laboratories within the Intramural Program, expert clinicians from numerous institutions throughout the country, and representatives from the biotechnology and pharmaceutical industries.

NCI Clinical Center researchers have initiated two clinical trials examining a **vaccine that activates cytotoxic (killer) T-cells** to attack tumor cells in patients with advanced colorectal, pancreatic, and lung carcinomas. Another group is conducting a similar trial for prostate cancer patients. In a Phase III randomized trial, investigators are testing an individualized

- Promote the early assessment of molecular targets in clinical trials and the discovery of drugs for potential combination trials through increased support for the Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA). \$2.00 M
- Accelerate intervention development through expanded support for the Rapid Access to Intervention Development (RAID) program. \$3.00 M
- Evaluate the effects of dietary and pharmaceutical anti-oxidants and anti-inflammatories on the effectiveness of radiation therapy. \$3.00 M
- Develop a clinical proteomics initiative, with supporting bioinformatics, to use patient biopsies to develop new laboratory tools for clinical proteomic applications in human cancer and drug toxicity detection. This resource would be available to cooperative groups to provide data or use the data generated. \$2.00 M
- Support an intramural Molecular Targets Development Program. \$2.00 M

3. Facilitate the steps necessary to develop therapies using targeted clinical agents alone or in novel combinations with radiation therapy. \$11.50 M

- Accelerate the movement of agents from the laboratory through clinical trials for efficacy by increasing funding to the Rapid Access to Preventive Intervention Development (RAPID) program. \$1.00 M
- Expand development of novel methods of drug formulation and drug delivery through new Small Business Innovation Research (SBIR) initiatives. \$2.00 M
- Expand assistance to small business drug research and development through the Flexible System to Advance Innovative Research (FLAIR) program. \$3.00 M
- Increase support to individual investigators and industry for the development of treatment programs using new agents with radiation therapy. Collaborate with industry and individual investigators to establish a system for alerting clinical investigators when agents are ready for clinical trials. \$0.50 M
- Provide infrastructure support to Cancer Centers and other research institutions for staff and facilities dedicated to clinical cancer prevention research. \$5.00 M

Management and Support		\$ 1.40 M
	Total	\$47.65 M

vaccine against B-cell follicular lymphoma. This trial is being conducted through an arrangement with a biotechnology investment group.

Intramural laboratories have been collaborating on early-phase clinical trials of prophylactic HPV-16 vaccine in unaffected volunteers for the prevention of cervical cancer. The vaccine has been found to be safe while producing an immune response. NCI and a pharmaceutical partner will conduct a large-scale trial in Costa Rica. Another intramural laboratory is developing new targeted approaches to replace standard, cytotoxic chemotherapy for the AIDS-related malignancy Kaposi's sarcoma.

Quality Patient Care Includes Radiation Oncology That Is Crosscutting and Multidisciplinary

Radiation oncologists are providing care for increasing numbers of cancer patients at some point during the course of their disease. Radiation is used both alone and in combination with other modes of therapy. For example:



Proton radiation therapy is used to treat melanoma cancer of the choroidea, the middle layer of the vertebrate eye, between the retina and sclera.

- Radiation oncology is at the forefront of image-guided therapy. Beam-shaping techniques such as 3D-conformal therapy and intensity-modulated radiation therapy (IMRT) allow health care providers to administer higher doses of radiation to the tumor while exposing normal tissue to reduced amounts.
- Technological advances in brachytherapy permit radiation sources to be placed within certain tumors.
- Proton particle beam therapy allows more precise administration of radiation to cancerous tissue.
- Radioimmunotherapy involves the use of radioactive molecules attached to monoclonal antibodies to attack cancer cells throughout the body.
- Combination radiation and chemotherapy permits organ-sparing curative treatment and has increased patient survival rates for a number of diseases, compared to using either type of therapy alone.
- New molecularly targeted anti-cancer drugs are often more effective when administered in combination with radiation therapy. Basic and clinical researchers are studying cancer-related molecular pathways to design improved chemo-radiation approaches.

NCI places a high priority on crosscutting research into new radiation technologies.

NCI's intramural researchers collaborate with universities and industry, linking studies in molecular imaging, molecular biology, and molecularly targeted therapy. This multidisciplinary research is helping oncologists to understand molecular processes affected by radiation, improve tumor control, and lessen injury of normal tissue. Research in normal tissue radiation toxicity will also help the Nation to prevent and/or treat possible injury from radiological or nuclear terrorism.

Beyond intervention development, NCI has been a leader in radiation oncology quality assurance, pioneering the Patterns of Care studies over three decades ago to investigate adoption of recommended treatments for the most common cancers. (See page 52.) NCI is now implementing shared quality assurance programs that will improve the technological sophistication of radiation oncology, worldwide, and create data sharing abilities via telemedicine. This improvement in technological resources is the backbone of the new cancer disparities research partnership program,¹ designed to enable research at institutions that primarily serve low-income, underserved, and ethnic and minority populations. (See also page 59.) NCI's radiation oncology research embraces the goal of ensuring that highly effective cancer interventions are accessible to all who need them.

¹Supported through the Cooperative Planning Grant for Cancer Disparities Research.

Cancer Imaging and Molecular Sensing

Cancer care is critically dependent on imaging technologies, which are used to detect tumors early, when they are easier to treat, and to guide therapy or surgery. As our knowledge of the molecular basis of cancer increases, so does the need for imaging methods that provide clinicians with telling details about the molecular environs of patients' tissues. We must also focus resources on the imaging of precancerous conditions so that more cancers can be diagnosed and treated before there is any evidence of anatomic change.

Computed tomography and magnetic resonance imaging permit remarkable accuracy in detecting whether a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs. Molecular or "functional" imaging is increasingly used in place of patient biopsy. Imaging guided interventions allow precise delivery of tumor-destroying approaches (e.g., chemicals and radiation) minimizing trauma and damage to healthy tissue, shortening recovery times, and reducing healthcare costs.

Investment in cancer imaging technologies is pivotal to achieving NCI's challenge goal of eliminating the suffering and death due to cancer. Oncologic imaging guided intervention (OIGI), for example, is a rapidly evolving area of interest that may be used not only to cure some cancers and precancerous lesions, but in many more cases to provide minimally invasive, well-tolerated palliative therapies. This latter, easily achievable objective will help transform certain cancers from debilitating and deadly illnesses into chronic, well managed diseases that have little or no adverse effect on the daily lives or life expectancies of patients.

To ensure the speedy movement of lifesaving new cancer interventions to patient care, NCI must also invest in imaging and molecular sensing techniques that help the preclinical researcher. For example, micro-imaging technologies will permit researchers fuller use of the increasing number of mouse models of human cancer to uncover the genetic basis of specific tumors and examine response to experimental therapies. The development of functional imaging methods for mouse models and molecular biosensors for use in animal models will help determine how newly discovered defects in genes and proteins interact to cause cancer.

As scientists make exponential progress in understanding the molecular basis of cancer, this is an opportune time for NCI to invest in cancer imaging and molecular sensing technologies that will increasingly save and improve lives.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

Discovering Better Imaging Technologies and Techniques

NCI has played a major role in fostering functional imaging through initiatives such as *In Vivo Cellular and Molecular Imaging Centers* (ICMICs). Each ICMIC brings together experts from diverse scientific and technological backgrounds to conduct multidisciplinary research on cellular and molecular imaging in cancer. Seven ICMICs operate nationwide, including two new centers established in 2003. At one of the new centers, researchers will use their expertise in magnetic resonance (MR), positron emission tomography (PET), and optical imaging to understand cancer vascularization, invasion, and metastasis — knowledge that can be applied to achieving effective cancer therapies. Scientists at the second new center will apply their radiochemistry expertise, integrated with molecular and biochemical techniques, to design and generate new molecularly targeted cancer agents. The **Small Animal Imaging Resource Programs** (SAIRPs) at 10 centers around the country increase the efficiency, synergy, and innovation of small-animal imaging research. Launched in

As small animal imaging becomes an increasingly valuable tool in cancer research, NCI seeks to optimize its availability to investigators.

1999, SAIRPs make the necessary equipment and personnel available to investigators, improve and enhance technologies and techniques for imaging small animals, and foster cross-disciplinary collaborations. For example, SAIRP researchers have established research techniques for imaging apoptosis in tumors in real-time; imaging elusive protein-protein interactions; tracking lymphocytes involved in immunotherapy approaches; and monitoring the response of tumors to experimental therapies. Collaborations between SAIRPs and other animal research groups allow researchers to study *in vivo*, molecular intricacies of cancer development not otherwise observable. An **Imaging Working Group** is enhancing collaborations between SAIRPs and the **Mouse Models of Human Cancers Consortium (MMHCC)**.

In a separate effort, launched in 2003, NCI is increasing **researcher access to small-animal imaging equipment** by providing funds for purchasing or upgrading equipment to NCI-funded small-animal imaging researchers with a history of collaborating with other investigators. The recipients will share the equipment and provide imaging expertise to a number of other NCI-funded researchers.

ICMIC Scientists Develop a Biosensor to Permit Imaging of Molecular Interactions

Cancer researchers seek to understand how interactions among molecules such as genes and proteins sometimes go awry, transforming a normal cell into a cancer cell. Laboratory scientists routinely design and use biosensors that interact chemically with a tissue sample to allow study of the almost instantaneous interactions occurring among such molecules. These assays often require investigators to carefully isolate

and prepare from the biological sample the type of molecules they want to study — a costly, time-consuming process that uses up quantities of precious sample.

Recently scientists supported by NCI's *In Vivo* Cellular and Molecular Imaging Centers (ICMICs) created a biosensor that allows researchers to slow down the activity of molecules so that their interactions can be imaged, rather than studied by chemical assay. These biosensors contain magnetic relaxation switches (MRSs), tiny probes made up of nanoparticles with magnetic properties that will slow down, or “relax,” the activity of nearby molecules enough for their activity to be captured by magnetic resonance imagery or nuclear magnetic resonance imagery. The MRS biosensors worked well regardless of sample turbidity, variations in temperatures, or solution type — permitting researchers to use MRSs without costly sample preparation. ICMIC investigators also demonstrated that MRSs work well in a high-throughput assay format. Furthermore, several features of MRSs highlight their potential as *in vivo* biosensors to detect molecular targets of cancer: materials used to make the probes have little or no toxicity; the necessary imaging techniques are commonly used *in vivo*; and magnetic nanoparticles can be modified to be internalized by cells.

With further development of MRSs and accompanying imaging systems, this ICMIC advance should have broad biomedical applications, including widespread use by investigators developing molecularly targeted cancer interventions.

Development

Developing Promising Imaging Advances

NCI realizes that the discovery of new imaging agents will have limited clinical impact without the resources to help move promising agents through the development phase. Researchers often lack the resources to conduct preclinical testing (e.g., tests for safety, pharmacology, toxicology, etc.). These data must be submitted to the Food and Drug Administration (FDA) in an Investigational New Drug (IND) application before the agent can be tested in humans. NCI's **Development of Clinical Imaging Drugs and Enhancers (DCIDE)** program fills this gap by providing, on a competitive contract basis, NCI resources to perform this preclinical testing. A relatively new program, DCIDE has already reviewed 15 compounds, has completed preclinical evaluation for one agent, and has three others in various stages of synthesis and testing. DCIDE resources also permit NCI to file INDs for agents that have withstood preclinical testing and are highly promising, but for which an IND has not yet been filed. Currently, INDs for two such agents are in progress and two others are under consideration.

In another effort to shorten the time it takes to move a promising new agent from discovery to clinical testing, NCI recently developed a **contract program to validate imaging methodologies** for preclinical testing of new drugs. Through this program, scientists have developed a variety of methods for using dynamic contrast-enhanced magnetic resonance imaging (MRI) and MRI blood-volume measurement to visualize the effects of anti-angiogenic agents in animal models. In 2003, researchers applied these new techniques to preclinical testing of several therapeutic anti-angiogenic agents. Researchers have now begun examining PET in a similar manner for use in assessment of blood flow, blood volume, and metabolism in preclinical drug studies.

Following preclinical testing, new cancer imaging technologies and techniques are often evaluated through one of NCI's clinical trials cooperative groups. These groups are networks of health care professionals affiliated with medical schools, teaching hospitals, and community-based cancer treatment centers.

The American College of Radiology Imaging Network (ACRIN), supported by NCI, is conducting the **Digital Mammography Imaging Screening Trial (DMST)**. This large-scale effort is comparing the diagnostic power of digital mammography to conventional, film-based mammography. More than 32,000 women have enrolled in DMST at 31 sites across the United States and Canada. In another large-scale trial, ACRIN and NCI collaboratively launched the **National Lung Screening Trial (NLST)** in September 2002. This 8-year study conducted at 30 sites nationwide will determine whether lung cancer screening using low-dose spiral computed tomography in high-risk populations reduces mortality from this disease compared with standard x-ray screening. NLST scientists will also assess the stage of tumors when first detected, quality-of-life and psychological issues for people who test positive for lung cancer, economic consequences, and other potential differences between the two screening methods. NLST researchers have enrolled over 21,000 of the 50,000 smokers and former smokers¹ needed to conduct this study.

¹ Participants must be between the ages of 55-74 with a current or previous smoking history of at least 30 pack-years; former smokers must have quit within the preceding 15 years.

GOAL

Accelerate discovery and development of imaging methods, biosensors, and minimally invasive image-guided interventions for cancer and pre-cancerous conditions.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

1. Expand the discovery and development of novel imaging agents, devices, and methods for cancer.	\$15.00 M
<ul style="list-style-type: none"> ■ Foster multidisciplinary research through support of <i>In Vivo</i> Cellular and Molecular Imaging Centers (ICMICs). ■ Increase the number of imaging agents supported by the Development of Clinical Imaging Drugs and Enhancers program from three to five per year. \$2.00 M ■ Increase collaborations between Small Animal Imaging Resource Programs (SAIRPs) and other NCI programs, such as the Mouse Models of Human Cancers Consortium. \$2.00 M ■ Establish a repository of imaging agents, available to investigators, at NCI-Frederick. \$2.00 M ■ Establish a research resource of databanks of standardized digital image or spectroscopy data associated with known clinical outcomes. \$3.00 M ■ Expand the NCI-funded, publicly available Molecular Imaging Database of imaging agents. \$1.00 M ■ Expand the Network for Translational Research in Optical Imaging (NTROI). \$3.00 M ■ Support an intramural Molecular Imaging Program (MIP) to develop novel imaging biosensors and techniques. \$2.00 M 	
2. Integrate advanced imaging methods into therapeutic clinical trials.	\$14.00 M
<ul style="list-style-type: none"> ■ Support correlative imaging studies, such as monitoring response to therapy, with supplements to Clinical Trials Cooperative Groups. \$4.00 M ■ Increase the contract support for early clinical trials of imaging agents. \$2.00 M ■ Develop imaging cores within NCI-funded Cancer Centers. \$4.00 M 	

In other efforts, ACRIN and partners are studying:

- Whether **contrast-enhanced breast MRI** can be used as a biomarker that can predict patient outcome and guide individualized treatment — in partnership with the NCI-sponsored cooperative group, Cancer and Leukemia Group B, and NCI breast cancer Specialized Programs of Research Excellence (SPORE).
- The potential role that **breast ultrasound**, using standardized technique and interpretation criteria, should play in screening women at high risk for breast cancer — in partnership with the Avon Foundation.
- Whether **PET measurement** of changes in tumor volume in non-small cell lung cancer patients, before and after treatment, can help predict long-term patient outcome.
- Whether **whole body MRI and FDG²-PET** are valuable for detecting metastatic disease in common primary tumors in children.
- Whether combined **MR/magnetic resonance spectroscopic (MRS)** imaging performs better than MR imaging alone for localizing prostate tumors prior to radical prostatectomy.

² FDG-PET utilizes the radioisotope 18F-2-fluoro-2-deoxy-D-glucose.

■	Validate imaging methodologies in preclinical testing of new drugs through an expanded contract program. \$1.00 M	
■	Support an intramural Radiation Oncology Molecular Assessment and Technology Program (ROMAT) integrating multiple imaging approaches in clinical studies. \$3.00 M	
3.	Accelerate the development and clinical testing of image-guided interventions (IGI).	\$11.25 M
■	Develop an IGI Animal Laboratory Network. \$2.25 M	
■	Develop an IGI Clinical Centers of Excellence Program. \$6.00 M	
■	Establish an Imaging-Guided Oncologic Trials Network. \$3.00 M	
4.	Stimulate research on components and systems integration of devices for <i>in vivo</i> molecular sensing (biosensors).	\$4.00 M
■	Develop biosensors or components of biosensors for <i>in vivo</i> use by funding supplements to investigators in the Innovative Molecular Analysis Technology Program and the Unconventional Innovation Program. \$2.00 M	
■	Fund a Center for Biosensors in Oncology, based on the National Science Foundation Engineering Research Center model. \$2.00 M	
	Management and Support	\$ 0.50 M
	Total	\$44.75 M

NCI is also supporting a large project to assess the emerging technologies of **fluorescence and reflectance imaging spectroscopy** for diagnosing cervical cancer. (See page 74.)

Advancing *In Vivo* Biosensor Research

Investigators in the **Unconventional Innovations Program (UIP)** and the **Fundamental Technologies for Biomolecular Sensors (FTBS)** Program are developing molecular biosensors that can be either injected into the bloodstream or taken orally, for the purpose of detecting and destroying cancer cells. These biosensors are multifunctional nanoparticles that range in size from 10 to 250 nanometers in diameter (a typical human hair is about 50,000 nanometers wide). To build a molecular biosensor, researchers first construct a base particle to which they attach ligands, such as peptides or monoclonal antibodies that recognize and bind to cells that overexpress specific cancer-related proteins (e.g., PSA, Her-2).

Once attached to the cancerous cell, a contrast enhancing agent that is also carried by the biosensor is used to obtain a high quality image. The particle then releases a therapeutic compound to kill the cell. To date, several of the participating researchers have synthesized and characterized suitable base particles and have developed the chemistry needed to attach ligands, contrast enhancement agents, and therapeutics. They have performed *in vitro* and *in vivo* testing for binding, image contrast, therapeutic delivery, and cell killing. Many of the researchers are now scaling up production of the biosensors for larger testing, and are in some cases actively pursuing clinical trials at various Cancer Centers.

Delivery

Delivering Imaging Advances to Patient Care

NCI is supporting **partnerships to accelerate commercialization** of tested new technologies to help move them into mainstream clinical use. In 2003 NCI initiated a program to build academic/industry partnerships to ensure development of promising cancer-specific biomedical imaging systems and methods. Using seed grants, this program supports large and small companies in their efforts to optimize imaging devices and agents developed on a small scale, but with promise for production on a commercial scale. These companies might, for example, integrate informatics platforms into imaging systems, adapt systems to perform specialized molecular imaging, refine software developed by lay researchers, or develop and validate “orphan” imaging technologies.

One NCI-funded research team, in collaboration with Advanced Magnetix, Inc., has developed a non-invasive imaging technique that appears to be superior to existing clinical methods for staging prostate cancer. This new investigational procedure is used to evaluate an important staging criterion: whether, and to what extent, malignant cells have reached surrounding lymph nodes. Investigators employ **contrast-enhanced MRI**, which uses a contrast agent to make lymph nodes in the imaged area appear bright. The procedure also uses the compound Combidex,[®] which is composed of nanoparticles that attach only to cells in normal lymph nodes and are unable to attach to malignant cells. Combidex[®] causes the normal lymph nodes to appear dark on an MRI, while malignant cells in affected lymph nodes remain bright and are easily located. FDA expects to release this new technique soon for clinical use. Other potential applications include the staging of cancers of the breast, bladder, head and neck, and cervix.



Cancer Advocates Help Put a Human Face on Cancer Research

“I was invited to be the patient representative on an NCI peer review panel for a proposed clinical trial. The other members of the panel were well respected scientists who focused with diligence and purpose on the scientific merit of the clinical trial. I, by raising issues related only to the patients, sharpened that focus. As one scientist said, ‘You remind us why we are here.’” — **Cancer Advocate**

You remind us why we are here.

Cancer advocates may be cancer survivors, family members or life partners, or people integrally involved in cancer-related activities, such as support group leaders or hotline workers. They come from diverse age groups, races, ethnicities, educational levels, and geographic locations. Cancer advocates are intimately familiar with the hopes, struggles, joys, losses, and successes of cancer patients, those at risk for cancer, and their loved ones. Their advocacy helps present the human face of cancer to scientists, administrators, and the general public, reminding us of the “why” in cancer research.

NCI draws upon the expertise of cancer advocates through two major vehicles. The Director’s Consumer Liaison Group (DCLG)¹ is made up of 15 cancer advocates, each representing a unique constituency in the advocacy community. DCLG members advise the Director of NCI on a wide variety of issues, programs, and research priorities. The Consumer Advocates in Research and Related Activities (CARRA)² links cancer advocates with opportunities to help NCI, for example through participation in the peer review process for research proposals; participation on Progress Review Groups; and review of patient-oriented materials for readability and relevance.

NCI is highly dependent on cancer advocates and the perspectives they bring to all aspects of the cancer research planning process, and cancer advocates are impacting NCI’s research efforts. For example, recent advocacy efforts have contributed to:

- Expanded research focus on quality of cancer care, quality of life for cancer patients and survivors, and cancer health disparities
- A more streamlined clinical trials process designed to move promising agents to the market earlier
- An improved informed consent process for clinical trials that helps patients better understand the potential risks and benefits of participation
- More consistent use of plain language in NCI consumer publications and Web sites
- Better public understanding of the importance of, and NCI’s role in, cancer research.

¹ For more information on DCLG, go to deainfo.nci.nih.gov/ADVISORY/dclg/dclg.htm.

² For more information on CARRA, go to la.cancer.gov/carra.

Research on Tobacco and Tobacco-Related Cancers

Much is known and documented about the harmful effects of tobacco. Tobacco use is the leading preventable cause of illness and death in the United States. Cigarette smoking is the primary reason people die from lung cancer, coronary heart disease, chronic obstructive pulmonary disease, and stroke. Cancers of the lung, oral cavity, pharynx, larynx, esophagus, pancreas, urinary bladder, and renal pelvis all have been scientifically linked to tobacco use. More recent research connects tobacco use to still more cancers. A 2002 International Agency for Research on Cancer (IARC) monograph established a causal association between cigarette smoking and cancers of the nasal cavities and nasal sinuses, stomach, liver, kidney, and cervix, as well as myeloid leukemia. Why then do people choose to begin and continue smoking in spite of these health risks? This is the challenge for NCI and other research organizations and institutions as we work to reduce tobacco's staggering burden on our Nation's health.

- Approximately 440,000 deaths per year in the United States are caused by tobacco use.
- Worldwide, more than 3 million people die every year because of tobacco use.
- Approximately 46.5 million American adults, or 23.3 percent of the population, are current smokers; approximately 44.3 million adults, or 22.2 percent of the population, are former smokers.
- Approximately 28.5 percent of high school students identified themselves as smokers in 2001.
- In the United States, almost one-third of the approximately 750,000 youth who become regular smokers each year will ultimately die as a result of a smoking-related illness.

Of the many obstacles that confront the research community in the fight against tobacco-related disease, two are particularly complex: (1) the addicting nature of tobacco products, and (2) the impact of tobacco advertising and marketing. These factors drive the continued use of tobacco products even when the users are fully aware of their increased risk of disease and premature death. Adolescents are particularly vulnerable; almost 90 percent of adult current smokers began smoking before the age of 18. At this age, individuals tend to be less than fully aware of the risks and their implications and less able to make an informed, educated decision independent of external influences. Therefore, research on preventing youth smoking must focus on increasing young people's awareness of the harmful consequences of tobacco use and addiction; deflecting the presence of tobacco industry advertising messages; and decreasing the acceptability of tobacco use in physical and social environments. Equally important is the role of genetics and its interaction with psychosocial and environmental factors in the development or onset of tobacco dependence.

