



The National Cancer Institute

# The Nation's Investment in Cancer Research

*A Plan and Budget Proposal  
for Fiscal Year 2003*

Prepared by the Director  
National Cancer Institute

National Institutes of Health

# The National Cancer Institute

... bringing together the resources to stimulate and support scientific discovery and its application to achieve a future when all cancers are uncommon and easily treated.



Each year our work involves the efforts of a multitude of dedicated people across the United States and around the world.

- Almost 5,000 principal investigators lead research projects to understand cancer and develop better ways to prevent, detect, treat, and control it. These people conduct studies at NCI and at nearly 650 universities, hospitals, and other sites in our country and abroad.
- More than 10,000 physicians and 200,000 patients participate in NCI-sponsored clinical trials for cancer treatment, prevention, and early detection interventions. About 1,300 trials will be conducted in 2001 at 1,700 hospitals and cancer centers around the country.
- Thousands of scientific, health care, technical, and other specialists carry out the vital day-to-day laboratory, clinical, and administrative work of cancer research.
- Nearly 2,000 students and postdoctoral fellows pursue the specialized research training required to become part of the next generation of cancer scientists and research leaders.
- Hundreds of scientific and medical experts and representatives of advocacy groups help NCI identify research needs and opportunities, set priorities, and assess progress.

# Director's Message

The National Cancer Institute is a remarkable enterprise that represents a unique confluence of history, politics, science, technology, and even philosophy. It is a public institution dedicated to reducing the burden of cancer for all our Nation's citizens and people around the world. Through basic intellectual inquiry, the generation of new knowledge and tools, and the application of discovery, it has the capacity to change the course of history by reducing the terrible toll placed on people and society by that group of diseases we call cancer. NCI is successful because we are part of an extensive network of biomedical and broad scientific research and technology that gives us the tools to ask questions, find and interpret answers, and turn those answers into useful ways of enhancing health and reducing disease.

Each year, my colleagues and I prepare this plan and budget proposal, as prescribed by the National Cancer Act of 1971. To set forth new goals and objectives for the "Nation's investment in cancer research," we first examine the gaps in our understanding of cancer and our ability to translate and apply what we know for the benefit of people. This analysis helps us determine the larger context in which we carry out our mission.

The primary gap upon which all of our efforts are predicated is the one between ignorance and knowledge about this disease. Attempting to address the many unanswered questions about cancer is an incredibly challenging intellectual exercise and an essential step in successfully and predictably reducing its burden. Increasing our knowledge about cancer is difficult, complex, and often confusing. The road to discovery often takes us in unexpected directions and brings us to unexpected outcomes or insights. We must explore blind alleys, question and change old knowledge and beliefs, and figure out how seemingly unrelated pieces of information fit

together. Working as part of a community, we constantly draw on new talent, evolve and use new tools, and capitalize on creativity, intelligence, persistence — and very often, luck!

Our second task is to close the gap between knowledge gained through science and the translation of that information to the actual experience of people at risk for, diagnosed with, or surviving cancer. This requires moving new knowledge directly into the setting of the disease. We must establish new insights into individual risks for developing cancer; new, more targeted approaches to early detection; a new molecular view of diagnosis; and entirely new approaches to the prevention, treatment, and control of cancer and its consequences. This type of translational research is our first step in the transformation of cancer medicine and public health to more certainty and precision. It is our road to transforming therapy from trial and error to rational design and the development of targeted interventions.

Third, our NCI activities must address the gap between this translational work and actually reducing the burden of cancer between what *might work* or *looks promising* and what really *does work*. We need to move research results to their application in clinical practice and public health by conducting extensive clinical trials that will define the details of how new approaches will work and determine what the benefits and risks of specific interventions are. This clinical research establishes or refutes the extent of benefit to patients of new approaches to reducing the risk of, preventing, detecting, diagnosing, and treating cancer — and provides the bridge to better, less invasive, and longer-term solutions.

The final gap that we strive to close is one of the most frustrating because it seems to be due to things that we should have the power to influence and change. This is the discontinuity between what we

have already established as effective in reducing the burden of cancer and the practice and availability of that hard-won knowledge for *all* people regardless of where they live, whether they are rich or poor, or what their cultural backgrounds are. Bridging this divide requires better understanding the unequal burden of this disease, addressing disparities in the quality of cancer care, and implementing the most effective interventions to address them.

We must work to bridge each of these gaps through the dissemination, diffusion, and adoption of new insights. This means finding the most effective ways to share findings and encourage collaborations among researchers. It means applying the best communications technologies to facilitate translational and clinical trial activities. And it means arming practitioners with the information and tools they need to achieve a level of comfort that will allow them to successfully use new approaches in their work with cancer patients, people at risk, and survivors.

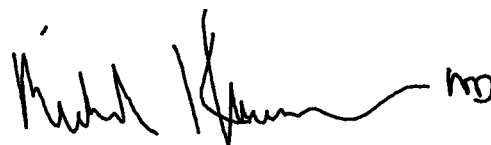
The true measure of excellence for an enterprise is both where it can go and where it has been. With our future planning, we look back to the myriad of initiatives supported by NCI and how these have begun to close the gaps, and we look ahead to the many important next steps needed to continue. As stewards of the public trust, we have a grave responsibility to chart a course and develop a plan and budget that will allow us to maintain the superior quality of all of our research programs. In addition, we must meet the challenges that come with new approaches, technology, and knowledge and build on past discovery in areas of “extraordinary opportunity” that address all cancers as well as the specific needs of different types of cancer. And through all of these efforts, we must remain vigilant in addressing the barriers to full

implementation of new interventions that will bring quality cancer care to *all* people.

Our plans emerge through the insights and wisdom we gain from the input, questioning, feedback, and collective experience of all involved in the cancer research enterprise. The future plans and priorities we identify now set the rationale for our decisions along the way, give us a systematic framework for assessing progress, and provide a clear and credible means for reporting our performance and results to the public.

But these plans, these strategies, these technologies provide only a framework. The real work begins with people, people who are at the heart of delivering the full promise of our plans and investments. These people, be they patient or health care provider, scientist or administrator, advocate or lawmaker are the ones we must count on to close the gaps between ignorance and knowledge, knowledge and application, and burden and access to or availability of care.

Though the focus and methods have changed as the science has evolved, our goal to improve the plight of all people everywhere is unwavering. With the courage of our cancer research and care community and the continued strength of our resources, hope is stronger and more certain than ever, and the years to come hold promise beyond our imaginations!

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  
September 2001

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# Executive Summary

The National Cancer Institute's goal is to stimulate and support scientific discovery and its application to achieve a future when all cancers are uncommon and easily treated. NCI works toward this goal in two major ways. We provide vision to the Nation and leadership for NCI-funded researchers across the United States and around the world, and we work to ensure that the results of research are used in clinical practice and public health programs to reduce the burden of cancer for all people.

Each year, we support some 5,000 principal investigators in the pursuit of a broad range of research from studies of the causes and incidence of cancer to translational research and clinical trials to survivorship and end-of-life issues. NCI also funds cancer centers; collaborative research teams; cancer control; and training, education, and career development activities.

Our future planning encompasses three key components required for a strong cancer research enterprise. These are to maintain a sound research infrastructure and build capacity for the future (NCI's Challenge), to capitalize on opportunities in broad scientific areas (Extraordinary Opportunities for Investment), and to assess and plan for research related to specific types of cancer such as breast or lymphoma (Planning National Agendas for Disease-Specific Research).

Our total Fiscal Year 2003 Budget Request is \$5,690,000,000. This represents an increase of \$1,512,796,000 over the Fiscal Year 2002 President's Budget. Of this increase, \$305,753,000 will be provided to continue NCI commitments into 2003 (Core Budget). An additional \$878,193,000 will be used for NCI's Challenge, and \$328,850,000 will support Extraordinary Opportunities for Investment. Funding for disease-specific research is included in nearly all of the Challenge and Opportunity areas.

## NCI'S CHALLENGE

Major breakthroughs depend on building and sustaining the strong research mechanisms, support structures, and collaborations that will enable us to pursue rapidly evolving discoveries in all areas of cancer research. NCI must provide the vision, creative environments, and diverse resources needed to ensure a smooth flow between advances in knowledge and their application.

### Enhancing Investigator-Initiated Research

Investigator-initiated research has always been the driving force behind advances in biomedical research. Our challenge is to provide scientists with opportunities to pursue as many promising research ideas as possible while at the same time supporting each project with sufficient funds to cover the growing costs of research. NCI gives special consideration to proposals from clinical researchers and those who respond to announcements of priority research areas. We seek to maximize the pace of discovery by providing a broad range of flexible funding options and promoting collaborations and resource sharing. With increased funding in 2003, we will be able to support research projects at the full levels recommended by peer reviewers and fund the top 35 percent of competing grant applications. We will continue to allocate the first 80 to 90 percent of available funds for research project grants through conventional selection processes while ensuring that proposals from new investigators are also funded and that exceptions funding is available to support particularly innovative and potentially high reward projects.

## Centers, Networks, and Consortia

The rapid pace of scientific and technological discovery is creating opportunities that require interaction among scientists of diverse backgrounds sometimes located in physically distant sites. The challenge for NCI is to create research settings that encourage the multidisciplinary collaborations needed to address the big picture problems in cancer research. To meet this challenge, we continue to support NCI-designated Cancer Centers, Centers of Research Excellence, and various research networks and consortia that enable scientists from different disciplines to work together, share information and resources, and experience the synergism that often catalyzes new discovery. In 2003, NCI will use new funding to increase support to Cancer Centers for new technology development, improved informatics capabilities, and clinical and population research infrastructure; expand and enhance the Specialized Programs of Research Excellence based on needs for disease-specific research; and implement a Strategic Supplement Program to take advantage of high priority opportunities that can be completed in short time frames.

## National Clinical Trials Program in Treatment and Prevention

Our intricate clinical trials system relies on cooperation and collaboration among patients, investigators, industry, academia, and NCI. Adding to this complexity, cancer clinical trials have undergone dramatic changes in recent years, the result of progress in cancer biology, imaging technology, and advances in informatics and electronic communications generating both the need and the possibility for more trials involving much larger numbers of health care providers and patients. While NCI-supported clinical trials have incorporated many changes, reimbursement to health care providers has not kept pace and participation in clinical trials remains lower than ideal. Our challenge is to minimize the barriers to participation in clinical trials while ensuring that we capitalize on the latest developments in cancer research, informatics, and management. With adequate funding in 2003, NCI will be able to improve patient access to and the rate at which trials are completed by increasing the per patient reimbursement for trials, doubling the number of patients accrued to trials, providing follow-up funding for healthcare providers to follow patients and report outcome and other data, and expanding the Clinical Trials Support Unit. We also

will be able to expand funds for clinical correlative studies; fund tissue and specimen banks; create collaborations for multi-institutional clinical trials; and step up development and assessment of promising targeted prevention and treatment agents.

## Studying Emerging Trends in Cancer

NCI must continue to build a versatile cancer surveillance system that fully represents the diversity of our nation's population and more accurately tracks the Nation's cancer burden. This information is needed to help researchers form hypotheses and to provide communities with the information they need to strengthen cancer prevention and control. NCI works with partners to develop a more robust system, create analytical tools for research and cancer control, and find effective ways to disseminate surveillance information. In 2003, we will use additional funding to augment and refine our surveillance system to keep pace with a rapidly changing cultural, social, and technological milieu and continue to build systems that better track cancer trends, highlight research needs, explain causes of cancers, identify individuals at greatest risk, and support community cancer control.

## Quality of Cancer Care

The quality of cancer care is a major national concern. Evidence suggests that some patients with cancer do not receive the newer, more effective treatments, and there is often uncertainty about what constitutes optimal care. To address these concerns, NCI is helping to enhance the information base for cancer care decision making through improvements in data collection and the development of better measures for comparing cancer treatments and outcomes. Furthermore, we are also investing in studies to examine the quality of cancer care and in demonstration projects to ensure that the delivery of care reflects the latest findings from cancer research. With funding increases in 2003, NCI will engage in activities to improve measurement of patient-centered outcomes in cancer; support innovative research on the diffusion, quality, and outcomes of cancer interventions; and enhance quality-of-care research within the NCI clinical trials program.

## Reducing Cancer-Related Health Disparities

To effectively reduce cancer-related health disparities, NCI must make new research investments to explain social, cultural, environmental, biological, and behav-

ioral determinants of cancer, the interactions among them, and the mechanisms by which they contribute to disparities in cancer care and prevention. Our efforts include support to the NCI-sponsored Special Populations Networks for Cancer Awareness Research and Training, examination of specific ways in which cancer incidence and mortality are disproportionate for certain populations (e.g., cervical cancer in rural U.S.), development of patient education materials for low-literacy populations, collaborations to increase access to and involvement in clinical trials, and training for new scientists focused on health disparities. In 2003, we will use funding increases to expand our research efforts in gap areas, foster better dissemination and use of research findings, and further increase access to clinical trials by special population groups. We will support new Centers for Population Health and Cancer and special grants for continuing education of health care providers.

### **Informatics and Information Flow**

To assist the cancer research community in keeping pace with the flood of information stemming from new scientific discovery, NCI needs to develop and provide informatics systems that facilitate resource sharing and the translation of emerging findings into public health benefits. NCI has built a Cancer Informatics Infrastructure to supply standardized bioinformatics support and integration of NCI's diverse research initiatives. Within this framework, we are developing the innovative tools required to connect people with the information they need. In 2003, we will use funding increases to enhance integration of the data and tools resulting from NCI's priority initiatives, establish informatics applications and services based on a common set of operating principles and standards and make them available to cancer researchers, support planning and public communication activities, establish a network of bioinformatics research centers, provide funding supplements to NCI-supported research organizations for development of informatics systems, and promote informatics training for biomedical research settings.

### **Cancer Research Training and Career Development**

Scientists of the future will need to be trained in multiple disciplines, able to work in teams to understand the multifaceted nature of cancer, and better prepared to translate discoveries into public benefit. NCI is employing a variety of individual and institutional

training and career development awards to meet the needs of new and established investigators and NCI's anticipated research priorities. We have focused increased resources on career development for M.D.s in cancer research, behavioral and population scientists, minority scientists, and scientists in highly technical fields important to the future of cancer research. We also are more effectively integrating education programs for health practitioners and the public through improved national networking and use of communication technologies. NCI will use new funding in 2003 to more adequately prepare scientists to work in multidisciplinary environments; reverse the migration of physicians from research to practice; increase the number of population, behavioral, and public health scientists; create a research workforce that is ethnically and racially diverse; and attract and integrate technical and informatics experts into cancer research.

## **EXTRAORDINARY OPPORTUNITIES FOR INVESTMENT**

Our focus on six priority areas with extraordinary potential to impact the pace and direction of cancer research have shown significant results and will be continued into 2003.

### **Genes and the Environment**

As we better understand the interplay between inherited susceptibility to cancer and environmental risk factors, we will be able to develop more meaningful approaches to cancer prevention, early detection, and treatment. NCI has begun building capacity in this area through consortia of investigators who are pooling data and resources to compile the large data sets required for this kind of study. We also are examining approaches for assessing and measuring environmental exposures, advancing research to discover and characterize cancer predisposing genes, and supporting the development of a number of tools for use in gene discovery and characterization such as mouse models of human cancers. We also have established an infrastructure to support intervention trials on inherited susceptibility to cancer. In 2003, NCI will use new funding to support studies to identify additional environmental risk factors and susceptibility genes and determine their interactions, develop new ways to assess and measure environmen-



tal exposures, and identify and investigate how other genes and environmental factors modify the expression of cancer predisposing genes.

### **Cancer Imaging**

With the power of new imaging technology, researchers and health care providers can generate much clearer and more detailed pictures of organs and tissues, and they can use “functional imaging” for the visualization of physiological, cellular, or molecular processes in living tissue. NCI has supported *In vivo* Cellular and Molecular Imaging Centers to provide essential infrastructure and career stability to investigators in this emerging field. We also are fostering the development of new imaging contrast agents and molecular probes, making equipment and personnel available to improve technologies and techniques for imaging small animals, and assessing the value of computed tomography scanning in screening patients for colon cancer (“virtual colonoscopy”). With new funding in 2003, NCI will be able to advance imaging technology development and use by expanding the discovery, design, and development of novel imaging agents and devices, integrating molecular and functional imaging methods into therapeutic clinical trials, increasing clinical trials of imaging methods and technologies, and accelerating the development and clinical testing of image-guided interventions.

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

With the aid of new technologies, scientists are working to read and understand the unique, identifiable characteristics of cancer cells known as molecular signatures. Our ability to read these signatures will allow us to differentiate among tumors at the molecular level and devise treatments targeted at specific cancers. NCI provides researchers with a variety of resources for study in this area such as catalogs of molecular changes in cancer, tissue resources, and informatics tools. The Early Detection Research Network has begun describing molecular signatures that may be used for the early detection of breast, esophageal, and other cancers. New funding in 2003 will be used to expand the development and availability of molecular and analytic resources, make tissue resources available to researchers, apply molecular signatures to the study and validation of animal models for human cancer, support new approaches for the

early detection and diagnosis of cancer, and characterize aberrant molecular interactions in cancer.

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

Our increasing knowledge of the molecular changes that cause a cell to become cancerous is opening a whole new avenue to drug development. Agents that target these molecular changes have potential to selectively delay, stop, or reverse the growth of cancer cells without harming surrounding healthy tissue and promise to be less toxic and more effective than current drugs. To respond to this research opportunity, NCI has rallied the necessary resources for laboratory, animal, and clinical studies and has begun to identify numerous potential molecular targets as an early step in cancer prevention and treatment drug discovery. NCI will use new funding in 2003 to distinguish and use cellular targets for the discovery of new anti-cancer agents; develop assays to identify possible treatments for cancer; acquire large libraries of natural and synthetic compounds; develop a translational research program that will closely link molecular imaging, cancer signatures and molecular targets; and facilitate the steps necessary to turn a compound into a targeted drug ready for clinical use.

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

The devastating impact of tobacco use and tobacco smoke exposure on the incidence of cancer is both compelling and conclusive. We need to better understand the genetic, biological, behavioral, and social components of tobacco use, addiction, smoking cessation, and how to prevent, detect, and treat tobacco-related cancers. New evidence is helping to better explain why some people are more vulnerable than others to DNA damage caused by tobacco exposure. Research on the early detection of lung cancer suggests that it may soon be possible to identify cancers in smokers and former smokers at a much earlier and more treatable stage. Recent studies of teen smokers have identified psychological factors that increase the risk of becoming addicted. NCI will use new funds in 2003 to expand efforts to define the biological, behavioral, and social bases of tobacco use and addiction; accelerate progress in understanding the interplay among tobacco, other exposures, and genetic susceptibility; and develop, test, and disseminate more effective interventions to prevent and

treat tobacco use and tobacco-related cancers.

### Cancer Communications

People now have more ways than ever to get information, and the future holds even more choices. NCI is working to optimize the use of communications tools to meet the information needs of various groups while enhancing the absolutely essential interaction of patients with their doctors and nurses. Digital Divide Pilot Projects have demonstrated the potential for using computer technology to address the information needs of underserved populations. Five new Centers of Excellence in Cancer Communications Research will be established in 2002 to encourage focused interdisciplinary studies, increase the number of investigators, and train scientists to conduct cutting-edge research directly. In 2003, NCI plans to expand activities to more fully address the communication needs of underserved populations, continue the Centers of Excellence, provide support for the dissemination of research results, and add to the menu of communication choices available for information about cancer.

### PLANNING NATIONAL AGENDAS FOR DISEASE-SPECIFIC RESEARCH

While we have learned much that is broadly applicable to cancer through our core research programs and Extraordinary Opportunity initiatives, NCI must be equally alert to the specific tendencies and behaviors of each unique type of cancer. This is why NCI plans, promotes, and carries out an ambitious program of disease-specific research, charting the course for these efforts primarily through advice from experts participating in Progress Review Groups (PRGs). NCI carefully addresses PRG recommendations by modifying and supplementing existing research programs, encouraging scientists to apply for disease-specific research funding, and developing new initiatives when needed. PRGs have been completed or are underway for breast, prostate, colorectal, pancreatic, lung, gynecologic, kidney and bladder cancers, brain tumors, and leukemia, lymphoma, and myeloma. PRGs on stomach/esophageal, liver/bile duct, and skin cancers are planned.

#### The Nation's Investment in Cancer Research

### NCI's Budget Request for Fiscal Year 2003

(dollars in thousands)

Fiscal Year 2002 President's Budget	\$4,177,204
Increase to Core Budget	305,753
<b>NCI's Challenge Increase</b>	
Enhancing Investigator-Initiated Research Centers, Networks, and Consortia	121,543
National Clinical Trials Program	81,250
Studying Emerging Trends in Cancer	433,000
Quality of Cancer Care	22,700
Reducing Cancer-Related Health Disparities	14,000
Informatics and Information Flow	52,700
Cancer Research Training and Career Development	95,000
Subtotal Challenge	878,193
<b>Extraordinary Opportunities Increase</b>	
Genes and the Environment	55,500
Cancer Imaging	69,800
Defining the Signatures of Cancer Cells	75,000
Molecular Targets of Prevention and Treatment	42,500
Research on Tobacco and Tobacco-Related Cancers	67,000
Cancer Communications	19,050
Subtotal Opportunities	328,850
<b>Total FY 2003 Budget Request</b>	<b>\$5,690,000</b>

# Highlights of Progress

One of every two men and one of every three women in the United States will develop some type of cancer over the course of their lives. Approximately 8.4 million Americans alive today have a history of cancer. The consequences are enormous:

- Nearly 25 percent of all deaths in our country are due to cancer. Cancer is the second leading cause of death in the U.S., ranking behind only heart disease.
- Medical care expenses for cancer patients and survivors add up to \$60 billion annually, about five percent of all dollars spent on health care in the U.S.
- The toll in pain, suffering, and loss of productivity and income is less easily measured, but keenly felt by the more than one million patients newly diagnosed with cancer each year, their families, and communities.

There is some encouraging news, however. Figures reported in the most recent *Annual Report to the Nation on the Status of Cancer*<sup>1</sup> show that from 1992 through 1998, cancer incidence rates declined in men and cancer death rates declined in both men and women. This promising trend is due to the earnest efforts and ardent determination of so many in our country to find better ways to prevent and more effectively treat cancer in all its forms. Recent advances reported here provide snapshots of a few of the thousands of research projects that NCI sponsors each year that together bring us ever closer to reaching our goal to achieve a future when all cancers are uncommon and easily treated.

## PREVENTING AND CONTROLLING CANCER

### Cigarette Promotions Influence Smoking Among Youth<sup>2</sup>

In a study of nearly 500 elementary and high school students in Vermont, researchers explored whether promotional activities for tobacco influence the smoking behaviors and beliefs of adolescents. Results of the study suggest that exposure to tobacco marketing does influence youthful attitudes and beliefs about smoking. Investigators found that the likelihood that adolescents will start smoking increases after they acquire cigarette promotional items such as hats or t-shirts with tobacco company logos. These findings underscore the harmful effects on adolescents of tobacco advertising and suggest that eliminating cigarette promotional campaigns could reduce adolescent smoking.

### Personality Variables Predict Adolescent Smoking<sup>3</sup>

A group of scientists recently determined that better understanding the personality characteristics of adolescents who become smokers can provide key insights for designing effective prevention strategies. These investigators evaluated more than 3,000 fifth graders for factors such as a propensity toward rebelliousness, risk-taking behavior, problem-solving abilities, and susceptibility to peer compliance and approval. Following up with the students at the end of high school, they found that rebelliousness and risk taking had the strongest predictive value for future smoking behavior. In light of these findings, the researchers suggested that smoking prevention

1 The *Annual Report to the Nation on the Status of Cancer* is a collaborative effort of the National Cancer Institute, the Centers for Disease Control and Prevention, the National Center for Health Statistics, the American Cancer Society, and the North American Association of Central Cancer Registries.  
2 & 3 See pages 83-87 for more information on NCI Tobacco and Tobacco-Related Research initiatives.

programs should address the needs and expectations of rebellious and risk-taking youth and should begin no later than fifth grade.

#### **Experts Recommend Continuing Promotion of Fruit and Vegetables<sup>4</sup>**

An outside panel of experts recently evaluated NCI's decade-long efforts to encourage Americans to include at least five servings of fruits and vegetables in their daily diets through the Five A Day Program. After considering the science underlying the program, its implementation, and accomplishments, the group recommended that it continue under NCI's leadership while partnering more closely with other NIH institutes, Federal agencies such as the Department of Agriculture and the Centers of Disease Control and Prevention, and the produce industry. In addition, the evaluation report recommends that NCI continue and expand monitoring of fruit and vegetable consumption in the U.S. as well as its research in related areas such as cancer communications, behavior change, and the mechanisms by which fruit and vegetable consumption reduce cancer risk.

## **DETECTING CANCER**

#### **New Technology May Improve Lung Cancer Detection<sup>5</sup>**

A major obstacle to understanding and treating the abnormal lesions that are the first sign of lung cancer is that they are often not visible with bronchoscopy, a technique by which physicians use a thin, lighted tube to examine the lungs. Some clinicians have reported, however, that bronchoscopy using ultraviolet (UV) light fluorescence may be a more sensitive technique for detecting these lesions. In an effort to explore this question, investigators in an NCI-funded Specialized Program of Research Excellence (SPORE) in Lung Cancer carried out the first controlled trial comparing the two techniques. Both approaches tended to pick up irregularities that were not associated with disease, but scientists found that UV fluorescence was more than four times as likely as white light bronchoscopy to correctly identify precancerous lesions.

#### **Genetic Testing of Stool Samples Detects Most Colorectal Cancers<sup>6</sup>**

Because colorectal cancer cells are shed into the stool, testing stool samples can be an easy and non-invasive way to detect colorectal cancer. Exploring this opportunity, one team of investigators has shown that the majority of colorectal cancers can be detected by screening stool samples for the presence of three genes with tumor-associated alterations — *TP53*, *K-RAS*, and *BAT26*. More studies now are needed to determine the specificity of these genetic tests for detecting colorectal cancer in patients without symptoms.

#### **“Optical Biopsy” Provides a Less Invasive Method for Detecting Cancer<sup>7</sup>**

Another investigator is developing an imaging technique that may permit patients of the future with certain types of cancer to undergo “optical biopsies,” allowing their physicians to diagnose or rule out cancer without the need for tissue samples. Using a technique known as optical coherence tomography (OCT), scientists have been able to capture ultra-high resolution images of esophageal and gynecologic tissues, allowing them to identify cancerous lesions in these sites. Other organs and surfaces that may be imaged with OCT include the gastrointestinal system, the bladder, the lungs, and skin. In the future, health care providers may be able to improve diagnosis and treatment by attaching catheters and endoscopes to OCT instrumentation, sparing patients the added time and pain associated with more invasive procedures.

#### **Proteomics Offers Hope for New Prevention, Detection, and Treatment**

NCI has teamed with the Food and Drug Administration to create a Clinical Proteomics Program. Proteomics is the systematic study of protein expression and function and an important next phase in our pursuit of molecular medicine. Proteins comprise the functional machinery of the cell, linking circuits and pathways that transmit information within the cell and the entire organism. In cancer, alterations in genes usually cause defects in the corresponding proteins, disrupting the normal communication network of the cell. Using proteomics, cancer

<sup>4</sup> See pages 88-92 for information on other NCI Cancer Communications initiatives.

<sup>5</sup> See page 28 for more information on the SPORE program and pages 66-70 for more information on Cancer Imaging initiatives.

<sup>6</sup> See page 75 for information on other initiatives to develop genetic testing strategies for the early detection of cancer.

<sup>7</sup> See pages 66-70 for more information on Cancer Imaging initiatives.

researchers are discovering and characterizing disruptions in the protein communication networks that drive the growth and spread of cancer, knowledge that will advance early detection, prevention, and drug development. For example, a group of NCI scientists has discovered more than 130 proteins that are altered during the transition from benign to malignant disease in breast, ovarian, prostate, and/or esophageal cancers. With additional research, these proteins may serve as early cancer biomarkers or offer possible targets for therapeutic drug development.

### Center of Excellence Advances Ovarian Cancer Biomarker Discovery

The earlier ovarian cancer is treated, the better a woman's chance for recovery. Currently, most ovarian tumors are diagnosed after they have advanced beyond cure, spurring researchers to look for reliable, minimally invasive techniques for earlier detection. For example, tumor markers that can be measured in blood or used in combination with imaging may allow health care providers to detect ovarian cancer sooner. Scientists in an NCI-funded Specialized Program of Research Excellence have conducted an extensive search for genes that play a role in ovarian cancer and identified a number of genes never before associated with this cancer. These include *mesothelin*, *HE4*, *ESE-1*, *SLPIa*, and *GPR39*. Scientists now are studying the molecules associated with these genes to determine whether they can be useful as early detection markers. If so, and tests can be developed to detect these markers in blood, this research could have a significant impact on women's ability to survive ovarian cancer.

## TREATING CANCER

### Breast-Conserving Therapy Is At Least As Cost Effective as Mastectomy

The choice of treatment for breast cancer depends on many factors, including the size and stage of the tumor, a woman's age, other medical conditions, and costs. In a study of nearly 1,700 breast cancer patients 35 and older with early-stage breast cancer, researchers compared the cost of care for mastectomy with that of breast-conserving therapy (BCT). At six months after diagnosis, the medical care costs associated with BCT were higher than for mastectomy.

The cost difference disappeared over time, however, and by five years after surgery, the medical care costs of BCT were less than those for mastectomy, possibly due to the expenses associated with the higher complication rates of mastectomy or later surgical reconstruction of the breast. This study suggests that breast-conserving therapy is at least as cost-effective as mastectomy and should be weighed equally in treatment considerations about cost. The larger lesson, however, is that short-term and longer-term expenses associated with cancer care may be quite different, and that both considerations should inform health care policy decisions.

### Phase I Trials Suggest Vaccines for Lung and Colon Cancers

Although the idea of treating cancer with a vaccine that stimulates the body's immune system to kill tumors is generating exciting results for several cancers, success with lung and colorectal cancers has been more elusive. Recently, scientists have taken a new approach that has produced promising results in a Phase I clinical trial. Researchers first isolated from tumor tissue a portion of carcinoembryonic antigen, a protein usually found only in fetal tissue but abundantly expressed in non-small cell lung, colon, and other cancer cells. They next delivered the isolated antigen to the immune system using an innovative method that seems to heighten the immune response. Researchers hoped that vaccinated patients would produce antibodies to attack the novel antigen and consequently the tumor cells that express it. Five of the twelve patients in the study did respond to the vaccine, two with dramatic tumor regression. These are promising findings for a Phase I trial, and if more extended clinical trials demonstrate its effectiveness, this approach could lead to a new therapy for lung, colorectal, and perhaps other cancers.

### Early Hairy Cell Leukemia Trial Results In Complete Remissions

A new immunotherapy for hairy cell leukemia, a cancer of the immune system, has produced impressive results in a preliminary clinical trial. The treatment works by using a specially designed molecule known as BL22 to deliver a deadly toxin directly to the hairy cell leukemia cells. Scientists made BL22 by joining portions of an endotoxin made by the bacteria *Pseudomonas aeruginosa* with an antibody that recog-



nizes and binds to CD22, a protein found on the outside of hairy cell leukemia cells. BL22 is a small molecule designed to get to the tumor quickly and with less toxicity to the body. When BL22 reaches its target, the cancer cell internalizes the deadly toxin by natural mechanisms and dies. Of the 16 patients with hairy cell leukemia who participated in this preliminary trial, 11 experienced complete remission and another two partial remission after BL22 immunotherapy. These early clinical results show promise for BL22 treatment of hairy cell leukemia and other cancers that express CD22.

### Metastatic Melanoma Patients Experience Regression with Immunotherapy

Melanoma is the most rapidly increasing cancer in the United States and is virtually lethal once it has spread beyond the initial site. Recent metastatic melanoma studies provide some of the first examples of the successful application of specific immunotherapy for human cancer based on an understanding of the molecular basis of the immune response against the disease. For example, many patients vaccinated with gp100 melanoma antigen,<sup>8</sup> found on the outside of melanoma cells, have produced immune cells that attack their cancer. In a preliminary trial, one-third of all metastatic melanoma patients experienced tumor regression when this vaccine was administered along with the immune stimulating cytokine,<sup>9</sup> Interleukin-2 (IL-2). Patients are experiencing substantial tumor regression in pilot studies of vaccination with a number of other antigens characteristic of melanoma cells, without the help of IL-2 or other immune boosting cytokines. In recent studies, some of the cancer attacking immune cells were removed from patients and allowed to increase in number in a laboratory culture. Transferring larger quantities of the immune cells back to the patient resulted in additional cancer regressions. Researchers have begun exploring molecular and genetic characteristics of antigens for breast, ovarian, prostate and lung cancers, and similar treatment approaches are being applied to forms of these cancers.

## UNDERSTANDING CANCER AND ITS CAUSES

### Tumor Growth May Be Stopped By Depriving Cancer Cells of Oxygen

One strategy for stopping tumor growth is to selectively starve cancerous tissue for oxygen. *Angiogenesis* refers to the body's ability to grow new blood vessels to supply tissues low in oxygen, a process necessary for tumor growth but not for routine bodily functions. If we learn how to stop this process, we should be able to arrest tumor growth. Scientists have learned that the mammalian cell uses the protein hypoxia-inducible factor (HIF) to help turn angiogenesis on and off. When HIF is present, it turns on the genes that start the angiogenesis process. At normal levels of oxygen the cell has a mechanism that continuously breaks down HIF. During hypoxia, such as occurs during tumor growth, another mechanism makes a small change to the structure of HIF so that it is resistant to degradation. HIF levels increase, blood vessels grow, and the new tumor thrives. Scientists are searching for possible drugs to target the HIF oxygen sensing and signaling pathways to stop angiogenesis without harming healthy cells.

