

The National Cancer Institute

# The Nation's Investment in Cancer Research

*A Budget Proposal for  
Fiscal Year 2001*

Prepared by the Director  
National Cancer Institute

National Institutes of Health

# In Brief

**Special Populations** In our country, some populations are more severely affected by cancer than others. NCI has an aggressive program of research, training opportunities, and organizational structures dedicated to understanding and addressing the unequal burden of cancer in the United States – see [page 34](#).

**Information** NCI provides the Nation with the most up-to-date cancer information 24 hours a day, 7 days a week – through the Internet, and by phone, fax, and more than 600 print and audiovisual materials. Turn to [page 33](#) to learn the many ways you can access NCI's information services.

**Molecular Targets** Using “molecular targets,” we may be able to design cancer treatments that are “customized” for many patients, determine immediately whether or not a particular treatment is working, and even decipher the mechanism of action by which a drug works. See [page 57](#) to find out what a “molecular target” is and how they're being used to transform cancer prevention and treatment.

**Training** Too few talented scientists are choosing careers in clinical oncology research, and those that do are experiencing increasing clinical and administrative pressures that impede their ability to conduct needed research. To learn more about NCI's plans to meet this challenge – and to attract much-needed basic and population scientists to cancer research – turn to [page 96](#).

**Colorectal Cancer** Colorectal cancer kills more than 50,000 Americans each year. Find out how NCI is fighting this disease – and the screening tests that are currently available – [page 22](#).

**Surveillance** Cancer surveillance – identifying and tracking trends in our national cancer burden, and monitoring the factors that influence these changes – is a crucial underpinning of our efforts to prevent and control cancer. For example, increased surveillance efforts can help us understand and address the unequal burden of cancer experienced by certain racial and ethnic groups in America. To learn about NCI's plans for all areas of cancer surveillance research, see [page 92](#).

**Centers** Progress in cancer research is more dependent than ever on the synergy of multidisciplinary teams of investigators and on government, academia, and industry collaborations. See [page 79](#) to learn how NCI's Centers, Networks, and Consortia are linking vital resources to address important questions about human cancer.

**Imaging** “Functional imaging” allows us to monitor physiological processes (such as blood flow, oxygen consumption, or glucose metabolism) and molecular activities as they take place in the body. Turn to [page 45](#) to find out how NCI is using new cancer imaging techniques to improve cancer detection, diagnosis, and even treatment.

**Highlights of Progress** Every day, NCI's nationwide programs for supporting cancer research are yielding new discoveries, new prevention and treatment approaches, and greater hope for people with cancer and those at risk – see [page 12](#) for highlights of recent progress.

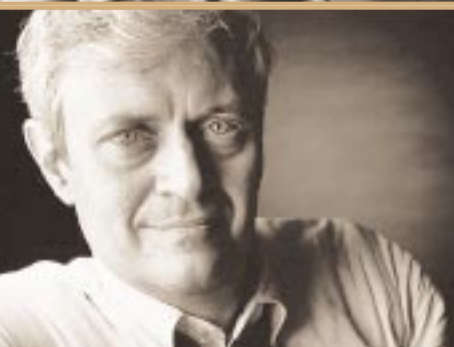
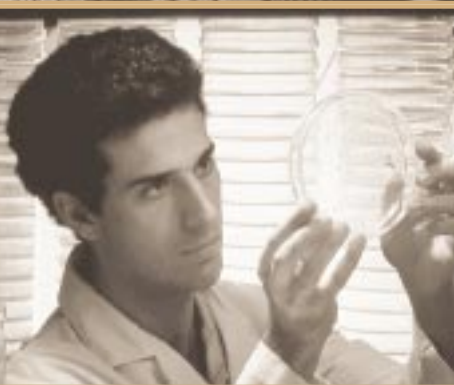
**Communications** The late-20th century revolution in communications has had a profound impact on how we convey important information about cancer detection, prevention, treatment, and risk to cancer patients and those at risk. Turn to [page 69](#) to find out how.

**Genes** How do our genes interact with environmental agents in the development of cancer? NCI-supported scientists are working to find out. See [page 38](#).

**Signatures** Scientists have learned that all cells – normal, precancerous, and cancerous – have unique molecular features, or “signatures.” Learn how we're using this knowledge to revolutionize cancer detection and diagnosis – [page 51](#).

**Clinical Trials** Our current clinical trials infrastructure is insufficient to handle the many exciting new drugs and drug combinations emerging from our Nation's laboratories. See [page 84](#) to learn about NCI's proposed National Clinical Trials Program that will pave the way for us to translate new discoveries into treatments and prevention strategies for patients.

**Tobacco** Did you know that tobacco use is directly responsible for 30 percent of all cancers, and 20 percent of deaths overall, in the United States? See [page 62](#) to learn about the NCI's planned program of basic and behavioral research on tobacco and addiction.



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*The Nation's Investment in Cancer Research*, the Bypass Budget, communicates the needs and plans of the National Cancer Institute, in accordance with the legislative mandate contained within the National Cancer Act of 1971 [Public Law 92-218, Sec. 407 (b)(9)(A)]. This request is provided directly to the President in the Fall of each year as he formulates his budget request to the Congress for the entire Federal government and more specifically for cancer research. The amount exhibited within the President's Budget may differ from the level included in this document. The Congress, through the appropriations process, is empowered to determine the final funding amount that is appropriated to the National Cancer Institute.

# Director's Message

As we stand on the threshold of the 21st century, we can marvel at how far we've come in the battle against cancer. A hundred – even fifty – years ago, cancer was a poorly understood disease that killed the great majority of people who had it. Today, we are learning more each day about how cancer arises from a single cell that behaves abnormally, dividing uncontrollably and leading, eventually, to the development of a tumor. We also are learning about the ways that genes, which direct the behavior of the cell, interact with a host of environmental agents to cause cellular malfunction and disease. This basic knowledge about the nature of cancer is providing us with critical insights into how we can prevent and detect cancer more effectively. And it is giving us the opportunity to improve treatment by enabling us to design therapies that target the machinery of the cancer cell.

Thanks in large measure to the dedication and hard work of scientists across the Nation, we are making real progress against cancer. The rate of new cancer cases has been declining and the cancer death rate falling. Powerful new technologies are permitting us to detect and diagnose cancer at an earlier stage, before it has had the chance to spread. People with cancer are living longer, and with a better quality of life, than ever before.

Truly, we are making progress, but for those who are touched by this disease, we are not making progress quickly enough. The declining incidence means little to Marisol, a mother of three, newly diagnosed with colon cancer, or to Paul, a retiree whose golden years are darkened by the specter of chronic lymphoma, or to the

parents of sixteen-month-old Andrew, who is fighting for his life against an aggressive neuroblastoma. The drop in the death rate is only an abstraction to the Corelli family, who were prematurely robbed of a loving wife and mother by her ovarian cancer, or to the classmates and friends of Minh, a college student whose life was cut short by leukemia. And although we have undoubtedly made tremendous strides in our ability to detect, diagnose, and identify people at risk for cancer, we have much to learn about what people who find themselves at increased risk should do. Just ask Rachel, who at age 31 has learned that she has a markedly increased risk of breast cancer due to an altered *BRCA1* gene, and now faces the agonizing choice of what preventive measures, if any, she is going to take to reduce her risk of this disease.

Furthermore, other recent trends threaten to overshadow our hard-won victories. The incidence of melanoma, an aggressive skin cancer, has been rising about three percent per year, although death rates have remained constant, and incidence rates for non-Hodgkin's lymphoma continue, inexplicably, to rise. In addition, adolescents are now smoking and using tobacco products – a major risk factor for lung and other cancers – at a troubling rate, which may well reverse the currently falling rates of lung cancer in coming years. Moreover, certain racial and ethnic groups continue to be disproportionately burdened by cancer.

How, then, can we continue to build on our recent accomplishments to make further much-needed progress against cancer? First, we must sustain the proven research programs that have enabled us to pursue a path of scientific excellence

and discovery in cancer research. At the National Cancer Institute (NCI), we have created an infrastructure that promotes discovery, worked with some of the most innovative and productive scientists in the Nation, and initiated ground-breaking programs that have yielded critical knowledge, improved patient care, saved lives, and improved the quality of life for many cancer survivors. We must continue to offer these programs our full measure of support.

At the same time, we cannot hesitate to seize extraordinary opportunities to further the progress brought about by our previous research successes. Three years ago, we identified four areas of investment that, if exploited, could produce dramatic progress against cancer. We have made tremendous strides in each of these areas, and our progress is highlighted in this Bypass Budget, *The Nation's Investment in Cancer Research: A Budget Proposal for Fiscal Year 2001*. In addition, we begin a new cycle of progress by identifying three additional areas of extraordinary scientific opportunity.

Finally, we must ensure that the full promise of our research findings is realized by translating our findings rapidly from the laboratory into practical solutions that will benefit everyone. We outline how this will happen in the "Challenge" section of this document for, indeed, our greatest challenge is to assure that the insights of science become advances in medicine and public health. This Bypass Budget outlines the progress we have made in this critical area and defines our plans for the future.

This document describes the budget we believe we will need to fund our research programs, as well as the support we need to train the next generation of top-flight scientists. It also details our activities in the crucial area of communicating up-to-date cancer information to patients, health professionals, and people at risk for cancer. Finally, it serves as our central planning document, laying out clearly our funding priorities and presenting our vision of the Institute's direction.

Since 1937, NCI has dedicated itself, through its scientists and its resources, to the defeat of cancer. We have made tremendous advances, but we cannot stop now. We must persevere in our work. For all of the Minhs and Marisols and Rachels and Pauls of the Nation and the world, we must persevere. Through the careful application of research and discovery, the 21st century can and will be the era in which cancer finally is conquered.

A handwritten signature in black ink, appearing to read 'Richard Klausner', with a stylized flourish at the end.

Richard D. Klausner, M.D.  
*Director*  
*National Cancer Institute*

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# Executive Summary

The National Cancer Institute (NCI) leads the Nation's fight against cancer by supporting and conducting ground-breaking research in cancer biology, causation, prevention, detection, treatment, and survivorship. Decades of work by NCI-supported scientists have produced real gains. The rate of new cancer cases declined an average of nearly one percent each year between 1990 and 1996, while the cancer death rate fell, on average, 0.6 percent per year during that same period. Powerful new technologies are enabling us to detect and diagnose more cancers at an earlier stage, before they have had the chance to spread. And many people with cancer are living longer, and with a better quality of life.

Even so, cancer continues to be a major health problem; for many Americans, it remains the most feared of diseases. In addition, the burden of cancer falls disproportionately on certain racial, ethnic and socioeconomic groups. Although we have made real and lasting progress against the disease, it is critical that we continue to push forward toward our ultimate goal – preventing and curing all forms of cancer.

To more rapidly achieve our goal, NCI has developed the following plan:

- Sustain at full measure proven, productive research programs.
- Seize extraordinary scientific opportunities made possible by our previous research discoveries.
- Create and sustain mechanisms that build the capacity to allow the scientific community to apply rapidly evolving discoveries and emerging technologies for the benefit of human health.

## **Sustain at full measure proven, productive research programs.**

In support of the entire community of cancer researchers, NCI has developed an infrastructure of mechanisms, organizations, and networks that link scientists, facilities, and information. Each year, through NCI support, the efforts of thousands of scientists yield scientific advances in all of these areas.

In addition to basic, population, and clinical research, we support investment in new research programs to address behavioral, surveillance, and communications research, as well as studies on the needs of cancer patients and survivors. We also support cancer centers, community-based clinical oncology programs, training opportunities, and communications, education, and outreach programs for both health professionals and the public.

## **Seize extraordinary scientific opportunities made possible by our previous research discoveries.**

In 1996, NCI began to systematically identify areas in which focused efforts and increased resources could help reduce the burden of cancer. Through this effort, we selected four areas of extraordinary opportunity for investment: Cancer Genetics; Imaging Technologies; Defining the Signatures of Cancer Cells; and Preclinical Models of Cancer. A plan of action addresses each of these opportunities.

This year, as we prepared to launch our “second generation” of efforts, we carefully evaluated our direction and progress in each investment area. We determined that the time is right to build on the foundations we have laid over the past three years



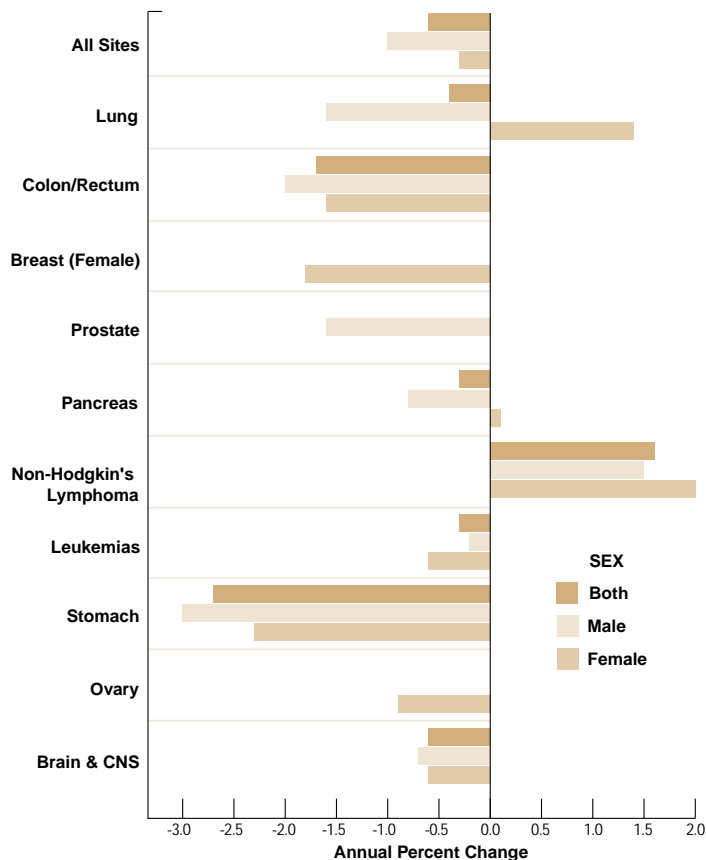
in each “opportunity area” to resolve fundamental questions about cancer and improve cancer detection, diagnosis, and treatment. From this evaluation, we also determined that we should broaden our Cancer Genetics investment area to include the complex ways in which genes interplay with the environment to affect cancer susceptibility and risk, and integrate our efforts in Preclinical Models into the other investment opportunities.

In this document, we identify three additional areas of extraordinary opportunity: Molecular Targets of Prevention and Treatment, Research on Tobacco and Tobacco-Related Cancers, and Cancer Communications. Each of these areas holds exceptional promise for advancing our knowledge of cancer and for helping patients and those at risk.

**Genes and the Environment**

The new challenge in the study of cancer causation is to apply the emerging tools of molecular genetics to understand how genes interact with an individual’s environment to cause cancer. These studies will, as a rule, involve large populations and will require new types of research mechanisms and strategies for interdisciplinary collaboration. Despite the complexities involved, this endeavor holds great promise in many ways: (1) Identifying cancer susceptibility genes with known pathways of action will point to previously unsuspected carcinogens.

**Annual Percent Change in U.S. Cancer Death Rates: Top 10 Sites 1990-1996**  
By Sex, All Ages, All Races



- (2) Studies of genetically susceptible groups will make it easier to detect small variations in risk posed by certain types of environmental exposures.
- (3) Understanding how cancer susceptibility genes interact with other genetic and environmental risk factors will result in new ways to diagnose,

prevent, and treat cancer. (4) Quantifying the cancer risks associated with susceptibility genes and environmental exposures will inform clinical and public health strategies against cancer.

### ***Cancer Imaging***

Over the last quarter century, refinements in imaging technology allow us to not only view structures anatomically, but to visualize physiological, cellular, or molecular processes as they take place in living cells of the body. Parallel developments in image enhancement agents are improving our ability to capture changes in the biochemical makeup of cells and other living structures. But despite our progress, we still have important work to do before imaging technology can be applied to its fullest potential – when it will enable physicians to precisely locate precancerous and cancerous lesions, biologically characterize a lesion to predict how it is likely to respond to a specific therapy, and directly monitor its response to treatment.

### ***Defining the Signatures of Cancer Cells: Detection and Diagnosis***

All cells have unique, identifiable signatures – specific characteristics such as genes that are active and proteins and other products that the cell manufactures. During the transformation of a normal cell to a cancer cell, the signature changes, signaling the presence of cancer. By identifying and “reading” the signatures of cells, we can detect and diagnose cancer early, before it has had a chance to spread and while it may still be easily curable. We also can use the information from a cancer cell’s signature to choose the most effective treatment, determine which cancers are likely to spread, and gain important insights into the etiology of the disease.

### ***Molecular Targets of Prevention and Treatment***

Until recently, scientists working to discover effective prevention and treatment agents have faced a formidable barrier: not knowing precisely what cancer is. No longer is this the case. With the evolution of molecular biology and the emergence of new technologies, we are gathering remarkable knowledge about the nature of a cancer cell and the molecular changes that occur during a tumor’s

development. The extraordinary opportunity before us – to discover and exploit molecular targets for cancer prevention and treatment – arises from the convergence of scientific advances in several areas. A research emphasis on molecular targets could lead to tremendous advances in prevention and treatment. Agents that target specific characteristics of a cancer cell presumably would leave normal cells alone and would be more effective and less toxic than most traditional chemotherapies. By understanding the changes, we can also develop targeted preventive drugs that can stop or even reverse those changes.

### ***Research on Tobacco and Tobacco-Related Cancers***

Tobacco-related diseases are the most preventable and costly cause of death in the Nation, claiming 450,000 lives each year. To respond to this ongoing crisis, we must comprehensively attack the problem of tobacco use – expanding our understanding of tobacco addiction, increasing our knowledge of biological mechanisms underlying tobacco-induced cancers, designing targeted approaches that prevent people of all ages from using tobacco, developing ways to prevent the onset of tobacco-related cancers in smokers and former smokers, and developing treatments for tobacco addiction and the cancers it causes. We will take full advantage of the constellation of recent scientific, public policy, social, educational, and legal advances that are providing an unparalleled opportunity to address the tobacco problem in ways that integrate biological and psychosocial models of tobacco and addiction.

### ***Cancer Communications***

Few health-related interventions have the potential of interactive health communications to improve health outcomes, decrease costs, and enhance consumer satisfaction. Indeed, effective communication is central to cancer care, from primary prevention through survivorship. Today, we are in the midst of a communications revolution. Experts are producing increasingly refined approaches to health communications, and changes in the role and accessibility of information are altering health care practices, patient-physician relationships, and the way consumers

acquire and use information. We need to refine and apply these advances to improve outcomes in cancer prevention, early detection, treatment, and survivorship.

**Create and sustain mechanisms that build the capacity to allow the scientific community to apply rapidly evolving discoveries and emerging technologies for the benefit of human health.**

We are learning more each day about the basic nature of cancer. Yet we are faced with the challenge of converting these findings into advances in cancer detection, prevention, and treatment. If the pace of discovery is like an eight-lane highway, our current ability to translate those discoveries into clinical application is like a country road. Where the two meet, a bottleneck of good ideas occurs. Our challenge is to expand the country road to an eight-lane highway that moves discoveries swiftly to their use in cancer care. Doing so means ensuring that sufficient technological resources, trained scientists, and expanded infrastructures exist, and providing the vision, creative environments, and diverse resources needed to ensure there is no delay between discovery and its application.

To respond to this challenge, we have identified six key areas for investment: (1) Investigator-Initiated Research; (2) Centers, Networks, and Consortia; (3) National Clinical Trials Program; (4) Informatics and Information Flow; (5) Studying Emerging Trends in Cancer; and (6) Training, Education, and Career Development. Increased support in these areas will enable us to strengthen our infrastructure and enable basic discovery to rapidly improve clinical practice.

***Investigator-Initiated Research***

Investigator-initiated research – research proposed and conducted by scientists in laboratories and clinics across the country and here at NCI – is the wellspring of scientific discovery. Discoveries made through investigator-initiated research are critical to reducing the cancer burden. We must create mechanisms that link basic, clinical, and population-based researchers with state-of-the-art resources and technologies, promote collaborations among researchers inside and outside of cancer research, and draw into cancer-related research

scientists from allied fields, such as chemistry, biology, physics, and mathematics. In addition, we must strive to expand our research portfolio to include a greater number of research proposals that may be somewhat riskier or highly speculative, or that pursue novel paths. We also must convert basic science discoveries into practical, affordable, and effective ways of restoring cancer patients to health and preventing cancer throughout our population.

***Centers, Networks, and Consortia***

We find increasingly that multidisciplinary teams are needed to solve the “big problems” in cancer research. It is necessary to create new kinds of functional links among scientists in diverse disciplines. We also need to ensure that these researchers have the tools and resources needed to conduct these essential studies. For these reasons, NCI must expand its Centers of Excellence and NCI-designated Cancer Centers programs and develop a variety of new research networks and consortia.

***National Clinical Trials Program***

The research investment of the past decade has brought about a dramatic increase in the number of new therapeutic and preventive agents showing enough promise to warrant testing in clinical trials. However, our present clinical trials system is failing to keep pace with these opportunities to improve cancer care. While fewer than three percent of patients with cancer participate in the clinical trials that define effective new prevention and treatment approaches, the number and complexity of trials needed to determine the therapeutic roles of the new generation of agents continues to grow. Many more patient-volunteers are needed to help establish the benefits of new agents and new combination treatments, and a sufficient infrastructure to support these studies is needed.

***Informatics and Information Flow***

The power of computer-based communications and the World Wide Web are making possible unprecedented research opportunities. Paper-based research systems are giving way rapidly to integrated systems that share information and knowledge effortlessly and enable new discoveries to be made

at the researcher's desk, not just in the lab. NCI must construct a new information architecture for the cancer research process. This Cancer Informatics Infrastructure will help speed the discovery process, translate the best discoveries into clinical trials, and transform cancer care through more effective and efficient information exchanges. By drastically reducing the time and effort required to make new discoveries or apply existing discoveries, this revolution will result in a dramatic acceleration of progress against cancer.

### ***Studying Emerging Trends in Cancer***

Appropriate decision making in science and in public health depends on accurate, reliable information about the incidence and impact of

disease. NCI uses data from the Surveillance, Epidemiology, and End Results cancer registry program to identify and study trends, track the impact of cancer on the general population, and provide information to help researchers find out why certain populations are affected by cancer more severely than others. However, recent changes in health care financing and delivery, the revolution in informatics and computer programming technology, and the social and cultural diversity of our country present new challenges and opportunities in surveillance research. We need to expand our data collection to include patterns of cancer care, as well as treatment and quality of life outcomes. In addition, new investments are required to find tools that will improve the

**TABLE 1**  
**National Cancer Institute - 2001 Bypass Budget Request** (dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Request	2001 Core and Investments Request	2001 Core, Investments & Challenge Request
Research Project Grants (RPGs):					
Ongoing	\$983,129	\$1,056,342	\$1,166,993	\$1,167,993	\$1,172,793
New (New and Renewal)	377,516	353,517	366,244	500,132	673,212
Small Business Innovation Research	57,808	60,978	63,173	72,173	83,173
Subtotal (RPG's)	1,418,453	1,470,837	1,596,410	1,737,298	1,929,239
Intramural Research	488,884	487,144	506,630	518,380	549,180
Cancer Centers	197,490	197,455	204,563	259,263	335,113
Clinical Trials Infrastructure:					
Cooperative Clinical Research	126,205	125,460	129,977	149,477	249,827
Community Clinical Oncology Program (CCOPs)	52,161	54,312	56,267	61,767	111,967
Subtotal (Trials Infrastructure)	178,366	179,772	186,244	211,244	361,794
Training and Education	112,123	117,256	122,097	134,097	173,172
Research Support Contracts	275,087	298,569	309,519	399,680	490,165
Cancer Control Management and Support	89,882	82,640	85,946	94,946	97,246
Research Management and Support	108,965	110,065	114,468	129,468	148,468
Other	26,866	29,181	32,124	50,624	50,624
<b>Total NCI</b>	<b>\$2,896,116</b>	<b>\$2,972,919</b>	<b>\$3,158,000</b>	<b>\$3,538,000</b>	<b>\$4,135,000</b>
<i>Cancer Control included above</i>	<i>\$301,259</i>	<i>\$312,719</i>	<i>\$334,278</i>	<i>\$462,778</i>	<i>\$565,578</i>

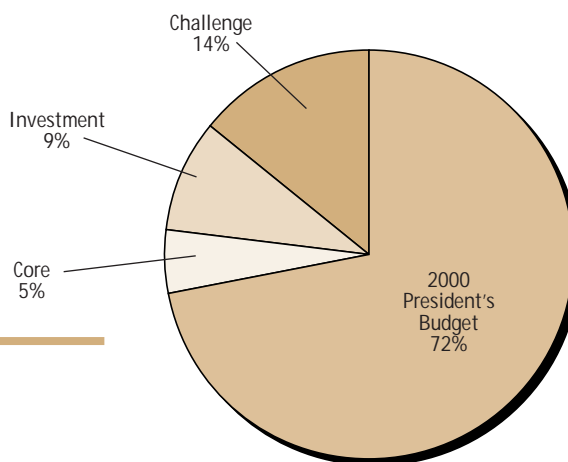
precision and expand the reach of cancer surveillance. NCI's surveillance efforts should encompass a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. Greater efforts are needed to disseminate the results of NCI's surveillance research, and, finally, we must create the training programs to prepare the next generation of surveillance researchers.

**Training, Education, and Career Development**

Currently, too few promising individuals are choosing careers in cancer research. Those who do are faced with a field of increasing complexity, yet they have decreasing amounts of time reserved from clinical and administrative responsibilities to conduct important research, mentor new scien-

tists, or obtain necessary continuing training for themselves. New ways of educating, training, and developing scientists are necessary to ensure that technology advances are integrated rapidly into the cancer research enterprise and that scientists are prepared to work together in team settings to unravel the complex factors contributing to human cancer.

To strengthen the infrastructure for discovery that supports all of our research efforts, continue progress in pursuing our Extraordinary Opportunities for Investment, and speed the flow of discovery into application, the National Cancer Institute requests the funding presented in Tables 1 and 2.



**TABLE 2**  
**2000 Base Amount with 2001 Increases**  
 (dollars in thousands)

	2000 President's Budget	2001 Core	2001 Investment	2001 Challenge	2001 Total
Research Project Grants	\$1,470,837	\$125,573	\$143,889	\$188,940	\$1,929,239
Intramural Research	487,144	19,486	11,750	30,800	549,180
Cancer Centers	197,455	7,108	54,700	75,850	335,113
Clinical Trials Infrastructure	179,772	6,472	25,000	150,550	361,794
Training and Education	117,256	4,841	12,000	39,075	173,172
Research Support Contracts	298,569	10,950	90,161	90,485	490,165
Cancer Control Management and Support	82,640	3,306	9,000	2,300	97,246
Research Management and Support	110,065	4,403	15,000	19,000	148,468
Other	29,181	2,943	18,500		50,624
<b>Total</b>	<b>\$2,972,919</b>	<b>\$185,081</b>	<b>\$380,000</b>	<b>\$ 597,000</b>	<b>\$4,135,000</b>

# Highlights of Progress

Scientific progress may sometimes seem to move forward at a frustrating pace. Because advances in basic research, prevention, and treatment are incremental, it often takes years to see the cumulative effects of our efforts on populations at risk, patient survival, and improved quality of life. Moving from an insight to a tested, successful intervention in people takes time, and there will always be a lag between our investment in developing a solid knowledge base and the payoff for a person with cancer or one at risk for the disease. Yet every day, thanks to the dedicated efforts of cancer researchers and clinicians, we are growing closer to our goal of overcoming cancer.

In these final years of the twentieth century, we have seen an explosion of progress against cancer. We have witnessed a number of important advances culminating from many years of intensive effort. We have begun to gather significant information from programs launched only two or three years ago. And with our recent funding increase, we have been able to launch innovative new programs that will have far-reaching effects into the next century. The following highlights of recent progress demonstrate how far we have come against cancer, and offer a glimpse of what is to come as we continue to build on our successes to conquer cancer in a future that is no longer so distant.

## ADVANCES IN SCIENCE AND TECHNOLOGY

### Preventing Cancer/Cancer Control

Finding effective ways to prevent cancer has long been a central focus for NCI and cancer researchers. Prevention can take many forms, from smoking cessation and other behavioral changes

to vaccines or antimicrobial agents against cancer-causing infections. Importantly, our increasing knowledge of cancer biology is enabling us to identify agents – both natural and man-made – that may prevent cancer by interfering with the biological processes underlying cancer development. In fact, more than 50 compounds currently are being investigated for their potential efficacy as cancer preventives.

Closely related to cancer prevention, cancer control encompasses research on the many diverse aspects of translating proven technologies and tested methodologies into routine practice in the community. For example, cancer control research may focus on identifying new ways to help people stop smoking, or to encourage people to adopt a healthier diet, or to communicate health risks to certain population groups. NCI's commitment to ground-breaking cancer control research is evidenced by its new Extraordinary Opportunities in Research on Tobacco and Tobacco-Related Cancers (see page 62) and Cancer Communications (see page 69).

■ In recent results from the Breast Cancer Prevention Trial, **tamoxifen**, a drug long used for breast cancer treatment, **led to a 49 percent reduction in the incidence of primary breast cancer** during the treatment period in women at high risk for the disease. This outcome marks an important landmark in this line of research. However, because tamoxifen may have serious long-term side effects, NCI recently began recruiting volunteers to participate in a **study to determine whether the drug raloxifene is as effective in reducing breast cancer risk as tamoxifen**, but with fewer undesirable side effects. The Study of Tamoxifen and Raloxifene (STAR) will compare the effectiveness and the long-term safety of these two medications in women at increased risk for breast cancer.

- Some women who are at high risk of breast cancer make the difficult decision to have both breasts surgically removed, a procedure known as **bilateral prophylactic mastectomy (PM)**. In a recent retrospective study of 639 women with a family history of breast cancer who had undergone the procedure, **PM was associated with a 90 percent reduction in the incidence of breast cancer**. And in another study, **prophylactic oophorectomy** – surgical removal of the ovaries – **was found to reduce breast cancer risk by about 40 percent** for women with cancer-predisposing *BRCA1* mutations.
- The sale of cigars in the U.S. has been increasing since 1993, but until recently little was known about their health effects. However, researchers have found that compared with nonsmokers, **cigar smokers were at increased risk of lung and upper aerodigestive tract cancer**, as well as heart and lung disease. These important findings highlight the need for prevention efforts aimed at cigar smokers.
- Because tobacco use is responsible for over 30 percent of all cancers, research on more effective **smoking prevention and cessation approaches** is a cornerstone of the Institute's cancer control efforts. Two recent studies have added to our knowledge. In one, researchers found that the passage of a **comprehensive ordinance ensuring merchant compliance with tobacco age-of-sale laws** in seven communities significantly reduced daily smoking among eighth, ninth, and tenth graders, compared to communities without such an ordinance. In the other, **women who participated in an exercise program** concurrently with a behavioral smoking cessation program had a **higher success rate** than women who underwent the behavioral program but did not exercise. In addition, women in the exercise program had gained less weight by the end of the program.

## Detecting Cancer

New technologies that will enable us to detect and diagnose cancer early, before it has had the chance to spread, are on the horizon. Imaging devices and modalities are being developed and tested that allow us to visualize the cell with greater precision than ever before (see page 45). In addition, new methods of reading the signatures of cells (see page 51) are enabling us to identify the subtle differences between normal and cancer cells, and are leading us to the day when only a simple blood test is needed to detect cancer anywhere in the body.

- Current methods for the non-invasive detection of small tumors are limited in their ability to distinguish small areas of abnormal cells from larger surrounding areas of normal tissue. Researchers have developed a new method to more precisely image tumor cells. They injected tumor-bearing mice with a unique imaging agent composed of near-infrared fluorescence imaging probes coupled with a novel copolymer that moves efficiently into tumor cells. When the agent was absorbed into the cancer cells, enzymes within the cells “activated” the agent and caused it to fluoresce. The fluorescence could then be detected non-invasively. The agent was not activated in non-tumor cells. Using this technique, investigators were able to image tumors smaller than three-tenths of a millimeter in diameter. Although this technique is in the early stages of development, it shows great promise for the detection of very small tumors.

## Treatment Advances

As recently as thirty years ago, when legislation launched the National Cancer Program, the idea of curing cancer seemed a remote ideal. This ideal is now a reality for a growing number of cancers and within our grasp for many others. Today, using insights gleaned from discoveries about cancer biology, we are learning to tailor treatments for a specific cancer in a specific individual, to optimize the effectiveness of traditional treatments, and to target treatments to the cellular machinery of specific tumors. Our great hope is that targeted treatments will prove to be more effective and less toxic than our current approaches.

- An exciting approach to cancer treatment is **immunotherapy**, or treatments in which the patient's own immune system is coaxed to recognize and eradicate cancer cells. One targeted immunotherapeutic approach that recently has met with exciting success involves the use of **monoclonal antibodies**, proteins derived from cells found in the body's own immune system, that attach to the surfaces of cancer cells and deliver a deadly substance directly to them. Based on clinical trial results, two monoclonal antibodies recently have been approved for use in cancer treatment: Rituxan® for B-cell lymphoma, and Herceptin® for metastatic breast cancer. Clinical trials are underway to determine whether these agents may be used or enhanced to combat other types of cancer. Another type of immunotherapy involves **cancer treatment vaccines**. NCI is sponsoring more than 70 vaccine therapy trials, including studies on using vaccines to treat melanoma and cancers of the breast, prostate, cervix, kidney, pancreas, and ovary.
- Another evolving treatment approach targets the process of angiogenesis. Presently, about 20 **angiogenesis inhibitors** – agents that block the development of tumor-nourishing new blood vessels – are being tested in human trials, and others showing promise in animal studies will soon enter human trials. For example, the drug **thalidomide**, long banned from medical practice for causing severe birth defects in chil-

dren born to mothers who took the drug during pregnancy, has been shown to be a potent angiogenesis inhibitor. In a small trial of prostate cancer patients, thalidomide caused a decline in the biomarker PSA in 68 percent of the patients – an indicator that **thalidomide could be effective against prostate cancer**. In a separate study, thalidomide was shown to induce **tumor shrinkage in 45 to 50 percent of patients with AIDS-related Kaposi's sarcoma**.

- Our success in treating childhood cancers, particularly leukemia, was the first proof that cancer could be treated and cured. Years of trials focused on improving chemotherapies for children with acute lymphocytic leukemia (ALL) resulted in our current ability to cure 75 to 80 percent of children diagnosed with this disease. For 20 percent of children with ALL, however, our treatments were ineffective and the children fared poorly. **Results of a new trial using a modified chemotherapy regimen have shown a 70 percent drop in the rate of treatment failure** in these high-risk children.
- Five clinical trials involving women with locally and regionally advanced cervical cancer showed that when cisplatin-based chemotherapy was given concurrently with radiation therapy, **the risk of cervical cancer death was reduced by 30 percent**. Based on these definitive results, NCI strongly urges that physicians consider adding chemotherapy to the treatment of women who require radiation therapy for cervical cancer.
- Results from clinical trials under the long-running National Surgical Breast and Bowel Project show that adding tamoxifen to lumpectomy and radiotherapy in women with ductal carcinoma *in situ* (DCIS) reduces the risk of subsequent invasive breast cancer. Taken together with results of an earlier trial, these findings suggest that **lumpectomy, breast irradiation, and tamoxifen can safely substitute for mastectomy in the treatment of DCIS**. In addition, women with DCIS treated with lumpectomy alone have a significantly increased risk of eventually developing breast cancer, and thus should be considered a high-



risk group that merits consideration for preventive treatment with tamoxifen.