Clearly, NCI cannot achieve its Challenge Goal to eliminate suffering and death due to cancer without dramatically reducing and treating tobacco use and tobacco-related cancers across all ages and populations. This requires an integrated, multidisciplinary approach to decipher the interplay of social, psychological, behavioral, environmental, and biological/genetic determinants of tobacco use and tobacco-related cancers. Because many tobacco-related cancers take years to develop, making investments consistent with the enormous burden of tobacco-related disease now will lead to substantial benefits in the future.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

The intransigence of tobacco use and its disease consequences, along with its complex, multidimensional determinants, led the scientific community to recognize the need for new research models and paradigms that are integrated across disciplines. Transdisciplinary research, a process by which researchers work jointly, using a shared conceptual framework that draws together discipline-specific theories,

Collaborative TTURC projects include:

- Development of a measure for nicotine dependence
- Joint studies related to genetic/cultural/environmental interactions in tobacco use
- Studies of the interrelationship of culture, mood, and smoking
- Adolescent studies investigating the influence of peer interaction, depression, and hostility on smoking initiation and maintenance
- Genetic studies of treatment response

concepts, and approaches to address common problems, was identified as the most promising approach to accelerate discovery. In 1999, NCI, the National Institute on Drug Abuse (NIDA), and the Robert Wood Johnson Foundation jointly funded Transdisciplinary Tobacco Use Research Centers (TTURCs) within seven academic institutions. As of 2003, over 100 researchers involved in nearly 100 major research projects, pilot projects, and cores (e.g., training, biostatistics, administrative and transdisciplinary) are involved in research at these seven centers.

At one TTURC, investigators generated the first empirical evidence that the *CYP2B6* gene may influence the effectiveness of treatment with bupropion. This research team, composed of scientists who study behavior, neuroscience, pharmacology, and genetics, gained insight into specific neuronal and pharmacological mechanisms that may explain genetic effects on individual response to smoking cessation treatment. In clinical testing at another TTURC, researchers developed a single-photon emission computed tomography (SPECT) radiotracer for imaging certain nicotine acetylcholine receptors in the brain. This breakthrough will open new directions for cross-disciplinary research on receptor response during smoking and smoking cessation, while considering the effects of environmental, emotional, and behavioral factors. TTURC-supported research revealed links between attention deficit hyperactivity disorder (ADHD) and susceptibility to tobacco industry marketing among adolescents. Based on findings that nicotine increases dopamine levels in animal and preliminary clinical studies, one TTURC sponsored a study of selegiline (an MAO-B inhibitor that inhibits dopamine metabolism) as a treatment for tobacco addiction. In an early trial, selegiline was superior to placebo for smoking cessation.

Supporting Clinical and Population Studies on Smoking and Cancer

Longitudinal, screening, and cohort studies that involve genetic and biomarker components from tissue, blood, urine, sputum, and other bodily fluids are providing new information about the interplay among one's cancer risk and tobacco and other exposures such as alcohol, diet, occupation, and radon. For example, one of the largest molecular epidemiology studies of lung cancer in the world, a **multi-center case-control study of lung cancer and tobacco use**, is under way in Milan, Italy. This trial includes collection of extensive questionnaire and biospecimen data, and is unique in collecting information on many other factors, including tumor tissue obtained in surgery, demographics, tobacco use, alcohol use, occupational exposures, diet, and medical illness. Investigators will apply advanced technologies to explore protein and expression patterns and the genomic correlates of lung cancer and tobacco use.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC), and the Shanghai Women's Study are all large cohort studies that include biospecimens and questionnaire data with a focus on tobacco-related cancers. Two studies using high-throughput genotyping are planned within the PLCO to examine genes involved in "ever" and current smokers and explore the relationship of genes to emphysema



Tobacco-Related Cancers in Women – Smoking Raises the Risk of Many Cancers

I started smoking when I was 16 and quit in my early 30s. I was shocked when the doctor told me that my bladder cancer may well have been caused by smoking. So far it's cost me the misery of four surgeries and the loss of my bladder. If only I had known . . .

For every woman who smoked in 1950, 600 women smoke today. And as more women smoke, more suffer and die from smoking related disease. Many American women are unaware of just how dangerous smoking can be. Here are the facts:

- Lung cancer has now replaced breast cancer as the number one cancer killer of women.
- Tobacco use is a major cause of cancers of the bladder, mouth, larynx, and esophagus.
- Tobacco use is a contributing cause of cervical cancer, myeloid leukemia, and kidney, colon, stomach, and pancreatic cancers.
- Nearly 20 million women have successfully quit smoking but remain at risk for many cancers.

NCI-supported research has shown that 14 percent of Hispanic women and 22 percent of White women smoke. Smoking rates are higher yet among African American women (about 24 percent) and much higher among Native American and Alaskan Native women (about 35 percent). Poor and less educated women are more likely to smoke. A better grasp of the underlying causes of these disparities is critical to developing effective interventions to help all women.

Tobacco industry marketing frequently targets young and minority women, and studies have revealed the effectiveness of this technique, especially for youths. Most women smokers begin as teenagers, before high school graduation. Of the millions of women who try to quit smoking each year, only a small percentage succeed. African American, Hispanic, younger, and less educated women have the lowest quit rates.

and lung cancer. The Shanghai study includes occupational data and urine samples. Additional case-control studies of renal, pancreatic, bladder, and brain cancers, colon polyps, and second tumors are in progress in various national and international settings. The **National Health and Nutrition Examination Survey (NHANES III)** provides a population-based sample, with available serum and DNA that may prove useful in the future to conduct studies of the genetics of smoking and related traits. Results from these cohort studies will provide critical information that can be translated into effective prevention and treatment practices.

Supporting Epidemiological and Genetic Research

Lead investigators in the area of individual susceptibility to tobacco-related cancers have established a large **database of epidemiologic, clinical, and laboratory data** from over 3,000 study participants with and without lung cancer. Using advanced technologies, the researchers are assessing biomarkers to track the damaging effects of cigarette smoking. Investigators have recently reported an increased risk of lung cancer in people with genetic polymorphisms in the genes that eliminate carcinogens or repair DNA damage. Emerging technological advances will permit investigators to analyze the network of relationships among genetic, molecular, and environmental elements that control how tobacco damages individuals. For example, genetic differences that affect lung cancer risk may be used to identify highly susceptible subgroups and facilitate development of targeted intervention and prevention strategies.



Lots of my friends smoke — me, too. It's social, it's relaxing, and it keeps the weight off. And it's not a problem, I could quit anytime.

In February 2003, NCI took the lead with other Federal and non-Federal partners to convene a meeting of experts to assess the state of knowledge about tobacco use and tobacco related cancers among women. They identified priorities for research, evidence-based interventions, and the application of new and proven interventions across several key areas:

- Toxicology, cancer susceptibility, and biologic gender differences related to tobacco and cancer
- The biology and behavior of addiction
- National surveillance of tobacco use and control efforts
- Prevention of tobacco use and treatment of addiction in women
- Public knowledge of tobacco addiction, health and addiction risks, and control interventions targeting women
- Community, policy, legal, and regulatory interventions
- International issues in tobacco use and control

Recommendations are being developed to serve as the basis for an action plan.

This People's Story is an amalgam of individual experiences.

The health of former smokers, who now comprise about half of those diagnosed with lung cancer, is a special concern to NCI. Through targeted initiatives released over the past several years, NCI is funding studies to identify newer, more potent agents to prevent cancers in former smokers. Preclinical studies focus on identifying and prioritizing agents that prevent cancers in tobacco-susceptible organ systems, and clinical researchers are evaluating the efficacy of chemopreventive agents in specific cohorts of former smokers.

Development

Developing and Evaluating Innovative Interventions

NCI supports translation of knowledge unveiled by research findings into interventions to benefit all people affected by or at risk for tobacco use and/or tobacco-related cancers.

- NCI recently established the **Tobacco Intervention Research Clinic** to conduct innovative, state-of-the-science research on behavioral and pharmacological tobacco-use treatment interventions in clinical patient populations. The clinic's streamlined funding and review process allows high-priority topics in tobacco-use treatment to be addressed in a timely fashion.
- NCI and the National Institute on Drug Abuse (NIDA) have established the **Working Group on Medication Development for Nicotine Addiction** for exploring ways to advance progress in treatment for nicotine addiction.

GOAL

Understand the causes of tobacco use, addiction, and tobacco-related cancers, and apply this knowledge to their prevention and treatment.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

1. Lead and conduct a vigorous research and public health effort consistent with the enormous burden of tobacco-related disease. \$33.50 M

- Continue support for the Transdisciplinary Tobacco Use Research Centers (TTURCs) program, in collaboration with relevant public and private organizations. \$10.00 M
- Support studies on the use of and cancer risk from tobacco products intended to reduce harm. \$2.00 M
- Support clinical and population studies that investigate the genetic, biological, and behavioral factors influencing vulnerability to tobacco dependence and tobacco-related cancers. \$6.00 M
- Continue support for including questions on tobacco use in the Current Population Survey and expand efforts to translate the questions into languages such as Chinese, Vietnamese, Korean, and others. \$2.50 M
- Capitalize on the breadth of expertise across NIH institutes by supporting collaborative projects such as the identification of new treatments to prevent weight gain following smoking cessation at NCI's Tobacco Intervention Research Clinic. \$1.00 M
- Support use of advanced technologies (e.g., genomics, proteomics, and bioinformatics) in population-based studies to elucidate the genetics of smoking, in collaboration with other NIH institutes and centers. \$5.00 M
- Support the Tobacco Etiology Research Network, a transdisciplinary network of scientists working to discover the causes of tobacco use and addiction among youth and young adults. \$3.00 M
- Support studies that systematically examine tobacco constituents, genetic factors, and environmental and psychosocial risks and their relative effects on trajectories in tobacco use, cessation, relapse, and addiction in understudied and underserved populations. \$3.00 M
- Collaborate with the American Cancer Society on tobacco use prevention and cessation research in China. \$1.00 M

Development

2. Support and develop innovative, integrated studies and interventions to understand, prevent, and treat tobacco use and addiction. \$23.00 M

- Accelerate the identification of new treatments for tobacco addiction through the implementation of a drug development and clinical trials collaborative group by NCI and other NIH institutes, as well as through linkage to existing clinical trial networks. \$2.00 M
- Develop and implement a rapid-response surveillance system for emerging trends in tobacco use and tobacco-related disease through collaborative efforts. \$1.00 M
- Expand the Cancer Intervention and Surveillance Modeling Network (CISNET) to develop models of tobacco use, dependence, relapse, and disease development. \$2.00 M
- Support interdisciplinary studies to accelerate development of new, molecularly based lung cancer treatments and chemoprevention interventions. \$10.00 M
- Accelerate the development of network-centric approaches, such as networks for monitoring tobacco use and reducing tobacco-related disparities, to assure maximal linkage and collaboration across tobacco control domains (e.g., surveillance, treatment). \$4.00 M

- Continue to support research and analysis of tobacco industry documents through reissuance of a program announcement with review (PAR).
- Support prevention intervention research that addresses the common risk factors for youth problem behaviors, including tobacco use. \$2.00 M
- Support tobacco use prevention and cessation research specifically addressing ethnically diverse underserved youth and young adults. \$2.00 M

Delivery

3. Apply cutting-edge research to prevent and treat tobacco use and tobacco-related cancers and to inform public health policy.	\$18.00 M
■ Develop integrated and coordinated efforts to implement the youth and adult cessation Blueprint recommendations ¹ in collaboration with the Centers for Disease Control and Prevention and other public and private organizations. \$2.00 M	
■ Award supplements to Cancer Centers to address disparities related to the clinical care of patients with tobacco-related cancers. \$2.00 M	
■ Enhance the Cancer Information Service's smoking cessation services and research infrastructure to improve treatment of tobacco addiction. \$4.00 M	
■ Fund community-based, participatory research on tobacco-use prevention and cessation. \$5.00 M	
■ As state tobacco control efforts decrease, support the development of multi-level secondary analyses, analytical tools, methodologies, and resources necessary to track and evaluate progress in state tobacco control and to benefit the delivery of tobacco control interventions in states. \$2.00 M	
■ Support the identification, development, and dissemination of effective tobacco-use prevention and cessation interventions to underserved populations. \$3.00 M	
Management and Support	\$ 0.50 M
	Total \$75.00 M

¹ National Blueprint for Disseminating Evidence-Based Clinical and Community Strategies to Promote Tobacco-Use Cessation, 2002.

- **The National Conference on Tobacco and Health Disparities**, held in December 2002, was the first scientific gathering to convene researchers and practitioners with the purpose of developing a research agenda to eliminate tobacco-related disparities.
- **Women, Tobacco, and Cancer: An Agenda for the 21st Century**, held in February 2003, provided a similar venue for a focus on current research on tobacco and tobacco-related cancers in women. (See pages 40-41).
- NCI-supported researchers have developed an online **guide to evidence-based measures** for use in youth tobacco research interventions.

Delivery

Delivering Evidence-Based Interventions

NCI's **Smoking and Tobacco Control Monographs** have provided timely information about emerging public health issues in smoking and tobacco control and accelerated its dissemination to the scientific and public policy communities. *Those Who Continue to Smoke: Is Achieving Abstinence Harder and Do We Need to Change Intervention?* was released in May 2003. The document is a result of a set of analyses funded jointly by NCI and the Tobacco Control Section of the California Department of Health Services. The *National Blueprint for Disseminating and Implementing Evidenced-Based Clinical and Community Strategies to Promote Tobacco-Use Cessation*, a document that resulted from the collaborative work of 10 public and private organizations, provides state-of-the-art research strategies for cessation interventions.

Smokefree.gov, launched in Fall 2002, offers science-driven tools, information, and support to smokers who want to quit. Cosponsored by NCI and CDC, the Website provides state and national resources, free materials, access to online cessation support, and a toll-free number (1-877-44U-QUIT) for telephone-based cessation support.

Smoking-related NCI publications available to the public include *Clearing the Air*, a manual designed to help smokers quit; *Clear Horizons*, a quitting guide for those older than 50; and the recently published Spanish-language guide on smoking cessation, *Guia para Dejar de Fumar*. In addition, through NCI's Multimedia Technology Health Communications Grants to Small Business, NCI has supported the development of a number of interactive CD-ROMs and Web-based applications designed to capture the attention of targeted population groups. Examples include *Rebels: The Battle for a Smoke-Free Future*, a CD-ROM game for high school students who smoke. The game includes a teacher's manual and student handouts. Two additional products are *Dig Deeper*, a CD-ROM for tobacco use prevention in 10- to 12-year-olds, and the *Appalachian Community Kit for Tobacco Prevention*, a second-hand smoke project. The community kit includes brochures, fact sheets, and videos designed for Appalachian women, who influence smoking cessation in their homes.

Optimizing Energy Balance to Reduce the Cancer Burden

The term “energy balance” refers to the integrated effects of diet, physical activity, and genetics on growth and body weight over an individual’s lifetime. Scientists are increasingly aware of the importance of understanding the effects of energy balance on the development and progression of cancer and on cancer patients’ quality of life after treatment.

A 2003 Institute of Medicine (IOM) report on cancer prevention and control assigns top priority to the development of a national strategy to prevent obesity and sedentary behavior, second only to efforts to curtail tobacco use.¹ However, because proven, evidence-based methods of preventing these unhealthful conditions are lacking, we must begin by learning more about energy balance through comprehensive and effective research.

At a time when almost two-thirds of the U.S. population is considered overweight or obese, international teams of scientists have assembled compelling evidence that as overweight and obesity increase, and physical activity decreases, the risk of developing many cancers rises. A comprehensive 2002 international review by the International Agency for Research on Cancer (IARC) summarized, for the first time, the compelling evidence that prevention of obesity reduces risk for many of the most common cancers such as colon, postmenopausal breast, uterine, and renal cell cancers and that physical activity reduces risk for colon and breast cancers. The IARC report further estimated that 20 to 30 percent of some of the most common cancers in the United States, including breast, prostate, colon, kidney, and uterine cancers, may be related to overweight and/or physical inactivity. Other international findings indicate that physically active people have a 50 percent decreased risk of colon cancer. Evidence from a large cancer cohort study based on results from almost 1 million subjects argues that overweight and obesity in our Nation account for 14 percent of deaths from cancer in men and 20 percent in women.

PROGRESS IN PURSUIT OF OUR GOAL

NCI is committed to providing leadership to advance energy balance research through targeted investments, as well as through collaborations with public and private partners. NCI-supported research has revealed a number of important findings, including: mechanisms by which diet, weight, and physical activity affect carcinogenesis; new methods for quantifying key health behaviors and their consequences; and innovative means for evaluating progress through national and regional health monitoring. Even so, much remains to be learned about research methods, mechanisms of energy balance-related cancer morbidity and mortality, and the interplay of multiple energy-balance risk factors on cancer development.

Discovery

Teams investigating energy balance employ resources ranging from preclinical models to epidemiologic studies and clinical interventions.

Improving Research Methods

NCI and its partners are improving diet and physical activity measures, including both self-reported and objective measures. Recent research includes the following:

- The Observing Protein and Energy Nutrition (OPEN) study, the largest of its kind, used biomarkers of dietary intake to assess the accuracy of dietary assessment methods commonly used in epidemiology, intervention, and surveillance research. The investigators found that self-reported intake measures used in many studies are not sufficiently accurate. Further research will examine whether these findings are true for diverse populations, for other dietary-report or physical activity instruments, and across varying nutrients and food groups, as well as how the measurement inaccuracies may affect ongoing prospective cohort studies.

¹ *Fulfilling the Potential of Cancer Prevention and Early Detection*. National Academies Press, 2003.

- The NIH Behavioral Change Consortium studies, cofunded by NCI, provided a setting for researchers to validate NCI-developed short screening questionnaires to assess changes in intake of fats, fruits, and vegetables. This and other research highlighted a need for innovation in measurement of diet and physical activity. In response, NCI is sponsoring the first NIH-wide program to improve diet and physical activity assessment methodology across culturally diverse populations.

Researchers are using breast density measurements as a marker for breast cancer risk to evaluate interventions that target pathways such as estrogen or insulin metabolism to reduce breast cancer risk.

Discovering Mechanisms

Researchers are discovering the mechanisms by which sedentary behavior or insufficient amounts of physical activity, poor diet, and overweight or obesity increase an individual's risk for cancer from infancy through adult life. For example:

- Investigators discovered that leptin, a hormone that tends to be elevated in obese people, provides researchers with a more precise means of studying the relationship between estimated total body fat and cancer. For example, using leptin measurements, researchers were able to establish a link between total body fat and the risk of developing prostate cancer. Prior studies using measurements such as weight or body mass had been unable to make this association.
- Preclinical investigators using Mouse Models of Human Cancers Consortium (MMHCC) mice discovered that increased activity was more protective in male than female mice.
- Intramural and extramural clinical researchers are exploring the ways that chemopreventive agents, diet, weight, and physical activity affect cancer development in humans.
- Another team of investigators found that postmenopausal women participating in a 1-year physical activity intervention program experienced beneficial changes in total body fat, body fat distribution, and levels of circulating hormones. This discovery may lead to interventions to prevent hormone-dependent cancers, such as breast and endometrial cancers.

Evaluating Multiple Risk Factors

Researchers evaluating multiple risk factors have found that the effect of women's body mass index on colon cancer risk changes, depending on estrogen exposure. In addition, results from the Women's Health Initiative, which examined the effects of obesity and physical activity on postmenopausal breast cancer risk, demonstrated that being physically active is most protective among women who remain of normal weight after menopause. This protection was not observed among obese women.

Understanding the Role of Physical Activity and Diet

In the last 5 years, scientists have improved their understanding of the relationship between physical activity and cancer, leading to critical insights into strategies to reduce the incidence and burden of cancer. For example:

- Recent discoveries highlight the role genetic differences may play in individuals' capacity to exercise as well as their risk for obesity. Now scientists must incorporate genetic information into large population studies to understand how the interplay of genetics with diet, obesity, and physical activity may alter cancer risk.

- Among cancer patients and survivors, anecdotal and research evidence suggests that physical activity benefits cardiopulmonary function and quality of life, reduces fatigue and depression, and improves muscular fitness. Low- to moderate-intensity regular physical activity programs may help breast cancer patients maintain functional ability and minimize weight gain. This in turn may help prevent disease recurrence and other comorbidities. NCI and partners are exploring the potential benefits of weight control and physical activity interventions among diverse groups of cancer patients with breast, prostate, and colon cancers, as well as among long-term survivors of childhood cancer.

Development

Learning How to Change Behaviors

As a first step in the development of energy balance interventions, NCI is researching key determinants of behavior change. This research has brought to light the difficulty of treating obesity once it has developed, and further reinforces the need for obesity prevention research, particularly among children and adolescents. Although much is known about how dietary and physical activity behaviors can be changed, attempts to develop behavioral interventions to effectively increase physical activity are relatively new. Therefore, NCI is sponsoring an NIH-wide effort to accelerate research on the mechanisms of physical activity behavior change. In addition, NCI has worked with groups such as the Agency for Healthcare Research and Quality and the National Academy of Sciences to conduct research reviews, providing information to aid evidence-based intervention development for dietary and physical activity behaviors.

Developing Health Monitoring Systems

NCI supports research to develop enhanced health monitoring systems at the national and regional levels to evaluate progress in cancer control across diverse populations, including minority and underserved populations. For example:

- NCI included physical activity monitoring in the 2003 National Health and Nutrition Examination Survey (NHANES) to address discrepancies discovered in previous studies between reported and objective measurements of physical activity. Researchers will compare reported physical activity levels to measurements such as body composition and cardiovascular fitness, generating the first critically objective examination of physical activity data on a nationally representative sample. In addition, NCI-supported research has enhanced methods for evaluating usual food and nutrient intake in national populations.
- NCI-sponsored research has demonstrated that the structure of neighborhood environment, such as availability of sidewalks, may enhance walking. NCI is partnering with the Centers for Disease Control and Prevention to collect data on diet, weight, physical activity, and neighborhood environment to determine whether there is a relationship among these factors in some communities.

GOAL

Understand the causes of adverse patterns of weight, physical activity, and diet; define their contributions to cancer; and apply this knowledge to cancer prevention and control.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

- 1. Discover how body weight, physical activity, and diet, along with genetic and environmental factors, interact over a lifetime to influence the cancer process. \$18.00 M**

 - Discover and characterize mechanisms leading to cancer by initiating transdisciplinary research centers in the areas of energetics, physical activity, nutrition, and genetics. \$6.00 M
 - Collect enhanced self-report and objective measures on diet and bioactive food components, body mass and composition, and physical activity and fitness by expanding and using existing population-level studies, including the Cohort Consortium. \$5.00 M
 - Advance understanding of cancer mechanisms by conducting studies in existing NIH clinical metabolic and nutrition research units. \$1.00 M
 - Document the influence of energy balance on the cancer process throughout life through the use of preclinical animal models. \$3.00 M
 - Study the impact of energy balance on cancer by initiating basic and clinical research utilizing proteomic approaches and molecular technology. \$3.00 M

- 2. Monitor trends in and determinants of diet, weight, and physical activity and their cancer-related consequences across diverse populations by expanding nationwide research and health surveillance infrastructure. \$12.50 M**

 - Expand nationwide surveys to enhance self-report, biologic, and genetic measures for monitoring and examining the impact of behaviors related to energy balance and cancer, in collaboration with the National Center for Health Statistics (NCHS). \$2.00 M
 - Advance knowledge about specific local populations by fostering community surveillance on individual behaviors and environmental factors, in collaboration with the Centers for Disease Control and Prevention and NCHS. \$3.00 M
 - Develop an infrastructure to train future national and international scientific leaders on the importance of energy balance across the cancer continuum by supporting interdisciplinary training in both basic and population sciences. \$2.50 M
 - Evaluate public comprehension of health recommendations on physical activity and nutrition through the NCI Health Information National Trends Survey (HINTS). \$0.50 M
 - Establish surveys of healthcare providers to evaluate knowledge, attitudes, and practice related to weight control in clinical practice. \$1.00 M
 - Identify opportunities for cancer control by developing a research resource on legislative policies related to nutrition, physical activity, and obesity. \$1.00 M
 - Initiate innovative research on economic factors related to diet, physical activity, and energy balance in at-risk populations, in collaboration with Federal partners, including the U.S. Department of Agriculture. \$2.50 M

Development
3. Develop improved measurement of body mass and composition, physical activity and fitness, and diet and bioactive food components through self-report measures and advances in technology for objective reference measures. \$13.50 M

- Expand validation research of diet, physical activity, and fitness measurement through the use of reference biomarkers and physical measures of fitness within national and international cohort studies. \$5.00 M
- Support research in collaboration with other NIH institutes in innovative technologies, such as electronic handheld monitoring devices and Internet surveys, in the assessment of diet, weight control, and physical activity behaviors. \$2.00 M
- Improve the ability to capture information on diet, weight, and physical activity behaviors across diverse cultural populations. \$5.00 M
- Develop surrogate (intermediate) biomarkers for use as predictors of the effectiveness of diet and physical activity interventions. \$1.50 M

4. Improve cancer-related health outcomes, especially in high-risk populations, by accelerating research on energy balance-related behaviors and developing interventions. \$13.00 M

- Support research on interventions that focus on weight control through diet and physical activity in cancer patients and in populations at high risk for cancer. \$4.00 M
- Support research to understand how sociocultural factors influence adoption of recommended behaviors, and develop approaches to improve interventions in specific populations. \$3.00 M
- Develop effective approaches to improving and targeting health messages in the areas of dietary guidance, physical activity recommendations, and food labeling by supporting health communication research in partnership with other NIH institutes. \$2.00 M
- Support research within transdisciplinary research centers on innovative and cost-effective obesity prevention interventions, with broad population impact at the social-environmental or policy level for children and adults. The research on efforts targeting adults should focus on critical periods when weight gain is likely to occur, such as with smoking cessation, pregnancy, stress, depression, injury, or cancer treatment. \$4.00 M

Management and Support

	\$ 0.80 M
Total	\$57.80 M



Energy In, Energy Out – A Critical Balance

I've struggled with my weight since I was about 13. I gain, I lose, I gain again. . . . I know the extra weight makes me more likely to have heart disease and diabetes, but now the scientists are saying I'm also at higher risk for many cancers.