### Reversing the Silence of a Gene May Make Cancer Therapy Effective

Neuroblastoma is the most common solid childhood tumor outside the brain area. Despite major advances in cancer chemotherapy and bone marrow transplantation, the long-term survival rate for children with aggressive forms of this disease remains very low. Cancer geneticists are working on a new treatment idea based on a recent finding about the gene *capsase 8*, which may be involved in a set of difficult to treat neuroblastoma cases. In these neuroblastomas, *capsase 8* does not do its job, because it is either missing or is chemically altered and rendered silent by a DNA methylation process. Scientists found that neuroblastoma cells without *capsase 8* activity grown in the laboratory are protected against a number of cancer therapy drugs directed against DNA targets. Researchers are now studying the possibility of using demethylation agents to reverse the chemistry that silences *capsase 8*, thus rendering the neuroblastoma

<sup>8</sup> An antigen is a protein or protein fragments located on the outside of a cell.

<sup>9</sup> A cytokine is a protein or protein-like substance naturally released by cells that have a biological effect on other cells. IL-2 is produced by certain white blood cells and can help boost immune response.

cells susceptible to the chemotherapeutic agents.

### No Connection Found Between Cellular Telephone Use and Brain Tumors

The use of hand-held cellular phones involves placing a small transmitter that emits radio frequency radiation next to the head. Given the unknown cancer risk posed by this radiation and the important public health implications, NCI scientists included cell phone use in a comprehensive study on the causes of brain tumors. Approximately 800 adult brain tumor patients and 800 controls (adults without brain tumors) from three medical institutions in the United States were questioned about their cell phone usage. Researchers found that regardless of years of use or number of minutes of use per day reported, there was no increased risk of brain tumors for cell phone users compared to non-users. Brain tumors also did not occur more frequently on the side of the head on which cell phone users reported holding their phone. While the NCI study (1994-1998) was conducted at a time when analogue phones were primarily used, there is no evidence at this time that cancer risk differs for the higher frequency digital phones more commonly used today.

### Scientists Identify Chemosensitive Gliomas

Gliomas are malignant tumors of the brain that arise from *glial* cells, a type of cell that provides support and insulation for neurons of the brain. Most are quickly fatal despite treatment, but the prognosis depends heavily on the specific type of glioma. Patients with oligodendroglioma, for example, respond well to combined treatment with the drugs procarbazine, lomustine, and vincristine with approximately two-thirds experiencing long-term remissions. Only recently, however, have scientists begun to identify which patients would respond to the combined treatment. They are learning how to predict response based on the genetic mutations present in the glioma tissue. For example, patients with altered portions of chromosome 1 and 19 tend to respond much better to chemotherapy than those with mutations in the genes *PTEN*, *EGFR*, and *CDKN2A*. This research will improve the ability of physicians to recommend appropriate treatment for patients. Patients with responsive tumors will increase their chances of survival when they are treated earlier. Other patients

may be spared ineffective and toxic chemical treatments and offered alternative therapies.

### Racial and Ethnic Differences in Prostate Cancer Need Further Study

The Prostate Cancer Outcomes Study is following over 3,000 men to learn more about the results of different therapies and their effect on quality of life. One recent report drawing on data from the study examined racial and ethnic differences found among men who developed advanced prostate cancer. Researchers found that African American men have the greatest risk of developing advanced disease (12.3 percent). This rate is higher than that of Hispanic men (10.5 percent) and about twice that of non-Hispanic Whites (6.3 percent). Differences in socioeconomic status, symptoms, and tumor characteristics seem to account for the differences between non-Hispanic Whites and Hispanics, but do not explain a significant portion of the African American disparities. Investigators suggested that further research on biologic markers, genetic susceptibility factors, and additional socioeconomic factors such as use of health care systems, distance from health care, diet, literacy, and health beliefs is needed to sufficiently describe these disparities.

### Other Research Highlights

Drugs for Prostate Cancer, page 95  
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# Our Role in Cancer Research

**The National Cancer Institute's goal is to stimulate and support scientific discovery and its application to achieve a future when all cancers are uncommon and easily treated.**

The NCI works toward this goal in two major ways. We provide vision and leadership for cancer research across the United States and around the world, and we work to ensure that the results of research are used in public health programs and clinical practice to reduce the burden of cancer for all people. Building on past discoveries and technological advances, we plan, conduct, coordinate, and support cutting-edge research and its application. We encourage creativity and innovation in all of our endeavors; support development of, access to, and use of new technologies by cancer researchers; and back up these approaches by providing research training and career development opportunities and maintaining support mechanisms and collaborative environments to link scientists with their colleagues and with critical technological and information resources.

As leader of the National Cancer Program, NCI provides the public with scientifically sound cancer information using all forms of communication carefully designed to meet the needs and preferences of cancer patients, persons at risk, their families, and those who care for them. The ultimate purpose of these activities is to help move research findings into clinical practice, chart and improve the quality of cancer prevention and care, and reduce disparities in the burden of cancer.

## HOW WE PLAN AND SET PRIORITIES

The NCI engages in a number of ongoing planning and priority setting activities to ensure that we are responsive to new discoveries and opportunities and make the best use of our resources. Our leaders work closely with NCI staff, the researchers we support,

and representatives from the scientific, medical, and advocacy communities to determine what is needed and how best to move the science forward.

We plan research that will comprehensively address critical unanswered questions covering the many forms of cancer and the various populations that experience them. We work to integrate basic, behavioral, population, and applied research through translational activities and strive to identify new opportunities as well as gaps and barriers to progress that help us create new programs and improve existing ones.

Program assessment is key to keeping our research portfolio balanced and our support structure strong. To implement recommendations arising from assessments, we convene scientists from diverse settings to assist NCI staff with redesigning programs and developing new initiatives. We track implementation and regularly report on our progress.

Our planning activities encompass three key components required for a strong cancer research enterprise:

- **Maintaining a sound research infrastructure and building capacity for the future.** We give priority to developing the technological and personnel resources needed to support changing scientific and resource needs and the translation of new knowledge and emerging technologies into clinical practice.<sup>1</sup>
- **Capitalizing on extraordinary scientific opportunities.** We seek opportunities that promise to provide profound insights into cancer – those opportunities that hold greatest potential to lead to major improvements in our ability to prevent, control, detect, diagnose, and treat cancer.<sup>2</sup>

<sup>1</sup> See page 20 for information on “NCI’s Challenge” and our current infrastructure development priorities.

<sup>2</sup> See page 60 for information on NCI’s “Extraordinary Opportunities for Investment,” the current scientific priority areas we are pursuing.

- **Disease-specific research** . We continually assess our portfolios and plan for the research needed to uncover the biological and other characteristics that are unique to specific types of cancer.<sup>3</sup>

## HOW WE WORK

### We sponsor and conduct cancer research.

The National Cancer Institute's primary mission is to sponsor and conduct cancer research, and we use our budget to support a broad range of research that will expand our understanding of cancer and develop improvements in prevention and care. Some investigators conduct basic laboratory research on genes that may cause cancer. Others are studying the incidence of cancer in specific populations, such as farm families and former smokers. Still other scientists focus on translational research, such as developing tests to identify patients who carry genes that may make them susceptible to cancer, or clinical trials to determine the effectiveness of new diagnostic tools or drugs for treating cancer.

The largest portion of research funds goes to support the work of scientists conducting research in universities, teaching hospitals, and other organizations outside the NIH. Proposals submitted by these **extramural investigators** are selected for funding by peer review, a process by which cancer experts from around the country identify outstanding science and the most needed areas of discovery by evaluating the approximately 5,000 new research proposals NCI receives every year. With guidance and oversight from program experts in NCI's Divisions of Cancer Biology, Cancer Treatment and Diagnosis, Cancer Prevention, and Cancer Control and Population Sciences, cancer research is conducted with NCI funding in nearly every state in the U.S. and more than 20 foreign countries.

Another portion of our research dollars stay at the NIH in Maryland, where some 400 NCI principal investigators are at work. These **intramural investigators** in NCI's Center for Cancer Research and Division of Cancer Epidemiology and Genetics focus on the rapid translation of basic laboratory research to clinical testing and long-term epidemiologic and genetics studies. Recent changes in the structure of

## New NCI Intramural Structure Maximizes Collaboration

The Center for Cancer Research (CCR) was recently established within NCI's Intramural Research Program to bring together previously separate basic and clinical science activities and allow translational research the best opportunity to flourish. By creating a highly interactive, interdisciplinary environment that maximizes the use of researcher expertise and technology, researchers are better able to perform cutting edge basic, translational, and clinical investigations and facilitate communication, interaction, and quick response to promising research findings.

The CCR facilitates translational research by providing a defined process for and support to researchers studying promising targeted treatments. "Faculties" bring together scientists who work in different disciplines but on similar cancer research problems across the Institute, both intramural and extramural. The faculties provide a venue for sharing information, informal peer review, and successful collaboration.

To further encourage interaction of scientists, both external and NCI researchers can become adjunct appointees within CCR laboratories. These appointments allow researchers to work more closely with other laboratories than would have been possible in traditional collaborations. Adjunct investigators attend meetings and become involved in the day-to-day work of the laboratory.

Interdisciplinary training programs are also under development through the CCR to encourage young investigators to explore promising new areas of science, such as those found at the intersection of chemistry and biology, statistics and biology, or pathology and genetics.

the intramural program promise to further enhance their role in the Nation's cancer research effort.

As the number of NCI's research initiatives has grown in recent years, so too have the responsibilities of our scientific managers and administrators. **Research management and support** budgets are used for the critical technical and administrative services required for NCI to carry out its work. They include central administration functions, overall program direction, grant and contract review and administra-

<sup>3</sup> See page 93 for more information on how Progress Review Groups (PRGs) assess the scientific needs and opportunities that are critical to advancing research on specific forms of cancer.

tion, personnel, program coordination, and financial management.

In addition to direct research funding, NCI offers cancer scientists a variety of useful research tools and services. Among the research resources made available to investigators at little or no cost are tissue samples, mouse models of cancers, statistics on cancer incidence and mortality, databases of genetic information, and software for analyzing statistical and genetic data.<sup>4</sup>

NCI devotes approximately four percent of its annual budget to preparing the next generation of cancer researchers and ensuring a steady flow of well trained investigators. Each year, we provide cancer research training and career development opportunities to more than 2,000 graduate students, postdoctoral fellows, and oncologists. Some of this research training takes place on the NIH campus, but most goes on in universities and teaching hospitals around the U.S.

### **We foster research through collaborations and partnerships.**

To ensure that we use public funds to greatest advantage, NCI encourages collaborative research and partners with other organizations in numerous ways. We began one of our longest-running partnerships by establishing the Cancer Centers Program in the early 1960s. Congress encouraged the expansion of the Program to improve the quality of cancer care by bringing cancer scientists and oncologists together in the same setting with patients and their families. Today, two-thirds of the 60 centers funded by NCI are Comprehensive Cancer Centers, so designated because of the breadth and depth of the research conducted by their investigators and their role in public education and outreach.

NCI's Centers of Research Excellence also bring together groups of cancer scientists from different areas of expertise. Centers of Excellence are smaller in scale than other NCI Cancer Centers and generally focus on one or a few types of cancer or scientific areas. For example, NCI's Specialized Programs of Research Excellence (SPOREs) focus on translational research for specific cancers. Other examples of NCI Centers of Research Excellence are the Transdisciplinary Tobacco Use Research Centers, *In Vivo* Cellular and Molecular Imaging Centers, and the soon-to-be established Centers of Excellence in

Cancer Communications Research. All of these centers support interactive, interdisciplinary research, make research resources and flexible exploratory funds available to investigators, and provide research training and career development opportunities.

The largest collaborative research activity sponsored by NCI is our clinical trials program for testing cancer treatments, diagnostic tests, and interventions for preventing cancer. With the participation of more than 10,000 medical school and private practice physicians in NCI's Clinical Trials Cooperative Group Program and Community Clinical Oncology Program, NCI supports over 1,300 clinical trials a year involving more than 200,000 patients.<sup>5</sup> NCI also brings investigators together through networks like the Early Detection Research Network, which assembles groups of scientists to identify markers and develop tests to detect early signs of cancer, and consortia like the Mouse Models of Human Cancer Consortium, in which scientists from around the world share their expertise and resources in creating strains of mice that develop cancers similar to those seen in humans.

NCI also fosters collaborative work through partnerships with other Federal and state agencies with roles in improving the Nation's health. For example, much of the data on cancer trends available today has been collected and analyzed through the combined efforts of NCI, the Centers for Disease Control and Prevention (CDC), and state cancer registries. In addition, NCI has joined forces with five other Federal agencies to work on a number of projects aimed at improving the quality of cancer care, such as efforts to raise the rates of colon cancer screening among veterans and the elderly.

Scientists, medical experts, and advocates also work together to help shape NCI's policies and programs through a number of standing and ad hoc advisory groups. The National Cancer Advisory Board provides overall guidance for NCI and a final assessment of the research proposals selected for funding through peer review. The Board of Scientific Counselors evaluates the progress, performance, and productivity of the Institute's intramural research programs and scientists through regular site visits to NCI. The Board of Scientific Advisors plays a similar role for NCI's extramural program, reviewing the progress of ongoing programs and providing feed-

<sup>4</sup> For a directory, go to [resresources.nci.nih.gov](http://resresources.nci.nih.gov).

<sup>5</sup> See page 29 for more information about the NCI National Clinical Trials Program.



back on proposed new research activities. On a regular basis, NCI convenes Progress Review Groups of scientific and medical experts and advocates to examine the research needs and opportunities for specific types of cancer. NCI also is strongly influenced by the President's Cancer Panel's assessment of progress and problems in the Nation's effort to reduce the burden of cancer.

In addition to their membership on other NCI advisory groups, advocates provide the NCI Director broad advice on program and research priorities through the Director's Consumer Liaison Group, an all-consumer advisory committee. NCI also solicits the advice of patients and their family members through the recently created Consumer Advocates in Research and Related Activities (CARRA) program. This pool of 150 advocates will participate in Progress Review Groups assessing research needs for specific cancers, provide advice on the design of clinical trials, and review education materials we develop.

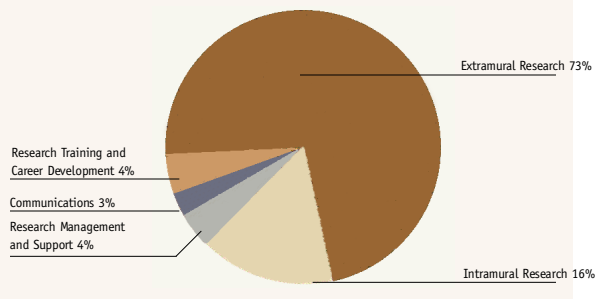
### **We work to ensure that people benefit from our research.**

The results of NCI-sponsored research consistently provide cancer patients and those who care for them with information, tools, and tests that impact cancer prevention and care and help people make better health choices. For example, once its effectiveness was confirmed in clinical trials, oncologists were quick to adopt the use of tamoxifen in the care of breast cancer patients. Likewise, since studies established the link between diet and cancer risk, more and more of us now strive to include five servings of fruits and vegetables in our daily diets.

Many of these advances reach the medical community and the public through medical journals and news reports, but NCI helps move the process along through a range of cancer communications activities. We provide information on scientific advances to the media and the public using an extensive array of information resources including a toll-free telephone service available in all regions of the country, printed brochures and educational packages, and Web-based information on cancer and clinical trials. NCI-sponsored researchers work to create the best methods for reaching all who need to learn about cancer, recent research findings, and opportunities to participate in clinical trials.

## **How We Spend Our Budget**

Nearly 90 percent of our budget is directly dedicated to cancer research, understanding how and why cancer strikes and developing improvements in its prevention and care. The remainder of our budget is used for research training and career development, the communication of cancer information, and research management and support.



When NCI-sponsored research results in discoveries that may lead to new drugs, devices, or diagnostic tests, federal laws encourage universities – and NCI – to pursue **commercialization** by licensing them to industry. In addition, NCI intramural investigators can also collaborate with industry through arrangements known as Cooperative Research and Development Agreements (CRADAs). It is through such an agreement between NCI and a major pharmaceutical company that investigators are continuing to follow chronic myelogenous leukemia patients treated with the recently approved anti-cancer agent Gleevec™, to determine its long-term effects.

Another way NCI makes a difference in peoples' lives is through our efforts in reducing the differences in the occurrence of cancer, its treatment and outcomes among various racial and ethnic groups. Our programs include research into the causes of **health disparities** as well as measures to translate research results into better health for groups at high risk for cancer. For example, NCI-sponsored investigators are using insurance data to examine the extent to which African American, Hispanic, and White patients are receiving recommended treatments for colon cancer. In addition, NCI is supporting field tests of smoking cessation and weight control programs targeted to the needs of specific racial and ethnic groups.

# The National Cancer Institute's Budget Request for Fiscal Year 2003

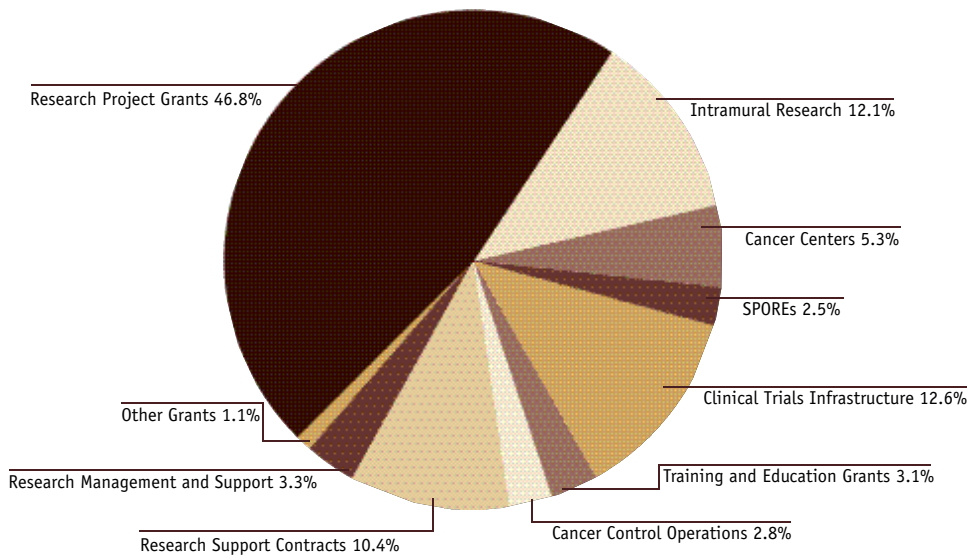
Each year, as mandated by the National Cancer Act of 1971 (P.L. 92-218), the National Cancer Institute (NCI) prepares a budget request for supporting the cancer research workforce with the technologies and resources it needs, building on research successes, and ensuring that research discoveries are applied to improve human health. This annual proposal is provided directly to the President of the United States in the fall of each year for formulating the President's budget request to Congress.

This document also serves as NCI's strategic plan and is intended for use by NCI staff; the researcher community; professional organizations; advisory groups; cancer information, education, and advocacy organizations; and public and private policymakers whose decisions affect cancer research and care in America. It is our hope that the information will inform and inspire all who read it to join the fight against cancer.

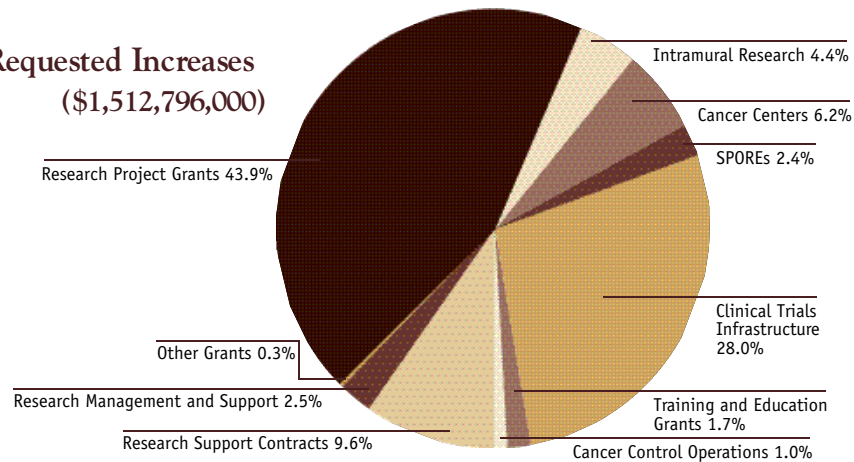
*. . . to achieve a future when all cancers are uncommon and easily treated.*

# The Nation's Investment in Cancer Research

Distribution of 2003 Budget Request (\$5,690,000,000) [View this graph as one continuous page](#)



## Distribution of 2003 Requested Increases (\$1,512,796,000)



### RESEARCH PROJECT GRANTS

Funding for extramural research, primarily through investigator-initiated Research Project Grants (RPGs), comprises the largest part of the NCI core budget. Increases through the NCI Challenge and Extraordinary Opportunity initiatives contribute to the expansion of research supported through RPGs. NCI funds about 4,500 RPGs each year to nearly 600 institutions across the United States at an average cost of approximately \$400,000 per grant. If fully supported, our budget request for Fiscal Year 2003 would add \$638 million to the funds available to support investigator-initiated research.

### INTRAMURAL RESEARCH

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

### CANCER CENTERS AND SPECIAL PROGRAMS OF RESEARCH EXCELLENCE (SPOREs)

Sixty NCI-supported Cancer Centers serve as hubs for cutting-edge research, high quality cancer care, and outreach and education for healthcare providers and patients. Centers of excellence like the 27 SPOREs use flexible funding to pursue questions related to specific forms of cancer and to move disease-specific research quickly from the laboratory to the patient. Funding increases will allow NCI to expand the number of Cancer Centers and SPOREs and broaden their range of activities.

# NCI Budget Request for Fiscal Year 2003

View this graph as one continuous page

## 2003 Budget Request

(dollars in thousands)	2001 Operating Budget	2002 President's Budget	Core	Core & Challenge	Core, Challenge, & Extraordinary Opportunities
<b>Research Project Grants (RPGs)</b>					
Ongoing	\$1,271,453	\$1,460,698	\$1,645,963	\$1,645,963	\$1,645,963
New (New and Renewal)	498,805	454,939	471,317	685,860	908,160
Subtotal	1,770,258	1,915,637	2,117,280	2,331,823	2,554,123
<b>Small Business Innovation Research</b>	74,593	85,120	110,120	110,120	110,120
Total RPGs	1,844,851	2,000,757	2,227,400	2,441,943	2,664,243
<b>Intramural Research</b>	593,581	619,443	641,743	683,243	686,243
<b>Cancer Centers</b>	205,507	206,202	213,625	286,375	299,375
Specialized Programs of Research Excellence (SPOREs)	91,475	107,452	111,320	140,320	143,320
<b>Clinical Trials Infrastructure</b>					
Cooperative Clinical Research	154,278	173,386	179,628	515,128	528,128
Community Clinical Oncology Program	26,208	119,482	123,784	188,784	188,784
Subtotal	180,486	292,868	303,412	703,912	716,912
<b>Training and Education Grants</b>					
National Research Service Awards	60,495	68,310	70,769	73,769	73,769
Research Career Program	54,970	57,828	59,910	74,610	74,610
Cancer Education Program	20,521	21,671	22,451	22,451	24,951
Minority Biomedical Research Support	3,479	4,638	5,138	5,138	5,138
Subtotal	139,465	152,447	158,268	175,968	178,468
<b>Cancer Control Operations</b>	141,110	144,461	149,662	152,662	159,862
<b>Research Support Contracts</b>	372,743	444,550	460,554	542,754	589,604
<b>Research Management and Support</b>	142,518	152,084	157,559	174,559	190,559
<b>Other Grants</b>	42,720	56,940	59,414	59,414	61,414
<b>Total NCI</b>	<b>3,754,456</b>	<b>4,177,204</b>	<b>4,482,957</b>	<b>5,361,150</b>	<b>5,690,000</b>
<i>Cancer Control included above**</i>	<i>457,965</i>	<i>511,058</i>	<i>538,431</i>	<i>648,881</i>	<i>783,431</i>

### CLINICAL TRIALS INFRASTRUCTURE

NCI supports clinical trials carried out by approximately 10,000 investigators at some 1,700 U.S. hospitals and cancer centers each year. Over 1,300 trials will be conducted in 2001 involving some 200,000 patients. Many of these trials make possible the testing of targeted agents like STI571 that hold promise for more effective, less invasive, cancer prevention and treatment. About three-quarters of this funding is for treatment trials and the other quarter supports prevention trials. The largest portion of additional funding will be used to increase physician reimbursement for participation in trials.

### TRAINING AND EDUCATION GRANTS

NCI funds approximately 170 institutions and 2,000 individuals each year through extramural cancer research training programs to prepare the next generation of scientists and clinicians to use new technologies and work effectively in interdisciplinary, collaborative research environments. Increased funding will be used to enhance these programs and to support the participation and growth of scientists within underserved populations.

### CANCER CONTROL \*\*

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

## Requested Increases for Fiscal Year 2003\*

(dollars in thousands)	Core	NCI's Challenge	Extraordinary Opportunities	Total
<b>Research Project Grants (RPGs)</b>				
Ongoing	\$185,265			\$185,265
New (New and Renewal)	16,378	\$214,543	\$222,300	453,221
Subtotal	201,643	214,543	222,300	638,486
Small Business Innovation Research	25,000			25,000
Total RPGs	226,643	214,543	222,300	663,486
<b>Intramural Research</b>				
Intramural Research	22,300	41,500	3,000	66,800
<b>Cancer Centers</b>				
Cancer Centers	7,423	72,750	13,000	93,173
<b>Specialized Programs of Research Excellence (SPOREs)</b>				
Specialized Programs of Research Excellence (SPOREs)	3,868	29,000	3,000	35,868
<b>Clinical Trials Infrastructure</b>				
Cooperative Clinical Research Community Clinical Oncology Program (CCOPs)	6,242	335,500	13,000	354,742
Subtotal	4,301	65,000		69,301
Subtotal	10,543	400,500	13,000	424,043
<b>Training and Education Grants</b>				
National Research Service Awards	2,459	3,000		5,459
Research Career Program	2,082	14,700		16,782
Cancer Education Program	780		2,500	3,280
Minority Biomedical Research Support	500			500
Subtotal	5,821	17,700	2,500	26,021
<b>Cancer Control Operations</b>				
Cancer Control Operations	5,201	3,000	7,200	15,401
<b>Research Support Contracts</b>				
Research Support Contracts	16,004	82,200	46,850	145,054
<b>Research Management and Support</b>				
Research Management and Support	5,475	17,000	16,000	38,475
<b>Other Grants</b>				
Other Grants	2,474	0	2,000	4,474
<b>Total Requested Increases</b>	<b>305,753</b>	<b>878,193</b>	<b>328,850</b>	<b>1,512,796</b>

\*Increases over the 2002 President's Budget.

### RESEARCH SUPPORT CONTRACTS

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

### RESEARCH MANAGEMENT AND SUPPORT

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

### OTHER GRANTS

Other grants go to support partnerships and shared resources, scientific evaluation, and workshop and conference support.



# NCI's Challenge

We are entering the 21st century with ever-expanding knowledge and an array of sophisticated tools for continuing the fight against cancer. The challenge before NCI is to build and continually enhance a research system that will allow the scientific community to apply new discoveries and emerging technologies. We need mechanisms that will promote and reward innovative thinking, aid cross-fertilization of ideas among disparate scientific disciplines, and enhance collaborations among government, academia, and industry. We must develop and maintain a cadre of trained scientists from a variety of disciplines. And we must address special societal concerns and other barriers that jeopardize our Nation's ability to provide the best possible treatment to cancer patients, ensure equal access to information and care, and offer current and future scientists sufficient opportunities to obtain research funding and other kinds of support.

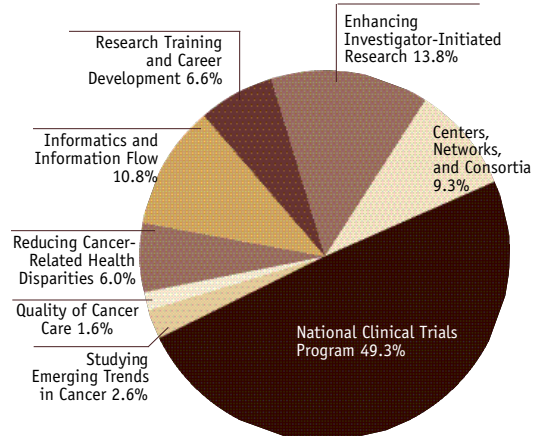
NCI must provide the vision, creative environments, and diverse resources needed to ensure an easy flow between the increasing number of discoveries and advances in cancer research and the scientific community's ability translate these findings into clinical application.

If the pace of discovery can be likened to speeding down a superhighway, our current ability to apply these findings still progresses at the slower pace of a country road. Where the two intersect, a bottleneck prevents a tremendous number of good ideas from moving forward. Our challenge is to continue to expand and smooth the country road, hastening discoveries to their application in interventions across the continuum of cancer care – from prevention and early detection to diagnosis, treatment, life after cancer, and the end of life.

To respond to this challenge, we identified six key areas for investment in our 2001 and 2002 proposals and will continue addressing these in 2003. Beginning with our 2002 proposal, we added new priority areas to address two persistent barriers to meeting our challenge: (1) inadequate quality of cancer care and (2) disparities in access to information, patient care, and research opportunities and careers. The plans proposed for these challenge areas describe new research awards or new and expanded programs and collaborations intended to help improve the prospects for patients and survivors of all types of cancers.

## NCI's Challenge FY 2003 Increase (dollars in thousands)

Enhancing Investigator-Initiated Research	\$121,543
Centers, Networks, and Consortia	81,250
National Clinical Trials Program	433,000
Studying Emerging Trends in Cancer	22,700
Quality of Cancer Care	14,000
Reducing Cancer-Related Health Disparities	52,700
Informatics, and Information Flow	95,000
Research Training and Career Development	58,000
<b>Total Challenge</b>	<b>\$878,193</b>



# Enhancing Investigator-Initiated Research

## THE CHALLENGE

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

Recent advances, such as the sequence of the human genome, new technologies for identifying molecular targets within cancer cells, and methods for discovering and analyzing promising drugs aimed at each cancer-causing pathway, have provided scientists with a wider arsenal of approaches and technologies for research than ever before. However, to take advantage of these advances, researchers often require additional resources, in the form of new research tools and equipment, collaborators from different disciplines, or special support for translational research. Providing these resources is NCI's challenge in the area of investigator-initiated research.

NCI has seen an enormous increase in the need for funding to allow scientists to fully exploit new technologies and approaches to conducting research. In Fiscal Year 2001, for example, the cost of research projects supported by NCI was nearly 15 percent higher than the year before. In response to this trend, we inevitably are forced to make some compromises in order to balance the growing number of research opportunities with the rising costs of research. These compromises result in NCI awarding fewer research grants than are endorsed by peer review and supporting each at a lower level than recommended. Though reviewer assessments of research applications consistently identify the top 35 to 40 percent as particularly worthy of support, the proportion actually funded (the

success rate) has averaged only 28 percent in recent years. Moreover, NCI has been able to maintain this success rate only by reducing individual grant budgets an average of 15 percent. A lack of funds — rather than a lack of exceptional ideas — remains a significant bottleneck in our fight against cancer.

Low success rates and less than optimal funding may prevent some of the brightest minds of the next generation from choosing to enter cancer research. But a sufficient infusion of resources and funding into investigator-initiated research will help to ensure that students considering a career in science, as well as current researchers, will perceive cancer research as an appealing and rewarding profession.

### GOAL

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

## PROGRESS TOWARD MEETING THE CHALLENGE

The NCI has sought to support and foster investigator-initiated research through a variety of policy decisions and flexible funding options.

### Identifying and Supporting High Priority Research

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

- Seeking out and supporting compelling research proposals that may have been overlooked in peer review, particularly those suggesting dramatically new or unconventional approaches to understanding cancer.
- Giving special consideration to proposals from clinical researchers and those who respond to NCI announcements of priority research areas, such as recommendations from Progress Review Groups for research related to specific cancers.

## THE PLAN — ENHANCING INVESTIGATOR-INITIATED RESEARCH

### Objectives and Milestones for Fiscal Year 2003

1. Accelerate the pace of discovery through increased funding for and larger numbers of competing research grants.
  - Support research projects at the full levels recommended by peer reviewers.
  - Fund, at a minimum, the top 35 percent of competing applications with (1) the highest scientific merit, (2) a less certain probability of success but potential to yield greater reward if they do succeed, (3) unconventional approaches but unique promise, (4) a focus on areas of extraordinary need in specific fields of investigation or model systems, and/or (5) the involvement of new investigators.
2. Encourage investigators to commit to careers in cancer research and to propose more innovative and higher reward projects.
  - Continue to allocate the first 80 to 90 percent of available funds for research project grants through conventional selection processes while ensuring that proposals from new investigators are also funded at a rate comparable to those of more established investigators.
  - Through a special evaluation process, fund particularly innovative and potentially high reward projects.
3. Facilitate rapid movement from discovery to application by using established mechanisms and creating novel special awards to encourage transdisciplinary and collaborative research.
  - Expand supplemental funding to grants to promote new interdisciplinary collaborations that bring together basic and clinical scientists, such as those fostered by NCI's Activities to Promote Research Collaborations Program.
  - Expand researcher access to central resources such as databases, tissue banks, and animal models using funding supplements; centers, networks, and consortia; and cooperative resource programs.