- **3-Dimensional Conformal Radiation Therapy (3DCRT)** is a new approach that employs sophisticated computer technology to fit the treatment field more tightly to the tumor, in three dimensions, than was possible using conventional techniques. Researchers used 3DCRT to treat patients with advanced prostate cancer and found that they could safely give **higher doses of radiation to the tumor and increase the probability of local tumor control**. Using an advanced form of 3DCRT, Intensity-Modulated Radiotherapy, **significantly decreased treatment complications** among the same group of men.

## Understanding Cancer and its Causes

With the knowledge that cancer is a genetic disease, we now look to our genes for clues about how the disease develops and progresses in the body. As a first step in this search, we are working to identify the mutated genes that give rise to cancer. A second – and equally important – step is to determine how these genetic changes contribute to cancer.

- Newly developed technologies now enable us to develop **mouse models of human cancers** by altering or inactivating mouse genes and introducing into mice the same mutations that occur in humans. Using such models, cancer researchers recently identified a gene, *Smad3*, that plays a role in the development of colorectal tumors. Researchers also elucidated the role of the normally functioning *PTEN* gene, whose mutated form is found in a large percentage of prostate, brain, breast, endometrial, skin, and kidney tumors. These discoveries will pave the way for further study of the biological changes that underlie cancer, and may even lead to new preventive or treatment interventions.
- As noted above, a number of angiogenesis inhibitors are now being tested in clinical trials. This is a result of our successful efforts to untangle the mysteries of cancer biology, and

the subsequent growth of our understanding of **angiogenesis**. The prevailing view holds that most tumors originate without blood vessels, and only induce angiogenesis once they grow to a specific size. Important new evidence suggests, however, that some tumors initially coopt existing vessels to form a well-vascularized tumor, but the coopted vessels quickly regress and the tumor loses many of its cells. Ultimately, the remaining cells are rescued by angiogenesis – through the collaboration of the angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) proteins – and the tumor continues to grow. These findings suggest that inhibiting VEGF, a powerful angiogenesis stimulator, can impede tumor growth by preventing this process and perhaps promoting the regression of fragile new tumor vessels. And Ang-2, apparently the earliest marker of blood vessels disturbed by tumor cells, may prove useful for early detection and as a treatment target.

- Newly developed tools are helping scientists perform large-scale analyses of the vast human genome to genetically characterize tumors, information that can help to explain why patients diagnosed with the same cancer differ dramatically in their responses to treatment, and in their prognoses. For example, the **Lymphochip**, a computer chip-like device with DNA from more than 15,000 genes important to both the immune system and lymphoid cancers, is enabling researchers to study the genes active in non-Hodgkin's lymphoma, a cancer rising in incidence. The lymphochip promises to be a useful tool for detecting lymphomas early, analyzing risk, and selecting targeted treatments. A similar device, an affinity-based biochip, was developed by NCI and FDA investigators to generate **biomarker profiles of normal, precancerous, cancer, and metastatic cells from esophageal, prostate, colon, and liver tissues**. Biomarker pattern profiles reveal changes in protein expression as tissue cells transition from normal, to premalignant, to invasive cancer; this new technology could be extremely useful in the discovery of disease-

related proteins, therapeutic assessment, and treatment toxicity monitoring.

- Our research on cancer also has revealed that elements in our environment play a significant role in cancer's development. Tobacco use, for example, accounts for about one third of cancer deaths in this country. Recently, several groups of scientists found intriguing evidence of a **possible genetic predisposition for smoking**, accounting for some peoples' inclination to smoke or inability to stop. Greater knowledge of how these genes influence smoking promises to provide important clues about how some people become addicted to nicotine, and how we can effectively help smokers stop smoking.

## CHARTING OUR FUTURE

NCI's mission to conquer cancer – to reduce and finally remove the burden of this disease on present and future generations – is the driving force behind the Institute's diverse research programs and activities. Planning for a future free from the fear of cancer requires that we leverage the value of our growing body of knowledge about cancer, and that we challenge the research community to go beyond its customary practices to achieve our ultimate objective. We must develop initiatives, programs, and new partnerships to most effectively use new discoveries, exploit scientific opportunities, and apply emerging technologies to prevent, detect, treat, and control cancer.

NCI has spent much time and effort developing and supporting an infrastructure that sustains the research programs that today are enabling us to pursue a path of scientific excellence and discovery in cancer research. In tandem, we have established a tradition of seeking better ways to inform the process of identifying needs and opportunities in the cancer field, setting priorities, and implementing decisions and recommendations that lead to new or improved research initiatives and programs.

- NCI recently assembled **Progress Review Groups** composed of researchers, health professionals, industry representatives, and lay advo-

ates to assess the state of our knowledge, identify scientific opportunity and need, and chart a course for future study in two high priority research areas: prostate cancer and breast cancer. NCI now is using the Groups' recommendations to help set a national research agenda in these areas. A colorectal cancer PRG is planned for this year.

- **Working Groups and Implementation Groups** also play a critical role in charting the course of research. For example, one such group, the **Tobacco Research Implementation Group (TRIG)**, was charged with establishing NCI's tobacco-related cancer research priorities for the next five to seven years. Another group, the **Surveillance Implementation Group (SIG)**, was charged with identifying priority cancer surveillance research areas and optimal strategies for using surveillance measures to advance our knowledge of cancer.
- NCI also has engaged groups of experts outside the Institute to perform **in-depth evaluations of various programs within the Institute** and recommend ways to enhance the structure and function of the programs under study. For example, a **recent review of the Developmental Therapeutics Program (DTP)**, NCI's organizational focal point for new cancer treatment development, highlighted the need for DTP to respond to the needs of rapidly changing science and technology. The review group emphasized that new basic knowledge and technologies must be integrated into the process of discovering and developing anti-cancer drugs to allow DTP to meet the challenge of drug development in the next decade. In addition, recommendations from a **review of the clinical trials program** resulted in a recently launched restructuring of our treatment clinical trials program. In this first major system reform in forty years, we hope to ensure the best science, improve physician and patient access to trials, and enhance program efficiency and effectiveness.

## FOUNDATIONS FOR FUTURE DISCOVERY

To conquer cancer, NCI must not only pursue new knowledge, but ensure that we have the **trained scientists, the technologies, and the necessary infrastructures** poised to take our considerable knowledge about cancer and apply it to reduce the burden of suffering it causes. These are the foundations for discovery that support our continued successes, and they must be continually evaluated, strengthened, and expanded to enable us to fully seize opportunities for progress. Important components of our foundations for discovery were launched or enhanced this year.

- The **Cancer Genome Anatomy Project (CGAP)** was established by NCI two years ago to systematically identify the gene expression patterns that characterize human cancer. We have made important progress in this project. For example, we have catalogued approximately 70,000 genes that are expressed in cancers and their precursors; of these, about 30,000 are previously unknown genes.
- Through the **Director's Challenge: Toward a Molecular Classification of Tumors**, NCI is challenging the scientific community to pursue research harnessing the power of molecular analysis to create a system for classifying tumors according to their molecular profiles. This "Director's Challenge" is intended to lay the groundwork, over a five year period, for changing our tumor classification system from one based on visual characteristics to one based on molecular characteristics. This information will fundamentally change our approach to diagnosing cancer, to choosing cancer therapy, and to predicting a patient's outcome.
- Over the past two years, CGAP also has enabled the discovery of hundreds of potential markers for cancer, bringing us closer to the possibility of sensitive, accurate, and predictive tests for early cancer detection. With new funds received this year, the Institute has established the **Early Detection Research Network (EDRN)**, a national scientific consortium of academic and industrial researchers who will work toward rapidly developing and testing such markers for cancer. Ultimately, this research is expected to yield simple tests for detecting all types of cancers that can be performed on easily sampled body fluids.
- To ensure that we not only fill but expand the pipeline to new cancer prevention and treatment approaches, NCI recently initiated the **Rapid Access to Intervention Development (RAID)** program. Through this program, we will be able to identify promising proposals and fund the rapid movement of new therapeutic reagents from the laboratory to the clinic. Because of its initial success, we have decided to expand RAID and to launch **RAPID**, a program offering the same process for potential preventive agents.
- Americans increasingly are turning to complementary and alternative medicine (CAM) for treatment and supportive care of numerous diseases and conditions, including cancer. In response to this growing trend, NCI has established the **Office of Cancer Complementary and Alternative Medicine**, which seeks to promote and support research in the various disciplines and modalities associated with CAM as they relate to cancer diagnosis, prevention, and treatment and the management of cancer patients.
- Because cancer strikes certain racial and ethnic minority groups disproportionately, NCI recently launched the **Special Populations Networks for Cancer Awareness Research and Training**. The Networks will fund a diverse group of research projects aimed at improving cancer prevention and control in minority and underserved communities. Principal goals of the new Networks will be to develop and maintain partnerships between scientific researchers and community leaders in an expanded range of minority and underserved populations, develop and test community cancer awareness activities, support minority enrollment in clinical trials, and encourage minority scientists to participate in cancer research. Initial awards under the program will be made in March 2000.

# The National Cancer Institute's Role in Cancer Research

The National Cancer Institute (NCI) is charged to lead our Nation's research effort to conquer this disease in all its forms. As the Federal focal point for cancer research in this country, NCI conducts, coordinates, and funds cancer research, and provides vision and leadership for the cancer research community. Each day, across the United States and around the world, thousands of NCI-funded researchers and clinicians are joined together by a common goal – they are working toward a day when cancers are an uncommon and easily treatable set of diseases.

NCI supports this vital work through research programs that seek answers to the many remaining questions about how best to prevent and treat cancer. Pursuing these answers can take one of two interrelated and complementary paths – studying the cancer cell itself to uncover biological processes broadly applicable to all cancers, or studying one of the more than 100 specific types of cancer. Though these research approaches appear to be divergent, they are inextricably linked, and in fact, most fruitful when there is extensive interplay and cross-fertilization between them. As we develop an understanding of biological processes common to many tumor types, we gain new knowledge that can be applied to cancer-specific research, and as we make discoveries about a specific cancer, new questions about themes common to all cancers are prompted.

Research on common biological processes, broadly applicable research, focuses on uncovering features that are common to all normal, precancerous, and cancerous cells. Basic research has taught us that one or more cellular mechanisms – cell growth, cell death, invasion, metastasis, avoidance of immune system attacks, and the accumula-

tion of genetic changes that lead to cancer – are, in different combinations, responsible for most cancers. In addition to providing us with new insights into mechanisms common to cancer cells, basic research helps us to better distinguish one cancer from another based on molecular characteristics. Distinguishing cancers according to their molecular characteristics is becoming as important as the traditional way of defining a cancer by the site in which it arose.

Basic research is not abstract; rather, it is the generation of essential knowledge that can be applied directly to each specific type of cancer that people experience. For example, scientists studying the process of angiogenesis, the formation of new blood vessels that tumor cells exploit to gain nutrients and growth factors, identified several potential anti-angiogenesis agents. The discovery of these agents, which may prove effective in combating a variety of human cancers, might not have occurred without broad research into the basic biological processes common to all cancers.

Disease-specific research is aimed at uncovering the biological characteristics that are unique to each specific cancer, such as breast or prostate cancer. Here the goals are to design effective methods of preventing, detecting, diagnosing, and treating the cancer, and to address disease-specific survivorship issues. Disease-specific research also yields information that applies to many diverse cancers. For example, researchers studying the very rare childhood cancer of the eye called retinoblastoma discovered a gene, *Rb*, that when altered is the trigger that leads to retinoblastoma development. Scientists continued to study *Rb* and discovered the interconnected molecular machinery of a cellular circuit called the *Rb* pathway.

This pathway is found in all cells, not just those that give rise to retinoblastoma, and at least one component of the *Rb* pathway is altered in every human cancer. Thus, a discovery unique to retinoblastoma eventually led to an understanding of a pathway that is found in all cells.

Our efforts to answer the key questions of cancer research through either broadly applicable research or disease-specific research involves four classes of investigation – laboratory, clinical, population, and translational. Laboratory research focuses on the biology of cancer, the fundamental properties of cancer-causing agents and processes, and the body's defense against and response to cancer. In the clinic, research is carried out on cancer prevention, diagnosis, treatment, and rehabilitation. Population research focuses on the causes, risks, predisposition, incidence, and behavioral aspects of cancer. Finally, translational research builds bridges and intersections between and among the classes of research. It facilitates the movement of discoveries from laboratory and population research into the clinic and, conversely, provides a way for clinical insights to help direct laboratory and population-based research. This flow of information among the laboratory, the clinic, and the community helps to drive research in new directions.

How do we know what questions to pursue in these four classes of research, be they broadly applicable or disease-specific? The keys to establishing this scientific direction are our planning and priority-setting processes; program review, progress review, and implementation efforts; and

input we receive from our advisory groups and the community.

## PLANNING AND PRIORITY SETTING

Planning – identifying needs and opportunities, setting priorities, implementing decisions and recommendations, and making sure that a reliable infrastructure supports all of our initiatives – is an integral part of all NCI activities. Setting NCI's funding priorities is a complex and dynamic process driven by several principles. We must support the full range of research activities necessary to conquer cancer; therefore, we strive for a balanced portfolio of research in behavior, epidemiology, control, prevention, detection, diagnosis, and treatment, as well as survivorship, rehabilitation, and end of life issues. This balance must include attention to the spectrum of distinct diseases we collectively refer to as cancer and the various populations that experience these diseases differently. We must not only balance these pieces of the cancer research enter-

prise but link them through translational research. In addition, we must rely on our diverse constituencies to help us identify new opportunities, gaps, and barriers to progress, and to help us create new programs and improve existing ones.

### Program Reviews

NCI supports research through a variety of mechanisms, many of which provide funds tailored to specific research processes. As part of an ongoing process of review and revitalization, NCI has instituted a series of external reviews to guide us

Program Review reports can be found at <http://deainfo.nci.nih.gov/advisory/boards.htm>

in strengthening our major research support programs. In the past few years, we have completed in-depth reviews of several programs: Cancer Centers, Cancer Control, Clinical Trials, Cancer Prevention, and the Developmental Therapeutics Program.

### Progress Reviews

One way NCI seeks the advice of experts is through Progress Review Groups (PRGs) composed of prominent members of the scientific, medical, and advocacy communities who know the state of the science intimately and can provide a thoughtful, considered assessment of our portfolio and recommend activities that will speed our progress. The overall goal of the PRGs is to provide recommendations for a national cancer research agenda. PRGs meet regularly over a period of months to review an NCI-prepared analysis of the Institute's current research program, review recommendations from the research and advocacy communities, define and prioritize unaddressed scientific opportunities that should be pursued, and to develop a plan of action for the research area.

In the past year, PRGs in Breast and Prostate Cancer completed their assessments of our research programs and we have begun considering and implementing their recommendations. A PRG in Colorectal Cancer is planned for 1999.

### Implementing Recommendations

Program reviews, progress reviews, and other assessment and advisory activities conducted at NCI generate not only insights, but also recommendations concerning how best to organize a program or pursue a field of research. Implementing these recommendations is key to successful planning, as planning alone does not bring about change. To implement changes, we have formed groups of outside scientists and NCI staff that grapple with the redesign of programs and development of new initiatives that are rec-

ommended by the Program Review Groups, Progress Review Groups, and extraordinary opportunity Working Groups. Ongoing Implementation Groups include those focused on Clinical Trials, Prevention, Surveillance, Diagnostics, Tobacco Research, and Early Detection.

## SEEKING ADVICE

To ensure the wise use of resources to meet the goals of the National Cancer Program, NCI actively seeks out expert advice from a variety of advisory bodies both within and outside the Institute.

The Breast  
Cancer Progress  
Review report  
can be found at:  
<http://www.wosp.nci.nih.gov/planning/prg/bprgtableofcontents.htm>

### National Cancer Advisory Board

NCI's principal advisory body is the Presidentially appointed National Cancer Advisory Board (NCAB). The NCAB, with a membership including scientific experts and advocates, advises NCI's Director on issues related to the entire National Cancer Program and provides a second level of review for grant applications referred to NCI.

### Board of Scientific Counselors

The Board of Scientific Counselors (BSC) advises the Institute leadership on the progress and future direction of NCI's Intramural Research Program. These scientific experts from outside NCI, along with consumer advocacy community representatives evaluate the performance and productivity of NCI staff scientists through periodic site visits to intramural laboratories, and evaluate and advise on the course of each Division's programs.

The Prostate  
Cancer Progress  
Review report  
can be  
found at:  
<http://www.wosp.nci.nih.gov/planning/prg/toc.htm>

### Board of Scientific Advisors

With the BSC, the Board of Scientific Advisors (BSA) represents the scientific community's voice in the science NCI conducts and supports. The BSA, composed of distinguished scientists from outside NCI and representatives from the consumer advocacy community, advises the NCI leadership on the progress and

future direction of the Institute's Extramural Research Program. The BSA evaluates Institute-awarded grants, cooperative agreements, and contracts, and reviews ideas for new research solicitations to ensure that the concepts are meritorious and consistent with the Institute's goals.

### NCI Executive Committee

The NCI Executive Committee, which includes NCI Division directors and other key advisors to the Director, meets regularly to make major policy and operating decisions for the Institute.

### Director's Consumer Liaison Group

Established in 1997, this first all-consumer advocate advisory committee at NCI consists of 15 consumer advocates who represent the diverse face of consumer advocacy across the U.S. Its purposes are to:

- Serve as a primary forum for discussing issues and concerns and exchanging viewpoints important to the broad development of NCI program and research priorities.
- Help develop and establish processes, mechanisms, and criteria for identifying appropriate consumer advocates to serve on NCI program and policy committees.
- Establish and maintain strong collaborations between NCI and the advocacy community.

### Community Input

Input from the community is very important to NCI. So that we can better understand the needs of cancer patients, those at risk for cancer, and interested parties in the lay community, NCI established the **Office of Liaison Activities (OLA)**. As NCI's public liaison office, OLA fosters and enhances communication with this community and addresses the concerns of Congress and the community about how NCI sets research priorities. OLA maintains ongoing communications and information exchange between the national cancer advocacy organizations and NCI,

encourages input and feedback from these organizations, and cooperates and collaborates with these groups in areas of mutual interest. The Office supports the Division of Extramural Activities in expanding representation of consumer advocates on NCI peer review panels and coordinates and supports the Director's Consumer Liaison Group. OLA also builds relationships with professional societies and other Federal agencies, and provides input and perspective to NCI on complex issues relevant to cancer patients and the public.

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## The Consumer Advocate's Role at NCI

Our work aims to support people with cancer, their families, their friends, and those at risk for developing the disease. We recognize this diverse community of people affected by cancer as key stakeholders in our quest to conquer the disease, and we are including those who represent the voices of this community – consumer advocates – in virtually all levels of NCI's decision making processes. Consumer advocates as members of NCI advisory committees and planning/oversight groups, play a vital role in program planning and implementation and help to set priorities and research agendas.

These advocates, often cancer survivors, provide the patient's view on a wide range of issues including those of special concern to minority and medically underserved populations. In addition, they often are advocate leaders who have a broad view of the cancer problem and are versed in the science. In 1999, NCI consumer advocates participated in the review of grant and contract applications and in site visits and review committees. They also provided ideas and recommendations for developing and disseminating templates for new, easier to understand informed consent documents.

NCI's Director's Consumer Liaison Group and our other consumer participation efforts, both coordinated through our Office of Liaison Activities, have served as models for the National Institutes of Health (NIH) community.

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## People's Story

# Colorectal Cancer

**I turned 50 this year. There's no history of colorectal cancer in my family, but my doctor said it's time to begin screening for the disease. Frankly, I found the idea of it embarrassing and, well...disgusting.**

Almost 130,000 people will be diagnosed with cancer of the colon or rectum this year, and some 56,000 will lose their lives to these cancers. Ninety percent of cases occur in people older than age 50, but colorectal cancer can occur at any age. Women and men are affected equally. Though mortality rates have been declining slowly over the past 20 years, colorectal cancer is the second leading cause of cancer death in America. Up to 90 percent of colorectal cancer deaths could be avoided, but sadly, people avoid the

available screening tests. Screening detects early cancers and the intestinal growths called polyps that can become cancerous. When detected at an early stage, colorectal cancer is highly curable.

**My friends who'd been screened had war stories to tell, but I decided this was too important to put off. So I did it – I went for my colon cancer screening.**

Colonoscopy is the standard for screening. However, advances in imaging may soon make colonoscopy for initial screening unnecessary. "Virtual" colonoscopy combines imaging and computer technologies to produce a three-dimensional image of the entire colon. At this point in its development, virtual

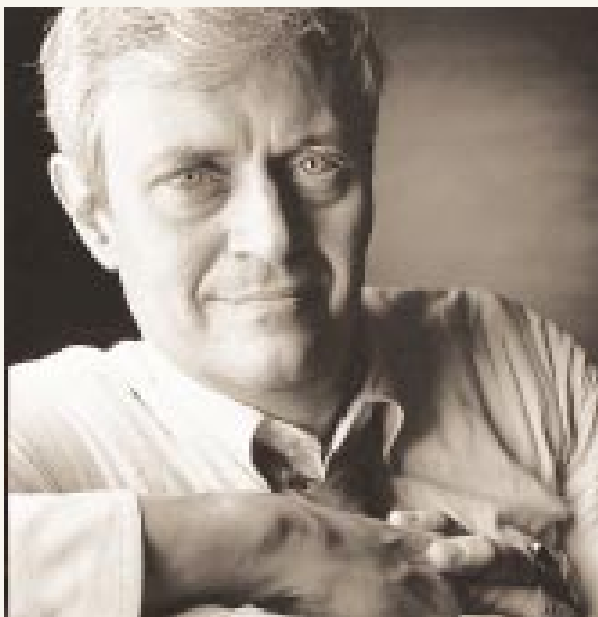
colonoscopy is still not accurate enough for use in routine screening, but it is hoped that continued advances in the required scanning and computer technologies will soon make this possible.

Knowing that many people hesitate to undergo screening, research is underway to find quicker,

non-invasive ways of detecting colorectal cancer at its earliest stages. For example, researchers are developing stool sampling methods able to detect genetic changes that signal the presence of cancer. The *p53* tumor suppressor gene and *K-ras* cancer gene are known to be altered in many colorectal cancers and can be detected in stool. Other genes have been discovered that identify people with an hereditary or other high risk of colon cancer; these individuals need especially close monitoring for early signs of cancer.

**My doctor also explained the risk factors for colorectal cancer and what a person can do to reduce the risk of getting it.**

Risk factors for colorectal cancer include a strong family history of colorectal cancer or polyps (in a first-degree relative – that is, parent or sibling – younger than age 60 or in two first-degree relatives of any age); a personal history of colorectal cancer, polyps, or chronic inflammatory bowel disease; or a family with an hereditary colorectal cancer syndrome (e.g., familial adenomatous polyposis, hereditary non-polyposis colorectal cancer). If a person has any of these known risk factors for colorectal cancer, screening should be considered earlier than age 50. Genetic tests are available to identify family members with an inherited predisposition to the disease. Since nine out of ten cases of colorectal cancers occur in those older than 50, aging also is considered a risk factor for the disease. Smoking and





frequent consumption of alcohol and red meat are associated with a higher colorectal cancer risk.

Eating a diet high in fruits and vegetables and regular moderate exercise may reduce risk. Aspirin use and hormone replacement therapy for women after menopause each may reduce colorectal cancer risk. Though it is too soon to recommend that people take supplements to prevent colorectal cancer, limited research suggests possible risk-reducing benefits of folic acid, vitamin E, selenium, and calcium supplements, as well as a diet containing low-fat dairy products. No one should begin taking aspirin or supplements to prevent colorectal cancer without consulting a doctor first.

**There are certain symptoms that may mean colorectal cancer.**

Symptoms, especially in people over age 40, include a change in bowel habits (constipation, diarrhea, black or pencil-thin stools) that lasts more than a few days; a feeling that you need to have a bowel movement that doesn't go away after you do; rectal bleeding or blood in stool; cramping or gnawing stomach pain; decreased appetite; weakness and fatigue; and jaundice (yellowing of the skin or white part of the eye). Symptoms don't mean you have cancer, but seeing a doctor is the only way to be sure. Since a person also can have no symptoms but still have colorectal cancer, the importance of regular screening cannot be overstressed.

## Colorectal Cancer Screening Tests

- *Fecal Occult Blood Test (FOBT)* – The patient applies samples from three separate stools on consecutive days to a card. The card is sent to a laboratory to check for any traces of blood. Many colorectal cancers cause minor bleeding that would otherwise go unnoticed. Annual or biennial FOBT screening has been proven to decrease the risk of dying from colorectal cancer.
- *Flexible Sigmoidoscopy* – A lighted scope is inserted as far as the lower third of the colon to check for growths, cancer, and inflammation. Performed in a doctor's office, the test takes about 10 minutes following bowel cleansing. While it is 90 percent accurate, it does not examine the entire colon.
- *Colonoscopy* – A lighted scope is used to visually examine the entire colon. Usually performed on a hospital outpatient basis, colonoscopy takes about 20 minutes after bowel cleansing. Any polyps found can be removed during the test. This test is highly accurate.
- *Double Contrast Barium Enema* – An x-ray of the colon is taken following administration of an enema containing barium sulfate and expansion of the colon with air; these two measures enhance the quality of the x-ray image.
- *Digital Rectal Examination* – A doctor manually checks the lower part of the rectum. This test is used to detect rectal and anal cancer.

To raise awareness that screening saves lives, NCI, the Centers for Disease Prevention and Control, and the Health Care Financing Administration have launched a public education campaign called *Screen for Life*.

**I understand that colorectal cancer treatments are improving, but I'm going to keep up the screening and do everything else I can to prevent it.**

For people who do get colorectal cancer, treatment and related care that enhances quality of life are improving. Thanks to surgical advances, fewer patients now need permanent colostomies (a bag outside the body to hold waste after colorectal cancer surgery). Chemotherapy for colorectal cancer has improved; new agents and new drug combinations are now available.

For patients whose cancer has spread, chemotherapy can be given directly into the artery that feeds the liver – this may stop further spread of the disease in the liver and increase survival for some patients. Other exciting treatments now in early clinical trials include gene therapies designed to deliver normal *p53* genes into colorectal tumors and halt their growth, and several approaches to boosting the patient's immune system to better fight colorectal cancer.

*This vignette is a composite of experiences.*

# How We Work

The national cancer research program represents our Nation's commitment to progress against cancer through science. Science cannot thrive – indeed, it cannot even take place – without the resources that support an enterprise of discovery. The engine that drives progress is the creativity, commitment, and hard work of researchers and clinicians whose discoveries and ideas are tested to find ways to understand, prevent, detect, diagnose, and treat cancer and to care for the people who have cancer, have survived it, or are at risk.

## SUPPORTING OUR RESEARCH

In support of the community of cancer researchers, NCI has built an infrastructure, or framework, of support mechanisms, organizations, and networks that link scientists, facilities, and information. It is this infrastructure that NCI's budget supports.

### Extramural Research

NCI's Extramural Research Program serves as our link to the greater scientific community and includes the Divisions of Cancer Biology, Cancer Treatment and Diagnosis, Cancer Prevention, and Cancer Control and Population Sciences. An essential component of the Extramural Research Program is NCI program staff. Their scientific expertise in cancer-related fields and national focus in a given research area enables them to work effectively with NCI-funded scientists in academia and industry to facilitate research progress. They synthesize the state of the science in important areas, identify priorities for new research directions, foster collaborations among scientists, keep abreast of the research program through active communication with investigators,

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## How We Spend Our Budget

- About 73% of our budget supports basic and clinical studies conducted by researchers and clinicians across the Nation through our Extramural Research Program.
  - We spend about 16% of our budget on our Intramural Research Program, in which NCI's own scientists conduct cancer-related research.
  - About 4% of our budget is devoted to training, education, and career development of researchers and clinicians at every stage of their careers.
  - We use about 3% of our budget to communicate the latest information about cancer risk, detection, prevention, treatment, rehabilitation, and control to people with cancer, health professionals, and the general public.
  - About 4% of our budget supports the administration and management of the Institute.
- 

organize scientific meetings to promote the interchange of information among investigators, and secure supplemental funds as deemed meritorious. Program staff are a resource for researchers, educating them on NCI policies and procedures, advising scientists new to the NCI system on the preparation of research grant applications, and reviewing and identifying gaps in our research portfolio that may lead to new areas of research emphasis. Finally, program staff monitor the progress of extramural grants through contact with individual investigators and annual research progress reports. Results of these NCI-funded projects are communicated to the scientific community and the public primarily through peer reviewed scientific journals, but also through major scientific meetings, workshops, and symposia, and through our other cancer communication outlets,

such as the Cancer Information Service, the Physician Data Query database, our press office, and our Web site.

### Research Project Grants

The main pool of funds expended by NCI for awards to extramural scientists is known as the Research Project Grant (RPG) pool. These funds foster the creativity of talented scientists by providing them with the freedom to pursue the best ideas that will yield progress against cancer.

NCI funds two main types of research project grants: **Single Research Project Grants**, awarded to institutions on behalf of individual principal investigators, and **Program Project Grants**, funded to foster collaborations among groups of scientists involved in related research projects. In FY 2000, NCI anticipates expending more than \$1.4 billion in support of over 4,300 separate research grants. More than 1,150 of these awards

A complete listing and description of NCI's grant mechanisms can be found at <http://deainfo.nci.nih.gov/flash/awards.htm>

will be new or competing renewal projects. The single investigator grant payline rose from the 15th percentile in FY 1995 to the 24th percentile in FY 1999. These grant awards and the dedicated researchers behind them constitute the largest single categorical investment of resources that NCI, through the extramural research community, makes annually to combat cancer. Collectively, the Single Research Project and Program Project Grants span the full range of basic, clinical, population-based, and translational studies of cancer etiology, biology, prevention, detection, diagnosis, treatment, control, and survivorship. The advances that come from these investments, such as the discovery and development of paclitaxel (Taxol®) and tamoxifen (Nolvadex®), and advances in the understanding of basic bone marrow transplant biology and clinical application, represent the future of cancer research and cancer care.

### Research Project Grants (RPGs)

(dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Budget
Ongoing	\$983,129	\$1,056,342	\$1,166,993
New	377,516	353,517	366,244
Subtotal	1,360,645	1,409,859	1,533,237
Small Business Innovation Research	57,808	60,978	63,173
<b>TOTAL</b>	<b>\$1,418,453</b>	<b>\$1,470,837</b>	<b>\$1,596,410</b>

### Other Grant Mechanisms

NCI also has special mechanisms for exceptionally high-risk, innovative, exploratory, and developmental research activities, to allow investigators to embark on projects of unusual scientific potential, and to support research and development ideas that are likely to result in the development of a commercial product or service.

### Support for Extramural Clinical Research

Clinical research is one of the cornerstones of the National Cancer Program. Every new treatment we use today, every preventive measure that is widely recommended, and every innovative detection strategy was, at one time, tested in cancer

## Clinical Trials Infrastructure

(dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Budget
TREATMENT:			
Clinical Cooperative Research	\$126,205	\$125,460	\$129,977
Community Clinical Oncology Program	6,565	6,007	6,009
Subtotal Treatment	132,770	131,467	135,985
PREVENTION:			
Community Clinical Oncology Program	45,596	48,305	50,258
<b>TOTAL</b>	<b>\$178,366</b>	<b>\$179,772</b>	<b>\$186,244</b>

patients or in people at risk for the disease. These heroes of the fight against cancer have allowed us to amass the body of information we are building upon every day. Even though trials often test the latest therapies, there is no guarantee of success – a person may be randomly assigned to a control group to receive standard therapy, or may participate in a Phase I or II trial which may be too early in the drug's development to know if it is effective. Nonetheless, trials provide patients and other participants access to cutting-edge interventions and provide researchers with information that ultimately will enable us to prevent and effectively treat all cancers.

A strong clinical research infrastructure, including a comprehensive program of clinical trials in treatment, early detection, and prevention, is a vital component of NCI's research program. NCI's Cancer Centers, Cooperative Groups, and Community Clinical Oncology Program are where findings from the laboratory are translated into new treatments, diagnostic tools, and preventive interventions, and where these measures are first tested for safety and effectiveness. These programs are fundamentally interrelated: every Cancer Center is a participant in at least one Cooperative Group, and Cooperative Groups serve as research bases for participants in the Community Clinical

Oncology Program. Hundreds of clinical trials are supported through these and other research mechanisms, such as Single Research Project Grants, Program Project Grants, cooperative agreements, and contracts.

NCI's programs in clinical research have enjoyed many notable successes over the years. NCI has been responsible for the early development and/or testing of many important treatments, including paclitaxel (Taxol®) for breast and ovarian cancer, interferon alpha-2b for malignant melanoma, and Herceptin® for breast cancer. Studies to test the effectiveness of certain drugs to prevent first occurrences of cancer include the ongoing Prostate Cancer Prevention Trial. The Breast Cancer Prevention Trial demonstrated a 49 percent reduction in breast cancer incidence during the treatment period among high-risk participants who took the drug tamoxifen (Nolvadex®). Based on the results from that trial, the Food and Drug Administration has approved the use of tamoxifen to reduce the chance that women at high risk of breast cancer will develop the disease.

Through our clinical research programs, we also have identified successful interventions for symptom management and continuing care of cancer patients, including treatment for mouth sores and hot flashes, both common side effects of chemotherapy. And based on the results of laboratory research, we now are exploring interventions for individuals whose genetic profile places them at increased risk of cancer.

However, our ability to conduct clinical trials is in danger of being compromised by changes in the health care system. In the past, institutions have used surplus revenues from patient care services to supplement government research support. The growth of managed care has all but eliminated those discretionary funds. As a result, institutions can no longer sponsor research activities requiring capital expenditures and cannot support essential training for young investigators. These changes pose a very real danger for the continuation of cancer research and our continued progress against cancer.

In response to the changing health care system, we are developing ways to improve access to and participation in clinical trials. To ensure that physicians have the time to conduct clinical trials,

# Understanding Clinical Trials

## What are Clinical Trials?

Clinical trials are research studies conducted to answer specific scientific questions about new ways to prevent, diagnose, detect, and treat cancer. Most clinical trials are designed to test new cancer treatments; concurrent or separate studies also may look at the psychological impact of cancer or ways to improve a patient's quality of life. In addition, the number of clinical trials to test drugs for cancer prevention has been increasing, because of success with large precedent-setting prevention trials, such as the Breast Cancer Prevention Trial.

Before a clinical trial of a promising new treatment or preventive agent can be launched, the agent must undergo rigorous laboratory testing to prove that it may be beneficial to patients and will be safe to use during testing. If the agent is promising and is safe for use, then researchers design a trial in an effort to answer a specific scientific question about the agent's use or efficacy. The researchers then establish strict entry criteria to help identify patients who are best suited for the trial. Only then can the researchers recruit volunteers to participate. Trials generally are conducted in three phases:

- **Phase I** — These are small trials designed to tell researchers how best to administer the new intervention and, in studies of new agents, the optimal dose of the drug to give with the least possible side effects.
- **Phase II** — Involving a small number of people, these studies determine if the treatment, delivered at the optimum dose, destroys or prevents cancer and against what types of cancer it works best.
- **Phase III** — Once a new therapy has been proven to have an anti-cancer effect and be safe, it then moves to a Phase III trial to compare its efficacy with that of a standard therapy. Phase III trials often are large, and may include hundreds or thousands of people from across the country.