The evidence is now clear that obesity is a significant risk factor in many cancers, including cancers of the colon, prostate, postmenopausal breast, uterine, and renal cell. It has been estimated that overweight and obesity in the United States may account for 14 percent of all cancer deaths in men and 20 percent in women, adding up to more than 94,000 deaths each year.

Researchers suspect that many of the mechanisms responsible for this increased risk are systemic in nature, simultaneously increasing the risk of cancer in many parts of the body. For example, overweight and inactivity have been shown to cause the body to secrete increasingly higher amounts of insulin and other growth factors. Cells exposed to high levels of these substances over an extended period are more prone to accelerated growth. This rapid growth increases the likelihood of random genetic mutations which, in turn, elevates the risk of cancer.

Other mechanisms related to energy balance appear to be specific to certain cancer types. For example, investigators have demonstrated that exercise decreases colon cancer risk, possibly by increasing the rate at which harmful waste products move through and exit the colon. Also, epidemiologic researchers have shown that overweight or obese women, especially those who gain weight throughout adulthood, experience increased risk for breast cancer after menopause. Even moderate regular exercise may help reduce this risk by decreasing estrogen levels in the breast tissue.

Scientists have identified obesity and sedentary lifestyle as two important and modifiable risk factors for cancer. Experts believe that it is particularly important to reach children with information about healthy eating and regular exercise while their lifestyle patterns are developing and before they experience excess weight gain.

I try to eat right and exercise regularly, but it's really hard for me to build new habits.

NCI is working to accelerate our understanding of the many aspects of energy balance and specific cancers and cancer in general, and to devise ways to communicate this information to all populations. Investigators are examining the relationship between cancer and the independent and combined effects of reduced energy intake (caloric restriction), various components of diet (e.g., carbohydrates, protein, fat), specific foods, micronutrients, food preparation methods, and types and intensity of physical activity. To further this research, NCI is hoping to support more transdisciplinary research dedicated to improving our understanding of how energy balance affects risk across the cancer continuum, from causation through survival, and on developing innovative approaches to obesity prevention, especially among children and in diverse populations.

This People's Story is an amalgam of individual experiences.

Improving the Quality of Cancer Care

Receiving the best possible medical treatment and care is the continuing hope for over 9 million cancer patients and survivors in the United States. Drawing from the Institute of Medicine's (IOM) National Cancer Policy Board (NCPB) report, we define quality cancer care as the provision of evidence-based, patient-centered services throughout the continuum of care in a timely and technically competent manner, with good communication, shared decision making, and cultural sensitivity. The ultimate aim is to improve a range of outcomes important to patients, families, and other decision makers, including patient survival and health-related quality of life.

Unfortunately, far too many will not receive the highest caliber of care. In many cases, there is substantial disagreement about what constitutes optimal care, especially from the patient's perspective, and about the best approaches for achieving improvement. Even where consensus appears to exist, there is often wide variation in practice patterns. Therefore, it is critical that we advance understanding of how to measure, monitor, and improve the quality of cancer care.

The reasons why some cancer patients do not receive the newer, more effective treatments or sufficient palliative and end-of-life care are not adequately understood. The NCPB has criticized the Nation's "ad hoc and fragmented cancer care system." Cancer patients, families, and providers gave testimony, summarized in the President's Cancer Panel Report, *Voices of a Broken System: Real People, Real Problems*,¹ which identified barriers to high quality cancer care. They include system and financial limitations, inadequate patient information and provider education, poor management of cancer-related symptoms, and lack of timely referral to palliative and hospice care.

NCI must strive to discover what constitutes quality cancer care. We must develop the measures and tools required to achieve improvements and evaluate performance. Finally, we must investigate and generate mechanisms, in collaboration with public and private policymakers, to ensure that quality care — based on outcomes research that identifies best practices — is delivered to all who need it.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

Discovering What Constitutes Quality Cancer Care

Several NCI-supported national data resources enable researchers to empirically explore important questions related to cancer quality of care. **Rapid Response Special Studies (RRSS)** allow NCI to quickly sponsor research on high priority topics. A recent RRSS study found that in children with cancer, 71 percent of patients younger than 15 received treatment through NCI-sponsored clinical trial protocols, but less than 24 percent of adolescents ages 15-19 received this highest quality pediatric cancer treatment.

¹ Institute of Medicine, National Research Council, *Improving Palliative Care for Cancer*, 2001. President's Cancer Panel, Report of the Chairman 2000-2001, *Voices of a Broken System: Real People, Real Problems*, September 2001.

Two new RRSS studies, the Experience of Care and Health Outcomes of Survivors of Non-Hodgkin's Lymphoma (ECHOS-NHL) and the Assessment of Patients' Experience of Cancer Care (APECC), will yield important new information about the follow-up care experiences and health outcomes of cancer survivors.

NCI's **Patterns of Care/Quality of Care (POC/QOC)** program draws from the Surveillance, Epidemiology, and End Results (SEER) registry data to investigate adoption of recommended treatments for the most common cancers. The results of POC/QOC studies are reported at professional meetings of oncology societies and are used to develop educational and training opportunities to improve the use of state-of-the-art cancer therapy in community practice. Currently, POC/QOC data are being analyzed to document the relationship between health insurance coverage and receipt of appropriate or complete cancer care.

Studies linking SEER and Medicare data continue to provide insights into quality of care issues:

- Hospice is used more frequently and for a longer period by persons enrolled in health maintenance organizations (HMOs), compared with fee-for-service patients.
- Patients diagnosed with superficial bladder cancer undergo significantly less postdiagnostic surveillance than generally recommended by leading cancer professional and research organizations.
- Disabled women with breast cancer are diagnosed at a later stage of the disease than nondisabled women, with the disparity greater for women with fee-for-service coverage compared with HMO coverage.

To better understand the causal factors and mechanisms that underlie the patterns of care described in these investigations, NCI has established large national-level studies that track patterns of care and outcomes for cohorts of newly-diagnosed cancer patients. The first of these, the **Prostate Cancer Outcomes Study (PCOS)**, provided a wealth of information about treatment outcomes for 3,500 men diagnosed with tumors confined to the prostate gland.

In 2001, NCI launched the **Cancer Care Outcomes Research and Surveillance Consortium (CanCORS)**, combining data from registries, medical records, insurance claims, and patient and provider surveys to create an unusually rich longitudinal picture of the care received by a sample of 5,300 colorectal and 4,800 lung cancer patients across the United States. Treatment settings include fee-for-service, large nonprofit HMOs, and the relatively centralized health care system of the Department of Veterans Affairs.

The **Breast Cancer Surveillance Consortium (BCSC)** investigates factors associated with high quality screening mammography in community practice. Evidence from a study involving over 300,000 women, including 2,200 women with cancer, examined the combined and individual effects of breast density, age, and hormone replacement therapy on the accuracy of screening mammography. Research examining

the biologic characteristics of cancers that are not detected by screening has found that screening mammography may miss some rapidly growing, high-grade tumors and those of lobular or mucinous histology. BCSC is actively collaborating with Federal regulatory agencies, radiological professional societies, and private-sector vendors to reduce the cost and improve the quality of data collection for mammography quality control.

The **Cancer Research Network**, a consortium of researchers affiliated with 11 major not-for-profit HMOs, is providing the mechanism for NCI to quickly obtain better data on patterns of cancer care from multiple perspectives. Recent findings include:

- Support for tobacco cessation is both variable and suboptimal.
- The most important factor predicting oncologists' ability to recruit patients to clinical trials was having sufficient organizational infrastructure to support trial participation.
- The majority of late-stage breast and invasive cervical cancer cases appear to be associated with an absence of screening or failures in detection.

The **NCI National Clinical Trials Program** provides an ideal venue to deepen our understanding about the quality of cancer care from both biomedical and patient-reported perspectives by incorporating clinical and health-related quality of life endpoints into clinical study design.

Development

NCI initiatives are significantly expanding our understanding of how to measure and improve the quality of cancer care in a variety of specific, community-based practice settings. But we need additional research on health system-level interventions. The organizational and informatics infrastructure of clinical and patient decision making requires improvement, and patient care will benefit from incentives rewarding the delivery of evidence-based cancer care.

Developing Core Measures to Support Discovery and Delivery of Quality Cancer Care

In 2001, NCI convened the **Cancer Outcomes Measurement Working Group (COMWG)**, composed of 35 internationally recognized experts in measurement, oncology, and the social sciences. This group assessed alternative approaches for improving patient-centered outcome measures such as health-related quality of life, economic burden, and satisfaction with care. The lack of standardization in measuring such patient-reported outcomes is a major barrier to comparing findings in quality of care research. In the forthcoming volume *Outcomes Assessment in Cancer* (Cambridge University Press, 2004), the working group emphasizes the potential value of survey item banks and computer-adaptive data collection.

NCI is collaborating with other Federal agencies and the private sector to create standards for process measures of cancer care quality. The centerpiece of this **Cancer Care Quality Measures Project (CanQual)**, conducted under the auspices of the nonprofit National Quality Forum (NQF), is consensus development of core process measures and recommendation of topics for further measures development. The high-priority areas identified by NQF are: diagnosis and treatment for breast, colorectal, and prostate cancers; access to care; communication and coordination of care; and symptom management across the cancer continuum, including end of life.

Developing Approaches to Improve Symptom Management and Palliative Care across the Cancer Continuum

The *Improving Palliative Care for Cancer* report² identified gaps in symptom management and palliative care research. Information on how to better measure, evaluate, and improve symptom management is now emerging. Basic and clinical researchers are currently:

- Determining which symptoms occur most frequently according to tumor type and treatment choice.
- Developing new methods for assessing symptoms.
- Working to improve communication about symptoms between patients and their health care teams.
- Developing and comparing strategies of symptom management.
- Finding ways to better integrate symptom management as a vital part of all cancer care.

Delivery

A workshop on the diffusion of medical innovations will be held in 2004, setting the stage for studies to examine why some highly promising therapies successfully move into clinical practice while others do not.

Delivering on the Promise of High Quality Cancer Care through Evidence-Based Decision Making

Since it was established in 2000, NCI's **Quality of Cancer Care Committee (QCCC)** has sought to improve Federal-level decision making on cancer care. Through the QCCC, NCI is currently supporting three interagency projects:

- The Health Resources and Services Administration, the Centers for Disease Control and Prevention, and the nonprofit Institute for Health Care Improvement are collaborating with NCI to improve screening and follow-up for breast, cervical, and colorectal cancers in community health centers for the medically underserved. In the project's pilot phase, 12 health centers helped develop and test a core set of quality performance measures, which are now being evaluated in 20 additional centers.
- The Centers for Medicare and Medicaid Services is working with NCI to increase the awareness and improve the delivery of Medicare-covered colorectal cancer screening services.
- The Department of Veterans Affairs (VA), with NCI support, has established a Quality Enhancement Research Initiative (QUERI) to improve screening, follow-up, treatment, and end-of-life care for colorectal cancer in the VA health system.

² Institute of Medicine, National Research Council, *Improving Palliative Care for Cancer*, 2001.



Symptom Management Research – Improving Quality of Life for Patients and Their Caregivers

Each time my colon cancer comes back, it seems to hit me harder. The pain is worse, I have more trouble sleeping, and I just get so tired. The pain is the biggest problem. I get depressed because I can't control it. When the doctors and nurses ask me how the pain is, I don't know how to describe it, except that it's worse than it was the week before. I'm afraid to say too much, because they might stop the chemo, and then the cancer would get even worse.

Symptoms of cancer and side effects of related treatments can be severe in patients with advanced-stage disease, especially in those receiving aggressive and experimental therapies. Research has shown that symptoms affect patients' overall quality of life, including their ability to do many of the things most people take for granted, such as caring for themselves, doing household chores, sleeping, or going to work. We know that intense and uncontrolled symptoms lead to poor emotional and physical health. We also know that patients are sometimes hesitant to report they have bothersome symptoms for fear their therapy will be slowed or stopped. More symptom management research is needed to ensure that patients receive quality, effective cancer care that does not disrupt their quality of life. (See pages 54 and 57.)

NCI-supported researchers are exploring ways to help patients and their families better manage symptoms and improve their quality of life. Investigators are seeking a better understanding of the interaction between common symptoms of advanced cancer. For example, when patients experience pain, are they more likely to have fatigue? And which symptoms are particularly troubling to caregivers and patients?

My husband has been battling cancer for a year and a half. I know he's in a great deal of pain because I can see it in his face. The doctor gave him pain medication, but I wonder if he's taking the full dose — he's told me before he doesn't like how "out of it" he feels when he takes it. It seems like it's a never ending cycle — as the pain gets worse, he gets more tired, he can't eat or sleep, which makes the pain even harder to take. I wish I knew what to do to help him be more comfortable.

Caregivers are partners in care, part of the patient's team, and a vital resource to the patient. They are often responsible for accessing information, communicating with the patient's health care team, and providing hands-on care to alleviate troublesome symptoms. Caregivers are more likely to feel a greater sense of burden and to be depressed, frustrated, and overwhelmed in their role when patients' symptoms are out of control, particularly when the patient has severe pain or fatigue. Through symptom management research, we will be able to better prepare caregivers to manage patients at home and ultimately improve caregivers' emotional and physical health as they continue to help their family members live with cancer.

This People's Story is an amalgam of individual experiences.

GOAL

Improve the quality of cancer care by strengthening the scientific basis for public and private decision making in care delivery, coverage, purchasing, regulation, and standards setting.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

1. Strengthen the methodological and empirical foundations of cancer care quality assessment. \$17.50 M

- Investigate factors associated with high-quality screening mammography in community practice, by renewing support for the Breast Cancer Surveillance Consortium (BCSC). \$6.00 M
- Support intervention studies and programs for improving referral patterns and treatment where suboptimal performance has been documented, such as in cervical and ovarian cancer. \$2.00 M
- Investigate the feasibility of implementing new data systems to monitor the outcomes and economic cost of cancer care in healthcare systems, including:
 - Linkage of tumor registry information with additional public and private health claims data and with patient outcomes and satisfaction surveys. \$5.00 M
 - Establishment of physician networks and databases for tracking and monitoring cancer screening practices. \$1.50 M
 - Creation of a provider survey initiative to collect nationally representative data from practitioners and health care organizations. \$1.00 M
- Conduct new studies to strengthen the methodological foundations of outcomes research and quality of care assessment. \$2.00 M

2. Enhance quality-of-care research within, and beyond, the NCI clinical trials program. \$2.00 M

- Conduct an international state-of-the-science conference on the benefits of adding quality of life and outcome measures to cancer trials, in collaboration with the Food and Drug Administration and community-based practitioners. Recommend new guidelines for NCI-supported treatment and prevention trials. \$0.50 M
- Examine the adoption of therapies across delivery systems, using knowledge gleaned from a workshop on the diffusion of medical innovations. \$1.00 M
- Support economic studies paralleling cancer treatment and prevention trials and other cancer control intervention studies. \$0.50 M
- Strengthen the evaluation of proposals to use health-related quality of life and economic endpoints in NCI-sponsored Phase III trials, by establishing protocol review teams consisting of both NCI and non-NCI experts.

Development

3. Identify, develop, and test core process and outcome measures for assessing the quality of cancer care. \$6.50 M

- Improve patient-centered outcomes measurement, including health-related quality of life and patient satisfaction, by (1) developing and testing tools and instruments; (2) supporting statistical studies to facilitate the “cross-walking” of scores among competing instruments, and determining clinically meaningful change scores; and (3) conducting pilot investigations of new or enhanced outcome measures. \$2.00 M
- Identify and test additional core process measures by providing supplemental funding for the Cancer Care Quality Measures Project (CanQual). \$2.00 M

- Test the ability of core process and outcome measures to improve the quality and patient safety of cancer care, strengthen provider accountability, and enhance informed decision making. \$2.50 M

4. Incorporate symptom management and palliative care into the full spectrum of cancer quality improvement research and translation efforts, from initial treatment, through survivorship, and at the end of life. \$3.00 M

- Assess approaches for effective symptom management and palliative care by collaborating with other NIH institutes to support research on new interventions (e.g., for lymphedema, cachexia, pain, and sleep disorders). \$2.50 M
- Assist in the coordination of Department of Health and Human Services end-of-life research through the creation of a symptom management and palliative care consortium within NCI Cooperative Groups, and cosponsor an NIH End of Life interest group.
- Increase the number of interdisciplinary-trained researchers in symptom management, rehabilitation, and palliative care through individual mentor and career development awards. \$ 0.50 M

Delivery

5. Ensure that the best scientific evidence about quality measures and assessment informs Federal, state, and private-sector decision making about cancer care. Sponsor collaborative projects on core measures of cancer care quality and translate research evidence into better quality care. \$6.50 M

- Provide technical assistance and advice to public agencies and private organizations, through continued support for the Quality of Cancer Care Committee (QCCC) and the clinical and policy expertise of the QCCC. \$2.00 M
- Implement core process measures of cancer quality and monitor progress through collaboration with public agencies and private organizations. Such measures would include symptom management and palliative care. \$1.00 M
- Incorporate and disseminate evidence-based symptom management and palliative care practices more fully into NCI's education and information products for health professionals. \$0.50 M
- Support ongoing development of a national cancer data system for tracking trends in cancer care and outcomes and identifying population disparities, through collaboration among QCCC members, the states, and private organizations.
- Strengthen the science of cancer care by:
 - Implementing and evaluating evidence-based interventions to improve cancer care through collaborative teams within NCI-designated Cancer Centers and other organizations. \$1.50 M
 - Addressing the delivery of cancer care at the health systems level, including approaches to improve cancer care coordination, patient navigation, and provider decision support, by issuing joint solicitations with other NIH institutes and Federal agencies. \$1.50 M

Management and Support		\$ 0.80 M
	Total	\$36.30 M

Reducing Cancer-Related Health Disparities

Overcoming cancer health disparities is one of NCI's top priorities for reaching our Challenge Goal of eliminating suffering and death due to cancer. It is well known and documented that the burden of cancer is not borne equally by all population groups in the United States. One's gender, ethnicity, and socioeconomic status influence cancer incidence, morbidity, and mortality. For example:

- Men have about a 50 percent higher annual death rate from cancer than women.
- African Americans and Alaskan Natives experience a higher incidence of colorectal, lung, and bronchus cancers than any other ethnic group.
- The death rate from prostate cancer among African American men is approximately twice that of White men.
- Asian and Pacific Islanders, including Native Hawaiians, have a substantially higher incidence of stomach cancer than other populations.
- People living in areas of low socioeconomic status generally have higher cancer death rates than those in areas of higher socioeconomic status.

The scientific community has a critical and unique role in addressing the moral and ethical dilemmas posed by the unequal burden of cancer in our society. We must use our overall knowledge and understanding of cancer and our knowledge of the fundamental causes of health disparities to develop and deliver effective interventions to all Americans, particularly those who bear the brunt of the burden. This is an especially opportune time for NCI to commit additional resources to address cancer health disparities. Innovations include the availability of new technologies such as telemedicine, bringing screening and diagnostic services to people where they live, the exciting potential for scientific advances in cancer prevention and treatment, and new developments in addressing the cancer communications needs of specific communities.

PROGRESS IN PURSUIT OF OUR GOAL

From Discovery to Delivery

Over the past several years, NCI has increased its support for research to address the gaps in the delivery of research advances to all populations regardless of their age, gender, race, ethnicity, or socioeconomic status.

Bridging the Gap between Discovery and Delivery to Address Disparities

NCI-supported **Special Population Networks (SPNs)** at 18 institutions across the country are building long-term relationships between large research institutions and community-based programs to learn more about the causes of cancer disparities in minority communities and to develop and test ways to address and eliminate these causes. The SPNs are located in institutions that serve American Indian populations in the Southwest, rural underserved populations of Appalachia, Asian and Pacific Islanders in the West, and underserved and immigrant minority groups in inner cities. The programs promote cancer awareness through culturally tailored education programs, encourage cancer screening and participation in clinical trials, and conduct community-based cancer research.

To bring new radiation-related treatments for cancer to underserved communities, NCI is providing support and resources for **radiation oncology clinical research** in institutions that traditionally have not been involved in NCI-sponsored research, but that care for a disproportionate number of medically underserved, low-income, and ethnic and minority populations. Supported through the

The use of telemedicine in communities such as Native American reservations can significantly improve access to care.

Cooperative Planning Grant for Cancer Disparities Research, this initiative also has established partnerships between institutions that are actively involved in NCI-sponsored research. This support also provides for the use of **telemedicine and teleconferencing systems** between institutions and partners, including patient exam cameras and remote-controlled microscope capability to examine biopsy specimens, allowing for simultaneous examination and discussion.

The **Patient Navigator program**, a new approach to providing individualized assistance to newly diagnosed cancer patients, is being piloted at two institutions supported through the Cooperative Planning Grant for Cancer Disparities Research. Patient navigators are trained, culturally sensitive individuals who help cancer patients manage the complexities of medical care by providing information and guidance on screening, diagnosis, and treatment options. Results of this pilot will provide NCI with a model for examining the effectiveness of promising interventions to address gaps in the delivery of cancer health services.

NCI, in collaboration with four institutes and offices within the National Institutes of Health, recently provided support to establish **Centers for Population Health and Health Disparities**. Interdisciplinary in focus, these centers provide environments conducive to collaborations among biomedical, social science, and environmental research investigators working with communities serving low-income and racially diverse populations. The centers will accelerate knowledge about social, cultural, biological, behavioral, and environmental factors that contribute to health disparities, and the development of effective interventions to reduce them.

Initiated in 1990, the **Minority-Based Community Clinical Oncology Program (CCOP)** continues to provide minority cancer patients with access to state-of-the-art cancer treatment, prevention, and control technology in their own communities. The current program includes 11 minority-based CCOPs and involves more than 40 hospitals and over 100 minority investigators. Greater involvement in clinical trials research by African American, Hispanic, Asian American, American Indian, and other racial and ethnic minority patients is needed to ensure that advances in clinical research are extended to all groups and subsequent results can be generalized to the entire population. NCI issued an announcement in Spring 2003 to continue support for this program.

Broadening Our Understanding of the Causes of Cancer Disparities

Despite a three-fold reduction in **cervical cancer mortality** nationwide in the past 50 years, counties stretching from Maine southwest through Appalachia to the Texas/Mexico border, in many Southeastern states, and in the Central Valley of California have experienced persistently higher cervical cancer mortality rates. To address these high mortality rates, NCI has implemented a partnership demonstration project in eight states to increase cervical and breast cancer screening among women who have never or rarely been screened, in collaboration with the Centers for Disease Control and Prevention (CDC), the United States Department of Agriculture (USDA), and the American Cancer Society (ACS). Using NCI analyses of county mortality rates

NCI assembled a think tank to synthesize research knowledge and identify core findings to provide Federal, state, and local policymakers with evidence-based recommendations to reduce disparity in cervical cancer mortality rates.

to identify high-rate counties, the partners are working together to train staff of CDC's Breast and Cervical Cancer Early Detection Program; USDA's Cooperative State Research, Education, and Extension Service; ACS's regional cancer control programs; and NCI's Cancer Information Service to use evidence-based cancer screening promotion programs to increase screening among high-risk women.