### Maximizing the Ability to Start New Projects and Collaborations

NCI seeks to maximize the pace of discovery by providing a broad range of flexible funding options and promoting collaborations and resource sharing wherever possible by:

- Providing opportunities for collaborative study through awards such as program project grants (P01s) and cooperative agreements, in addition to the traditional research project grants (R01s) that make up the bulk of NCI's research portfolio.
- Expanding the use of award mechanisms that provide seed funds for promising research. In Fiscal Year 2000, the number of small (R03)

and exploratory/developmental (R21, R33) grants awarded increased more than 25 percent over the previous year.

- Making "administrative supplement" funds available to investigators to allow them to take advantage of unanticipated opportunities or to pursue interdisciplinary collaborations. For example, through NCI's Activities to Promote Research Collaborations Program, grantees can apply for funding to support collaborations to initiate novel research that pursues unforeseen opportunities, share resources, develop new technologies, or organize cross-disciplinary meetings or workshops.

- Expand researcher access to technologies that promote interdisciplinary research and collaborations and to the expertise needed to move discoveries to application.
  - Encourage the development of information technology tools to foster and enhance interdisciplinary communication and collaboration.
  - Double the funding for collaborative research awards such as program project grants and cooperative agreements for networks in cancer genetics, imaging, early detection, and other areas.
  - Expand the use of exploratory grants to encourage more patient- and population-based research.
  - Allow peer review to be the primary determinant of appropriate funding levels for individual awards.
4. Use regular and special award mechanisms to encourage investigation in priority areas identified by advisory committees, NCI staff, Progress Review Groups, and extraordinary opportunity working groups.
- Monitor investigator-initiated research to assess whether these projects alone are meeting programmatic objectives, such as those identified in specific disease areas.
  - Set aside 10 to 15 percent of funds for Requests for Applications in specifically targeted areas of need.
  - Support Program Announcements and investigator-initiated projects that target identified gaps and/or emerging opportunities.
  - Enhance coordination within and among initiatives, and increase direct contact with applicants and grantees by increasing levels of extramural staff commensurate with the growth of the portfolio.

Total	\$121.5 M
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- Promoting collaborative studies and sharing of resources through various networks and consortia. (See page 25.)

### Reviewing Research Proposals Better and Faster

We review grant applications more effectively and make awards more rapidly than in the past. This is possible in large part because of changes such as:

- The establishment of a clinical oncology study section in April 2000 by NIH's Center for Scientific Review to ensure that applications for clinical research funding are reviewed by those familiar with the special issues related to such research.

- Electronic approval of grant applications by National Cancer Advisory Board members between their regularly scheduled meetings, permitting Institute staff to notify recipients earlier and, in many cases, allowing research projects to begin sooner than anticipated. This new procedure reduces the standard nine-month funding cycle by more than a month for most applications.

## Today's Research Investments Shape the Number of Researchers Tomorrow

When, as in recent years, the percentage of research proposals that NCI funds (the success rate) averages less than 30 percent, and grants routinely are less than fully funded, young people may be discouraged from pursuing careers in cancer research and opt for professions in more stable or well-paying fields. Faced with such odds, many clinicians in particular may choose a career in private practice over clinical research. Basic cancer biology scientists may choose another career altogether.

Thus, it is not just funds for training per se that influence the number of future researchers. (See page 20.) The success rate of the Research Project Grant (RPG) pool also makes its mark. First, many trainees depend on RPGs awarded to their mentors, rather than formal training awards, for financial support of their training. If their mentors' grants are not funded, trainees often have no immediate means to continue. Second, upon completion of their training, new investigators today generally cannot expect much financial support from the university or medical school where they work, but instead must depend on RPG awards for their salaries as well as for research support. Without such grants, these investigators are unable to pursue their chosen career in an academic setting. Clearly, then, reductions in the numbers of awards and the percent of recommended dollars actually awarded have profound effects on the next generation of cancer researchers.

To continue to address the many questions remaining in cancer research, NCI must assure a steady supply of future researchers in the training pipeline. This requires more than support for the training itself. It also requires maintenance of the light at the end of the tunnel, in the form of reasonable odds for obtaining grants to sustain the careers of future cancer researchers.

## NCI Research at Your Fingertips

"What research is NCI supporting in pancreatic cancer?" "How much of this research is devoted to biology or etiology versus treatment and prevention?" "How much of NCI's total research effort is in early detection, diagnosis and prognosis?" These are all easy questions, but until recently very difficult to answer.

In the spring of 2001, NCI launched a new Web site, the ***Cancer Research Portfolio***, the most comprehensive, easy to use source of information about current NCI-supported research. Investigator-initiated grants, contracts, clinical trials, and NCI's intramural research are for the first time accessible in one place, one database, and, now, available to the public on a Web site. Viewers can search, browse, and sort NCI research in ways never possible before. For example:

- Cancer patients and advocates can see exactly what NCI is funding by cancer site and disease as well as across broad scientific areas.
- Scientists can more easily identify investigators doing similar work, as well as contacts for multidisciplinary research and collaborations.
- Congressional staff can view cancer research supported in their states as well as assess the status of research support across disease site and scientific area.
- Science policy advisors and NCI staff can use this tool to facilitate cancer research planning and resource allocation.

Visit [researchportfolio.cancer.gov](http://researchportfolio.cancer.gov) to learn more about this NCI tool.



# Centers, Networks, and Consortia

### THE CHALLENGE

Our efforts to translate scientific knowledge into more effective cancer interventions increasingly are challenged by the conventional ways in which research is conducted. With today's rapid pace of scientific and technological discovery, NCI must help researchers create integrated research environments that foster the multidisciplinary collaborations needed to address the "big picture" problems in cancer research. We must functionally link basic, clinical, population, and behavioral scientists to each other and to newly developing, diverse fields of science and technology. Investigators must have easy access to many different patients and at-risk populations, tissue banks, new technologies, and state-of-the-art informatics. They must be able to work together with ease and flexibility in multi-institutional research settings as well as within the same institution.

NCI must continue to create and nurture an overarching structure for research composed of NCI-designated Cancer Centers, Centers of Research Excellence, and research networks and consortia. These centers, networks, and consortia are enhancing the traditional research enterprise in ways that promote and facilitate complex scientific interactions, provide the critical resources essential for the research, and encourage the easy exchange of information and ideas through new communication linkages. While these interactive structures are critical to progress, this challenge also requires that NCI find ways to integrate these centers and networks with each other when broader interactions will allow investigators to seek answers to major questions more efficiently and effectively.

NCI-designated Cancer Centers organize and integrate multidisciplinary research across departments and schools within a single institution. They provide scientists access to the most advanced technologies and new research opportunities and bring the benefits of their research directly to the public in the form of patient care. They link state-of-the-art research and clinical

care activities within the institution and form key partnerships with industrial, community, and state health organizations outside the institution. (See [cancer.gov/cancercenters](http://cancer.gov/cancercenters) for more information.)

For example, the disease-specific Specialized Programs of Research Excellence, designed to move discoveries between the laboratory and patient and population research settings, had their origins in Cancer Centers. The new Special Populations Networks for Cancer Awareness Research and Training are designed to link local, community, and regional problems of cancer in underserved populations to the broad-based research capabilities of NCI-designated Cancer Centers. Centers are critical in a new NCI initiative to incorporate Minority-Serving Institutions (MSIs) into NCI's cancer research, education, training, and outreach activities. The Cancer Genetics Network sites are headquartered in Centers. Nearly all the participants in the Mouse Models of Human Cancer Consortium are in NCI-designated Cancer Centers. Centers have worked closely with industry in developing new cancer therapeutic agents and are rapidly becoming significant partners with industry for new technology development. Approximately 70 percent of cancer clinical trials are conducted in Cancer Centers.

NCI is planning to establish Regional Enhancement Cancer Centers to facilitate partnerships between smaller institutions and the large, existing NCI-designated Comprehensive Cancer Centers. These partnerships will provide patients and populations with much improved access to the newest trials in early detection, prevention, and therapeutic research. NCI anticipates that the centers also will play a key role in integrating and coordinating NCI-supported centers of excellence and networks into one overarching, unified research framework.

Centers of Research Excellence bring together interdisciplinary and translational research teams focused on a specific disease, modality, biologic

#### G O A L

Create and sustain research infrastructures for collaboration, technology support and development, and access to resources.

## THE PLAN — CENTERS, NETWORKS, AND CONSORTIA

While NCI's goal for collaborative research applies to all NCI-designated Cancer Centers, networks, and consortia, this plan focuses primarily on the objectives and resources for the Centers and SPOREs. Many other research networks are budgeted and discussed in the Extraordinary Opportunities and NCI Challenge sections throughout this document.

### Goal

Create and sustain research infrastructures for collaboration, technology support and development, and access to resources that enable multiple scientific disciplines to address large problems in cancer that could not be solved by individual investigators.

### Objectives and Milestones for Fiscal Year 2003

1. Increase the number and broaden the geographic distribution of NCI-designated Cancer Centers and create partnerships between Minority-Serving Institutions and NCI Cancer Centers. \$7.3 M
  - Designate one new Cancer Center to bring the total number of centers to 61. \$1.25 M
  - Award two new Cancer Center Planning Grants. \$0.50 M
  - Establish formal affiliations between Cancer Centers and Minority-Serving Institutions (MSIs) in the form of 2 comprehensive partnerships and 1 planning grant for a comprehensive partnership to enhance the research capabilities of MSIs, and improve the effectiveness of Cancer Centers in serving minority communities. (See page 57, Objective 3 for the training component of these partnerships.) \$5.50 M
  
2. Expand the capacity of Cancer Centers to engage in newly developing areas of research and technology and to act as platforms for translating discoveries into interventions. \$28.5 M
  - Increase funding to all Cancer Centers to encourage scientists in Centers to develop new technologies and methodologies for entirely new approaches to answering important cancer research questions. \$6.00 M

process, or scientific area. They are awarded sizeable amounts of flexible funding to enable them to rapidly address emerging scientific opportunities.

The first of these centers, the Specialized Programs of Research Excellence (SPOREs), were created in 1992 and focus on specific cancers. They serve as highly effective hubs for translational research, moving discoveries back and forth among laboratory, clinic, and population research settings. To date, SPOREs have been established in breast, lung, gastrointestinal, ovarian, prostate, genitourinary, and skin cancer. (Go to [spores.nci.nih.gov](http://spores.nci.nih.gov) for further information.)

The SPORE blueprint has been used to establish

similar programs in other cancer research areas, including NCI-sponsored Transdisciplinary Tobacco Use Research Centers, *In Vivo* Cellular and Molecular Imaging Centers, Interdisciplinary Research Teams for Molecular Target Assessment, and the soon-to-be established Centers of Excellence in Cancer Communications Research. Like the SPOREs, all of these centers support interactive multidisciplinary research and provide research resources and flexible exploratory funds, as well as research training and career development opportunities.

Networks and consortia link the expertise and innovation of scientists from different disciplines and

<ul style="list-style-type: none"> <li>■ Establish 10 Informatics Planning Activities in Cancer Centers to build, in partnership with NCI, critical informatics capabilities in data acquisition, analysis, integration, and coordination. \$7.50 M</li> <li>■ Provide additional funding to build the clinical research and population research infrastructure of Cancer Centers. Fund databases that conform to NCI's clinical informatics infrastructure; support the development and expansion of population databases; provide more core staff to conduct innovative translational therapeutic and prevention trials; and strengthen the auditing and data safety and monitoring of human subjects research. \$15.00 M</li> </ul>	
<p>3. Expand and enhance the research of Specialized Programs of Research Excellence (SPOREs).</p> <ul style="list-style-type: none"> <li>■ Expand the SPORE program by adding one in genitourinary cancer, one in lung cancer, two in leukemia, one in myeloma, one in ovarian cancer, one in prostate cancer and one in skin cancer. \$24.00 M</li> <li>■ Support development of an Internet platform and research database to enable SPOREs to exchange research results and to foster communications for sharing resources and developing collaborative inter-SPORE research projects. \$1.00 M</li> <li>■ Provide supplements to SPOREs for planning and developing inter-SPORE research projects. \$4.00 M</li> </ul>	\$29.0 M
<p>4. Implement a Strategic Supplement Program for taking advantage of high priority scientific opportunities that can be completed in a short time frame (1 to 2 years):</p> <ul style="list-style-type: none"> <li>■ In response to opportunities identified by NCI program managers of Cancer Centers, Centers of Excellence, Networks, and Consortia \$5.00 M</li> <li>■ In response to scientific advice from outside advisory groups (e.g., Progress Review Groups) \$10.00 M</li> </ul>	\$15.0 M
<p>Management and Support</p>	\$1.5 M
<b>Total</b>	<b>\$81.3 M</b>

diverse research backgrounds to address important questions and issues about cancer. For example, the Cancer Genetics Network addresses the issue of inherited predisposition to cancer and is linking its goals and objectives to those of SPOREs and NCI-designated Cancer Centers. The Mouse Models of Human Cancer Consortium will work closely with SPOREs to develop mouse models that reflect various precancerous and cancerous stages of human cancer. The American College of Radiology Imaging Network, the newest of NCI's cooperative groups, is evaluating and developing a new generation of imaging concepts and tools with device manufacturers and other technology developers.

The Early Detection Research Network, which facilitates the discovery, development, and initial steps in clinical validation of molecular markers and assays that detect early signs of cancer, is already interacting with SPOREs and other interdisciplinary teams of scientists. The Special Populations Networks are involving underrepresented communities in establishing research priorities and conducting research that will benefit these populations. Investigators in several brain tumor consortia are exploring new biologic approaches to pediatric and adult brain tumors, testing promising new treatments, and evaluating innovative ways of administering existing therapies.

## PROGRESS TOWARD MEETING THE CHALLENGE

Through its Cancer Centers Program, NCI has established the foundation for an overarching research framework that will bring diverse scientific disciplines together across institutional boundaries. NCI-designated Cancer Centers continue to evolve as key strategic partners of NCI. In 2001, NCI added a Center in Missouri and will fund a new planning grant for developing a Center in South Carolina. In addition, the number of Cancer Centers with the “Comprehensive” designation increased in 2001 to 38. NCI has also been working with institutions in more than 10 other states to develop Cancer Centers.

NCI launched the **Minority Institution/Cancer Center Partnership (MICCP)** Program in Fiscal Year 2001 by funding 2 comprehensive partnerships, 2 planning grants for comprehensive partnerships, and 12 planning grants dedicated to more focused collaborative projects and programs ranging from research to training. This program reaches out to the 5 major minority institutions with medical schools, as well as to more than 300 smaller institutions dedicated to educating African Americans, Hispanics, Native

Americans, and other groups underrepresented in biomedical research. Research-intensive NCI Cancer Centers, together with culturally sensitive MSIs, offer an entirely new set of opportunities for training more minority scientists, expanding the cancer research capability of MSIs, and focusing more research and community outreach programs of Cancer Centers on understanding and addressing minority health disparities. In the next year, the MICCP will seek ways to integrate its efforts with NCI’s Special Populations Networks for Cancer Awareness Research and Training and the Minority Biomedical Support Grant Program, sponsored by the National Institute of General Medical Sciences at the NIH.

As NCI’s **Specialized Programs of Research Excellence (SPOREs)** have become more established, SPORE investigators have begun to make significant contributions to translational research. Similarly, the multidisciplinary collaborations fostered by other centers of research excellence are starting to yield some impressive results. Research advances from Transdisciplinary Tobacco Use Research Centers are described on page 86; those from *In Vivo* Cellular and Molecular Imaging Centers can be found on page 67.

### SPOTLIGHT ON RESEARCH

## Results Show Value of SPOREs

Since their start in 1992, NCI’s Specialized Programs of Research Excellence (SPOREs) have grown to include 27 centers focused on translational research for breast, lung, gastrointestinal, ovarian, prostate, genitourinary, and skin cancer. Recent advances testify to their value:

- The discovery that smokers who carry certain gene types are less likely than others to successfully quit. This finding raises the possibility that specially tailored cessation programs may help these smokers.
- A better approach to detecting the early signs of lung cancer. Investigators found that the use of fluorescent light in bronchoscopy dramatically improved physicians’ ability to identify the early signs of lung cancer.
- Confirmation that family clusters of pancreatic cancer have a genetic basis. After tracking relatives of pancreatic cancer patients since 1994, researchers recently confirmed that those with two or more relatives with pancreatic cancer are at higher risk for the dis-

ease. This finding provides important information for these relatives and their physicians and supplies scientists with a vital first step toward identifying the responsible genes.

- Promising results in an initial clinical trial of a treatment vaccine that stimulates the immune system of pancreatic cancer patients to take action against their tumors. Investigators have now expanded testing of this new treatment to a larger number of patients.
- Confirmation that variations in the molecular profiles of different types of breast tumors can yield important clues about the prospects for relapse and long-term patient survival.

In the coming years, the program will continue to establish centers on the cancers currently under study while expanding to include centers devoted to every major cancer site. The expected schedule for expansion can be found at [spores.nci.nih.gov](http://spores.nci.nih.gov).

# National Clinical Trials Program in Treatment and Prevention

## THE CHALLENGE

Clinical trials, a crucial component of NCI's research program, are the final, definitive step in testing new approaches to cancer prevention, diagnosis, and treatment. Our National Clinical Trials Program essentially is a laboratory without walls, through which NCI has a tangible and direct impact on the survival and quality of life of patients with cancer.

NCI's clinical trials system is complex, involves many participants, and requires collaboration at all levels – between investigators and physicians, industry and academia, academia and NCI, and NCI and industry. Adding to this complexity, cancer clinical trials have undergone a number of dramatic changes in recent years. Progress in cancer biology, genetics, immunology, molecular biology, and imaging technology has accelerated, creating new opportunities to improve clinical practice. As cancer researchers around the country have identified the molecular changes that cause a normal cell to become cancerous, the number of new anti-cancer agents that target these changes has rapidly grown, triggering an entirely new approach to the development of cancer drugs and a rapid growth in NCI-sponsored clinical trials for treating and preventing cancer.

At the same time, advances in informatics and electronic communications have led to new approaches to communication and data reporting and analysis in the clinical research setting, providing new opportunities to enhance the efficiency of clinical trials and speed their results to the care of cancer patients. NCI's cooperative groups — networks of investigators who conduct clinical trials — have begun to incorporate many of these advances into their clinical trials, but much work remains to be done.

Despite progress made to date, many barriers to clinical trials participation persist. In particular, the reimbursement that NCI provides physicians for their

role in clinical trials often falls far short of their costs and is well below what the pharmaceutical industry provides. Physicians who take part in clinical trials often must hire additional nursing and data management staff to ensure that patients fully understand the risks and benefits of participation, track participating patients, and collect and report the necessary data. A 1999 survey of oncologists by the American Society of Clinical Oncology found that although many physicians preferred NCI-sponsored cooperative group clinical trials, inadequate reimbursement for the costs and time required for data reporting were barriers to participation.

While NCI has improved the availability of clinical trials information to patients and health care professionals (see page 89) and has doubled its reimbursement over the past several years, it still lags far behind actual costs and industry standards. This problem is compounded in cancer prevention trials because many thousands of patients often are needed to evaluate preventive measures and these patients must be followed for longer periods of time.

NCI's challenge is to ensure that we overcome the barriers to participation in clinical trials and that we capitalize on the latest developments in cancer research, informatics, and management to address our most important questions in cancer prevention and treatment.

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## PROGRESS TOWARD MEETING THE CHALLENGE

In our ongoing efforts to improve the speed and efficiency with which cancer clinical trials are conducted, NCI recently centralized the common administrative, financial, and data collection activities of its clinical trials cooperative groups. Through an online Cancer Trials Support Unit site unveiled in 2000, cooperative group investigators can now download

**G O A L**  
Ensure that clinical trials address the most important questions in treatment and prevention and are broadly accessible.



clinical trial protocols and other information, enroll patients in clinical trials, arrange for reimbursement of research costs, and receive alerts when new trials begin. In 2002, oncologists outside the cooperative groups also will be permitted to enroll their patients in these clinical trials.

Similarly, the four cooperative groups conducting studies on cancer in children merged into a single new Children's Oncology Group. This consolidation is expected to potentially double the number of doctors and hospitals involved in any given study and allow trials to be completed more quickly. With cure rates for new childhood cancers now reaching 70 percent, the new cooperative group will be able to devote more of its energies to the less common childhood cancers, for which cures have not been as forthcoming.

Over the past two years, clinical trials have continued to contribute to improvements in survival and quality of life for patients with a wide variety of cancers. For example, recently completed clinical trials have determined that:

- Cervical cancer, still the second leading cause of cancer death in women around the world, can be treated more effectively by combining cisplatin chemotherapy with radiation treatment. It is estimated that this treatment can save 2,000 additional lives each year in the United States and considerably more – perhaps hundreds of thousands – worldwide.
- The combination of chemotherapy and radiation following surgery substantially prolongs the survival of patients with stomach cancer.
- For patients with metastatic kidney cancer, surgery to remove the kidney can add months to patients' lives.
- Preoperative chemotherapy prolongs the survival of patients undergoing bladder cancer surgery.
- In the most aggressive cases of prostate cancer, radiation therapy combined with the optimal application of hormone treatments leads to longer survival.
- The use of cyclooxygenase-2 (COX-2) inhibitors reduces the number of colon polyps in patients with the genetic disorder Familial Adenomatous Polyposis. Without treatment, patients with this condition typically develop numerous polyps, increasing their risk for colon cancer.

The recent improvements in cancer therapy described above generally combine advances in conventional anti-cancer treatments with surgery, chemotherapy, or radiation. But the past decade also has seen an explosion in our understanding of tumor biology and immunology, which has led to the identification of a vast array of new molecular targets at which to direct treatment and prevention interventions. The cellular pathways and interactions involved in these molecular targets are extraordinarily complex and inter-related, and they require scientists to develop new techniques and tests to identify patients whose tumors contain the relevant targets.

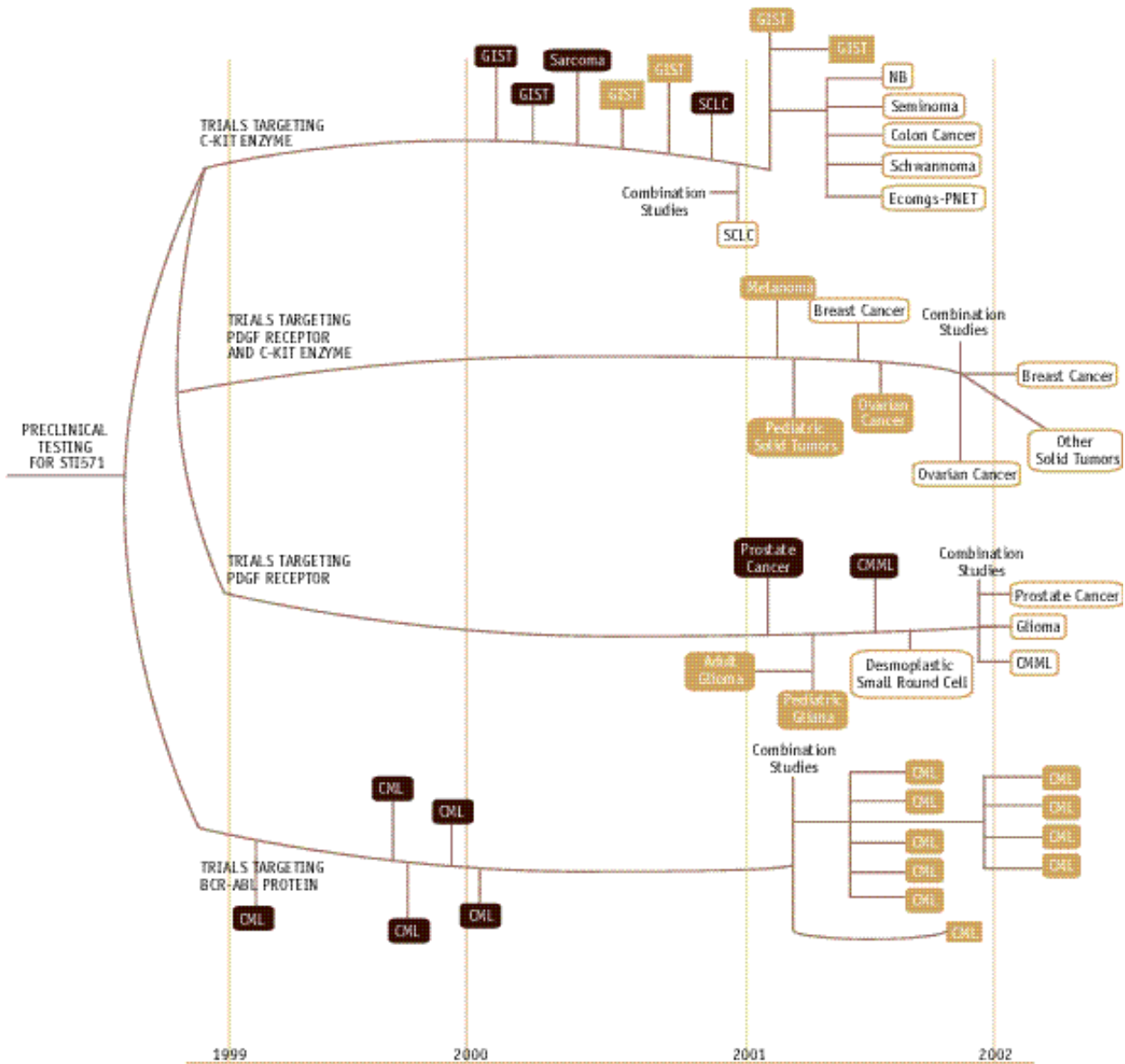
As a result, clinical trials of targeted agents often involve laboratory studies to better define the presence of targets and drug effects in the tumors of individual patients undergoing treatment. Indeed, more than half the cancer treatment trials initiated by NCI's cooperative groups over the last two years have included correlative studies. This trend is also increasingly seen in cancer prevention trials involving chemopreventive agents.

Along with the discovery of more and more therapeutic targets for cancer, there has been a huge increase in the number of new anti-cancer agents in drug development. According to the Pharmaceutical Research and Manufacturers of America, more than 400 anti-cancer agents were in development in 2001, up from fewer than 100 in the late 1980s. Similarly, the number of pharmaceutical and biotechnology companies developing anti-cancer agents nearly quadrupled over the same period, rising from 45 to 170.

Despite this large increase in corporate involvement, NCI's role and the public-private partnerships it brokers continue to be essential. NCI collaborates with industry in the development of many promising investigational agents for treatment and prevention by sponsoring clinical trials for them. Because pharmaceutical companies tend to seek FDA approval or licensing of a new agent only for a single tumor type, NCI's involvement in the drug development process helps ensure that new agents are evaluated against the full range of cancers for which they may be effective and in combination with treatments such as surgery and radiation therapy. These collaborations bring new treatments and prevention strategies to patients years earlier than would otherwise occur. Figure 1 illustrates the rapid expansion of clinical tri-

# Clinical Trials for STI571 Have Mushroomed Since Early 1999

After success with a small Phase I clinical trial to test the safety of STI571 (Gleevec™) for treating chronic myelogenous leukemia, clinical investigators began testing the drug in a variety of cancers that share common molecular abnormalities. A rapid and broad expansion of clinical trials followed.



- NCI Sponsored
- Company Sponsored
- NCI, Company, or Both

Boxes with rounded corners indicate Phase I or II preliminary clinical trials to assess factors such as toxicity, dosage, and activity of a new drug.

Boxes with square corners indicate Phase III larger, more in-depth trials that, for example, look at long-term effects to compare the drug to standard therapies.

- GIST  
Gastrointestinal stromal tumors
- CML  
Chronic myelogenous leukemia
- CMML  
Chronic myelomonocytic leukemia
- SCLC  
Small cell lung cancer
- NB  
Neuroblastoma

## THE PLAN — NATIONAL CLINICAL TRIALS PROGRAM IN TREATMENT AND PREVENTION

### Goal

Ensure that NCI's clinical trials program is poised to address the most important medical and scientific questions in cancer prevention and treatment quickly and effectively through state-of-the-art clinical trials that are broadly accessible to cancer patients, populations at risk for cancer, and the physicians who care for them.

### Objectives and Milestones for Fiscal Year 2003

1. Identify and address compelling clinical questions confronting physicians and their patients struggling with cancer or at high risk of cancer. \$17.0 M
  - Expand clinical trials planning so that critical treatment and prevention questions are addressed across the major types of conditions experienced by patients. \$1.00 M
  - Expand State of the Science meetings to identify important research questions and define a scientific research agenda to address them. \$1.00 M
  - Provide additional research funds for scientific leadership support for researchers who chair studies in addition to caring for patients and for statisticians; together they are responsible for writing, monitoring, and analyzing NCI-sponsored, high-priority Phase III trials. \$3.00 M
  - Increase translational research funds for clinical correlative studies to uncover the mechanisms of action, response, and resistance underlying new treatments and preventive strategies and to translate basic biology from the laboratory to clinical practice. \$8.00 M
  - Support a national tissue resource system to facilitate rapid evaluation of new assays and relevant clinical correlations as new targets are identified. (See page 72, Objective 2.)
  - Fund tissue and specimen banks to store material from cancer patients undergoing treatment and from those at risk of developing cancer to allow later studies of drug effectiveness, molecular abnormalities, and clues to tumor initiation and progression. \$4.00 M
  - Develop and make widely available molecular assays required to characterize/classify tumors. (See page 80, Objective 2.)
  
2. Enhance the ability and flexibility of the clinical trials system to respond quickly and effectively to scientific opportunities emerging from the vast expansion of molecular targets discovery, new drug discovery, and translational research. \$5.5 M
  - Create flexible collaborations among investigators to facilitate multi-institutional clinical trials, projects, and consortia.
  - Integrate scientific strategic planning to include cross-disciplinary input (e.g., oncology and diagnostic imaging) and project teams.
  - Incorporate other relevant research questions into treatment and prevention trials, and utilize the clinical trials infrastructure more broadly.
  - Incorporate behavioral, epidemiologic, outcomes, and other relevant research to effectively address cancer questions in specific tumor types and patient populations.
  - Incorporate the evaluation of relevant biomarkers into clinical trials.

<p><b>3. Increase the pace of development and clinical testing of promising new therapeutic and preventive agents.</b></p> <ul style="list-style-type: none"> <li>■ Over 2 to 3 years, substantially increase the number of promising agents entering NCI-sponsored clinical trials, triple annual patient accrual to early clinical trials of promising agents, and substantially increase the number of pivotal or proof-of-principle early clinical trials.</li> <li>■ Expand resources for the Rapid Access to Intervention Development (RAID) and Rapid Access to Preventive Intervention Development (RAPID) programs. (See page 81, Objective 4.)</li> <li>■ Increase funding for early treatment and prevention agent development and for Interdisciplinary Research Teams for Molecular Target Assessment to develop the necessary assays, tools, and approaches to assess the effects of promising new agents on their molecular targets. \$20.00 M</li> <li>■ Support a rapid grant review process for mechanism-based clinical trials.</li> <li>■ Support the NCI intramural clinical trials program by increasing the numbers of data managers, research nurses, biostatisticians, and clinicians available to support a critical mass of clinical investigators; continue to develop the net-Trials database system (see page 52); and continue the Tissue Array Research Program to identify key molecular alterations in cancers. \$15.00 M</li> </ul>	<p><b>\$35.0 M</b></p>
<p><b>4. Double the rate at which Phase III trials are completed.</b></p> <ul style="list-style-type: none"> <li>■ Shorten the duration of patient accrual to national trials (approximately 5 years at present) by 50 percent, thereby substantially increasing the number of new treatments or interventions that can be evaluated.</li> <li>■ Provide funds to adequately support data management and enable substantially greater physician and patient participation in clinical trials. \$350.00 M <ul style="list-style-type: none"> <li>■ Increase physician reimbursement to \$3,500 per patient for treatment and prevention trials to adequately cover the additional nursing and data management costs required to participate in clinical trials.</li> <li>■ Double the number of patients accrued to treatment and prevention trials over 1 to 2 years.</li> <li>■ Provide follow-up funding to allow physicians to follow patients, report outcome data, and address important long-term treatment and epidemiology issues.</li> </ul> </li> <li>■ Expand the Clinical Trials Support Unit to consolidate the administrative tasks associated with clinical trials and to provide a single interface for investigators enrolling patients. \$20.00 M</li> <li>■ Provide extensive information about prevention and treatment clinical trials to enable patients and physicians to make informed choices. (See page 90, Objective 2.)</li> <li>■ Facilitate clinical trials participation by developing uniform electronic case report forms and data reporting systems (See page 52, Objective 1.)</li> </ul>	<p><b>\$370.0 M</b></p>
<p><b>5. Reduce outcome disparities in special populations by increasing access to state-of-the-art clinical trials in cancer prevention and treatment.</b> (See page 47, Objective 5.)</p>	<p><b>\$5.5 M</b></p>
<p>Management and Support</p>	<p><b>\$5.5 M</b></p>
<p><b>Total</b></p>	<p><b>\$433.0 M</b></p>

als in many different tumors, made possible by the collaboration between Novartis Pharmaceuticals and NCI-supported researchers to develop Gleevec™.

As scientists discover more and more about the basic mechanisms of cancer, they also add to our knowledge about its prevention, allowing experts to explore the possibility of averting cancer through chemoprevention. Unlike conventional approaches to preventing cancer, which often focus on avoiding exposure to cancer-causing agents (such as tobacco and excessive sunlight), chemoprevention actively intervenes against cancer with drugs or other agents that stop the transformation of normal cells into cancer cells.