As each phase of testing is completed, the data collected are analyzed and the results published. Based on this analysis, the researchers determine whether the agent is showing enough of a benefit to continue testing. Once a therapy has successfully completed these three phases of testing, a New Drug Application is submitted to the U.S. Food and Drug Administration. The testing and approval process can take many years; however, the approval process can sometimes be accelerated, particularly if the agent is beneficial for patients with a form of cancer that has few treatment or prevention options. Occasionally, additional trials (called **Phase IV** trials) are conducted after the approval of the drug to provide longer-term safety data or to collect new types of information, such as quality of life assessments.

## Ensuring Diversity in Clinical Trials Participation

Ensuring participation in clinical research, particularly among women and members of special population groups, is a high priority for the Institute; several programs help us ensure that all populations are well represented. The Minority-Based Community Clinical Oncology Program, begun in 1990, has been successful in accruing minority cancer patients to trials and provides for studies in minority populations that may lead to better understandings about the dynamics of patient accrual. In addition, two new grant programs are supporting research on ways to draw more women and minority participants into prevention and screening studies. The Institute also has funded a number of conferences aimed at sharing current information and strategies to maintain and enhance its good record of minority accrual to clinical trials.

As a result of our efforts, analysis of accrual patterns in Cooperative Group cancer treatment trials has shown that women and ethnic/racial minorities are proportionally represented in NCI cancer treatment trials. Nearly 20 percent of the more than 20,000 patients entering treatment clinical trials every year are members of an ethnic/racial minority group.

we have developed a Midcareer Investigator Award in Patient-Oriented Research that offers subsidies to clinicians, allowing them protected time to devote to vital patient-oriented research. Further, through agreements with private insurers and other government agencies, we are working to assure insurance coverage for individuals participating in trials. We have two government interagency agreements, one with the Department of Defense (DoD) that provides coverage for DoD health plan beneficiaries to participate in NCI-sponsored cancer treatment trials, and a second with the Veteran's Administration that covers the full range of NCI-sponsored clinical trials. This year, we signed a new agreement with the DoD, marking the first time a health plan has agreed to provide coverage for participation in cancer prevention trials. Based on these initial successes, several organizations have enacted agreements at the local, state, and national levels to provide greater access and coverage for clinical trials. For example, in 1999 the United Health Care Corporation began piloting a program providing coverage of the patient care costs associated with cancer treatment trials conducted by the NCI-supported Coalition of Cooperative Groups. Several states also have enacted legislation designed to provide greater access and coverage for clinical trials. In addition, NCI is working with patient advocates, local communities, and non-profit organizations to increase awareness of and education about clinical trials. Together with other clinical trials efforts, we hope these initiatives will serve as national models and provide access for more individuals interested in participating in clinical trials.

### **Cooperative Group Clinical Trials Program**

The sheer number of different types of cancer and their biological complexity make the process of efficiently identifying and evaluating new treatments or other anti-cancer strategies extremely challenging. To test potential treatment advances in patients more rapidly, NCI maintains the Cooperative Group program, a national network

of 12 consortia (Cooperative Groups) that seek to define the key unanswered questions in cancer and then conduct clinical trials to answer them. Each year, 1,700 institutions throughout the United States and Canada, and approximately 8,000 investigators in these institutions participate in these trials. This kind of cooperation makes it possible to centralize administration and data collection for trials taking place at a large number of sites around the world. The Cooperative Groups differ in structure and research organization, but they share the common purpose of developing and conducting large-scale trials in multi-institutional settings.

Cooperative Groups frequently work together when the cancer in question is so rare that one group working alone would be unable to accrue enough patients to conduct a meaningful study. For example, six Cooperative Groups worked together on the landmark study establishing that all-*trans* retinoic acid (ATRA) significantly improves disease-free survival time for patients with acute promyelocytic leukemia. Cooperative Groups collaborate regularly on clinical trials for solid tumors in children, breast cancer, colorectal cancer, lung cancer, prostate cancer, and cancers of the head and neck.

Approximately 20,000 patients participate in Cooperative Group clinical trials each year, principally in large Phase III trials that help establish the state of the art for cancer therapy. Many new anti-cancer drugs are tested in patients for the first time under NCI Investigational New Drug (IND) sponsorships through the Cooperative Group program. Nearly 200 investigational agents or treatment strategies, ranging from new chemotherapy drugs and cancer vaccines to agents that prevent tumor blood vessel development, are currently being studied under NCI INDs.

An agreement between the U.S. Office for Protection from Research Risks and the European Organization for Research and Treatment of Cancer (EORTC) promises to improve the ability of NCI's Cooperative Groups to collaborate with the EORTC and other international cancer research groups.

To learn more about the Cooperative Group program, visit the Cooperative Group Web site at [http://ctep.info.nih.gov/CoopGroup/Coop\\_Group\\_Prog.html](http://ctep.info.nih.gov/CoopGroup/Coop_Group_Prog.html)

## Community Clinical Oncology Program (CCOP)

The Community Clinical Oncology Program is a network of 49 central offices in 31 states that provides the infrastructure to link more than 2,500 community cancer specialists and primary care physicians with clinical Cooperative Groups and Cancer Centers. In addition, CCOPs support scientific development and the implementation of ongoing cancer treatment, prevention, and control clinical trials among community Cooperative Group members and Cancer Centers.

This network enables individuals to participate in state-of-the-art clinical research trials at over 340 community hospitals without the burden of traveling to a distant site. Each year, the Program enrolls more than 5,000 patients in cancer treatment clinical trials and an additional 3,500 patients in cancer prevention and control clinical trials. An additional seven Minority-based CCOPs increase the participation of minority individuals in clinical trials research. Each year, over 700 patients enter clinical trials through these specialized CCOPs. Located in six states and Puerto Rico, these programs bring an additional 33 hospitals and 250 physicians into the clinical trials network. By increasing the number of patients and physicians who participate in clinical trials, the program helps transfer the latest research findings to the community.

More information on the Community Clinical Oncology Program is available at <http://dcp.ni.nih.gov/corb/CCOP.html>

The Minority-based CCOP Web site is located at <http://dcp.ni.nih.gov/corb/MBCCOP.html>

Center, it is awarded a Cancer Center Support Grant. These funds enable the institution to coordinate multidisciplinary approaches to research questions, to gain access to the most advanced research technologies, and to take rapid advantage of new research opportunities. Support for the Cancer Centers helps ensure a close association between state-of-the-art research and state-of-the-art care activities within the institution. Moreover, it allows each Center to develop key collaborations with industrial, community, and state health organizations, and to link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions.

Three types of centers exist: Cancer Centers have specific research foci, such as epidemiologic or basic research;

Clinical Cancer Centers integrate basic science with clinical science; and Comprehensive Cancer Centers demonstrate both significant scientific strength in basic, clinical, and population studies and strong interdisciplinary collaboration. Comprehensive Cancer Centers also must have in place effective cancer information, education, and outreach activities for the regions and communities they serve.

Traditionally, Cancer Centers have had broad scientific bases, and most have been developed within a single institution. Changes in the program, however, are

The Cancer Centers program Web site is located at <http://www.ni.nih.gov/cancercenters/>

## Cancer Centers

Fifty-nine research-oriented institutions throughout the Nation have been designated NCI-supported Cancer Centers in recognition of their scientific excellence. The Centers are key partners in NCI's efforts to speed the process of discovery and bring the benefits of cancer research directly to the public. Located throughout the country, each Cancer Center is a hub of cutting-edge research, high quality cancer care, and outreach and education for both health care professionals and the general public.

When an institution meets the rigorous competitive standards to become an NCI Cancer

**Cancer Centers** (dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Budget
Basic	\$13,504	\$18,765	\$19,441
Clinical/ Comprehensive	134,738	137,014	141,947
Subtotal	148,242	155,779	161,387
Core Grants			
Planning	1,131	787	815
SPOREs (P50)	48,117	40,889	42,361
<b>TOTAL</b>	<b>\$197,490</b>	<b>\$197,455</b>	<b>\$204,563</b>

enabling the planning of new consortia of institutions, often linking free-standing clinical and academic centers with community hospitals to form networks with tremendous research strength and the ability to deliver quality care in a managed care environment. In addition, more focused scientific concepts are being developed for Cancer Centers. For example, some Centers are focusing on population sciences and others are concentrating on translational research opportunities within a specific scientific discipline, such as immunology. Overall, such changes in the Cancer Centers program promise to increase the scientific versatility, translational research capabilities, and geographic distribution of NCI-supported Cancer Centers.

### Intramural Research

The NCI Intramural Research Program (IRP), consisting of more than 400 principal investigators in the Divisions of Basic Sciences, Cancer Epidemiology and Genetics, and Clinical Sciences, is dedicated to the comprehensive understanding of cancer and to finding cures for these diseases. Organized to complement ongoing research in universities and in industry, the IRP

### Intramural Research

(dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Budget
Basic	\$173,218	\$172,602	\$179,506
Clinical	117,039	116,623	121,288
Epidemiology & Genetics	48,987	48,823	51,156
NIH Central Services	149,640	149,097	154,681
<b>TOTAL</b>	<b>\$488,884</b>	<b>\$487,144</b>	<b>\$506,630</b>

has been involved in pivotal discoveries in cancer research: the first successful treatments for childhood leukemias; establishing the principles for curative chemotherapy for lymphomas; developing effective therapies for HIV; defining the foundations for tumor vaccines; identifying the genetic causes for familial cancers; and uncovering environmental causes of cancer.

The IRP's epidemiology research program is a national program of population-based studies to identify environmental and genetic determinants of

## SPOTLIGHT ON RESEARCH

### NCI's Intramural Program

NCI's Intramural Research Program (IRP) is a critical part of the effort to understand and find cures for the many types of cancer. New programs include:

Our recently established **Advanced Technology Center (ATC)**, home to the Cancer Genome Anatomy Project (CGAP), two high throughput genotyping and sequencing centers, and a microarray facility, that uses new technologies to address biological, clinical, and genetic questions pertinent to human cancers. The ATC, which focuses on clinical and molecular medicine, houses investigators from NCI and from the National Human Genome Research Institute, whose research centers on human cancer genetics, molecular epidemiology, and cell biology. Through the efforts of CGAP and array projects, ATC has become a premier facility for the development of tools for molecular expression profiling studies.

NCI is initiating a joint effort with the National Institute of Neurological Disorders and Stroke to develop a **Neuro-Oncology Branch** at the NIH Clinical Center. Researchers will study both adult and childhood brain tumors from a translational perspective, applying advances in the understanding of the basic biology of central nervous system malignancies to novel, targeted treatments.

In support of NCI's long tradition of using mice as models for human cancers, a new **Mouse Genomics Program** will bring together scientists with varied but related expertise in the field to create an environment for rapid progress in this area. The program will develop new disease models based on advances in the development of high-resolution genetic and physical linkage maps of the mouse genome, transgenic technology, and array technologies. These models will offer a potentially important resource for preclinical testing of different treatment strategies.



cancer. This IRP component supports epidemiologic and interdisciplinary research to ensure that the momentum of recent and ongoing discoveries in molecular genetics and cancer biology is accelerated and broadened through population-based studies into the etiology of cancer and its prevention.

The intramural clinical research program is conducted principally in NIH's Warren G. Magnuson Clinical Center. It provides the opportunity for patients from across the country to be treated through ground-breaking research protocols. The Clinical Center is a unique environment in which investigators throughout the NIH community develop and test novel therapies derived from our growing body of knowledge; in this environment new information can be transferred quickly from the laboratory to the patient and back to the laboratory for additional analysis.

The Intramural Research Program is uniquely structured to address cancer research problems whose resolution requires long-term commitments and that may be considered unsuitable for many extramural funding mechanisms. Another unique aspect of the Intramural Program is its framework for cooperation between basic researchers and investigators performing clinical trials. These interactions, fostered by common research interests, topic-specific focus groups and retreats, and close physical proximity of basic and clinical research efforts, result in rapid translation of new basic research discoveries into early clinical trials.

Because of its national stature and unique structure, NCI's IRP also is a center for basic, clinical, and population-based oncology training for researchers, clinicians, research fellows, and visiting scholars from around the world. NCI plays a major role in fostering the education and careers of a growing number of nurses, doctors, and physician assistants, as evidenced by the approximately 500 participants each year in the summer intramural research training program. Many of the current leaders in cancer research received some of their training at NCI, and we anticipate that the IRP will continue to be an important resource for training the next generation of investigators.

For more information on the NIH Clinical Center visit <http://www.cc.nih.gov>

## Cancer Control

Cancer control research encompasses basic and applied research in the behavioral, social, and population sciences aimed at creating or enhancing interventions that, by themselves or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity, and mortality, and improve quality of life. For example, a cancer control study might investigate the use of a medical intervention, such as a nicotine patch, in combination with a behavioral intervention, such as a counseling program to help smokers overcome their barriers to quitting. Interventions may be directed at patients, physicians, and/or other health care providers. Cancer control research seeks to improve interventions across the human lifespan and over the entire cancer continuum, and to move research findings into clinical and public health practice. The foundation of cancer control research is epidemiology, and surveillance and outcomes research are the fundamental mechanisms for assessing progress.

NCI maintains a firm commitment to cancer control research through the Division of Cancer Control and Population Sciences (DCCPS), the focus for NCI-sponsored research programs aimed at studies in populations, behavior, surveillance, special populations, outcomes, and other aspects of cancer control. Our wide-ranging cancer control research efforts include research in epidemiology and genetics, tobacco research, tailored communications, and theoretical models for studies of human behavior and behavior change.

## Cancer Control

(dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Budget
Grants	\$107,549	\$113,671	\$127,734
Contracts	103,828	116,408	120,599
Cancer Control Management & Support	89,882	82,640	85,946
<b>TOTAL</b>	<b>\$301,259</b>	<b>\$312,719</b>	<b>\$334,278</b>

Cancer surveillance – tracking and analyzing trends in cancer incidence, mortality, and survival rates – is a critical component of cancer control. The keystone of NCI’s surveillance efforts is the Surveillance, Epidemiology, and End Results (SEER) program, which monitors the Nation’s cancer burden and provides the basis for assessing individual, organizational, and societal factors that can reduce cancer rates. (See page 92 for further information on cancer trends.)

### AIDS Research

Malignancies occur in more than 30 percent of AIDS cases and contribute greatly to AIDS morbidity and mortality. Many areas of fundamental biology developed in NCI programs, including virology, immunology, and cellular and molecular biology, are directly applicable to understanding HIV and AIDS. Research efforts in AIDS malignancies begins with basic science that provides new insights in cancer biology that can lead to hypotheses to test in epidemiologic studies, the development of treatment targets, and new treatments to prevent and control AIDS malignancies. But basic science, even with associated drug development programs, would not make progress without clinical programs in which to test potential discoveries. Work in this area is necessarily collaborative and one of NCI’s major roles is to foster these collaborations, create research groups, and provide infrastructure, including clinical trials support, central specimen banking, international scientific meetings, and new investigator training.

Today, research into the fundamental biology of HIV and AIDS, AIDS treatment, and particularly AIDS-related malignancies takes place throughout all programmatic mechanisms of NCI. The Intramural Research Program is an internationally recognized center for research in HIV and AIDS, housing the HIV Drug Resistance Program, the HIV and Malignancies Branch, and the NIH Vaccine Research Center, a joint project with the National Institute of Allergy and Infectious Diseases. The Extramural Research Program also has been a vital and innovative force in this area of research. Among its programs are the AIDS Malignancy Consortium, the AIDS Malignancy Bank, the AIDS Oncology Clinical Scientist Training Program, and an annual international

forum on AIDS malignancies.

NCI, in coordination with other NIH Institutes and the NIH Office of AIDS Research, continues its commitment to meeting the challenge of AIDS and is working to ensure that NCI-supported AIDS and AIDS-related research is integrated with national AIDS strategies.

### Training and Education

In the past decade, we have made stunning advances in our understanding of cancer. Our ability to bring these new discoveries to the communities and clinics where they benefit cancer patients and those at risk for developing cancer depends on physicians and other scientists who are specially trained in cancer research. While resources for training are shrinking at many institutions, NCI is committed to ensuring that a national cadre of trained cancer researchers exists by continuing to provide essential training to our Nation’s scientific and medical workforce.

To address this crucial requirement, NCI has developed a strategic plan for extramural training, education, and career development. This plan focuses on attracting young scientists into cancer research, on providing stability and protected research time for researchers in disciplines critical to translational research, on creating more opportunities for underserved ethnic and minority scientists, and on encouraging research program diversification. In pursuit of these objectives, NCI has

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### Training and Education

(dollars in thousands)

	1999 Operating Budget	2000 President’s Budget	2001 Core Budget
National Research Service Awards	57,135	58,026	60,115
Research Career Program	34,881	38,915	40,316
Cancer Education Program	17,319	16,692	17,293
Minority Biomedical Research Support	2,788	3,623	4,373
<b>TOTAL</b>	<b>\$112,123</b>	<b>\$117,256</b>	<b>\$122,097</b>

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implemented a number of new training and career development programs in basic, clinical, population, and diversified sciences, as well as for underserved ethnic and minority groups who are underrepresented in the research workforce. These programs aid investigators in stabilizing and sustaining productive research careers, and offer opportunities for engaging in translational research (see page 96 for more information on training).

NCI's research divisions also are developing training programs. For example, the Division of Clinical Sciences' Clinical Intramural Research Award supports innovative and collaborative clinical research projects emphasizing novel approaches or promising new outcomes of current research; the Division of Cancer Epidemiology and Genetics' Cancer Genetics and Epidemiology Fellowship Program provides interdisciplinary training in clinical, molecular, and quantitative genetics, and genetic epidemiology; and the Division of Cancer Prevention Fellowship provides training in cancer prevention and control for individuals from many health science disciplines.

### Other Research Support

In addition to its many types of grants and awards, NCI employs a variety of other research support mechanisms. These mechanisms include: contracts to provide support for research, information

### Other Research Support

(dollars in thousands)

	1999 Operating Budget	2000 President's Budget	2001 Core Budget
Research Support Contracts	\$275,087	\$298,569	\$309,519
Scientific Evaluation Grants	3,528	3,742	3,877
Research Resource Grants	19,437	21,338	22,106
Construction	3,000	3,000	5,000
Conference Grants	901	1,101	1,141
Research Management & Support	108,965	110,065	114,468
<b>TOTAL</b>	<b>\$410,918</b>	<b>\$437,815</b>	<b>\$456,111</b>

## Informing Professionals and the Public — NCI's Information Services

Every day, thousands of people – health professionals, cancer patients and their families, and the general public – benefit from NCI's broad array of information and public education services. Using basic printed materials, sophisticated Internet technology, and everything in between, NCI provides millions of people each year — often in Spanish as well as English — with the complete, reliable information they need to make decisions about cancer prevention, detection, treatment, and follow-up care. NCI's services include:

- **The Cancer Information Service (CIS).** This nationwide cancer information and education network, available in all 50 states, Puerto Rico, and the U.S. Virgin Islands, receives more than 2,000 calls each day. By calling 1-800-4-CANCER (1-800-422-6237), cancer patients, their families, people at risk for cancer, and health professionals can receive information confidentially on all aspects, including prevention, treatment and clinical trials. Callers with TTY equipment can dial 1-800-332-8615.
- **NCI's Internet Services.** Patients and health professionals with access to the Internet may search for accurate, up-to-date information about cancer on: NCI's Web site (<http://www.nci.nih.gov>) or the International Cancer Information Center's **CancerNet™** Web site (<http://cancer.net.nci.nih.gov>) and **cancerTrials™** (<http://cancertrials.nci.nih.gov>).
- **Physician Data Query (PDQ®).** The CancerNet™ searchable PDQ® data base contains current information on cancer prevention, screening, treatment, and supportive care, as well as descriptions of active clinical trials and directories of physicians, health professionals who provide cancer genetics services, and organizations involved in cancer care.
- **CANCERLIT®.** This bibliographic data base contains more than 1.4 million records on cancer literature from 1963 to the present. It can be searched from the CancerNet™ Web site.
- **The PDQ/CANCERLIT® Service Center.** Physicians and other health professionals can make requests for PDQ and CancerLit information through a toll-free telephone service (1-800-345-3300), e-mail ([cancermail@icicc.nci.nih.gov](mailto:cancermail@icicc.nci.nih.gov) with the word "help" in the body of the message, users receive a contents list and ordering instructions by return electronic mail.), or fax (301-402-5874).
- **Print Publications.** NCI makes available nearly 600 publications and audiovisual materials, many published both in English and Spanish. They are available from the toll-free number 1-800-4-CANCER or from the NCI Web site. NCI is also working to develop materials in several Asian languages.

dissemination, and management; conference grants to fund meetings, conferences, and workshops; resource-related research projects to improve the ability of resources to serve biomedical research; scientific evaluation awards to support the scientific review of grant and contract proposals; and construction grants and contracts

to provide partial support for the modernization or development of cancer research facilities throughout the Nation.

NCI also sustains, guides, and monitors both the extramural and intramural activities of the Institute through its research management and support activities. These activities include overall

## SPOTLIGHT ON RESEARCH

### Addressing the Unequal Burden of Cancer — Special Populations Research

Not all populations are affected equally by cancer. Cancer statistics and numerous studies have shown that some population groups develop cancer more often, have poorer survival, and are more likely to die from cancer than others. These “special” populations, which are not mutually exclusive, include ethnic minorities, geographically isolated and other medically underserved populations, the elderly, women, people of diverse cultures and lifestyles, and people with lower income, education, and literacy levels. We know that major differences in cancer burden exist between these groups and the general population. Moreover, disparities exist within and between special populations, who likewise are affected more severely by many specific types of cancer.

Research also is demonstrating that differences in cancer morbidity and mortality previously attributed to race are not due to supposed biological differences between populations or between the tumors individuals develop. Rather, these differences actually reflect the too-frequent biological and medical consequences of socially-defined race – lower socioeconomic status and educational level, and less access to high quality cancer care. For example, recent data from NCI’s **Black-White Study of Cancer Survival** showed that compared with white women, black women with breast cancer (as well as poor and older women) were less likely to receive appropriate treatment after diagnosis. They also are more often diagnosed at a later stage of disease and are less likely to have a regular source of health care. Similar disparities in appropriate treatment have been demonstrated between various population groups with prostate, lung, colorectal, and cervical cancers. Analyses of NCI clinical trials have shown however, that equal treatment yields equal outcome, and that race is not a factor when there is equal treatment.

NCI has long supported and is committed to a broad array of research and related activities to pinpoint, understand, and address cancer disparities. NCI plans and coordinates these activities through organizational units dedicated to special populations issues. The **Office of Special Populations Research** was established in 1996 to advise the Director of NCI and provide a focal point for leadership and coordination on minority and other special populations research. NCI’s **Comprehensive Minority Biomedical Branch** creates and coordinates programs to broaden participation in all aspects of cancer-related research and training activities by minorities and other special populations. The **Applied Sociocultural Research Branch (ASRB)** promotes grant-supported cancer prevention and control research in populations that experience a greater burden of cancer. The ASRB also offers training to help potential applicants prepare scientifically competitive research applications in cancer control science. Special populations initiatives at NCI now are expanding even further to encompass a larger spectrum of special populations, and to create new opportunities to attract and train cancer researchers and clinicians from special populations.

For more than 20 years, NCI’s **Surveillance, Epidemiology, and End Results (SEER)** cancer registry program has monitored the Nation’s cancer burden and been a world model for tracking population trends in cancer incidence, survival, morbidity, and mortality. SEER data are used by researchers to develop studies designed to explain cancer trends and identify study populations, by health planners and policy makers at all levels, by public health practitioners, and by the public. SEER now is being expanded to collect data on a wider range of population subgroups and on socioeconomic and other factors that underlie cancer trends. As many as four new state registries will be added to SEER, and up to ten additional states will receive sup-

scientific program direction and administration by the Office of the Director, with assistance from grant and contract science managers, finance, human resources, legislation, science program direction and assessment, and technology transfer staff. The review and oversight activities of the National Cancer Advisory Board and President's

Cancer Panel also are included. This part of the budget also supports a share of central NIH facilities and operations, and extramural program staff salaries (intramural staff salaries and intramural facilities maintenance are included under the intramural research budget).

plementary funding to upgrade their existing registries to meet SEER standards. This expansion will be achieved in partnership with the Centers for Disease Control and Prevention, and will capture data on a broader spectrum of Native American and Hispanic population subgroups, rural African Americans and whites, and others.

NCI recently launched the **Special Populations Networks for Cancer Awareness Research and Training**, for which \$30 million has been earmarked over five years. Funding a diverse group of research projects aimed at improving cancer prevention and control in minority and underserved communities, the Networks will build upon and expand the scope of NCI's three **National Leadership Initiatives** that now are drawing to a close. The Leadership Initiatives were instrumental in launching collaborative efforts to raise cancer awareness, improve access to care, and reduce the cancer burden in African American, Hispanic, and Appalachian populations. Principal goals of the new Networks will be to develop and maintain partnerships between scientific researchers and community leaders in a broader range of minority and underserved populations, develop and test community cancer awareness activities, support minority enrollment in clinical trials, and encourage minority scientists to participate in research. Initial awards under the program will be made in March 2000.

Also responding to the need to attract, develop, and support researchers and cancer care givers from minority and underserved populations, NCI recently organized and expanded special populations biomedical training opportunities under the **Continuing Umbrella of Research Experiences (CURE)** initiative. CURE reaches minority students as young as high school age, develops under-

graduate, graduate, and postdoctoral scientists, and supports young minority investigators as they establish their research careers. CURE also provides training support for individuals with disabilities and for scientists re-entering an active research career after taking time off for child care or other family responsibilities. In addition, **long-term partnerships between NCI Cancer Centers and both minority and minority-serving institutions** are being established. The partnerships are expected to enhance the cancer centers' approaches to outreach and education for underserved communities as well as the institutions' approaches to conducting cancer research and training future cancer scientists.

In July 1999, NCI convened a meeting of key staff and identified experts to discuss how best to describe underserved populations to aid NCI in planning, research, and related activities to address cancer issues in these populations. In addition, NCI has appointed a **Special Populations Working Group** to enhance its priority-setting and information dissemination processes and strengthen communication with the many groups, organizations, and institutions involved in special populations issues. Its membership is drawn from a variety of medical and non-medical disciplines, individuals knowledgeable about the cancer experience, and diverse communities. The Working Group is charged to raise and articulate special populations concerns and issues, make recommendations for addressing special populations issues at the NCI, suggest NCI-community partnerships to reach common goals, and provide an ongoing communication channel with diverse minority and special populations communities. This important group met for the first time in May 1999 and will meet approximately three times per year.

# Extraordinary Opportunities for Investment

Over the past thirty years, we have witnessed dramatic changes in our fight against cancer. The revolution in molecular biology, along with the emergence of powerful new technologies, have enabled us to gather an impressive body of knowledge about cancer's very nature. Today we are able to identify many of the biochemical pathways in a cell that become disrupted in cancer, and we are gaining a fuller understanding about how such changes contribute to a cancer cell's abnormal and dangerous behavior in the body. We also are gaining important insights into how the vulnerability of DNA – our genetic material – and elements in our environment and lifestyle interact to give rise to this disease. For the many who struggle with cancer, these striking changes in the science and technology of cancer research are reflected in marked improvements in treatments and a heightened chance for survival. They also are reflected in more effective prevention, particularly for those who may be at increased risk for the disease. These are important advances, yet as long as people continue to suffer from cancer, our work is not complete.

Three years ago, NCI acknowledged that to conquer cancer, we must choose a path that not only maintains our pace of discovery but one that speeds progress and optimizes our ability to overcome this disease. This path is great science – science that is anchored in exceptional quality, marked by vision, imbued with imagination – a path that tenaciously follows opportunities for discovery. In 1996, NCI identified areas of extraordinary opportunity for investment in cancer research. We defined areas of discovery in which focused efforts and increased resources could produce dramatic progress toward reducing the burden of cancer. If pursued, these extraordinary opportunities for investment – new doors to discovery opened by past successes – would provide profound insights into how cancer devel-

ops, paving the way for better techniques to prevent, detect, diagnose, and treat the disease.

Four areas originally were chosen as investment areas – Cancer Genetics, Preclinical Models of Cancer, Imaging Technologies, and Defining the Signatures of Cancer Cells. Since selecting these areas in 1996, we have focused on putting into place several dozen innovative projects – the Cancer Genetics Network, the Mouse Models of Human Cancers Consortium, *In Vivo* Cellular and Molecular Imaging Centers, and the Cancer Genome Anatomy Project (CGAP), to name a few – that provide the infrastructure for basic discovery. Many of these projects are described in the following pages.

This year, we intensively evaluated our current direction and progress in each investment area to chart a course for our second generation of efforts. We determined that our primary focus for each of these extraordinary opportunities should be to move from process to product in the coming years – to use the infrastructure established in each area to resolve fundamental questions about cancer and produce tangible improvements in cancer detection, diagnosis, and treatment. For example, our charge now will be to take cancer genes identified through CGAP and determine how they contribute to cancer, how they can easily be detected in people at risk, and how they can be targeted through new treatments. From this evaluation, we also determined that we should broaden our Cancer Genetics investment area to Genes and the Environment, and integrate our efforts in Preclinical Models into the other investment opportunities.

We also identified three new areas of extraordinary opportunity for investment: Research on Tobacco and Tobacco-Related Cancers, Cancer Communications, and Molecular Targets of Prevention and Treatment. As with the opportunities identified originally, each of these areas is

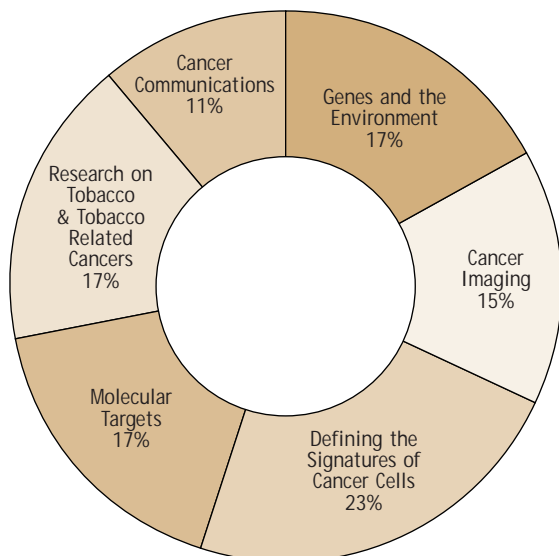
rife with possibilities for taking us to a new era in cancer prevention and cancer care.

An investment in each of these six areas promises to drive forward our understanding and control of cancer. Although the needed resources are not trivial, our failure to respond quickly with investment in all of these areas will slow the pace of cancer research at all levels – and more importantly – will impair our ability to better care for those whose lives have been touched by cancer.

### Extraordinary Opportunities for Investment Increase

(dollars in thousands)

	Amount
Genes and the Environment	\$65,036
Cancer Imaging	58,700
Defining the Signatures of Cancer Cells	93,000
Molecular Targets	66,375
Research on Tobacco & Tobacco-Related Cancers	66,000
Cancer Communications	43,000
<b>Total</b>	<b>\$392,111*</b>



\* \$12,111 towards Investment areas included in Core budget level.

## Selecting Extraordinary Opportunities

In 1996, NCI, with formal input from over 60 cancer scientists, educators, advocates, and community leaders, identified four research areas of exceptional promise in the cancer field – Cancer Genetics, Preclinical Models of Cancer, Imaging Technologies, and Defining the Signatures of Cancer Cells – and pledged to focus increased attention and investment on these areas for a three-year cycle.

In 1998, as this first cycle drew to a close, NCI again approached scientific, professional, and lay experts in the cancer field to revisit the “extraordinary opportunities” and select emerging investment research areas for the next three-year cycle. NCI received over 250 responses from our grantees, members of our advisory boards, and advocacy groups. We then assessed the responses, blended related meritorious ideas from the initial selected extraordinary opportunities, and selected three additional new investment areas for a total of six – Genes and the Environment, Cancer Imaging, Defining the Signatures of Cancer Cells: Detection and Diagnosis, Molecular Targets of Prevention and Treatment, Research on Tobacco and Tobacco-Related Cancers, and Cancer Communications.

These extraordinary opportunities are different from the other important research areas supported by NCI; they are areas where focused efforts and increased resources could produce dramatic progress toward reducing the burden of cancer. To qualify as extraordinary opportunities, these research initiatives must:

- Respond to important recent developments in knowledge and technology;
- Offer approaches to cancer research beyond the size, scope, and funding of our current research activities;
- Be implemented with specific, defined investments;
- Be described in terms of achievable milestones, with clear consequences for not investing; and
- Promise advances for making progress against all cancers.

In addition, these investment areas will result in new extramural grant or contract awards; collaborative efforts with other institutes, government agencies, or the private sector; and new or expanded scientific programs within NCI divisions. They promise to take us to a new era in cancer prevention and care.

# Genes and the Environment

## THE OPPORTUNITY

Dramatic scientific advances have led to new and fundamental insights into the causes of cancer. Fueled by conceptual and technical breakthroughs, the often breathtaking pace of scientific discovery has engendered a tremendous sense of optimism among cancer researchers that new avenues will be found to detect, treat, and prevent cancer. Nowhere is this sense of promise greater or the potential implications more profound than at the interface of the fields of epidemiology and genetics. By marrying the epidemiologic approach – study of the distribution and causes of cancer in human populations – with cutting-edge genetic and related molecular technologies, we will be able to:

- Identify genes that predispose people to cancer (cancer susceptibility genes) whose pathways of action will point to previously unsuspected environmental carcinogens, including those related to lifestyle exposures.
- Detect the slight to moderate elevations of risk resulting from certain types of exposures by studying genetically susceptible subgroups.
- Design new approaches to diagnose, prevent, and treat cancer based on an understanding of how genes modify and interact with environmental exposures.
- Quantify cancer risks associated with gene-environment interactions, which will direct individual and public health strategies aimed at preventing and controlling cancer.

The importance of lifestyle and other environmental exposures as causes of cancer is unquestionable. The pivotal role of environment is reflected in the substantial variation in cancer incidence around the world, and in the changes in risk observed among groups that migrate and become acculturated in the host country. Furthermore, epidemiologic research has succeeded in identifying a wide range of cancer-causing

exposures, including tobacco use, dietary components, sunlight, ionizing radiation, environmental chemicals, infectious agents, obesity, exercise, hormones, and reproductive factors. Nevertheless, the causes of many cancers remain elusive. While better approaches to measuring exposures will provide new insights, it is clear that the environment represents only part of the equation in determining who will get cancer. It also is important to understand cancer susceptibility. For example, why does one person with a cancer-causing exposure (such as smoking or infection with human papillomavirus) develop cancer, while another does not?

Viewing such questions through the lens of genetics promises to provide insights into these apparent paradoxes. The scientific investment in cancer genetics, initially focused on the intensive study of rare cancer-prone families, already has paid huge dividends. These studies have opened a unique window into the basic mechanisms of cancer, with benefits extending well beyond the rare families from which they were derived. This is because the genes identified by these studies are altered forms of normal genes involved in key biochemical chains of events (pathways) controlling fundamental cell processes. It has become clear that these same pathways contribute to the development and progression of the more common, non-hereditary forms of cancer. Yet even among individuals who have inherited cancer-predisposing genes, the risk of developing cancer appears to be modified by other genetic and environmental factors. There is mounting evidence that one's genetic make-up may influence susceptibility or even resistance to cancer-causing exposures. Opportunities now exist to determine how variations in these genes combine with environmental and other factors to induce cancer in the general population.