Published studies in leading medical journals show that Black patients tend not to receive the same level of treatment quality as White patients of similar socioeconomic status, insurance coverage, health status, and diagnosis. Other studies show that other race and ethnic minorities experience similar **treatment disparities**. The unsettling nature of these conclusions led NCI to more thoroughly explore the mounting evidence of racial bias, prejudice, and intolerance in the Nation's health care system. NCI conducted think tank meetings composed of experts from a variety of disciplines who could help shed light on a complex set of issues. The purpose of the first think tank was to plan an approach to understanding why patients of similar financial resources, health status, access, and other factors but of differing racial and ethnic backgrounds do not receive the same level of health care. A subsequent think tank addressed participants' concerns regarding the depth and complexity of the problem in science and society. This think tank examined how evolution, migration, genetics, and social history have contributed to the problems associated with race in science.

NCI supports numerous **studies to identify risk factors for disease and describe racial and ethnic differences in cancer rates**. For example:

- The Southern Community Cohort Study (SCCS) is a landmark study that will further determine why African Americans are more likely to develop and die from cancer. A collaborative effort with public and private research-related organizations, the SCCS will examine disparities in lung, breast, colorectal, and prostate cancers by recruiting 70,000 African American and 35,000 non-African American residents in the southern United States.
- The association of diet and other factors contributing to gastric cancer is being studied in a 5-year, population-based case-control trial. Ethnic groups receiving special emphasis include Caucasians, Chinese, Filipinos, Hawaiians/part Hawaiians, and Japanese.
- A study of the causes of illness in Black women will examine multiple risk factors for cancer, cardiovascular disease, and other major illnesses. Possible risk factors to be examined include obesity, cigarette smoking, physical activity, alcohol use, diet, estrogen use, and reproductive factors.
- Through the NCI-supported Center for Psycho-Oncology, investigators are looking at the interrelationships among biological processes, cognition, emotion, and physical health in ethnically and culturally diverse survivors of breast cancer, prostate cancer, and AIDS-related cervical cancer.

In Spring 2003, NCI and DHHS announced a **national campaign to reduce the risk of chronic diseases among African American men**, encouraging the consumption of nine servings of fruits and vegetables a day. African American men are among the most seriously affected by diet-related chronic diseases such as cancer and have the lowest overall consumption of fruits and vegetables. The campaign includes national radio advertisements, brochures, and a new Website for African American men (9aday.cancer.gov).

Encouraging Minority Investigator Involvement in Cancer and Cancer-Related Disparities Research

NCI continues to support **opportunities to improve recruitment and retention of minority researchers** in cancer and cancer-related health disparities research through a variety of programs. The Network for Cancer Control Research among American Indian/Alaska Native Populations focuses on increasing the number of Native American researchers, scientists, and medical students involved in cancer control activities. The Minority Institution Cancer Center Partnership reaches out to over 300 minority institutions to offer new opportunities for training minority scientists and to promote more research and community outreach on minority health at Cancer Centers. Interest in health disparities research within the Cancer Prevention Fellowship Program continues to grow.



Trans-HHS Initiative Applies Progress Review Approach to Health Disparities

NCI's Progress Review Group process is serving as a model for a Trans-Department of Health and Human Services (HHS) effort to address health disparities. The purpose of the Trans-HHS Cancer Health Disparities Progress Review Group (CHD PRG) is to identify new opportunities for HHS agencies to address cancer health disparities,

implement new initiatives toward that end, and evaluate their progress. This effort will serve as a demonstration project for possible replication in addressing health disparities in other diseases as well.

The process is designed to:

- Comprehensively define and describe issues related to cancer health disparities.
- Identify areas of strength, gaps, opportunities, and priorities to address cancer health disparities in research and intervention development.
- Facilitate the adoption and implementation of evidence-based research, policy, community programs, and clinical interventions, and evaluate their impact on specific cancer health disparities.
- Ensure unbiased access to standard and continuous preventive care, early detection, and treatment of cancer for every American.

A report and recommendations from the CHD PRG will be issued in early 2004 and will form the basis for HHS's future planning to reduce cancer health disparities. Go to www.chdprg.omhrc.gov for more information on this trans-HHS initiative.

GOAL

Discover the fundamental causes of health disparities in cancer, develop effective interventions to reduce these disparities, and facilitate their delivery. Collaborate through the discovery-development-delivery continuum to ensure continuous access to evidence-based and high quality cancer prevention, early detection, and treatment services for all Americans.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

1. Implement recommendations from the Trans-DHHS Cancer Health Disparities Progress Review Group. (See page 61.) **\$5.00 M**

Discovery

2. Expand research on the magnitude and causes of health disparities in cancer. **\$19.00 M**

- Support international collaborative studies on social determinants of cancer and cancer-related disparities through supplements to NCI-supported Centers for Population Health and Health Disparities. \$2.00 M

 - Expand epidemiologic studies exploring racial/ethnic cancer disparities. \$2.00 M

 - Conduct methodological research to ensure cross-cultural equivalence in survey, epidemiological, and clinical research involving cancer risk factors. \$1.00 M

 - Collect risk factor and screening data for small populations defined by geographic, racial/ethnic, socioeconomic, and other characteristics. \$4.00 M

 - Examine the genetics of race, and develop policies that define the role of race in science through a trans-NIH study in partnership with the National Human Genome Research Institute. \$5.00 M

 - Examine the national costs associated with cancer health disparities, and the cost of not treating all patients equally, by conducting a multidisciplinary study on the economics of cancer with the NIH Office of Behavioral and Social Sciences Research. \$5.00 M
-

Development

3. Develop effective interventions to reduce cancer health disparities. **\$41.00 M**

- Establish new and strengthen current collaborative research partnerships among the Special Populations Networks (SPNs), NCI Divisions, and other Federally funded research networks. \$2.00 M

 - Test community-based interventions leading to the reduction of disparities in cervical cancer mortality through collaborations with NCI's SPNs in Appalachia, the South, and the Texas border. \$5.00 M

 - Reduce cancer health disparities through community partnerships, outreach, and training by continuing support for SPNs. Recompetition of the SPNs will emphasize bridging the gap between the discovery and development continuum of research and the delivery system of medical care in minority and underserved communities. \$20.00 M

 - Support research on planning, development, implementation, and evaluation interventions that provide access to timely and accurate cancer information, screening, early detection, and treatment in a variety of health care service delivery sites (e.g., examine the Patient Navigation Model as an effective intervention in populations experiencing serious cancer-related health disparities). \$4.00 M

 - Establish a Dissemination/Diffusion Research Grants Program to:
 - Study social, environmental, and behavioral barriers to the adoption of evidence-based cancer prevention and control interventions by public health officials and community clinicians.
 - Test new hypotheses for reaching underserved populations in under-resourced community health settings.
 - Develop, apply, and evaluate dissemination and diffusion interventions to reduce cancer health disparities. \$4.00 M
-

- Increase the number of scientists with a focus on health disparities research by recruiting four additional minority scientists and/or physicians through the Cancer Prevention Fellowship Program. \$1.00 M

- Encourage high school to graduate-level minority students to enter careers in health disparities research by expanding the Continuing Umbrella of Research Experiences Program and the Science Enrichment Program. \$3.00 M

- Support efforts to improve recruitment and retention of minorities in NCI-supported clinical trial programs. \$1.00.M

- Increase minority participation in clinical trials through an NCI fellowship training program for health-care providers and through other forums. \$1.00 M

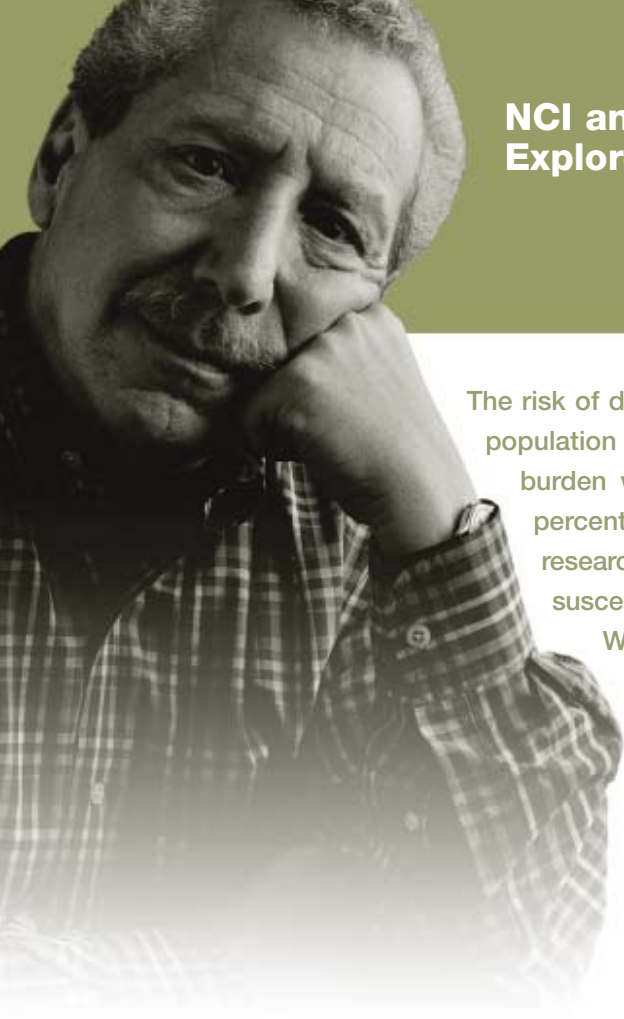
Delivery

- 4. Facilitate implementation of new policy, community, and clinical interventions, and evaluate their impact on health disparities. \$5.50 M**
-
- Customize cancer information materials for targeted audiences by expanding NCI's integrated low-literacy program. \$1.50 M

 - To address health disparities among medically underserved populations, support local and regional science/practice partnership demonstration projects, and disseminate models of success to communities with similar infrastructure barriers. \$2.50 M

 - To help move science into practice, expand Cancer Information Service Partnership Program resources to build new collaborations with staff from the American Cancer Society's Division of Cancer Control and the Centers for Disease Control and Prevention-funded State Health Department Comprehensive Cancer Control Program. \$1.50 M

Management and Support		\$ 0.80 M
	Total	\$71.30 M



NCI and NIA Launch New Efforts to Explore the Interface of Aging and Cancer

The risk of developing cancer significantly increases with age and — as the population of older Americans expands in the next decade — the cancer burden will escalate. Close to 60 percent of all new cancers and 70 percent of deaths from cancer are in persons older than 65. Moreover, research shows that older patients differ from younger patients in their susceptibility to disease progression and their response to treatment.

We also know that current healthcare practices frequently fall short of providing the best available early detection, treatment protocols, and quality care for aging patients. Finally, as increasing numbers of older people develop cancer, and younger cancer survivors live to an older age, the ranks of survivors will grow. The difficulties this group will experience include a greater chance of developing other health problems, disabling conditions, and recurrent cancers.

All of these factors point to a clear need to continue to advance our understanding of the relationships between aging and the development and progression of cancer.

Percent of Cancer Deaths in the United States among People 65 Years and Older

	% Male	% Female
All Tumor Sites	70.9	71.1
Lung & Bronchus	70.4	72.2
Colon and Rectum	73.1	80.1
Pancreas	68.7	79.9
Urinary Bladder	84.2	88.0
Stomach	69.4	77.1
Non-Hodgkin's Lymphoma	38.9	48.6
Leukemia	68.8	72.6
Brain	45.4	54.2
Prostate	92.5	
Breast		58.9
Ovary		67.2

In addition to numerous studies referenced throughout this document, NCI and the National Institute on Aging (NIA) have partnered to further invigorate the research community's focus on the intersection of aging and cancer. Two separate initiatives, one directed to the scientific community at large and the other to NCI-designated Cancer Centers, will support efforts in seven areas of emphasis that emerged from the 2001 NCI/NIA Cancer Centers Workshop on Integrating Aging and Cancer Research:

- **The Biology of Aging and Cancer.** Researchers 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.
- **Patterns of Care.** Investigators will expand efforts to identify and analyze existing and new data from numerous sources, including studies focusing on communities, patient management, and specific cancer sites. The goal of these patterns of care studies is to determine current cancer care practices and identify where changes are needed to improve the quality of care for older patients.
- **Treatment Efficacy and Tolerance.** Researchers will focus renewed efforts on investigating the effectiveness of available treatments, including radiation therapy, surgery, and standard technology; the pharmacology of anti-cancer drugs; limitations on admitting older patients to clinical trials; age-related treatment outcomes; and methods to prevent or offset unfavorable outcomes in older persons.
- **The Effects of Comorbidity.** New studies will further demonstrate or verify effective management of older cancer patients with pre-existing chronic conditions and concurrent diseases, including secondary cancers.
- **Prevention, Risk Assessment, and Screening.** Investigators will increase efforts to identify the impediments that prevent older people, both with and without symptoms, from receiving preventive, assessment, and screening services.
- **Psychosocial Issues and Medical Effects.** Researchers will determine the characteristics of early and late effects of treatment, quality cancer care, tumor recurrence, and multiple primary tumors in older patients, and develop interventions to improve quality of life, cancer survival, and family and caregiver resources.
- **Symptom Management and Palliative Care.** Researchers will focus on the development of evidence-based interventions and guidelines for the management of pain and other symptoms in patients with cancer, as well as family and caregiver support.

Cancer Survivorship: Optimizing Health and Quality of Life after Cancer

NCI's Challenge Goal of eliminating the suffering and death due to cancer is squarely aligned with the interests of the 9.6 million cancer survivors in the United States today. While the ultimate goal of eliminating cancer continues to be our long-term commitment, the capacity to dramatically reduce the suffering caused by cancer is within our immediate grasp. Advances in our ability to detect, treat, and support cancer patients have turned this disease into one that is chronic or readily managed for many, and curable for increasing numbers.

Despite the fact that the majority of survivors (62 percent) are 5 years or more posttreatment, few studies addressed long-term outcomes until NCI began to sponsor such research, a direction that is now actively pursued by the wider scientific community. Research grants that seek to evaluate and improve the posttreatment experience of cancer survivors have increased almost 30 percent in the last year, including a significant focus on interventions that improve psychosocial and health-related outcomes. A growing number of grant applications (15 percent in Fiscal Year 2002) are being submitted by investigators new to cancer survivorship research.

NCI leads the nation in championing research on the health and functioning of our growing population of cancer survivors. We are learning more about many things: the nature and scope of problems encountered by young adult survivors of childhood cancer; the differences between younger and older adults in their responses to treatment; who is at risk for adverse health outcomes; and provocative new interventions for treatment effects such as fatigue, memory difficulties, and pain. To take advantage of this momentum, we need to advance the science in several areas. NCI must work with partners to:

- Expand our capacity to track the health and well-being of cancer survivor populations and their families or caregivers.
- Understand the underlying biologic and genetic mechanisms that may increase survivors' risk for adverse outcomes.
- Broaden the scope of interventions development and testing to include the reduction of cancer-related late morbidity and mortality.
- Explore approaches to promoting optimal posttreatment health behaviors.
- Understand patterns of follow-up care for cancer survivors, including available community resources to deliver care.
- Communicate our findings to both the survivor and healthcare practitioner communities.

The population of cancer survivors continues to grow, a testament to NCI's many successes in preventing cancer from progressing to its later and more virulent stages. These successes include important progress in the delivery and use of cancer screening; enhancement of early detection technologies; discovery and use of more effective and often multimodal therapies; provision of a broadening array of supportive care and rehabilitative options; and, increasingly, wider adoption of active screening behaviors and healthier lifestyles by those at risk for cancer, as well as by those with a history of the disease. Nevertheless, we are also deeply committed to addressing the needs of, and providing hope for, those living with and beyond a cancer diagnosis.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

Exploring the Genetics of Survivorship

The recent decoding of the human genome is increasing scientists' ability to decipher the genetics of survivorship issues, such as hereditary cancer risk patterns that affect family members and genetic susceptibility to treatment-related late effects. Researchers will increasingly be able to identify, based on the genetic profile of

individual patients, potential therapies that will best treat the cancer while preventing unwanted late effects of treatment.

For example, the e4 allele of the *Apolipoprotein E (apoE)* gene has been identified as a potential genetic marker for increased risk of neurocognitive deficits among adult survivors of cancer (breast and lymphoma) who have undergone chemotherapy. NCI is funding research to investigate mechanisms of risk for these late effects using noninvasive techniques such as morphometric magnetic resonance imaging (MRI), functional MRI, diffusion tensor imaging, MR spectroscopy, and positron emission tomography.

Exploring the Impact of Cancer on the Family

As cancer care migrates into the outpatient setting, the economic, physical, and emotional burden on family members is increasing. NCI needs to explore the impact on family members affected by this illness, many of whom may themselves be at increased risk for cancer due to shared cancer-causing genes, lifestyle choices, and/or toxic exposures. Over the next several years, NCI will collect population-based data on the impact of major cancers on U.S. families of diverse racial/ethnic and socioeconomic backgrounds. This survey will generate basic descriptive statistics on the percentage of family households with cancer survivors and caregivers, by demographic characteristics. In addition, the survey will provide data on the medical, familial, psychosocial, and economic factors that may affect family outcomes. The data will be made available to researchers and program planners to monitor the success of interventions and educational resources.

Expanding Research Addressing Underrepresented/Underserved Survivors

In September 2002, NCI convened a meeting to address survivorship issues in minority and medically underserved survivor populations. Held in conjunction with the semiannual board meeting of the Intercultural Cancer Council, the meeting provided an opportunity to discuss research challenges and solutions. Participants reached a consensus on recommendations for collaboration between academic research centers and community organizations, including guidelines for research studies and successful subject recruitment.

The **Cancer Disparities Research Partnership (CDRP)** program will support 5-year cooperative agreements to investigate survivorship in underserved patient populations in locations where health disparities exist. The first two awards were given to sites serving Native American and Hispanic populations. Four additional sites will receive funding in 2003.

Understanding Research Gaps

A review of survivorship research of underserved populations identified only 65 studies with sample sizes sufficient to permit detailed comparisons among diverse groups. Populations requiring further study include diverse ethnic groups, those diagnosed at age 65 or older, rural populations, low-income groups, those with limited education, and survivors with less commonly studied types of cancer.

Discovering Long-Term and Late Effects

The Common Terminology Criteria for Adverse Events represents the first comprehensive, multimodality grading system for reporting the incidence of both acute and late effects of cancer treatment, as well as their duration. Educational tools will be made available to the scientific community. This new scoring system will enable investigators to compare newer treatments for all cancers with the current regimens; investigate molecular mechanisms for late tissue damage based on the severity of effects experienced by patients; facilitate the development of interventions for use in clinical trials to prevent, reduce, or possibly reverse late effects of cancer treatment; and permit the standardized reporting of adverse events and of comparisons of outcomes between trials and institutions.

Development

Delivering Best Practices through Partnerships and Consensus Building

Many Cancer Centers and academic institutions have developed specialized follow-up care clinics and programs for survivors of childhood cancer. In the adult arena, a range of models are being used for follow-up care for survivors in Cancer Centers, community oncology practices, and primary care settings. However, there has been little consensus about what constitutes optimal care, no coordination of efforts to deliver such care, and no attempts to evaluate program effectiveness, specifically the impact of such programs on survivor outcomes and the cost of care. NCI is bringing people together to focus on the problem through initiatives such as the following:

- NCI, in collaboration with the American Cancer Society, established a **Biennial Cancer Survivorship Conference**, inaugurated in June 2002. The papers from this conference addressed such topics as cancer survivorship and aging; promoting posttreatment adaptation; pathways to psychosocial care; family outcomes; and improving survival in the setting of advanced disease. Designed to bring the consumer's voice to the scientific proceedings, the meeting was attended by more than 100 cancer survivors.
- Two **International Workshops on Long-Term Follow-Up Care Programs for Survivors of Pediatric Cancer** were convened to formulate a research agenda and establish a working group to advance the science of follow-up care by identifying and examining the efficacy of models for posttreatment care; determining the optimal frequency, content, setting, and provider for such care; developing best practices for follow-up care for both pediatric and adult survivors; and creating a database on survivor care and outcomes across follow-up programs and clinics.
- A National Institutes of Health state-of-the-science meeting, **Symptom Management in Cancer: Pain, Depression, and Fatigue**, identified key gaps in our knowledge and delivery of state-of-the-art palliative care, including recognition that pain is often undertreated, despite the availability of effective interventions; cancer-related depression and fatigue are extremely common and have a profound impact on a patient's well-being; insufficient resources are allocated to studying the occurrence, causes of, and impediments to effective treatments for these symptoms; and healthcare professionals, caregivers, and patients need to focus on symptom management throughout the course of cancer. (See also page 55.)

Childhood Cancer Survivor Study Informs Intervention Development

The NCI-supported Childhood Cancer Survivor Study is a cohort of over 14,000 5-year survivors of childhood cancer — the largest and most extensively characterized group of childhood survivors in North America. This cohort is a unique resource for addressing issues faced by the ever-growing population of childhood survivors, including risk of second cancers; adverse endocrine, reproductive, and psychosocial outcomes; and cardiopulmonary problems. A model of collaboration, the study is coordinated by researchers at the University of Minnesota and includes 27 participating centers in the United States and Canada.

Significant findings from the Childhood Cancer Survivor Study include the following:

- Many adult survivors of childhood cancer cannot recall basic aspects of their diagnosis and treatment, which could impair their ability to seek and receive long-term follow-up care.
- Childhood survivors are at increased risk for developing second cancers, but the degree of risk varies markedly by initial cancer diagnosis and treatment. Associated risk factors include an initial diagnosis of Hodgkin's disease or soft-tissue sarcoma, younger age at diagnosis, and certain types of chemotherapy.
- Survivors of childhood leukemia and lymphoma have a somewhat increased risk for depression compared to their siblings.
- Most chemotherapy treatments do not lead to pregnancy problems, but women who received radiation to the pelvis during childhood are more likely to have low birthweight babies.
- Radiation to the brain during childhood, especially at high dosages, is associated with an increased likelihood that survivors will need special-education services.
- Survivors of childhood leukemia and lymphoma who received high doses of radiation to the brain are at increased risk for obesity.
- When compared to the U.S. population, childhood survivors are less likely to smoke. If they do smoke, they are more likely to quit. Even so, the rate of smoking among study participants is far too high: 28 percent are smokers or former smokers.

Delivery

We must ensure that sufficient numbers of investigators and clinicians are committed to understanding and caring for cancer survivors. Continued training opportunities assist clinicians with acquiring the knowledge and skills necessary to keep pace with the rapidly changing needs of tomorrow's cancer survivors.

Disseminating Research Findings: Communication Tools and Resources

NCI has created several products that enable us to more accurately track who is surviving cancer and to communicate more effectively with diverse audiences:

- The **Prevalence Statistics Website** provides updated information about cancer survivors in the United States. The site will be expanded to track minorities and to provide information on survivors' second malignancies, quality of life, and prevalence data by state.
- The **Facing Forward series** for cancer survivors, family members, and medical professionals is designed to educate and empower cancer survivors as they face the challenges associated with life after cancer treatment.
- In partnership with Cancer Care, the Intercultural Cancer Council, the Lance Armstrong Foundation (LAF), and Living beyond Breast Cancer, NCI created a three-part **teleconference series** to provide survivors and their loved ones with a better understanding of what to expect after treatment ends.
- The **NCI Cancer Survivorship Website** (dccps.cancer.gov/ocs) is a comprehensive resource for researchers, advocates, cancer survivors, and the public.

CANCER SURVIVORSHIP: OPTIMIZING HEALTH AND QUALITY OF LIFE AFTER CANCER

GOAL

Reduce the adverse effects of cancer diagnosis and treatment, and improve health-related outcomes for cancer survivors and their families.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

- 1. Expand research efforts to understand the biological, physical, psychological, and social mechanisms, and their interactions, that affect a cancer patient's response to disease, treatment, and recovery. \$12.75 M**

 - Support investigators with access to extant cohort and case-control studies that include cancer survivor populations to leverage these databases through collaborative efforts. \$0.25 M
 - Conduct behavioral and epidemiological studies of cancer and its treatment on survivors who are posttreatment, by examining both negative and positive physiologic and psychosocial effects, and their correlates. \$5.00 M
 - Continue to support Long-Term Cancer Survivor studies and the associated investigator working group. \$4.00 M
 - Identify the genetic and/or phenotypic markers of susceptibility to treatment-related adverse effects and gene-environment interactions, using molecular epidemiological research. Expand understanding of the biologic and physiologic mechanisms in the adverse chronic and late effects of current and new cancer treatments. \$3.00 M
 - Synthesize the research with respect to the role of sociocultural, behavioral, emotional, and spiritual factors in survivor and family outcomes and survivor's willingness to adopt appropriate surveillance and health maintenance behaviors posttreatment. \$0.50 M

- 2. Expand the development and use of tools to assess the health-related quality of life and quality of care of posttreatment cancer survivors and their family members, as well as NCI's capacity to track outcomes for these populations. \$5.00 M**

 - Promote the testing and routine use of instruments to assess health-related quality of life beyond the active treatment period. Include efforts to accelerate the adoption of newly established common toxicity criteria for late effects of cancer treatment. \$2.00 M
 - Develop measures to evaluate comorbidities that are both cancer- and noncancer-related, in collaboration with other NIH institutes (e.g., National Institute on Aging; National Heart, Lung, and Blood Institute). \$1.50 M
 - Conduct national surveys of physicians and survivors of pediatric and adult cancer regarding follow-up care. \$1.50 M
 - Assess the health-related information needs and resources of cancer survivors through the Health Information and National Trends Survey (HINTS). (See page 102.)