One of the most widely used chemopreventive agents today is tamoxifen, a drug that interferes with the activity of estrogen and was initially introduced as a treatment for breast cancer. After physicians began to report that women who had received tamoxifen following breast cancer surgery were less likely to develop cancer in their other breast, NCI initiated the first large breast cancer prevention trial in the United States to determine whether the use of tamoxifen could prevent breast cancer in high-risk women. Initial results from that trial, announced in 1998, indicated that tamoxifen did indeed reduce the risk for breast cancer, and that its use could be especially beneficial for young women at significant risk for the disease. But because tamoxifen also carries potentially serious risks, such as blood clots and stroke, NCI continues to sponsor other clinical trials in breast cancer prevention. A major NCI-supported study is comparing tamoxifen with raloxifene, an osteoporosis prevention drug that also appears to lower the risk for breast cancer.

A number of other NCI-sponsored studies are examining the potential for the arthritis drug celecoxib (Celebrex™) to prevent colon and other cancers. For arthritis sufferers, celecoxib reduces inflammation and alleviates symptoms by inhibiting the body's production of COX-2 enzymes. Researchers suspect that celecoxib might play a valuable role in cancer prevention because precancerous tissues, such as colon polyps, also produce COX-2 enzymes, and because epidemiologic studies have shown that arthritis sufferers who regularly use anti-inflammatory drugs have lower rates of colon cancer. In NCI-sponsored studies thus far, celecoxib has been found to reduce the number of colon polyps in patients with Familial Adenomatous Polyposis, an inherited syndrome that predisposes them to colon cancer. Other NCI-funded clinical tri-

als are investigating whether celecoxib can prevent esophageal, bladder, and skin cancers.

## What Are Clinical Trials?

Clinical trials are research studies involving patients, designed to determine whether new drugs or treatments are safe and effective. Clinical trials are also routinely conducted to answer questions about new or existing ways to prevent, diagnose, and detect diseases such as cancer and may examine questions such as the psychological impact of cancer or ways to improve a patient's quality of life. In addition, as we learn more about the mechanisms of cancer, the number of cancer chemoprevention trials has been steadily increasing.

New treatments or chemopreventive agents are tested on patients only after laboratory and animal tests have shown promising results. Once patients are involved, clinical trials generally proceed through four phases. As each phase of testing is completed, the data collected are analyzed to determine whether the agent is showing enough of a benefit to continue testing. 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.

**Phase I** – These small trials, generally involving 20-80 patients, focus on determining the safety of a new agent, identifying side effects, and establishing a safe dosage range.

**Phase II** – With a larger group of patients (100-300), Phase II trials are intended to evaluate the effectiveness of a new treatment, as well as to continue to test its safety.

**Phase III** – These large trials, often involving 1,000-3,000 people, provide more definitive information about a new therapy's effectiveness, monitor the occurrence of side effects, and compare the new therapy to standard treatments. It is only after a Phase III trial has been successfully completed that the Food and Drug Administration considers whether to approve a new drug or treatment for general use.

**Phase IV** – After FDA approval has been granted, Phase IV trials continue to collect information about treatment outcomes in various populations of patients and any side effects associated with long-term use.

For more information about cancer clinical trials or details about how to participate in a cancer clinical trial, go to [cancertrials.nci.nih.gov](http://cancertrials.nci.nih.gov).



# Studying Emerging Trends in Cancer

## THE CHALLENGE

Over the past few decades, NCI has worked with other agencies to create a national cancer surveillance system for tracking cancer trends: the monitoring of cancer incidence, cancer mortality, cancers that are declining and those on the rise. At this time, our challenge is to develop a surveillance system that not only tracks cancer statistics but also helps us form hypotheses for cancer research, make critical scientific and public health decisions, develop and monitor prevention and control measures, and assess whether or not interventions are making a difference. Advances in information technology, increasing diversity in the U.S. population, and changes in health care delivery present new challenges to this task.

To continue our pivotal role in effective and comprehensive national surveillance, we must improve surveillance in ways that help communities identify research needs and develop effective cancer planning and health policy. NCI's Surveillance, Epidemiology, and End Results (SEER) program must cover a broader spectrum of the population and compare information on why people get cancer, how it is treated, and with what outcomes. We must improve the measures we use to track cancer risk, screening practices, treatment, quality of life, quality of care, and morbidity. Surveillance must also integrate information on health care providers, health systems, cancer communities, and policy into local and regional databases. We must develop research tools that track cancer trends more completely and precisely. We must change the way we make surveillance data available electronically to ensure privacy and confidentiality. We need new modeling techniques to help us explain trends across the full range of concerns about cancer. We need geographic information systems to study data on individuals in relation to potential environmental exposures. We must refine maps to allow easier appli-

cation of statistical analyses for measuring patterns and identifying clusters. And, we must strengthen dissemination of surveillance data to scientists, the public, and policy makers in a timely manner and in a readily usable format.

## PROGRESS TOWARD MEETING THE CHALLENGE

The NCI has worked with many partners to *build a broader surveillance program* that is easily used for cancer research, planning, and health policy decisions. We have expanded SEER (see Spotlight on Research, p. 38) and made other important improvements.

We have augmented our data collection on risk, health behaviors such as smoking and diet, and screening. For example, we have collected nationwide tobacco tracking data and conducted an in-depth evaluation, through the Cancer Research Network, of tobacco control activities conducted within medical practices across the United States. We have enhanced dietary data collected by the National Center for Health Statistics. These modifications help us track progress made towards achieving the Healthy People 2010 nutrition objectives relevant to cancer control. We released a survey of cancer risk, health behaviors, and screening conducted in collaboration with the National Center for Health Statistics in the fall of 2001. This provides data for tracking progress in cancer control health practices, genetic testing issues, and other cancer-related health objectives. We also have linked mammographic screening data in diverse communities to cancer outcomes to provide national measures of mammography performance.

NCI has added to its research on the adoption of new advances in cancer risk assessment, screening, and treatment and how their use impacts the lives of patients. For example, a completed national survey on

### G O A L

Expand cancer surveillance to improve monitoring of progress in cancer control and explain potential causes of cancer across all populations.

## THE PLAN — STUDYING EMERGING TRENDS IN CANCER

### Goal

Expand cancer surveillance data systems, methods, communications, and training to improve capacity for monitoring progress in cancer control and to explain potential causes of cancer nationally and among diverse populations.

### Objectives and Milestones for Fiscal Year 2003

1. Improve cancer registry data by expanding Surveillance, Epidemiology, and End Results (SEER) coverage, improving the quality of all population-based cancer registries, and enhancing SEER as a research resource. \$4.0 M
  - Refine and harmonize 4 new expansion registries added to SEER to meet data quality standards and use the data for reporting and for cancer control activities. \$2.00 M
  - Implement and improve SEER quality assurance procedures and use of data quality profiles. \$0.50 M
  - Increase coordination of Federal cancer registry programs through innovative information technology systems for SEER programs. \$0.75 M
  - Support innovative statistical survey research methodology and models for combining data from diverse sources of the evolving national cancer surveillance data. \$0.75 M
  
2. Expand systems and methods to enhance the quality of cancer control data on risk, health and behaviors, and screening practices linked to high quality data on cancer outcomes. \$10.7 M
  - Continue the Current Population Survey (CPS) Tobacco Use Supplements. (See page 84, Objective 1.)
  - Improve data quality and measurement of key cancer issues in national and regional data systems. Initiate data tracking systems for cancer control and treatment drugs and for over-the-counter prescription drugs and complementary and alternative therapies. \$1.50 M
  - Support development of a restricted access research data center required for linked databases containing potentially identifiable information. \$1.00 M
  - Continue supporting surveillance screening initiatives. \$3.00 M
    - In collaboration with the Agency for Healthcare Research and Quality, develop a surveillance and behavioral colorectal cancer screening initiative to raise levels of compliance with screening and monitor performance in primary care practices.
    - Explore data systems to monitor the use and side effects of spiral computed tomography for lung cancer screening and the role of Pap smears versus Human Papilloma Virus testing for cervical cancer screening.
  - Expand the Cancer Research Network as a population laboratory for evaluating progress in cancer control and care within integrated health care delivery systems. \$0.50 M

<ul style="list-style-type: none"> <li>■ Collaborate with private and public partners to facilitate transition for obtaining cancer stage and care data that is not currently part of routine cancer registration. \$1.00 M</li> <li>■ Update linked databases for tracking cancer care, such as the linked SEER-Medicare database, and develop new linked databases related to cancer control and treatment at the population level for people under age 65. \$0.70 M</li> <li>■ Use statistical and methodological research to add to the accuracy and reliability of cancer relevant measures — including self-report and various behavioral determinants — for use in surveillance and epidemiologic research. \$2.00M</li> <li>■ Develop statistical and graphical methods, software applications, and other technologies relevant to geospatial<sup>1</sup> and mapping research. \$1.00 M</li> </ul>	\$2.5 M
<p>3. <b>Expand systems and methods to enhance exploration of causes of cancer, generate new hypotheses on risk, and identify new opportunities for cancer control interventions.</b></p> <ul style="list-style-type: none"> <li>■ Encourage use of the NCI <i>Atlas of Cancer Mortality</i> and other population-based data systems.</li> <li>■ Provide critical tools for cancer control, especially at the community level in three ways. \$2.00 M               <ul style="list-style-type: none"> <li>■ Develop a Web-based Internet lecture series on use of Geographical Information Systems (GIS) and other data sources.</li> <li>■ Work with the National Science Foundation on use of geographical data.</li> <li>■ Develop software for visualizing disease patterns and advancing use of disease-exposure GIS applications.</li> </ul> </li> <li>■ Support workshops and pilot studies on enhancing surveillance systems for research in gene-environment interactions and identifying the potential for cancer control interventions at the population level. \$0.50 M</li> </ul>	\$3.5 M
<p>4. <b>Improve dissemination of information on cancer trends and progress in cancer control and care to all interested audiences. Enhance training opportunities in surveillance, health services, and applied research.</b></p> <ul style="list-style-type: none"> <li>■ Continue to strengthen local and national surveillance data dissemination for research and health policy planning, applying information technology to boost visual quality, user interaction, and clarity for a diverse audience. \$2.00 M</li> <li>■ Continue the NCI <i>Cancer Progress Report</i> as a vehicle for disseminating summaries of cancer progress, including new measures and a 2003 feature on dissemination of cancer treatment advances. \$0.50 M</li> <li>■ Support training of state health department and American Cancer Society personnel in using surveillance and intervention evidence data in cancer control planning.</li> <li>■ Fund existing surveillance and applied research networks and consortia to conduct intensive training programs, provide sabbatical opportunities for research professionals, and initiate and develop academic curricula. \$1.00 M</li> </ul>	\$2.0 M
<p>Management and Support</p>	\$22.7 M
<b>Total</b>	<b>\$22.7 M</b>

<sup>1</sup> Geospatial is a statistical term referring to information associated with a geographic location, features (such as health care systems), and boundaries (such as cities and states) as well as selected attributes. Attributes in this case would refer largely to cancer surveillance data.

colorectal cancer screening practices among 2,212 physicians helps identify potential targets for improving compliance with recommended screening. A national physician survey on cancer susceptibility Testing explored comfort with and use of genetic susceptibility testing among 1,250 physicians.

We have evaluated the use of many new treatment advances highlighted by successful clinical trials, NIH consensus development conference reports, and NCI clinical alerts. For example, patterns of care studies are drawing from SEER registry data to study adoption of recommended treatments for breast and colon cancer. These ongoing studies and the **Cancer Care Outcomes Research and Surveillance Consortium** are expected to provide the basis to evaluate cancer treatments, quality of care, and their effect on quality of life and other patient-centered outcomes. We have also supported projects focused on the economics of cancer and on using claims data for evaluation of cancer health services.

NCI scientists have also been using modeling to study the impact of interventions on cancer trends

at state, local, and national levels through support of the **Cancer Intervention and Surveillance Modeling Network (CISNET)**. CISNET modeling explores the causes of cancer incidence and mortality trends, analyzes whether recommended interventions are working, predicts the impact of new interventions, and studies optimal control strategies. As requested through state health departments and American Cancer Society (ACS) divisions, and in collaboration with the Centers for Disease Control and Prevention (CDC) and ACS National, we are building relationships between cancer control planners and CISNET to model the impact of disseminating effective interventions on cancer trends.

We have strengthened our research among cancer survivors, assessing lifestyle and quality of life in relation to treatment and survival. A seminal workshop co-sponsored by public and private organizations examined the role of physical activity across the cancer continuum. An NCI-funded study investigated lifestyle factors among ethnically diverse breast cancer survivors.

## SPOTLIGHT ON RESEARCH

### SEER Increases Coverage and Forms Partnerships

NCI expanded its Surveillance, Epidemiology, and End Results (SEER) program in 2001 to improve surveillance coverage of the full spectrum of the U.S. population. New coverage in four states increases overall surveillance from about 35 million to over 65 million people and improves coverage of several populations that were previously underrepresented including ethnic minorities, low-income Whites in rural areas and other areas of high poverty, and regions with high cancer death rates.

Several partnership activities with state registries, which capture a wealth of information not directly covered by SEER, have also broadened SEER surveillance. For example:

- NCI, CDC, and the State of California collaborated to plan specialized cancer control strategies geared toward reducing the local cancer burden. They used a survey to collect health data and local health systems and policy measures from diverse ethnic, social, and cultural communities in California. This standardized data can be used in developing local

cancer control programs and will allow comparison with national cancer control data, providing insight into the direction of future cancer trends.

- NCI, CDC, and other partners are working to establish guidelines that address the technical difficulties of sharing such as differences in the types of data each registry collects and how the data is stored. Simpler, standardized rules will enable better comparability among data sets and increase opportunity for collaboration.
- NCI is working with others to develop computer applications that will be able to pool and analyze data from multiple cancer registries and disseminate the findings to the cancer community.

The more we can share surveillance data among state and national agencies and the more data we can amass through broader coverage of the U.S. population, the better picture we will have of the cancer burden in the U.S. and the better equipped we will be to find ways to reduce that burden.

To better track emerging trends in cancer and apply the data to reduce the national cancer burden, we have been providing new tools for exploring patterns and generating hypotheses for research which examines the causes of cancer. The Geographic Information Systems (GIS) for cancer control, already used for database storage and mapping in conjunction with the *Atlas of Cancer Mortality* in the United States ([www.nci.nih.gov/atlasplus/](http://www.nci.nih.gov/atlasplus/)), have been upgraded for use as an analytical tool via two major additions.<sup>2</sup> The Geographic-Based Research in Cancer Control and Epidemiology, supports use of the *Cancer Atlas* and GIS among other applications. A collaboration with the National Science Foundation supports development for better visualization of data.

Cancer Profiles, an advanced statistical system for identifying areas in greatest need of cancer control activities, is being constructed in collaboration with CDC and other partners. The Web-based design will allow people who plan, implement, and evaluate cancer control programs to identify regions matching user-specified comparison criteria. The system will provide high quality data that relate the effects of physical and social environments to cancer trends.

Analytic tool kits, accessible on the Web, make SEER and other surveillance databases easier to use and provide innovative statistical measures as well as improvements to existing measures.

To communicate and promote the use of important information about cancer trends, NCI has been improving dissemination and use of data resources and methods.

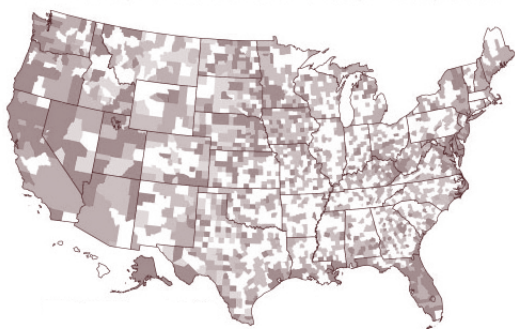
NCI is examining the use of workshops to teach researchers how to use and apply surveillance tools and data. Topics might include using analytic methods for complex medical claims data in the SEER-Medicare Linked Database and exploration of innovations in statistical methods.

We are collaborating with public and private partners to organize and streamline data collection, statistical methods, and reporting processes. For example, a major international publishing company is helping to make a “core engine” that can be used online to retrieve cancer statistics. The Breast Cancer Surveillance Consortium and the Breast Imaging Reporting and Data System Committee of the American College of Radiology are streamlining and standardizing data collection instruments and software systems to enhance the research potential of national mammography screening data.

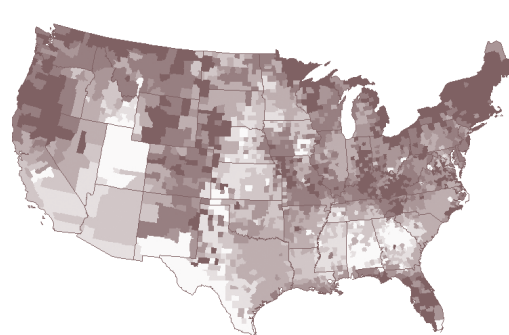
NCI published the *Cancer Progress Report* in December of 2001 ([progressreport.cancer.gov](http://progressreport.cancer.gov)) to inform the public, advocates, and other health professionals of progress in the Nation’s fight against cancer, using information drawing on recent surveillance research.

<sup>2</sup> While the *Atlas of Cancer Mortality* shows geographic patterns of cancer death rates and makes it easy to uncover patterns. GISs provide tools for exploring patterns and generating hypotheses.

Cancer Mortality Rates for White Females. Lung, Trachea, Bronchus, and Pleura. 1970-94



Proportion of Women Who Ever Smoked Cigarettes 1992-98



Cancer mortality maps viewed alongside maps showing incidence of smoking can provide clues to researchers working to solve the puzzle of what causes cancer and its relationship to tobacco use.



# Quality of Cancer Care

## THE CHALLENGE

About nine million Americans living today have had a diagnosis of cancer, and another 1.3 million will be diagnosed in 2001. Of these, a large percentage are undergoing active treatment for their disease, and all require life-long quality care to detect and treat recurrences, new cancers, treatment side effects, and to meet their supportive care needs. In 2001, direct medical care costs attributable to cancer will exceed \$50 billion. The toll in human pain, suffering, and fear cannot be captured in dollars, but will be keenly felt by the millions of people touched by cancer.

The quality of cancer care is a major national concern. Evidence suggests that some patients with cancer do not receive the newer, more effective treatments. Moreover, in some cases, there remains substantial disagreement or uncertainty about what constitutes optimal care, especially from the patient's perspective. This was underscored by reports from the Institute of Medicine's National Cancer Policy Board — *Ensuring the Quality of Cancer Care and Improving Palliative Care for Cancer* — and by the President's Cancer Panel meetings held across the country to explore why not all Americans get the best available cancer care. Clearly, too many patients face significant financial and other barriers to obtaining appropriate and timely care. But even as society wrestles with how to make health care more accessible to more people, it is critically important to advance a comprehensive research agenda that includes finding ways to improve the quality of the cancer care, as well as deepening our understanding of factors that impede access.

To meet this research challenge, we must:

- Define a core set of cancer outcome measures to enhance our ability to compare interventions across studies and over time. Chosen measures must be patient-centered, acceptable to providers and payers, span the continuum of care from pre-

vention to treatment and post-treatment care, including palliative care, and meet the highest technical standards.

- Define a core set of process measures to identify those interventions that have been convincingly shown to improve cancer care outcomes. Process measures are focused on how care is delivered in comparison with accepted standards.
- Build a stronger data and methods “infrastructure” for conducting quality of care analyses, including studies to determine which interventions improve patient-valued outcomes, identify geographic or racial/ethnic variations in receipt of quality care, and monitor quality over time, both at the individual and population levels.
- Ensure that therapies shown to be effective in clinical trials are incorporated into community practice.
- Enhance the quality of cancer communications by gaining a better understanding of the information needs of patients, families, and other decision makers involved in the choice of cancer interventions.

### G O A L

Enhance the state of the science on the quality of cancer care and inform decision making on care delivery, coverage, and regulation.

## PROGRESS TOWARD MEETING THE CHALLENGE

The following are examples of some specific research activities underway related to key elements of NCI's quality of care research plan.

### Developing Core Measurements

#### Outcome Measures

Identifying clinical and patient-centered endpoint measures that are valid, reliable, sensitive, and feasible for use in quality of care studies is critical if these studies are to appropriately inform decision makers. In response, NCI has convened the Cancer Outcomes Measurement Working Group — 35 internationally recognized experts in measurement,

oncology, and the social sciences — to assess the strengths and limitations of alternative approaches to measuring health-related quality of life, economic burden, and satisfaction with care for the major cancer sites and for every phase of cancer care, and to make recommendations about core measures for use across studies.

A set of papers reviewing and analyzing the published literature in cancer outcomes research over the past decade will be published as a monograph of the *Journal of the National Cancer Institute* in early 2002. This monograph will critically appraise the current and potential use of cancer outcome measures across a broad array of applications — from national level surveillance, to the evaluation of prevention and treatment interventions in trials or observational studies, to monitoring the progress of individual patients undergoing cancer treatment. The monograph focuses not only on the most prevalent adult cancers, but also the special challenges in measuring and monitoring the outcomes of care for childhood cancer patients and survivors.

### **Process Measures**

For some elements of cancer care, there is such strong evidence linking provider and health services performance to better outcomes that providing such care is presumed to enhance quality. Identifying a body of core process measures of cancer care quality is an important element for ongoing and future research to monitor the performance of providers and health systems. To move this effort forward, NCI is working closely with the **National Quality Forum (NQF)**, created recently to foster voluntary consensus standards on the quality of health care, focusing on treatment, survivorship, and palliative care. NCI has actively collaborated with a number of Federal agencies and private-sector organizations to assist the NQF in shaping the objectives, agenda, framework, and timeline, as well as to provide financial and technical assistance.

### **Strengthening the Science Base**

NCI's **Surveillance, Epidemiology, and End Results (SEER) program**, a well known and highly respected surveillance system, continues to provide a wealth of information to the private and public research enterprise on the cancer burden, as well as data resources for assessing the impact of research advances on cancer outcomes. **SEER Pattern of Care Studies** are ongoing investigations to monitor the diffusion of cutting-edge interventions into community practice,

with special attention to population disparities in the receipt of cancer care. Benchmark studies from 1987 to 1995 on patterns of care for patients with breast and colorectal cancer will be published in 2001.

The **Prostate Cancer Outcome Studies (PCOS)**, initiated in 1994, have extended our ability to understand treatment patterns by collecting information directly from patients and their physicians, as well as data from medical records, for more than 3,500 men diagnosed with prostate cancer and followed for up to 5 years. Results from a PCOS study looking at health outcomes after radical prostatectomy or radiotherapy for clinically localized prostate cancer show that rates of impotence are high among men receiving radical prostatectomy (79 percent) and radiation (62 percent). Among the men ages 55 to 59 years, the prostatectomy patients were more bothered by loss of sexual function than were the radiotherapy patients. Also, men in the radical prostatectomy group recovered some urinary and sexual function during the second year after treatment, while men in the radiotherapy group remained the same or slightly worse. PCOS results also are providing information on racial and ethnic differences in advanced-stage prostate cancer.

The approach of using large cohorts of newly diagnosed cancer patients to study treatment patterns and monitor the quality of care, has been extended to the study of colorectal and lung cancers. NCI is providing support for research teams across the country under the sponsorship of the **Cancer Care Outcomes Research and Surveillance (CanCORS) Consortium**. CanCORS will support the development and application of an expanded set of core process and outcome measures and will examine methodological issues in outcomes research conducted in community settings. The potential value of such large cohort studies for quality assessment is being increasingly recognized within the oncology community. For example, the American Society of Clinical Oncology has launched such a study, focusing on breast and colorectal cancer, as part of its **National Initiative on Cancer Care Quality**.

Studies linking **SEER and Medicare data** are also extremely useful to the research community and other stakeholders assessing the quality of cancer care. A study looking at age and adjuvant chemotherapy use following surgery for colon cancer reports that more than 70 percent of colon cancer patients age 65-74 initiated postoperative chemotherapy during the period 1991-1996. However, rates of use declined

## THE PLAN — QUALITY OF CANCER CARE

### Goal

Enhance the state of the science for defining, measuring, monitoring, and improving the quality of cancer care, and inform both public- and private- sector decision making on cancer care delivery, coverage, regulation, and standards setting.

### Objective and Milestones for Fiscal Year 2003

1. Develop core process and outcome measures for assessing the quality of cancer care. \$2.5 M
  - Support research to improve the theory and practice of patient-centered outcomes measurement in cancer, including the development and testing of new instruments, item banking, and computer adaptive testing to improve the efficiency and accuracy of data collection as well as statistical studies to facilitate the “cross-walking” of scores between competing instruments. \$1.50 M
  - Continue to participate in and provide supplemental funding for the National Quality Forum in order to identify core process measures of cancer care quality. \$1.00 M
  
2. Strengthen the methodological and empirical foundations of quality of cancer care assessment. \$8.0 M
  - Sustain support at \$7.5million per year for Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) studies of dissemination of state-of-the-science therapies and palliative care into community practice, the influence of modifiable risk factors, and disparities in the delivery of quality cancer care.
  - Sustain support for Cancer Research Network population laboratories for cancer control research, with additional emphasis on studies of the quality of cancer care in community settings. (See page 36, Objective 2.)
  - Sustain support for Surveillance Epidemiology and End Result program (SEER) pattern of care studies to produce regular and timely information on levels, trends, variations, and dissemination of treatments of proven efficacy and effectiveness. Integrate results from these studies with Cancer Intervention Surveillance Modeling Network (CISNET) models to predict effects of treatment dissemination on population trends in cancer survival and mortality. (See page 38.)
  - Increase support for analyses of the SEER-Medicare database to investigate the diffusion and outcomes of selected cancer interventions. \$2.00 M
  - Support the creation of databases that link tumor registry information with private payer administrative data to expand capacity to investigate whether cancer interventions are reaching and improving the health of individuals under age 65. \$2.00 M
  - Continue support for innovative research on economic and health care delivery system determinants of quality of cancer prevention, screening, and treatment services at the community level. \$2.50 M
  - Sponsor new studies to strengthen the methodological foundations of outcomes research and quality of care assessment. \$1.50 M

<p><b>3. Enhance quality of care research within the NCI clinical trials program.</b></p> <ul style="list-style-type: none"> <li>■ Sponsor a symposium and follow-up workshop to bring together leading researchers, patient advocates, and the relevant Federal agencies to assess the current state of the art, identify key research questions, and develop a decision strategy for encouraging comprehensive assessment of patient outcomes for clinical trials. \$0.50 M</li> <li>■ Using knowledge gleaned from a workshop on the determinants of diffusion of medical innovations, expand support for studies of diffusion patterns and the overall diffusion rates of important clinical trial findings into community practice. \$0.50 M</li> </ul>	<p><b>\$1.0 M</b></p>
<p><b>4. Improve the quality of cancer care by strengthening the quality of cancer communications.</b> (See Cancer Communications Opportunity, pages 88-92.)</p> <ul style="list-style-type: none"> <li>■ Assess the current status of cancer communications.</li> <li>■ Support the Centers of Excellence in Cancer Communications Research.</li> <li>■ Create new communications products for cancer care decision making.</li> <li>■ Convene an interdisciplinary group of scholars, organization gatekeepers, and funders to identify research strategies and opportunities for collaboration.</li> </ul>	
<p><b>5. Ensure that the best available scientific evidence about quality measures and assessment informs Federal decision making on cancer care. Share new knowledge with public and private partners on ways to translate quality of care research into better medical practice. Collaborate with these partners to identify core measures of cancer care quality.</b></p> <ul style="list-style-type: none"> <li>■ Continue to support interagency demonstration projects organized through the Quality of Cancer Care Committee, a forum for coordinating Federal activities to improve the quality of cancer care.</li> <li>■ Capitalize on the collective clinical and policy expertise of the QCCC to provide technical assistance and advice to public agencies and private organizations upon request.</li> </ul>	<p><b>\$2.0 M</b></p>
<p>Management and Support</p>	<p><b>\$0.5 M</b></p>
<b>Total</b>	<b>\$14.0 M</b>

markedly for older patients, even after adjusting for measures of comorbidity. Also, African American patients were found to be less likely to receive chemotherapy than Whites, even among patients with no major comorbidities. Further investigation is necessary to determine whether patient preferences, physician attitudes, or other factors in the health care system explain the care patterns.

In an effort to develop analogous information and data on patients under 65 years of age, NCI has been working with managed care systems to promote collaborative cancer research. Through the **Cancer Research Network (CRN)** initiative, a consortium of researchers affiliated with 10 major not-for-profit HMOs is conducting studies of late-stage breast and invasive cervical cancer cases to identify patient, provider, and system factors that affect advanced disease.

### **Enhancing Quality of Care Research within the NCI Clinical Trials Program**

The NCI clinical trials program provides an ideal venue to assess quality of care by incorporating valid, reliable, quality-of-life endpoints into clinical study design. NCI staff are working with clinical trials investigators around the country to assist them in decisions about the appropriate inclusion of quality-of-life endpoints in NCI-sponsored trials.

### **Improving the Quality of Cancer Care by Strengthening Cancer Communications**

Ultimately, improved cancer care depends on our ability to translate messages about prevention, treatment, patient care, survivorship, and end-of-life issues to the research community, providers, patients, and payers. As part of NCI's investment in Cancer Communications as an Extraordinary Opportunity, several efforts already underway focus directly on the quality of cancer care. (See pages 88-92.)

## **Ensuring the Best Available Scientific Evidence To Inform Federal Decision Making on Cancer Care**

In 1999, the Department of Health and Human Services created the Quality of Cancer Care Committee (QCCC), a trans-agency task force with representatives from Federal agencies involved in cancer care delivery, coverage, regulation, and research. The QCCC, currently chaired by NCI, was created on the principle that Federal-level decisions about cancer care should be consistent with the best scientific evidence available on quality outcomes. NCI is working directly with:

- **The Department of Veterans Affairs**, on the Quality Enhancement Research Initiative Center, to promote the use of evidence to foster better patient outcomes and promote ongoing system wide improvements in detection and treatment of colorectal cancer.
- **The Centers for Medicare and Medicaid Services**, on a project to improve the quality of cancer care by increasing colorectal cancer screening rates within the Medicare beneficiary population and their primary care physicians in North and South Carolina.
- **The Health Resources and Services Administration (HRSA) and the Centers for Disease Control and Prevention**, on a project to improve cancer screening, referral, and follow-up in Federally supported primary care health clinics. One objective of this project is to reduce health disparities for the underserved population cared for by HRSA-supported community health centers throughout the United States.
- **The Food and Drug Administration**, in an effort to determine the benefit of selected endpoints, including clinically oriented and patient-reported outcomes, to help judge drug efficacy and health marketing claims. The aim is to understand the value added — in terms of information important to patients and other decision makers — from using measures of health-related quality of life in addition to, or instead of, symptom-based indicators of patient status and improved survival.



# Reducing Cancer-Related Health Disparities

## THE CHALLENGE

The unequal burden of disease in our society is a challenge to science and a moral and ethical dilemma for our Nation. Cancer-related health disparities occur among all people. This is because cancer develops due to a combination of factors related to genes, individual behaviors, and social and environmental circumstances. The interaction among these determines who is born healthy, who grows up healthy, who sustains health throughout his or her life, who survives disease, and who maintains a good quality of life after diagnosis and treatment.

NCI-supported research has helped us make enormous strides in understanding how biological and behavioral factors determine risks for developing or dying from cancer and how interventions can modify these risks. We know much less, however, about the effects of social position, economic status, cultural beliefs and practices, and environmental exposures on cancer risk. Further research is needed for us to separate myth from reality and explain the relative importance of these social, cultural, and environmental determinants of cancer, how they interact with biological and behavioral determinants, and by what mechanisms they may increase cancer incidence and mortality and contribute to disparities in cancer incidence, prevention, care, and outcomes.

## PROGRESS TOWARD MEETING THE CHALLENGE

As a result of external and internal reviews of cancer health disparity issues and research programs, NCI is working in several high priority areas to better understand the relationship between what we know about cancer care and how and to whom it is provided.

- NCI-sponsored Special Populations Networks for Cancer Awareness Research and Training

(SPNs) were established at 18 research institutions in 2000 to build relationships with community-based programs, foster cancer awareness activities, increase minority enrollment in clinical trials, and develop junior biomedical researchers in minority and underserved communities.

In the first year of this program, each SPN has (1) developed new culturally and educationally appropriate cancer awareness campaigns focused on African American, Asian American, Pacific Islander, Latin American, Native American, and low-income Appalachian white populations and (2) built collaborative, community-based infrastructures for cancer control research.

Fourteen of the SPNs have worked to increase the competitiveness of junior and minority investigator-initiated research applications submitted for peer review by participating in developmental research grant programs sponsored by NCI.

- Two new series of cancer patient education materials for low-literacy populations focus on information in two areas important to these groups, pain management and clinical trials. The clinical trials series was created specifically for African American and Native American groups.
- NCI collaborated with two Minority-Serving Institutions to increase access to and involvement in clinical trials by underrepresented populations, minority researchers, and patients and physicians. NCI provided support for the development of culturally appropriate patient education materials and for clinical trials data management.
- NCI is focusing increased attention on how best to translate research into improved outcomes for all populations. NCI leadership helped organize the Department of Health and Human Services (DHHS) task force on the dissemination of health promotion and disease prevention interventions.

### G O A L

Understand the causes of cancer health disparities and develop effective interventions to reduce or eliminate them.



## THE PLAN — REDUCING CANCER-RELATED HEALTH DISPARITIES

### Goal

Understand the causes of health disparities in cancer and develop effective interventions to reduce these disparities.