Three years ago, we identified cancer genetics as an area of extraordinary opportunity. We recognized that to exploit fully this area's potential – to move it forward at the accelerated pace that accu-



culated knowledge and powerful technological advances now permit – new initiatives were needed. Many of today’s new opportunities in the area of genetics are a direct benefit of these scientific investments. For example, NCI’s Cancer Genome Anatomy Project (CGAP) has resulted in the discovery of approximately 30,000 new genes. New technologies have permitted scientists to determine which genes are expressed (active) in normal and cancerous tissues. There has been an exponential increase in the pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body as well as environmental agents. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public data bases contain millions of entries describing gene sequences, their expression in different tissue types, and their location in the human genome.

These advances are ushering in a new generation of epidemiologic research that will lead to a comprehensive understanding of environmental and genetic determinants of cancer. However, the exciting opportunities of this emerging field – referred to as “molecular epidemiology” – are accompanied by enormous challenges. Population studies sufficiently powerful to examine the complex interactions of multiple genetic and environmental factors will involve unprecedented numbers of participants and will require new research infrastructures and strategies for interdisciplinary collaboration. At the same time, we must strive to ensure that individuals will be helped, not harmed, by their knowledge of risk. What psychosocial, legal, ethical, and clinical issues will arise from being able to determine cancer risk? How can we help people to cope with the information and to take appropriate action? What will be the impact on the individual, the family, and the medical care system? These critical questions must be addressed with the same urgency and dedication with which we pursue the scientific opportunities.

## THE GOALS

- Identify environmental causes of cancer using new epidemiologic and genetic approaches.
- Identify genes that modify (increase or decrease) cancer risk, including the risk resulting from environmental exposures.
- Integrate information on genetic susceptibility and environmental exposures to estimate cancer risks for individuals, families, and populations.
- Develop new strategies for cancer prevention, early detection, and treatment, building upon new knowledge about the genetic and environmental determinants of risk.

## THE PLAN

### Objectives

- 1. Conduct large-scale studies of cancer in human populations to identify new susceptibility genes, environmental risk factors, and their interactions with one another.**
  - Form a consortium of investigators directing large, prospective cohort studies of the general population.
  - Develop a network of cohorts totaling one million individuals under active follow-up by coordinating studies in which genetic and exposure information is collected; add biologic specimen collections where needed. Use this resource to study gene-environment interactions for common cancers (e.g., breast, prostate, lung, colon, and lymphoma), particularly those related to exposures that are best studied prospectively (e.g., diet, endogenous hormones).
  - Develop the infrastructure within existing population-based cancer registries to conduct a coordinated series of large-scale case-control studies that include biospecimens and in-depth exposure data collection. Specifically:
    - Collect biospecimens and detailed exposure information on 12,000 cancer cases and 8,000 members of the general population in the initial three years of this program.

- Use this resource to study gene-environment interactions for cancers of intermediate or lower incidence (e.g., pancreas, ovary, kidney, leukemia) and for studies of the more common tumors that require intensive assessment of exposures and biological markers.
  - Give special attention to studies of tumors with rising incidence and mortality rates, racial and ethnic disparities, and unusual geographic patterns.
  - As appropriate, integrate population-based components of the Cancer Genetics Network (CGN) and the Cooperative Family Registries (CFRs).
  - Establish regional biospecimen repositories and high throughput genotyping facilities to ensure high quality, cost-efficient handling of biologic samples from molecular epidemiology studies.
  - Form a network of resource laboratories to develop and conduct specific laboratory tests (e.g., hormonal, gene expression, immunological, nutritional, toxicological) on biologic samples from various study populations.
  - Develop informatics systems that collect, store, analyze, and integrate the vast amounts of epidemiologic, clinical, and laboratory data generated by large-scale studies, and safeguard the confidentiality of all research data.
- 2. Develop new ways of assessing and measuring environmental exposures for use in population studies.**
- Develop new epidemiologic methods for assessing complex exposures over a lifetime (e.g., diet, nutrition, occupational, and other environmental hazards), including computer-assisted interviewing techniques and improved data bases for nutritional and environmental exposures.
  - Expand the NCI's Unconventional Innovation Program and other funding mechanisms to develop new techniques for using very small amounts of biologic samples to quantify exposures (e.g., pesticides, nutrients).
  - Expand the Phased Innovation Award and Small Business Innovation Research program to develop non-invasive methods of collecting DNA for molecular studies (e.g., buccal cells) and techniques to maximize the use of small quantities of genetic material.
  - Supplement ongoing research programs to develop and validate measures of cumulative cellular genetic and molecular exposure to environmental carcinogens in non-tumor tissue.
  - Expand and supplement research programs including CGAP to develop and validate molecular approaches to define in tumor cells the characteristic mutation pattern of DNA damage – the “molecular fingerprint” – that implicates a specific carcinogen.
  - Use emerging technologies to develop molecular and immunologic techniques that will enable screening of large numbers of biologic samples to identify infectious agents relevant to human cancer.
  - Work with academic centers, including schools of public health, to train highly skilled scientists needed to carry out molecular epidemiology studies.
- 3. Identify and characterize gene variations involved in key molecular pathways important in cancer.**
- Expand the CGAP programs to identify all cancer-relevant genes and common variants. As part of this effort:
    - Increase the scope of gene discovery efforts within the Tumor Gene Index (TGI); expand the capacity of the Genetic Annotation Initiative (GAI) infrastructure to delineate, characterize, and validate gene variants.
    - Recruit additional collaborators through CGAP partnerships to accelerate GAI validation and confirmation efforts.
    - Extend efforts to identify genetic variants into clinically and epidemiologically defined groups.
    - Assess the relevance of gene variations in the context of population studies of gene-environment interactions.
  - Extend the GAI's efforts to define key molecular pathways by increasing CGAP's capacity to assess gene expression profiles and by establishing working groups to develop and curate information on cancer genes and their related pathways.
  - Accelerate new technology development and application by expanding the GAI Technology Partners initiative and the Unconventional Innovation Program.

#### **4. Develop new experimental models that parallel human cancer-related genes, pathways, and processes.**

- Augment the Mouse Models of Human Cancers Consortium (MMHCC) to derive and refine mouse models of all known human hereditary cancer genes.
- Generate valid mouse models based on epidemiologic observations on genetic and environmental modifiers of cancer risk. Specifically:
  - Support a GAI for the mouse in a systematic effort to identify common DNA-based genetic variants.
- Augment the Web-based forum within the MMHCC to integrate emerging knowledge about cancer susceptibility from experimental models and studies on human populations.
- Support the MMHCC to discover mouse genes that modify cancer susceptibility to illuminate cancer pathways in humans.
  - Augment MMHCC repository support to derive and distribute consomic and recombinant inbred congenic mouse strains.
  - Use susceptible mouse models to evaluate environmental factors for their potential to modify cancer development.
  - Use mouse cancer models to discover biomarkers and *in vivo* approaches for early detection and to develop and test new prevention strategies.
- Develop and use non-mammalian organisms as models of complex interactions among the pathways and processes that contribute to cancer etiology.

#### **5. Identify and characterize cancer-predisposing genes in high-risk families and investigate how the expression of these genes is modified by other genetic and environmental factors.**

- Enhance high-risk family recruitment through mechanisms such as the CGN, CFRs, cancer centers, and cooperative groups. In addition, develop common research tools such as family history instruments, model informed consent documents, and research data protection standards; expand mechanisms (e.g., Internet) to aid family identification and referral into research programs.

- Use these resources to initiate large collaborative interdisciplinary studies of high-risk families to quantify cancer risk among carriers of identified major genes (e.g., *BRCA1*, *BRCA2*, *APC*, *VHL*) and to investigate genetic and environmental modifiers of risk.
- Foster consortia of investigators to identify the genetic basis for specific familial aggregations of cancers that have not yet been linked to genes.
- Expand the capability and use of the NIH Center for Inherited Disease Research (CIDR) and other resources to accelerate familial cancer gene identification.

#### **6. Develop risk assessment models that integrate information on genetic and environmental determinants of cancer.**

- Augment selected population-based studies and clinical trials to design and validate statistical models that predict individual cancer risk for specific cancers. Develop strategies to communicate the resulting information to both health professionals and high-risk persons.
- Use these models to identify high-risk individuals for diagnostic, preventive, or therapeutic interventions.
- Develop statistical methods and models to assess the population's cancer burden that is attributable to susceptibility genes, specific exposures, and their interactions.
- Use these population burden models to inform public policy.
- Use new and existing NCI initiatives, including transition career development and established investigator awards, to train investigators in clinical and population risk assessment methodologies.

#### **7. Enroll high-risk individuals into clinical protocols, and conduct studies to address the clinical, behavioral, and societal issues associated with cancer susceptibility.**

- Through the CGN, CFRs, cancer centers, and cooperative groups, recruit high-risk individuals into clinical studies to assess diagnostic and preventive interventions (e.g., the use of innovative breast imaging strategies or preventive agents among *BRCA1/2* carriers).

- Expand and extend selected NCI-supported therapy trials to enable long-term follow-up of survivors for late treatment effects, particularly risk of second cancers. Include biospecimen collections to evaluate the role of genetic susceptibility and other mechanisms of cancer development.
- Through the NCI Biobehavioral Research Program, the CGN, CFRs, interagency collaborations, and other mechanisms, conduct research into the genetics of specific behavioral traits related to cancer risk (e.g., smoking initiation and cessation).
- Supplement existing genetic screening programs and other consortia to conduct behavioral research to assess the impact of predictive genetic testing and cancer risk assessment on high-risk individuals and their families, and to develop interventions for coping with the implications of genetic information.
- Develop and employ model procedures to protect the confidentiality of participants in NCI-sponsored research, and prevent disclosure of identifying information. Implement recommendations from the Fall 1999 NCI Conference on Confidentiality, Data Security, and Cancer Research.

## PROGRESS IN PURSUIT OF OUR GOALS

NCI has initiated a broad range of projects that are providing many new opportunities for studying genetic and environmental determinants of cancer. Recent progress in several efforts is highlighted below.

- NCI launched the **Cancer Genetics Network**, a collaborative multicenter infrastructure that will study the genetic basis of cancer susceptibility and clinical outcomes; apply new genetic information in medical practice; and address psychosocial, ethical, legal, and public health issues. In addition, NCI established the **Cooperative Family Registries for breast/ovarian and colon cancer** to foster interdisciplinary research in the genetic epidemiology of these cancers.
- The **Genetic Annotation Initiative (GAI)**, part of the Cancer Genome Anatomy Project (CGAP), has been established to expand the array of tools available for genetic analysis. The GAI identifies variations in genes discovered through the CGAP. Over 10,000 gene variations have been discovered and in June 1999, NCI made this information available on a pub-

### SPOTLIGHT ON RESEARCH

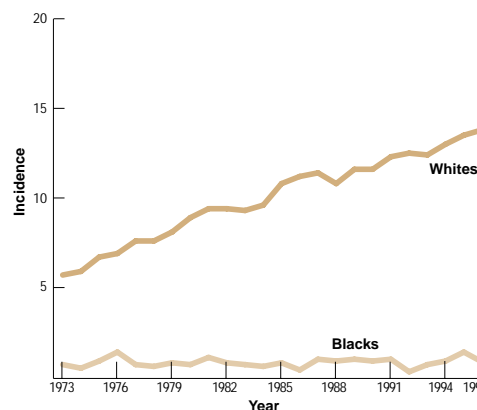
## Malignant Melanoma

The year is 2000. Due largely to sun exposure, one in 75 people can expect during his or her lifetime to develop a disfiguring and potentially deadly cancer of the skin, mucous membranes, eyes, and central nervous system – malignant melanoma. In the United States, cases of melanoma have more than doubled since 1970, and the incidence of this disease is increasing dramatically in persons with light-colored skin in all parts of the world.

Unaware of the danger, people who were sun-worshippers in their teens and early 20s, and people doing outdoor work without sun protection, are now, at 40 or 50 years of age facing the consequences of irreparable DNA damage the sun's ultraviolet light has caused in their skin. Unlike basal cell and squamous cell carcinomas, common skin cancers that typically can be removed surgically and require no further treatment, malignant melanoma is

### Melanoma Incidence 1973-1996

Blacks and Whites (per 100,000 people)



lic Web site for investigators to validate and use.

- The **Cancer Chromosome Aberration Project**, also part of CGAP, has developed tools for characterizing in detail the distinct chromosomal alterations associated with cellular transformation to malignancy. Studies recently funded include a repository of **bacterial artificial chromosomes (BACs)** mapped at high resolution across the human genome.
- This year, NCI funded the development of a prototype **geographic information system (GIS) for breast cancer studies**. The GIS will use existing data bases from Federal, state, and local government and private sources to integrate environmental data on drinking water contaminants, ambient air pollution, electromagnetic fields, ionizing radiation, pesticides, and other toxic chemicals. The system will be piloted as part of the **Long Island Breast Cancer Study**.
- This year, NCI funded the **Mouse Models of Human Cancers Consortium**, a program designed to develop and refine experimental models that reflect the etiology and progression of human cancer. These models

To find out more about confidentiality issues, visit <http://www.nci.nih.gov/confidentiality.html>

will accelerate the discovery of genes that modify susceptibility to cancer and permit the design and testing of new approaches for prevention, early detection, and treatment.

- Under the auspices of the **Mouse Cancer Genome Anatomy Project (MCGAP)**, studies are underway to investigate molecular determinants of cancer in the mouse for comparative studies in human tumors. NCI will make the MCGAP reagents publicly available in support of efforts to identify mouse modifier genes involved in cancer etiology.
- The success of research in cancer epidemiology and genetics depends critically on our ability to **safeguard the confidentiality of genetic and other sensitive information** collected in research studies. NCI is calling for a national discussion engaging the scientific, bioethics, and advocacy communities to address these issues, which have profound implications for the conduct of future research. To stimulate public discourse, NCI has developed a “white paper” on confidentiality, data security, and cancer research.

invasive – and therefore quite serious – even if it only penetrates the skin to a depth of less than a single millimeter. Many patients whose melanoma has not penetrated into surrounding tissue can be cured by surgery alone. For those with more advanced melanoma, new and emerging treatments hold promise for arresting the progress of the disease, or even curing it.

Drugs that enhance the immune system’s response to tumor cells and drugs that attack the tumor cells are being studied in patients with high-risk and metastatic melanomas. One such treatment, high-dose interferon alpha-2a, has been approved by the Food and Drug Administration for treatment following surgery for melanoma patients who are at high risk of disease recurrence.

In addition, NCI is researching new approaches to cancer treatment vaccines. In the vast arsenal of the human

immune system, there are special white blood cells that can infiltrate tumors, and scientists have identified within these cells specific molecules involved in cancer rejection. Researchers are now able to take a melanoma patient’s own tumor infiltrating white blood cells, grow or “amplify” the cells, their associated genes, or gene products, and use them to treat the cancer. This individualized therapy, alone and in combination with the immune response modifier interleukin-2, has shown promising results in initial studies in patients with metastatic melanoma. Other early studies suggest that similar new immunologic approaches will prove useful not only in treating melanomas, but in treating certain groups of patients with breast cancer, colon cancer, ovarian cancer, and lymphomas. Such treatment, called immunotherapy, may lead to a major advance in our progress against the family of persistent and deadly diseases known as cancer.

## Resources: Genes and the Environment

<b>Conduct population-based studies of gene-environment interactions.</b>	<b>\$20.0 M</b>
<ul style="list-style-type: none"><li>■ Create a network to coordinate prospective studies involving a total of one million participants.</li><li>■ Develop infrastructure for case-control studies initially involving 20,000 participants.</li><li>■ Develop repository, laboratory, and informatics infrastructures.</li></ul>	
<b>Assess and measure environmental exposures for use in population studies.</b>	<b>\$8.0 M</b>
<ul style="list-style-type: none"><li>■ Develop epidemiologic methods to assess complex exposures.</li><li>■ Develop non-invasive DNA collection methods and technologies.</li><li>■ Develop molecular measures of cumulative exposure to environmental carcinogens in non-tumor tissue.</li><li>■ Develop and validate molecular approaches to define molecular fingerprints in tumor cells that implicate specific carcinogens.</li><li>■ Develop immunologic and genotypic approaches to identify infectious agents in human cancers.</li><li>■ Support interdisciplinary training programs in molecular epidemiology.</li></ul>	
<b>Identify and characterize gene variants in key molecular pathways.</b>	<b>\$5.0 M</b>
<ul style="list-style-type: none"><li>■ Expand CGAP programs to identify, characterize, and validate gene variants relevant to cancer.</li><li>■ Extend efforts to identify cancer-related molecular pathways.</li><li>■ Accelerate new technology development and application.</li></ul>	
<b>Develop animal/experimental model systems.</b>	<b>\$5.0 M</b>
<ul style="list-style-type: none"><li>■ Develop mouse models of human cancer-related genes.</li><li>■ Develop organisms as models of gene-gene and gene-environment interactions.</li></ul>	
<b>Conduct family-based studies.</b>	<b>\$10.0 M</b>
<ul style="list-style-type: none"><li>■ Enhance recruitment of high-risk families into research studies.</li><li>■ Initiate large collaborative studies to quantify cancer risk and to investigate genetic and environmental modifiers of risk.</li><li>■ Support consortia to study familial clusters of cancers not yet linked to genes.</li><li>■ Support use of CIDR and other resources to identify familial cancer genes.</li></ul>	
<b>Develop risk assessment models.</b>	<b>\$2.0 M</b>
<ul style="list-style-type: none"><li>■ Develop population-based and clinical studies to design and validate risk assessment models.</li><li>■ Develop methodologic approaches incorporating genetic and environmental determinants.</li><li>■ Train investigators in clinical and population risk assessment methodologies.</li></ul>	
<b>Expand clinical research.</b>	<b>\$12.0 M</b>
<ul style="list-style-type: none"><li>■ Recruit high-risk individuals into studies assessing diagnostic or preventive interventions.</li><li>■ Evaluate late effects of cancer treatment, including gene-environment interactions.</li><li>■ Conduct research into the genetics of specific behavioral traits related to cancer risk.</li><li>■ Assess the impact of predictive genetic testing and cancer risk assessment on high-risk individuals and their families; develop interventions for coping with genetic information.</li><li>■ Develop procedures to protect participant confidentiality.</li></ul>	
<b>Management and support.</b>	<b>\$3.0 M</b>
<b>TOTAL</b>	<b>\$65.0 M</b>

## Cancer Imaging

### THE OPPORTUNITY

As recently as 25 years ago, a physician or surgeon who suspected the presence of a tumor in a patient had few options. Order x-ray studies to define and localize the tumor as accurately as the pictures would permit. Schedule the patient for surgery and examine the tumor directly, excise a portion of the unhealthy tissue for biopsy, remove the tumor if possible, and explore surrounding tissues to determine whether the cancer had spread.

Over the last quarter century, refinements in imaging technology have substantially broadened the range of medical options. Current imaging tests now provide much clearer and more detailed pictures of organs and tissues than were possible previously. Imaging already has had a lifesaving effect in detecting some early cancers. X-ray mammography, for example, has saved the lives of many women by revealing the presence of very small cancers before they could be detected by physical examination. Computed tomography (CT) and ultrasound permit physicians to guide long, thin needles deep within the body to biopsy organs, often eliminating the need for an open surgical procedure. CT can reveal whether a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs; important information that can help guide treatment choices.

But the power of imaging technology allows us to do more than simply view structures anatomically, such as visualizing bones, organs, and tumors in the body. Functional imaging – the visualization of physiological, cellular, or molecular processes in living tissue – allows us to see such things as blood flow, oxygen consumption, or glucose metabolism in real time, as *they take place* in living cells of the body. As we gain a better understanding of the fundamental nature of cancer, cellular and molecular imaging will be a key tool in translating this knowledge into better ways of

diagnosing, treating, and preventing the disease. Imaging can identify the kinds of molecular structures/receptors that cover the surface of a tumor, information that potentially can predict how it may behave and respond to certain treatments. Or, by providing a picture of glucose utilization in tumor cells, imaging can demonstrate – without the need for a biopsy – how a tumor is responding to a recently administered treatment.

And seeing how the processes and pathways inside a cell change as the cell transforms from normal to cancerous will allow us to detect this change in people earlier in the cancer process, perhaps before a tumor has even had the chance to become fully malignant. Eventually we expect to be able to visualize the actual molecular signatures of a cancer. We will be able to tell, in the radiology suite of a hospital, which genes are being expressed in a person's cancer, and we will be able to translate this information directly into better management of the disease. In other words, the ability to detect, through imaging, the molecular changes associated with a tumor cell will vastly improve our ability to detect and stage tumors, select appropriate treatments, monitor the effectiveness of a treatment, and determine prognosis.

The potential of imaging to improve cancer treatment extends well beyond using imaging information to help select effective treatments or preventives. For example, combining precise imaging techniques with radiation sources and high performance computing is significantly improving our ability to shape radiation treatments to the tumor's three-dimensional contours. In principle, imaging techniques can be interfaced with other tumor-killing approaches – toxic chemicals, gene therapy, heat, and cold – to more precisely guide tissue destruction at the tumor site. Being able to distinguish between cancerous and normal tissue and deliver treatments only to diseased tissues in a minimally invasive way will potentially minimize surgical trauma, shorten

recovery time, and reduce health costs.

Parallel developments in image enhancement agents are improving our ability to capture changes in the biochemical makeup of cells and other living structures. Enhancement agents contribute to image formation in three ways. They may localize in certain body organs or structures (anatomic localization); they may attach to specific molecules in the body (receptor localization); or they may become activated by certain biochemical or physical conditions, such as the presence of a specific enzyme or low oxygen concentration in the cell (activatable agents). We anticipate that contrast agents of the future will be able to reveal the functional characteristics of tumors that determine clinical behavior and response to therapy.

In imaging, as elsewhere in cancer research, animal models of cancer will make possible certain kinds of studies that are difficult or impossible to perform in people. In addition to learning more about cancer, work with animal models can enable imaging technology improvements that then can be applied in the clinic. Imaging permits repetitive observations of the biological processes underlying cancer growth and development, and the level of resolution with some imaging modalities is now approaching the size of individual cells. Imaging also can help assess the effectiveness of new instruments, and animal studies will be crucial in developing a new generation of clinically useful imaging agents to assess drug effects in patients.

Although it seems clear that better imaging tools will improve patient care, we need better ways of measuring that improvement. In evaluating new therapies, a cure or prolonging the patient's life are often important measures of effectiveness. For diagnostics, however, these measures are relatively insensitive. The problem is that survival is a global reflection of all diagnostic and therapeutic interventions that a patient experiences; it often is difficult or impossible to ascribe improvements in survival to a particular diagnostic test. More appropriate measures of effectiveness might include, for example, greater efficiency of testing, less cost, fewer hospital days, less morbidity, and the need for less extensive or disfiguring treatment. In short, we need improved methodologies to assess the ultimate value of diagnostic tests.

Three years ago, NCI recognized the great untapped potential that imaging technology holds for cancer and identified it as an area of extraordinary opportunity. With this designation, we began a three-year effort aimed at significantly advancing imaging to more fully exploit its promise for cancer research and care. By establishing an Imaging Working Group, we stimulated constructive communication among experts from diverse disciplines who have advised NCI about how we can quickly and effectively move imaging research forward. The efforts of this group helped us define research needs and opportunities. In the past year, we launched a national network to evaluate diagnostic imaging technologies. We also have established several small-animal imaging research centers.

Still, we have much important work to do before the full promise of the imaging sciences is realized for cancer. Having laid the groundwork, we now will target tangible improvements in cancer detection, diagnosis, and treatment – results that will provide real clinical benefits for people with cancer and those at risk.

## THE GOALS

- Develop and validate imaging technologies and agents (e.g., probes, radiocontrast agents) that have the sensitivity to detect precancerous abnormalities and very small cancers.
- Develop imaging techniques that identify the biological properties of precancerous or cancerous cells that will predict clinical course and response to interventions.
- Develop minimally invasive imaging technologies that can be used in interventions and in assessing treatment outcomes.
- Foster interaction and collaboration among imaging scientists and basic biologists, chemists, and physicists to help to advance imaging research.
- Create infrastructures to advance research in developing, assessing, and validating new imaging tools, techniques, and assessment methodologies.



## THE PLAN

### Objectives

- 1. Accelerate development of clinically useful technologies for detecting malignant and precancerous cells and for visualizing their functional characteristics.**
  - Expand the number of *In Vivo* Cellular and Molecular Imaging Centers. (See Progress section for description)
  - Expand the Small Animal Imaging Resources Program to improve access to researchers testing new approaches to diagnosis, treatment, and prevention in animal models of cancer. NCI will foster collaborations between this program and the Mouse Models of Human Cancers Consortium.
  - Support multidisciplinary centers of expertise to develop optical technologies and perform clinical feasibility tests of instruments able to visualize epithelial tissue at risk for common cancers and recognize the optical signatures of precancerous abnormalities.
- 2. Develop, synthesize, validate, and distribute to the research community novel imaging agents.**
  - Create a program similar to NCI's Rapid Access to Intervention Development initiative (designed to accelerate the movement of novel interventions from the laboratory to the clinic) for imaging agents. NCI will, on a competitive basis, synthesize, test, and distribute probes that image the physiological and functional status of tumor tissue in the human body.
  - Establish a publicly available data base of agents available to the research community, together with information on their properties.
- 3. Expand and improve clinical studies of imaging modalities and image-guided interventions.**
  - Establish centers for developing and clinical feasibility testing of technologies enabling minimally invasive, image-guided therapy for localized malignancies (e.g., brain, breast, prostate).
  - Enable collaborations between the clinical cooperative groups and the Diagnostic Imaging Network (see Progress section for description) for definitive testing of minimal-
- ly invasive, image-guided interventions that appear promising in early feasibility studies.
  - Expand the Diagnostic Imaging Network to permit it to develop a full menu of clinical trials relating to all major cancers.
  - Develop methodologies to assess the medical value of diagnostic tests in clinical trials. Support the full development of outcomes research as applied to the evaluation of imaging diagnostics.
- 4. Integrate molecular and functional imaging technologies into drug development and early clinical trials.**
  - Support the development of *in vivo* and clinical imaging research tools for assessing the biologic effect of cancer drugs on their intended target or pathway. (See Molecular Targets)
- 5. Establish information archives and repositories needed by the research community.**
  - Establish data banks of standardized digital images associated with known clinical outcomes.
  - Provide resources to develop and test image processing and analysis algorithms on these standardized data sets.
- 6. Provide innovative imaging equipment to the research community for limited scale feasibility testing.**
  - Establish a competitive program in which innovative equipment prototypes developed in industry or academia will be provided to selected academic institutions for feasibility testing, in close collaboration with the developer.

## PROGRESS IN PURSUIT OF OUR GOALS

Over the past year, NCI launched several exciting new initiatives and achieved important progress in ongoing programs. The following describes some of our new programs and activities as well as the progress made in programs already underway.

- Advances in both structural and functional imaging technologies have produced remarkable tools for understanding, detecting, and diagnosing cancer. Yet the power of these tools

could be amplified appreciably if advances in imaging technology could be merged with the myriad new discoveries in cancer-related genes and proteins. A scientific gulf still exists between basic scientists who discover new cancer genes and intracellular pathways – any of which could serve as a diagnostic or therapeutic target – and imaging scientists who focus on non-invasive approaches to transform these discoveries into a greater understanding of cancer. To narrow this gap, NCI will award two to three grants in the coming year to support **In Vivo Cellular and Molecular Imaging Centers (ICMICs)**. ICMICs will facilitate interaction among scientists from a variety of fields to conduct multidisciplinary research on cellular and molecular imaging. Because the integration of this breadth of expertise is still in its early stages, the NCI also will award six pre-ICMIC planning grants. The pre-ICMIC planning grants will provide time and funds for investigators and institutions to prepare themselves, organizationally and scientifically, to establish an ICMIC.

- **Digital mammography** is considered one of the most promising technologies for use in large-scale screening programs to improve early breast cancer detection. To advance the state-of-the-art in digital mammography displays and workstation design, NCI has set aside funds to encourage studies that focus on

research and development in critical areas to make digital mammography a more useful device in clinical settings.

- Small animal models, particularly genetically engineered mice, are powerful discovery tools, but we have yet to capitalize fully on their potential in cancer research. NCI will fund four to five **Small Animal Imaging Resource Programs** this year. This initiative will support activities to develop and apply a wide variety of imaging modalities that focus on functional, quantitative imaging. Quantitating image data for small animals will lead the way to quantitative methods that can be applied in humans.
- Preclinical models of human cancer can be valuable tools for developing and testing new therapeutic, preventive, early detection, and diagnostic imaging strategies. NCI will develop and use a **Preclinical Models Imaging Forum** (a mechanism that will include meetings and a Web site) to link the expertise of participants in the Mouse Models of Human Cancer Consortium, imaging technique developers and users of the small animal imaging centers, the Diagnostic Imaging Network, investigators using imaging techniques to observe patients, and investigators who use model systems other than mice. The information generated through this forum will be helpful for designing and testing imaging techniques to detect human cancers and in developing and validating new

#### SPOTLIGHT ON RESEARCH

## How Can Spiral CT Improve Early Detection of Lung Cancers?

**F**inding lung cancers early is believed to be a missing key to combating this deadly disease – the leading cause of cancer death for men and women in the United States. Yet despite intensive research, a reliable screening technique for early detection of lung cancers has eluded discovery. Now, however, advances in imaging technology have led to the development of a screening technique, spiral computerized tomography (spiral CT), that may prove to be the first screening method to find some of these cancers early and reduce lung cancer deaths.

With spiral CT, the entire lungs, from the neck to the diaphragm, can be scanned in less than 20 seconds – a single breath-hold. Rapid scanning improves the detection of smaller lesions since they are not moving in and out of the field of view due to breathing; moreover, rapid scanning minimizes radiation exposure. Preliminary studies of spiral CT have shown promise in detecting small cancers. For example, adenocarcinomas, the most common lung cancer, can be detected more readily with spiral CT than with standard chest x-ray. However, this technology may be less useful for detecting central airway tumors, such as

preclinical models.

- Before new or refined imaging tools can be used as cancer diagnostic instruments, they must be evaluated for their safety and effectiveness. In March 1999, NCI funded the **Diagnostic Imaging Network** to bring together imaging experts from around the Nation to perform a broad spectrum of multi-institutional clinical trials on diagnostic imaging tools related to cancer. The Diagnostic Imaging Network will establish collaborations with NCI Cooperative Groups to expedite the integration of diagnostic imaging technologies into clinical trials aimed at assessing new therapies.
- Improved imaging techniques can enable clinicians treating prostate cancer to accurately localize and stage a tumor, information that can be useful for choosing treatments. NCI has set aside funding to launch a new initiative aimed at **developing non-invasive imaging technologies for the localization, biopsy, and minimally invasive treatment of prostate cancer.**
- New drug discovery programs are producing an ever increasing number of molecules for investigation, in turn stimulating a need for research that integrates imaging techniques into preclinical and clinical studies to assess newly devel-

For information on the Diagnostic Imaging Network visit <http://www.acrin.org>

oped therapeutic agents. NCI has set aside funding for the **development and application of labeled therapeutic agents as compounds for imaging studies and imaging agents that serve as metabolic markers of response to newly developed therapeutic agents.**

- NCI, the National Electrical Manufacturers Association, the FDA, and the Health Care Financing Administration are collaborating to develop **partnerships with the imaging industry.**

- To stimulate the discovery, development, and advancement of highly innovative new areas of imaging science, NCI has made available **Exploratory/Development Grants for Diagnostic Cancer Imaging.** These grants are designed to provide investigators with the initial resources required to accomplish feasibility and pilot testing of innovative ideas. Some of these feasibility studies will help

generate new research programs in previously unexplored areas. This ongoing program already has been used to fund studies in a wide variety of imaging areas, including new MRI technology to diagnose head tumors, and a system employing both MRI and ultrasound in minimally invasive detection of prostate abnormalities.

squamous cell carcinomas, and very rapidly growing carcinomas, such as small cell lung cancers.

NCI is funding clinical trials to determine the size and types of abnormalities that can be detected by spiral CT. But many lesions detected with this technology may not be malignant. Therefore, to avoid invasive, potentially dangerous biopsy procedures such as open lung surgery, we must consider carefully how we will evaluate the abnormalities found with spiral CT. Two technologies are available to aid in diagnosis: high-resolution CT, which

helps to distinguish between cancerous and non-cancerous tissue, and positron-emission tomography (PET), which shows the differing uptake of radioactive isotope "tracers" in benign growths and malignant tumors. Other diagnostic techniques are being studied. But the potential physical and psychological complications arising from evaluation of what eventually is found to be benign disease must be recognized and addressed. NCI will also fund studies to assess the benefits and risks of routine lung cancer screening.

## Resources: Cancer Imaging

<b>Develop clinically useful technologies for detecting malignant and precancerous cells.</b>	<b>\$27.2 M</b>
<ul style="list-style-type: none"><li>■ Fund 2 Centers and 8 four-year planning grants for <i>In Vivo</i> Cellular and Molecular Imaging Centers.</li><li>■ Support 10 additional Small Animal Imaging Resource Programs.</li><li>■ Support 4 multidisciplinary Centers of Excellence for Optical Technologies.</li></ul>	
<b>Develop, synthesize, validate, and distribute novel imaging agents.</b>	<b>\$4.0 M</b>
<ul style="list-style-type: none"><li>■ Create a RAID-like program for imaging agents – fund 3 to 6 agents.</li><li>■ Establish a publicly available data base of agents.</li></ul>	
<b>Conduct clinical trials of imaging modalities and image-guided interventions.</b>	<b>\$16.5 M</b>
<ul style="list-style-type: none"><li>■ Establish 4 centers for development and clinical feasibility testing of image-guided therapy for localized malignancies.</li><li>■ Support collaborations between clinical cooperative groups and the Diagnostic Imaging Network.</li><li>■ Expand the Diagnostic Imaging Network.</li><li>■ Develop methodologies to assess medical value of diagnostic tests in clinical trials.</li></ul>	
<b>Integrate molecular and functional imaging technologies into drug development.</b> (Budgeted in the Molecular Targets Opportunity.)	<b>\$ 0 M</b>
<ul style="list-style-type: none"><li>■ Support development of <i>in vivo</i> and clinical imaging research tools for assessing drug effects on intended targets.</li></ul>	
<b>Develop information archives and repositories.</b>	<b>\$1.5 M</b>
<ul style="list-style-type: none"><li>■ Establish data banks of standardized digital images associated with known clinical outcomes.</li><li>■ Develop and test image processing and analysis algorithms on standardized data sets.</li></ul>	
<b>Evaluate innovative imaging equipment.</b>	<b>\$7.5 M</b>
<ul style="list-style-type: none"><li>■ Establish a competitive program for feasibility testing of innovative prototypes.</li></ul>	
<b>Management and support.</b>	<b>\$2.0 M</b>
<b>TOTAL</b>	<b>\$58.7 M</b>

## Defining the Signatures of Cancer Cells: Detection and Diagnosis

### THE OPPORTUNITY

In the 19th century, the light microscope opened a new frontier in the study of disease by opening a window on the inner workings of the cell. The science of pathology – the branch of medicine that deals with the essential nature of disease – expanded to include the study of structural changes in cells. For the first time, disease could be linked to visible, recognizable changes in the cells of the body.

At the cusp of the 21st century, new molecular-based technologies are bringing us to a similar epiphany. These new technologies are enabling us to identify features of individual cells in ways unimagined by our 19th century predecessors. For example, all cell types, depending on their functions, have unique, identifiable “signatures” – special characteristics such as which genes are active and what proteins or other cellular products are manufactured by the cell. Our new technologies are enabling us to read and understand those signatures. We have learned that during the transformation of a normal cell to a cancer cell, the signature changes, and that change becomes a signal of the presence of cancer.