Development	
3. Accelerate intervention research in order to reduce cancer-related chronic or late morbidity and mortality.	\$9.00 M
<ul style="list-style-type: none"> ■ Expand research on the most promising and cost-effective interventions to address cancer survivor needs for improved quality of life — e.g., reducing cancer-related symptoms such as distress, pain, and nausea; minimizing posttreatment organ dysfunction; treating infertility; promoting healthy practices such as exercise, smoking cessation, and diet change; and addressing individual needs. This research includes investigating the impact of well-characterized and controlled interventions (type, intensity, and length) on appropriate intermediate biomarkers — e.g., immune functioning, cortisol levels, PSA levels. \$5.00 M ■ Develop interventions that promote the health and well-being of family members or caregivers as well as interventions that target minority and medically underserved populations. \$2.00 M ■ Develop screening tools that identify individuals who are at high risk for poor outcomes, and assess the impact of such screening on patterns and outcomes of care. \$2.00 M 	
Development and Delivery	
4. Ensure the delivery to relevant audiences of new information, interventions, and best practices, in collaboration with other Federal and health- or cancer-related professional and nonprofit organizations.	\$3.00 M
<ul style="list-style-type: none"> ■ Develop and disseminate best practice guidelines for follow-up care, surveillance, and monitoring of cancer survivors who have completed initial cancer treatment. \$1.00 M ■ Study the adoption and impact of best practices in posttreatment care. \$1.50 M ■ Develop and disseminate curricula and standards for the delivery of effective psychosocial and supportive care across the illness continuum. \$0.50 M ■ Develop and disseminate educational materials for family members and healthcare providers of cancer survivors. 	
Management and Support	\$ 0.50 M
Total	\$30.25 M

Platforms for Discovery, Development, and Delivery: Building Synergy through Interdisciplinary Team Science

Bringing the benefits of cancer research to the American people depends on building and sustaining the strong research mechanisms, support structures, and collaborations that make it possible for us to pursue rapidly evolving discoveries. NCI must provide the vision, creative environment, and diverse resources needed to ensure a fast paced and synergistic flow of innovative thinking among scientists in disparate scientific disciplines. We must also leverage our collaborations with other government agencies, academia, and industry, focusing on steering major breakthroughs toward the delivery of effective cancer interventions.

Investigator-Initiated Research builds on the synergism at medical schools, hospitals, universities, and research centers for asking the critical questions, exploring the options, and developing and testing innovative technologies. *Centers, Networks, and Consortia* created and supported by NCI comprise a model framework in which investigators can work effectively in teams, collaborate for progress, and ensure that results advance from discovery to intervention development and delivery. NCI-supported *Clinical Trials* provide the crucial infrastructure for moving new cancer interventions from the laboratory to studies in people with, or at risk for, cancer and then to the healthcare setting. NCI's *Intramural Research Program*, which complements our robust Extramural Research Program, also provides a unique venue for innovative investigation, as well as translation, and application of research findings.

We must continue to use these platforms to build and enhance a research system that will allow and encourage the scientific community to share and apply new discoveries and emerging technologies. We need new funding arrangements that will promote and reward innovative thinking; speed cross fertilization of ideas across scientific disciplines; facilitate collaborations among government, academia, and industry; and bring advances in cancer care to all populations. And we need to foster and coordinate efforts that would be too large for the individual investigator by promoting team endeavors and encouraging scientific integration without inhibiting individual creativity.

To streamline progress for cancer in as many ways as possible, we need to:

- Guide, support, and leverage the work of the individual investigator and that performed within NCI-supported Cancer Centers, networks, and consortia.
- Maximize physician and patient access to clinical trials for prevention, diagnostic, and therapeutic interventions.
- Train top researchers in oncology and arm them with the finest technologies and tools available.
- Build and sustain the interdisciplinary connections so vital to 21st century science.

Enhancing Investigator-Initiated Research

Investigator-initiated research — research independently conceived and developed by scientists — has always been the primary means by which biomedical research is funded and conducted. Driven by the synergism at medical schools, hospitals, universities, and research centers, these investigators ask the critical questions, explore the options, develop and test innovative technologies, and make the discoveries that lead to better cancer science and its application to patient care.

Investigator-initiated research is the principal means by which scientists address high-priority goals, such as those identified by the Progress Review Groups focused on specific types of cancer. It is also a mainstay for cancer research training and for enabling multidisciplinary collaboration.

Providing Resources to Maximize Investigator Productivity

Science is changing rapidly, and the promise and problems of research are changing along with it. In many areas, a single laboratory can easily accomplish goals that would have been unapproachable only a few years ago. This is due to the availability of vast amounts of information as well as new tools and techniques for analysis. The genetic makeup of cells and tissues, as well as complex gene expression patterns, can be analyzed in exquisite detail, and methods to analyze proteins and other cellular components are developing rapidly. Methods for discovering and analyzing promising drugs aimed at cancer-causing pathways have outfitted scientists with an arsenal of research approaches and technologies more comprehensive than any previously available.

Although new research tools increase productivity, their costs place an extra burden on grant budgets, threatening to decrease the number of grants that can be supported. The increasing complexity of research projects demands that researchers work in an interdisciplinary team environment, rather than in isolated laboratories with occasional collaborators. NCI is striving to ensure that the resources needed for maximum productivity are widely available and that the support mechanisms facilitate, rather than hinder, the kind of research that can and should be done.

Balancing Research Opportunities and Costs

NCI has seen an enormous increase in the funding needed to allow scientists to fully exploit new technologies and approaches to conducting research. In Fiscal Year 2003, for example, the number of applications submitted to NCI increased by 9 percent, and the total NCI spending on research projects was nearly 8 percent higher than the year before. This cost increase reflects a larger number of total active awards as well as some growth in the average cost of awards. While we expect this trend to moderate, we must balance the growing number of research opportunities with the rising costs of research. Reviewer assessments of research applications consistently identify the top 35 percent to 40 percent of grants as highly meritorious; the proportion actually funded (the success rate) has averaged 26 percent in recent years. To maintain this success rate, NCI carefully reviews individually approved grant applications for programmatic efficiencies, reducing the cost of a grant by an average of 10 percent. In addition to leveraging our Federal dollars, we must ask researchers to complement this funding from other sources as much as possible.

For the next generation of scientists to choose to enter cancer research, they must perceive opportunities for discovery with the potential to change our world. A sufficient infusion of resources and funding into investigator-initiated research will help to ensure that science students, as well as current researchers, undertake cancer research.

PROGRESS IN PURSUIT OF OUR GOAL

NCI supports and fosters investigator-initiated research through a variety of policy decisions and flexible funding options.

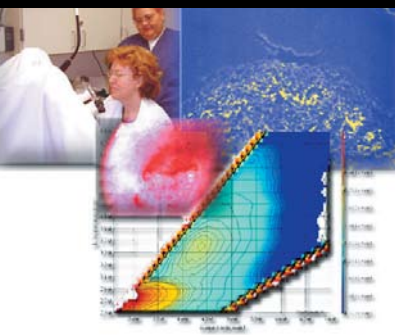
Identifying and Supporting High-Priority Research

NCI takes extra steps to identify and support high-priority research by:

- Seeking out and supporting compelling research proposals with exceptions funding, particularly projects that employ dramatically new or unconventional approaches to understanding cancer.
- Giving special consideration to proposals responsive to high-priority research areas identified by NCI advisory groups, NCI Program Announcements of priority research areas, and recommendations from Progress Review Groups (PRGs) for research related to specific cancers.

We are also exploring better ways to define and promote the exploration of uncharted areas of research and to give them heightened consideration when reviewing grant applications.

Imaging Researchers Develop Promising Cervical Cancer Screening Technique



Computer analysis of fluorescence and reflectance spectroscopic imaging of the cervix

NCI-supported scientists are developing a noninvasive test for the screening of cervical neoplasia (abnormal and uncontrolled cell growth). Preliminary testing suggests that this screening method may be more accurate, as well as more acceptable to patients, than standard methods. The current standard of care calls for screening to begin with a routine Pap smear. If the results are abnormal, the physician may recommend repeating the test at a later date or performing a colposcopy (examination of the cervix with a special magnification tool) and/or biopsy, depending on the specific results and patient history.

NCI-supported basic and clinical researchers are assessing emerging imaging technologies that use fluorescence and reflectance spectroscopy to noninvasively detect cervical neoplasia. Basic scientists have demonstrated that this imaging approach accurately detects the intracellular changes that occur as cells progress from a normal to a neoplastic state. The scientists have also made major progress in understanding the biological basis of cervical tissue fluorescence and have applied this knowledge to develop mathematical models to accurately distinguish between normal and neoplastic tissue.

Scientists recently carried out clinical trials showing that the imaging techniques are feasible for use in large populations. For example, one team experimented with using different wavelengths of fluorescent light to design relatively simple, inexpensive imaging systems for use in screening trials worldwide. Another team showed that fluorescence and reflectance spectroscopy can be used anytime during the menstrual cycle except during menstruation. Participants in this trial reported significantly less pain and anxiety and were more satisfied with spectroscopy than with the usual care procedures. NCI investigators will continue to develop this promising new technology in a large randomized trial comparing fluorescence and reflectance screening with standard cervical cancer screening techniques.

Investigator-Initiated Research in Bone Marrow Transplantation Spans the Discovery-Development-Delivery Continuum

Investigator-initiated research is the engine of scientific discovery. It is also much more. Bone-marrow transplantation research, traditionally carried out under investigator-initiated program projects and traditional (R01) research grants, is an excellent example of cancer intervention research that spans the discovery-development-delivery continuum.

Over the past 15 years, a number of outstanding research groups have produced a quiet revolution in this field. In cancer therapy, bone marrow (or peripheral stem cell) transplantation was originally viewed largely as a supportive therapy that would allow the use of larger, more effective doses of chemotherapy and radiation. It is now clear that this conception understates the potential benefits of this therapeutic intervention. In transplants from related donors, where transplantation has been most effective in leukemias and lymphomas, much of the benefit derives from an immune response of donor white blood cells against residual tumor cells. This recognition has led to new transplant strategies, including the use of donor leukocyte (white blood cell) infusions for the treatment of relapse. Preparative regimens for both donors and recipients have been modified to maximize the immune-mediated benefit, improving efficacy while greatly reducing the toxicity in the recipient. As a result, the treatment is now available to

older patients, extending the number of people who can benefit. Moreover, the focus on immune cell reactivity to cancer has provided important new directions for pursuit of immunotherapeutic strategies outside the transplant setting.

Ultimately, all research progress stems from the creativity and drive of the cancer research community. NCI maintains a balanced portfolio of diverse support mechanisms to maximize the progress achieved through a remarkably wide range of investigational approaches. Within this portfolio, investigator-initiated research remains critical not only to discovery, but also to the development and delivery of cancer interventions.

Maximizing the Ability to Start New Projects and Collaborations

NCI maximizes the pace of research by providing a **broad range of flexible funding options** and promoting **collaborations and resource sharing** wherever possible. NCI is:

- Providing opportunities for collaborative study through awards such as program project grants (P01s) and cooperative agreements, in addition to the traditional research project grants (R01s) that make up the bulk of NCI's research portfolio.
- Providing seed funds for promising research. In Fiscal Year 2002, the number of small (R03) and exploratory/developmental (R21, R33) grants awarded increased more than 17 percent over the previous year.
- Enabling investigators to take advantage of unanticipated opportunities or to pursue interdisciplinary collaborations with administrative supplement funds. For example, through NCI's Activities to Promote Research Collaborations Program, grantees request funding for collaborations that will pursue novel, unforeseen opportunities and embrace resource sharing; develop new technologies; or organize cross-disciplinary meetings or workshops.
- Promoting collaborative studies and sharing of resources through innovative networks and consortia.

GOAL

Accelerate discoveries and their application by expanding and facilitating researcher access to resources and new technologies.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

1. Accelerate the pace of discovery through increased funding for, and greater numbers of, competing research grants.

- Move research projects toward funding at the full levels recommended by peer reviewers.
- Fund, at a minimum, 35 percent of competing applications, with the following areas of emphasis: (1) the highest scientific merit; (2) a less certain probability of success, but potential to yield greater reward if they do succeed; (3) unconventional approaches but unique promise; (4) a focus on areas of extraordinary need in specific fields of investigation or model systems; and/or (5) the involvement of new investigators.

2. Facilitate rapid movement from discovery to development to delivery by using established mechanisms and creating novel special awards to encourage transdisciplinary and collaborative research.

- Expand supplemental funding for grants to promote new interdisciplinary collaborations for bringing together basic, clinical, and population scientists, such as those fostered by NCI's Activities to Promote Research Collaborations Program.
- Expand researcher access to central resources, such as databases, tissue banks, and animal models, by using funding supplements; centers, networks, and consortia; and cooperative resource programs.
- Expand researcher access to: (1) technologies that promote interdisciplinary research and collaborations, and (2) the expertise needed to move discoveries to application.
- Develop and make available information technology tools to foster and enhance interdisciplinary communication and collaboration.
- Expand the funding for collaborative research awards, such as program project grants and cooperative agreements, for consortia that facilitate translational research.
- Encourage more patient- and population-based research by expanding the use of exploratory grants.

Enabling Research Across the Discovery-Development-Delivery Continuum

The undirected nature of investigator-initiated research requires **grant mechanisms with substantial flexibility**. Investigators use this flexibility to carry out development projects, all the way to and through Phase III clinical trials. (See page 75.) While researchers supported by investigator-initiated grants do not have immediate access to specialized resources provided by NCI under such targeted mechanisms as the Cooperative Group clinical trials program or SPOREs, informal alliances are encouraged by NCI staff and can be particularly beneficial for research carried out at NCI-supported Cancer Centers.

3. Encourage investigators from a variety of scientific backgrounds to commit to careers in cancer research and to propose more innovative and higher-reward projects.

- Continue to allocate the first 80 percent to 90 percent of available funds for research project grants through the well-established peer review selection process, while ensuring that proposals from new investigators are also funded at a rate comparable to those of more established investigators, utilizing exceptions as necessary.
 - Use a special administrative evaluation process to fund particularly innovative and potentially high-reward projects.
-

4. Encourage investigation in priority areas identified by advisory committees, NCI staff, Progress Review Groups (PRGs), and other groups, through regular and special award mechanisms. Leverage resources for these efforts through collaborative initiatives.

- Monitor investigator-initiated research to assess whether these projects alone are meeting programmatic objectives, such as those identified in specific disease areas.
 - Set aside 10 to 15 percent of funds for Requests for Applications in specifically targeted areas of need.
 - Support Program Announcements and investigator-initiated projects that target identified gaps and/or emerging opportunities (e.g., those identified by the PRGs and other priority setting and strategic planning activities).
 - Enhance coordination within and among initiatives, and increase management and support commensurate with the growth of the portfolio.
 - Encourage outreach to establish public-private partnerships and to leverage current NCI-funded activities with new, complementary, non-NCI sources of support, through supplemental awards.
-

Management and Support		\$ 0.80 M
	Total	\$123.50 M

Training Scientists for Cancer Research

By providing salary support on research grants, investigator-initiated research is now the single largest training support mechanism for scientists. Training programs are critical, but have not expanded as rapidly as other grant mechanisms. To compensate, trainees are increasingly supported directly on grant budgets. In addition, the special attention accorded to research grants to new investigators eases their transition to independent research careers.



NCI Addresses Obstacles to the Development of New Treatments for Pediatric Cancer

Researchers face distinct obstacles to the development of new treatments for cancer in children.

For example:

- Even cancers that are common in children are rare compared to most adult malignancies. Accumulating enough cases to test a new treatment requires collaboration among multiple research organizations.
- Drug development costs for developing agents that specifically target pediatric tumors can be prohibitive for the pharmaceutical industry given the relative rarity of childhood cancers.
- Twenty-first century anti-neoplastic drug development often focuses on agents that target specific molecular pathways in adult cancer cells. These same molecular pathways may also promote the growth and survival of childhood cancers. However, the drugs targeting these pathways need to be tested in the laboratory against pediatric cancer models to identify those drugs that might be effective for treating childhood cancers.

NCI is addressing these obstacles through a research strategy focused on the development of new treatments for pediatric cancers — treatments that are not a by-product of drug development for adults. The new strategy spans the spectrum from preclinical drug discovery through Phase III studies aimed at obtaining FDA approval. For example:

- The newly established Pediatric Preclinical Testing Program aims to annually screen 10 to 15 new agents, or combinations of agents, against a panel of pre-clinical models for common pediatric tumors (e.g., mouse models). In this way, researchers can rapidly identify agents with activity against pediatric tumors. These preclinical models will also allow researchers to screen cancer drugs developed for adults for their potential applicability to pediatric tumors.
- NCI's Pediatric Oncology Preclinical Protein-Tissue Array Project (POPP-TAP) and the Children's Oncology Group Phase I Consortium are characterizing the molecular features (RNA and protein expression) of pediatric tumors in children and in corresponding preclinical models. This information will help preclinical researchers to select the model that most resembles the childhood cancer under study. Molecular characterization of preclinical tumor models will also point to critical signaling pathways that can be targeted by specific anti-cancer agents.
- NCI-funded Cooperative Groups have successfully brought together pediatric oncologists worldwide to enroll children with cancer into clinical trials. This international cooperation allows oncologists to learn from each case and to accomplish the kind of high quality clinical research that most effectively assesses the safety and efficacy of experimental treatments.

NCI is committed to surmounting current obstacles through focused discovery initiatives that ensure children are not left behind — that they survive cancer through tailored, safe, and effective treatment.

Transforming the Capacity of Centers, Networks, and Consortia

The centers, networks, and consortia created and supported by NCI over the past 10 years comprise a model framework in which investigators can work effectively in teams, collaborate for progress, and ensure that results advance from discovery to intervention development and delivery.

The interdisciplinary nature of today's cancer research requires new infrastructures that support team science and enable the sharing of a multitude of resources.

- NCI-designated Cancer Centers¹ are highly effective platforms that span the discovery-development-delivery continuum. These Centers organize and integrate multidisciplinary research across departments and schools within a single institution or consortium of local institutions. Emphasizing the cancers that represent the greatest health threat to their communities, NCI-designated Cancer Centers provide scientists with the most advanced technologies and promote new research opportunities; work collaboratively with industry; perform state-of-the-art translational research; and conduct education, outreach, and information programs. NCI-designated Cancer Centers are highly effective at leveraging additional resources for cancer research and education from organizations in the public as well as private sectors.
- NCI Centers of Excellence, usually evolving within Cancer Centers, connect specialized groups of scientists in collaborative, interdisciplinary research. Projects are closely integrated with the efforts of other centers of excellence, research networks and consortia, and institutions throughout the Nation. NCI Centers of Research Excellence are usually devoted to discovery and development of new interventions and are often linked to private industry.
- Networks and consortia are geographically dispersed multidisciplinary groups whose goals require inter-institutional collaborations. Networks and consortia usually focus on the development or validation of new interventions, ranging from new therapies to genetic risk counseling to outreach.

The new research paradigm hinges on interdisciplinary science, strategic partnerships, immediate application of new technologies, optimal information sharing, and close links to health delivery systems.

Embracing an Evolving Paradigm in Cancer Research

This infrastructure is now poised to exploit an evolving paradigm in cancer research that will help attain NCI's Challenge Goal of eliminating the suffering and death due to cancer. To move forward, by realigning existing resources and incorporating new ones, NCI must:

- Employ progressive bioinformatics and communication systems.
- Encourage collaborative, multidisciplinary research, and require integration and sharing of results.
- Realize economies of scale, avoid duplications, and exercise regional sharing.
- Promote growth in strategic areas of research and technology development.
- Strategically broaden the geographic impact of the centers, networks, and consortia.
- Improve the access of minority and underserved populations to state-of-the-art research and resources.
- Create and strengthen partnerships with government agencies and community organizations.
- Broadly provide expertise, facilities, and other resources to caregivers, patients and families, and appropriate health agencies.

¹ In this document, "NCI-designated Cancer Centers" is sometimes abbreviated as "Cancer Centers."

PROGRESS IN PURSUIT OF OUR GOAL

NCI is strengthening the capacity of NCI-designated Cancer Centers to audit research, ensure data safety, and monitor human research. A broad new NCI bioinformatics initiative will pave the way for investigators at NCI-designated Cancer Centers to participate in a national network for collaborative research and sharing of research results, while ensuring the safety of patients and populations. (See page 96.)

Strategic Expansion of NCI's Centers, Networks, and Consortia

NCI-designated Cancer Centers are now present in 31 states and the District of Columbia, and NCI has planning grants in place for developing Cancer Centers in another five states. NCI is actively working with institutions in five additional states that have the capability to develop strong research and outreach programs, with the goal of creating a Cancer Centers program that benefits the entire Nation. NCI is also creating new Cancer Center models to serve states that do not have the institutional infrastructure to sustain a more traditional NCI Cancer Center. These innovative models will address geographic expansion, education and outreach activities, partnerships for research and delivery, and aids for underserved populations. For example, Cancer Centers are now engaged in a unique partnership, Overcoming Barriers to Early Phase Clinical Trials, with several major pharmaceutical companies.

Specialized Programs of Research Excellence (SPOREs), the original Centers of Excellence created by NCI in 1992, focus entirely on discovery-to-delivery research dedicated to specific cancers. There are now 50 SPOREs in place across the Nation, with all major cancer sites represented. These SPOREs are poised to rapidly conduct early-phase clinical studies, sharing information via a protected Web-based system. The SPOREs effectively work together across institutional boundaries and have begun productive collaborations with NCI networks and consortia, as well as through public-private partnerships. For example, a partnership with the Avon Foundation has generated over 15 early-phase clinical trials in breast cancer. A new supplement program for early-phase trials in all cancer sites is also working well. Fifteen new early-phase clinical trials are ongoing in the longest-standing

**Cancer Centers Speed
the Delivery of Research
Benefits to Cancer
Patients and
To Populations at
Risk for Cancer**



A Comprehensive Cancer
Center Designated by the
National Cancer Institute

NCI-supported Cancer Centers, networks, and consortia are natural hubs for national leadership in the war against cancer. They also provide a means for fostering coalitions and partnerships with other cancer funding organizations, professional societies, businesses, industry, communities, and local and state governments. NCI's leadership will accelerate the pace of delivery of effective cancer interventions to the public.

NCI-designated Cancer Centers will be particularly important in future strategies to improve the delivery of new state-of-the-art interventions to the public. In the last 5 years, more than 40 of the 60 Cancer Centers have received the "comprehensive" designation. This includes most medical institutions in the United States with major biomedical research programs. Directors and investigators at these Comprehensive Cancer Centers participate with NCI in outreach activities in order to speed the benefits of research to patients, physicians and other caregivers, and communities, especially to those in under-represented geographic regions of the Nation.

National Cancer Advisory Board Working Group Confirms Central Role of Cancer Centers and SPOREs in Delivery of Cancer Interventions

In 2003, the National Cancer Advisory Board completed a report of an ad hoc working group charged with establishing a blueprint for NCI-designated Cancer Centers and Specialized Programs of Research Excellence (SPOREs). The report confirmed the central role of Cancer Centers and SPOREs in future strategies for improving the delivery of cancer interventions. The report lists recommended strategies for balancing the breadth and depth of these programs, maximizing translation of research discoveries, developing objectives for a national cancer agenda focused on reducing the cancer burden, and facilitating partnerships with other governmental, private, philanthropic, and business entities. Specific recommendations include the following:

- Consolidate shared resources in Cancer Centers to create greater economies of scale.
- Look to Cancer Centers for piloting new research, education, dissemination, and delivery strategies.
- Provide greater support for critical activities such as tissue banks, clinical data management and safety, and conformance to regulatory requirements.
- Encourage greater geographic distribution of Cancer Centers by creating programs for institutions that cannot currently meet all the requirements of the more research-intensive institutions that are currently supported by NCI.
- Provide the means for Cancer Centers to actively establish strategic, programmatic links with state health departments, other state agencies, local governments, and Federal agencies such as the Centers for Disease Control and Prevention.
- Encourage Centers to develop the infrastructure to test and implement novel methods for disseminating new knowledge in clinical, cancer control, and early detection research.
- Adopt as a top priority an integrated clinical research informatics system that will serve Centers and industry.
- Work with the Federal Office of Human Research Protections to engage Institutional Review Boards to develop a centralized review of multicenter trials.