### Objectives and Milestones for Fiscal Year 2003

1. Create and implement a comprehensive plan for NCI activities in health disparities research, education, training, and health services support. \$4.5 M
  - Expand the capacity of the NCI Center to Reduce Cancer Health Disparities to support NCI health disparities research opportunities. \$2.00 M
  - Disseminate findings on the relationship between disparity factors and cancer care including the cost of untreated cancer to society, the cost/benefit of extending Medicare coverage to cancer patients without insurance, and the influence of the concept of race on scientific inquiry. \$1.50 M
  - Further develop and implement NCI's integrated low-literacy program by customizing materials with cultural and language appropriateness for different audience groups. \$1.00 M
  
2. Improve capacity and accelerate knowledge through fundamental cancer control and population research. \$12.5 M
  - Establish Centers for Population Health and Cancer to:
    - Expand understanding of the social and environmental determinants of cancer and the psychosocial, behavioral, and biologic factors that mediate them.
    - Develop hypotheses for cancer control research at social, institutional, and policy levels.
    - Develop, apply, and evaluate interventions to improve cancer outcomes and reduce outcome disparities. \$8.00 M
  - Expand epidemiologic investigations to explore racial and ethnic cancer disparities with a focus on cancers for which these disparities are greatest (e.g., breast, cervix, kidney, prostate). \$1.50 M
  - Support research on the biologic variability in cancer in terms of tumor aggressiveness, differential response to therapy, genetic polymorphism, and psychoneuroimmunologic factors as mediators of social environment. \$2.00 M
  - Build on findings from the Prostate Cancer Outcomes Study to examine risk factors associated with late-stage disease — lifestyle, biological and clinical characteristics, and access to care — while accounting for state-of-the-art measures of socioeconomic status. \$1.00 M
  
3. Expand our ability to define and monitor cancer-related health disparities. \$3.5 M
  - Develop new data collection methods for socioeconomic and cultural factors including measures, data sources, and data linkage. \$1.00 M
  - Examine informed consent provided with prostate cancer screening and treatment in different age, race-ethnicity, and socioeconomic groups as a measure of quality of care in situations where there is uncertainty about the efficacy of interventions. \$1.00 M

- Conduct methodological evidence-based research to ensure that survey, epidemiological, and clinical research involving cancer risk factors exhibits cross-cultural equivalence. \$1.00 M
  - Enhance use of the NCI Cancer Progress Report ([progressreport.cancer.gov](http://progressreport.cancer.gov)) process to monitor health disparity reductions and reach Healthy People 2010 goals. \$0.50 M
- 4. Expand cancer control intervention research in prevention, early detection, treatment, and communications. \$7.5 M**
- Expand the developmental research grant support for the Special Populations Networks for Cancer Awareness Research and Training program. \$2.00 M
  - Collaborate with the Centers for Disease Control and Prevention to support new intervention research on barriers to screening for women who underuse or never use breast and cervical screening and on sociocultural determinants in planning, implementing, and evaluating these interventions. \$3.50 M
  - Develop formal affiliations between NCI Cancer Centers and Minority-Serving Institutions. (See page 26, Objective 1.)
  - Provide supplemental funding to Cancer Centers for health disparities research that will reduce the heaviest cancer burdens among disadvantaged populations and address disparities in risk factors, access to prevention interventions (e.g., smoking cessation, dietary change, physical activity), quality cancer care, and clinical trials. \$2.00 M
- 5. Reduce outcome disparities in special populations by increasing access to state-of-the-art clinical trials in cancer prevention and treatment. \$6.5 M**
- Expand Clinical Trials Outreach Programs to increase participation by underrepresented populations, establish clinical trials units at minority-serving medical institutions, and strengthen clinical trials units at minority-based community oncology sites. \$3.00 M
  - Increase clinical trials participation by implementing an NCI fellowship training program for healthcare providers and forums for minority scientist input into the development of clinical trials that address issues of special importance for minority and special populations. \$1.00 M
  - Use the radiation oncology-based Cancer Disparities Research Program to expand clinical research infrastructure in communities with disproportionate cancer-related health disparities and examine novel approaches to more closely link these groups with cancer researchers. \$2.50 M
- 6. Expand the channels for research dissemination and diffusion. \$5.5 M**
- Expand support for advanced training of state health department staff and American Cancer Society volunteers in best practices for using surveillance and intervention evidence data in comprehensive cancer control planning. \$2.00 M
  - Establish and maintain local and regional partnerships to understand and overcome cancer control infrastructure barriers that contribute to health disparities. Establish new comprehensive cancer control program initiative with the Washington, D.C. Department of Health. Develop and demonstrate approaches for bringing the latest interventions in cancer screening, care, and treatment, including access to clinical trials, to Native American populations through national and regional Indian health boards, tribal organizations, the Indian Health Service, and established Native American investigators. \$1.50 M
  - Fund supplements to NCI research grants for dissemination of evidence-based interventions specifically aimed at reducing health disparities. \$2.00 M

7. Expand minority investigator competition for and minority population involvement in health disparities research.	\$11.2 M
<ul style="list-style-type: none"> <li>■ Recruit two additional minority scientists and physicians to the Cancer Prevention Fellowship Program to specifically focus on health disparities research. \$0.50 M</li> <li>■ Fund 30 new cancer education grants for the continuing education of healthcare providers, outreach and education programs in underserved and minority communities, and the accrual of minority and underserved populations to NCI-sponsored treatment and prevention trials. \$9.00 M</li> <li>■ Develop community-based participatory research in cancer control through partnerships among NCI-funded Comprehensive Cancer Centers, Special Populations Networks, and Minority-Serving Institutions. \$1.00 M</li> <li>■ Further expand underserved and minority-based clinical investigator training under the radiation oncology-based Cancer Disparities Research Program. \$0.70 M</li> </ul>	
Management and Support	\$1.5 M
<b>Total</b>	<b>\$52.7 M</b>

Through collaboration with the American Cancer Society (ACS) and the Centers for Disease Control and Prevention (CDC), NCI has contributed to the training of state health department staff and volunteers from 17 divisions of ACS in best practices for using data to improve cancer control planning. We also have worked with the CDC to develop a targeted dissemination plan for evidence-based cancer control interventions to be included in the *Guide to Community Preventive Services*.

NCI has worked with the Agency for Healthcare Research and Quality and CDC to promote the adoption of best practices for clinical and public health approaches to tobacco control. The Institute is working with the ACS and NCI-funded researchers to disseminate a dietary intervention through faith-based organizations, tested with NCI 5-A-Day research grant support, and

found to be effective in two studies conducted among six African American churches in North Carolina and Georgia. Working with ACS regional and African American church volunteers, NCI is supporting dissemination research of a unified *Body and Soul* program in nine matched pairs of African American churches in three regions, and ACS will provide sustained support for the intervention.

- NCI is providing training for new scientists focused on health disparities through the Cancer Prevention Fellowship Program and the Special Population Networks for Cancer Awareness Research and Training (SPNs). Opportunities for new scientists include working through the NCI-funded Latin American Cancer Research Coalition SPN and working closely with investigators in new prevention and control programs targeted to African American men.

## Highlights of Recent Research on Cancer Related Health Disparities

**Treatment Disparities for Lung Cancer Related To Surgical Practices.** An NCI-funded study found that the lower survival rate among African American patients with early-stage, non-small-cell lung cancer, as compared with White patients, is largely explained by the lower rate of treatment through surgery among African Americans. This study of 10,984 patients 65 years of age or older, of whom 860 were African American and 10,124 were non-Hispanic White, showed that:

- The rate of surgery was 12.7 percentage points lower for African American patients than for White patients (64.0 percent versus 76.7 percent).
- The 5-year survival rate was also lower for African Americans (26.4 versus 34.1 percent).
- For patients who had surgery, survival was similar for the two racial groups.
- For patients who did not have surgery, survival was also similar.

Study results suggest that increased use of surgery for African American patients would improve survival.

### **Unnecessarily High Cervical Cancer Mortality Must Be Addressed.**

Research is needed to determine why, despite a three-fold reduction in cervical mortality nationwide in the past 50 years, counties stretching from Maine southwest through Appalachia to the Texas/Mexico border as well as in many Southeastern states and in the Central Valley of California have experienced persistently higher cervical cancer mortality rates. To address this 50-year disparity for a cancer from which no woman in this Nation should die, NCI and its national, state, and local partners are working to: (1) synthesize research knowledge, (2) identify core findings, (3) articulate program and policy options, and (4) disseminate this information to Federal, state, and local policy makers.

### **HPV Clinical Trials Expected To Help Improve Control of Cervical Cancer.**

Comprehensively controlling the human papillomavirus (HPV) would virtually eliminate cervical cancer, which disproportionately affects economically and socially disadvantaged women around the world. For the past 2 years, NCI has been following the medical condition of more than 5,000 women in Guanacaste, Costa Rica, who are enrolled in a randomized clinical trial to evaluate HPV DNA testing and visual and automated cytology techniques and determine the optimum strategy for managing low-grade cervical abnormalities. An HPV vaccine trial to compare the efficacy of two vaccines developed by NCI also is underway in Costa Rica. From 15,000 to 20,000 women will be invited to participate in the trial, which is expected to run for the next 8 years.

### **Cancer Survivorship in Minority and Under served Addressed by Cancer Centers.**

Investigators at NCI-supported Comprehensive Cancer Centers are using supplemental funding to examine:

- The physical and psychosocial needs of medically underserved cancer survivors and/or their families and how these needs compare with those found in cancer survivors and/or their families from majority populations
- Sociocultural variables that affect cancer survivorship, particularly those that affect quality of life
- The nature and effectiveness of existing post-treatment medical and support services designed for cancer patients from underserved communities
- The effectiveness and feasibility of behavioral measures and interventions aimed at assessing and reducing secondary physical and psychological consequences for minority or underserved cancer survivors and their families

See also page 92 for a report on the Digital Divide Pilot Projects initiative through the Cancer Communications Extraordinary Opportunity.

# Informatics and Information Flow

## THE CHALLENGE

Informatics involves the use of information technology to integrate and make available emerging biomedical information. NCI needs innovative informatics systems to ensure that the flood of information stemming from scientific discovery is available to those who need it. For example, the approximately 30,000 genes within the human genome along with millions of possible variations have been mapped and made available to cancer researchers. Furthermore, a number of genes can be expressed differently among thousands of different cancers. To add to this information, the number of drugs targeted to interact with certain genes and related proteins is multiplying every day. Other areas of cancer research are generating a comparable avalanche of information. NCI's challenge is to develop systems to effectively integrate and share this knowledge.

We envision meeting this challenge with a Cancer Informatics Infrastructure (CII) composed of three interrelated components.

- The first is a knowledge management core that works to standardize information and data use by all NCI programs.
- The second consists of information technology tools which link to the core and allow the capture, analysis, application, and re-use of information.
- The third component is the experts from diverse areas of scientific research, including informatics, who apply these tools to problem solving in cancer research and care.

The CII will create electronic interfaces reaching and connecting the entire cancer research community. Strategic partnerships with commercial, academic, and other governmental groups will broaden the base of interoperable<sup>1</sup> tools, data, and infrastructure. Scientists

must broker the application of this infrastructure in all fields of cancer research. We must ensure that the infrastructure can evolve to reflect the ever-changing research landscape and provide for cross-training of scientists who will bridge the gap between the informatics and biomedical research communities. The efficient, comprehensible, and easy access to varied collections of cancer knowledge will dramatically improve the rapid translation of research observations into clinical and public health interventions.

## PROGRESS TOWARD MEETING THE CHALLENGE

### GOAL

Create an informatics infrastructure that enhances information and resource exchange among researchers.

The NCI has made much progress in creating and implementing its informatics system. Our progress includes the following important achievements.

### Standards-Based Knowledge Management

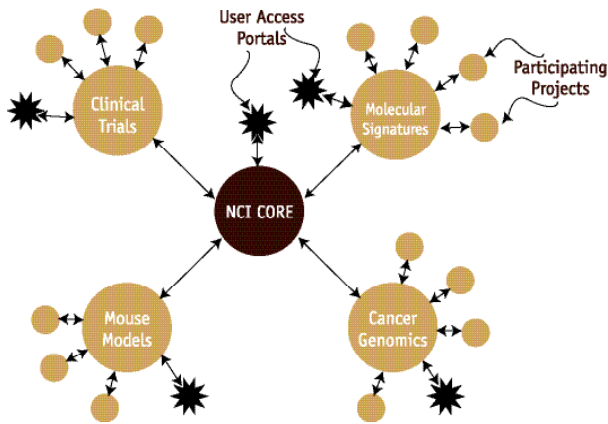
NCI's Center for Bioinformatics (NCICB) ([ncicb.nci.nih.gov](http://ncicb.nci.nih.gov)) was established in 2001 to ensure that diverse databases can be used together seamlessly, making data maximally accessible and easy to use. The Center provides standardized bioinformatics support and integration to allow for the smooth progression of investigative efforts from the level of molecular biology and molecular genetics through pre-clinical animal modeling to the informed design of clinical trials.

To ensure that the needs of the cancer community are recognized in the standards-setting process, the NCICB has joined several national standards groups. We are building a repository to comprehensively store the data used by our programs in adherence with the international standards used by many other Federal organizations. This keystone effort will ensure that all data from NCICB supported programs can be easily

<sup>1</sup> In an interoperable system, diverse individual components are made to communicate with one another and to function as a common database.



## NCI's Center for Bioinformatics



shared, whether from clinical trials, animal model programs, basic research, or any other discipline. We are also creating a unified national repository of health-related data needed for efficient sharing. Regular seminars keep NCI and the public up to date on developments in informatics techniques, practices, and standards.

Through the NCICB, NCI has developed and put into use *common data elements* — standard ways of referring to scientific phraseology — for several cancers, and has provided electronic interfaces among our cancer research communities for information exchange. For example, the NCI Enterprise Vocabulary System (EVS) serves our science communities by organizing and translating their respective distinct, but overlapping terminology. One database is used for translating among vocabularies used in different scientific specialties, and another builds a common vocabulary. Other EVS services support easy, user-friendly access to diverse collections of cancer information.

Four inter-related research initiatives supported by the NCICB represent key areas of knowledge in cancer research. The Center supports and integrates the efforts of these initiatives with one another and with the larger cancer community.

- NCI's new clinical trials infrastructure has increased information sharing among many clinical trials and with other types of research efforts and has helped researchers organize and launch clinical trials faster and run them more efficiently.
- The Cancer Genome Anatomy Project (CGAP) informatics team has made dramatic strides in making genomic data from the broader scientific community easily available to cancer researchers

in a format familiar to them, integrating genetics information not easily accessible elsewhere.

- The Mouse Models of Human Cancer Consortium (MMHCC) informatics team has been instrumental in providing critical information and tools to MMHCC researchers and quickly integrating the results of MMHCC efforts for use by the cancer community.
- The Director's Challenge — Towards a Molecular Classification of Cancer was issued by the NCI Director in 1998 to stimulate the use of molecular technology for classifying tumors based on distinguishing molecular characteristics. The success of this effort is dependent on NCI's informatics tools and the flow of standardized information to and from other NCI initiatives and the greater research community.

## Cancer Informatics Tools

NCI's informatics tools are promoting the efficient and safe delivery of effective cancer agents to the American public. Business support tools have been implemented to **streamline procedures and processes in the clinical trial system**. This effort has dramatically reduced the administrative burden on researchers and permitted stable staffing requirements in the face of increasing, sometimes doubling, workloads.

NCI has developed informatics tools to ensure clinical trial safety. Our standardization of business rules and toxicity terminology has improved reporting and assessment of previously unknown or severe toxicities from NCI-supplied investigational drugs. Success was such that the oncology community has asked that the improvements be applied to non-NCI cancer agents and to other research areas.

NCI is developing integrated informatics to promote scientific planning. These tools are flexible and scalable to help databases remain current as new therapies and further advances in cancer biology are discovered. These tools are applied in numerous areas of research from refining sophisticated cancer agents based on their mechanisms of action and planning their clinical use to reallocating staff to areas of scientific importance and recruiting minority participants into clinical trials.

NCI is focusing on all aspects of software development for **scientific management systems**. We have introduced a process to manage all phases of NCI

## THE PLAN — INFORMATICS AND INFORMATION FLOW

### Goal

Create a cancer informatics infrastructure that enhances information and resource exchange and integration among researchers working in diverse disciplines, to facilitate the full spectrum of cancer investigations.

### Objectives and Milestones for Fiscal Year 2003

1. Through the NCI Center for Bioinformatics (NCICB), expand NCI's backbone informatics infrastructure to enable support and integration of NCI-supported basic, clinical, translational, and population research initiatives. \$49.0 M
  - Expand the NCICB to provide additional support, enhance integration of data and development of tools emanating from NCI's Extraordinary Opportunities. Facilitate information exchange within and between NCI-supported research initiatives. Support the Cancer Molecular Analysis Project's specialized bench-to-bedside information integration and display. \$29.00 M (See page 72, Objective 1)
  - Establish a toolbox of open-source<sup>2</sup> informatics applications and services based on a common set of operating principles and standards that support NCI's diverse cancer research activities. \$5.00 M
  - Develop a research infrastructure that uses a "standards stack," assembling common vocabulary, standard data elements, and information models to further the exchange of all types of cancer information and data among the cancer community. \$5.00 M
  - Expand information technology-based support services to enhance planning, execution, and communication of the wide-ranging research portfolio supported by NCI. \$10.00 M

<sup>2</sup> With "open source" software, the computer source code may be copied and/or modified.

<sup>3</sup> Plug-and-play means that the hardware or software does not have to be configured, but can be used immediately upon installation.

## SPOTLIGHT ON RESEARCH

### CGAP Is a Gateway to New Exploration and Discovery

NCI's Cancer Genome Anatomy Project (CGAP) was established in 1997 to determine the gene expression profiles of normal, pre-cancer, and cancer cells and to provide public access to this information for all cancer researchers. The project is now providing a wealth of human and mouse genomic data, informatics tools to query and analyze the data, information on methods, and access to biologic materials developed through the project. With public data and analysis tools, researchers can now find "in silico" answers to biological questions in a fraction of the time it used to take in the lab.

Researchers have started mining the CGAP databases (at [cgap.nci.nih.gov](http://cgap.nci.nih.gov)) and are discovering new potentially cancer-causing genes, identifying candidates for molecular targeting research, and helping to build microarrays for cancer cell signature research. For example:

- Because cancer is such a complex disease, finding the many cancer-causing genes involved and understanding their role is crucial to developing new treatments to combat the disease. Cancer researchers in collaboration with CGAP, examined the expression of more than 24,000 genes in the oxygen-deprived (hypoxic) cells of glioblastoma multiforme, a form of brain cancer. They identified ten genes believed to play a significant role in allowing this tumor to thrive under hypoxic conditions. Scientists are working to find the function of these genes with the long-term goal of developing targeted inhibitors that may be used in formulations against the cancer.
- Until recently, diffuse large B-cell lymphoma (DLBCL) had been traditionally classified as a single cancer, but patients suffering from this disease show diverse responses to

<p>2. Create a community matrix of interoperable data sources, analytic tools, and computational resources that provide an extensible plug-and-play <sup>3</sup> informatics capability for the cancer research community .</p> <ul style="list-style-type: none"> <li>■ Expand the informatics capacity of the larger cancer research community with partnerships to develop a standards-compliant infrastructure that can be used readily in conjunction with NCI applications and each partner's information systems. Establish a minimum of five academic, government, and commercial strategic partnerships in a research park setting where all partners can work together to address bioinformatics questions. \$15.00 M</li> <li>■ Use a minimum of 20 investigator-based awards that build on the NCI informatics backbone to 1) deploy the standards-based resources to the cancer research community to serve as the foundation for additional infrastructure and 2) facilitate rapid deployment of related new research initiatives. \$10.00 M</li> </ul>	<p>\$25.0 M</p>
<p>3. Expand the cancer research community's capacity to perform informatics research on a local institutional basis.</p> <ul style="list-style-type: none"> <li>■ Establish a network of bioinformatics research centers to work with and through the NIH Biomedical Informatics Science and Technology Initiative, using a novel interdisciplinary management team to select and coordinate the centers. \$5.00 M</li> <li>■ Expand standards-compliant institutional infrastructure by providing infrastructure supplements to NCI-supported research organizations, supporting the growing need of investigator-initiated research to access state-of-the-art biocomputing tools and data. \$10.00 M</li> <li>■ Promote informatics training by encouraging recruitment of new scientists and cross training in a variety of life science research domains through 20 development and transition awards. \$3.00 M</li> </ul>	<p>\$18.0 M</p>
<p>Management and Support</p>	<p>\$3.0 M</p>
<p><b>Total</b></p>	<p><b>\$95.0 M</b></p>

chemotherapy. Only 40% of patients respond well to treatment, while the remainder succumb quickly to the disease. Using CGAP data, NCI and NCI-supported scientists developed a microarray called a *lymphochip* that contained 18,000 genes, which included those preferentially expressed in lymphoid cells as well as in cancer and the immune system. The expression analysis showed that DLBCL can be categorized into two distinct classes that broadly correlate with the clinical outcomes.

These results have already begun to contribute to our goal to improve detection, diagnosis and treatment of cancer. Since these discoveries come from early application of CGAP resources, CGAP's impact on the future of cancer research and clinical advances promises to be substantial.

software development from start to finish. This project maximizes the effectiveness of the spectrum of NCI resources, including information flow, human resources, grant management, and space management.

### **Informatics for Cancer Research and Care**

Net-Trials™ is a Web-based clinical trials information system that supports every aspect of the trial, including information management, data analysis, and secure Internet access allowing real-time collaboration of multiple centers. Net-Trials™ streamlines operations and improves data quality, patient safety monitoring, and analysis of much larger groups of data across the entire clinical trials portfolio. Still under development, Net-Trials™ is being used by at least six clinical branches of NCI's Center for Cancer Research and has been piloted at several sites outside NCI's intramural program.

## Cancer Research Training and Career Development

### THE CHALLENGE

Training and career development for the next generation of scientists remains one of our most important challenges. The scientists of the future will need to be more versatile in their use of new technologies, able to work in teams to understand the complicated environmental, lifestyle, genetic, and molecular variables contributing to human cancers, and better prepared to translate discoveries into public benefit. We need to implement and sustain multiple long-term strategies to attract the most talented individuals to cancer research. We need to create a stable cadre of well trained technical, biological, behavioral, medical, and public health scientists dedicated to the cancer research enterprise, who can and will work together.

Our success will depend on our ability to move beyond traditional educational and research cultures, overcome health financing constraints, and address socioeconomic inequities that have proven to be barriers to progress in the past. The theme for the future is to train scientists to work on problems as integrated, multidisciplinary teams.

To meet these challenges, we must continue to implement training and career development strategies to address a number of crucial issues.

- We need to more adequately prepare basic scientists and offer them more attractive career paths by providing the background to conduct cancer research and preparing them to collaborate on multidisciplinary research teams. Increasing trainees stipends to levels more reflective of their education and skills will help ensure that careers in basic science will continue to remain attractive.
- It is critical that we reverse the migration of talented and creative physicians from research to practice. This is the single most threatening consequence to cancer research from the shifting economics of the health care system. We need to use

more effective means to train clinical investigators and ensure they have protected time to conduct research that will translate basic discoveries into better methods for cancer prevention, diagnosis, and treatment. Intensive training and education are necessary to guarantee informed consent and provide maximum safety for patients participating in research.

- We need to increase the numbers and stabilize the careers of cancer prevention, control, population, behavioral, and public health scientists.

The discoveries of scientists dedicated to prevention, early detection, behavior modification, and risk factor analysis will have a major impact on reducing future cancer incidence and mortality. We must develop better ways to train these scientists to function in interdisciplinary research settings and work effectively with patient-oriented and basic scientists. We also must provide these scientists with protected time in which to conduct research.

- We need a research community that is ethnically and racially diverse. These scientists must be sensitive to the factors that lead to disproportionate cancer incidence and mortality and prepared to conduct research to help overcome the cultural and socioeconomic barriers responsible for the unequal burden of cancer.
- We must attract and integrate technical and informatics experts into cancer research. Specialists in these disciplines will provide a critical driving force for future progress.

### G O A L

Prepare a stable, diverse cadre of scientists to work together and use technologies for building knowledge and translating discoveries into application.

### PROGRESS TOWARD MEETING THE CHALLENGE

The NCI is employing a variety of individual and institutional training and career development awards to meet the needs of new and established investigators and NCI's anticipated research priori-

ties. We have focused increased resources on career tracks for M.D.s in cancer research, behavioral and population scientists, minority scientists, and scientists in highly technical fields important to the future of cancer research.

NCI gives **individual awards** to scientists at various stages in their careers.

- **Individual National Research Service Awards** continue to provide a stable cadre of well trained basic scientists. Many of the awards NCI makes through this program are for postdoctoral fellowships, which allow new Ph.D.s an opportunity to begin the transition to becoming independent investigators.
- **Individual mentored 5-year awards** provide special opportunities for M.D.s in basic or clinical research and for individuals pursuing cancer prevention, control, behavioral, and population science. Interest in these awards has increased dramatically over the last 2 years, resulting in a three-fold increase in the number granted – evidence of both the need for and effectiveness of these programs.
- **Bridging awards** encourage basic and minority scientists to pursue careers in cancer research. These awards require recipients to undertake mentored and independent research, providing them protected time to develop independent research programs. These special bridging awards have increased steadily since their inception 5 years ago and are on target for achieving their strategic objectives.
- **Transition awards** provide for 3 years of protected time for people completing mentored postdoctoral training or for new investigators to initiate successful research programs. These awards are now in place for NCI's two most critical areas of need: MD's in basic and clinical research and population scientists. A new transition award is now available for minority scientists. Because we have not been able to achieve our targeted objectives for these awards during their first few years, we are taking new measures to increase their accessibility and attractiveness.
- **Established investigator awards** provide seasoned investigators in the clinical sciences and in cancer prevention, control, behavioral, and population sciences protected time to conduct research and mentor new scientists. The number of these awards has increased since their introduction, and their avail-

ability appears to be helping to curtail the migration of physicians from research to patient care.

- **New diversified sciences career development awards** attract technology developers and scientists in disciplines not traditionally associated with cancer research but clearly needed for the future.

**Institutional awards** are 5-year awards for developing and conducting training and career development programs. These awards achieve special goals by establishing specific requirements and assembling mentors whose skills support program objectives.

- **National Research Service Awards**, NCI's mainstay for training basic scientists, include special provisions for curricula and research environments that expose all trainees to cancer-related opportunities and important new research approaches of the future.
- **Institutional Clinical Oncology Career Development Programs** prepare the next generation of clinical scientists to design and implement hypothesis-based clinical trials and to collaborate with basic scientists. There are now nearly 20 of these programs in place throughout the nation.
- **Institutional Education and Career Development Programs**, initiated in 2000, prepare participants for multidisciplinary team research settings. This program is proving to be extremely successful in stimulating new, forward-looking training programs in prevention and control, imaging sciences, outcomes research, and molecular pathology.
- The **Continuing Umbrella of Research Experiences Program** engages minority high school and undergraduate students and provides them with assistance through all stages of training and career development needed to become independent investigators.
- **Minority Institution/Cancer Center Partnerships** have the potential to link over 300 Minority-Serving Institutions<sup>1</sup> with NCI Cancer Centers to increase the number of minority students in cancer research; strengthen the research capabilities of minority institutions; reduce cancer incidence and mortality in minority populations. Several comprehensive partnerships are now operating, and many are in the planning stages.

For more information on these programs and career tracks, go to [cancer.gov/cancertraining](http://cancer.gov/cancertraining).

<sup>1</sup> Colleges and universities whose enrollments include a significant proportion of students from minority groups that are underrepresented in science



## THE PLAN — CANCER RESEARCH TRAINING AND CAREER DEVELOPMENT

### Goal

Build a stable, racially and ethnically diverse cadre of basic, clinical, behavioral, and population scientists trained to work together effectively and to use the most advanced technologies in building our knowledge base and in translating discoveries into more effective cancer prevention, detection, diagnosis, and treatment strategies.

### Objectives and Milestones for Fiscal Year 2003

1. Continue to provide training, career development opportunities, and protected research time to developing and established cancer scientists. \$18.0 M
  - Maintain a stable National Research Service Award (NRSA) program to train pre-doctoral and post-doctoral basic scientists through traditional institutional and individual awards. Increase the stipends of trainees by 10 percent in order to make research careers more attractive. \$3.00 M
  - Continue to increase the participation of clinically trained individuals in basic and in patient-oriented research by funding 20 new individual mentored awards, 20 new transition awards, and 10 new established investigator awards. \$7.00 M
  - Expand the number of well trained population, behavioral, and public health scientists in cancer research by funding 20 new individual mentored awards, 15 transition awards for junior independent scientists, and 10 awards to established investigators. \$5.00 M
  - Expand the role of the NCI Intramural Program in training extramural investigators by funding five additional trainees in the NCI Scholars Program and by creating two new intramural training and career development programs that partner and network with extramural institutions and focus on underdeveloped areas that can benefit by integrating sparse resources (e.g., radiation oncology, informatics, prevention). \$3.00 M
  
2. Continue to provide and refine special training and career development opportunities that prepare new and established scientists to function in collaborative, team research settings and that integrate new technical disciplines into the cancer research enterprise. \$18.0 M
  - Increase the number of basic scientists who focus on human cancer research and who can collaborate effectively with clinical and population scientists in translational research by funding 30 new special bridging career awards. \$4.00 M
  - Fund five new Institutional Clinical Oncology Career Development Programs to prepare clinically trained individuals to become expert in all aspects of clinical trials design and implementation as well as effective partners of basic scientists in moving discoveries in the laboratory to improved clinical tests and therapies. \$3.00 M
  - Implement 10 new Institutional Career Development Programs for training scientists for highly complex interdisciplinary team research settings. \$5.00 M

<ul style="list-style-type: none"> <li>■ Support five new individual Diversified Sciences Career Development Awards to attract new disciplines (e.g., physics, engineering, informatics) into multidisciplinary cancer research settings. \$1.00 M</li> <li>■ Expand and initiate career development opportunities in highly specialized interactive, translational, and research consortia and networks (e.g., Specialized Programs of Research Excellence, Imaging Centers, Tobacco and Tobacco-Related Centers) that are accessible to new and established investigators. \$5.00 M</li> </ul>		
<p>3. Expand programs to recruit, train, and sustain underserved racial and ethnic minority individuals in cancer research and provide partnership opportunities for training and career development.</p> <ul style="list-style-type: none"> <li>■ Expand the Continuing Umbrella of Research Experiences (CURE) Program by: adding 50 trainee positions on institutional NSRAs; providing new supplemental funding to 10 cancer centers for high school and undergraduate student research experience; adding 10 minority training positions in Clinical Oncology Career Development Programs; funding 10 new positions for Cancer Education and Career Development Programs in the population sciences; funding 50 new Minority Investigator Supplements to NCI research project grants; funding 20 new mentored career development awards for basic and clinically trained scientists; and funding 10 new Career Transition Awards for basic, clinical, behavioral, and population minority scientists in their first junior faculty positions. \$15.00 M</li> <li>■ Promote collaborations between scientists and educators in MSIs and in NCI-designated Cancer Centers through 15 planning grants for developing MSI/Cancer Center research training programs for minorities and outreach education programs for minority communities. \$3.00 M</li> <li>■ Increase minority access to training and career development opportunities by improving NCI Internet information services, establishing linkages between public and private agencies that provide related services, and establishing 20 new positions in NCI Cancer Centers that will “broker” the connections between minority individuals seeking research experiences and Cancer Center scientists. \$2.00 M</li> <li>■ Integrate the NCI CURE and Minority Institution/Cancer Center Partnership Programs more effectively into the Minority Biomedical Support Grant Program in the National Institute of General Medical Sciences.</li> </ul>		\$20.0 M
Management and Support		\$2.0 M
	<b>Total</b>	<b>\$58.0 M</b>

## Mouse Models of Human Cancers Consortium — Modeling Human Cancers in the Mouse

Animal models — laboratory animals that have specific characteristics resembling a human disease or disorder — play an invaluable role in cancer research. Technologies available today allow scientists to create animal models of cancer by transferring new genes into animals or inactivating certain existing genes. This makes the animals susceptible to specific cancers via the same genetic and environmental factors that affect humans. With these models, scientists can study the biological changes associated with every stage of tumor development, test new approaches to detection and diagnosis, and evaluate prevention and treatment strategies.

For a variety of reasons, mice are particularly well suited for cancer research. To start, mice and humans are similar in their genetic makeup and susceptibility to cancer. As a result, the development of tumors in mice largely parallels that in humans. Further, mouse tumors develop over the course of months rather than the years usually required for cancer to develop in larger animals and humans.

But the complexity of cancer makes the development of mouse models a far more challenging task for cancer than for some other diseases. Fortunately, cancer researchers today have a wide range of resources to bring to bear on this task. Scientists have access to increasingly detailed databases containing the details of mouse and human genes and a growing body of information on the molecular characteristics, or *signatures*, of tumors. This expanding knowledge — coupled with tools for modifying the genes of laboratory mice and a battery of tests to identify relevant cancer genes and proteins — ensure that cancer mouse models parallel the development, progression, and clinical course of human cancers.

To improve the pace and efficiency with which mouse models of cancer are developed and tested, and to ensure they are readily available to scientists, NCI created the **Mouse Models of Human Cancers Consortium** in late 1999 by funding 20 multidisciplinary groups of investigators. Consortium scientists are working to develop and evaluate mouse models for breast, prostate, lung, ovary,

cervix, pancreas, skin, blood and lymph system, colon, and brain cancers.

### How Mouse Models Are Advancing Cancer Research

Throughout the Consortium and in other NCI-supported laboratories, researchers are using mouse models to do the following: examine the interplay of genetic and environmental factors in cancer susceptibility; test novel approaches to detection, diagnosis, and imaging; and advance the use of genetically engineered mice for prevention, therapy, and population research.