Further, we have learned that cells surrounding the incipient tumor may also undergo changes indicating that cancer is present. For example, tobacco-induced molecular changes in the mouth may predict the risk of developing lung cancer, and cancers of the urinary tract may be signaled by cancer cells that are “shed” in the urine. Reading the signatures of these easily accessed cells may enable us to develop simple, non-invasive tests to find cancers located deep within the body.

The implications of these findings are profound. By reading cellular signatures accurately, we may be able to detect and diagnose cancers before they have had a chance to invade nearby tissues. In fact, with the tools we are developing, a single drop of blood from a patient’s finger may be all

that is needed to find a cancer, assess the threat it poses by comparing its traits to profiles in an on-line library of tumor characteristics, choose the best possible treatment, and monitor the patient’s recovery. By assessing the meaning of individual changes in the cell’s signature, we will be able to determine which cancers are most likely to progress and which are less likely to do so – a dilemma that confronts, for example, doctors treating patients with prostate cancer – thereby avoiding the consequences of unnecessary treatment. By studying the sequence of changes a cell undergoes as it transforms from normal to cancerous, we will gain important insights into the etiology of the disease. And by applying what we have learned, we will be able to identify new targets, at the molecular level, for effective prevention and treatment. (For more on this exciting area of scientific opportunity, see page 57.)

“Defining the Signatures of Cancer Cells” was first identified as an area of extraordinary scientific opportunity in 1996, and it continues to be an area rich in scientific promise today. For example, we now are in a position to learn new ways to characterize tumors more efficiently – that is, to determine which genes are active and inactive, and the levels of specific proteins that are present in a particular tumor. Such “molecular fingerprinting” will greatly enhance the specificity of cancer diagnosis by allowing us to differentiate among tumors at the molecular level, and will enable us to devise treatments targeted at cellular subtypes of different cancers. We can now use changes in molecular signatures to help us identify infectious and environmental agents that may be responsible for the development or progression of a tumor. In addition, while many of our previous efforts have centered on identifying genes involved in cancer, we are very interested in learning more about the functions of the proteins produced by these genes. Finally, there has been a gap between the identification of preclinical tumor changes, early evalua-

tion of new identification techniques, and their clinical application. We now have the opportunity to synthesize these disparate findings into a body of knowledge that will translate into real health benefits. Our ultimate goal is to push back the detection and diagnosis of cancer to the earliest stages, thereby offering the potential to focus intervention efforts at preventing overt disease, rather than at treatment.

Clearly, we have made substantial progress. However, much remains to be done if we are to take full advantage of the opportunities in this area. The diagnostic value of molecular-based methods must be confirmed and their practical benefits established against the background of conventional medicine. New technologies must be developed, and new preclinical models must be created and validated to establish our findings. Finally, it is crucial that we develop the sophisticated computer systems, data bases, and statistical methods needed to integrate the complex information being generated by the new technologies with the biologically relevant data. In this way we will be able to validate the predictive value of the new approaches.

## THE GOALS

- Complete the molecular catalogue of cancer by characterizing the molecular profiles of precancerous and cancer cells at all stages of clinical disease, associated host cells, and surrounding tissue and body fluids.
- Develop improved methods for detecting precancerous lesions and cancers at their earliest stages, when cure is most possible.
- Develop a new taxonomy for cancer based on the molecular signatures of cells and use it to develop improved strategies for cancer diagnosis and prognosis.
- Develop preclinical models that reflect the molecular basis of human cancer etiology and progression; use the models to inform the design of new molecularly based approaches for early detection, diagnosis, prognosis, and treatment of cancer, and to test and refine these approaches.

- Develop integrated technologies to detect defined molecular signatures that predict cancer occurrence or progression and provide a seamless interface with intervention.

## THE PLAN

### Objectives

- 1. Continue to characterize the molecular profiles of precancerous and cancer cells at all stages of clinical disease, associated host cells, and surrounding tissue and body fluids.**
  - Complete the Tumor Gene Index of genes expressed in cells at all stages of tumor development.
  - Enhance the Director's Challenge to establish molecular profiles of human cancer and develop molecular classification schemes for all human cancers.
  - Fund the development of data bases and analytic tools for comprehensive molecular analysis.
- 2. Establish and make available tissue resources to maximize the practical application of molecular signatures to problems in cancer.**
  - Establish a national tissue resources system for all major cancers, including cancers of the lung, breast, prostate, colon, head and neck, brain, soft tissue, blood, bone, the gynecologic and genitourinary systems, and childhood malignancies.
  - Develop tissue arrays and implement a system for distributing tissue and tumors.
  - Publicize the existence and capabilities of tissue resources to the research community.
  - Partner with the advocacy community to develop a public education program on issues surrounding tissue donation for research.
- 3. Develop and deploy a robust informatics system for molecular pathology.**
  - Establish pathology standardization and agreement on common data elements.
  - Develop query and search capability for the national tissue repositories.
  - Provide automatic encryption features for personal identifiers associated with tissue resources.

- Establish linkages to population data bases, such as SEER and other registries, to aid in acquiring outcome and follow-up information.
4. **Create a classification system for cancer and pre-cancer based on the molecular signatures of cells; use it to model improved approaches to early detection, diagnosis, and prognosis.**
    - Initiate a “Director’s Challenge” to fund consortia to identify molecular signatures of preneoplastic lesions associated with cancer development.
    - Fund the development of tissue repositories of precancerous lesions.
    - Support the development of standards for correlating molecular and pathologic criteria used to define stages of human cancer development.
    - Expand the Early Detection Research Network to expedite the discovery, validation, and development of new early detection tests for all major human cancers.
    - Support the development of high throughput technologies for isolating and enriching cells shed in body fluids.
    - Support the development of high throughput assays for the molecular characterization of proteins and for detecting informative markers in body fluids.
  5. **Validate molecular signatures for their potential value in cancer diagnosis and prognosis, and in predicting intervention response.**
    - Create a Diagnostics Validation Network to provide the research community with a means to evaluate and validate signatures with possible diagnostic value. Establish linkage to clinical information (i.e., pathology, histology, treatment response, stage, and grade) to establish surrogate molecular endpoints for application in cancer prevention and treatment studies.
    - Provide supplemental funding to groups conducting prevention and therapy studies to evaluate biomarkers for their ability to predict response to therapeutic and prevention interventions.
  6. **Develop preclinical models that reflect the genetic and molecular changes implicated in human cancer etiology and progression.**
    - Accelerate the Mouse Cancer Genome Anatomy Project to define the molecular anatomy of mouse cancer models.
    - Provide funds to validate mouse models of human cancer by systematic analysis and phenotyping.
    - Develop Mouse Models Application Funds to test early detection, diagnostic, imaging, preventive, and therapeutic interventions in mouse models.
    - Fund Phased Innovation Awards to develop new tissue, cellular, and computational models of cancer.
  7. **Support the development of new technologies.**
    - Expand the Unconventional Innovations Program to develop biosensors of human cancer and cancer development.
    - Fund an Unconventional Innovation Access Program to apply technology discoveries to clinical testing.
    - Initiate a collaboration with the National Aeronautics and Space Administration (NASA) to develop minimally invasive molecular biosensors.

## PROGRESS IN PURSUIT OF OUR GOALS

The past several years have seen an explosion of discovery in this area. NCI’s new and ongoing initiatives include:

- The Institute’s flagship program for molecular discovery is the **Cancer Genome Anatomy Project (CGAP)**. CGAP’s overall goal is to determine the complete profile of expressed (active) genes in normal, precancerous, and cancer cells, with the aim of making it possible to recognize all major steps of tumor development. Thus far, we have established the platform for building the complete molecular catalogue of cancer. Initially, we focused on cells that directly give rise to tumors and placed emphasis on five major types of cancer. Now that the necessary infrastructure has been established, we are positioned to examine a much wider variety of cancers and to extend our dis-

covery process to include cells that play key supporting roles in cancer development, such as the cells that form the tiny blood vessels that feed tumors, cells that metastasize and the tissues that support those metastases, as well as body fluids that might contain early indications of cancer development. This new information will greatly enrich our molecular catalogue of cancer and make it even more useful to the research community.

CGAP is composed of five initiatives. The most established of these is the **Human Tumor Gene Index (TGI)**. Its primary goal is to identify the genes expressed during the development of human tumors. Data from the CGAP have been used to discover approximately 30,000 new human genes. Other components of CGAP include the **Mouse Tumor Gene Index**, the **Cancer Chromosome Aberration Project**, the **Genetic Annotation Initiative**, and **Molecular Profiling**. Each of these is described in greater detail on the CGAP Web site.

- NCI is creating a multi-institutional **Early Detection Research Network** to develop sensitive and specific tests for the earlier detection of cancer. The Network will link centers of expertise in tumor biology, diagnostic technologies, and clinical trials methodology in academia and industry to develop high throughput assays suitable for clinical application. To expedite the discovery and development of more sensitive and specific markers for early disease, NCI also will establish links between Network activities and programs in academia and industry.
- In 1998, the NCI Director issued his **Director's Challenge: Toward a Molecular Classification of Tumors**, a challenge to the research community to revolutionize the classification of human tumors. Traditionally, tumor classification has been based on morphology, or the tumor's structure. But morphological classification alone does not always accurately predict biological behavior, treatment response, or prognosis. We anticipate that the research community will rise to this challenge and discover new ways to

For more CGAP information, visit <http://www.ncbi.nlm.nih.gov/CGAP>

combine technological advances in molecular detection with rapidly advancing knowledge of tumor biology to provide a more clinically predictive and useful tumor classification system.

- Success in developing molecular diagnostics depends on the availability of **specimen banks for tissue analysis**. NCI has several programs designed to collect and disseminate tissue, such as the **Cooperative Breast Cancer Tissue Resource**. NCI also will develop a **national prostate cancer tissue resource**. In addition, NCI sponsors the **Tissue Expediter**, a scientist whose role is to identify sources of human tissue specimens and to help researchers locate the tissue and related data they need.
- Models that truly reflect the behavior of human cancer and its response to preventive and therapeutic maneuvers would profoundly improve our ability to understand the process of malignant transformation, and could enhance our ability to evaluate a range of biomarkers prior to their clinical application. To meet the need for animal models in a variety of settings, NCI is soliciting applications for establishing a **consortium that will develop and validate mouse models for human cancer**.
- New technology development is key to success in this area. Many new technologies will be supported through NCI's **Phased Innovation Award**, developed last year to support technology research from the evolution of innovative concepts, through feasibility testing, and ultimately to subsequent full-scale development. In its first year, this mechanism already has reduced significantly the time lag between the review process and application funding, and is expected to continue accelerating the pace of technology development for profiling molecular characteristics of preneoplastic cells. A similar award, the **Phased Technology Application Award**, has been created to support the pilot application of instrumentation, techniques, and analytic tools (e.g., computer software) relevant to research on the molecular biology of cancer.



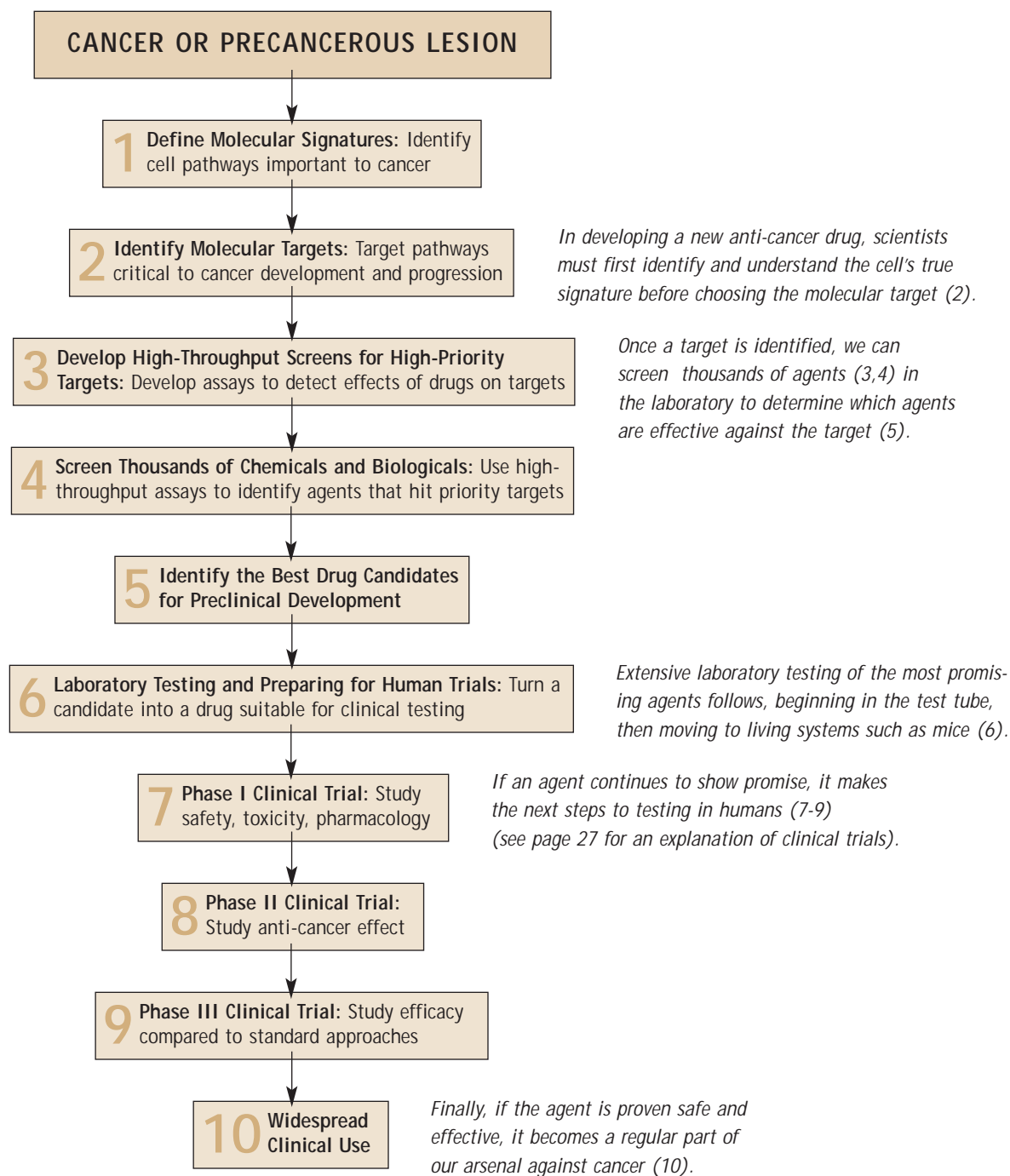
# Resources: Defining the Signatures of Cancer Cells

<b>Characterize the molecular profiles of precancerous and cancerous cells.</b>	<b>\$16.0 M</b>
<ul style="list-style-type: none"> <li>■ Complete the Tumor Gene Index.</li> <li>■ Enhance Director's Challenge to establish molecular profiles of human cancer and develop molecular classification schemes for all human cancers.</li> <li>■ Develop data bases and analytic tools.</li> </ul>	
<b>Establish and make available tissue resources.</b>	<b>\$7.0 M</b>
<ul style="list-style-type: none"> <li>■ Establish and promote a national system.</li> <li>■ Develop public education materials about tissue donation for research.</li> </ul>	
<b>Develop and deploy molecular pathology informatics system.</b>	<b>\$3.0 M</b>
<ul style="list-style-type: none"> <li>■ Establish standardization and common data elements.</li> <li>■ Provide automatic encryption features.</li> <li>■ Establish linkages to population-based data resources.</li> </ul>	
<b>Create new classification system for cancer; use it to model improved approaches to detection, diagnosis, and prognosis.</b>	<b>\$20.5 M</b>
<ul style="list-style-type: none"> <li>■ Initiate a Director's Challenge to identify molecular signatures of preneoplastic lesions.</li> <li>■ Expand the Early Detection Research Network.</li> <li>■ Develop repositories, assays, and new technologies.</li> <li>■ Develop standards for correlating molecular and pathologic criteria used to stage cancer.</li> </ul>	
<b>Validate potential molecular signatures.</b>	<b>\$16.0 M</b>
<ul style="list-style-type: none"> <li>■ Create Diagnostics Validation Network.</li> <li>■ Provide supplemental funding to groups to evaluate biomarkers.</li> </ul>	
<b>Develop preclinical models.</b>	<b>\$15.0 M</b>
<ul style="list-style-type: none"> <li>■ Accelerate the Mouse Cancer Genome Anatomy Project.</li> <li>■ Develop Mouse Models Application Funds to test early detection, diagnosis, prevention and treatment interventions.</li> <li>■ Develop new tissue, cellular, and computational models of cancer.</li> </ul>	
<b>Support technology development.</b>	<b>\$11.5 M</b>
<ul style="list-style-type: none"> <li>■ Expand the Unconventional Innovations Program to develop biosensors.</li> <li>■ Fund an Unconventional Innovation Access Program to apply discoveries to clinical testing.</li> <li>■ Collaborate with NASA to develop minimally invasive molecular biosensors.</li> </ul>	
<b>Management and support.</b>	<b>\$4.0 M</b>
<b>TOTAL</b>	<b>\$93.0 M</b>

## The Path to a New Cancer Drug

The pathway to the development of a new treatment or preventive drug begins at the cell. All cells have unique signatures composed of all the genes that are active, proteins that are secreted, processes that are followed, and pathways that are present. A cancer cell's signature differs from that of a normal cell; different genes are active or

inactive, for example, or different pathways may be present. Certain components of a cancer cell's signature – genes, pathways, or patterns of behavior – may be especially vulnerable to the action of treatment or preventive agents. These components are the molecular targets at which treatments or preventives can be aimed.



# Molecular Targets of Prevention and Treatment

## THE OPPORTUNITY

Our systematic search for drugs to combat cancer began about 60 years ago. During most of this search, our understanding of cancer has been limited by technologies available at the time – the microscope enabled us to see the structure of the cancer cell, but our ability to discern the once normal features and internal pathways that had become corrupted was incomplete. As a result, our techniques for identifying drugs to prevent or treat cancer were rate-limiting, involving tests that measured inhibition of cancer's development or its growth in animals or test tubes. Despite these limitations, scientists have identified drugs that, alone or with surgery, can cure some cancers in people and can significantly ease symptoms in others.

Yet anyone who has ever undergone treatment for cancer – or watched a loved one undergo treatment – knows that our ability to treat the disease leaves much to be desired. Most of the common tumors of adults – the ones that cause most of the suffering and death from cancer – do not respond well to the treatments available today. And even when these treatments succeed in shrinking tumors or eliminating them from the body, they can cause a variety of short- or long-term side effects that can have a devastating impact on a patient's quality of life.

Many of the serious side effects of cancer treatments stem directly from their non-selective nature. Until recently, we were unable to detect the differences between the molecular features of normal and cancerous cells, and thus, a compound that inhibited the growth of a tumor cell also inhibited the growth of a healthy cell. This is what causes many of chemotherapy's most severe toxic effects. However, drugs that target the molecular differences between tumor and normal cells – the altered genes or proteins or the corrupted pathways – would be less toxic and more effective than the drugs we currently have.

The situation for prevention is similar. The recent findings that the anti-estrogen tamoxifen can reduce the risk of invasive breast cancer suggests that cancer prevention is a realistic possibility. If we know the precise molecular steps that characterize premalignant change, we can attempt to find agents that reverse these changes or prevent next steps critical to the full development of cancer from occurring. This new generation of chemopreventives will be optimized and made more efficient by clinically testing the effect of a preventive on its intended target.

Until recently, scientists working to discover effective prevention and treatment agents have faced a formidable barrier: not knowing precisely what cancer is. No longer is this the case. With the evolution of molecular biology and the emergence of new technologies, we are gathering remarkable knowledge about the nature of a cancer cell and the molecular changes that occur during a tumor's development. The extraordinary opportunity before us – to discover and exploit molecular targets for cancer prevention and treatment – arises from the convergence of scientific advances in several areas.

### Cancer Biology

We continue to make astounding strides in our understanding of how molecules and pathways in premalignant or fully malignant cells differ from their normal counterparts. This new knowledge is enabling us to understand and classify human tumors in terms of molecular changes and also has given us a new strategy for cancer drug discovery. Today, every difference between cancerous and normal cells is not only a biological fact or a point of interest to the biochemist, it is a potential target of opportunity for drug discovery.

### Synthetic Chemistry

Traditionally, the chemicals used in anti-cancer drugs have come from nature – from tropical rain

forests or organisms in the sea or the soil. Using recently developed techniques, chemists now are able to create in the laboratory enormously diverse collections of compounds. Now, both naturally and synthetically derived chemicals can be screened for possible anti-cancer effects. The ability to test the effectiveness of large numbers of structurally diverse compounds – using highly informative cancer-relevant techniques that exploit our knowledge of cancer biology – is now a reality.

### **Biosynthetic Chemistry**

Synthetic chemists have long been able to manipulate small molecules to produce useful medicines. The recent biotechnology revolution has cleared the way for biochemists to mix and match genes to design synthetic proteins. Changing proteins in cells is an important breakthrough, since proteins form the “messages” that make up communication pathways that determine a cell’s healthy or aberrant behavior. Historically, scientists have been unable to alter these messages since they only had access to proteins produced naturally within cells. Now scientists can change the messages sent by protein molecules, creating a whole new class of drugs to be tested for anti-cancer activity.

### **High Throughput Screening**

Over the past decade, advances in biotechnology have made it possible to devise highly sensitive, highly efficient tests for virtually any biological process. These tests, or “smart” assays, can be used many different ways. For example, they can be used to screen cell lines and tissues for the presence of particular genes, proteins, or entire pathways – an essential step in identifying the chain of events involved in every stage of cancer development. These assays also can be used to screen potential drugs for anti-cancer effects; thousands of compounds can be screened in this manner each week. Moreover, these assays can be performed on a micro scale with tiny quantities of material, using computer-driven robots to maximize efficiency.

### **Medical Imaging**

Until now, imaging has been used in cancer research and care to gain information about the occurrence, size, and location of tumors.

Refinements in imaging technology are allowing us to watch molecular processes within the cell unfold, as they occur, with unprecedented vividness and accuracy. Imaging techniques are being developed to tell us not only the location of a tumor but the kind of molecules it contains and how its biochemical pathways work. Further advances will have a profound impact on the testing of potential cancer interventions. For example, new imaging technologies have the potential to track where drugs go in the body, or visualize a drug’s immediate effects on abnormal collections of cells and on normal tissues. These uses of such functional imaging approaches are likely to be as common in the future as the use of the CT scan is now.

The convergence of these advances presents us with the opportunity for a real revolution: to place the discovery and development of drugs for cancer prevention and treatment on a firm scientific footing. There is good reason to think that doing so may, within the next decade, lead to a whole new generation of cancer treatments and preventives. Yet, to ensure our success, we need to create conceptual and functional links among drug discovery, development, and clinical testing in ways that are completely unprecedented.

To understand why, consider the main questions that researchers need to pursue about a new drug’s effect on malignant or precancerous cells. Does the drug kill the cancer, or at least effectively block its growth and spread? What part of the cell’s complex machinery does it disrupt and how is this disruption related to its anti-cancer effect? Until now, with our incomplete knowledge of cancer, we had neither the knowledge nor the tools to address this second question, and thus, our clinical testing focused only on the first.

It is crucial that we gather the knowledge and develop the tools to answer both of these questions. When we can, we will finally be able to address some of the most important questions in cancer therapeutics. If a drug is working well, why is it working, and if not, why not? Are we giving a person the right amount, or too much, or too little? Do we have to give people the maximum amount of a drug that they can tolerate, or can we judge the right amount by whether the drug is getting to the tumor and affecting its target? Will the drug harm the patient, now or in the future? Only when we can answer these questions will we be

able to predict who is likely to respond to a particular treatment and who will not. Moreover, information from the clinic and from the laboratory will reinforce each other, providing the basis for the design of even better drugs in the future.

Timely investment in this area is critical. If the NCI does not invest now, engaging academically-based cancer biologists will depend on the alignment of their discoveries with the product development goals of individual companies. This process will be incomplete and will not necessarily emphasize the compounds, hypotheses, or approaches that are likely to yield the most far-reaching advances. Because most companies' efforts are highly focused, many important scientific opportunities will not be explored in a timely manner. Most importantly, development of the practical tools needed to enable assessment of a drug's effects on its molecular target *in vivo* will not happen quickly or systematically, and information and reagents will not be made publicly available as soon as they might have been.

## THE GOALS

- Transform the process by which cancer therapeutics and preventives are discovered, developed, and tested in the clinic.
- Base discovery and development on interference with specific molecular targets in premalignant and malignant cells and in the tissues surrounding the malignancy that sustain its growth and spread.
- Expand the involvement of the entire cancer research community in the discovery and development process.

## THE PLAN

### Objectives

#### 1. Identify and characterize molecular targets for drug discovery.

- Fund Molecular Target Discovery Grants to provide researchers working on cancer mechanisms with the resources to develop the evidence that a new cancer-relevant molecule or pathway is, in fact, a promising target for drug discovery. Such evidence will establish the

credentials of a molecule or pathway as a suitable target for prevention or treatment discovery efforts.

- Supplement existing grants to support the synthesis of target molecules in sufficient quantities necessary to characterize them biologically and determine their physical structure.
  - Supplement existing grants for structural studies involving collaborations between cancer biologists and structural biologists to determine the physical structure of target molecules through x-ray crystallography or nuclear magnetic resonance.
  - Convene a panel of experts to assist NCI in prioritizing the targets emanating from this program, to pinpoint those worthy of further research and development.
- #### 2. Develop assays (tests) for molecular targets.
- Contract with organizations expert in state-of-the-art drug screening technology to develop sensitive, high throughput assays for priority molecular targets to assess the effects of compounds on a target. The result of this effort will be a practical screen for every high priority target, through which thousands of compounds can be tested daily.
- #### 3. Establish chemical and biochemical diversity libraries.
- Assemble and curate a "Library of Libraries" – a rich collection of small molecule chemical libraries derived from combinatorial synthesis programs. The library, assembled in collaboration with chemists from academia and industry, will complement NCI's existing repositories of natural product extracts and synthetic chemicals. These libraries will be formatted to be suitable for screening and will be widely available to researchers.
- #### 4. Foster interactions between assay developers and diversity libraries.
- Make diversity libraries widely available to researchers with assays. Create a sophisticated informatics system annotating the chemical repositories to ensure researchers' access to libraries most appropriate for their scientific orientation. NCI staff and outside experts will work together to match biologists with innovative assays to chemists having libraries of potential relevance to those assays.

- Double the number of Chemistry-Biology Centers in which chemists and biologists create highly integrated programs that combine chemical diversity generation with the use of these compounds in “smart” high throughput screens.
- 5. Screen compound libraries.**
- Fund contracts for drug screening to identify chemicals or biologics that hit our priority targets. Use the assays developed with our support to screen compound libraries from our collections. The most promising compounds identified from this process will undergo chemical optimization, and the best optimized compounds will be developed into drugs suitable for clinical testing.
- 6. Create the tools and methods to make possible target-based clinical testing.**
- Establish Centers of Excellence for Drug Development organized around a mechanism of particular relevance to cancer prevention or therapy, such as angiogenesis, cell-cycle control, immunotherapy, DNA-damage repair, cell signaling, differentiation, metastasis, or apoptosis. These multidisciplinary research groups of chemists, biologists, pharmacologists, imagers, clinicians, and informatics experts will create the tools necessary to clinically assess and validate the effects of drugs on molecular targets. All reagents developed in these centers will be made available to the research community.
  - Provide supplements to Centers of Excellence for Drug Development. Supplements will enable a Center to work with other investigators and NCI to develop specific compounds. Companies will be able to provide resources to the Centers for similar collaborations.
  - Increase support to the National Cooperative Drug Discovery Group program. This NCI-funded program supports consortia of academic institutions and pharmaceutical companies discovering and developing targeted drugs.
- 7. Expedite the steps that turn a chemical or a biologic into a drug suitable for initial clinical testing.**
- Fund contracts for drug-lead optimization and drug development. Contracts with chemists in academia and industry will support optimizing lead structures produced by target-based discovery activities that result in candidate compounds for clinical testing. NCI’s contracts program for pharmacology, synthesis, formulation, and toxicology will support the advancement of these drug candidates to the clinic. Fast-response contracts will assist in developing assays for particular agents in NCI’s development pipeline.
  - Support optimization of target-directed biomolecules. NCI will increase support for optimization of the interaction of biomolecules (for example, monoclonal antibodies) with their targets by exploring the effects of sequence diversity on important properties like target affinities and selectivity.
  - Competitively fund Rapid Access to Intervention Development (RAID and RAPID) contracts for academic drug discovery laboratory needs. The contracts will support novel discoveries through the development steps necessary to take a new discovery into the clinic for proof-of-principle testing as a potential therapeutic or preventive.
- 8. Expand Resources and infrastructure.**
- Create standards and expedite access to biological resources. The availability of standardized reagents (cell lines, growth factors) or assay conditions is critical to further progress. In collaboration with the investigator community and with industry, NCI will create standards for assays and reagents. If access is a significant research barrier, NCI will create a distribution system to expedite access to crucial reagents at reasonable cost.
  - Fund synthesis of chemicals and biologicals and provide them to the research community, on a competitive basis, to advance the drug discovery effort and move promising compounds to clinical trials.
  - Develop data bases of drug screening results and create a publicly accessible Web site that advertises the availability of chemical and biological resources and expedites interactions between research groups.

## Resources: Molecular Targets of Prevention and Treatment

<b>Identify and characterize molecular targets for drug discovery.</b>	<b>\$7.5 M</b>
<ul style="list-style-type: none"><li>■ Fund Molecular Target Discovery Grants (R01, R21/R33, SBIR/STTR).</li><li>■ Fund up to 5 grant supplements to support the synthesis of target molecules.</li><li>■ Fund up to 5 grant supplements to determine the physical structure of target molecules.</li><li>■ Convene a panel of experts to assist in prioritizing targets.</li></ul>	
<b>Develop assays for priority molecular targets.</b>	<b>\$0.5 M</b>
<ul style="list-style-type: none"><li>■ Develop sensitive, high throughput assays.</li></ul>	
<b>Establish chemical and biochemical diversity libraries.</b>	<b>\$2.0 M</b>
<ul style="list-style-type: none"><li>■ Assemble and curate a collection of small molecule chemical libraries derived from combinatorial synthesis programs.</li></ul>	
<b>Foster interactions between assay developers and diversity libraries.</b>	<b>\$6.5 M</b>
<ul style="list-style-type: none"><li>■ Make diversity libraries widely available to researchers with assays.</li><li>■ Double the number of Chemistry-Biology Centers (U19).</li></ul>	
<b>Screen compound libraries.</b>	<b>\$0.6 M</b>
<ul style="list-style-type: none"><li>■ Fund drug screening contracts to identify chemicals or biologics that hit priority targets.</li></ul>	
<b>Create tools and methods for target-based clinical testing.</b>	<b>\$22.5 M</b>
<ul style="list-style-type: none"><li>■ Establish 10 Centers of Excellence for Drug Development (P50).</li><li>■ Supplement P50 grants for Centers of Excellence for Drug Development to support collaborations.</li><li>■ Increase support to the National Cooperative Drug Discovery Group program.</li></ul>	
<b>Expedite steps that turn a chemical or biologic into a drug suitable for initial clinical testing.</b>	<b>\$20.5 M</b>
<ul style="list-style-type: none"><li>■ Fund contracts for lead optimization and drug development.</li><li>■ Support optimization of the interaction of biomolecules with their targets.</li><li>■ Fund RAID and RAPID contracts for drug development needs of academic discovery laboratories.</li></ul>	
<b>Expand resources and infrastructure.</b>	<b>\$4.3 M</b>
<ul style="list-style-type: none"><li>■ Create standards and distribution system for biological resources.</li><li>■ Synthesize and provide chemicals and biologics to research community.</li><li>■ Develop data bases of drug screening results; create publicly accessible chemical and biological resources Web site.</li></ul>	
<b>Management and support.</b>	<b>\$2.0 M</b>
<b>TOTAL</b>	<b>\$66.4 M</b>

## Research on Tobacco and Tobacco-Related Cancers

### THE OPPORTUNITY

The numbers are truly alarming. Every day, across this country, more than 3,000 youths will begin to smoke, placing themselves at increased risk for a host of cancers – lung, mouth, pharynx, larynx, esophagus, pancreas, cervix, kidney, and bladder – as well as heart disease and a range of other conditions. Of those who continue to smoke, approximately one half will die prematurely, losing an average of 20 to 25 years of their life expectancy. And an estimated 450,000 people in the U.S. will die this year alone from tobacco-related diseases – the *most preventable and costly cause of death in our Nation*. The global picture is even more sobering: More than one billion people smoke worldwide and an estimated three million die annually from tobacco-related illness. By 2025, the number of deaths is expected to reach ten million per year.

These statistics illustrate dramatically that tobacco – through the use of cigarettes, cigars, pipes, and smokeless products – poses an extremely serious threat to people’s health worldwide. They also underscore the urgency of addressing this threat. Evidence demonstrates strongly that people who stop smoking – regardless of age – live longer than those who continue to smoke, although their risk for lung cancer remains somewhat higher than if they never had smoked. To respond to this major threat to life and health, NCI has established decreasing tobacco use as an area of extraordinary opportunity.

Seizing this opportunity, however, presents a significant challenge to NCI and to the research and public health communities. In a field where every need seems pressing, we must identify where research is most needed and how best to prioritize and achieve scientific objectives with the greatest benefit. As a first step, NCI established the Tobacco Research Implementation Group

(TRIG), bringing together two dozen leading scientists and experts to identify tobacco-related research priorities for the next five to seven years. The TRIG identified and prioritized a set of nine overarching research opportunities. Pursuing these priorities promises to alter dramatically the way tobacco research is conducted on a national scale and to speed the pace of discovery to help reverse today’s epidemic of tobacco use and tobacco-related cancers.

### Developing Optimal Prevention and Cessation Strategies

Studies indicate that the majority of smokers want to stop smoking completely but struggle to quit. And most adolescents who smoke regret ever starting. Thus, developing strategies that prevent people from ever starting to smoke and help those who currently smoke to stop is a critical need.

In the last three decades, we have witnessed many achievements in this area of research: the development and implementation of physician training and office protocols for smoking cessation programs; the confirmation of the effectiveness of primary care medical and pharmacologic interventions; the development of effective self-help interventions; and the development of new tailored, proactive interventions designed to meet the needs of individual smokers. In addition, mass media interventions capable of reaching large numbers of people with prevention and cessation messages have been developed and strategies aimed at reaching minority, ethnic, and high-risk populations have been tested. Recent large programs, like the Community Intervention Trial for Smoking Cessation (COMMIT) and the American Stop Smoking Intervention Study (ASSIST), have shown both the potential and the limitations of community and state tobacco control interventions for changing attitudes about

For more information on TRIG, visit <http://dccps.nci.nih.gov/tcrb/TRIP/>



tobacco use, changing tobacco use behaviors, and reducing the tobacco-related cancer burden. Yet we still do not fully understand the most critical elements of tobacco prevention and treatment strategies, their timing, how best to target high-risk subgroups and settings, and how to tailor messages and materials appropriately for different populations.