Many of these recommendations are reflected in NCI's ongoing programs and plans for centers, networks, and consortia. The report will be a valuable resource to NCI in its continued strategic planning.

SPOREs, focusing on prostate, gastrointestinal, and lung cancers. These achievements mark the end of the rapid expansion phase of the SPOREs and a transition to strategic growth.

Other Centers of Excellence founded on the SPOREs model are spearheading interdisciplinary research in a number of specialty areas. For example:

- **The Transdisciplinary Tobacco Use Research Centers (TTURCs)** support a broad array of studies related to tobacco use, including genetic and behavioral research. (See page 39.)
- ***In Vivo* Cellular and Molecular Imaging Centers** bring together experts from diverse scientific and technological backgrounds to conduct research on cellular and molecular imaging in cancer. (See pages 31-32.)
- **Interdisciplinary Research Teams for Molecular Target Assessment** study critical biological processes to uncover high-priority targets for cancer intervention strategies. (See page 26.)
- **Centers of Excellence in Cancer Communications Research** focus on advancement of cancer communication science. (See page 99.)
- **Centers for Population Health and Health Disparities** research the interaction of social, cultural, and physical environmental determinants of cancer incidence and outcomes, and the behavioral and biologic factors that contribute to them. (See page 59.)

GOAL

Integrate research infrastructures and collaborations that enable multiple scientific disciplines to address large problems in human cancer that cannot be solved by individual investigators. Promote networks, partnerships, and coalitions that increase the pace of translational research and the rate at which the results of research are translated into clinical practice and public health benefit.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

1. Promote strategic growth of the NCI Cancer Centers, incorporating and realigning resources to accelerate discovery, development, and delivery of cancer interventions.	\$27.50 M
<ul style="list-style-type: none"> ■ Develop regional strategies for maximizing the impact of NCI Cancer Centers. \$0.50 M ■ Deploy new Cancer Center consortium models to two regions of the country in which no single institution has the research strength to become an NCI-designated Cancer Center. \$3.00 M ■ Develop Research Enhancement and Cancer Health (REACH) programs that will draw more institutions into a collaborative network with NCI Cancer Centers, promote partnerships with local communities to disseminate research benefits, and influence more rapid delivery of state-of-the-art cancer prevention and treatment. \$5.00 M ■ Develop and implement state Cancer Plans and improve public health practice for the prevention, control, and cure of cancer by establishing units within NCI Cancer Centers – including Centers with and without the “comprehensive” designation – to work with the Centers for Disease Control and Prevention and state and local governments. \$16.00 M ■ Continue to develop a biomedical informatics system common to all Cancer Centers to increase collaborations between Centers and further the sharing of research results. (See page 97.) ■ Pilot new outreach and education strategies at Cancer Centers to reach the broadest possible population. \$3.00 M 	
2. Increase the effectiveness of collaborations to improve access of minority populations to state-of-the-art clinical and population studies, cancer treatments, technologies, and care.	\$10.00 M
<ul style="list-style-type: none"> ■ Enhance the research capabilities of minority and minority-serving institutions (MSIs) and improve the effectiveness of Cancer Centers in serving minority communities by strengthening formal partnerships between Cancer Centers and MSIs. \$8.00 M ■ Integrate NCI-designated Cancer Centers and Minority Institution/Cancer Center Partnerships with the NCI Special Populations Networks for Cancer Awareness Research and Training. \$2.00 M 	

The **Cancer Genetics Network** is a nationwide system of research sites located within NCI-designated Cancer Centers. The CGN specializes in the study of inherited predispositions to cancer. This ambitious program now has its essential databases in place and has achieved adequate participation from patients. Poised as a major research arm in genetics, the CGN has begun collaborating on several projects with the SPOREs and with individual investigators. (See page 11.)

The **Mouse Models of Human Cancers Consortium** is a powerful system for engaging researchers in a wide spectrum of basic, translational, clinical, and epidemiological investigations. (See page 18.) For the first time, a resource is available to the scientific community that documents the characteristics of mouse models and supplies the most valuable cancer models to the scientific community. The Consortium investigators are collaborating with independent investigators supported by traditional research grants and with SPORE and Early Detection Research Network investigators. (See page 18.)

3. Expand the capacity of NCI Cancer Centers, Centers of Excellence, networks, and consortia to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions.	\$58.50 M
<ul style="list-style-type: none"> ■ Build the clinical and population research infrastructures of NCI-designated Cancer Centers. Fund databases that conform to NCI's clinical informatics infrastructure; support the development and expansion of population databases and other resources; provide more core staff to conduct innovative translational therapeutic and prevention trials; and strengthen the auditing and data safety and monitoring of human subjects research. \$25.00 M ■ Expand the conduct and impact of translational research by promoting and developing partnerships among NCI-designated Cancer Centers and industry; national, private, state, and community organizations; and other cancer funding organizations. \$2.50 M ■ Maximize collaborative research opportunities and facilitate integration of best practices, sharing of protocols, and consolidation of functions to avoid duplication of resources, by providing leadership and coordination to NCI-designated Cancer Centers, Centers of Excellence, networks, and consortia. \$0.50 M ■ Expand and refine the tissue banks and tissue procurement systems of Cancer Centers in order to meet a national standard and increase the potential for collaborations in translational research. \$17.50 M ■ Strategically expand SPOREs by adding two to three SPOREs to cancer disease sites that lack a critical mass to function maximally in translational research. \$8.00 M ■ Stimulate inter-SPORE research, early phase clinical trials, and collaborations with other NCI networks, Centers of Excellence, and consortia by expanding the supplement programs for SPOREs. \$5.00 M 	
Management and Support	\$ 0.80 M
	Total \$96.80 M

Interactions among the Early Detection Research Network, SPOREs, and other interdisciplinary groups are facilitating the discovery and development of molecular markers and assays that detect early signs of cancer.

Through its **Minority Institution/Cancer Center Partnership Program (MICCP)**, NCI is helping to increase the competitive research grants obtained by minority institutions. All major U.S. minority institutions with medical schools now participate in the program. Over 30 other institutions that have never been involved in cancer research are also participating. New inter-institutional models are emerging that provide direction for minorities as they develop their skills in cancer research. (See page 61.) In another NCI effort, **Special Populations Networks for Cancer Awareness and Training** are building relationships between minority communities, NCI-designated Cancer Centers, and NCI Cooperative Groups to address cancer health disparities in specific populations. (See page 58.)

NCI Partners To Advance Cancer Research

NCI is increasingly looking beyond its institutional boundaries to engage in diverse partnerships with public, private, and academic sectors.

NCI's partnership goals aim to:



Medical researchers examine a sequence gel x-ray to determine the pattern of DNA.

- Eliminate bottlenecks and foster an “enabling culture” to accelerate progress against cancer.
- Leverage funding to take advantage of expertise outside of the Institute.
- Build synergy and create a feeling within the cancer community that we are all in this fight together.

A few of these partnerships are described here to illustrate the depth and breadth of our partnership portfolio.

Among intra- and extramural investigators . . .

At the heart of the Leukemia/Lymphoma Molecular Profiling Project (LLMPP) is a consortium of NCI intramural and extramural investigators who have pooled resources and talent to define the molecular classification of lymphomas. In one project, the group used the tissue collections of member institutions to define subtypes of diffuse large B-cell lymphoma that are associated with differing clinical responses to treatment. The large number of samples, substantially more than any single institution could have acquired, have allowed the researchers to draw reliable conclusions about how best to diagnose and treat patients based on the molecular subtype of their disease.

With other Federal agencies . . .

Through an interagency agreement, NCI and the Food and Drug Administration (FDA) recently collaborated to share knowledge and resources to facilitate the development of new cancer drugs and speed their delivery to patients. A task force, with chairs from both NCI and FDA and other senior staff from both agencies, will oversee implementation of this agreement. (See page 88.)

With pharmaceutical companies . . .

In 1999, NCI and the pharmaceutical company Genentech entered into a cooperative research and development agreement (CRADA). Under this CRADA, NCI and Genentech conducted a clinical trial to test treatment of renal cell carcinoma (RCC) patients with the monoclonal antibody AvastinTM (bevacizumab). Avastin targets a protein involved in the angiogenesis (development and maintenance of new blood vessels) that is required for renal cell tumor growth. Cancer progression was slower in patients treated with Avastin in addition to standard interferon therapy than in patients given interferon and a placebo. These preliminary findings provide the basis for a larger trial to determine whether Avastin treatment can improve survival in RCC patients. Avastin also looks promising for treatment of breast and colorectal cancers. (See page 87.)

**Other partnerships
highlighted in
this document**



- National Surgical Adjuvant Breast and Bowel Project, page 13
- Massively Parallel Signature Sequencing, page 17
- Quality Enhancement Research Initiative, page 54
- Transdisciplinary Tobacco Research Centers, page 39
- Avon Foundation and Breast Cancer SPORes, page 80
- Advanced Magnetics Inc., and Combidex®, page 36
- Novartis and Gleevec™, page 87
- Searle and Pfizer, Inc., and celecoxib, page 87
- Asian American/Pacific Islander mammography education resource, page 101
- Research Tested Intervention Programs, page 101

A partnership with Millenium Pharmaceuticals yielded Velcade™, a drug that inhibits a class of proteins known as proteasomes, which are implicated in cancer development. The NCI/Millenium partnership is allowing Velcade to rapidly move through the drug development pipeline, expediting its availability to patients. In 2003, FDA approved Velcade for treatment of multiple myeloma patients who have received at least two prior therapies. NCI-sponsored clinical investigators are now evaluating Velcade therapy for newly diagnosed multiple myeloma patients. For more information, see page 89.

With bioinformatics companies . . .

NCI, FDA, and Correlologic Systems Inc., a bioinformatics company, are engaged in scientific collaboration in clinical proteomics (the study of protein structure and function). The partners are developing an approach for early detection of ovarian and prostate cancers based on protein profiling, a complex analysis of proteins present in individual blood samples. A clinical trial using protein profiling to monitor ovarian cancer recurrence is underway. This technology also shows promise for diagnosing cancer, monitoring toxicity, determining the efficacy of therapy, and conducting follow-up surveillance.

Beyond traditional partnerships . . .

NCI, with Cancer Care, the Intercultural Cancer Council, Living Beyond Breast Cancer, and the Lance Armstrong Foundation partnered to produce the teleconference series “Cancer Survivorship: Living with, through, and beyond Cancer.” Over 1,000 people participated in each of three sessions in spring 2003. The interest in this series underscores the importance of collaborations for the diffusion and dissemination of evidence-based information to the public.

A new initiative, called the Academic Public Private Partnership Program (AP4), is supporting the discovery of new cancer agents and their rapid translation to human clinical trials. Through this program, NCI fosters collaborations among universities, pharmaceutical companies, biotech companies, and nonprofit organizations. A new funding mechanism to support such broad-based collaboration was called for by several NCI Progress Review Groups. (See page 6.) The AP4 initiative represents a new paradigm in drug discovery, development, and delivery for NCI.

NCI has partnered with the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, and the American Cancer Society to provide evidence-based tools to help communities better understand and address their cancer burden. The Web-based tools are available through a Web portal called Cancer Control PLANET (Plan Link Act Network) located at cancercontrolplanet.cancer.gov. The Agency for Healthcare Research and Quality will be adding links to more cancer prevention Web sites. States and communities can use these tools to plan, implement, and evaluate evidence-based comprehensive cancer control programs.

National Clinical Trials Program in Treatment and Prevention

NCI-supported clinical trials provide a crucial infrastructure for moving new cancer interventions from the laboratory to studies in people with, or at risk for, cancer and then to the health care setting. These clinical trials have always included investigations of a broad set of interventions — chemoprevention, chemotherapy, radiation, and surgery — sometimes used alone and sometimes in combination. With recent advances in deciphering the molecular changes that cause cancer, a new paradigm of cancer treatment and prevention research is emerging and bringing with it the promise of an exponential growth in effective cancer interventions. Increasingly, new anti-cancer agents are directed at distinct molecular targets within cancer cells, leaving healthy cells unharmed.

NCI currently provides leadership, resources, and expertise at all stages of clinical development for molecularly targeted agents. In the early stages of research, when candidate drugs are first identified and shown to have promise, NCI forms collaborations and partnerships that help researchers from public, industrial, and academic settings develop anti-cancer agents for a broader array of tumor types and at a faster pace than would otherwise be possible. Partners work together to establish “proof-of-principle” in early clinical trials. Then they move rapidly to verify the presence of relevant molecular targets in populations of patients and persons at risk for cancer and to test for improvements in outcomes such as prevention, tumor response, and improved quality of life and survival. For Phase III trials, NCI provides resources to test promising leads in large numbers of patients.

While much has been accomplished to streamline cancer clinical trials, NCI must further accelerate movement of promising research discoveries into clinical development and delivery to the public. We must:

- Identify the most important questions in prevention and treatment that can be addressed through clinical trials.
- Create flexible mechanisms that allow for easy collaboration among basic scientists, clinicians, industry, academia, and NCI.
- Explore the use of combinations of molecularly targeted agents for treating cancer by targeting several critical points in cancer causing molecular pathways. (See page 92.)
- Develop surrogate endpoints to identify the most promising treatment or prevention agents for movement into large, easily accessible trials.
- Improve support to physician researchers.
- Improve access to clinical trials by physicians, patients, and those at risk of cancer.
- Help ensure that treatments are made available to all patients who need them, including minority and underserved populations.

PROGRESS IN PURSUIT OF OUR GOAL

Building Public-Private Partnerships for Clinical Trials Research

NCI is expanding its role in public-private partnerships as more private-sector companies begin to develop anti-cancer drugs. Because pharmaceutical companies tend to seek FDA approval or licensing of a new agent for one or a few tumor types, NCI can help ensure that new agents are evaluated against a fuller range of cancers (or precancers) and in combination with treatments such as surgery, radiation therapy, or other drugs. In one recent success, the collaboration between Novartis and NCI-supported researchers led to the development of **Gleevec™** (imatinib mesylate) to treat chronic myelogenous leukemia and now gastrointestinal stromal tumors, in both adult and pediatric patients. In an ongoing partnership with Genentech, NCI-supported clinical investigators are testing a promising molecularly targeted drug, **Avastin™** (bevacizumab), in patients with advanced colorectal cancer who were previously treated by chemotherapy.¹ In a partnership with Searle and Pfizer Inc., researchers found that the arthritis drug, **celecoxib**, can reduce the number of precancerous colon polyps in patients with familial adenomatous polyposis, an inherited syndrome that predisposes them to colon cancer. Researchers are also testing celecoxib for prevention and/or treatment of head and neck and other cancers.

Building Collaborations among Laboratory and Clinical Scientists

NCI also recognizes the increasing need for collaboration with laboratory scientists in conducting clinical trials for molecularly targeted agents. The cellular pathways and interactions involved in these molecular targets are extraordinarily complex and interrelated, and they require scientists to develop new techniques and tests to identify patients whose tumors contain the relevant targets and to monitor drug effects during treatment. More than half of NCI-sponsored cancer treatment trials initiated over the last 2 years have included correlative studies with laboratory scientists, and this trend is increasingly seen in cancer prevention trials.

Simplifying Administration of Clinical Trials

NCI continues to simplify the administration of NCI-supported clinical trials to make it easier for physicians and their patients to participate. In 2000, we launched the online Cancer Trials Support Unit (CTSU) Website to centralize the common administrative, financial, and data collection activities of NCI's clinical trials cooperative groups. Since May 2002, physicians outside NCI cooperative groups have also been able to enroll patients into these NCI-sponsored clinical trials.

¹ Irinotecan, 5-fluorouracil (5-FU), and leucovorin

NCI and FDA Partner to Streamline Cancer Drug Development

“The collaboration will help our two agencies take full advantage of our combined knowledge base at a time when many new kinds of anti-cancer agents are in the pipeline. Molecularly targeted drugs and other novel agents offer great promise, but they also present new challenges that require more collaboration.”

— Andrew C. Von Eschenbach, M.D.
Director, NCI

“FDA is committed to finding better ways to get safe and effective treatments to patients with life-threatening diseases as quickly as possible. At a time when the opportunities to reduce the burden of cancer are greater than ever, sharing tools and resources with our colleagues at the National Cancer Institute will help us fulfill that mission.”

— Mark B. McClellan, M.D.
Commissioner, FDA

In May 2003, NCI and the Food and Drug Administration (FDA) announced a joint effort to streamline cancer drug development. Under a multi-part Interagency Agreement, the two agencies will share knowledge and resources to enhance the efficiency of clinical research and the scientific evaluation of new cancer medications. Federal researchers and regulators will be working more effectively than ever before to facilitate the development of new cancer drugs and speed their delivery to patients.

This new partnership will broaden existing and create new joint programs to:

- Develop biomarkers for use as surrogate markers in clinical trials.
- Create a cancer bioinformatics infrastructure to improve data collection, integration, and analysis for preclinical, pre-approval, and post-approval research.
- Address joint technology development issues in proteomics and other areas.
- Advance the process for developing and evaluating cancer chemoprevention agents, including the development of clinically meaningful endpoints.
- Improve consumer awareness of the consequences of their choices about diet and nutrition for cancer prevention.
- Enhance staff capabilities through collaborative training, joint rotations, and joint appointments.
- Conduct a systematic review of current policies to identify other ways in which NCI-FDA collaborations can enhance the development and regulatory process for cancer technologies.

Making Strides in Cancer Treatment through Clinical Trials

NCI’s focused investment in treatment trials is paying off with increased survival and better quality of life for patients with a variety of cancers. Just a few of the advances emerging from recent clinical trials are listed here:

- In breast cancer patients who have experienced metastasis to at least one lymph node, adding the drug **paclitaxel** to standard adjuvant chemotherapy of **adriamycin** and **cytoxan** (AC) improved disease-free survival by 17 percent. Furthermore, patients treated with a dose-dense chemotherapy regimen, where treatments are given over shorter intervals, received the most benefit from paclitaxel (82 percent versus 75 percent disease-free survival compared to standard administration). As a result of this discovery, 4,000 more women could be alive and disease-free 4 years after diagnosis.

Velcade is the first in a new class of molecularly targeted anti-cancer agents known as proteasome inhibitors. See “Story of Discovery: Harnessing Apoptosis to Destroy Cancer Cells” in *The Nation’s Investment in Cancer Research: A Plan and Budget Proposal for Fiscal Year 2004* (plan2004.cancer.gov).

From years of scientific research, we know that cancers are not caused by a single, catastrophic event, but result from a complex and long-evolving process.

- A Phase III clinical trial demonstrated that adjuvant chemotherapy can improve survival in women with endometrial cancer. Following hysterectomy, staging, and tumor debulking, women with advanced endometrial cancer who received systemic chemotherapy with the drugs **cisplatin** and **doxorubicin** survived, on average, 33 percent longer than those treated with standard radiation treatment. Approximately 4,000 to 5,000 women per year may benefit from this new treatment approach.
- In partnership with Millennium Pharmaceuticals, Inc., NCI has been studying the use of **Velcade™** (bortezomib) in patients with refractory or relapsed myeloma. In a recently completed Phase II clinical trial, 30 percent of patients responded well to Velcade over the course of about a year. Investigators are now conducting follow-up studies and have begun evaluating Velcade in newly diagnosed multiple myeloma patients. Other investigators are discovering anti-tumor effects of Velcade in breast, non-small cell lung, neuroendocrine, and renal cancers, as well as in melanoma, sarcoma, chronic myelogenous leukemia, and non-Hodgkin’s lymphoma.

Making Strides in Cancer Prevention through Clinical Trials

Since many cancers take decades to develop, we have the time and opportunity to intervene to stop or reverse their progress. NCI’s prevention trials seek to determine which person is at risk for cancer, define ways to prevent or reduce that risk, detect cancer at its earliest stages, and actively intervene to prevent invasive cancer. The following represent a small sampling of the progress in these areas:

- In June 2003, researchers of the Prostate Cancer Prevention Trial presented the first-ever findings that prostate cancer can be prevented, at least in part, by drug intervention. Men in the study who took the drug **finasteride** for 7 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. Further study of finasteride therapy is needed.
- Daily **aspirin** may be an appropriate supplement to regular surveillance procedures for many men and women at increased risk for colorectal cancer. Through two large randomized trials, investigators confirmed earlier observational studies that daily aspirin can reduce the development of colorectal polyps. On average, patients at increased risk for colorectal cancer who took daily aspirin for as few as 3 years reduced their colorectal polyp development by 35 percent. People considering aspirin therapy should consult their physician to discuss risks and benefits.
- Data from the landmark Breast Cancer Prevention Trial show that women at high risk for breast cancer who received **tamoxifen**, especially women under age 50, developed fewer cases of benign breast disease and, consequently, were better able to avoid invasive follow-up biopsies.

GOAL

Ensure that NCI's Clinical Trials Program is poised to address the most important medical and scientific questions in cancer prevention, treatment, and quality of life quickly and effectively through state-of-the-art clinical trials.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

<p>1. Identify and accelerate development of the most promising new agents for cancer treatment and prevention.</p>	<p>\$84.70 M</p>
<ul style="list-style-type: none"> ■ Expand partnerships and create flexible collaborations with industry, the FDA, and other public, private, and academic organizations to bring together the best laboratories, institutions, and investigators (including surgeons, pathologists, and radiologists, in addition to traditional participants) for early translational research. \$4.00 M ■ Expand resources for the Rapid Access to Intervention Development (RAID) and Rapid Access to Prevention Intervention Development (RAPID) programs. (See pages 28-29, Objectives 2 and 3.) ■ Facilitate early proof-of-principle clinical trials by expanding capacity to file Investigational New Drug Applications and New Investigational Technology Applications. \$0.70 M ■ Create broadly-based working groups to identify clinically relevant surrogate endpoints and develop standardized resources to validate these endpoints. \$2.00 M ■ Expand translational research capacity to use correlative studies more extensively. \$8.00 M ■ Develop resources to assess the effects of promising agents on their molecular targets through increased funding of Interdisciplinary Research Teams for Molecular Target Assessment. \$20.00 M ■ Develop molecular assays required to characterize/classify tumors, and make them widely available. Support a national tissue resource to facilitate rapid evaluation of new assays and relevant clinical correlations as new targets are identified. (See page 28, Objective 2.) ■ Increase the pace of development and clinical testing of promising new therapeutic and preventive agents by: 1) increasing the number of promising agents entering clinical trials, 2) increasing the number of, and tripling patient accrual, to pivotal early clinical trials, 3) providing financial incentives for timely initiation and conduct of clinical trials, and 4) expanding the rapid grant review process, Quick Trials, for mechanism-based clinical trials. \$35.00 M ■ Support the NCI intramural clinical trials program by increasing the number of data managers, research nurses, biostatisticians, and clinicians available to support a critical mass of clinical investigators, and continuing the Tissue Array Research Program to identify key molecular alterations in cancers. \$15.00 M 	
<p>2. Strengthen scientific planning and leadership for the large, definitive clinical trials that evaluate and define the efficacy and clinical benefit of new treatments and prevention strategies.</p>	<p>\$25.00 M</p>
<ul style="list-style-type: none"> ■ Identify and address compelling clinical questions confronting physicians and their patients under treatment for cancer or at high risk of cancer. \$17.00 M ■ Expand state-of-the-science meetings to identify important research questions and develop scientific strategic plans to address them in disease settings not currently covered, including pediatric tumors. Continue to include broad representation from the scientific community, both basic and clinical, as well as the advocacy community. \$1.00 M ■ Expand clinical trials planning to address critical questions across the major types of conditions experienced by patients by: 1) integrating cross-disciplinary and patient advocate input into scientific strategic planning, 2) supporting multidisciplinary scientific leadership of clinical trials, and 3) integrating biomarker, behavioral, epidemiologic, outcome and other research into existing clinical trials. \$1.00 M 	

- Provide additional research funds for leadership support of scientists who are responsible for writing, monitoring, and analyzing NCI-sponsored, high-priority Phase III trials, including researchers who chair studies in addition to caring for patients, and study statisticians. \$5.00 M

- Enable correlative studies and long-term follow-up for future evaluation of new assays and biomarkers by increasing funding for tissue banks. \$1.00 M

3. Double the rate at which Phase III trials are completed. \$223.50 M

- Increase the number of patients accrued to national trials and shorten the duration of accrual by: 1) increasing funding for nursing, data management, and other infrastructure costs at local clinical trial sites and for operations, data management, and statistical offices, and 2) increasing the number and capacity of existing Community Clinical Oncology Programs.