Mouse models provide a unique opportunity to **explore how genetic and environmental factors interact** to give rise to cancer. With such models, scientists can test the effects of a particular chemical in a controlled environment using animals with a known genetic makeup. For example, researchers are using a recently developed mouse model of lung cancer to investigate the role that genetic factors play in determining why some smokers develop lung cancer and others do not. The model also is being used to test whether tobacco smoke accelerates tumor formation, and to define the genes that confer susceptibility to tobacco-related cancers.

Because samples of human cancers at their earliest stages can be difficult to obtain, mouse models also are **invaluable in cancer detection studies**. Tumors in these mice can be examined to verify the role that each genetic alteration plays in causing cancer and in its progression, and may also reveal changes informative to human cancer diagnosis or early detection. An example of this type of research is a newly developed mouse model that closely mimics inflammatory bowel disease, a condition associated with increased cancer risk. Researchers are using this model to test the effect of known and suspected causal factors — such as the *Helicobacter* bacteria — on the timing and severity of cancer. By taking biopsies at varying times after infection, they are looking for the earliest changes indicating increased risk for gastric, intestinal, or colon cancer.

Defining the changes associated with cancer is fundamental for successful early detection, as well as for finding potential targets for early intervention. Once these targets have been identified, scientists depend on mouse models to **test the efficacy of new drugs**, and to **understand why a drug does — or does not — work as expected**. Indeed, one of the most important roles of mouse models is in the development of drugs to treat cancer.

In one recent example of using mouse models to **test treatments**, investigators used a model of one type of childhood leukemia to help solve the mystery of why some children respond to the standard therapy of retinoids while others do not. As they studied the problem in the model, scientists discovered that the mice that did not respond to treatment had an unexpected gene rearrangement. With this information, the researchers then developed a new treatment that blocks the action of the rearranged gene. It was effective in combination with retinoids in mice, and these investigators are now assessing the combined treatment in childhood leukemia patients who do not respond to retinoid therapy alone. Models also are valuable for **studying a host of treatment questions**, such as determining mechanisms of drug resistance and defining new treatment targets.

With specialized equipment and techniques for imaging mice and other small animals, investigators are using mouse models to **explore improvements in cancer imaging and treatment** in order to determine whether anti-cancer drugs have reached their targets and to track response to therapy. Since 1999, much of this research has been fostered by Small Animal Imaging Resource Programs that NCI has established at a number of research centers around the country. (See page 67 for more information.)

As Consortium investigators develop more mouse models of cancer, collaborations between them and small animal imaging specialists are expected to grow. Already, Consortium scientists involved in developing mouse models for prostate cancer have teamed with colleagues from the NCI-funded Small Animal Imaging Resource Program to use positron emission tomography imaging to study prostate

cancer development, from its beginnings in the prostate to its metastasis (spread) to bones and other organs. Similarly, investigators testing mouse models of brain tumors are collaborating with small animal imaging experts to use magnetic resonance imaging to test approaches to gene therapy for brain tumors. Experiments of this kind are already revealing new avenues for human therapy.

## The Future of Mouse Models

If the research community is to employ mouse models to their greatest advantage, extensive collaborations are needed among those who can best inform the design of the models and their ultimate use in cancer research. NCI is facilitating the formation of collaborative groups — e.g., for ovarian, brain, pediatric, and pancreatic cancer modeling — to ensure rapid incorporation of human cancer research discoveries into mouse model design and application. With NCI's help to organize conferences and symposia, Consortium investigators are spearheading the dissemination of information about mouse engineering tactics, development of validation standards for cancer models, and the practical application of models to inform many aspects of cancer research.

The achievements of Consortium investigators and the need to deploy models to the research community prompted NCI to establish the Mouse Models of Human Cancers Consortium Mouse Repository ([web.ncifcrf.gov/researchresources/mmhcc/default.asp](http://web.ncifcrf.gov/researchresources/mmhcc/default.asp)), to which interested scientists are invited to contribute models. When it opened in February 2001, the NCI repository had three mouse strains available for distribution. The number of mouse models offered is expected to quickly increase, reaching at least 30 by early 2002. NCI will expand the repository in the future to accommodate the growing requirements of the cancer research community for well-designed and thoroughly tested mouse models. For more information about Consortium programs and projects, and access to its databases, go to [mmhcc.nci.nih.gov](http://mmhcc.nci.nih.gov).

# Extraordinary Opportunities for Investment

The NCI's "extraordinary opportunities for investment" are broad-based, overarching areas of scientific pursuit that hold tremendous promise for significantly expanding our understanding of cancer. With focused efforts and increased resources in these areas, we can build on past successes and technological breakthroughs to stimulate dramatic progress in addressing some of our most difficult questions. 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 impair our ability to find better ways to care for those whose lives are touched by cancer.

NCI seeks formal input from cancer experts representing a broad spectrum of perspectives to help identify these areas of exceptional promise. Every three years, we ask members of the research community, advisory groups, and advocacy organizations to revisit the "extraordinary opportunities" and recommend important areas of research into which additional resources should be infused over the next three-year

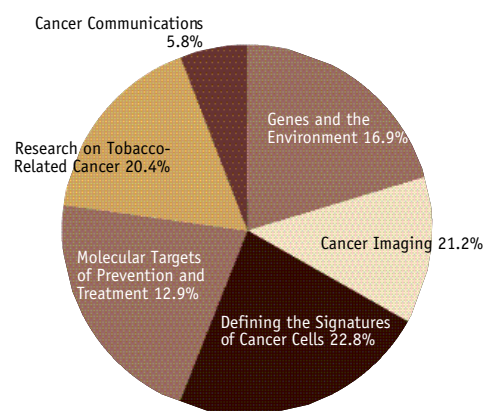
cycle. We thoroughly assess these responses, blend related ideas, and, with our advisors, select new investment areas. The current six extraordinary opportunities were first outlined in NCI's Fiscal Year 2001 budget proposal and are continued in this proposal for Fiscal Year 2003.

The purpose of the extraordinary opportunities is to identify areas of discovery that build upon important recent developments in knowledge and technology and that hold promise for making significant progress against all cancers. Extraordinary opportunities must involve approaches to cancer research beyond the size, scope, and funding of our current research activities, be implementable with specific defined investments, and be described in terms of achievable milestones.

The plans proposed for these extraordinary opportunity areas describe new research awards and new or expanded programs and collaborations intended to help improve the prospects for patients and survivors of all types of cancers.

## Extraordinary Opportunities 2003 Budget Increase Request (dollars in thousands)

Genes and Environment	\$55,500
Cancer Imaging	69,800
Defining the Signatures of Cancer Cells	75,000
Molecular Targets of Prevention and Treatment	42,500
Research on Tobacco and Tobacco-Related Cancers	67,000
Cancer Communications	19,050
<b>Total</b>	<b>\$328,850</b>





## Genes and the Environment

### THE OPPORTUNITY

As we better understand the interplay between inherited susceptibility to cancer and environmental risk factors, we will be able to develop more meaningful approaches to cancer prevention, early detection, and treatment. Until recently, we have pursued separate lines of inquiry for cancer genetics and environmental risk factors for cancer. As such, we have been able to identify some of the human genes that make people susceptible to cancer, to apply increasingly sophisticated molecular technologies to analyze genetic changes, and to examine the relationship between disease development and individual genetic profiles. We have learned about a variety of carcinogenic environmental factors not only in the outdoors but also in the home and workplace. These include pollutants in air, water, and soil; components of food, tobacco, alcohol, and drugs; sunlight and other forms of radiation; and infectious agents.

Early efforts to discover how genes and environmental factors interact to cause cancer are showing promise but also highlight the complexity of the puzzle. Some genes have proven to be so powerful that their presence in an individual makes cancer highly predictable. For example, carriers of the gene for Familial Adenomatous Polyposis are almost certain to develop colon cancer. But an inherited predisposition to other types of cancer requires other factors for cancer to occur, such as the presence of other genes or exposures to chemicals in the environment. For example, mutations in the susceptibility genes BRCA1 and BRCA2 are risk factors for breast cancer that may be related to a combination of factors. Similarly, some environmental exposures — tobacco use, for example — can be strong, but not certain, predictors of cancer.

NCI's opportunity is to uncover elements of the gene-environment interaction that can lead to tangible improvements in our ability to prevent and con-

trol cancer. For example, we expect to identify previously unsuspected carcinogens through the study of newly discovered genes that predispose people to cancer. We also want to learn how certain environmental exposures increase the cancer risk for genetically susceptible subgroups. When we can define the cancer risks associated with specific environmental and genetic factors and their interactions, we can develop new individual and public health strategies to avoid adverse exposures, check genetic susceptibility earlier, identify appropriate treatment regimes, and take special precautions for people at high risk.

To progress in this area, NCI needs to develop new ways to study cancer genetics, environmental exposures, and their interaction and to maximize the availability and use of large amounts of research data and other resources. Large-scale studies that require new levels of cooperation and innovation from the cancer community will be needed to achieve tangible improvements in medical practice and public health.

#### G O A L

Discover genetic, environmental, and lifestyle factors and their interactions that define cancer risk and inform strategies for cancer control.

### PROGRESS IN PURSUIT OF OUR GOAL

The NCI is pursuing research opportunities in five growth areas to better understand cancer-related genes, environmental factors, and their interaction. First, we are *building the capacity* to understand genetic variation, identify important biologic exposures, and explore the complex interaction among them through research collaborations with many partners.

- Investigators already involved in 15 separate prospective studies of large population groups are pooling high quality environmental exposure data along with tissue, blood, and other body fluid samples suitable for genetic analysis to form a combined study size of 700,000 participants, large enough to yield significant findings. Some members of this

## THE PLAN – GENES AND THE ENVIRONMENT

### Goal

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

### Objectives and Milestones for Fiscal Year 2003

1. Identify new environmental risk factors and susceptibility genes and determine their interactions in cancer causation. \$16.0 M
  - Utilize the unique advantages of the Cohort Consortium to investigate exposures best studied in large populations and their interactions with susceptibility genes.
    - Continue the five-center gene-environment risk factor discovery study of breast and prostate cancers while adding studies of other common cancer sites. \$3.00 M
    - Expand the number of participants, population diversity, and types of biospecimens. \$2.00 M
  - Support Case-Control Consortium investigators to address specific gene-environment interactions in detail. Establish formal resources for discovery efforts by initiating large population-based and hospital-based studies to develop comprehensive data and specimen resources by cancer site. Encourage use of the NCI Atlas of Cancer Mortality and other public use data systems (e.g. Long Island Breast Cancer Study) as source of study from high risk areas. \$4.00 M.
  - Continue improving infrastructure to meet the needs of large, collaborative human population studies.
    - Maximize the utility of specimen resources for human population studies with improved efficiency and cost-effectiveness of specimen collection, processing, storage techniques, and high-throughput assays. \$2.00 M
    - Continue developing informatics systems to capture, store, analyze and integrate the massive amount of information generated by these studies. \$3.00 M
    - Facilitate the use of new genomic technologies by funding supplements to existing gene-environment focused studies. \$2.00 M
  
2. Develop new ways to assess and measure environmental exposures for use in population studies. \$6.0 M
  - Support development of new methods for characterization of internal dose resulting from complex lifetime exposures. \$2.00 M
  - Continue expanding NCI's Innovative Molecular Analysis Technologies Program to develop new non-invasive techniques for collecting and measuring DNA and proteins in very small amounts of biologic material. \$2.00 M
  - Continue support for applying and validating measures of the cumulative cellular, genetic, and molecular effects of environmental exposure through funding supplements for ongoing research programs. \$2.00 M
  
3. Identify cancer-predisposing genes in high-risk families and investigate how other genes and environmental factors modify expression of these genes. \$8.0 M
  - Fund two new consortia of investigators to identify unknown cancer susceptibility genes (e.g., pancreatic cancer). \$4.00 M

<ul style="list-style-type: none"> <li>■ Support interdisciplinary studies for gene discovery and characterization for additional cancer sites by new collaborative family registry groups. \$2.00 M</li> <li>■ Support collection of fresh-frozen tumor tissue and other biospecimens from genetically cancer-prone families for microarray-based molecular signature analyses in NCI-supported large population research resources such as a Cancer Family Registry Web site. \$2.00 M</li> </ul>	
<b>4. Develop tools for the study of gene and environment interactions in human populations.</b>	<b>\$5.0 M</b>
<ul style="list-style-type: none"> <li>■ Extend the Genetic Annotation Initiative to identify new gene variants relevant to cancer in clinically and epidemiologically defined populations, and for various molecular applications. (See page 72, Objective 1.)</li> <li>■ Augment the Mouse Models of Human Cancers Consortium to more rapidly localize interesting genetic regions, increase the number of models for human hereditary cancer genes, decipher environmental factors that modify cancer development, and test biomarkers for early detection. \$2.50 M</li> <li>■ Provide the framework for productive use of genetically engineered mouse models to study human cancer genetics by integrating the study of mouse and human molecular genetics and by cataloging mouse single nucleotide polymorphisms to facilitate genotyping of commonly used mouse strains. \$2.50</li> </ul>	
<b>5. Support collaborative studies of high-risk individuals to address the clinical, behavioral, and societal issues associated with cancer susceptibility.</b>	<b>\$17.5 M</b>
<ul style="list-style-type: none"> <li>■ Sustain the Cancer Genetics Network (CGN) as a resource for studies of clinical care for early detection, diagnosis, and treatment of genetically high-risk individuals, including those from minority and underserved populations. \$10.00 M</li> <li>■ Expand support for studies in cancer genetics that examine psychosocial responses to cancer risk communication within average and high-risk populations in order to inform the development of effective educational strategies and resources for patients, providers, and the public. \$4.00 M</li> <li>■ Continue to support research in cancer survivorship to evaluate physiologic and/or psychosocial effects of cancer or its treatment among survivors of cancer, and examine the role of genetic factors in these sequelae. \$2.00 M</li> <li>■ Refine cancer risk prediction methods/models to integrate genetic and environmental determinants of cancer by developing methods to estimate individual risk. Merge models that are primarily genetic based with those that are primarily environmental. Refine models that predict cancer risk and other outcomes among diverse populations to estimate population burden and policy implications. \$1.00 M</li> <li>■ Collaborate with the Centers for Disease Control and Prevention Genomics and Public Health Centers to develop methodological standards specific to the collection and reporting of data from NCI consortia on gene-environment interactions, effectively relating these results to medical practice and public health. \$0.50M</li> </ul>	
Management and Support	\$3.0 M
<b>Total</b>	<b>\$55.5 M</b>

Cohort Consortium of investigators are involved in a collaboration to uncover gene-environment interactions by compiling and examining more than 7,000 cases each of breast and prostate cancer.

- Two other groups of investigators are using the case-control approach to identify genetic and environmental determinants of non-Hodgkin's lymphoma (NHL) and brain cancer. These Case-Control Consortia of investigators are pooling data from more than 5,000 patients with NHL and more than 3,000 with brain tumors.
- Two groups of researchers are partnering to collect high quality cancer registry data on environmental exposures of patients and a variety of biologic specimens from these patients for use in genetic analysis. These data and analyses will be compared with those of non-cancer patients, and the resulting information will serve as a resource for the research community in its search for susceptibility genes and environmental carcinogens.

Second, NCI is *examining a broad spectrum of approaches* to assess and measure environmental exposures.

- Non-invasive methods for detecting cancers, carcinogenic exposures, and genetic susceptibility can ease the stress on patients and make screening for environmental exposures and early signs of cancer more thorough and affordable. These methods also are well suited to use in large-scale research studies. Researchers are examining options that would allow doctors to detect cancer, carcinogenic exposures, or genetic susceptibility by screening for lung cancer using a molecular marker in sputum samples; sampling DNA from cheek cells; using saliva samples instead of blood to test for body nutrient levels, hormones, and environmental chemicals; or using urine samples to validate patient responses to questions about dietary habits.
- New and easier methods, such as biodosimetry and direct versus surrogate measures, may provide improved ways of assessing difficult-to-measure environmental exposures.
- Collaborative studies with the National Institute for Occupational Safety and Health are improving assessment measures for studying cancer resulting from exposure to low-dose radiation and agricultural pesticides. Sophisticated monitors designed for workers in specific occupations can be used in large groups of workers.

- Techniques using geographic information systems to support the Long Island Breast Cancer Study of complex toxicological and environmental exposures and breast cancer incidence can be applied to other areas of research as well.

Third, we are *advancing research to discover and characterize cancer predisposing genes* by building on NCI-supported cancer family registries and promoting collaborations among investigators who have studied large numbers of families with cancer.

- The Cancer Family Registry (CFR), a large international registry of more than 8,500 ethnically diverse families and 21,000 participants, focuses on highly penetrant breast and ovarian cancer genes by recording information on cancer family history, demographics, environmental and lifestyle risk factors, and clinical data and by maintaining a bank of biological specimens. The CFR is supporting several studies to provide the information needed to make prevention and treatment decisions. One such study examines the effects of hormones as well as diet, body size, physical activity, alcohol consumption, and radiation on breast cancer risk among carriers of BRCA1 and BRCA2 mutations.
- A second large resource, the Colon Cancer Family Registry, has assembled data on more than 5,000 families, including more than 150 families with hereditary non-polyposis colon cancer and more than 300 with two or more first-degree relatives who have the cancer.
- Other groups of investigators are working to discover and characterize highly penetrant familial genes associated with melanoma, ataxia telangiectasia, and prostate and lung cancers.

Fourth, NCI is *supporting the development of a number of tools for use in gene discovery and characterization*. These efforts are needed to advance our understanding of gene-environment interactions and the application of that knowledge.

- Through the Mouse Models of Human Cancers Consortium (MMHCC), scientists are capitalizing on the remarkable correspondence between the human and mouse genomes to identify human cancer-related genes and are facilitating rapid cancer gene discovery by adding mouse models of known familial cancer susceptibility genes. In collaboration with population scientists studying cancer families, MMHCC researchers applied a

new timesaving strategy of mouse cross-breeding to quickly pinpoint the BRCA1 breast cancer susceptibility gene. The mouse studies soon revealed the function of the gene and enabled scientists to verify its role in altering susceptibility to breast cancer. Furthermore, a model for the gene PTEN/MMAC1 may shed light on several types of cancer, including Cowden disease, a syndrome that predisposes family members to breast, brain, prostate, endometrial, and bladder cancers.

- NCI used a risk assessment model that combines several known risk factors in the Tamoxifen Breast Cancer Prevention Trial. The success of the model exemplifies how we can substantially increase our ability to predict breast cancer risk. Scientists have greatly expanded information on risk factors among African American women and are incorporating data from the Women's Health Initiative Trial. Using this Gail Model as a pattern, researchers are now constructing models for both ovarian cancer and colorectal malignancies built on pooled data from large multi-center studies.
- Through the efforts of the Genetic Annotation Initiative (GAI), the genetic information generated by the Cancer Genome Anatomy Project (CGAP) is being made available for research use. More than 30,000 gene-based polymorphisms – DNA variations among individuals – have been identified, and GAI scientists have established high-throughput laboratory assays to detect more than 7,000 of these variants. As with all of the CGAP resources, materials are available free of charge through the World Wide Web ([cgap.nci.nih.gov](http://cgap.nci.nih.gov)). Scientists can use these tools to investigate the roles of these genes in families and populations.

Fifth, NCI *has established a productive infrastructure to support intervention trials on inherited susceptibility to cancer.* Such trials are vitally important to improving our ability to detect and treat cancer earlier. Through the Cancer Genetics Network (CGN), researchers are conducting a number of these studies. (1) A pilot study of an early detection technique for ovarian cancer screening in genetically susceptible women involves a CGN partnership with several NCI-supported programs, including the Gynecologic Oncology Clinical Trials Group. (2) In another study, researchers are comparing the effectiveness of several existing biostatistical models for

estimating breast cancer risks. (3) Another group is developing innovative analytical methods to identify colon cancer genes that are as yet undiscovered. (4) A pilot study will improve methods for recruiting and retraining individuals and families at high risk of cancer into clinical trials. (5) Finally, a pilot collaborative is coordinating a multi-institutional study of genetic and environmental modifiers of cancer risk in women with BRCA1 and BRCA2 mutations.

To apply the latest findings in human epidemiologic and clinical investigations, the CGN is promoting active collaboration with the Mouse Models of Human Cancers Consortium, the Genetic Annotation Index, and the Cancer Genome Anatomy Project. In addition, CGN is collaborating with the NCI Special Populations Networks for Cancer Awareness Research and Training to ensure wider opportunities for people from diverse communities, including investigators representing those communities, to participate in research on genetic susceptibility to cancer.

### Environmental Exposures and Inherited Susceptibility in Cancer

Scientific studies point to three main categories of environmental exposures that contribute to the development of cancer.

#### Chemicals

- Chemicals in the diet
- Home or workplace exposures
- Drugs
- Pollutants in the air, water, or soil

#### Radiation

- Low strength radiation such as ultraviolet radiation from sunlight
- High strength radiation as from x-rays or radioisotopes

#### Viruses and bacteria

- Epstein-Barr virus — Burkitt's lymphoma
- Human papillomavirus — cervical cancer
- Hepatitis B virus — liver cancer
- Human T-cell lymphotropic virus — adult T-cell leukemia
- Kaposi's sarcoma associated herpes virus — Kaposi's sarcoma
- H. pylori bacteria — associated with stomach cancer

A person's chances of developing cancer can also be influenced by the inheritance of certain kinds of genetic alterations. Specific inherited mutations increase a person's risk of developing some cancers including breast, colon, kidney, bone, and skin. As we better understand the interplay between inherited susceptibility to cancer and environmental risk factors, we can develop more meaningful approaches to cancer care.



2

## 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. The normal course of events would be to order x-ray studies to find the tumor’s exact location, schedule the patient for surgery, excise a portion of the unhealthy tissue for biopsy, remove the tumor, and explore surrounding tissues to determine if the cancer had spread. But over the last quarter century, improvements in imaging technology have substantially broadened the range of medical options. With the power of imaging technology now available, physicians can get much clearer and more detailed pictures of organs and tissues, and they can view far more than anatomical structures such as bones, organs, and tumors. Using “functional imaging” for the visualization of physiological, cellular, or molecular processes in living tissue, physicians can examine activities such as blood flow, oxygen consumption, or glucose metabolism as they take place.

Modern imaging technology already has had lifesaving effects on our ability to detect cancer early and more accurately diagnose the disease. X-ray mammography, for example, has revealed the presence of very small cancers in thousands of women before the tumors could be detected by physical examination. And computed tomography (CT) can show if a tumor has invaded vital tissue, grown around blood vessels, or spread to distant organs. As the science continues to advance, we will be able to detect changes in the workings of a cell as it becomes malignant and use this information to diagnose cancer earlier.

Eventually, we may be able to detect changes in the activity and function of specific genes in a patient’s cancer cells, and use that information to choose the best treatment option. In addition to using CT and other imaging technologies to guide treatment choices, scientists have developed methods for combining imaging techniques with radiation

sources and high-performance computing. This serves to better target radiation treatments to a tumor’s three-dimensional contours, thus minimizing damage to surrounding, healthy tissue. Moreover, with today’s technology, we can also identify the molecular characteristics of a tumor and use that information to predict how it will respond to certain treatments. With a visual image of how glucose is being used in cancer cells, we can tell – without the need for a biopsy – how a tumor is responding to a recently administered treatment.

Oncologists also increasingly rely on image-guided therapy, in which imaging is combined with various tumor-killing approaches (toxic chemicals, gene therapy, heat, and cold). By allowing physicians to better distinguish between cancerous and normal tissue and target treatments to diseased tissues, image-guided therapy can minimize surgical trauma, shorten recovery time, improve patients quality of life, and reduce health care costs.

NCI’s opportunity is to further improve cancer imaging technologies with the goal of ensuring earlier and more accurate diagnoses for more cancer patients, reducing the number of invasive therapies needed to treat their illnesses, and improving physicians’ abilities to monitor patient responses to treatment. With investments in research and development, significant advances in cancer imaging are now possible and will ultimately save more lives.

**G O A L**  
 Accelerate discovery and development of imaging methods that will predict clinical course and response to interventions.

### PROGRESS IN PURSUIT OF OUR GOAL

Advances in cancer imaging research and technology over the last 25 years have demonstrated their potential to profoundly affect the practice of oncology and extend patients’ lives, and NCI’s continued investment is yielding further tangible progress in developing better imaging technologies for both cancer research and clinical practice.



## Developing Better Imaging Technologies and Techniques

NCI has played a major role in fostering molecular or functional<sup>1</sup> imaging. Through initiatives such as *In vivo* Cellular and Molecular Imaging Centers (ICMICs), NCI has nurtured and promoted molecular imaging by supporting essential infrastructure and providing career stability to investigators in this emerging field of research. Each Center brings together experts such as biomedical engineers, cellular and molecular biologists, pharmacologists, and imaging scientists to conduct a program of multidisciplinary research on cellular and molecular imaging in cancer.

One of the ICMICs has led the way in developing “smart contrast agents.” When smart contrast agents are injected into the body, they are undetectable. However, when they come into contact with tumor-associated enzymes called proteases, the smart agents change shape and become fluorescent. The fluorescent signal can then be detected using sophisticated imaging devices. This first generation of smart agents are being further refined and developed by ICMIC investigators and will have important applications in tumor detection and therapy assessment in the future.

At the start of 2000, NCI established ICMICs at three sites around the country. The Institute has also awarded planning grants to 16 universities and research centers to begin to bring together investigators from a range of fields and initiate research projects in molecular imaging. NCI will select two of these to become full-fledged Centers by the end of 2001. In addition to their research activities, ICMICs will train new investigators and provide established investigators an opportunity to develop a multidisciplinary understanding of imaging, the basic science of cancer, and cancer care.

NCI is also helping to foster the development of new imaging contrast agents and molecular probes to improve the diagnosis and treatment of cancer through the Development of Clinical Imaging Drugs and Enhancers (DCIDE) program. In the first year of DCIDE, two agents were selected for further development: (1) a new contrast agent that enhances positron emission tomography (PET) imaging by targeting elevated levels of an enzyme present in prostate and other cancers and (2) a probe that can improve the accuracy with which magnetic reso-

nance imaging (MRI) can reveal the earliest stages of the new blood vessel growth that accompanies a developing tumor.

Animal models of cancers play an invaluable role in research, enabling scientists to investigate the development and progression of cancer; test new approaches to detection, diagnosis, and imaging; and evaluate prevention and treatment. With improved, genetically engineered mouse models for cancer becoming more widely available, investigators are able to use laboratory mice to study the development and spread of cancer and to test improvements in cancer imaging through the use of specialized equipment and techniques for imaging small animals. Since 1999, NCI has funded Small Animal Imaging Resource Programs at five research centers around the country to make the necessary equipment and personnel available to investigators and to improve and enhance technologies and techniques for imaging small animals.

Investigators working with the Small Animal Imaging Resource Program at one university, for example, have been exploring the use of diffusion MRI, which measures the movement of water through and between cells for imaging brain tumors. After validating their approach in small animals, imaging specialists have begun to test this new form of MRI in patients with brain tumors and other cancers. Initial results in patients, especially children, look very promising. If proven effective, diffusion MRI could dramatically reduce the time required to determine whether cancer patients are responding to therapy.

Given the success of the Small Animal Imaging Resource Programs to date, NCI funded five additional programs in 2001. In addition, the Institute is actively working to foster broader use of these technologies. For example, NCI will co-sponsor a conference on the techniques of small animal imaging in September 2001, and has awarded supplemental funding to a number of scientists involved in the Mouse Models of Human Cancers Consortium to incorporate imaging research into their work.

NCI, with the National Science Foundation, is cultivating further advances in the development of noninvasive imaging, monitoring, and therapeutic systems, with two projects focusing on the development of miniaturized optical probes. These probes,

<sup>1</sup> Molecular imaging techniques do not actually reveal molecules themselves, but detect signals that indicate the presence of biochemical activity and changes, such as cell growth or death. Thus, molecular imaging is often described as “functional”, because the processes being imaged are active and constantly changing.

## THE PLAN — CANCER IMAGING

### Goal

Accelerate discovery, development, validation, and clinical feasibility of imaging methods to identify the biological and molecular properties of precancerous or cancerous cells that will predict clinical course and response to interventions.

### Objectives and Milestones for Fiscal Year 2003

1. Expand the discovery, design, and development of novel imaging agents and devices. \$25.1 M
  - Establish two additional *In Vivo* Cellular and Molecular Imaging Centers (ICMICs) to foster multidisciplinary research on cellular and molecular imaging in cancer. \$4.00 M
  - Establish a Network for Optical Technologies Development. \$4.00 M
  - Increase the number of imaging agents supported by the Development of Clinical Imaging Drugs and Enhancers Program from 6 to 10 per year. \$4.00 M
  - Use research supplements to increase collaborations between Small Animal Imaging Resource Programs (SAIRPs) and other NCI programs such as the Mouse Models of Human Cancers Consortium. \$2.00 M
  - Speed the development of specific imaging agents by funding grantees in a variety of NCI programs, such as ICMICs, SAIRPs, Interdisciplinary Research Teams for Molecular Target Assessment, Molecular Target Drug Discovery, and Molecular Target Laboratories. \$2.00 M
  - In collaboration with the developers, provide to academic institutions for feasibility testing, innovative imaging device prototypes, selected through a new competitive program, that have a limited market or face other barriers to commercialization. \$5.00 M
  - Support and add information to a publicly available database of imaging agents for the research community. \$0.10 M
  - Establish data banks of standardized digital image data (such as virtual colonoscopy, digital mammography, digital chest imaging, and optical imaging for applications such as cervical, prostate, and oral cancers) associated with known clinical outcomes to provide research resources for a variety of investigators. \$2.00 M
  - Fund six to eight grants to develop and test image processing and analysis algorithms (artificial intelligence) using these standardized data sets. \$2.00 M

which provide very high-resolution images, are capable of detecting changes at the molecular level.

### Bringing Advances in Imaging to Cancer Care

As new cancer imaging technologies and techniques emerge and are refined, they often undergo further evaluation through one of NCI's clinical trials cooperative groups. These are networks of health care professionals affiliated with medical schools, teaching hospitals, and community-based cancer treatment

centers. For example, NCI's newest cooperative group, the American College of Radiology Imaging Network (ACRIN), is assessing the value of computed tomography (CT) scanning in screening patients for colon cancer, a technique sometimes known as "virtual colonoscopy." Because patient cooperation is critical to the success of any type of cancer screening, another group of NCI-funded investigators is also looking at patient preferences as one component of their comparisons of virtual colonoscopy and more traditional methods of colon cancer screening.

<p><b>2. Integrate molecular and functional imaging methods into therapeutic clinical trials.</b></p> <ul style="list-style-type: none"> <li>■ Increase the contract support for early clinical trials of imaging agents (safety and efficacy studies) from 8 to 12 trials per year. \$2.00 M</li> <li>■ Provide expertise to clinical trials that use imaging by funding supplements or grants for 10 to 15 imaging cores within NCI-funded Cancer Centers. \$4.00 M</li> <li>■ Support expert panels to develop consensus criteria for using imaging results as endpoints in clinical trials. \$0.20 M</li> </ul>	<p><b>\$6.2 M</b></p>
<p><b>3. Increase clinical trials of imaging methods and technologies.</b></p> <ul style="list-style-type: none"> <li>■ Expand a large randomized clinical study of spiral computed tomography as a screen in the detection of lung cancer, if initial data show a larger study is needed. \$20.00 M</li> <li>■ Initiate clinical studies to: compare CT colonography (virtual colonoscopy) with endoscopic colonoscopy for early detection of colon cancer and polyps in a large multi-institutional setting; evaluate magnetic resonance spectroscopy for the early detection and assessment of prostate cancer; and evaluate the role of FDG-PET studies for monitoring tumor response to therapy. \$4.00 M</li> <li>■ Support corollary imaging studies, such as monitoring response to therapy, with 10 funding supplements to Clinical Trials Cooperative Groups. \$4.00 M</li> <li>■ Support the development of the tools and infrastructure for the use of functional and molecular imaging in conjunction with radiation therapy, using novel treatment approaches including intensity modulated radiation therapy. \$2.00 M</li> </ul>	<p><b>\$30.0 M</b></p>
<p><b>4. Accelerate the development and clinical testing of image-guided interventions.</b></p> <ul style="list-style-type: none"> <li>■ Use 6 to 10 funding supplements to enhance programs such as the SPOREs for image-guided therapy research that emphasizes a problem-solving, organ-specific approach and promotes interactions between clinicians and bioengineers. \$3.00 M</li> <li>■ Increase collaborations between the other Clinical Trials Cooperative Groups and the American College of Radiology Imaging Network (ACRIN) for testing promising, minimally invasive, image-guided interventions with four to six funding supplements. \$2.00 M</li> </ul>	<p><b>\$5.0 M</b></p>
<p>Management and Support</p>	<p><b>\$3.5 M</b></p>
<b>Total</b>	<b>\$69.8 M</b>

ACRIN investigators are also evaluating the use of CT, MRI, and traditional tests for determining the spread of cervical cancer. To definitively answer questions about the value of digital mammography for breast cancer screening, ACRIN investigators have launched the largest study ever to compare conventional and digital mammography. They plan to compare the two methods in nearly 50,000 women over the next few years.

At the same time, other NCI-sponsored networks are also evaluating the use of imaging technologies.

Another cooperative group, the **American College of Surgeons Oncology Group**, is actively studying the use of PET scanning in patients with lung and esophageal cancer, to determine how far the disease has advanced. In addition, investigators involved in the **Lung Cancer Screening Study** are comparing the use of spiral CT with traditional chest x-rays in screening for lung cancer. A number of other investigators

## Highlights of Recent Advances in Cancer Imaging

### **High-Powered Microscope Tracks Cell Changes.**

With funding from NCI, a multidisciplinary team of physicists, biologists, optical experts, and chemists has developed a new type of microscope combining the capabilities of nuclear magnetic resonance imaging with those of a traditional microscope. Using the combined microscope, investigators can examine how living cells react to changes in their environment, track the development of cancer, and study how cancer cells respond to treatment. In light of its potential significance for biomedical research, *Discover Magazine* recognized the new microscope and the leader of the research team that developed it with its 2001 Award for Technological Innovation in Health.