### **Identifying and Targeting Populations at High Risk for Tobacco-Related Cancers and Nicotine Addiction**

We have made enormous progress in understanding the molecular and genetic factors that underlie the transformation of a normal cell to a cancer cell following exposure to tobacco carcinogens. For example, scientists have identified many cancer-causing agents contained in tobacco smoke and shown that different tobacco products and methods of nicotine delivery influence the type and quantity of exposure to these agents.

Researchers also have determined that these multiple agents seemingly induce similar changes in a cell, regardless of the cell's location in the body. The challenge now is to learn more about

how and why elements in tobacco smoke target particular genes and how tobacco-induced cellular damage initiates and promotes cancer's development. Such knowledge, gained through studies using preclinical models, will help us identify pre-cancerous lesions and markers that may predict tobacco-induced cancer. Identifying markers that detect DNA damage and other antecedents of cancer will enable us to test different prevention and treatment strategies and develop new early detection methods. It also will enable us to determine the amount of carcinogens in different tobacco delivery systems, the effects of burning temperatures on tobacco additives, and how tobacco smoke components interact with each other.

This research also could provide important insights into why some people may be particularly vulnerable to harm from tobacco. For example, women develop more lung cancers than men per cigarette smoked. Certain ethnic groups appear to be at increased risk for lung cancer as well. While the reasons for these differences are not clear, smokers with certain gene variants are more likely to be lung cancer victims. Therefore, we need to develop preclinical models that will enable us to identify the harmful variants that lead to increased susceptibility to tobacco-related cancers to help determine why some individuals exposed to tobacco are particularly susceptible to cancer, while others are spared. Using this information and knowledge of how inherited susceptibilities and tobacco exposure contribute to cancer in combination, we can develop specific prevention and detection strategies and target them to vulnerable individuals.

Further, there is increasing evidence that genes interact with environmental factors to influence whether an individual will start smoking, how early he or she will start, and how difficult it will be for him or her to quit. Just as we now know more about the biological bases of tobacco-related cancers, we also have learned a great deal about the psychosocial, biobehavioral, and biological determinants of tobacco use and addiction. We know, for example, that adolescent tobacco use is tied to peer and family influences and low self-esteem. We also know that continued smoking by adults is associated with nicotine addiction, depression, and stress. More recently, major research breakthroughs have provided important

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### **About Tobacco**

- Tobacco is responsible for more than 30 percent of all cancers and nearly one in five deaths in the U.S. every year.
- In the last decade, more than four million people in this country lost their lives to tobacco-related diseases, including, according to Environmental Protection Agency estimates, more than 30,000 nonsmokers who died of lung cancer caused by breathing smoke from others' cigarettes.
- The number of tobacco-related deaths in the U.S. continues to rise, particularly among women.
- The financial costs of tobacco also are rising. Over the course of their lives, current and former smokers generate an estimated \$501 billion in excess health care costs. Tobacco costs Medicare a staggering \$10 billion each year and Medicaid more than \$12.9 billion annually.
- Smoking among U.S. adolescents has increased by 73 percent in the last 10 years, and the declines in adult smoking appear to have leveled off.
- Rates of smoking are disproportionately high among certain population groups, such as African Americans.

## People's Story

# Lung Cancer

**My father was just diagnosed with lung cancer. He quit smoking twenty years ago — we never dreamed he would still be at risk.**

Cigarette smoking is by far the single greatest risk factor for lung cancer, which will cause nearly 160,000 deaths this year. Current smokers are at highest risk, but lung cancer does occur in former smokers even years after they have quit. Research is urgently needed to determine how to decrease the risk of tobacco-related cancers in former smokers, who now number nearly 50 million. Research also is needed to find these cancers when they are small and curable. Lung cancers can occur in people who have never used tobacco. Other factors shown to increase lung cancer risk include recurrent lung inflammation, air pollution, exposure to radon gas

(especially in combination with tobacco smoke), and exposure to asbestos and other industrial carcinogens.

**We found out about a clinical trial of a new treatment for people with the kind of lung cancer my father has — the early results look promising.**

Treatment for both major types of lung cancer — small cell and non-small cell — remains extremely difficult, but we are achieving modest incremental improvements. Advances in combination chemotherapy and radiation regimens have played the most significant role in treating small cell lung cancers, while refined surgical techniques have been most important in improving the outlook for some patients with early non-small cell lung cancer. Other advances may be on the horizon. Early study results

suggest that photodynamic therapy — the use of lasers and light-activated drugs to kill tumors — may hold promise for certain groups of patients with early lung cancers and for some patients who cannot withstand surgery. In another early clinical trial, administration of a genetically altered

virus successfully replaced faulty *p53* tumor suppressor genes in patients with advanced lung cancer, leading to disease stabilization or tumor shrinkage for some patients, and in one case, complete remission of disease. Though more research is needed to demonstrate their benefit, approaches such as these may eventually offer lung cancer patients new treatment options.

**I smoke. I know it sends the wrong message to my daughter.**

Each day, 3,000 American youth become smokers. If they continue to smoke, as many as half will eventually die a premature, tobacco-related death — many of these deaths will result from lung and other smoking-related cancers. Cigarette smoking is again increasing among teenagers, and recent evidence indicates that smoking rates also are rising markedly among college students. New studies show that people who begin smoking as adolescents are more susceptible to long-term DNA damage associated with lung cancer. Smoking among women continues to escalate, as does their lung cancer incidence and mortality, which exceeds that of breast cancer. Moreover, cigar smoking, which increases risks of lung and oral cancers, is increasing among both women and men. Recently, a gene has been discovered that appears to affect how easily a person becomes addicted to nicotine.



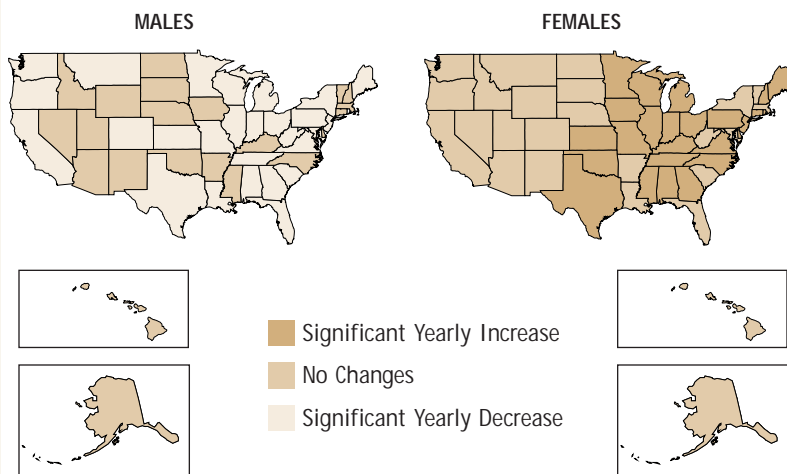
Especially now, since my father's diagnosis, I want to try to quit smoking. I've failed so many times before, but I think this time will be different.

Nearly a quarter of the U.S. adult population smokes, but most smokers want to quit. Furthermore, nearly one third of all cigarette smokers attempt to quit each year, but only a small percentage actually succeed. New smoking cessation aids have become available in recent years to help smokers – nicotine gum, the nicotine skin patch, the antidepressant drug bupropion, and smokeless nicotine inhalers. A recent study found that after one year, almost 36 percent of those using the patch and bupropion together remained abstinent, compared to those using bupropion alone (30 percent) or the patch alone (just over 16 percent). Evidence also indicates that quitters using a cessation aid who also get counseling from their health care provider have better success than those who do not.

Following the recommendations of its Tobacco Research Implementation Group (TRIG), NCI, in collaboration with the National Institute on Drug Abuse, will soon launch a network of Transdisciplinary Tobacco Research Centers to study tobacco use initiation and prevention, tobacco addiction and its treatment, and the treatment of tobacco-related cancers. The TRIG also has recommended targeted research initiatives to identify cultural, psychological, and genetic factors that influence smoking behavior in children and adults. Other initiatives will focus on improving the dissemination of proven prevention and

### Annual Percent Change in Mortality Lung & Bronchus Cancers 1990-1996

All Races



treatment interventions at the state and community levels, and on tailoring tobacco control programs for populations at high risk.

**I've learned that even if I never smoke again, my lung cancer risk may always be higher than someone who never smoked. My doctor told me some signs of trouble to watch for.**

Though most lung cancers cause no symptoms until they are advanced, smokers and former smokers should be especially alert for symptoms that may signal early lung cancer. These include a persistent cough, hoarseness, chest pain, loss of appetite and weight loss, bloody or rust-colored sputum, shortness of breath, fever without apparent reason, recurring bronchitis or pneumonia, and wheezing. Any of these symptoms can be caused by other diseases, but seeing a doctor promptly is the only way to find out if they are being caused by a lung cancer.

Watching for such signs is especially important since no reliable procedure for routine lung cancer screening is yet available. Encouraging results from an early trial of spiral computed tomography (spiral CT) for lung cancer detection suggest that further developing this technology may lead to an affordable, accurate lung cancer screening test in the coming years.

Research also is being conducted to learn more about former smokers' long-term risk for lung and other cancers. In addition, for those lung cancers not attributable to tobacco use, NCI is continuing research to learn more about how genes, the environment, and other factors may contribute to lung cancer development and progression.

*This vignette is a composite of experiences.*

insights into the biological bases of tobacco use and nicotine addiction, including the role of genetic factors and ethnicity in nicotine metabolism. For example, researchers have identified genes that modify nicotine metabolism and regulate brain chemicals that affect the pleasurable feelings triggered by nicotine. These discoveries provide unique opportunities for studying the links between biology and behavior and will help identify preexisting vulnerabilities to tobacco use. By determining how these vulnerabilities interact with sociocultural and psychological influences on tobacco use, and by improving our ability to assess risks quantitatively, we can develop more effective prevention and cessation interventions and tailor these interventions to the people most likely to benefit from them. We also can identify effective new drugs and combinations of already proven drugs for treating nicotine addiction. The combination of pharmacologic and behavioral tailoring may be particularly important in accelerating major improvements in smoking cessation rates.

### **Capitalizing on Social, Legal, and Public Policy Developments**

A number of social, legal, and public policy developments are converging with scientific advances to create a unique opportunity to tackle tobacco use. Public attitudes reflect decreasing acceptance of tobacco use as a social norm. For example, concerns have been raised about the targeted marketing of menthol cigarettes in the African American community. Government agencies, academic institutions, and professional and voluntary organizations are making major commitments to reduce tobacco use and exposure to tobacco carcinogens. Through lawsuits, states are recovering billions of dollars lost to the treatment of diseases caused by smoking. However, while state political leaders have been urged to use these funds to expand tobacco control programs, they almost certainly will use most of the funds to address other priorities. This dilemma underscores the need for NCI to expand its investment in tobacco control research to ensure that the best scientific evidence informs state and community programs. How can we help policy makers develop effective programs when we do not know the full impact on tobacco use of clean indoor air policies, marketing restrictions, and youth access restrictions, all of which

are pillars of tobacco control but face stiff and sometimes passionate resistance?

In summary, we have an unprecedented opportunity to reduce the enormous burden of tobacco use on our Nation's public health. The investment proposed here will enable us to gather knowledge that will inform policy makers and public health practitioners about the best strategies for prevention and treatment; this is of special concern because states must decide how best to use tobacco company settlement funds for tobacco control efforts. Our collaborations with Federal and state officials will help ensure that these funds are spent in ways that will maximize tobacco control benefits and save lives.

More effective smoking cessation programs alone could save many of the nearly 160,000 lives lost to lung cancer each year. An expanded tobacco control research program covering biological and biobehavioral research; clinical, epidemiologic, surveillance, and policy research; and support for research infrastructure, will be essential to achieving our goals.

## **THE GOALS**

- Define the biological, behavioral, and societal bases of tobacco use and addiction.
- Reduce tobacco use rates among youth and adults, and especially among high-risk groups including low income, minority, and medically underserved smokers.
- Define the relationship between exposure to tobacco products and carcinogenesis.
- Prevent cancer in former smokers.

## **THE PLAN**

### **Objectives**

#### **1. Develop more effective interventions to prevent tobacco use.**

- Initiate trans-NIH efforts to determine the interdependent causes of tobacco use, especially among youth. These efforts should include epidemiological studies, such as longitudinal cohort designs, to track familial, environmental, and biological risk factors within the same individuals over time,

enabling us to better understand the determinants and health consequences of tobacco use in children and adults.

- Fund a consortium of prevention scientists to develop targeted tobacco use prevention strategies for high-risk populations.
- Establish a tobacco policy research consortium to determine the impact of pricing policies, clean air policies, marketing and access restrictions, and tobacco product and nicotine replacement regulation on tobacco use.

## **2. Develop more effective strategies for tobacco cessation, including those tailored for high-risk individuals.**

- Develop more powerful pharmacotherapies by discovering new drugs, combining proven drugs to determine additive effects, and studying long-term use to improve cessation maintenance.
- Develop new behavioral techniques and technologies that will amplify the effects of other treatments; tailor therapies to smoker characteristics such as age, race and ethnicity, culture, income, education level, psychiatric co-factors, other diseases, and even genetic makeup.
- Conduct controlled intervention trials to identify optimal ways to disseminate and implement proven tobacco-use prevention and treatment strategies.

## **3. Expand initiatives exploring genetic/environmental interactions that influence smoking behavior and increased risk for cancer.**

- Support research to identify genes related to addiction.
- Fund studies to understand how environmental and other factors interact with genes to influence the likelihood and age of smoking initiation, intractability of addiction, and risk of tobacco-related disease, such as lung cancer.
- Encourage collaborations with international investigators to enable us to pursue unique research opportunities involving resources not available in the U.S.

## **4. Develop approaches to prevent cancer in former smokers.**

- Expand NCI's Early Detection Research Network to identify and validate markers of tobacco exposure and tobacco-induced cellular events leading to carcinogenesis.
- Support preclinical model development and small clinical trials to test preventive agents or cancer therapies for people with a history of tobacco exposure and the highest risk of developing cancer.
- Fund innovative studies to determine the mechanisms by which tobacco use contributes to the development of non-aerodigestive cancers such as pancreas, cervix, and bladder cancers.

## **5. Expand the national research infrastructure to support tobacco use research across disciplines, provide training to new investigators, and monitor trends in tobacco use and tobacco-related cancers.**

- Expand support for transdisciplinary tobacco use research and training.
  - Use the Transdisciplinary Tobacco Use Research Centers (TTURCs) to bring together and foster collaboration among transdisciplinary teams of scientists. Establish new TTURCs to expand the scope of research conducted at existing TTURCs.
  - Support transdisciplinary research through other mechanisms and increase support for training in tobacco research, especially among minority investigators.
  - Establish a clinical research program at NCI where scientists from NIH and the extramural community can collaborate and rapidly implement cutting-edge research on nicotine addiction and tobacco use.
- Expand surveillance systems to monitor tobacco use behaviors, the implementation and durability of tobacco-related interventions, and other factors that influence tobacco use.

## Resources: Research on Tobacco and Tobacco-Related Cancers

<b>Expand research on tobacco use prevention.</b>	<b>\$11.0 M</b>
<ul style="list-style-type: none"> <li>■ Initiate trans-NIH effort to determine interdependent causes of tobacco use.</li> <li>■ Fund a consortium to develop targeted prevention strategies for high-risk populations.</li> <li>■ Establish a tobacco policy research consortium.</li> </ul>	
<b>Develop improved tobacco-use treatment strategies.</b>	<b>\$12.0 M</b>
<ul style="list-style-type: none"> <li>■ Develop and evaluate new drug and drug combination treatments for tobacco addiction.</li> <li>■ Develop tailored behavioral techniques, technologies, and treatments.</li> <li>■ Conduct controlled intervention trials.</li> </ul>	
<b>Conduct genetic epidemiology research.</b>	<b>\$6.0 M</b>
<ul style="list-style-type: none"> <li>■ Supplement research grants to accelerate the discovery of nicotine addiction-related genes.</li> <li>■ Establish cohorts to study the etiology of tobacco use.</li> <li>■ Initiate international collaborative studies to identify genes-environment interactions influencing tobacco use initiation, cessation, and cancer development.</li> </ul>	
<b>Prevent cancer in former smokers.</b>	<b>\$4.0 M</b>
<ul style="list-style-type: none"> <li>■ Expand Early Detection Research Network to identify and validate markers of tobacco exposure and carcinogenesis.</li> <li>■ Support pilot projects to develop and test preventive agents or therapies.</li> </ul>	
<b>Conduct basic biological research.</b>	<b>\$7.0 M</b>
<ul style="list-style-type: none"> <li>■ Initiate prospective studies to identify genetic and biological factors affecting vulnerability to tobacco-related cancers.</li> <li>■ Fund innovative studies to determine how tobacco use contributes to non-aerodigestive cancers.</li> <li>■ Develop and use a Tobacco Carcinogenesis Models forum to link Mouse Models of Human Cancer Consortium participants to investigators with expertise in behavioral and other models of tobacco carcinogenesis.</li> </ul>	
<b>Expand surveillance.</b>	<b>\$3.0 M</b>
<ul style="list-style-type: none"> <li>■ Expand surveillance systems to monitor tobacco use behaviors, tobacco-related intervention, implementation and durability, and other factors.</li> </ul>	
<b>Enhance national research infrastructure.</b>	<b>\$20.0 M</b>
<ul style="list-style-type: none"> <li>■ Double the number of TTURCs to expand the scope of research and capitalize on new discoveries.</li> <li>■ Fund transdisciplinary research and training programs.</li> <li>■ Create a NCI clinical research program on nicotine addiction and tobacco use.</li> </ul>	
<b>Management and support.</b>	<b>\$3.0 M</b>
<b>TOTAL</b>	<b>\$66.0 M</b>

## Cancer Communications

### THE OPPORTUNITY

We are in the midst of a communications revolution unparalleled since Gutenberg introduced movable type to the western world in the 15th century. At no other time in history has it been so easy for so many people to access such a vast wealth of information. In particular, the Internet has multiplied exponentially our ability to make large amounts of information available to a wide audience quickly and easily.

Communication is central to effective, quality cancer care, from primary prevention to survivorship and end of life issues. Communication empowers people; it can raise awareness of health problems and recommended actions, and give people the information they need to make informed cancer-related decisions. Effective communications can move people to engage in behaviors that will improve their health, such as stopping smoking or undergoing screening for certain types of cancer. The Department of Health and Human Services' Science Panel on Interactive Communications and Health has concluded that few other health-related interventions have the potential of interactive health communications to simultaneously improve health outcomes, decrease health care costs, and enhance consumer satisfaction.

Scientists and communications experts have been studying the process of effective communication and its impact on health for more than 25 years. They have produced increasingly refined theories of health communication, including those that focus on how people process health information and how they respond to cancer-related risks. These theories have enabled us to refine messages for people who differ in their readiness to take responsibility for their health. For example, inter-

vention research on effective health communications has contributed to declining smoking rates among many groups in the U.S. Likewise, it has influenced the increasing proportions of Americans who are eating five fruits and vegetables per day, and getting screened for breast, cervical, and other cancers.

Moreover, changes in the role and accessibility of information are altering health care practices, patient-physician relationships, and the way consumers and patients acquire and use information. Where once physicians were the main source of health information, now many consumers are actively seeking information to meet their needs. The commercial sector has responded to this paradigm shift by developing new communications technologies at a dizzying rate. As we enter the 21st century, consumers and professionals alike have, or will have, a host of new opportunities for creating, distributing, and acquiring health information from the World Wide Web, individually-tailored print and multimedia materials, interactive computer games, interactive kiosks, and wireless pagers, among others.

It is impossible to overstate the impact of these "new media" on health communications.

Consider, for example, the fact that:

- In 1998, 22.3 million adults in the U.S. searched on-line for health and medical information, and cancer was one of the most sought-after topics.
- Also in 1998, 1.3 million pieces of e-mail were processed each week by cancer-related listservs (e-mail groups devoted to a specific topic) hosted by the Association of Cancer On-line Resources.
- In 1997, 41 percent of U.S. households had at least one personal computer, and that number continues to increase.

But this new world of expanded communications capabilities remains in many ways uncharted territory. Important questions confront us. How can we promote the demand for, access to, and use of cancer information, given the high national rates of medical illiteracy? How can we ensure that cancer communications are salient, accurate, relevant, and culturally sensitive to diverse audiences? How can we better design our interventions to use what works, to know what does not work, and to understand why? How can we help physicians to maximize their communication about cancer? How can we redesign information systems so they give people the information they want, how they want it, when and where they want it?

In addition, substantial barriers prevent major segments of the population from seeking and/or using cancer information. Some people continue to lack access to the medium. Others are faced with content that is unintelligible (i.e., in the wrong language or in language that is too complex), culturally inappropriate, or simply ineffective.

Furthermore, despite our progress in refining health communications theories, major gaps remain in our understanding of how consumers use health information. We must learn how to help people distinguish important from insignificant health risks and deal with contradictory health messages so that they can make informed choices. We must provide accurate and balanced information about all areas of cancer treatment and care, including complementary and alternative therapies. We must find the best ways to inform doctors of emerging “best practices” in patient care. And we must find ways to help physicians be more effective communicators and integrate cancer communications into all aspects of cancer care.

Cancer communication must be used to narrow the enormous gap between what we know and what we do at all levels and to reduce health disparities among our people. For example, new avenues are needed to reach children, especially those in vulnerable, high-risk populations. NCI is committed to improving demand for, access to,

and use of cancer information for all, regardless of race, ethnicity, health status, education, income, age, gender, or geographic region.

Finally, new information technologies must complement, not replace, older but effective strategies, such as the mass media, one-to-one counseling, and targeted print communications. We know, for example, that many people still want to talk with a knowledgeable and supportive person. As we develop new technologies, we must not lose sight of the importance of the human bond.

To be effective, cancer communications must be integrated into the cancer continuum – from prevention through treatment to survivorship and to end of life issues, including palliative care and pain management. Communication should be an integral component of quality cancer care. NCI and its grantees and contractors have traditionally been leaders in health communication, but it is time to go beyond what we have done before – to take advantage of new knowledge about health behavior and new technology – to reduce the burden of cancer. If NCI takes the lead now, we have the opportunity to use both proven strategies and new communications technologies to help people increase their knowledge, enhance their ability to negotiate the health care system, understand and modify their health risk behaviors, speed the pace of discoveries, and increase access to and participation in clinical trials. Moreover, we will have a far richer understanding of how people use communications technologies of all kinds. Ultimately, we will improve outcomes in cancer prevention, early detection, treatment, and survivorship.

By investing now, we will seize a crucial opportunity to shape the emerging national information infrastructure to improve cancer communications. At this pivotal juncture, there is a need for a public institution such as NCI to provide leadership in the cancer communications arena; the broad and reasoned perspective that NCI brings to patients and health care providers alike is essential to successfully implement communications strategies to reduce the cancer burden.



## THE GOALS

- Accelerate reductions in the U.S. cancer burden through the use of cancer communications.
- Integrate cancer communications into the cancer continuum so that it is an accepted and practiced component of quality care.
- Increase the demand for, access to, and use of cancer communications by diverse populations including the public, high-risk persons, underserved and disabled populations, children, patients, survivors, and health professionals.

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### Fundamental Assumptions of Cancer Communications

- Proactive communication strategies are needed across the cancer continuum to rapidly accelerate a reduction in the cancer burden and across the life span.
- A successful strategy requires that we reach a broad cross-section of the U.S. population.
- NCI's cancer communications should be based on scientific evidence obtained through high quality research and its products should be evaluated for efficacy, impact, and use by the target audiences.
- Access includes removing cost barriers and improving ease of use, familiarity, cultural appropriateness, and appeal of the medium.
- Comprehension is essential, and messages must be perceived as salient, appropriate, and relevant.
- We must offer a flexible and adaptable menu of communication choices to reach the public, patients, underserved populations, survivors, and health providers in diverse settings.
- The new media should complement more "traditional" media such as mass media, the telephone, and one-to-one interpersonal communications.
- We must forge effective partnerships with other NIH Institutes, the Centers for Disease Control and Prevention, voluntary health organizations such as the American Cancer Society, and advocacy and self-help groups.
- Partnerships with industry and academia are essential to identify and gain access to emerging communication technologies. These partnerships should include computer, telecommunications, pharmaceutical, insurance, and new media companies.

- Use cancer communications to speed the dissemination of "best practices" across the cancer continuum from prevention through treatment and survivorship or end of life.
- Strengthen and monitor the use and efficacy of NCI's own communications and communication products.
- Develop the infrastructure needed to accelerate advances in cancer communications, such as the testing of strategies, models, and tools; and dissemination of results to researchers, clinicians, patients, practitioners, advocacy groups, other partners, and the public, including emerging on-line communities of interest.

## THE PLAN

### Objectives

- 1. Establish new data collection and analysis strategies to obtain data at regular intervals for cancer communications planning, research, evaluation, and marketing.**
  - Sponsor a triennial survey of a nationally representative sample of the U.S. population that is conducted on a recurring basis with input from investigators in the field.
  - Add questionnaire items to the National Health Interview Survey and the CDC Behavioral Risk Factor Surveillance Survey to more effectively monitor national trends related to cancer communications.
  - Track promising new product development, monitor software developers and hardware manufacturers as well as market research firms that monitor developers and manufacturers and often are the first to spot new product uses.
  - As technology evolves, monitor emerging information needs and ensure that mechanisms are in place to conduct the appropriate research to address unmet and perhaps previously unarticulated needs.

2. **Create Cancer Communications Centers of Excellence to provide interdisciplinary units for communications research.**
  - Facilitate rapid advances in knowledge about cancer communications.
  - Develop new theories of health and cancer communications that are appropriate to underserved populations.
  - Develop strategies to improve the penetration, efficacy, effectiveness, and dissemination of cancer communications.
  - Identify optimal formats for communicating cancer risks.
3. **Develop an integrated cancer knowledge management strategy, including an adapted Cancer Information Service (CIS) that offers a menu of communication choices designed to meet and respond to people's diverse information needs.**
  - Integrate NCI's information services.
  - Infuse new media technologies into all NCI information services.
  - Disseminate best processes.
  - Support and use new research methodologies and approaches to respond to the swift pace of change inherent in the communications revolution.
  - Create an extended enterprise knowledge base at NCI that integrates linkages to appropriate external resources.
  - Foster cooperative relationships with other public health agencies, advocacy groups, support organizations, and industry.
4. **Develop new communication products to improve cancer communications to diverse audiences.**
  - Develop and update regularly practical toolkits for the public, patients and their caregivers, underserved populations, advocacy groups, health professionals, and cancer communicators to improve the state of cancer communications.
  - Fund research to develop practical decision aids to improve patient-provider communication and to help people make better cancer-related decisions.
  - Fund workshops and seminars to promote dissemination and use of these practical tools and to solicit information concerning current levels of use and barriers.
5. **Identify, create, and nurture the newest and most promising communication technologies.**
  - Collaborate with academia and the private sector to encourage the development or new uses of software and hardware to improve cancer communications.
6. **Train the health communications scientists, researchers, and practitioners needed to achieve our scientific and health communications objectives.**
  - Encourage the development of interdisciplinary training programs that, at a minimum, include people in health behavior, marketing, engineering, communications, public health, and medicine.
  - Fund existing health communications research laboratories to conduct training programs and provide opportunities for research professionals in growing areas, including risk communication.

## Resources: Cancer Communications

<b>Expand data collection.</b>	<b>\$5.0 M</b>
<ul style="list-style-type: none"> <li>■ Sponsor a nationally representative triennial survey and make results publicly available.</li> <li>■ Add questions to established surveys to monitor national trends in cancer communication.</li> <li>■ Track promising new product development.</li> </ul>	
<b>Establish 6-8 Cancer Communication Centers of Excellence.</b>	<b>\$12.0 M</b>
<b>Develop an integrated cancer knowledge management strategy.</b>	<b>\$10.0 M</b>
<ul style="list-style-type: none"> <li>■ Integrate new media technologies into NCI information services; link to external resources.</li> <li>■ Support new research methods/approaches and disseminate best processes.</li> <li>■ Integrate new information technologies for easier, more efficient, and less costly organization, packaging, and communication of cancer information for users with diverse needs.</li> <li>■ Foster relationships with public health agencies, advocacy groups, and industry.</li> <li>■ Expand communication choices available through CIS.</li> <li>■ Integrate the restructure of PDQ and the CIS activities into NCI's clinical research program.</li> </ul>	
<b>Develop practical tools for cancer communications.</b>	<b>\$3.5 M</b>
<ul style="list-style-type: none"> <li>■ Develop toolkits for media, public, patients, underserved populations, advocacy organizations, health professionals, and cancer communicators to improve cancer communications.</li> <li>■ Support development of decision tools, appropriate for underserved populations.</li> </ul>	
<b>Identify, create, and support promising communications technologies.</b>	<b>\$1.5 M</b>
<ul style="list-style-type: none"> <li>■ Expand JOLT (Joining Organizations with Leading Technologies).</li> <li>■ Co-sponsor state-of-the-art meetings on emerging technologies.</li> </ul>	
<b>Foster interdisciplinary training and educational programs.</b>	<b>\$6.0 M</b>
<ul style="list-style-type: none"> <li>■ Develop interdisciplinary training programs to prepare needed personnel in cancer-related consumer health informatics and cancer communications.</li> <li>■ Fund existing health communications research laboratories to conduct short- or longer-format training programs for research professionals.</li> <li>■ Develop a Master's Program in health communications and media technology delivery.</li> </ul>	
<b>Develop NCI infrastructure in cancer communications research.</b>	<b>\$4.0 M</b>
<ul style="list-style-type: none"> <li>■ Recruit staff expert in health communications and media development, use, and research.</li> <li>■ Create an in-house laboratory for testing cancer communications.</li> <li>■ Implement freestanding science bureau to improve reporting in cancer communications.</li> </ul>	
<b>Management and support.</b>	<b>\$1.0 M</b>
<b>TOTAL</b>	<b>\$43.0 M</b>

# NCI's Challenge: Building the Capacity of the Future

As we begin the 21st century, we are without doubt in a position to make real improvements in human health and disease. We made remarkable progress in the 20th century in our knowledge of cancer biology, dramatically expanding our understanding of what is required to turn a normal cell into a cancer cell. Recently developed molecular-based technologies are providing even greater insights into the steps involved in the transformation of cells from normal to precancerous to cancerous, allowing us to detect and diagnose cancers much earlier. Other advances in technology, such as new and enhanced imaging tools and techniques, coupled with new drugs, targeted therapeutic interventions, and new insights and discoveries into the fundamental nature and causes of cancer, present unprecedented opportunities for advancing our understanding of cancer and improving quality of life for people diagnosed with cancer.

The challenge before us is to establish the mechanisms that will allow the scientific community to apply these discoveries and emerging technologies to the field of cancer research. We need mechanisms that will promote and reward innovative thinking, the cross-fertilization of ideas among disparate scientific disciplines, and enhanced collaborations among government, academia, and industry. We also must develop and maintain the cadre of trained scientists from many disciplines needed to undertake this essential work.

NCI's role is to provide the vision, creative environments, and diverse resources needed to ensure a smooth flow between the increasing num-

ber of discoveries and advances in cancer research and the scientific community's ability to apply these findings to prevent and treat the many forms of cancer. Yet if the pace of discovery is like an eight-lane highway, our current ability to translate those discoveries into clinical application is like a country road. Where the two meet, a bottleneck of good ideas occurs. Our challenge is to expand the country road to an eight-lane highway that moves discoveries swiftly to their use in interventions across the continuum of cancer care.

To respond to this challenge, we have identified six key areas for investment – Investigator-Initiated Research; Centers, Networks, and Consortia; National Clinical Trials Program; Informatics and Information Flow; Studying Emerging Trends in Cancer; and Training, Education, and Career Development. Each of these investment areas will play a unique role in our fight against cancer.

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## Challenge Program Increase (dollars in thousands)

	Amount
Investigator-Initiated Research	\$ 146,015
Centers, Networks, and Consortia	62,350
National Clinical Trials Program	201,335
Informatics and Information Flow	70,000
Studying Emerging Trends in Cancer	56,600
Training, Education, and Career Development	60,700
<b>Total</b>	<b>\$597,000</b>

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# Investigator-Initiated Research

## THE CHALLENGE

Investigator-initiated research – research proposed and conducted by scientists in laboratories and clinics across the country and here at NCI – is the wellspring of scientific discovery. Funded and sustained by a variety of NCI grant mechanisms, our investigator-initiated research is continually yielding discoveries and insights into the mechanisms and causes of cancer and its prevention, detection, diagnosis, treatment, control, and survival. These discoveries, and their application in interventions of all kinds, are critical to reducing the burden of cancer and are resulting in real progress against cancer.

Through the dedicated work of these NCI-supported scientists over the past 50 years, we stand at the threshold of understanding a great unknown – how cancer develops at the molecular level. Because of our continued national commitment to cancer research, we are poised to expose more rapidly than ever before the inner workings of cancer cells, their genes, and the ways in which they behave. We must push forward as quickly as possible with this work. The absolute number and pace of our discoveries, and the speed with which we bring them to bear to benefit people, are directly linked to the level of resources available to support the exploration of new leads across the cancer research continuum. Moreover, we must strive to expand our research portfolio to include a greater number of research proposals that may be somewhat riskier, highly speculative, or pursue novel paths. We also must continue to expand the translational research that converts basic science dis-

coveries into practical, affordable, and effective ways of restoring cancer patients to health and preventing cancer throughout our population.

As we promote innovative research, we must create mechanisms that link basic, clinical, and population-based research with state-of-the-art resources and technologies; promote collaborations among researchers inside and outside of cancer research; and draw into cancer-related research scientists from allied fields such as chemistry, biology, physics, and mathematics. By bringing together researchers from allied fields, we will galvanize the complementary knowledge these individuals possess to most quickly answer the crucial questions in basic, clinical, population, and translational research. It is under this broad scientific umbrella that discoveries in the 21st century will be made.

The Nation waits eagerly for the day when cancer is no longer a threat to health and life, when most cancers are prevented, and when those that occur are cured or controlled rapidly and successfully. To meet this challenge, we must fuel the drive to discover the unknown by increasing our support of innovative research and providing the support needed to exploit the discoveries it yields. Our research base should bring to bear the best of our developing knowledge, as well as the best ideas and technologies, to address the full spectrum of cancer research questions – from basic research to prevention and care. Continued investment in this crucial aspect of the research infrastructure will span the gap between discovery and application and transform the processes by which we bring discoveries to the benefit of people.

## THE GOALS

- Increase the rate of discovery.
- Increase investigators' access to state-of-the-art resources, technologies, and infrastructures that promote collaboration and speed the pace of discovery.
- Accelerate the application of discoveries to benefit people.