- Facilitate greater investigator participation in clinical trials by: 1) initiating a “start-up” loan program for new investigators to fund training, research nurse support, and data management, 2) reducing administrative burdens of clinical trials participation, and 3) shortening development and activation of new clinical trials through broader implementation of the Central Institutional Review Board, more rapid protocol development and review, and other mechanisms.

- Provide extensive information about treatment and prevention clinical trials to enable patients and physicians to make informed choices by: 1) incorporating NCI educational materials into marketing and communications strategies (working with the NCI Offices of Communications and Education, patient advocacy groups, professional societies, and others), and 2) developing novel strategies, including the use of alternative media, for working with minority and underrepresented patient populations and their primary care physicians.

- Consolidate administrative tasks and improve quality assurance functions by 1) providing a single interface for investigators to enroll patients, 2) expanding the Cancer Trials Support Unit, 3) developing uniform electronic case report forms and data reporting systems, and 4) expanding NCI’s audit program.

- Facilitate efficient collection, analysis, and sharing of clinical trials data for current and future use in association with tissue specimens in tissue repositories and banks, by maintaining state-of-the-art informatics systems.

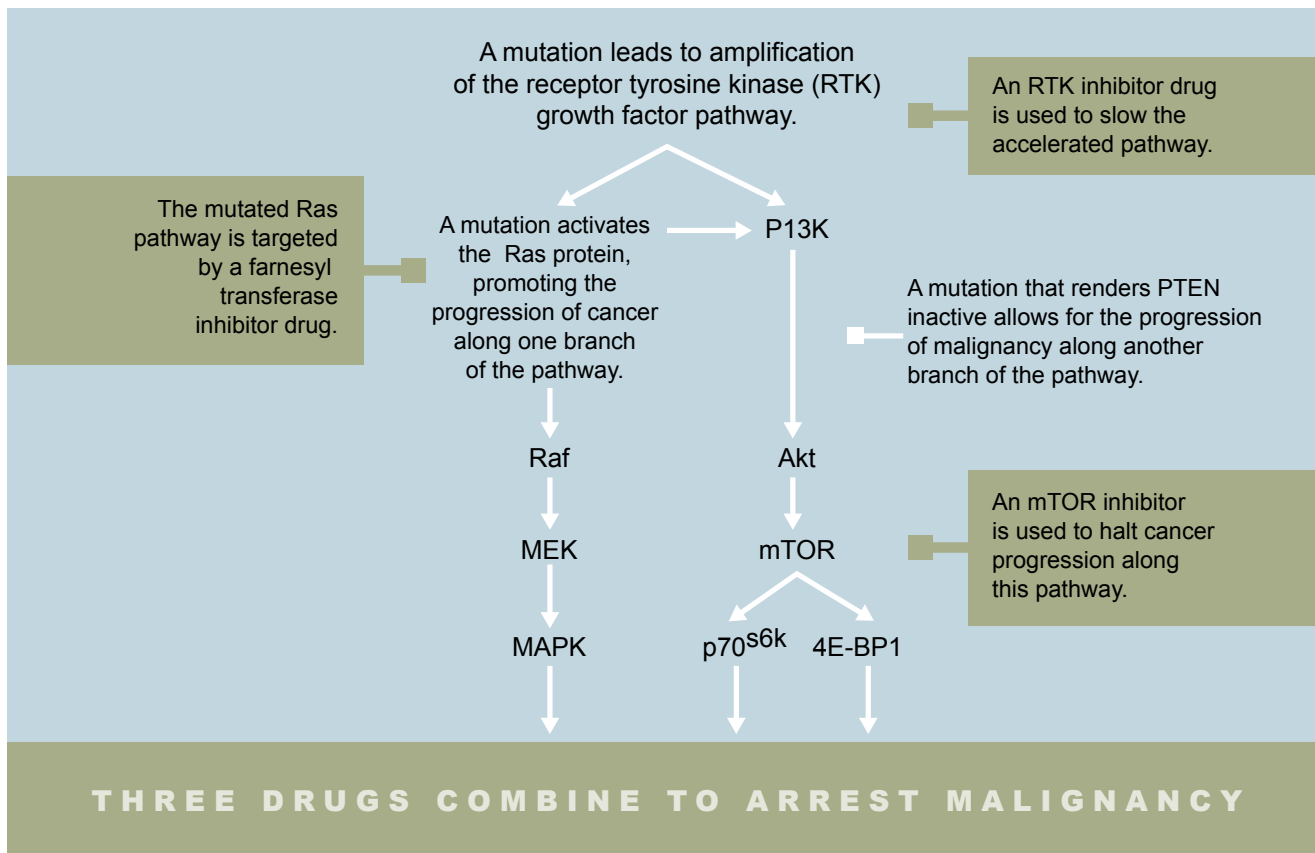
4. Ensure that clinical trials are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for these groups.

- Increase access for minority and underserved populations to state-of-the-art clinical trials. (See pages 62 and 63, Objective 3.)

- Provide funding directly to patients with special needs to cover costs associated with travel, child-care, and other relevant expenses that might limit participation. Address barriers to access for patients dependent on state and Federal health agencies for healthcare coverage by working with state and local government agencies, the Indian Health Service, and other gatekeepers.

- Encourage local sites to identify existing resources to help minority and underserved patients receive appropriate follow-up care and ensure that follow-up care is offered.

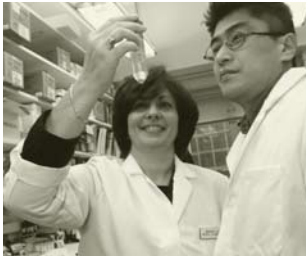
Management and Support		\$ 1.70 M
	Total	\$334.90 M



Targeting Signaling Pathways with Drug Combinations

Cancer is caused by mutations in genes that in turn alter the structure of proteins that regulate molecular pathways for cell growth and other important functions. To improve patient outcomes, researchers hope to develop and test in the clinic, therapies that use combinations of drugs to target several critical points in cancer-causing molecular pathways. This diagram shows how three drugs might be used in combination to shut down a pathway with multiple proteomic changes.

NCI Intramural Research Program Provides a Platform for Innovation, Translation, and Application



NCI's Intramural Research Program (IRP), which conducts research at NIH research laboratories and clinics, provides a unique venue for innovation, translation, and application, and complements our robust Extramural Research Program. The intramural environment promotes and encourages innovation and serves as a proving ground for longer-term, high-risk/high-impact projects. This is possible because the IRP can make long-term funding commitments and support. The Program provides exceptional translational research opportunities that exploit the close linkages among investigators conducting basic, clinical, and population research. It allows immediate application of technological advances to biomedical research and enables rapid response to urgent public health needs. Clinical researchers have access to the facilities of the NIH Clinical Center, and with them, the quality medical care that is provided without charge to patients enrolled in NCI clinical trial protocols.

The intramural environment promotes and encourages innovation and serves as a proving ground for longer-term, high-risk/high-impact projects.

IRP plans include objectives to:

- Enhance the unique value of the Program by facilitating more interactions and collaborations among intramural investigators.
- Increase interactions and collaborations with extramural investigators, and expand interactions with the public and private sectors.
- Develop innovative new technologies and approaches for cancer discovery, prevention, detection, diagnosis, and treatment.
- Facilitate the development of a unique clinical research program for delivery of novel interventions for prevention and therapy.
- Foster training to ensure excellence and to address the need for new, interdisciplinary approaches to cancer research.
- Implement a review and reward structure that will encourage innovation and collaboration while maintaining scientific excellence.

The opening of the new NIH Clinical Center facility in 2004, the establishment of new consortia linking extramural and intramural investigators, the development of new technologies, and new efforts to foster interdisciplinary approaches to scientific discovery will strengthen the work of NCI's Intramural Research Program. Its unique contributions will help us meet our Challenge Goal to eliminate the suffering and death due to cancer.

Enablers of Discovery, Development, and Delivery: Strengthening Tools for Analysis, Resource Sharing, and Dissemination

Case control and cohort studies rely on high throughput genotyping, studies in integrative cancer biology require computational models, large clinical trials require the recording and tracking of enormous amounts of information, and protein pattern analysis puts to use the latest developments in artificial intelligence.

It is vital that investigators carrying out state-of-the-art studies have access to the *Bioinformatics* tools that will support these and other needs for data analysis and resource sharing. The cancer research community must act now to harness contemporary bioinformatics tools for integrating diverse data types, conducting analyses with accuracy and speed, capturing and sharing research outcome data, and providing user-friendly tools that permit patients and their advocates to interact more directly with the cancer research community. NCI will accomplish this by using requested funding to establish a network of information technology partners and support development of a shared bioinformatics infrastructure and tools that facilitate data mining and integration.

The explosive rise of the Internet continues to fuel the demand for accessible health information, but substantial research reveals gaps between the information people want and what they receive. Moreover, people with less income and education are disadvantaged with respect to health communication. This is especially evident with patient-provider communication. NCI leads our Nation's *Cancer Communications* research and development efforts and plays a central role in delivering vast amounts of information to diverse audiences every day. The research focuses on how people inform, persuade, relate to, and influence each other in various contexts and cultures. Larger investments in cancer communications will enable the translation of successful intervention research into practice. In particular, we must apply what we have learned through research to strengthening communications with and improving the health of underserved populations. And optimizing communications to speed the process from discovery to the dissemination of evidence-based interventions is at the forefront of our responsibilities. We must ensure that every person gets needed information at the appropriate time and in a form that is comprehensible and useful as well as culturally and linguistically appropriate.

Bioinformatics

The exponential expansion of biomedical knowledge is generating a tidal wave of data. As biomedical research becomes an increasingly collaborative undertaking, the research arena is finding itself hampered by the “silo” approach to solving data management challenges. Most existing databases have developed independently, with tremendous variability in rules, processes, vocabularies, data content, and analytical tools. There is no unifying architecture to support the essential interoperability among databases and exchange of data. Parallel advances in bioinformatics are needed to address these issues and to accelerate the pace of discovery within and across scientific research centers.

NCI’s bioinformatics strategy is to use information technology to integrate biomedical information in order to make it accessible to researchers across disciplines. Such harmonization will have a major national impact. For example, collaborations among individuals and institutions will become easier to initiate and carry out, clinical trials will be completed more quickly in multi-institutional settings, and the critical new frontier of genotype-phenotype correlative analyses will be greatly facilitated.

Our long-term goal for bioinformatics is to redefine how research is conducted, care is provided, and patients and participants interact with the biomedical research enterprise. We will do this by building an interconnected web of data, individuals, and organizations and making it accessible to all who need it.

To achieve this goal, NCI will:

- Create and implement an informatics platform that integrates diverse data types and analytic tools and facilitates the sharing of data among investigators within and across disciplines.
- Capture and share data from clinical studies by linking networks of community practitioners, clinical research organizations, managed care providers, advocates, academic centers, and individuals.
- Create a consortium for developing a novel infrastructure and tools to facilitate complex biomedical data mining and integration.

NCI’s Center for Bioinformatics Serves as an Integrator for Cancer Research



Bioinformatics technology ensures that the growing tide of cancer information is made available to individuals, groups, and institutions for research and clinical practice. The goal of NCI’s Center for Bioinformatics (NCICB) is to maximize interoperability and integration of research-related information resources to support NCI research initiatives. This support includes bioinformatics platforms, services, tools, and data. The Center participates in the evaluation and prioritization of NCI’s bioinformatics research portfolio, conducts and facilitates bioinformatics research, and serves as the locus for strategic planning to address expanding informatics needs. The Center establishes information technology and exchange standards both within and outside of NCI.

PROGRESS IN PURSUIT OF OUR GOAL

Support to Discovery, Development, and Delivery

Developing New Bioinformatics Tools and Infrastructure

Unprecedented amounts of data and information — clinical trial results, molecular signature information, and preclinical and animal models — are available to current researchers. However, many of the systems in which this rich and sophisticated collection of data is stored are incapable of communicating with other systems. NCI is committed to developing a means to address this complexity by integrating and synthesizing data. NCI is currently developing a spectrum of infrastructure, tools, templates, and standards for biomedical informatics that can meet the needs of the cancer research community. We collaborate with a variety of institutions and make our products and services available at no cost to scientists.

Biomedical informatics systems are integral to NCI's Cancer Therapeutics Evaluation Program, the NCI Center for Cancer Research, the Cancer Biomedical Imaging Program, the Specialized Programs of Research Excellence, the Director's Challenge microarray initiative, the Cancer Genome Anatomy Project, and the Mouse Models of Human Cancers Consortium, as well as numerous cancer prevention trials. Through the Cancer Molecular Analysis Project (CMAP), NCI facilitates the identification and evaluation of molecular targets by integrating comprehensive molecular characterizations of cancer and making the data and infrastructure publicly accessible. CMAP permits investigators to discover molecular targets, assess their validity and interaction with other targets, determine if there are therapeutic agents that can act on specific targets, screen for possible toxicity, and determine whether there are clinical trials evaluating these agents.

Setting Standards That Allow Systems to “Talk” with One Another

NCI's Center for Bioinformatics has developed the cancer Common Ontologic Reference Environment (caCORE), a system for combining and generating knowledge. A key component of the caCORE is NCI's Enterprise Vocabulary Services (EVS). Collaboratively developed, the EVS team organizes and translates the distinct and overlapping vocabularies of scientific projects via one common vocabulary and two broadly used vocabulary resources, the NCI Thesaurus and Metathesaurus. The EVS team also works with vendors to create and improve tools for vocabulary development and curation.

Partnering to Leverage Resources and Encourage Growth

New strategic partnerships are underway to promote the integration of disparate bioinformatics efforts throughout the cancer research community, establish common language, and promote sharing of bioinformatics infrastructure and data. One such partnership is between NCI and the NCI-supported Cancer Centers. The focus of this partnership is on building a coordinated program to leverage existing infrastructure and inform future development across NCI and the entire community of Cancer Centers. In its pilot phase, the program will fund a small number of representative Cancer Centers that will be responsible for broadly assessing requirements,

GOAL

Redefine how research is conducted, care is provided, and patients and participants interact with the biomedical research enterprise by building the necessary interconnected web of data, individuals, and organizations and making it accessible to all who need it.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Support to Discovery and Development

1. Enable data generated among investigators in diverse disciplines to be transparently connected and shared by creating and implementing an informatics platform that integrates diverse data types and analytic tools. \$20.00 M

- Complete the pilot of an NCI-developed informatics platform in a selected group of Cancer Centers, Specialized Programs of Research Excellence (SPOREs), and NCI intramural laboratories. \$5.00 M
- Refine current and develop additional modules, software bridges, and infrastructure extension based on the results of the pilot. \$2.50 M
- Expand NCI help desk capabilities to better serve the needs of the project. \$2.50 M
- Make the resources available to additional Cancer Centers, SPOREs, and intramural groups. \$10.00 M

2. Facilitate complex biomedical data mining and integration by creating a consortium charged with developing a novel infrastructure and tools. \$10.00 M

- Identify academic, government, and industrial developers who are willing to produce open-source tools that are interoperable with NCI's architecture and support community identified needs and NCI-determined priorities.
- Establish a mechanism for working together to develop data mining and data integration tools.

Support to Delivery

3. Link networks of community practitioners, clinical research organizations, managed care providers, and academic centers by capturing and sharing data from clinical research investigations. \$10.00 M

- Capture clinical research data through a Web-based reporting system piloted with volunteers from SPOREs, Cancer Centers, and NCI intramural groups. \$5.00 M
- Extend the infrastructure to permit integration with and sharing of other data types and to support clinical research beyond therapeutic and prevention trials. \$1.00 M
- Pilot in additional cancer research settings a Web-based clinical trials support infrastructure developed in the NCI Intramural Program, SPOREs, and Cancer Centers. \$2.00 M
- Develop open source clinical trials modules that can be freely distributed to other academic research centers, community practices, and private practices. \$2.00 M

Management and Support \$ 0.80 M

Total \$40.80 M

caBIG Will Expedite Access to Bioinformatics Resources

NCI plans to deploy a biomedical informatics infrastructure called the cancer Biomedical Informatics Grid or caBIG. As part of this effort, NCI, in partnership with others in the cancer research community, is creating a common, extensible informatics platform that integrates diverse data types and supports interoperable analytic tools. This platform will allow research groups to tap into the rich collection of emerging cancer research data while supporting their individual investigations.

Because Cancer Centers provide the institutional framework around which much of NCI-supported research is conducted, NCI is working with a representative sample of these Centers in the pilot phase of the project. Center resources will be joined into a common web of communications, data, and applications.

The caBIG pilot includes:

- “Co-developers” that contribute mature infrastructure and applications
- “Adapters/adopters” that take contributed infrastructure and applications and implement or adapt them for local needs
- “Users” that utilize the applications and infrastructure provided, contribute data sets and study populations, and assist in establishing the needed functionality of the caBIG effort

NCI is soliciting ongoing feedback from the Cancer Centers through working groups engaged in specific development areas, workshops to review models and system development, and a project Website (caBIG.nci.nih.gov) and mailing list. The workshops and Website are available to the entire cancer research community. As consensus is achieved, projects are executed and implemented, initially at the funded pilot centers and then more broadly across the Cancer Centers, Specialized Programs of Research Excellence, new NCI research initiatives, and intramural research programs.

The caBIG pilot effort strives to:

- Maintain the current momentum of the informatics efforts at NCI.
- Create tools and systems that are adaptable to different institutional settings, meet Food and Drug Administration compliance requirements, and can retrieve common information important to biomedical research from existing biomedical information systems.
- Involve all Cancer Centers through updates of progress and solicitation of comments and feedback, while working directly with a few Centers for pilot development.

existing infrastructure, and development priorities. New tools and infrastructure will be deployed at test sites. Feedback gathered during the pilot will drive improvement priorities. Finally, the tools and infrastructure will be fully deployed to the cancer center community.

Cancer Communications

From primary prevention to survivorship or end-of-life care, communication provides people with the vital link to the information they need to make good decisions. Effective communication motivates people and communities to take actions that reduce their cancer risk. It can be used to encourage people to eat healthy, wear sunscreen, exercise regularly, stop smoking, and get screened for cancer. In every cancer diagnosis, communication plays a key role in helping patients and physicians with the information they need to make the best decisions about treatment options, risks, and benefits. And those who live beyond cancer experience a better quality of life when they have access to information and support in dealing with post-treatment effects. Culturally and linguistically appropriate communication helps people make decisions that are compatible with their values and beliefs.

NCI actively pursues research to examine the processes and mechanisms through which cancer information is delivered, understood, and used. Specific initiatives focus on such topics as cancer risk perception, information processing, and decision making. The knowledge gained allows us to develop, evaluate, and deliver communication resources and interventions.

Yet research reveals substantial gaps between the information people want and need and what they receive. The explosion in information delivery systems such as the Internet has given people access to information from any number of sources, but the inconsistent quality and reliability of the information jeopardizes the ability of patients and their caregivers to sort out which information to use in making critical, sometimes lifesaving, decisions. Research shows that people perceive information based on their prior knowledge, beliefs, and experiences. America's increasing cultural diversity and a pervasive pattern of disparities that limit access to and use of information only add to the complexities of effective cancer communications.

NCI is committed to helping Americans better understand news about cancer — whether the news comes in the form of a diagnosis, media report, or Website communication. A better understanding of cancer improves communications between patients and health-care professionals and helps them work together to make good decisions and minimize inappropriate ones. NCI promotes cancer prevention and detection through communication activities that provide the information, tools, and encouragement people need to embrace actions known to reduce cancer risk. We also promote the use of age-appropriate cancer screening and early detection tests — e.g., mammograms, Pap tests, and colorectal cancer screening tests. People who are empowered with knowledge can make informed decisions about treatment, disease management, palliative care, and end-of-life options.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

Increasing Knowledge through Discovery

The Centers of Excellence in Cancer Communications Research (CECCRs) serve as the centerpiece of NCI's communications research. The Centers foster the advancement of cancer communication science by examining the processes and mechanisms through which communication plays a role in cancer control. Four centers were funded in July 2003 to carry out a variety of projects such as facilitating information seeking related to prostate, breast, and colorectal cancers; developing decision aids concerning tamoxifen use among women at high risk for breast cancer; promoting fruit and vegetable intake among African Americans; examining media coverage of cancer-related issues in African American newspapers; and developing and evaluating new interactive health communication systems.

As a first step toward understanding the nature, extent, and depth of media coverage on cancer, NCI is conducting a pilot study to examine how news media reported the 2002 controversy on the efficacy of mammography in saving lives. An analysis of news stories published in the Nation's top 50 newspapers will reveal how reporters framed the controversy in terms of risks and benefits and which sources, among scientists and the advocacy community, were used in reporting the debate. This study will serve as a complement to surveys that assessed women's reactions to the controversy. Both media content analysis and surveys will help NCI understand how media coverage of cancer could influence audience perceptions of risk and risk-related behaviors. The findings will enable NCI to take appropriate actions to influence people's risk behaviors as well as proactively work with the media to provide accurate and timely information on cancer. These studies will also help inform future communications planning.

Development

NCI has taken an important first step in bridging the gap between development and delivery by funding grant supplements for investigators to disseminate promising interventions and products to the broader population. The first seven supplements address sun safety, 5 A Day promotion, smoking cessation, dietary patterns in preschool children, cancer screening, interventions for use in managed care settings, and interventions for underserved populations.

Developing and Evaluating Communication Resources and Interventions

To promote increased participation in cancer clinical trials, NCI developed a Web-based course for health professionals, *Incorporating Clinical Trials into Your Practice*. The course emphasizes the importance of health professional participation in clinical trials, either through referral or by becoming a clinical trials investigator, and provides practical information and guidance on conducting and locating trials. It complements NCI's **Clinical Trial Education Series (CTES)**, a set of 13 educational resources designed to educate health care professionals and the public (cancer.gov/clinicaltrials/resources/clinical-trials-education-series). Course participants may receive Continuing Medical Education credits for course completion.

NCI held a workshop on health behavior theories in May 2002 to examine actions individuals can take to prevent cancer and speed its early detection. A group of experts with backgrounds in risk communication, risk behaviors, cancer screening, diet, and tobacco addiction discussed how our understanding of health behaviors can be improved in order to help inform health interventions.

Delivery

Partnering to Deliver Evidence-Based Cancer Interventions

NCI encourages all Americans to eat 5 to 9 servings of fruits and vegetables a day for better health. This advice is especially critical for African American men, who suffer a disproportionately high incidence of and mortality from many chronic diseases related to diet, including cancer. In 2003, NCI launched a 9 A Day campaign for African American men. The campaign includes national radio programming on more than 230 affiliate urban stations through a faith-based initiative, and outreach and partnership opportunities with national African American organizations and television programming outlets. In a related campaign, a National Basketball Association sports celebrity helped NCI spread the message to all men to "Shoot for 9" via public service announcements and media interviews that aired during the 2003 playoffs. For more information, go to 9aday.cancer.gov and 5aday.gov/shootfor9.

One of NCI's most powerful communication arms is the Cancer Information Service (CIS).

CIS helps people become active participants in their health care by providing the latest scientific cancer information in understandable language. Through a network of 14 regional offices located at Cancer Centers or major medical centers throughout the country, CIS serves the entire United States, Puerto Rico, the U.S. Virgin Islands, and the U.S. Territories. In 2002, CIS handled over 1.4 million requests for service from patients, their families, the general public, and health professionals. The Cancer Information Service offers smoking cessation assistance (1-877-44U-QUIT), cancer-related publications, and recorded information about cancer 24 hours a day, 7 days a week (1-800-4-CANCER). In addition, through its Partnership Program, CIS collaborates with national, state, and regional organizations to develop appropriate cancer education programs for minority and medically underserved populations.

New Online Tool Puts U.S.- and U.K.- Sponsored Cancer Research Information at Your Fingertips

The International Cancer Research Portfolio Web site (www.cancerportfolio.org) was launched in June 2003 to provide public access to information about approximately 13,000 cancer-related research projects. The project is the result of collaboration among the NCI, the Congressionally Directed Medical Research Programs of the Department of Defense and the National Cancer Research Institute of the United Kingdom. This new online resource allows scientists, patient advocates, and the public to search and browse research portfolios of U.S. and U.K. cancer research organizations by specific cancer and type of cancer research, providing information about the funding organization, awardee institution, and principal investigator along with a detailed research abstract.