### **New Imaging Tools Provide More Accurate and Complete Diagnosis.**

Two groups of NCI-supported investigators working to improve cancer screening recently received Food and Drug Administration approval for computer-aided diagnosis systems to help radiologists assess the results of mammograms and chest x-rays. In these systems, computers are programmed to identify and highlight suspicious "hot spots" to ensure that all potentially cancerous points are examined.

### **Optical Biopsies an Option for the Future.**

NCI-funded scientists are developing imaging systems that may permit patients to undergo "optical biopsies" in the future and allow physicians to diagnose cancer without the need for tissue samples. By modifying endoscopes and similar instruments to provide very high-resolution images for examining the gastrointestinal system, lungs, and other internal organs, investigators can now identify the cellular changes typical of early cancer when it is most treatable. In cases where these more powerful images can rule out cancer, such optical biopsies will allow patients to avoid unnecessary and painful tissue biopsies.

around the country are working to improve diagnostic imaging and image-guided therapy for prostate cancer.

In addition to evaluating the use of various imaging technologies and screening and treatment procedures, NCI-supported scientists are using sophisticated imaging to assess the effects of new cancer drugs. For example, with many drugs that prevent the growth of new blood vessels, tumor shrinkage may not be readily apparent for some time. In cases such as these, functional imaging techniques can reveal whether the tumor is responding to therapy.

The integration of new imaging technologies in radiation oncology will not only improve the targeting of a tumor but will allow for the delivery of a more exacting radiation dose to areas within the tumor defined by functional imaging. This targeting has the potential to not only improve tumor control but also minimize toxicity. This complex technology requires enhanced treatment planning, quality assurance, and data transfer. NCI is supporting a consortium to develop the necessary tools through the **Advanced Technology Radiation Therapy Clinical Trials** program.

Biomedical opportunities and scientific advances drive technology development in cancer imaging, but NCI recognizes that the regulatory environment in which this development takes place is critically important. To facilitate the transition of emerging cancer imaging technologies into medical practice, NCI created and coordinates a "sounding board" of Federal agency staff that advises investigators and manufacturers seeking to bring new imaging technologies to the marketplace. This group, the **Interagency Council on Biomedical Imaging in Oncology**, consists of staff from NCI, the Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services (formerly the Health Care Financing Administration). Council members provide advice to technology developers from academia and industry and discuss the evaluation of emerging technologies. Since September 1999, NCI has also co-sponsored with industry an annual national conference on biomedical imaging in oncology that focuses on the research, regulatory, and reimbursement pathways of technology development.

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

### THE OPPORTUNITY

Our bodies are made up of many different kinds of cells, and each is suited to its particular function as a part of the whole. Scientists are discovering that every cell type has a unique *molecular signature* – identifiable characteristics such as levels or activities of a myriad of genes, proteins or other molecular features. Today researchers are using new technologies to read and understand the signatures of normal cells and how they can change to become cancerous. They are learning to identify signature changes in developing tumors, in surrounding cells, and sometimes at more distal, more easily sampled sites of the body – such as sampling cells in the mouth instead of the lung or sampling urine to detect urinary tract cancer. Molecular signatures can also be used to identify cancer-causing infectious and environmental agents.

The extraordinary opportunity of molecular signatures is expected to help the cancer community learn how to diagnose cancer early before it has a chance to do harm, to compose highly effective treatments tailored to the features of each case, and to monitor the patients recovery.

To succeed in this effort we will need a full understanding of how cancer starts and progresses, especially focusing on how small changes in only a few genes or proteins can disrupt a variety of cellular functions. This work will require new technologies, new pre-clinical models and heightened cooperation between investigators from all disciplines of cancer research. Our ultimate objective is to push back the detection and diagnosis of cancer to the earliest stages when prevention of overt disease can be most successful.

### PROGRESS IN PURSUIT OF OUR GOAL

The NCI is providing resources needed to study the molecular signatures of cancer including catalogs of molecular changes in cancer at the chromosomal

and gene levels, genes, tissues, and other biologics for study, new technologies, and informatics tools.

### Molecular and Analytic Resources to Stimulate Research

NCI is creating molecular and analytic resources through genetic profiling and technology development. The Cancer Genome Anatomy Project (CGAP) ([cgap.nci.nih.gov](http://cgap.nci.nih.gov)) is a multi-initiative NCI program to build a complete profile of genes expressed in normal, precancerous, and cancer cells. This resource is helping investigators to elucidate major steps of tumor development, develop molecular diagnostic techniques, and identify molecules that can be used for early detection or drug discovery. Researchers throughout the world have used CGAP to identify molecular signatures of prostate, colon, ovary, breast, pancreas, brain, and other cancers.

One CGAP initiative, the Tumor Gene Index (TGI), containing more than five million gene-based DNA sequences, is the most complete public catalog of gene expression for human cancers and for mouse models of cancer. Scientists already are using TGI to classify tumors according to their molecular features for improved cancer prevention, early detection, diagnosis, and treatment strategies. Through TGI we hope to build a complete index of cancer-related genes.

CGAP's Mammalian Gene Collection (MGC) is extending the TGI to focus on identifying and cloning the full set of human and mouse genes to enable more rigorous study of individual genes, their protein products, and the role they play in human disease. Currently, potentially full gene sequences have been identified for about 15,000 human genes and 8,000 mouse genes.

The CGAP Genetic Annotation Initiative (GAI) has characterized and cataloged more than 30,000 human genetic polymorphisms. Polymorphisms are variations, sometimes quite subtle, in the DNA

#### GOAL

Catalog distinguishing molecular signatures of cells to develop new diagnostic and therapeutic approaches and predict response.



## THE PLAN — DEFINING THE SIGNATURES OF CANCER CELLS: DETECTION, DIAGNOSIS, AND THERAPY

### Goal

Generate a complete catalog of the distinguishing molecular signatures of normal, precancerous, and cancer cells at all stages in all tissues, and use the catalog to develop diagnostic techniques for the earliest detection of precancerous lesions and cancers; develop signature-based therapies; and identify subsets of patients with different prognoses to predict therapeutic response.

### Objectives and Milestones for Fiscal Year 2003

1. Expand the development and availability of molecular and analytic resources. \$18.5 M
  - Initiate the Cancer Molecular Analysis Project to integrate molecular signatures, targets, and interventions. \$5.00 M
  - Complete the Mammalian Gene Collection for full-length human and mouse cDNAs. \$3.00 M
  - Continue to develop technologies relevant to discovering and measuring molecular signatures of cancer and precancer and the dissemination of technologies to the scientific community \$1.00 M
  - Continue to develop biosensors for detecting human cancer and cancer development through the Unconventional Innovation Program. \$6.50 M
  - Extend the Genetic Annotation Initiative to identify new cancer related gene polymorphisms in defined populations, define key molecular pathways by thoroughly characterizing genetic variations on numerous gene and protein expression profiles, and develop human gene expression profiles from specific tissues with measured exposure times to study epigenetic targets and cell pathways that lead to tumor formation. \$3.00 M
  
2. Establish and make available to researchers tissue resources to maximize the practical application of molecular signatures to problems in cancer research. \$14.5 M
  - Establish a national tissue resource system for all major cancers, including lung, breast, prostate, colon, head and neck, brain, soft tissue, blood, bone, the gynecologic and genitourinary, and childhood malignancies. \$4.00 M
  - Expand tissue repositories of precancerous lesions in all major cancers. \$4.00 M
  - Use Phased Innovation Awards to develop tissue preservation and sample preparation methods to increase their utility and compatibility with new research technologies. \$4.00 M
  - Enhance the Web-based system to query pathology information systems, including pathology standardization and agreement on common data elements. \$2.50 M
  
3. Identify molecular signatures and apply them to the study and validation of animal models for human cancer. \$5.0 M
  - Continue to develop preclinical mouse models and fund systematic analysis and phenotyping to validate them. Use these models to validate new molecular-based approaches for early detection, diagnosis, treatment, and prognosis of human cancer. \$5.00 M



<p><b>4. Support new approaches for early detection of cancer and to determine biomarkers of precancerous lesions.</b></p> <ul style="list-style-type: none"> <li>■ Identify easy-to-sample sites remote from the tumor itself, for more cost-effective, earlier cancer detection and risk assessment. \$2.00 M</li> <li>■ Study molecular signatures to discover the causes of cancer, including infectious and environmental agents. \$1.00 M</li> <li>■ Identify and validate biomarkers to develop effective, reliable tools for early cancer detection and to assess their potential for predicting cancer. \$2.00 M</li> <li>■ Develop a program that uses the patterns of very small proteins in serum for early diagnosis of prostate, breast and ovarian cancer. Expand marker identification to predict disease stage and risk of recurrence. \$2.00 M</li> <li>■ Expand studies to identify and validate epigenetic markers of cancer. \$1.00 M</li> <li>■ Develop applied algorithms and statistical methods to analyze multiple biomarkers and patterns of molecular changes and link those changes with clinical outcomes. \$1.00 M</li> <li>■ Develop analytical prediction tools for risk assessment, incorporating molecular, genetic, and family history information. \$1.00 M</li> <li>■ Implement within the Early Detection Research Network, a Network-Wide Knowledge and Informatics Center. \$1.00 M</li> </ul>	<p><b>\$11.0 M</b></p>
<p><b>5. Validate molecular classification schemes of cancer, and develop new diagnostic tests.</b></p> <ul style="list-style-type: none"> <li>■ Expand validation programs for each major cancer site as results emerge from the Director's Challenge and other programs.</li> <li>■ Validate new diagnostic approaches through the Program for Assessment of Clinical Cancer Tests to provide the research community with a means to evaluate and validate signatures with possible diagnostic value.</li> </ul>	<p><b>\$13.0 M</b></p>
<p><b>6. Support basic research aimed at characterizing aberrant molecular interactions in cancer.</b></p> <ul style="list-style-type: none"> <li>■ Generate a comprehensive map of all cellular signal transduction pathways<sup>1</sup> and their links to one another through a Signal Transduction Annotation Consortium. \$5.00 M</li> <li>■ Support basic research efforts for analysis of: important cell structure that may be disrupted in cancer; organization and location of chromosomes during cell reproduction; structure and function of molecular machines; and structure and function of membranes. \$2.00 M</li> <li>■ Develop technologies for analyzing cell-cell interactions and communication that might be disrupted in cancer by funding 10 Phased Innovation Awards. \$2.00 M</li> </ul>	<p><b>\$9.0 M</b></p>
<p>Management and Support</p>	<p><b>\$4.0 M</b></p>
<b>Total</b>	<b>\$75.0 M</b>

<sup>1</sup> Molecular pathways that translate a signal from outside the cell to a functional change in the cell.

sequences of a gene that may affect its function. The GAI provides scientists with insights about genetic variants associated with certain cancers and those that occur more frequently in some populations.

The **Cancer Chromosome Aberration Project (CCAP)** was established by CGAP to generate a “Human Cancer Chromosome Aberration Map” – a genetic map that defines distinct chromosomal alterations that lead to cancer. Investigators are using a molecular tool known as BAC (bacterial artificial chromosomes) clones. BAC clones are derived from bacteria and contain fluorescent probes as well as inserts of human DNA sequences. The human DNA inserts are designed to bind to aberrant sections of DNA in the samples being tested in the laboratory. Researchers are able to confirm the presence of an aberration by measuring fluorescence in the sample. In 2001, CCAP passed a major milestone by producing an online version of the Mitelman Database of Chromosomal Aberrations in Cancer, a well-established and exhaustive reference of chromosome changes in human tumors. In 2002, CCAP will complete a map that integrates structural mapping of the human genome with chromosomal maps. (See page 52 for more information on CGAP.)

The **Innovative Molecular Analysis Technologies Program (IMAT)** supports the development of technology to detect molecular signatures in small numbers of cells. This technology is needed to detect cancer at its earliest stage and to study its origins. More than 100 research projects are under way, focusing on new approaches to analyze DNA, RNA, and proteins, as well as new methods to detect interactions of macromolecules in the cell.

Through the **Unconventional Innovations Program**, NCI is supporting creative technological improvements in cancer treatment and detection in the 21st century. This program aims to generate radically new technologies in cancer care to make attainable the goal of detecting, diagnosing, and intervening in cancer at its earliest stages. It targets improvements in existing technologies or new approaches and actively stimulates the interest and involvement of investigators from disciplines not traditionally focused on NCI’s technology challenges.

### **Tissue Resources for Signatures Research**

Clinical specimens are a critical resource for the discovery and application of molecular signatures to cancer detection, diagnosis, and treatment. NCI has established and made readily available to researchers

a variety of tissue repositories.

The **Cooperative Human Tissue Network (CHTN)**, **Cooperative Breast Cancer Tissue Resource**, and **Cooperative Prostate Cancer Tissue Resource** all provide researchers with easy access to high-quality tissue specimens. For example, the CHTN alone is now providing close to 50,000 samples per year. More than 1,000 investigators have been served by the CHTN, and about 200 new investigators request tissue each year.

The **Shared Pathology Informatics Network**, a consortium of institutions connected by a model Web-based system, is working to improve scientists’ access to human specimens and relevant clinical data. The system will automatically access information from medical databases and respond to queries by identifying, obtaining, and returning data for specimens that meet the defined search criteria, after removing information that could compromise patient privacy.

The **Tissue Array Research Program (TARP)** ([cancer.gov/tarp](http://cancer.gov/tarp)) stemmed from collaboration among scientists at NCI and the National Human Genome Research Institute and is responsible for the development of multi-tumor, tissue screening microarray slides. The slides contain up to 600 tissue core samples from different tumor tissues as well as normal tissue and specific cell lines grown in the laboratory. Researchers use the slides for high-throughput, comprehensive analysis of the molecular profile of each tumor type represented on the slide, including characterization of DNA, RNA, and proteins. The slides also can be used to further characterize molecules as potential molecular targets unique to each tumor tissue (see page 78). As of 2002, approximately 11,000 array slides were distributed to researchers nationwide. TARP plans to scale up production of these slides and is establishing a knowledge transfer and training program to disseminate this technology to interested scientific investigators.

### **Using Molecular Signatures to Study and Validate Animal Models of Human Cancer**

Models that accurately reflect the behavior of human cancer promise to improve our ability to identify and understand the molecular changes that characterize cancer as well as enhance our ability to evaluate a range of biomarkers prior to clinical use. NCI launched the **Mouse Models of Human Cancers Consortium** to develop and make available to researchers validated mouse models that mimic human cancers. See page 58.

## **Molecular Signatures and New Approaches for Early Detection**

NCI established the Early Detection Research Network (EDRN) in 1999 as a research program aimed at the discovery and development of novel biomarkers for all cancers and for precancerous lesions. Separate EDRN laboratories cooperate to streamline the development, validation, and clinical testing of promising biomarkers and technologies for cancer screening and detection. This comprehensive, collaborative approach merges genetic pursuits with protein approaches, providing a systematic view of how the molecular signatures of specific cancers can be used as unique, identifying markers.

EDRN researchers have discovered biomarkers for the early detection of several types of cancer, including breast, esophageal, and prostate. In breast cancer studies, researchers are hoping to develop a noninvasive detection test for breast cancer based on proteins present in nipple aspirate fluid (NAF). NAF circulates in the breast ducts and contains proteins produced by the breast. An easily extractable fluid, NAF may provide a “snapshot” of the breast environment. Investigators have identified differences in proteins in NAF samples from a cancerous breast compared with a normal breast in the same patient and are now testing the validity of this approach with a large number of specimens. Other studies are exploring new approaches to detect esophageal cancer at its earliest stages, when the disease is most amenable to intervention. Preliminary EDRN data suggest that gene microarrays may be used to detect premalignant and malignant esophageal lesions with a high degree of accuracy. If validated, these expression profiles offer the potential of classifying esophageal lesions by their aggressiveness and by their responsiveness to chemoprevention. Other researchers are using protein microarray technology to improve the sensitivity and specificity of tests for prostate cancer. Through this research, they have observed that the serum protein PSMA is superior to PSA, the marker currently used for prostate cancer screening, in distinguishing prostate cancer from benign growth.

## **Better Classification of Tumors to Improve Diagnostic Tests**

Tumors have traditionally been classified according to structural characteristics and not on molecular features that would better predict their biological behavior, treatment response, and prognosis.

Through the **Director’s Challenge: Toward a Molecular Classification of Tumors** initiative, investigators are developing profiles of molecular alterations in human tumors using DNA, RNA, or protein-based analysis technologies. These efforts will shift the focus of tumor classification from structure to molecular-based schemes which may be used to define clinically important subsets of tumors, helping health care providers choose the best individual prevention and treatment options.

Director’s Challenge teams are working on several cancers including breast, prostate, lung, brain, ovary, colon, and leukemia and lymphoma. One team is working to subclassify node-negative breast cancer patients. Node negative/positive is a traditional classification based on whether cancer can be detected in local lymph nodes. While it is known that node positive patients have a considerable risk of cancer recurrence, this classification scheme cannot predict this risk for node negative patients. This molecular subclassification appears to address this problem and researchers are working to validate their findings for use in a clinical setting.

The **Program for the Assessment of Clinical Cancer Tests (PACCT)** facilitates the translation of new knowledge about cancer and new technologies to clinical practice. Activities include the generation of reference sets of clinical specimens, which will be made available to academic and industry researchers working to evaluate new markers and validate the utility of some known markers and tests.

## A Story of Discovery: Making the Connections for a Targeted Cancer Treatment Takes Time and Perseverance

**M**ay 10, 2001, marked an important milestone in the fight against cancer. News outlets all over the country announced that a promising drug called Gleevec™ had been approved to treat a serious blood cancer known as chronic myelogenous leukemia (CML). The drug is one of the first of its kind to be approved — a **targeted** agent that hones in on specific molecules in cancer cells, leaving healthy cells unharmed.

But the development of Gleevec™ is far from an overnight breakthrough. The road to its discovery was paved through knowledge culled from more than 40 years of studies probing the molecular events associated with cancer development, the use of new technologies that enabled scientists to move in directions previously beyond reach, and quite often, unanticipated opportunity. The story involves four key steps: learning the unique chromosomal abnormalities of CML, identifying the related cancer-causing protein, finding a treatment agent that targets that protein, and testing and proving its effectiveness and readiness for use in treating cancer.

### The Philadelphia Chromosome: Uncovering the Fundamental Nature of CML

**1960** The story really began in 1960 when Drs. Peter Nowell and David Hungerford, two Philadelphia-based physicians, made a curious discovery. They noticed that cells from CML patients were missing a short segment on one member of the 22nd pair of chromosomes. This shortened chromosome became known as the “Philadelphia chromosome.” It was the first chromosome abnormality ever found to be associated with a specific cancer and the first indication that tumors might indeed arise from changes beginning in just one cell. While the link between the Philadelphia chromosome and CML led scientists to suspect a causal relationship, the location of the missing DNA from chromosome 22 and how it might lead to CML was a mystery to be solved over the next three decades.

**1970** In the early 1970s, new staining techniques offered a way to more precisely visualize band patterns, characteristic markings that

can be used to identify individual chromosomes. With this technique, Dr. Janet Rowley determined that chromosome 9 in CML patients was lengthened by the same amount that chromosome 22 was shortened. From this observation, Rowley proposed that the genetic material from the two chromosomes was reciprocally exchanged, or “translocated.”

**1980** Using newly developed approaches for molecular analysis, scientists in the early 1980s determined that the genetic rearrangement that leads to the Philadelphia chromosome occurs when genetic mistakes cause breaks in the middle of two vital genes located on chromosomes 9 and 22. They found that the break on chromosome 22 occurs in the middle of the *bcr* gene and that the break on chromosome 9 occurs in the *abl* gene. On the shortened end of chromosome 22, the genetic rearrangement produces the abnormal *bcr-abl* gene, the source of CML development.

In 1986, Dr. David Baltimore and his research group determined that, like the normal *abl* gene, the defective *bcr-abl* gene carries the code for a tyrosine kinase, a class of proteins that plays an important role in regulating cell growth and division. The normal *abl* gene will turn on or off, producing tyrosine kinase to promote cell growth as needed. The aberrant *bcr-abl* gene, however, is always turned on and lacks the critical piece that enables the gene to turn itself off. As a consequence, *bcr-abl* floods the cell with the instruction to divide constantly and also prevents the leukemia cells from undergoing normal programmed cell death or apoptosis, a process that helps to regulate white blood cell numbers. Several laboratories confirmed the link between the defective gene and CML through studies showing that the *bcr-abl* gene was all that was needed to induce leukemia in mice.

### Developing a Targeted Treatment

During this same time period, advances in molecular biology were revolutionizing the field of drug discovery. In the laboratories of Ciba-Geigy (later, Novartis), scientists were able to apply unfolding knowledge about the workings of cellular pathways and communications systems in a number of drug development

efforts. In one research program, scientists were looking for agents to inhibit protein kinases, a group of cell signaling proteins that includes the Abl protein. A number of such agents were found, including one that they labeled STI571.

**1990** Meanwhile, American oncologist Dr. Brian Druker was interested in determining how the Bcr-Abl protein, the product of the *bcr-abl* gene, fits into the complicated circuitry of cell signaling. His research led him to believe that the Bcr-Abl protein could be a powerful target for a drug that could impede the activity of the protein and be an effective treatment for CML. When he learned about Ciba-Geigy's complementary research, Druker asked scientists there for candidate protein kinase inhibitors that he could test against leukemia cells. At the end of 1993, the pharmaceutical company sent him several candidates, including STI571. Druker screened the chemicals and found that STI571 halted the growth of the leukemia cells but had little effect on healthy ones.

While this was an exciting outcome, there were still many obstacles to overcome. The process of developing a new drug and getting it approved for use is lengthy and expensive. Scientists must identify a possible agent; study and test it for efficacy, pharmacology, and toxicology; file with the Food and Drug Administration; and finally evaluate it through large-scale clinical trials. STI571 posed an additional business problem because the incidence of CML is quite low, limiting the potential demand for the drug, and two moderately effective treatments already were available for CML, although both held potential for serious side effects.

Despite reservations, Novartis agreed to produce enough STI571 for an initial clinical trial. Dr. Druker began the Phase I trial, conducted to identify a safe dose level, in June of 1998. By December of 1999, he and his colleagues reported that white blood cell counts for all of the 31 patients receiving a high dose of STI571 had returned to normal, an effect that was sustained for the eight months that the patients stayed on the drug. In 9 of the 20 patients who were treated for five months or longer, no leukemia cells could be found, confirming that the drug was eliminating the source of the cancer and with minimal side effects. Rarely are

such dramatic results seen in a Phase I trial.

**2000** In response to these exciting findings, Druker and his colleagues conducted a larger study and reported in April 2001 that STI571 restored normal blood counts in 53 of 54 CML patients, all of whom had resisted previous chemotherapy. Of these patients, 51 were still doing well after a year on the medicine, with most reporting few side effects. Following "fast-track" review, the Food and Drug Administration approved STI571, now known as Gleevec™, as a treatment for CML in May 2001, beginning with patients not responding to standard therapies.

### The Story Continues

But the story of Gleevec™ as a treatment for CML is not complete. Patients receiving the drug need to be followed for longer periods to determine whether the positive effects will last and whether long-term treatment can cause side effects. Unfortunately, most patients with advanced disease relapse within a year. The cause of resistance is now known, so scientists are trying to overcome it. Like most successful treatments, Gleevec™ will undoubtedly spawn a host of refinements.

The story does not end with CML. In addition to the Bcr-Abl signaling protein, the drug appears to target two other protein kinases, the c-kit receptor and the PDGF receptor. The c-kit receptor is active in gastrointestinal stromal tumor (GIST) and the PDGF receptor associated with many types of cancer, including a form of brain cancer called glioblastoma. NCI-supported and private-sector scientists are investigating the effectiveness of Gleevec™ against cancers of the breast, ovary, and lung. See page 31 for more information.

The success of Gleevec™ offers substantial hope that molecular targeting can be a highly effective strategy to thwart the growth of specific cancers. It is likely that Gleevec™ is the first of many potent, but safer, targeted preventive and treatment drugs to be developed as a result of advances in our understanding of cancer at the molecular level.

4

## Molecular Targets of Prevention and Treatment

### THE OPPORTUNITY

We are entering an era in cancer research that holds the potential for an exciting new approach to drug development for cancer prevention and treatment. These drugs will be designed to target specific molecular features of cancer cells, such as small but critical errors in genes or proteins that lead to tumor growth. By selectively attacking cancer cells, these revolutionary agents promise to be less toxic and more effective than current drugs. This extraordinary opportunity of molecular targeting has been generated by knowledge gained through recent advances in multiple research disciplines from basic cancer biology to synthetic and biosynthetic chemistry.

Our ability to treat cancer is integrally linked to our understanding of cancer. Historically, using available technology scientists could tell by features such as the shape or size of the cell whether it was cancerous, but not why it was cancerous or how its inner workings might differ from normal cells. Yet investigators applied what they could see to produce the drugs now in use that, alone or with surgery or radiation, can cure some cancers and ease symptoms in others. However, these drugs tend to be *non-selective* – while treating the cancer they also attack a number of healthy cells. Consequently, cancer chemotherapy is often accompanied by a variety of sometimes devastating short- or long-term side effects. It has also been hard to pinpoint why many tumors do not respond well to available drugs.

Scientists are now harnessing recent advances in technology to learn more about the nature of cancer and to identify ways that cancer cells differ from healthy cells at the molecular level. This knowledge creates the potential for cancer drugs that target these differences to more effectively attack the cancer while sparing healthy tissues. To harness this potential we need to create better ties between laboratory and

clinical research to integrate drug discovery, development, and clinical testing. In this cooperative setting researchers can effectively identify molecular targets in the cell, find drugs that will “hit” the targets, test these drugs for safety and efficacy in the laboratory and in animal studies, and test the use of successful candidate drugs in clinical trials. Ultimately these drugs will be used by health care providers to more effectively prevent and treat cancer, with far fewer side effects.

### PROGRESS IN PURSUIT OF OUR GOAL

The NCI is advancing the molecular targeting approach to drug discovery through a number of exciting initiatives.

#### Identifying and Validating Molecular Targets for Drug Discovery

Through the Molecular Target Drug Discovery (MTDD) program investigators are identifying novel molecular targets, validating these targets as sites that can be exploited for cancer therapy, and developing tests that determine how well potential agents work on these targets. The 41 research groups currently supported are studying a number of molecular targets. One group of scientists is investigating Bcl-xL, an aberrant protein that enables cancer cells to

evade apoptosis, or programmed cell death – a process that normally eliminates damaged cells from the body. Another group is investigating Heat Shock Protein (HSP) 90, a “stress response” protein that is overexpressed in tumors and may play an important role in cancer growth. Still another team is studying how DNA methylation can lead to cancer. Methylation is a specific type of chemical alteration that can prevent or reduce the expression of affected genes. Researchers have found that in some cancers DNA repair genes and tumor suppressor genes are

**G O A L**

Accelerate discovery, development, and testing of prevention and treatment agents that target the molecular changes of cancer.



silenced by this mechanism and unable to do their job in preventing cancer.

### Resources for Exploiting Molecular Targets for Drug Discovery

The **Molecular Targets Laboratories (MTLs)** was first funded in FY 2002 to capitalize on the opportunities emerging from advances in genomics, molecular biology, combinatorial chemistry, informatics, and imaging. Through this initiative scientists are applying advances to create a resource of biological assays and chemical probes to study cancer-related targets. This work enables biological studies of cancer, including physiological and biochemical monitoring, and provides a platform for drug discovery.

Through the **Mouse Models of Human Cancers Consortium** groups of academic researchers have created and are making available to researchers mice with defined genetic alterations that predispose the animals to certain types of cancer. Six strains were available as of 2001, and up to 30 more may be added annually. These models could serve as a basis for testing new molecular targeting treatment and prevention strategies. As more models are added, it will be possible to create subsequent generations of mice with more than one genetically defined alteration to resemble human tumors even more closely. Academic members of the consortium are developing ties to pharmaceutical industry sponsors to facilitate the testing and evaluation of new compounds in these mouse strains. For more information about this initiative, see page 58.

We are working with the National Institute for General Medical Sciences on the **National Beam Program** to provide technology to quickly identify the structure of important molecular targets in cancer cells and efficient computer modeling to identify potential anti-cancer agents suited to “hit” the targets based on these structures. Partners are constructing “the x-ray beamline” at the Argonne National Laboratories. This cutting-edge technology will greatly improve scientists’ ability to determine the complex structure of proteins and larger multi-molecular complexes.

### Identifying Compounds That Hit the Targets

Through several NCI initiatives, chemists and biologists are collaborating to create libraries of synthetic, biological, and natural compounds that will be tested for therapeutic potential against validated molecular

targets. These scientists are developing “smart” assays, or tests used to screen the compounds to identify those that “hit” defined target molecules.

The **National Cooperative Drug Discovery Groups** program supports innovative, multidisciplinary, multi-project approaches to discover new anticancer treatments. Thirteen funded groups are progressing in a variety of areas, including an innovative effort to design and evaluate novel anti-cancer drugs that inhibit the enzyme geranylgeranyltransferase I (GGTase I). This enzyme is involved in activating a cellular pathway involving the Ras oncogene, which has been implicated in a number of human cancers. Researchers hope to identify an agent that will selectively suppress GGTase I and the cancer-promoting activity of the Ras pathway. This research is an excellent example of how a basic discovery generated through an NCI grant can be expanded into clinical development with support from special NCI initiatives.

In **Biology-Chemistry Centers** multidisciplinary teams of scientists use a combination of chemical and biological techniques to create libraries of chemically diverse structures with potential anti-cancer effects. Using “smart” assays, scientists screen the compounds to identify those that will interact with cancer-specific molecular targets. The six teams funded through this initiative have screened hundreds of thousands of compounds for anti-cancer activity. Promising compounds include the newly designed GFB-111 molecule. This novel molecule binds to growth factors — proteins that help to regulate new tissue growth — and has been shown to significantly inhibit new blood vessel formation (angiogenesis), and thereby growth of human tumors studied in mice.

NCI supports the collection of **natural extracts** from plants throughout the world. Using high-throughput screening, scientists are testing these extracts for use either as targeted cancer drugs or as probes to study targets in the cell. One chemical, Halichondrin B, which occurs naturally in a Pacific Ocean sponge, has been found to have considerable anti-tumor activity. Because of the scarcity of Halichondrin B in its natural form, researchers have started designing promising synthetic analogs. Two such analogs have shown significant anti-tumor activity against human breast, colon, melanoma, and ovarian tumors grown in laboratory animals and will next be studied for clinical usefulness.

The **Rapid Access to NCI Discovery Resources**

## THE PLAN — MOLECULAR TARGETS OF PREVENTION AND TREATMENT

### Goal

Facilitate the expanded exploration of the causes of cancer and the discovery and development of agents that specifically “target” these causes to treat and prevent cancer.

### Objectives and Milestones for Fiscal Year 2003

1. Identify, characterize, and validate the combinations of deregulated cellular proteins and pathways that cause cancer in precancerous and cancerous cells. \$6.0 M
  - Through the Molecular Target Drug Discovery Grants (MTDD), increase support for research to identify cellular targets and discover related anti-cancer agents. Continue support for the MTDD Grants and previously awarded Biology-Chemistry P01s. Provide screening assistance and informatics management. \$6.00 M
  
2. Determine the cancer-causing deregulated pathways that can be targeted by prevention or treatment agents. \$6.0 M
  - Amplify support for the Molecular Target Laboratories to bolster the systematic search for new preventive and therapeutic agents. 1) Develop assays to identify possible treatments for cancer and 2) acquire large libraries of natural and synthetic compounds. \$5.00 M
  - Support the Mouse Models of Human Cancers Consortium to accelerate the pace of making available accurate, reproducible mouse models of human cancers. \$1.00 M
  
3. Provide the infrastructure for researchers to develop assays to test large numbers of potential drugs against validated “drugable” deregulated proteins and pathways. \$15.0 M
  - Expand support for the National Cooperative Drug Discovery Groups. \$5.00 M
  - Expand the availability of NCI discovery resources to academic laboratories through the Rapid Access to NCI Discovery Resources program (RAPID). \$1.00 M
  - Expand efforts to collect, inventory, and distribute diverse compounds — synthetic chemicals, natural products, and biological materials, and provide informatics support for anti-cancer research. \$3.00 M
  - Develop a translational research program to closely link molecular imaging, cancer signatures and molecular targets. This would allow serial imaging and serial biopsies used to assess genomics and proteomics, to be coupled with therapeutic interventions which use systemic agents, radiation therapy, immunologic treatment and chemopreventive agents. The ability to

(R\*A\*N\*D) is a new program that expedites the development of drug research capabilities in academic institutions. R\*A\*N\*D focuses on laboratory-based studies that are the starting points for new drug development, supporting early formulation, pharmacokinetic, pharmacology, and toxicology studies. R\*A\*N\*D assists in the development of high-throughput laboratory assays to screen large numbers of promising chemicals. The program supports the

development of libraries of chemicals that scientists can draw upon for study. One of the five initial R\*A\*N\*D projects uses microarray technology to study molecular profiles of leukemia cells and to identify more targets. Another exciting project is creating a library based on a compound that targets an important cellular protein involved in angiogenesis, or generation of new blood vessels – an integral component of tumor growth.