## THE PLAN

### Objectives

- 1. Increase investment in research to ensure a higher and sustainable success rate for competing grant applications.** Today, NCI funds just over 30 percent of competing grant applications through the Research Project Grant (RPG) pool. To ensure that a greater number of excellent ideas have the chance to be tested as quickly as possible, we need to:
  - Fund 40 percent of competing applications, including those that have the highest scientific merit, carry great risk but may yield potentially greater reward, are unconventional but hold unique promise, are in areas of extraordinary need in specific fields of investigation or model systems, or encourage new investigators.
- 2. Encourage investigators to commit to careers in cancer research and to propose more innovative and higher risk/higher reward projects.**
  - Continue to allocate the first 80 to 90 percent of available RPG funds to competing applications that fall within conventional merit rank order paylines.
  - Assure that applications from new investigators and applications that are particularly innovative and high risk/high reward have a reasonable funding rate.
- 3. Enhance the opportunity for outstanding applications that fall just beyond established paylines to receive more rapid reconsideration.**
  - Allocate up to 20 percent of available RPG funds to award meritorious applications that are outside conventional paylines, including set-aside funds for Requests for Applications (RFAs), Program Announcements (PAs), and applications under other grant mechanisms.
- 4. Invest in areas that NCI consensus planning processes (e.g., Progress Review Groups, Extraordinary Opportunity Working Groups, Advisory Committees) have identified as presenting special opportunity or need.**
  - Continue Accelerated Executive Review (AER) to fund single project applications in patient-oriented and basic research that are near the payline and for which reviewer criticisms can be addressed rapidly; apply a similar approach to other application types, such as Program Project Grants.
  - Monitor investigator-initiated research applications to assess whether these projects alone are meeting programmatic objectives.
  - Use as needed regular, novel, and special award mechanisms and incentives announced through competitions (e.g., PAs, RFAs) to encourage investigation in particular areas.
  - Provide sufficient staff, resources, and enhanced electronic communications to improve information dissemination, enhance coordination within and between initiatives, and increase direct contact with applicants and grantees.
- 5. Optimize each award to accelerate the pace of discovery.** In 1999, NCI grant awards averaged four years in duration and were awarded 90 percent of recommended funds. This level of funding and project duration slows discovery because fewer experiments can be conducted and fewer patients accrued to clinical trials.
  - Provide funding at full peer-reviewed recommended budget levels for up to five years of support.
  - Ensure that investigators have access to NCI-sponsored resources, infrastructure, and technologies that facilitate discovery, both to make progress as quickly as possible, and to create breakthrough opportunities.
  - Set aside funds to award as administrative supplements to current awardees whose research is going better than expected, or who are poised to test new ideas.
  - Expand award mechanisms that provide seed funds and resources to pilot promising leads.

## 6. Facilitate rapid movement from discovery to application by encouraging interdisciplinary and collaborative approaches.

- Use established mechanisms and create novel and special mechanisms to encourage collaborative and translational research. Broaden the Phased Innovation Award to include an application phase.
- Expand administrative supplements to encourage new collaborations that bring together basic and clinical scientists; promote additional interdisciplinary collaborations and access to central resources such as data bases, tissue banks, and animal models.
- Foster and expand novel opportunities for access to resources and technologies that promote interdisciplinary research and collaborations through centers, networks, and consortia.
- Expand cooperative resource programs that give investigators access to technologies and expertise needed to move their discoveries to application.
- Encourage the development of information technology tools to facilitate interdisciplinary communication and collaboration.
- Increase funding for collaborative research awards such as Program Project Grants and cooperative agreement networks in cancer genetics, imaging, early detection, and other areas.
- Expand use of exploratory grants to encourage patient- and population-based research.

## PROGRESS TOWARD MEETING THE CHALLENGE

Over the past four years, NCI has **increased substantially the number of investigator-initiated grant applications funded**. In 1995, the overall success rate for grants funded from the RPG pool was 23 percent. In 1999, we anticipate funding more than 1,200 new and competing grant applications from the RPG pool, for an overall success rate of 33 percent. This increase has resulted in and will continue to yield many research rewards, but this improved funding level is still insufficient to support the wealth of innovative, high quality proposals received each year. In fact, as we attract new researchers to the cancer problem the number of excellent, innovative applications can only be expected to grow.

To encourage both the development of new technologies and innovative approaches to specific areas with special needs, NCI has implemented several new or expanded mechanisms. For example, the **Quick-Trials program** was designed to speed the translation of ideas to early stage clinical trials. The **Phased Innovation Award** program supports novel technology development for molecular analyses of cancer. Both programs promise to encourage innovative approaches and increase the speed at which discoveries are translated to clinical application. Through a **special exceptions process**, NCI ensures that new investigators share the same success rate as more established R01 applicants. In addition, the **Accelerated Executive Review** process ensures rapid reconsideration of applications ranked within a few percentile points of the payline, especially those involving patient-oriented research.

## Resources: Investigator-Initiated Research

### Ensure sustainable success rate for competing applications.

- Fund 40% of competing applications.

### Encourage investigators to commit to cancer research careers and to propose more innovative and higher risk/higher reward projects.

- Continue to allocate the first 80 to 90% of RPG funds to competing applications falling within conventional merit rank order paylines.
- Ensure reasonable funding success rate for high risk/high reward applications and a success rate at least equal to traditional R01 grants for applications from new investigators.

### Enhance opportunities for rapid reconsideration of outstanding applications that fall just beyond established paylines.

- Allocate up to 20% of RPG funds for meritorious applications outside conventional paylines.
- Expand AER to include Program Project Grants.

### Invest in areas of special opportunity or need.

- Use regular, novel, and special award mechanisms to encourage investigation in priority areas.
- Provide staff, resources, and enhanced electronic communications to improve information dissemination, enhance coordination within and between initiatives, and increase direct contact with applicants and grantees.

### Optimize awards to accelerate discovery.

- Fund at full peer-reviewed recommended budget levels for up to 5 years of support.
- Ensure access to NCI-sponsored resources, infrastructure, and technologies.
- Set aside funds for administrative supplements.
- Expand R03, R21, R33, and other awards to provide seed funds and resources.

### Facilitate rapid movement from discovery to application through interdisciplinary and collaborative approaches.

- Use established and novel mechanisms to encourage collaborative and translational research. Add application phase to R21/R33 Phased Innovation Award.
- Expand administrative supplements to encourage collaborations and promote access to resources.
- Expand access to resources and technologies that promote interdisciplinary research and collaborations through centers, networks, and consortia.
- Expand cooperative resource programs (e.g., RAID, RAPID, CGAP, EDRN) to improve access to technologies and expertise.
- Encourage development of information technology tools to expedite interdisciplinary communication and collaboration.
- Double funding for collaborative research awards.
- Expand exploratory grants for patient- and population-based research.

### Management and support.

\$2.0 M

### TOTAL

\$146.0 M



## Centers, Networks, and Consortia

### THE CHALLENGE

The rapid pace of scientific and technological discovery has created enormous opportunities. Along with them come some very significant challenges. The most obvious one – how to turn scientific knowledge into more effective cure and control of cancer – is NCI’s mission. To do this most effectively, the research community must first successfully address another challenge – one having to do with the culture of the research community itself.

For decades, laboratory-based biological investigation – the “basic science” of cancer research – has flourished in the familiar departments of our medical schools, universities, and research institutes. It has always been a kind of “cottage industry” in which small, cohesive laboratory groups are the units that do the research, sometimes working with similar groups in *ad hoc* collaborations. As biomedical science has advanced, however, it has become clear that certain kinds of scientific problems cannot be addressed in this way. This has long been the case for certain epidemiologic studies and clinical and populations research, which often require teams of substantial size that may straddle multiple institutions. What is really new, however, is the sheer extent to which the need for “team research” has come to pervade biology and medicine, particularly for those problems that require back-and-forth movement between the laboratory and clinics or populations.

Multidisciplinary teams are needed to solve virtually all of the “big” problems in cancer research – sequencing the genome, creating the next generation of sensitive and specific imaging devices, or discovering and testing target-specific therapeutics and preventives. Increasingly, single institutions do not have the scientific breadth, patient resources, or regional outreach to populations to enable them to address the major scientific questions upon which really effective cancer control will depend. The cultural challenge to the scientific community,

therefore, is to go beyond customary ways of thinking and organizing, beyond traditional academic departments and faculties, to establish whatever kinds of cross-disciplinary and multi-institutional collaborations are needed to get the work done.

More specifically, we need to create quite new kinds of functional links – not only among basic, clinical, and population scientists, but also across very diverse fields of science and technology. We need productive interfaces among and between mathematicians, biologists, computer scientists, epidemiologists, imaging scientists, chemists, physicists, and clinicians. Similarly, as scientific and technological development provides us with new tools to intervene at many points along the entire trajectory of malignancy, the actual testing of these new interventions – whether for prevention, detection, diagnosis, or treatment – will require the collaboration of many scientists with diverse backgrounds. These scientists will require access to many different kinds of resources, such as patients, at-risk populations, tissue banks, new technologies, and state-of-the-art informatics. These many requirements will best be satisfied by specialized networks, centers, and consortia that incorporate diverse expertise and flexibility in funding and in administration.

For these reasons, NCI proposes to expand its programs for Centers of Research Excellence and Cancer Centers and to develop a variety of new research networks and consortia. Centers can serve as platforms for developing and providing access to technologies, for promoting and facilitating complex scientific interactions, and for providing the critical resources essential for research studies of great scope. NCI will enable more specialized research networks and consortia to develop novel capabilities and link with NCI Cancer Centers.

### NCI-designated Cancer Centers

The NCI-designated Cancer Centers are key partners in NCI’s efforts to speed the process of

discovery and bring the benefits of cancer research directly to the public. Centers coordinate multi-disciplinary approaches to research questions, provide access to the most advanced research technologies, and take rapid advantage of new research opportunities. Support of the Cancer Centers helps ensure a close association between state-of-the-art research and clinical care activities within the institution. It also allows each Center to develop key collaborations and partnerships within industrial, community, and state health organizations, and link the research capabilities and expertise of scientists within the institution to problems of cancer incidence and mortality in their communities and regions.

Establishing partnerships between and among NCI-supported centers and research institutions is equally important. NCI will create Regional Enhancement Centers that will work closely with existing NCI-designated Comprehensive Cancer Centers; these partnerships will provide patients and populations with much improved access to studies in early detection, prevention, and therapeutic research. NCI also has recently launched the Special Populations Network for Cancer Awareness Research and Training. This initiative will develop and maintain partnerships between scientific researchers and community leaders from a broad range of minority and underserved populations. In addition, the Cancer Centers will be enhanced by placing a stronger emphasis on the need for collaborations between the Cancer Centers, industry, and non-traditional academic sites lying outside the orbit of cancer research. These will enable the Centers to function more effectively as platforms for broad-based early technology development, and ensure that the research community can gain access to these technologies.

### Centers of Research Excellence

Centers of Research Excellence are multidisciplinary and translational research teams focused on a specific disease, modality, biologic process, or scientific area of particular significance. They are awarded sizeable amounts of flexible funding to enable them to rapidly address emerging scientific opportunities or specific challenges. NCI's SPORE

program (Specialized Programs of Research Excellence) is one highly successful example of this approach. Each SPORE group focuses on a specific cancer site. Their goal is translational: they aim to move discoveries and observations back and forth among laboratory, clinic, and population settings. Research in the SPOREs focuses on approaches for reducing cancer incidence and mortality and improving survival and quality of life. Recent findings from the SPORE program include the identification of several tumor suppressor gene mutations that lead to pancreatic cancer, and the first human gene therapy approaches for advanced prostate cancer. NCI is supporting SPOREs in cancers of the breast, prostate, lung, and gastrointestinal tract,

and one soon will be awarded in ovarian cancer. We plan to expand the SPORE program to all cancer sites; each SPORE will continue to focus on a specific cancer.

Additional examples of the centers of excellence concept that we have recently implemented or will shortly implement include those in tobacco research, molecular and *in vivo* imaging, communications, population health, and interventions directed against molecular targets.

For a list of  
Cancer Centers  
visit  
[http://www.  
nci.nih.gov/  
cancercenters/  
centerslist.html](http://www.nci.nih.gov/cancercenters/centerslist.html)

### Consortia and Networks

Many of the most innovative ideas emerge from groups of scientists who link their expertise and resources to address important questions about human cancer. NCI has taken steps to facilitate just this sort of complex collaborative effort. For example, we recently established the Cancer Genetics Network (CGN), which is dedicated to studying inherited predisposition to cancer. The CGN consists of eight centers and an informatics and information technology group. It builds on recent progress in isolating genes linked to inherited cancer and promotes the application of this knowledge to the clinical setting. The CGN not only will integrate discoveries into medical applications such as prevention, detection, and cancer control, but will address psychosocial, ethical, legal, and public health implications of inherited cancer susceptibility. The Diagnostic Imaging Network creates, for the first time, a multi-center research group to systematically evaluate new imaging technologies and their impact on cancer management and health care outcomes. We

expect that strong collaborative relationships will develop between the Diagnostic Imaging Network and industrial device manufacturers, as well as between the imaging network and our clinical cooperative groups that perform treatment and prevention studies. Networks for early detection studies and for developing better animal models of human cancer are additional examples of specialized consortia that the NCI recently has begun.

Centers and networks actively reinforce each other. For example, NCI recently has supported innovative proposals from several collaborating SPOREs to study the molecular characteristics of breast duct carcinoma *in situ* and to create a common language and data bases that will pave the way for joint studies in lung cancer prevention and early detection.

## THE GOALS

- Refine the organizational framework of centers, consortia, and networks to stimulate and expedite interdisciplinary collaborations.
- Promote collaborations among and between basic, clinical, and population scientists by providing the infrastructure to support a critical mass of expertise and a variety of study populations.
- Stimulate unique forms of research that can be conducted only by interinstitutional, interdisciplinary teams of investigators.
- Support centers and consortia as platforms for technology development and application.

## THE PLAN

### Objectives

- 1. Increase the number and broaden the geographic distribution of NCI-designated Cancer Centers.**
  - Establish new NCI-designated Cancer Centers.
  - Award new cancer center planning grants.
- 2. Expand NCI Cancer Center linkages to increase their research capabilities and broaden their access to populations that currently lack access to centers.**
  - Create new Regional Enhancement Cancer Centers that will collaborate with existing NCI-designated Comprehensive Cancer Centers to expand the base of patients and populations available for early detection, prevention, and therapeutic research studies.
  - Establish formal affiliations between cancer centers and minority institutions to strengthen the research capabilities of minority institutions and to enable collaborative research programs focusing on the burden of cancer in minority groups.
  - Establish a program of competitive cancer center supplements to foster new collaborations among centers, particularly when the centers are competing for the same populations or patient bases or when combining resources can address important questions more effectively.
- 3. Expand the capacities of NCI-designated Cancer Centers to engage in newly developing areas of research that are critical to solving the cancer problem.**
  - Establish Advanced Technology Programs in cancer centers to enable center investigators to access cutting-edge technology developed in industry and to develop applications and pilot projects to solve particular problems in cancer research.
- 4. Expand the research programs in NCI's Specialized Programs of Research Excellence (SPOREs) and other Centers of Research Excellence.**
  - Expand the scope of the SPORE program to include all cancer sites.
  - Create and expand Centers of Research Excellence to support multidisciplinary and translational research teams focused on modalities, biological processes, or scientific areas of particular significance.
  - Provide supplements to SPOREs and other Centers of Research Excellence to develop and initiate complex inter-institutional exploratory research initiatives.
  - Support the development of an Internet platform for SPOREs to exchange research results and to foster the communications needed for sharing resources and conducting inter-SPORE collaborative research.

5. **Enhance the capacity of NCI Centers to act as platforms for translating discoveries into interventions.**

- Provide funding for research nurses and data managers.
- Develop clinical trials informatics to conform with NCI's Cancer Informatics Infrastructure.
- Address regulatory issues.

## PROGRESS TOWARD MEETING THE CHALLENGE

In the past year, NCI has taken a number of steps to strengthen and expand research support mechanisms designed to foster multidisciplinary and multi-institutional collaborations. These collaborations are bringing together diverse scientific disciplines across institutional boundaries, improving access to new technologies and patient populations.

The emergence of new and improved medical imaging technologies is an area of cancer research that will depend on effective multidisciplinary collaboration. NCI has created **In Vivo Cellular and Molecular Imaging Centers** that will provide the infrastructure to foster the interaction and collaboration of imaging scientists with basic biologists, chemists, immunologists, computer scientists, and physicists to focus imaging research on the detection of genotypic and phenotypic abnormalities in oncology. Similarly, NCI is providing support for the **Diagnostic Imaging Network** to bring together imaging experts from across the country to perform a broad spectrum of multi-institutional clinical diagnostic imaging trials related to cancer.

Increasingly, tobacco control and addiction research must rely upon scientists with expertise in diverse areas including molecular biology, genetics, neuroscience, epidemiology, imaging, behavioral science, primary care, and communication. To further transdisciplinary research in tobacco control and addiction research, NCI and the National Institute on Drug Abuse have created **Transdisciplinary Tobacco Use Research Centers**.

Two areas of extraordinary opportunity identified by NCI in this document are Defining the Signatures of Cancer Cells: Detection and Diagnosis, and Molecular Targets of Prevention and Treatment. Possibly no other opportunities challenge us to work more collaboratively in multi-institutional settings with multidisciplinary

teams than these. As stated in the Extraordinary Opportunities section, new molecular-based technologies are enabling us to identify features of cells and the transformation of normal cells to cancerous cells in unprecedented ways. The implications of these discoveries for cancer detection, diagnosis, and treatment are profound. The NCI-supported **Early Detection Research Network (EDRN)**, a multi-institutional network, links centers of expertise in tumor biology, diagnostic technologies, and clinical trials methodology in academia and industry to develop, evaluate, and validate biomarkers for early cancer detection.

To develop and test target-based therapeutics and preventives, NCI will create a series of multidisciplinary research groups, each organized around a mechanism of particular relevance to cancer therapy, such as angiogenesis, cell cycle control, immunotherapy, DNA repair, metastasis, and apoptosis. These consortia will bring together chemists, biologists, pharmacologists, imagers, clinicians, and informatics experts to create tools such as assays, probes, and reagents necessary to assess the effects of cancer drugs on their molecular targets in patients with cancer.

Developing experimental models that mimic the wide variety of human cancers is critical to understanding how a cancer gene disrupts the normal processes of a cell. The challenge has always been the lack of infrastructure to develop and distribute efficiently to the research community the range of models necessary to represent human cancer and to validate these as predictive models of human cancer. NCI has undertaken a major effort to overcome these challenges by creating the **Mouse Models of Human Cancer Consortium**, a consortium of scientific laboratories and teams of scientists dedicated to developing, validating, and characterizing mouse models of human cancer.

Other recently established or expanded NCI-sponsored consortia include the **Pediatric Brain Tumor Consortium**, a network of medical centers that will evaluate promising treatments for children with brain malignancies; and the **Community Clinical Oncology Program** and the **Minority-Based Community Clinical Oncology Program**, which provide the infrastructure to link community cancer specialists and primary care physicians with NCI's Clinical Cooperative Groups and Cancer Centers.

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## Resources: Centers, Networks, and Consortia

<b>Broaden geographic distribution of NCI-designated Cancer Centers.</b>	<b>\$5.1 M</b>
<ul style="list-style-type: none"><li>■ Designate 3 new Cancer Centers.</li><li>■ Award 3 new Cancer Center Planning Grants.</li></ul>	
<b>Link NCI Cancer Centers to populations.</b>	<b>\$9.5 M</b>
<ul style="list-style-type: none"><li>■ Establish 2 Regional Enhancement Cancer Centers.</li><li>■ Establish formal affiliations between NCI Cancer Centers and minority institutions.</li><li>■ Award Cancer Center supplements to support inter-center collaborations.</li></ul>	
<b>Expand capacity of NCI-designated Cancer Centers.</b>	<b>\$16.0 M</b>
<ul style="list-style-type: none"><li>■ Establish 10 Advanced Technology Programs in Cancer Centers.</li></ul>	
<b>Expand NCI's Specialized Programs of Research Excellence (SPOREs) and other Centers of Research Excellence.</b>	<b>\$15.3 M</b>
<ul style="list-style-type: none"><li>■ Establish 6 new SPOREs/Centers of Excellence.</li><li>■ Provide supplements to SPOREs and Centers of Research Excellence for inter-institutional exploratory research initiatives.</li><li>■ Support development of Internet platform for SPOREs.</li><li>■ Support Centers of Research Excellence.<sup>1</sup></li></ul>	
<b>Enhance capacity of NCI Centers to act as platforms for translating discoveries into interventions.</b>	<b>\$14.5 M</b>
<ul style="list-style-type: none"><li>■ Provide funding for research nurses and data managers.</li><li>■ Develop clinical trials informatics to conform with NCI's CII.</li><li>■ Address regulatory issues.</li></ul>	
<b>Management and support.</b>	<b>\$2.0 M</b>
<b>TOTAL</b>	<b>\$62.4 M</b>

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<sup>1</sup> See Cancer Imaging, Molecular Targets for Prevention and Treatment, Research on Tobacco and Tobacco-Related Cancers, Cancer Communications, and Studying Emerging Trends in Cancer for specific budget items.

# 3

## CHALLENGE

### National Clinical Trials Program

#### THE CHALLENGE

The research investment of the past decade has produced major advances in our understanding of tumor biology and molecular targets – the tumor-related molecules that can be selectively targeted to treat or prevent cancer. It also has brought about a dramatic increase in the number of new preventive, diagnostic, and therapeutic agents being tested in clinical trials. But our present clinical trials system is failing to keep pace with the growing number of agents that will merit testing in people. Currently, an estimated 354 new cancer treatments are in development by industry, a three-fold increase during the 1990s. In 1999, NCI

entered into clinical trials approximately 30 novel agents discovered through its own drug discovery programs or in collaboration with academic institutions or industry. This is in addition to 78 promising new interventions for treatment and 32 for prevention that NCI already is testing in people.

As these potential treatments and prevention strategies emerge from early clinical testing, NCI is faced with a backlog of agents that need to enter large Phase III trials – the final crucial step in the translation of new discoveries into effective new treatments and prevention strategies for patients. (See page 27 for more information.) At present, NCI and its grantees are able to initiate only about 30 Phase III trials each year. Compounding this

#### SPOTLIGHT ON RESEARCH

### Viruses, Vinegar, and Vaccines – Preventing Cervical Cancer

Without question, our ability to prevent cervical cancer through regular Papanicolaou screening tests – also called the Pap smear – is a major public health success story in the United States and many other countries with established screening programs. But in developing countries, few women receive this life-saving screening, and invasive cervical cancer still strikes an estimated 350,000 women each year, killing 200,000. And even with the success of cervical cancer screening in the U.S., about 15,000 women each year will learn that they have this disease. Some older women fail to be screened because they believe they are no longer at risk, or because their physicians do not recommend screening. HIV-positive women, whose immune systems are weakened, are at greater risk of infection with the human papillomavirus (HPV) that has been discovered to be the primary cause of 90 percent of cervical cancers. In addition, some populations of women still avoid screening, or live in medically under-

served areas where screening rates are as low as those in developing nations. For these reasons, population, laboratory, and clinical researchers are working to discover more effective, less invasive, and less costly ways to prevent, diagnose, and treat cervical cancer here and around the world.

Population and laboratory studies led to discovery of the HPV-cervical cancer link, and clinical studies have shown that while sexually transmitted HPV infection is widespread in the population, most infections go away by themselves within six months. Moreover, we now know that only a small percentage of women with HPV – even those infected with the HPV types most associated with cervical cancer – actually develop the disease. Further, even moderately severe cell proliferation believed to be a precursor of invasive cancer may regress spontaneously, suggesting new approaches to monitoring and treating these early lesions.

problem is the fact that for a variety of reasons – e.g., limited access, lack of insurance coverage, patient-physician communication issues, therapy choice – only about 20,000 patients enter Phase III trials each year. Overall, fewer than three percent of patients with cancer participate in the clinical trials that define effective new treatment approaches. Thus, it can take over four years just to recruit enough patients for the average Phase III trial. In addition, more than 80 Phase II and III prevention trials have been initiated, but progress in this area is limited by lack of methods, such as biomarkers, to determine the effect of a preventive over a short period of time, lack of technologies to improve precision in characterizing precancerous lesions, and the growing number and complexity of trials needed to determine the roles of this new generation of agents.

How can we more efficiently convert recent scientific discoveries into effective interventions, eliminate the backlog of agents for testing, and increase patient access? We must invest in, restructure, and increase the capacity of our national clin-

ical trials program. NCI has reconfigured major aspects of its clinical trials program to increase the speed and smooth the path for entering promising agents into trials. While the time from initiation of clinical trials to Food and Drug Administration (FDA) approval has improved over the past decade, the clinical development required to establish the best uses of new agents still occurs over a much longer period. For example, paclitaxel (Taxol®), approved for use in ovarian cancer in 1992, also has a potentially life-saving role in several other cancers, including cancers of the breast, lung, prostate, head and neck, esophagus, and bladder. Even so, the clinical trials to define its use in these diseases are still ongoing seven years after FDA approval for ovarian cancer treatment.

The changes we propose in the following plan will substantially increase the number of trials and number of patients who enroll in trials each year by easing the way for physicians to communicate with patients and enroll them in clinical trials. The plan also calls for funding the kinds of laboratory studies that will help determine why particular

These and other findings are leading to much-needed interventions for women. A refined Pap test is slowly gaining acceptance in community practice; more cells are sampled, cell preparation errors are less likely, and the sample can be saved and reused if a reading is questionable. The new test also is easier to read and substantially more accurate. In developing nations, an easily performed screening test in which the cervix is swabbed with a vinegar solution that discolors only abnormal cells is being studied in selected populations. It could bring affordable screening to millions of women in countries where health care resources and personnel are so scarce that currently, only five percent of women are screened for cervical cancer. HPV DNA testing for women who have a questionable Pap smear shows promise as a reliable, less invasive, and less costly method of determining a woman's cervical cancer risk and catching early disease, compared with current approaches. Prevention vaccines are being developed that will prime the immune system to recognize both cancer-linked and other HPV types and attack if infection occurs. If given to men as well as women, these vaccines will prevent cervical can-

cer and also may prevent sexually transmitted HPV diseases like genital warts that affect both genders.

There also is encouraging news for women who do develop suspicious cervical dysplasia or invasive cervical cancer. To better guide the treatment of precancerous cervical changes, a refined and simplified system of classifying these early lesions – the Bethesda system – has been established. Treatment vaccines that spur the immune system to attack existing HPV infection are on the near horizon. Of great importance, NCI recently issued a special announcement to physicians to inform them of the results of five clinical trials involving women with locally and regionally advanced cervical cancer. These trials showed that women achieved significantly improved survival when cisplatin-based chemotherapy was given concurrently with radiation therapy – the risk of cervical cancer death was reduced by 30 percent. Based on these definitive results, NCI strongly urges that physicians consider adding chemotherapy to the treatment of women who require radiation therapy for cervical cancer.

drugs are effective in some patients and not in others. The results will help us tailor treatments for cancer patients in the future. These enhancements will help speed development of agents and alleviate the backlog of agents awaiting evaluation.

## THE GOALS

- Create a more effective and efficient clinical trials system.
- Accelerate clinical evaluation of the best scientific ideas and approaches for treatment and prevention.
- Study a broader range of clinically relevant questions.
- Enhance collaborations between NCI, academia, industry, and other agencies in developing promising therapeutic and preventive approaches.
- Make access to clinical trials a realistic possibility for many more patients with cancer.
- Achieve better short-term assessment of promising strategies by developing and validating molecular and imaging risk biomarkers.

## THE PLAN

### Objectives

1. **Increase pace of development and clinical testing for new therapeutic and preventive agents.**
  - Triple the number of promising agents entering Phase I and II clinical trials annually.
  - Implement a new rapid-review grant support program for mechanism-based clinical trials (Quick-Trials) to support trials of novel agents and the associated laboratory studies that assess a drug's effects on its target.
  - Include correlative laboratory studies in clinical trials to elucidate the molecular mechanisms of response and drug effects.
2. **Address compelling clinical questions confronting physicians and patients struggling with cancer.**
  - Conduct disease-specific State of the Science Meetings to bring together the Nation's leading multidisciplinary experts, to identify the important research questions for a given disease and help define the scientific research agenda that will assist us in addressing those questions.
3. **Maximize the use of existing clinical trials infrastructure to study prevention and treatment outcomes and other clinically relevant questions.**
  - Sponsor clinical trials of the best scientific concepts from individual academic sites or investigators, pharmaceutical or biotechnology companies, or others through NCI's national network of cooperative groups and community practice sites.
  - Provide Concept Evaluation Panels for NCI Phase III trials conducted through our national accrual network
  - Provide scientific leadership funding to permit academic investigators the time necessary to develop and conduct clinical research protocols.
  - Provide funds for correlative studies to elucidate the mechanisms underlying new treatments and preventive strategies.
  - Support the broad acquisition of tumor specimens/tumor banks to facilitate rapid evaluation of new assays and relevant clinical correlations as new targets are identified.
  - Use Centers of Excellence to develop the molecular assays required to characterize/classify patient tumors.
  - Develop reference laboratories so that appropriate assays are widely available.
4. **Develop common informatics systems, shared data bases, and information resources that allow physicians to enroll patients in trials and report data from any site nationwide.**
  - Integrate treatment with prevention, early detection, epidemiology, behavioral, and other relevant research areas to most effectively address the burden of cancer in specific tumor types and patient populations.
  - Establish common data elements so that all clinical trials are written in the same "language" and so that results can be easily combined and compared.
  - Develop common forms and interfaces for physicians participating in trials.
  - Create electronic protocol authoring tools to speed protocol generation.
  - Create electronic update and reporting systems.
5. **Increase the number of referring physicians and patients who participate in clinical trials.**
  - Create a national accrual network that allows physicians to enroll patients in any of the Phase III trials sponsored by NCI.



- Extend outreach efforts to physicians in busy and competitive practice settings; provide the data management and research support they need to enroll their patients on clinical trials.
- Extend outreach to minority patients and physicians to improve their access to state-of-the-art cancer therapy.
- Use a variety of media to increase substantially the information available to patients about clinical trials.
- Provide extensive electronic information about available treatment and prevention protocols to physicians.

#### 6. Create collaborations to optimize resources.

- Facilitate new partnerships with academia, industry, patient advocacy groups, professional societies, and other organizations to accomplish research objectives, share resources, and avoid duplication.
- Provide opportunities for industry to invest in and use the national clinical trials infrastructure to perform important clinical trials.

#### 7. Identify relevant biomarkers.

- Identify novel response-related biomarkers by measuring tumor burden.
- Conduct research on molecular profiling of cancer cells to identify patients most likely to benefit from specific treatments. Monitoring biomarkers can more quickly identify patients with a suboptimal response who may require a change or discontinuation of treatment.
- Fund intergroup studies to evaluate biomarkers for monitoring treatment response.

#### 8. Support intramural clinical trials.

- Support high priority clinical trials conducted at the NIH Clinical Center.

tions regarding review, funding, design, oversight, and administration of our clinical trials system. In September 1998, a plan for implementing these recommendations was approved. Since that time a number of pilot projects have been initiated:

- **State of the Science Meetings** are being held on prostate cancer (November 1999 and February 2000), lung cancer (September 1999), leukemia (March and September 2000), and colorectal cancer (January 2000).
- This year, **Concept Evaluation Panels**, expert panels of nationally renowned scientists, were formed to review and prioritize Phase III clinical trials proposals in lung and genitourinary cancers.

- A **Cancer Trials Support Unit (CTSU)** was created to centralize administrative and data management functions now duplicated in numerous clinical trials organizations. A Request for Proposals was issued in March 1999 with awards planned for September 1999.
- **New Cooperative Group peer review criteria and procedures** were implemented in March 1999.

For more information on the clinical trials review visit <http://ctep.info.nih.gov/Armitage/>

Along with the launch of several new pilot projects, NCI has **increased funding for its Cooperative Groups** (see page 28), which have been funded below peer review recommended levels for many years. A 29 percent increase in funding was provided in 1999, reducing the gap in funding by 33 percent overall.

Finally, we are implementing **new information systems**, such as an electronic Adverse Event Reporting System that captures information on severe toxicities experienced on clinical trials, and a Physician Communication Module in collaboration with the Howard University Cancer Center. This computer-based tool will facilitate clinical trials data collection, help physicians in office settings identify trials for eligible patients, and provide educational information. This project should increase minority physician and patient participation in NCI clinical trials.

For more information on clinical trials implementation visit [http://cancertrials.nci.nih.gov/NCI\\_CANCER\\_TRIALS/zones/Tools/Booklets/Plan/index.html](http://cancertrials.nci.nih.gov/NCI_CANCER_TRIALS/zones/Tools/Booklets/Plan/index.html)

## PROGRESS TOWARD MEETING THE CHALLENGE

In 1996, an external review group conducted an **in-depth review of NCI's clinical trials system**. The review group made major recommenda-

and patient participation in NCI clinical trials.

## Resources: National Clinical Trials Program

<b>Accelerate new agent development and clinical testing.</b>	<b>\$121.8 M</b>
<ul style="list-style-type: none"><li>■ Increase funding for Early Therapeutics Development contracts.</li><li>■ Implement Quick-Trials.</li><li>■ Establish Centers of Excellence in interventions directed to molecular targets.</li><li>■ Establish Translational Research Fund for correlative laboratory studies in clinical trials.</li><li>■ Establish Group Developmental Fund to support Cooperative Group pilot correlative studies.</li><li>■ Provide adequate funding to Cooperative Groups and practice sites for data management and to double or triple physician participation in clinical trials.</li><li>■ Provide information about treatment and prevention options and clinical trials needed to enable patients and physicians to make informed treatment choices. (See Informatics)</li><li>■ Increase contracts for prevention drug development; accelerate patient accrual to prevention trials.</li></ul>	
<b>Address the most compelling clinical questions.</b>	<b>\$31.6 M</b>
<ul style="list-style-type: none"><li>■ Conduct State of the Science meetings for genitourinary and lung cancers.</li><li>■ Establish Concept Evaluation Panels for NCI Phase III trials.</li><li>■ Provide Scientific Leadership Funds to study chairs and statisticians who write, monitor, and analyze high priority Phase III trials approved for conduct in the national accrual network.</li><li>■ Fund correlative studies to elucidate and translate basic biology from bench to bedside.</li><li>■ Fund tissue banks to store tissues from patients in studies of drug effects, molecular abnormalities in tumor and normal tissue, and tumor initiation and progression mechanisms.</li></ul>	
<b>Maximize use of existing infrastructure.</b>	<b>\$5.0 M</b>
<ul style="list-style-type: none"><li>■ Conduct multidisciplinary meetings to explore possible Cooperative Group studies.</li><li>■ Involve multidisciplinary planning teams from NCI Divisions in State of the Science meetings.</li><li>■ Increase the number of CCOPs to increase prevention clinical trials capacity.</li></ul>	
<b>Develop common informatics systems, shared data bases, and resources.</b> (Budgeted in the Informatics Challenge.)	<b>\$ 0 M</b>
<b>Increase number of physicians and patients participating in clinical trials.</b>	<b>\$9.0 M</b>
<ul style="list-style-type: none"><li>■ Expand Participation Project to enable new participating physicians, including new minority physicians, to hire the necessary research nurses and data managers.</li><li>■ Establish CTSUs to consolidate administrative tasks associated with conducting clinical trials.</li><li>■ Use Physician Communication Module to provide protocol and patient education information.</li></ul>	
<b>Create effective collaborations.</b>	
<ul style="list-style-type: none"><li>■ Encourage pharmaceutical/biotechnology industry to submit concepts for high priority Phase III trials to Concept Evaluation Panels; conduct trials through the national accrual network; and invest in CTSUs to reduce administrative redundancy.</li><li>■ Encourage private foundations and other government agencies to co-fund clinical trials.</li></ul>	
<b>Identify relevant biomarkers.</b>	<b>\$3.0 M</b>
<ul style="list-style-type: none"><li>■ Identify novel response-related biomarkers.</li><li>■ Conduct research on molecular profiling of cancer cells to predict treatment response.</li><li>■ Fund intergroup studies to evaluate biomarkers of treatment.</li></ul>	
<b>Support intramural clinical trials.</b>	<b>\$25.0 M</b>
<ul style="list-style-type: none"><li>■ Support high priority clinical trials conducted at the NIH Clinical Center.</li></ul>	
<b>Management and support.</b>	<b>\$6.0 M</b>
<b>TOTAL</b>	<b>\$201.4 M</b>

## Informatics and Information Flow

### THE CHALLENGE

Around the globe, cancer researchers are benefiting from advances in computing and telecommunications that, coupled with the explosive growth of the World Wide Web, help make unprecedented research opportunities possible. As never before, these advances in technology enable scientists to collaborate and to generate incredible amounts of information – the raw data from which knowledge is created. But vast amounts of knowledge that already exist often go unused due to an inability to access and organize information from diverse sources. Therefore, we must ask ourselves, how do we best collect, manage, and share this information?