MPCAI in a unique public-private partnership with the Centers for Medicare and Medicaid Services (CMS) and the National Asian Women's Health Organization, NCI adapted, tested, and disseminated nationally an Asian American/Pacific Islander (AAPI) mammography education resource. Developed for Chinese, Vietnamese, and Pacific Islander women in their 40s and older, this breast health screening brochure was adapted from CMS-funded intervention research. NCI collaborated with five AAPI community organizations to pilot test this educational resource. A multipronged distribution strategy focused on 10 U.S. geographic areas with the largest concentrations of AAPI populations. Evaluation of the distribution strategy is underway.

With the newly revised *Making Health Communications Programs Work: A Planner's Guide*, NCI has provided a resource for health communicators that emphasizes a practical approach to the communications process and reflects recent advances in knowledge and technology such as the Internet. This highly popular publication has been an essential communications tool for many professional associations, private organizations, and government agencies. Communicators can use the *Guide* to assess community needs, create messages, identify appropriate audiences and media, conduct market research, create partnerships, and evaluate and improve programs.

Research Tested Intervention Programs (RTIPs), a collaboration between NCI and the Substance Abuse and Mental Health Services Administration, was launched as part of the Web portal, Cancer Control PLANET. RTIPs provide access to examples of evidence-based intervention programs and products developed and evaluated by researchers in the field. Cancer Control PLANET provides access to data and resources that can help cancer control planners, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. (See also page 85.)

GOAL

Understand, apply, and disseminate effective communication approaches that maximize access to and appropriate use of cancer information by all who need it.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

1. Increase knowledge about cancer information needs, beliefs, decision making processes, and behaviors, and the relationships between these factors among different publics, including general populations, the underserved, patients and their caregivers, high-risk groups, and health providers. \$12.50 M

- Investigate and monitor the commercial communication, consumer technology, and health technology industries to identify developments that are likely to influence access to, the means for, and the effectiveness of cancer-related communication 3 to 10 years into the future. \$0.50 M
- Identify the information, communication, and decision making factors related to the etiology of cancer disparities, and develop an evidence base to support population-specific strategies for overcoming cancer disparities. \$2.50 M
- Analyze data from a variety of sources, including the Health Information National Trends Survey (HINTS) to understand public knowledge, attitudes, beliefs, and information-seeking behaviors related to cancer and screening practices, with an oversampling of underserved groups. \$2.00 M
- Investigate high-priority cancer communication issues among different population subgroups on such issues as risk communication, health literacy, informed decision making, provider-patient communication, perceptions of cancer clusters, communication of cancer statistics, perceptions of cancer as a chronic disease, the information needs of cancer patients as they undergo and recover from various treatment modalities, exit communication strategies for patients who are leaving clinical trials, and perceptions and practices of various population groups with regard to genetic testing for cancer. \$4.00 M
- Examine the fundamental processes and mechanisms of cancer communication science through continued funding of the Centers of Excellence in Cancer Communications Research (CECCRs).
- Analyze NCI's intramural clinical trials recruitment methods to develop a model for Phase I and II clinical trials recruitment and follow-up care. \$0.75 M
- Identify how various population groups understand recommendations on diet, physical activity, and weight for the purpose of informing the development of communication programs. \$2.00 M
- Survey health and science journalists to understand contemporary methods and strategies used in health reporting. \$0.75 M

Development

2. Develop and evaluate communication resources and interventions for use in reducing the cancer burden, including overcoming barriers to access and completion of cancer treatment, particularly among underserved populations. \$18.50 M

- Study the nature of information provided to different audiences through various media and the availability of these media to underserved communities and individuals. Measure the public's response to cancer information in the media through development of a Cancer Information Surveillance System (CISS). \$4.00 M
- Establish and apply methods to ensure that communication tools, products, and programs used by NCI and its partners are evidence-based. These methods will include syntheses of research, consumer research, product development research, and systematic evaluation. \$3.00 M
- Complete the development of HINTS as a public access database for research and program planning, and expand HINTS to include a survey of cancer survivors. \$1.00 M

- Evaluate the effectiveness of the CIS in increasing the public's knowledge of cancer topics and positively influencing healthful behaviors and decisions. \$2.00 M
- Evaluate CIS partners for satisfaction with collaboration, success at reaching underserved populations, and organizational capacity to disseminate cancer information. \$1.00 M
- Foster a more integrated and coordinated approach to media campaigns across NIH and in partnership with other Federal agencies, such as the Centers for Disease Control and Prevention, to develop important behavioral messages on health issues that cross multiple diseases. \$1.50 M
- Cultivate relationships with the commercial communication, consumer technology, and health technology industries to foster improved access to and provision of effective cancer-related information, including decision making aids. \$2.00 M
- Partner with advocacy groups, state health departments, and other Federal agencies to develop a strategy to help the public understand cancer clusters and to assist partners in communicating effectively about the issue. \$2.00 M
- Collaborate with organizations to support and evaluate the outcomes of promoting accurate cancer information messages in popular culture (e.g., movies and television shows). \$2.00 M

Delivery

3. Engage with partners and the media to deliver evidence-based cancer interventions in clinical and public health programs. \$10.50 M

- Support dissemination research to identify optimal means for NCI and grantees to increase the adoption of NCI-funded evidence-based interventions. \$3.00 M
- Facilitate the media's effective use of NCI's resources (for example, statistical reports) through outreach including annual workshops and toolkits. \$1.00 M
- Translate findings and lessons learned from large prevention trials into key messages, tools, and products that can be used to inform and educate the public about cancer prevention. \$1.50 M
- Strengthen collaborations with Federal agencies and other organizations to further reduce the burden of highly preventable cancers such as colorectal and lung cancers. \$2.00 M
- Expand the dissemination of NIH and NCI grant resources, policies, and funding opportunities to the extramural scientific community engaged in cancer research. \$2.00 M
- Expand efforts to communicate research findings to the public via the news media, using strategies and tools that reach ethnically diverse populations. \$1.00 M

Management and Support		\$ 2.00 M
	Total	\$43.50 M

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* See also Table of Contents on page v for major topics covered in this document.

Glossary

allele — Any of the alternative forms of a gene that are located together on a chromosome. For autosomal chromosomes, each allele will normally have two copies of the same gene, one inherited from the mother and one from the father.

angiogenesis — Growth of new blood vessels.

antibody — A type of protein made by certain white blood cells in response to a foreign substance (antigen). Antibodies bind to the antigen and either destroy the foreign substance directly or make it easier for the body to do so.

antigen — A foreign substance that causes the immune system to make a specific immune response.

apoptosis — A type of cell death where the cell is “programmed” to “commit suicide” when it has been sufficiently damaged or is no longer needed.

autosomal — Pertaining to a chromosome not involved in sex determination.

autosomal dominant — Requires that only one affected parent have the trait to pass it to offspring.

biomarker — A substance sometimes found in the blood, other body fluids, or tissues that can be used to assess the presence of cancer.

biosensor — A type of biomolecular probe that measures the presence or concentration of biological molecules, biological structures, etc., by translating a biochemical interaction at the probe surface into a quantifiable physical signal such as light or electric pulse.

biospecimen — Sample taken from a patient such as blood, tissue, urine, or sputum.

cachexia — The loss of body weight and muscle mass frequently seen in patients with cancer, AIDS, or other diseases.

candidate gene — A gene researchers suspect may be related to a certain condition, such as cancer.

case-control study — An epidemiological study in which the risk factors of people with a certain disease (cases) are compared with those without the disease (controls).

cell line — Cells of a single type taken from an animal or human and grown in the laboratory.

cohort study — A research study that compares a particular outcome, such as lung cancer, in groups of individuals who are alike in many ways but differ by a certain characteristic — for example, female nurses who smoke compared with those who do not smoke.

combinatorial chemistry — The systematic creation of large numbers of small molecules in “libraries” that can be screened *in vitro* for potential as cancer drugs.

comparative genomic hybridization — A method of identifying and mapping differences in DNA sequencing data between normal cells and tumor cells.

computer adaptive data collection/testing — A computer administered test that tailors the content of the test to the skills of the test taker.

correlative study — A type of study that tests for a relationship between a condition and a potential causal factor of the condition — e.g., cancer and obesity.

cytotoxic — Cell killing.

deregulated pathway — A molecular pathway that is not regulated in a normal manner by the cell.

dietary crucifer — Any of a family (Cruciferae) of plants including cabbage, broccoli, cauliflower, brussels sprouts, and greens such as mustard greens.

DNA — Deoxyribonucleic acid. The molecule that encodes genetic information in the nucleus of cells. It determines the structure, function, and behavior of the cell.

dopamine — A neurotransmitter and hormone. Dopamine levels have been associated with mood state.

enzyme — A protein that speeds up chemical reactions in the body.

epidemiology — The study of the patterns, causes, and control of disease in groups of people.

epigenetic effects — Changes in cellular biochemistry that influence the phenotype produced from a genotype. Epigenetic effects differ from genetic effects, which are caused by DNA mutation.

epithelium — The thin layer of tissue that covers organs, glands, and other structures within the body.

etiology — The study of the cause or origin of disease.

expression — The process by which a gene’s coded information is converted into the structures present and operating in the cell.

extracellular matrix — Any material produced by cells and secreted into the surrounding medium.

fibroadenoma — A benign solid growth, usually found in the breast.

fibrosis — The formation of fibrous tissue.

functional genomics — Study of the function of individual genes and interactions among groups of genes to address biological questions.

functional imaging — Sometimes called molecular imaging. Imaging techniques for detecting molecular signals that indicate the presence of biochemical activity and changes, such as cell growth or death.

gene variant — A gene that is essentially the same as another, but has mutational differences.

genetic profile — DNA analysis of a person’s body tissue or body fluid.

genome — The complete genetic material of an organism.

genotype — Referring to the genetic constitution (makeup) of an individual or group.

genotyping — Measuring features of an individual’s genotype — e.g., testing for genetic mutations.

germline — The body’s reproductive cells (egg or sperm). Germline DNA becomes incorporated into the DNA of every cell in the body of offspring.

haplotype — A group of alleles of different genes that are linked closely enough to be inherited as a unit.

histology — The study of cells and tissues at the microscopic level.

histone — A type of protein found in chromosomes that help give them their shape and help control the activity of genes.

hyperplasia — An abnormal increase in the number of cells in an organ or tissue.

immune-mediated benefit — A benefit that results from activity of the immune system — e.g., mobilization of white blood cells against cancer cells.

immunotoxin — An antibody linked to a toxic substance. Some immunotoxins can bind to cancer cells and kill them.

in silico analysis — Analysis performed using computers in conjunction with informatics capabilities.

in vitro — In the laboratory (outside the body).

in vivo — In the body.

late effect — Side effects of cancer treatment that only become apparent with long-term monitoring of the patient.

ligand — Any molecule that binds to another; usually a soluble molecule such as a hormone or neurotransmitter that binds to a protein receptor.

longitudinal study — A study that involves the repeated observation or examination of a set of subjects over time with respect to one or more study variables.

lymphedema — A condition in which excess fluid collects in tissue and causes swelling.

MAO-B inhibitor — A type of drug that inhibits the function of the enzyme, monoamine oxidase B. MAO-B inhibitors are commonly used to treat depression and Parkinson's disease.

methylation — The addition of a chemical group (methyl) to DNA that epigenetically alters gene expression.

microarray — A powerful technology that allows simultaneous measurement of expression levels for up to tens of thousands of genes.

microdissection — Dissection of tissues under a microscope.

microenvironment — Local and systemic architecture surrounding a cancer cell. Includes other cells, growth factors, enzymes, and parts of the blood and lymphatic systems.

microsatellite — A repetitive stretch of short DNA sequences that occur in increased numbers in cancer cells.

molecular beacon — A type of biosensor that emits a signal, such as light, when it encounters a particular feature, such as a particular type of protein.

molecular epidemiology — Epidemiology that focuses on measurements of molecular features.

molecular imaging — See “functional imaging.”

molecular signature — Characteristic features of the molecular composition of a cell or its surroundings.

molecular target — Molecular features in a cancer cell or its surroundings critical to cancer development or progression that can potentially be disrupted to prevent or treat the disease.

monoclonal antibody — Laboratory-produced protein that can locate and bind to a particular feature of cancer cells in the body. Monoclonal antibodies can be used to deliver drugs, toxins, or radioactive material directly to a tumor.

mucinous — Pertaining to cells that line certain internal organs and produce mucin (the main component of mucus).

multimodal therapy — Therapy that combines more than one method of treatment.

mutation — A permanent change in the genetic material, usually in a single gene.

mycochemical — A chemical derived from fungi.

nanometer — A metric unit of measure. Approximately 25.4 million nanometers equal one inch.

nanoparticle — Small clusters of atoms about 1 to 100 nanometers long.

nanotechnology — Technology development at the atomic, molecular, or macromolecular range of approximately 1-100 nanometers to create and use structures, devices, and systems that have novel properties.

neoplastic — Abnormal and uncontrolled cell growth.

nicotinic acetylcholine receptor — A type of neurotransmitter receptor in the hippocampus (a part of the brain) that naturally responds to acetylcholine.

nucleotide — Molecules that comprise the building blocks of DNA.

oncogene — A gene that normally directs cell growth, but is altered to promote or allow uncontrolled cellular growth.

open-source — Of or relating to source code (e.g., computer code) that is available to the public.

patient navigation — The recruitment and training of persons from underserved communities to assist in navigating patients through standard cancer diagnosis and treatment services.

peptide — Any compound consisting of two or more amino acids, the building blocks of proteins.

pharmacogenomics — The study of individual genetic differences in response to drug therapy.

pharmacology — The study of the properties and reactions of drugs, especially with relation to their therapeutic value.

phenotype — The visible or measurable properties of an organism that are produced by the interaction of the genotype and the environment — e.g., eye color.

polymorphism — Common variation or mutation in DNA, not always harmful.

process measure — An index of the degree to which a service or procedure is performed correctly and appropriately; that is, the service or procedure's likely benefit exceeds its likely harms or risks.

proof of principle study — A study that demonstrates an agent to have the desired biological effect on its target.

prospective study — A study in which participants are identified and then followed forward in time.

proteasome inhibitor — Drugs that block the action of proteasomes, cellular complexes that break down proteins.

proteomics — The comprehensive study of proteins and their functions.

quantum dots — Tiny crystals that glow when stimulated by ultraviolet (UV) light; an *in vivo* application of nanotechnology.

radiolabeled — Labeled for detection with a radioactive material.

radiotracer — A radioactive substance that can be traced in the body.

reference clone — The sequence for a particular gene that is accepted as the true sequence.

resequencing — A specific application of gene sequencing that precisely determines the sequence of bases in DNA. Resequencing is used to identify single nucleotide polymorphisms (SNPs).

retrospective analysis — A study that looks backward in time, usually using medical records and interviews with patients who already have or had a disease.

RNA — Ribonucleic acid, one of the two types of nucleic acids found in all cells. (The other is DNA.) RNA transmits genetic information from DNA to proteins produced by the cell.

RNAi — RNA inhibitor.

sequencing — Determination of the order of nucleotides in a DNA or RNA molecule or the order of amino acids in a protein.

single nucleotide polymorphism (SNP) — A genetic change that is caused by substitution of a single nucleotide.

stem cell — A cell from which other types of cells can develop.

stroma — The supporting connective tissue of an organ.

suicide genes — Genes that, when expressed, cause cell death through apoptosis.

surrogate biomarker — A biomarker used to assess a surrogate endpoint.

surrogate endpoint — A laboratory measurement of some biological indicator of a drug's effectiveness, used in place of longer-term outcome measures.

survey item bank — A collection of commonly used questionnaire items and scales.

telemedicine — Delivery of health services via remote telecommunications.

toxicology — The study of the chemistry and effects of poisonous substances and the treatment of poisoning.

vascularization — Formation of blood vessels.

von Hippel-Lindau syndrome — A rare inherited disorder in which blood vessels grow abnormally in the eyes, brain, spinal cord, adrenal glands, or other parts of the body. People with this syndrome have a higher risk of developing some types of cancer.

well-differentiated — A tumor which is superficially similar in appearance to the parent tissue.

yttrium — A rare elemental metal. A radioactive form of yttrium is used in radiation therapy and some types of immunotherapy.

Acknowledgments

Each year, countless people at NCI; on our advisory boards; and in research, other professional, and advocacy organizations around the country provide their insights, perspectives, and expertise for the development of this document. Members of the Office of Science Planning and Assessment provide leadership and guidance for plan development from conceptualization to production. They work alongside the core group of NCI leaders who serve as Champions for the various priority areas and with staff of the Office of Budget and Financial Management and the Office of Communications. Numerous other people at NCI contribute information, review drafts, and identify new areas of emphasis.

The following people made major contributions to this document:

NCI Office of Science Planning and Assessment: *Lead Staff:* Cherie Nichols, Kathie Reed, Kathy Sorrow, and Marianne Kost. *Priority Area Contacts:* Anne Tatem, Jane Lockmuller, Lisa Stevens, Samir Sauma, and Margaret Ames

NCI Priority Area Champions: Jeff Abrams, Rachel Ballard-Barbash, Carl Barrett, Linda M. Brown, Martin Brown, Ken Buetow, Neil Caporaso, Nelvis Castro, Steve Chanock, Michael Christian, Norm Coleman, Jim Crowell, Bob Croyle, Ellen Feigal, Michele Forman, Harold Freeman, Paulette Gray, Lee Helman, Bob Hoover, Lenora Johnson, Gary Kelloff, Jon Kerner, Brian Kimes, Scott Leischow, Joe Lipscomb, Ed Maibach, Mary McCabe, John Milner, Lori Minasian, Julia Rowland, Ed Sausville, Arthur Schatzkin, Jeff Shilling, Dinah Singer, John Sogn, Bob Strausberg, Dan Sullivan, Ed Trapido, and Vish Viswanath

NCI Office of Budget and Financial Management: Jim Dickens and Ngan Nguyen

NCI Office of Communications: Jo-Ann Kriebel, Tamara Maze-Gallman, Donna Bonner, Paul LaMasters, and Diane Reid

NCI Office of the Director: John Hartinger and Jim Mathews

Other NCI offices: Jane Daye, Matt Fritts, Elisabeth Handley, Jill Johnson, and Stacey Vandor

Michigan State University: Barbara Given, Charles Given, and Paula Sherwood

Other contributors include:

NCI Staff: Alan Rabson, Noreen Aziz, Ann Barker, Joseph Fraumeni, Peter Greenwald, Norma Davis, Kevin Callahan, Anna Levy, Jim Corrigan, Marilyn Duncan, Buddy Clark, Lauren Christopher, Christine Moretto, Julie Schneider, Kevin Wright, Heather Burns, Michelle Bennett, Kelly Blake, Barbara Croft, Gregory Downing, Andrea Denicoff, Kay Flemming, Dorothy Foellmer,

Barbara Galen, Neil Goldman, Lakshmi Grama, Ernie Hawk, Steve Hazen, Marianne Henderson, Steven Hewitt, John Hoffman, Jim Jacobson, Diana Jeffery, Kathy Kelly, Geoffrey Kidd, Lance Liotta, Guoying Lui, Cheryl Marks, Anne Menkens, Suresh Mohla, Ed Monachino, Kathleen Schlom, Sudhir Srivastava, James Tatum, Sheila Taube, Gina Tesauro, Tracy Thompson, Robert Yarchoan, Sheila Zahm, and Katherine Zoon.
National Institute on Aging: Rosemary Yancik.
University of Pennsylvania: Gillies McKenna. **University of Michigan:** Theodore Lawrence. **M. D. Anderson Cancer Center:** Michele Follen

The following people and organizations provided input prior to the development of this document.

NCI Director's Consumer Liaison Group: Vernal Branch, Kathy Giusti, Ruth Lin, Barbara LeStage, Gena Love, Michael Katz, Karen Packer, Nyrvah Richard, Doug Ulman, and Marisa Weiss

NCI-Designated Cancer Centers: Dave Alberts, Ralph Freedman, Gary Giovino, and John Mendelsohn

Professional and Advocacy Organizations: American Association for Cancer Research, American Society for Clinical Oncology, American Society for Therapeutic Radiology and Oncology, The Children's Cause, and Federation of Practice Based Research Networks

Individual Reviewers: Edith Balbach, Steve Booth-Butterfield, Judith Brook, Gregory Connolly, Dave Haaga, Dorothy Hatsukami, Bruce Hillman, Wendy Hobbie, Judy Hopkins, Lawrence Hunter, Ferenc Jolesz, Herb Kressel, Nancy Krieger, Ed Lichtenstein, Pamela Ling, Ruth Malone, Timothy Rebeck, Barbara Stillwater, and Tom Vogt

A special thank you goes to the following people who provided **writing, design, editing, proofing, and printing support** for the production of this document: Suzanne Reuben of Progressive Health Systems; Lynne Komai, Don Wheeler, and Claudia Smith of The Watermark Design Office; Paula Zeller; Kathy Hollen; and Walt Burroughs.

Valuable World Wide Web Locations

National Cancer Institute cancer.gov
National Institutes of Health www.nih.gov
Department of Health and Human Services www.hhs.gov
Cancer Research Portfolio researchportfolio.cancer.gov
International Cancer Research Portfolio www.cancerportfolio.org
Cancer News newscenter.cancer.gov
Cancer Science newscenter.cancer.gov/sciencebehind

Cancer Information Service (CIS)

By phone
1-800-4-CANCER (1-800-422-6237)
For deaf and hard-of-hearing 1-800-332-8615

On the Web
cis.nci.nih.gov

This Document Online

Access expanded content for this Plan and Budget Proposal, including links to key Websites, at plan.cancer.gov.
Online links related to the chapters in this book include the following.

National Agendas for Disease-Specific Research

- Progress Review Groups prg.cancer.gov
- Research Initiatives cri.cancer.gov

Investigator-Initiated Research

- Research Portfolio researchportfolio.cancer.gov
- International Portfolio www.cancerportfolio.org
- Research Resources resresources.nci.nih.gov
- Funding www.cancer.gov/researchfunding

Centers, Networks, and Consortia

- Cancer Centers www.cancer.gov/cancercenters
- SPOREs spores.nci.nih.gov

National Clinical Trials Program

- Cancer Clinical Trials www.cancer.gov/clinicaltrials and www.cancer.gov/clinicaltrials/understanding

Bioinformatics for Cancer Research

- Center for Bioinformatics ncicb.nci.nih.gov

Genes and the Environment

- Family Registry epi.grants.cancer.gov/CFR
- Genetics Network epi.grants.cancer.gov/CGN

Signatures and Microenvironment

- CGAP cgap.nci.nih.gov
- EDRN www.cancer.gov/prevention/cbrg/edrn
- Director's Challenge dc.nci.nih.gov

Molecular Targets

- Developmental Therapeutics dtp.nci.nih.gov
- Intramural Initiatives ccr.cancer.gov/initiatives

Cancer Imaging and Molecular Sensing

- Biomedical Imaging www.cancer.gov/bip and www.cancer.gov/clinicaltrials/understanding/science-explained-imaging

Cancer Communications

- Extraordinary Opportunity cancercontrol.cancer.gov/eocc

Quality of Cancer Care

- Applied Research appliedresearch.cancer.gov

Cancer-Related Health Disparities

- NCI Center crchd.nci.nih.gov

Cancer Survivorship

- Survivorship Research survivorship.cancer.gov

Tobacco and Tobacco-Related Cancers

- Tobacco Research tobaccocontrol.cancer.gov

Research Training and Career Development

- Opportunities cancertraining.nci.nih.gov

Emerging Trends in Cancer

- Progress Report progressreport.cancer.gov
- Mortality Maps www.cancer.gov/atlasplus
- SEER seer.cancer.gov

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By email sisocc@pop.nci.nih.gov
By Internet www.cancer.gov/publications
By phone 1-800-4-CANCER
By fax 1-301-330-7968

Telephone Assistance for Smoking Cessation

NCI provides telephone-based assistance for smokers who want to quit through the Cancer Information Service (CIS) at 1-800-4-CANCER. Callers can speak with someone in English or Spanish in the United States, Puerto Rico, the U.S. Virgin Islands, and territories in Guam and Saipan.

Smoking cessation service representatives:

- Assess the caller's individual smoking behavior.
- Provide brief educational messages.
- Help callers develop a personalized action plan for quitting.
- Reinforce the information with written materials.



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NIH Publication No. 03-5446
October 2003