The answer to this question lies in knowledge management – in designing a framework to help capture, analyze, apply, and reuse knowledge to make possible faster, smarter, and better applications. This framework will serve as a tool to create an interface among the research communities – basic, translational, clinical, and population-based – that participate in the research discovery process. NCI is addressing the challenges presented by the revolution in electronic communications and computing by developing a knowledge management system – a Cancer Informatics Infrastructure (CII) – that will unify these research communities. Employing knowledge management will reduce drastically the time and effort needed to create and use existing or new information, making research discoveries possible at a scientist's desk, in addition to the lab. By speeding the discovery process and translation of the best discoveries into clinical interventions, the CII will transform cancer care through more effective and efficient information exchanges among all involved in cancer research. Finally, a knowledge management system will create new synergies within and among the fields of research described in this document, resulting in a dramatic acceleration of our progress against cancer.

The first step being taken by the CII project is developing a knowledge management system to increase the speed with which we carry out clinical trials in cancer prevention, diagnosis, and treatment. We are revising our criteria and standards for reporting all data collected during a clinical trial, and are developing common forms, terminology, and reporting requirements across all types of clinical trials. This uniformity will increase the speed, efficiency, and accuracy of results reporting. Special data bases of medical and scientific terminology will help researchers, clinicians, and other users of NCI information systems to find and understand the information they seek. The accomplishments achieved in developing these common definitions can be applied to all areas of the research discovery process to accelerate scientific discovery. Once in place, the components of the clinical trials knowledge management system will be applied in the basic, translational, and population-based research fields to manage information and share knowledge within and among these communities.

By investing in the CII and its broad public-private partnerships, we have the opportunity to fundamentally improve our clinical trials system and establish an infrastructure that supports comprehensive knowledge management across diverse research disciplines. NCI's leadership in this area will enable us to establish a national clinical trials effort that realizes maximum benefit from the information revolution through increased patient accrual, common reporting practices, and greater sharing of knowledge with the public and the research community. We must work quickly to establish this infrastructure, however, as industrial and academic institutions are investing individually in automated systems to speed discovery, lower costs, and capture data electronically. As individual systems are established, it will become increasingly difficult, and eventually impossible, to institute a common knowledge management system. The CII

will help us address the issue of compatibility, enable us to manage the explosive growth in fundamental discoveries, and help alleviate the serious bottleneck that exists between discovery and its application for the benefit of patients with cancer.

## THE GOALS

- Create a common infrastructure that enables cancer research through enhanced information and resource exchange among researchers, clinicians, and the public.
- Reduce the barriers experienced by patients, survivors, families, at-risk individuals, and physicians seeking information about cancer prevention, diagnosis, and treatment.

## THE PLAN

### Objectives

1. **Design an information infrastructure and enhance information exchange to accelerate administration of the full range of clinical research activities.**
  - Develop a comprehensive clinical trials informatics infrastructure that ensures data compatibility and access, enhances clinical trials recruitment, and promotes scientific knowledge exchange among all participants.
  - Develop an electronic Protocol Authoring Toolbox that contains clinical trials “building blocks,” including a comprehensive set of clinical trials templates, to reduce the time needed to create a new protocol.
  - Develop a common, on-line protocol review process for all clinical trials that will “shepherd” approved concepts through the approval process within three months of submittal.
2. **Ensure widespread availability of all types of cancer information.**
  - Create a usable, comprehensive cancer information system for the public using the PDQ redesign as a model.
  - Encourage voluntary electronic submission of information on non-NCI sponsored clinical trials to PDQ.
  - Streamline and automate research results and clinical trials information management.

3. **Extend the informatics infrastructure developed for clinical trials to basic, translational, and population research.**

- Apply the information gained and processes used to achieve common data definitions to the areas of extraordinary opportunity.
- Create mechanisms that foster interaction between the public and private sectors for joint development of these informatics infrastructures and knowledge exchanges across the cancer research discovery enterprise.

4. **Create a knowledge management system for cancer research information and resources.**

- Establish an NCI-wide approach to knowledge management encompassing the wide array of scientific and resource-related information generated through NCI research.
- Develop an inventory of research tools to publicize and enhance the accessibility of scientific tools and technologies developed by NCI that are useful and available to the broader scientific community.
- Develop a document management/workflow approach that streamlines the review and award process and portfolio management of all funding mechanisms.
- Provide necessary staffing and contract support to establish the labor infrastructure necessary to accomplish the stated objectives.

## PROGRESS TOWARD MEETING THE CHALLENGE

The CII project already is developing several computer-based components of its clinical trials knowledge management system to help capture, analyze, apply, and reuse knowledge generated through clinical trials. Components designed to help capture and manage data include:

- **Clinical Trials Informatics System.** Developed by NCI, this system provides point-of-care data collection, document management, and digital document capabilities. It links all phases of the clinical trial life cycle, from protocol development, patient recruitment and screening, and protocol implementation to publication of trial results.

## Resources: Informatics and Information Flow

<b>Accelerate the full range of cancer research activities via enhanced information exchange across a common infrastructure.</b>	<b>\$25.0 M</b>
<ul style="list-style-type: none"> <li>■ Complete data models of the Common Data Elements for interventional and cancer control trials in breast, prostate, lung, gastrointestinal, and gynecologic cancers.</li> <li>■ Use Common Data Elements in all NCI-sponsored clinical trials by cooperative groups, cancer centers, and the FDA.</li> <li>■ Implement a Protocol Authoring Toolbox to reduce time needed to create a new protocol.</li> <li>■ Increase the number of on-line protocol submissions.</li> <li>■ Implement an on-line review and approval process for electronically submitted protocols.</li> </ul>	
<b>Ensure widespread availability of all types of cancer information.</b>	<b>\$20.0 M</b>
<ul style="list-style-type: none"> <li>■ Implement the user-friendly version of PDQ.</li> <li>■ Submit at least 80% of non NCI-sponsored trials on-line to PDQ.</li> <li>■ Implement the comprehensive cancer information system.</li> </ul>	
<b>Extend informatics infrastructures developed for clinical trials to basic, translational, and population research.</b>	<b>\$15.0 M</b>
<ul style="list-style-type: none"> <li>■ Extend data models and definitions for clinical trials to genomics, molecular targets, and preclinical models of cancer.</li> <li>■ Implement 2 Research Partnership Platforms that use the CII for knowledge management.</li> </ul>	
<b>Create a knowledge management system for cancer research information and research resources.</b>	<b>\$7.0 M</b>
<ul style="list-style-type: none"> <li>■ Implement an automated application and portfolio management system.</li> <li>■ Publish an inventory of research tools.</li> </ul>	
<b>Management and support.</b>	<b>\$3.0 M</b>
<b>TOTAL</b>	<b>\$70.0 M</b>

- **Clinical Data Update System (CDUS).** This system achieves rapid, accurate, and secure capture of clinical trial data with minimal effort. CDUS successfully captures the majority of trial data within hours of submission – a process that previously took months.
- **Common Toxicity Criteria Interactive Application (CTC-IA).** This application identifies and grades adverse events experienced on clinical trials. An application is being developed to capture toxicity data at the patient's bedside to minimize errors and duplication.
- **Adverse Events Reporting System.** This system complements the CTC-IA and collects information on severe toxicities experienced on clinical trials to assure future patient safety.

- **Clinical Trials Monitoring Branch Audit Information System.** This system assists NCI and cancer researchers in ensuring the quality and scientific integrity of NCI-sponsored trials.

Additional CII components facilitate the protocol submission and approval process for clinical trials and help pharmacists manage, order, and track NCI investigational agents. Finally, we are creating **common data elements** that will simplify and standardize data collection for cancer trials.

NCI is also redesigning the **Physician Data Query (PDQ)** – its comprehensive cancer information data base – based on substantial usability testing to make the information in it more accessible and easier to navigate for all users. The new PDQ Universal Database stores any type of cancer-related information – images, sound, movies, and text – and delivers data in a wide variety of media.

## Studying Emerging Trends in Cancer

### THE CHALLENGE

Cancer surveillance – identifying and tracking trends in our national cancer burden, and monitoring the factors that influence these changes – is a crucial underpinning of our efforts to prevent and control cancer. Unequivocally, we are making real progress against cancer, and reduction in the cancer burden on people is a critical measure of that progress. Between 1990 and 1996, cancer incidence and death rates dropped for all cancers combined and for most of the top 10 cancer sites, reversing a decades-long trend of rising cancer incidence and death in the United States. These decreases are hard evidence of the wisdom of this Nation’s investment in cancer research.

Appropriate decision making in science and in public health depends on accurate, reliable information about the incidence and impact of disease. Established in 1973, NCI’s Surveillance, Epidemiology, and End Results (SEER) cancer registry program has been a world model for tracking population trends in cancer morbidity and mortality. The NCI cancer surveillance program uses SEER data to identify and study trends, track the impact of cancer on the general population, and provide information that researchers need to ask critical questions about why certain populations are affected by cancer more severely than others. SEER data have enabled us to identify environmental carcinogens, track cancer-related effects of tobacco on men and women, identify geographic areas with higher than average cancer rates, study patterns and outcomes of cancer care, and identify risk groups for research and public health intervention programs.

Recent changes in health care financing and delivery, the revolution in informatics and computer programming technology, and the social and cultural diversity of our country present new chal-

lenges and opportunities in surveillance research. Currently, our understanding about how risk factors, screening, and treatment may affect trends in the cancer burden is limited, and advancing our knowledge in these areas will require new data sources and statistical methods. To more fully assess the Nation’s cancer burden, we need data on patterns of care and quality of life outcomes, in addition to the incidence, survival, and mortality data now collected. Research is needed to improve methods for measuring quality of life, quality of care, health status, morbidity, family history, cancer risk behaviors, screening, and treatment as well as methods and models for relating variables and predicting outcomes. In addition, new investments are required to support the adoption of

methodologic tools that will improve the precision and expand the reach of our cancer surveillance efforts. These tools include geographic information systems that allow data linkage by geographic location, new approaches to modeling trends, and more refined cancer maps for assembling, analyzing, and disseminating cancer surveillance data.

NCI’s surveillance efforts should be expanded to cover a broader spectrum of the racial, ethnic, socioeconomic, and cultural diversity of our country. For example, certain minorities and medically underserved populations are not fully represented in SEER registries; these groups include American Indian and Alaskan Natives, rural whites and African Americans, and Hispanics of Caribbean origin. New investments in surveillance research on specific population groups such as these will make it possible to connect information on prevention, risk factors, screening, treatments, and patterns of care with outcomes such as incidence, quality of life, and survival.

Greater efforts are needed to disseminate the results of NCI’s surveillance research to policy makers, advocacy groups, and the general public.

For more information on SEER visit <http://www.seer.ims.nci.nih.gov/>

In addition, we must improve our ability to provide epidemiologists and other population-based investigators with the information crucial to developing new ideas for research on cancer's causes and developing interventions based on study findings. As the field of surveillance research expands and takes on these new challenges, it is clear that scientists with skills that encompass the disciplines of epidemiology, statistics, disease registration, geographic information systems, and informatics are in short supply. To strengthen this maturing scientific discipline and ensure that we have the data we need to guide cancer research activities of all types, we must create the training opportunities necessary to prepare the next generation of surveillance researchers. Finally, enhancing our investment in surveillance research will ensure that NCI continues to play an active and visible national leadership role in developing a comprehensive national surveillance program.

## THE GOALS

- Improve our ability to describe the cancer burden across a broader spectrum of the population, track changes in cancer rates, and explain observed changes in trends by their relationships to changes in risk factor and screening data.
- Enhance the value of the surveillance system as a research resource by including treatment measures and genetic studies.
- Improve and expand communications relating to cancer surveillance and trends to researchers, public health professionals, advocates, legislators, policy makers, and the public.
- Ensure a cadre of skilled surveillance researchers.
- Foster interdisciplinary studies within the population-based sciences to increase opportunities for applying new discoveries to improve public health.

## THE PLAN

### Objectives

**1. Expand studies to improve our understanding of the experience of cancer survivors, including patterns of care people receive, quality of life they experience during and after treat-**

**ment, and influence of various modes of health services delivery on their outcomes.**

- Support initiatives to expand patterns of care and outcome studies among cohorts of patients with specific types of cancer.
  - Initiate prospective cohort studies to monitor community practice patterns for screening, diagnosis, treatment, and health-related outcomes of men with prostate cancer.
  - Fully develop and staff a program in cancer outcomes research.
  - Develop the infrastructure needed to collaborate with our national partners in cancer surveillance to find better ways to measure cancer care quality across all populations.
- 2. Improve our ability to connect data on cancer risk factors (i.e., lifestyle behaviors and environmental exposures) and screening practices with cancer outcomes in defined populations with high quality cancer registration systems.**
- Expand the Breast Cancer Surveillance Consortium.
  - Support a Colorectal Cancer Surveillance Consortium.
  - Support initiatives for continuing methodologic linking studies.
- 3. Expand SEER data collection to include underrepresented U.S. population segments, including rural whites, rural African Americans, Hispanics of Caribbean origin, Alaskan Natives and American Indians.**
- Support feasibility studies for adding two to five new SEER areas (e.g., states, regions); provide technical assistance/quality control for seven to 21 non-SEER regions to enable them to meet national registry standards.
  - Fund selected high quality, non-SEER registries for special surveillance studies.
- 4. Create opportunities to develop and share methodologic tools for assessing, analyzing, and disseminating data.**
- Support studies of modeling methods.
  - Accelerate in-house development of measures of risk and screening for surveillance.
  - Support studies incorporating geographic information system methods for surveillance.
  - Support initiatives to develop new maps of the cancer burden and its determinants.

5. **Enhance the SEER program by initiating the collection of family history data and biologic specimens from cancer patients, and by incorporating new mechanisms that allow investigators to rapidly identify new cancer patients.**
  - Support feasibility studies for collecting biospecimens and assessing the U.S. prevalence of major familial cancers.
  - Support activities to expand the use of rapid case ascertainment methods.
6. **Develop new informatics initiatives for surveillance data on cancer patients to be collected and disseminated rapidly but confidentially.**
  - Support pilot informatics systems.
7. **Improve the dissemination of NCI's surveillance research results to researchers, policy makers, advocacy groups, and the public.**
  - Produce an annual "report card" to improve dissemination of data on the cancer burden.
  - Develop mechanisms to make surveillance information more readily available to the academic research community and more compelling to the public.
  - Increase development and dissemination of surveillance data bases for cancer research.
  - Make new products available (e.g., cancer maps).
8. **Create cancer surveillance research training opportunities to support the growing need for skilled scientists with expertise in epidemiology, statistics, disease registration, geographic information systems, and informatics.**
  - Develop and fund training programs for a new generation of surveillance researchers.
9. **Create and support Centers of Excellence for interdisciplinary studies in population-based sciences to move basic cancer research findings into population research and increase opportunities for applying discoveries to improve public health.**
  - Support an initiative to create Centers for Population Health to integrate epidemiologic, behavioral, and surveillance research in areas of the country with SEER-quality cancer registry programs.

For more information on surveillance implementation visit <http://dccps.nci.nih.gov/DCCPS>

## PROGRESS TOWARD MEETING THE CHALLENGE

The Plan put forth complements and extends recommendations of the **Surveillance Implementation Group (SIG)**, a review committee created by NCI to determine what cancer surveillance research is most needed and how best to advance our knowledge of cancer. The SIG, which included 42 leading scientists and experts from NCI, other Federal agencies, and the extramural community, was asked to identify research directions and priorities and to produce an implementation plan that represented a comprehensive, focused vision for NCI-supported surveillance research. In 1999, the SIG produced a Cancer Surveillance Research Implementation Plan. It identifies five priority areas and 12 recommendations for opportunities in the study of cancer trends.

NCI support through SEER for the **Patterns of Care and the Prostate Cancer Outcome studies** is enhancing our knowledge about the outcomes of cancer treatment, including quality of care and quality of life issues. In addition, the Prostate Cancer Outcome Study, which oversampled black and Hispanic men, will provide us with much-needed information on these population groups.

The **Breast Cancer Surveillance Consortium** supports eight sites throughout the U.S. that assess accuracy, cost, and quality of screening programs and their impact on cancer diagnoses and survival. Recompetition for this program will continue research support and allow for collection of more detailed risk factor data. It also will provide an opportunity for adding other sites that provide screening for ethnic minority and medically underserved populations.

SEER investigators and NCI staff are developing a cancer survival monograph for publication in 2000. It will reflect enhanced data collection and reporting on survival among ethnic minorities and the medically underserved.

A new program called the **Cancer Intervention and Surveillance Modeling Network (CISNET)** is in development. Modeling is the use of mathematical and statistical techniques to integrate and synthesize known biological, epidemiological, clin-



## Resources: Studying Emerging Trends in Cancer

<b>Collect additional data on cancer patients.</b>	<b>\$8.7 M</b>
<ul style="list-style-type: none"> <li>■ Conduct quality of care studies.</li> <li>■ Conduct SEER special studies.</li> <li>■ Implement Cancer Research Network project.</li> </ul>	
<b>Connect risk factor and screening data.</b>	<b>\$12.0 M</b>
<ul style="list-style-type: none"> <li>■ Fund a Colorectal Cancer Surveillance Consortium.</li> <li>■ Expand the Breast Cancer Surveillance Consortium.</li> <li>■ Continue linkage studies.</li> </ul>	
<b>Expand SEER coverage.</b>	<b>\$11.3 M</b>
<ul style="list-style-type: none"> <li>■ Add 2-5 registries.</li> <li>■ Provide technical assistance for allied/pooled data registries.</li> <li>■ Support special studies.</li> <li>■ Provide technical assistance and quality control for infrastructure.</li> <li>■ Enhance biomedical computing capacities.</li> </ul>	
<b>Expand methodologic studies.</b>	<b>\$6.0 M</b>
<ul style="list-style-type: none"> <li>■ Develop methods (e.g., CISNET).</li> <li>■ Develop measures for risk factor assessment.</li> <li>■ Improve outcomes methods and modeling.</li> <li>■ Use Geographic Information Systems and mapping.</li> </ul>	
<b>Enhance SEER as research resource.</b>	<b>\$2.3 M</b>
<ul style="list-style-type: none"> <li>■ Enhance data collection on self-reported family history of cancer.</li> <li>■ Develop biospecimen resource for surveillance.</li> <li>■ Expand use of rapid case ascertainment methods.</li> </ul>	
<b>Develop new informatics initiatives.</b>	<b>\$1.5 M</b>
<b>Improve surveillance data dissemination.</b>	<b>\$0.8 M</b>
<b>Create surveillance research training opportunities.</b>	<b>\$1.0 M</b>
<b>Establish Centers for Population Health.</b>	<b>\$10.0 M</b>
<b>Management and support.</b>	<b>\$3.0 M</b>
<b>TOTAL</b>	<b>\$56.6 M</b>

ical, behavioral, genetic, and economic information. Modeling techniques have been used to describe the impact of cancer interventions (i.e., screening and treatment) on hypothetical cohorts (groups), or in trial and other clinical settings. CISNET will promote the application and extension of these models to population-based settings to help answer “why” questions in the analysis of cancer trends.

Early progress is being made in working with cancer surveillance partners to develop a **National**

**Cancer Surveillance Program.** Efforts have intensified in the past year to disseminate public use tapes of SEER data, various software packages such as SEER\*Stat, and a broad range of Cancer Surveillance Research Program resources through the World Wide Web. Finally, the SEER program is working with Oxford University Press on its **Cancer Spectrum project** to make cancer statistics more widely available through its on-line *Journal of the National Cancer Institute*.

## Training, Education, and Career Development

### THE CHALLENGE

Training, education, and career development of the next generation of cancer scientists is one of our most important challenges. Scientists of the future will need to both assimilate and create new modalities and ways of thinking to keep up with the rapid pace of scientific discovery and technological advances. We will need a cadre of scientists who can use new research models to expedite the translation of basic scientific discoveries into interventions and treatments for people with cancer or those at risk. Preparing the cancer research scientists of the future is a long-term challenge that requires us to implement new concepts and multiple strategies, and to make targeted, sustained investments to move beyond the limitations of traditional research establishment cultures, health care financing constraints, and socioeconomic inequities. We must sustain the basic science that enables us to discover the molecular reasons that normal cells become cancerous. We also must harness the potential of new scientific disciplines such as informatics and innovative technologies for characterizing critical genetic and cellular functions. We must train scientists who can translate these discoveries into public benefit.

Scientists who work in different kinds of research settings (e.g., laboratory, clinic, community) must have training across these disciplines so they can take maximum advantage of every opportunity for translating discovery into real advances in cancer prevention, detection, diagnosis, treatment, and quality of life. Traditional administrative divisions that separate academic areas in the education and training of basic biological scientists, clinical scientists, public health scientists, and behavioral scientists can be diminished by employing more unified concepts. New ways of educating, training, and developing scientists are necessary to ensure that technology advances are

integrated rapidly into the cancer research enterprise and that scientists are better prepared to work collaboratively in team settings to unravel the complex factors contributing to human cancer.

Moreover, we cannot afford to lose a generation of talented new cancer researchers, or fail to attract established scientists to the cancer research endeavor. Delaying investment in programs that ensure the essential training of our cancer research workforce of the future will cause a critical gap in the momentum of scientific discovery.

Five crucial issues must be addressed to meet this challenge. *First*, while the pool of basic scientists is of the highest quality, few are conducting research directly related to human cancer. We must train and encourage more basic scientists to collaborate with clinical and population scientists. *Second*, the economics of the health care system are forcing clinical investigators away from research into revenue-generating care. We must develop better ways to train clinical investigators and we must ensure that our highest quality medical scientists have protected time (i.e., time reserved from clinical and administrative responsibilities) to conduct the research that will produce better methods of cancer diagnosis and treatment. Without a well trained and supported critical mass of clinical investigators, many of the most important opportunities in patient-oriented, translational research will go untested. *Third*, the number of population scientists with sufficient professional stability who conduct early detection, epidemiology, prevention, control, risk factor, and behavioral research is inadequate to sustain a high quality translational research enterprise. We must develop better ways to train population scientists in the new interdisciplinary paradigms and increase the number of scientists who work in these fields. *Fourth*, the involvement in cancer research of scientists practicing in or from medically underserved areas and populations, and of underrepresented racial and ethnic minority backgrounds, is inade-

quate. We must develop new, more effective strategies for attracting and training these individuals as scientists. *Fifth*, new, more powerful technologies, new disciplines, and improved bioinformatics infrastructures are likely to be critical driving forces for progress in the future. We must develop new career paths that effectively link these areas to the cancer research enterprise.

## THE GOALS

- Build and sustain a critical mass of basic, clinical, population, and behavioral scientists capable of taking full advantage of the vast spectrum of future cancer research opportunities.
- Create models for educating and training scientists to interact effectively in translating basic knowledge into productive cancer prevention, detection, diagnosis, and treatment strategies.
- Attract into cancer research scientists whose unique disciplinary orientations and/or special technical skills can be integrated with those of more traditionally trained scientists in biology and medicine to generate novel, more powerful approaches to cancer research.
- Increase the participation in cancer research of underrepresented racial and ethnic minority scientists and scientists from medically underserved areas and populations.

## THE PLAN

### Objectives

- 1. Provide a continuum of training and career opportunities and protected time for research for developing and established cancer scientists.**
  - Sustain an active, vibrant National Research Service Awards (NRSA) program to train predoctoral and postdoctoral *basic scientists* through traditional institutional and individual awards.
  - Increase participation of *clinically trained individuals* in basic research and clinical trials research through special individual “mentored” awards; provide transition awards that afford protected time for junior scientists to develop their own research programs, and for senior scientists to do research and mentoring.

- Expand the number of well-trained *population and behavioral scientists* in cancer research by exploiting the NRSA program, increasing the number of individual “mentored” awards, providing transition awards for junior scientists, and providing senior scientists with protected time to do research and mentor new scientists.
  - Use resources of the NCI Intramural Research Program in collaboration with extramural institutions to (1) enable new scientists to use NCI’s on-campus resources to develop independent research programs (i.e., the NCI Scholars Program) and (2) develop a critical mass of mentors and expertise for training and career development in areas in which few institutions have the full range of capabilities (e.g., prevention, radiation oncology).
  - Increase access to training and career development for basic, clinical, population, and behavioral scientists by improving the NCI Internet information services, linking NCI opportunities to those of other funding agencies and professional organizations, and participating more actively at national professional meetings.
- 2. Provide special training and career development opportunities that prepare new scientists to function in collaborative, team research settings.**
    - Prepare more *basic scientists* who will pursue research relevant to human cancer and who are able to work effectively with clinical and population scientists.
    - Expand institutional oncology career development programs that prepare *clinically trained individuals* to become expert in clinical trials design and implementation requiring collaboration with basic scientists.
    - Implement new programs for *population and behavioral scientists* that will prepare them to work in collaborative, team research settings with basic scientists and clinicians.
  - 3. Develop partnerships with academic institutions, industry, and other Federal and non-Federal organizations for general and specialized training.**
    - In academic institutions, enhance the role of NCI Cancer Centers in developing and implementing unified cancer research curricula across all of the biomedical, public health, and social science disciplines; use education grants to promote short-term research experiences in multiple research settings.

- Develop new training programs linking informatics to the biomedical sciences in collaboration with the National Library of Medicine and the National Science Foundation.
  - Create exchange programs that encourage NCI career award recipients to spend part of their training experience in industry to promote academic/industrial collaborations.
  - Establish National Forums for short-term courses in areas of emerging scientific importance (e.g., technology, genomics) that provide didactic and “hands-on” experiences to a broad range of biomedical cancer researchers.
  - Improve communication of information about NCI training and career development programs to the Nation’s graduate schools, medical schools, and schools of public health, including minority and minority-serving institutions.
  - Create a seamless information continuum by electronically linking NCI information systems with those of other Federal and non-Federal funding organizations.
- 4. Integrate new technical and research disciplines into the cancer research enterprise.**
- Develop and implement new *institutional* training instruments that can be used to integrate traditional biomedical researchers with other non-traditional sciences (e.g., physics, engineering, computer science) and technology developers.
  - Create the *individual* Diversified Sciences Career Development Award for established scientists in non-traditional cancer research areas who wish to switch to cancer research careers and work in multidisciplinary research settings.
- 5. Implement programs to recruit underserved ethnic and minority individuals into cancer research, help them begin training earlier in their education and career, and help sustain these individuals through each stage of career development until a high proportion are successful independent investigators.**
- Implement the Continuing Umbrella of Research Experiences (CURE) program that provides a continuum of training and research opportunities, beginning in high school and continuing through undergraduate, graduate, postdoctoral, and junior faculty levels.
  - Link CURE to complementary programs of other funding agencies and professional organizations, such as the National Science Foundation and the American Association for Cancer Research.
  - Increase the participation of minority and minority-serving institutions in cancer research, training, education, and outreach by supporting the establishment of long-term partnerships with NCI Cancer Centers and Community Clinical Oncology Programs.

## PROGRESS TOWARD MEETING THE CHALLENGE

During the past year, NCI developed a strategic plan for research training and career development. The plan is a blueprint for meeting most of our training and career development objectives in the basic, clinical, population, and behavioral sciences in the next decade. Progress toward meeting this challenge has been significant but will require concentrated attention for five years or more before all of our critical objectives are satisfied.

NCI has created clear **career tracks** offering a continuum of opportunities that stabilize the training and career development of basic scientists, M.D.s pursuing basic science careers, M.D.s pursuing clinical science careers, individuals pursuing population science careers, individuals working in or from underserved areas, and individuals from underrepresented racial and ethnic minority groups pursuing cancer research careers. Career tracks are strategically linked by individual “mentored” awards, bridging awards, transition awards, established investigator awards, and institutional program awards. NCI’s most recent progress toward achieving its training, education, and career development objectives include establishing these career tracks and implementing the strategies described below.

## Individual Awards

- A spectrum of **Individual “Mentored”** five-year award opportunities now are in place for M.D.s pursuing basic or clinical science career tracks and for individuals pursuing a population science career track.
- **Bridging Awards** have been created to help basic scientists and minorities successfully navigate the transition from a mentored scientist to an independent junior faculty position. These awards incorporate the concepts of “transition” and “protected time” for basic scientists who commit to a research career focused on human cancer or for minority scientists pursuing a career in any aspect of cancer research.
- **Transition Awards** are three-year awards that provide protected time for new investigators to initiate successful research programs. They now are in place for NCI’s two most vulnerable and critical areas of need: medically trained doctors in basic or clinical research, and population scientists. A transition award is being developed for minority scientists.
- **Established Investigator Awards** allow seasoned investigators to set aside up to 50 percent of their salary toward protected research time and to participate in mentoring new scientists. Those who already have independent research support can qualify for up to five years of funding with another five years renewal through this award. This award is in place for M.D.s in the clinical science career track. This has been NCI’s greatest priority as so many clinicians are migrating from research to patient care in the current health care delivery system. Another established investigator award is being developed for the population sciences career track and should be in place within a year.

## Institutional Awards

- **Institutional Program Awards** are five-year awards to institutions that select candidates for participation in programs designed specifically to train individuals to work in translational research and/or team research settings. The applications are evaluated based on the quality of the training program and the quality of the

mentors who will participate. Of these awards, the R25 education and career development institutional grant is unique and specific to the National Cancer Institute. It will be immediately important to the prevention, control, population, and behavioral sciences but can be applied to all types of specialized interactive training programs in the future.

- **Diversified Sciences Career Development Awards** are in the planning stages. They will be designed to attract scientists from different disciplines to cancer research and to help build teams of scientists who will work together to ask and answer complex questions about cancer.
- A spectrum of minority supplements is now available. Combined with the Minority Career Awards and Transition Awards, these supplements make up the new NCI **Continuing Umbrella of Research Experiences (CURE) program**. This unique NCI program will attract young individuals from underserved areas and populations, and underrepresented racial and ethnic minority groups into research beginning at the high school level and follow them proactively through each stage of their careers until they become independent investigators.
- **Minority Institution/ NCI Cancer Center Research, Training, Education, and Outreach Partnerships will be initiated.** The purpose of these partnerships will be to increase and stabilize the participation of minority and minority-serving institutions in the cancer effort. The expectation is that these partnerships will have a major influence on the way NCI Cancer Centers conduct outreach and education in underserved communities and on the ways minority institutions conduct cancer research and train future cancer scientists.

These career tracks and training strategies, now being planned and implemented along with improved Internet communications and an increased NCI presence at national meetings, will ensure that all training, career development, and education opportunities are employed fully by the scientific community.

## Resources: Training, Education, and Career Development

### Provide a continuum of training and career opportunities. \$27.5 M

- Support an array of career development awards and training programs for basic, clinical, population, and minority scientists, and for diversified sciences:
  - 20 K01 (Temin Award – basic scientists working on human disease)
  - 22 K22 (12 clinical and 10 population scientists)
  - 20 K24 (clinical science)
  - 10 K07 (population science)
  - 10 K05 (population science)
  - 24 K01 (translational research)
  - 5 K25 (high technology)
  - 2 K12 (institutional awards for clinical science; 10 positions each)
  - 5 R25 (institutional awards, 3 in population science and 2 in diversified sciences, each with multiple positions)

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118 New Awards in FY 2001

- Create new training programs and enhance existing programs that use NCI Intramural Research Program resources (6 new scientists, NCI Scholars Program; 1 new intramural/extramural training program)

### Expand training and education opportunities. \$11.0 M

- Establish 2 National Forums for short-term courses in areas of emerging scientific importance.
- Develop 2 new co-funded cancer research training models.
- Create exchange programs that encourage NCI career award recipients (100 awardees annually) to spend part of their research training experience in other research settings.

### Recruit and retain more individuals from underserved populations and underrepresented racial and ethnic minority populations. \$11.0 M

- Provide supplements to NCI Cancer Centers for 100 minority high school and undergraduate students.
- Provide supplements to Research Project Grants for an additional 12 minority scientists.
- Provide supplements to existing training programs for minority trainees (8 K01, basic sciences; 3 K12 positions; 10 R25 positions).
- Establish 10 Minority Institution/NCI Cancer Center Research, Training, Education, and Outreach Partnerships.

### Improve infrastructure for developing and enhancing programs and for communication about NCI training and career development opportunities. \$8.2 M

- Continue developing, refining, and integrating NCI Internet-based information systems.
- Improve communication with professional organizations about NCI training opportunities.
- Provide supplements to cancer centers to foster communication and outreach to scientists.
- Improve interactions with graduate schools, medical schools, and schools of public health.
- Recruit additional NCI staff to manage new activities.

### Management and support. \$3.0 M

**TOTAL \$60.7 M**

# Acknowledgments

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## Extraordinary Opportunity and Challenge Champions

This year each Extraordinary Opportunity and Challenge was represented by "champions" - members of NCI staff expert in these areas of special research investment who aided in crafting the vision, plans, progress, and resources for each opportunity or challenge. The efforts of these champions and countless NCI staff members who assisted them helped us to articulate this critical information.

### Extraordinary Opportunities

Genes and the Environment - *Dr. Richard Klausner, Dr. Joseph Fraumeni*  
Cancer Imaging - *Dr. Robert Wittes, Dr. Ellen Feigal*

Defining the Signatures of Cancer Cells: Detection and Diagnosis - *Dr. Richard Klausner, Dr. Peter Greenwald*

Molecular Targets of Prevention and Treatment - *Dr. Richard Klausner, Dr. Robert Wittes*

Research on Tobacco and Tobacco-Related Cancers - *Dr. Richard Klausner, Dr. Barbara Rimer*  
Cancer Communications - *Dr. Richard Klausner, Dr. Barbara Rimer*

### Challenges

Investigator-Initiated Research - *Dr. Marvin Kalt, Dr. Norka Ruiz Bravo*  
Centers, Networks, and Consortia - *Dr. Ellen Feigal, Dr. Brian Kimes*  
National Clinical Trials Program - *Dr. Robert Wittes, Dr. Michaele Christian*  
Informatics and Information Flow - *Mr. James Silva, Ms. MaryAnn Guerra*  
Studying Emerging Trends in Cancer - *Dr. Robert Hiatt, Dr. Brenda Edwards*  
Training, Education, and Career Development - *Dr. Brian Kimes*

### FY 2001 Editorial Board

*The Nation's Investment in Cancer Research* serves two important functions: it describes NCI's research portfolio and the future path we have identified as the most direct route to conquering cancer. With this in mind, we enlisted the help of several NCI staff with expert scientific knowledge, an over-arching perspective on the Institute's activities and goals, and keen understanding of promising opportunities in cancer research. These individuals, our Editorial Board, helped shape the content of this book.

*Dr. Norka Ruiz Bravo, Ms. Julianne Chappell, Dr. Ellen Feigal, Mr. John Hartinger, Dr. Barry Kramer, Dr. Alfred Knudson, Dr. Edison Liu, Dr. Barbara Rimer, Dr. Margaret Tucker, Mr. Paul Van Nevel.*

### FY 2001 Bypass Planning Committee

We thank the members of our planning committee who helped to ensure that this document clearly and accurately describes the excitement and promise of our research efforts, NCI's needs and plans, and the vision for the future of our research programs.

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