<p>conduct multiple studies will provide a robust data set to understand the biology behind the image needed to credential new molecular targets. \$3.00 M</p> <ul style="list-style-type: none"> <li>■ Support an intramural Molecular Targets Drug Discovery Program to develop screening assays for biomolecules that interact with molecular targets, conduct screens to test candidates for probes and inhibitors of molecular targets, characterize and validate compounds that hit the targets, and facilitate development of needed research chemicals as well as promising molecular target compounds. Support the isolation, purification and characterization of individual components of natural products extracts. \$1.00 M</li> <li>■ Develop a clinical proteomics initiative to use laser capture microdissection of human tissue specimens and to develop new laboratory tools, including a new protein array, 2D-PAGE, signal pathway profiling, and SELDI-TOF protein pattern fingerprinting for clinical proteomic applications in human cancer and drug toxicity detection. \$2.00 M</li> </ul>	
<b>4. Facilitate the steps necessary to turn a target-specific lead compound into a clinical agent.</b>	<b>\$7.0 M</b>
<ul style="list-style-type: none"> <li>■ Expand support for the Rapid Access to Intervention Development (RAID) program. \$3.0 M</li> <li>■ Increase funding to RAPID to develop prevention agents from the laboratory through clinical trials of efficacy. \$1.0 M</li> <li>■ Expand assistance to small businesses through Flexible System to Advance Innovative Research. \$3.0M</li> </ul>	
<b>5. Investigate the use of novel combinations of radiation therapy with molecular therapeutics.</b>	<b>\$ 0.5 M</b>
<ul style="list-style-type: none"> <li>■ Support individual investigators and industry to develop treatment programs using new agents with radiation therapy. Facilitate collaboration with industry and individual investigators and establish a system for alerting clinical investigators when agents are ready for clinical trials. \$ .50 M</li> </ul>	
<b>6. Fund Clinical Trials Networks that will take drug candidates into human trials designed to test whether or not the drug is working against the intended target and is affecting the progression of the cancer in the intended manner.</b>	<b>\$2.0 M</b>
<ul style="list-style-type: none"> <li>■ Widen support for the Interdisciplinary Research Teams for Molecular Target Assessment program. \$2.0 M</li> </ul>	
Management and Support	<b>\$6.0 M</b>
<b>Total</b>	<b>\$42.5 M</b>

NCI provides, at no cost, **samples of synthetic chemicals, collected natural products, and biological materials** to investigators who want to screen them against molecular targets. NCI has made available more than 140,000 synthetic chemicals, 80,000 natural products extracted from plants and marine organisms, and a variety of biological agents for use in studying the compounds.

### Turning Promising Target-Directed Compounds into Drugs for Human Use

Translating laboratory discoveries into agents for human use is an exacting task that requires very specific, interrelated activities. For example, sufficient quantities of the drug must be made for formulation, stability, and safety testing. Drug optimization and development studies enable scientists to determine the manner and amount of drug to be delivered based

on a drug's overall effect on an animal. NCI is supporting this critical arm of drug development through a variety of initiatives.

The **Rapid Access to Intervention Development (RAID)** program provides preclinical drug development resources to academic institutions in 50 current projects. Two interventions developed through RAID are now being tested in clinical trials. One intervention is a novel gene therapy approach that delivers a pair of therapeutic "suicide genes" to prostate tumors, thereby rendering malignant cells sensitive to specific drugs and radiation. The other is the anti-cancer agent 6-Diazo-5-Oxo-l-Norleucine (DON), which selectively inhibits growth of neuroendocrine tumor cells. As many as nine additional agents will be in clinical trials testing by the end of 2001.

The **Rapid Access to Preventive Intervention Development (RAPID)** program provides preclinical and early clinical drug development resources to academic investigators who are developing novel agents to prevent, reverse, or delay cancer development. The seven projects currently funded through RAPID include studies to develop certain marine-derived products as chemopreventive agents, a human papillomavirus vaccine, and work to determine the preventive effects of certain proteins.

The **Drug Development Group** provides support for academic and corporate-derived compounds when NCI is responsible for conducting and monitoring the drug's clinical development. A number of promising agents have been developed through this program. PS-341, a novel compound presented to NCI by Millennium Pharmaceuticals, is the first in a new class of agents that take aim at a new cellular target — the proteasome enzymes. These enzymes play an important role in the breakdown of proteins that regulate the cell cycle. PS-341 inhibits the breakdown of these proteins and leads to cancer cell suicide. In preliminary clinical trials, PS-341 produced promising effects in both multiple myeloma and prostate cancer patients. NCI and Millennium are pursuing further clinical testing.

Certain cancer-causing genes induce cancer when they block the normal expression of healthy genes. Histone deacetylase inhibitors relieve this suppression. In cooperation with extramural organizations, NCI has studied the anti-tumor effects of several such inhibitors, including pyroxamide, an inhibitor identified by scientists at an NCI-supported Cancer Center

as a candidate for drug development. Pyroxamide considerably reduced tumor growth in animal models of breast, lung, and prostate cancer without causing toxicity. Preliminary clinical trials are now underway at the Cancer Center.

The **Flexible System to Advance Innovative Research (FLAIR)** provides funds to small businesses to develop cancer therapeutic and prevention agents from basic discovery to clinical trials. There are currently 20 active FLAIR grants, including an investigation of a potential anti-cancer agent, PX-12. This agent targets thioredoxin, a cellular protein that is overexpressed in a number of human cancers and associated with aggressive tumor growth and poor patient prognosis. PX-12, which inhibits the growth-promoting activities of thioredoxin, has shown potent anti-tumor activity against leukemia, breast, and lung cancers in animal models. Phase 1 clinical trials supported by the FLAIR program are now under way.

The **Radiation Modifier Evaluation Module (RAMEM)** program will serve individual investigators and industry in the design and development of treatment programs for the use of novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. Integration of molecular imaging, molecular signatures, and molecular therapeutics with radiation therapy is a high priority of NCI's Intramural Program because many new anti-cancer agents may ultimately be used in combination with radiation therapy.

### **Developing Clinical Trials Programs To Study New Molecular Target Agents**

The **Interdisciplinary Research Teams for Molecular Target Assessment (IRTMTA)** is a new program that enables interdisciplinary teams of scientists to develop molecular assays, molecular and cellular imaging probes, and other tools to assess the effects of targeted interventions in preclinical models and in early clinical trials. The teams will study critical biological processes to uncover high-priority targets for cancer prevention or treatment and drug discovery. The first set of applications for this program was funded in early 2001.

## Research on Tobacco and Tobacco-Related Cancers

### THE OPPORTUNITY

The devastating impact of tobacco use and tobacco smoke exposure on the incidence of cancer, heart disease, and stroke is both compelling and conclusive. Tobacco use causes more premature death than do all drugs of abuse combined. Lung cancer, which is estimated to account for approximately 157,400 deaths in 2001, would be a rare disease in the absence of smoking. Cancers of the mouth, pharynx, larynx, esophagus, pancreas, cervix, kidney, and bladder are all associated with tobacco use.

A major challenge in the fight against tobacco-related cancers is that addiction to nicotine drives the continued use of tobacco even when the user is fully aware of increased risk of disease and premature death. Some people will continue to smoke even as they undergo treatment for a life-threatening disease. Furthermore, tobacco-related diseases such as lung cancer remain some of the most difficult to treat effectively.

We need to better understand the genetic, biological, behavioral, and social influences that explain:

- Why children and adults use tobacco.
- How they become addicted.
- Why those who become addicted have such difficulty quitting.
- How to prevent, detect, and treat cancers caused by exposure to tobacco and its constituents.

NCI's commitment to preventing, diagnosing, and treating tobacco-related cancers began more than 40 years ago and remains one of our highest priorities. Our research has benefited individuals and has improved the public's health. To remain at the leading edge of this important area of research, NCI must devote additional resources to address the complex challenges of tobacco use and tobacco-related cancers.

### PROGRESS IN PURSUIT OF OUR GOAL

The NCI has a unique role in supporting the entire range of tobacco research, from understanding why and how people use tobacco to developing and evaluating more effective treatments for nicotine addiction to detecting and treating tobacco-related cancers and metastatic disease. NCI has a special concern for the health of former smokers, people who followed advice to quit smoking, who now comprise about half of those diagnosed with lung cancer. The breadth of NCI's support is reflected in our investments both in basic biological research on the effects of tobacco exposures and in community-based studies of smoking prevention and cessation programs.

Recent advances in knowledge about tobacco use and tobacco-related cancers provide an unprecedented opportunity to reduce the disease burden from tobacco. New evidence is helping to better explain why some people are more vulnerable than others to DNA damage caused by tobacco exposure. Research on the early detection of lung cancer suggests that it may soon be possible to identify cancers in smokers and former smokers at a much earlier and more treatable stage. Recent studies of teen smokers have identified psychological factors that increase the risk of becoming addicted, as well as the need to provide younger smokers with specialized programs to help them quit. A new evidence-based guideline, which NCI helped to develop, enables healthcare providers to offer smokers practical, effective strategies to quit smoking. If applied widely, this could have a dramatic effect on the number of smokers who successfully quit. Also, new cancer treatments based on molecular targeting provide models for how to increase the effectiveness of therapies for tobacco-related cancers.

The following are examples of research initiatives underway related to the objectives of the Research on Tobacco and Tobacco-Related Cancers Opportunity.

#### GOAL

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

## THE PLAN – RESEARCH ON TOBACCO AND TOBACCO-RELATED CANCERS

### Goal

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

### Objectives and Milestones for Fiscal Year 2003

1. Expand efforts to define the biological, behavioral, and social bases of tobacco use and addiction. \$17.0 M
  - Initiate prospective observational studies of the quitting and relapse process, including the effectiveness of medications. \$4.00 M
  - Improve understanding of the social bases of tobacco use by supporting studies of economic, geographic, sociocultural, and policy-related factors. \$2.00 M
  - Continue support for including questions on tobacco use in the Current Population Survey. \$2.00 M
  - Support analytical tools, resources, and analyses of existing and new tobacco use data. \$5.00 M
  - Expand collaborative efforts aimed at the translation of research findings on the determinants of tobacco use to clinical and community intervention research. \$4.00 M
  
2. Accelerate progress in understanding the interplay among tobacco, other exposures such as alcohol and asbestos, and host susceptibility on cancer risk. \$22.0 M
  - Support clinical and population studies that include tissue and biospecimen resources to investigate the genetic, biological, and behavioral factors influencing vulnerability to smoking dependence and tobacco-related cancer. \$6.00 M
  - Integrate biospecimen collection into screening trials to better understand the molecular basis of early-stage lung cancer. \$6.00 M
  - In collaboration with other Federal agencies, synthesize the latest evidence regarding environmental tobacco smoke and identify critical directions for new research. \$1.00 M
  - Support studies of the mechanisms of susceptibility to tobacco-related cancers to understand the effects of specific forms of tobacco and types of tobacco exposure. \$5.00 M

### Preventing, Treating, and Screening for Tobacco-Related Cancers

Lung cancer studies are the focus of much of our research on tobacco-related cancers and may be applicable to other cancers as well.

- A chemoprevention and biomarker study involving lung cancer survivors and patients at high risk for lung cancer is underway. Strategies include the use of drugs, vitamins, or other agents to reduce the risk or delay the development or recurrence of cancer. Investigators in the **Lung Cancer Biomarkers and Chemoprevention Consortium** began recruiting patients in the summer of 2001 to participate

in two trials evaluating chemopreventive drugs. Researchers will perform biomarker analyses on tissues obtained during the studies and correlate these findings with patient outcomes.

- The **Lung Cancer Screening Study** began in 2000 to assess the feasibility of the spiral computed tomography (CT or CAT) scan to detect early lung cancers. As of the spring of 2001, 3,300 people were randomized to either a spiral CT or a chest x-ray at six screening centers across the country. Investigators are comparing the lung cancer detection rates; measuring how much and what kind of medical follow-up is needed; and tracking how



■ Integrate the use of mouse models into research on the development of tobacco-related cancers to identify the relative contributions among the genes related to susceptibility and resistance and other endogenous and exogenous factors. \$2.00 M	
■ Facilitate scientific collaborations between lung and head and neck cancer SPORE investigators and TTURC investigators to better integrate biological, pharmacological, and behavioral research on tobacco use and its impact on disease. \$ 2.00 M	
3. Develop, test, and disseminate more effective interventions to prevent and treat tobacco use and tobacco-related cancers, especially in high-risk individuals and groups.	\$24.0 M
■ Support the development of biomarkers of tobacco exposure and risk through collaborative work with National Institutes of Health laboratories and those at the Centers for Disease Control and Prevention's National Center for Environmental Health. \$2.00 M	
■ Provide supplements to the Transdisciplinary Tobacco Use Research Centers, State/Community Tobacco grants, and Cancer Centers to stimulate health disparities research, including clinical assessment and care of tobacco-related cancers, differential tobacco use, and quitting patterns. \$4.00 M	
■ Support collaboration with public and private tobacco research funding organizations to identify and disseminate successful tobacco use prevention interventions. \$3.00 M	
■ Support the development of NCI's new tobacco treatment and research clinic to speed the discovery and testing of new treatments. \$1.00 M	
■ Accelerate the identification of new treatments for nicotine addiction through the creation of an NCI/National Institute on Drug Abuse drug development and clinical trials collaborative. \$2.00 M	
■ Support research on smoking cessation and relapse prevention in cancer patients and survivors. \$2.00 M	
■ In order to accelerate the development of new, molecularly based treatments for lung cancer, support a molecular defects database, a tissue resource, and improved exposure assessments to enable more sophisticated studies of treatment outcomes. \$10.00 M	
Management and Support	\$4.0 M
Total	\$67.0 M

frequently participants receive spiral CT scans outside the study. Although spiral CT scans are advertised as a new way to find early lung cancer in both current and former smokers, questions remain unanswered regarding its risks and benefits making these results crucial for the design of larger, more definitive studies. The study builds on the infrastructure of the NCI-supported Prostate, Lung, Colorectal, and Ovarian screening trial, launched in 1992.

- Through two new initiatives begun in the summer of 2001, NCI will fund preclinical and clinical studies to identify newer, more potent agents that may prevent cancers in former smokers. Currently,

almost half of all new cases of lung and bladder cancer occur in former smokers. It is vitally important to identify molecular and imaging markers of cancer risk and abnormal and uncontrolled cell growth and to test agents that can prevent the development of cancer in this group.

### Understanding the Interplay Among Tobacco, Other Exposures, and Cancer

While costly, resource-intensive, and long, cohort studies that include genetic and biomarker components are invaluable tools for collecting large amounts of information critical to understanding

cancer risk and assessing exposures to carcinogens prior to cancer diagnosis.

- The Prostate, Lung, Colorectal, and Ovarian screening trial is examining emphysema in relation to smoking, how genetic factors influence smoking, and the differences between current and former smokers regarding genes that might be involved in nicotine dependency. This information will prove increasingly precious over time as cancer cases develop in the cohort and their biospecimens become available for special study.
- Through an NCI-supported study of a group of women in Shanghai, we have an unprecedented opportunity to prospectively collect data and biospecimens from both non-smoking women who are exposed to second-hand smoke and their husbands who tend to be active smokers. Similarly, we have incorporated major biospecimen collections into studies that compare groups of people with cancer to healthy control groups. Specific studies initi-

### **Tobacco and Tobacco-Related Cancers: Good News and Bad**

#### **The Good News**

- Comprehensive state/community tobacco control programs work. For example, Arizona's adult tobacco use dropped from 23 percent in 1996 to 18 percent in 1999.
- Smokers do want to quit. Approximately 39 percent of all adult smokers made an attempt to quit in the past year.
- Consumption of cigarettes continues to decline, dropping from 4,345 per capita in 1963 to 2,146 per capita in 1999.
- Lung and bronchus cancer deaths are estimated to drop from 158,700 in 1996 to 157,400 in 2001, primarily due to decreased smoking.

#### **The Bad News**

- Youth smoking increased from 28 percent in 1991 to 35 percent in 1997 although it has since declined somewhat.
- Those with the least education and income smoke the most: 11 percent of college graduates smoke compared with 34 percent of those who did not finish high school.
- Lung cancer now kills approximately 157,000 people each year in the U.S. alone. It would seldom occur if people did not smoke.

ated during the past year focused on smoking-related cancers such as lung, bladder, and renal cancers.

- NCI supports regional biorepositories, such as the expanded Frederick Biorepository and the Cooperative Human Tissue Network, which fill a critical need by housing and maintaining human biospecimens such as tissue, blood, and urine. Scientists collect these biospecimens from large-scale studies and make them available to researchers.

### **Understanding and Preventing Youth Tobacco Use**

Tobacco use arises from a variety of influences, including social factors such as peer and parental smoking, as well as biobehavioral and genetic factors. Because the majority of smokers begin using tobacco before the age of 18, understanding why youths use tobacco is a high priority for NCI.

We have substantially expanded our support for studies that test ways to prevent tobacco use among the young and to help users quit. NCI, in collaboration with other NIH institutes, is now supporting more than 50 research grants related to the prevention, dependence, and cessation of adolescent tobacco use. This wealth of cutting-edge research is beginning to yield new insights into youth tobacco use. In June 2001, NCI brought together more than 200 investigators from across the country to share the latest scientific evidence concerning tobacco use among youth. Their research indicates that both social influences and inherited factors are predictors of youth tobacco use.

- A recent study of fifth- and eighth-grade students from New England middle schools showed that students who view more tobacco use in movies are more likely to try smoking.
- Studies of twins show that inherited factors influence whether a person will smoke and how difficult it will be to quit.

Ongoing research supported through the Transdisciplinary Tobacco Use Research Centers (TTURCs) is beginning to provide information on youth tobacco use. NCI, the National Institute on Drug Abuse (NIDA), and the Robert Wood Johnson Foundation (RWJF) funded seven TTURCs at U.S. academic institutions in 1999. Each organized around a special theme, these centers have yielded significant research results.

- TTURC research has shown that smokers with a unique genetic makeup started smoking almost two years earlier than others. Investigations of genes important in smoking have focused on the dopamine system and on the brain chemical serotonin, which plays a role in depression and anxiety, both traits associated with smoking.
- Another study has assessed factors associated with high school students' decisions to smoke. High academic performance, perceived academic competence, and involvement in school-related clubs and sports teams were found to decrease the risk of smoking, while alcohol or marijuana use and novelty-seeking were associated with increased smoking.
- Another TTURC study is examining factors that affect the progression of smoking initiation and use among youth of diverse cultures. Early results of this research suggest that the patterns of smoking initiation in the United States and China are similar and that the optimal age for smoking prevention interventions is between 10 and 15, earlier than many of the programs aimed at youth currently start.

### Treating Tobacco Dependence

Smoking cessation remains among the most cost-effective approaches to reducing cancer risk, but despite the dramatic advances in understanding the nature of nicotine dependency during the past decade, the best treatments are effective for less than a third of all smokers who try to quit. NCI continues to support effective behavioral, pharmacological, and community treatment approaches.

- Understanding the genetic factors related to nicotine initiation and dependence will be critical to the development of new medications to help smokers quit. With NIDA, NCI created a working group to advise both Institutes on key areas where progress can be achieved in the development of new medications for smoking cessation.
- NCI has supported innovative smoking cessation interventions that are tailored to the unique needs of individual smokers. For example, one recent study found that an “expert system” intervention, which provided computer-assisted feedback and help, resulted in quit rates that were almost 33 percent higher than for those without it. Conducted in a health care system, this study opens the door for increased assistance to smokers in environments where maximum medical follow-up is possible.
- A recent study funded through the NCI SPOREs

initiative showed that those smokers who carried the DRD2-A1 genotype were more likely to relapse than those who carried the DRD2-A2 genotype, suggesting the possibility of developing tailored approaches to treatment that take into account unique genetic traits. (See p. 24.)

Smokers who do not wish to quit or who are unable to do so comprise a target market for the tobacco and pharmaceutical industries. The tobacco industry is developing and marketing new products intended to reduce the harm of continued smoking. The pharmaceutical industry is developing medications for smoking reduction, along with those for cessation. Nevertheless, there is little evidence to suggest that changing tobacco products or using medications for smoking reduction will result in decreased harm.

#### International Efforts

Our efforts to address tobacco control in the United States clearly can inform and be informed by research conducted in other countries. Of particular international importance are surveillance of the changing global patterns of tobacco use, development of scientific and public health networks to optimally address tobacco control, and development of interventions for preventing and treating tobacco use. In support of global tobacco research efforts, NCI has:

- Partnered on a Global Youth Tobacco Survey led by the Centers for Disease Control and Prevention to document and monitor the prevalence of and contributing factors of youth tobacco use.
- Contributed to the design and funding of a new research initiative led by the NIH Fogarty International Center that will support international tobacco and health research as well as capacity-building efforts and studies that emphasize tobacco control research in low- and middle-income countries.
- Initiated a new lung cancer study in Milan, Italy, to evaluate gene-environment interactions in the development of lung cancer. This study includes the genetics of nicotine addiction and the treatment of smoking dependence.

6

## Cancer Communications

### THE OPPORTUNITY

It is not unusual today for newly diagnosed cancer patients to go to their doctors' appointments armed with printouts from CancerNet or other Web sites and lots of questions. People have more ways than ever to get information: by telephone, fax, email, the World Wide Web, TV and radio, and in person. And the future holds even more choices: automated monitoring of vital signs, voice recognition software, wider use of wireless technology, and other technologic advances to make it easier and faster for people anywhere to access the best information about cancer.

NCI's opportunity is to optimize the use of these tools while enhancing the absolutely essential interaction of patients with their doctors and nurses. Indeed, new communication tools can facilitate partnerships between patients and their physicians. We must push forward the frontiers of technology in support of the public, patients, their families, and medical teams to ensure access to individualized, high quality, NCI-validated information. From primary prevention to survivorship and end-of-life issues, communication empowers people to make informed cancer-related decisions and to engage in behaviors that will improve their health.

To build on our progress in refining health communication theories and interventions, we must close major gaps in our understanding of how people access and use health information as well as the discrepancies between what is known and what is practiced. We must:

- Provide accurate and balanced information about all areas of cancer prevention, diagnosis, treatment, and care.
- Learn how to help people distinguish important health risks from insignificant ones and make informed choices despite exposure to contradictory or inaccurate health messages.

- Inform healthcare providers of emerging best practices, help them become more effective communicators, and integrate communications into all aspects of cancer care.
- Find and implement the best ways to disseminate research results to the cancer research community, medical practitioners, patients, individuals at risk, and the public.
- Increase communication with patients about access to and participation in high quality clinical trials.
- Reduce cancer-related health disparities through health communications research and activities.
- Expand the cadre of health communications scientists and practitioners who conduct research and apply results.

**G O A L**

Understand and apply the most effective communications approaches to maximize access to and use of cancer information by all who need it.

Through these efforts, we will gain a far richer understanding of how people use health information and access communications technologies of all kinds. We will use that understanding to improve outcomes in cancer prevention, early detection, and treatment and to improve the lives of cancer survivors and patients needing palliative care.

### Study Shows Perceptions Can Change

NCI-supported researchers have shown that the combination of tailored print materials and a call from a telephone health advisor can have several positive effects. This was the first study to show that women's perceived risks about breast cancer could be changed, and that the changes were maintained a year later. Women who received the combination of tailored communications also were more knowledgeable about breast cancer and mammography and were significantly more likely to get mammograms.

## PROGRESS IN PURSUIT OF OUR GOAL

To maximize the effectiveness of all our communications and to support communications research, planning, implementation, and evaluation, we are **taking steps to collect, more effectively analyze, and disseminate critical information about our audience groups.** Planning for the **Health Information National Trends Survey (HINTS)** is well underway. HINTS, to be launched in 2002, will be the only national survey focused on cancer communications. It will gather information from about 9,000 participants on health, sociodemographics, and access to health care; knowledge about cancer; risk perceptions; cancer-related behaviors such as cancer prevention and screening; as well as data on such topics as personal cancer experience, social ties, and self efficacy. The data will be analyzed and made quickly available to the research community to inform future communications research and program planning for cancer as well as other health issues. Data will also be shared with the advocacy community through briefings and special reports.

NCI staff are tapping a **health and lifestyle information database** to identify and disseminate data on the information needs of specific audiences, develop appropriate educational messages, and identify the best media, locations, and techniques for communicating cancer information. Staff also have developed and maintain a NewMediacy listserv that is narrowing the knowledge gap between the private and public sectors.

NCI-sponsored **pilot projects and educational materials focus on increasing access to and use of cancer communications by all populations.** Last year, NCI announced a new initiative and within the same fiscal year, funded four research and development projects to develop unique approaches for overcoming the cancer digital divide. The projects provide underserved groups with access to and the wealth of cancer information now available through computers. Each involves public-private partnerships, and one has resulted in a joint effort with the Markle Foundation for continued funding. (See the sidebar on this page for more information.)

NCI also is **developing a communications toolkit to guide the development of health communications programs for underserved communities.** It is designed to assist leaders and organizations in promoting health

## NCI Supports Digital Divide Pilot Projects

NCI is supporting four research and development projects to overcome the digital divide by testing the efficacy of new communications technologies in cancer prevention and education. These projects involve partnerships among NCI-supported Cancer Centers and Cancer Information Service (CIS) Centers at universities and a wide range of community organizations and programs including Head Start, urban and rural community groups, senior centers, and computer suppliers. We will assess the results of the pilot projects and disseminate information about promising interventions.

- A regional CIS office is partnering with a Cancer Center, a Head Start Center, a group concerned with urban policy, and a group that supplies computers to children to develop techniques for teaching Head Start parents how to use computers and access health information on the Web.
- Another Cancer Center and regional CIS office are partnering to increase access to cancer information and the use of technology by residents of an economically depressed area in the community.
- A university and two regional CIS offices are collaborating to promote the use of, and training by peer advocates for, a computer-based education program among underserved women diagnosed with breast cancer in a rural area in one state and an urban area in another. The project is helping some 280 African American women in the urban area play a larger role in their own care by providing them with access to online information. They are being trained in the use of laptop computers and are learning to get cancer information and support over the World Wide Web. These patients say it helps them connect with people and information at all hours of the day and night, especially when they are worried.
- A collaboration between a university and a regional office of the CIS is examining the use of a low-literacy cancer information computer program to determine its potential to increase the use of new communication technologies for health information by older adults in a group of senior centers.

(For more information, go to [cancercontrol.cancer.gov/eocc/ddpp.html](http://cancercontrol.cancer.gov/eocc/ddpp.html).)



## THE PLAN — CANCER COMMUNICATIONS

### Goal

Increase knowledge about, tools for, access to, and use of cancer communications by the public, consumers, patients, survivors, and health professionals – with a special focus on diverse populations – to accelerate reductions in the U.S. cancer burden.

### Objectives and Milestones for Fiscal Year 2003

1. Establish new data collection and analysis strategies to support cancer communications planning and evaluation. \$4.1 M
  - Analyze data from the Health Information National Trends Survey (HINTS) and make results available to researchers and program planners as early as possible. \$1.00 M
  - Explore the use of Internet-based data collection to follow a subset of people interviewed as part of HINTS. \$0.50 M
  - Conduct a HINTS survey of cancer survivors in parallel with the HINTS public survey to collect data on survivors' use of different media, their risk perceptions, cancer-related behaviors, personal cancer experiences, and use of complementary and alternative medicine. \$1.50 M
  - Explore the need for national data collection about health professionals' communication practices. \$0.35 M
  - Continue to operate the NewMediacy listserv and health and lifestyle database to inform NCI's planning and evaluation efforts about which audiences use which new media and how they use them. \$0.20 M
  - Create a searchable database of cancer-related communication research reports accessible to researchers and program planners. \$0.50 M
  
2. Increase access to and use of cancer communications by all populations, especially underserved populations. \$2.5 M
  - Analyze and disseminate the results of four Digital Divide Pilot Projects to test strategies to increase access to and use of online and other interactive cancer communications by underserved populations. \$0.50 M
  - Fund additional Digital Divide Pilot Projects and evaluate outcomes. \$1.00 M
  - Transform the clinical trials Web portal to enable visitors to more quickly find information and resources. \$1.00 M

in their communities and addressing inequities in the quality of and access to cancer care. The kit will contain instructional materials and examples of proven strategies for effective cancer communications.

We are *working to improve the quality and volume of communications related to clinical trials*. Research is underway to improve and assess the communication of risks, benefits, and other essential elements of the informed consent and decision making processes. A Web-based educational program is

assisting research teams with issues related to the protection of human participants in research ([cme.nci.nih.gov](http://cme.nci.nih.gov), [ohsr.od.nih.gov/cbt](http://ohsr.od.nih.gov/cbt)). And our new Cancer Clinical Trials Education Series provides clinical trials information to the public, healthcare professionals, and patient groups.

NCI has taken several steps for *accelerating research and development of interventions*. We solicited applications for grants to create up to five Centers of Excellence in Cancer Communications



<p>3. Accelerate the pace of research and development of interventions in cancer communications.</p> <ul style="list-style-type: none"> <li>■ Continue to support Centers of Excellence in Cancer Communications Research.</li> <li>■ Establish interdisciplinary training partnerships and fund health communications laboratories to develop and conduct training programs for researchers in growing areas, including risk communications and interactive health communications. \$1.5 M</li> </ul>	<p>\$1.5 M</p>
<p>4. Develop a menu of communication choices to meet the needs of all users, and especially to increase knowledge about, tools for, access to, and use of these choices by diverse populations.</p> <ul style="list-style-type: none"> <li>■ Develop new tools and products to facilitate cancer communications for the public, patients and their caregivers, underserved populations, advocacy groups, health professionals, and cancer communicators. \$2.00 M</li> <li>■ Continue work with the Agency for Healthcare Research and Quality to fund research on decision aids (“Making Quality Count for Consumers and Patients”). Link with Digital Divide Pilot Projects to promote dissemination and use of interactive communication tools and collect information on current levels of, and barriers to, use. \$2.00 M</li> <li>■ Assess the status of low-literacy research and national initiatives in order to develop a strategic plan for low-literacy programs and materials. \$1.00 M</li> <li>■ Develop and promote a media toolkit to facilitate the media’s use of NCI’s resources in preparing cancer-related stories. \$0.50 M</li> </ul>	<p>\$5.5 M</p>
<p>5. Improve the science of dissemination and the dissemination of science to assure that our citizens realize the benefits of research investments.</p> <ul style="list-style-type: none"> <li>■ Fund dissemination and diffusion supplements to grantees with proven interventions ready for dissemination. \$4.00 M</li> </ul>	<p>\$4.0 M</p>
<p>Management and Support</p>	<p>\$1.5 M</p>
<p><b>Total</b></p>	<p><b>\$19.1 M</b></p>

Research in Fiscal Year 2002. The response was excellent, showing that this initiative meets a real need in the research community. The Centers will encourage focused interdisciplinary studies to accelerate scientific developments in cancer communications, increase the number of investigators from a range of disciplines who focus on the study of cancer communications, and train investigators to conduct cutting-edge communications research directly relevant to the context of cancer prevention, detection,

treatment, control, and survivorship (cancercontrol.cancer.gov/communicationcenters).

NCI also supported a Community Clinical Oncology Program based project to collect data from newly diagnosed cancer patients to learn more about their special communication needs. This information will be used for program planning and to assess the need for additional research.

Through the use of technology and in response to various needs, we are *improving existing communica-*

tion channels and developing new ones. NCI's NewsCenter Web site, launched in May 2001, provides journalists with easy access to downloadable photos, graphics, video clips, and audio clips; transcripts of interviews with NCI scientists; traditional press releases and backgrounders; and customized links to other relevant NCI Web sites.

NCI also is using several new features on the Web including an instant messaging service to answer cancer questions submitted online ([cancer.gov/Livehelp/vp/vp\\_cq.html](http://cancer.gov/Livehelp/vp/vp_cq.html)), a natural language search system, the online NCI Publications Locator ([cissecure.nci.nih.gov/ncipubs](http://cissecure.nci.nih.gov/ncipubs)), and new minimum standards for improved navigability, consistency, and usability ([usability.gov](http://usability.gov)). A new Communication Technologies Research Center for usability testing, technology evaluation and demonstration, and training provides the tools needed to design evidence-based cancer information products and services, and a new Emerging Technologies Unit searches out and applies new and evolving technologies to cancer communications.

Several *activities illustrate our commitment to improving dissemination of NCI research results*. We are working to heighten researchers' understanding about the needs of end users of research products and to increase the usefulness of the products so they will benefit people.

We have put in place several mechanisms to assist scientists in the dissemination of research findings. To increase the likelihood that citizens will benefit from our investment in research, we are strengthening NCI's partnerships with voluntary health organizations, HMOs, and community organizations and are planning to fund in 2002 six to eight competitive supplements to NCI grantees who have effective cancer control interventions ready for dissemination. We are convening, in collaboration with private organizations and other Federal agencies, an interdisciplinary group to develop recommendations for intervention researchers and encourage new partnerships among researchers, funders, and receiving organizations. As a unique component of the Transdisciplinary Tobacco Use Research Center (TTURC) program, the Robert

## Research on Targeted and Tailored Communications Highlights Successes

A group of NCI-sponsored health communications researchers recently teamed up to prepare articles for a special issue of the *Journal of Family and Community Health*. They reported on their efforts to develop communications for special populations, such as Asians, African Americans and Hispanics, and to individualize cancer information. One team showed that focus groups could be conducted through the Internet and therefore could include people who would not otherwise participate. Another group tested the feasibility of a tailored, interactive computerized cancer pain program for patients. In pilot research, the majority of patients said the computer programs were easy, enjoyable, and informative tools. The computer programs extend the reach of health professionals and permit better reporting of patients' pain and tailored advice based on each patient's unique pain profile.

Wood Johnson Foundation, as a cosponsor, has funded hiring a specialist at each TTURC to facilitate communication with the public, researchers, and the media. (See page 86.) In partnership with the Agency for Healthcare Research and Quality (AHRQ), we have commissioned an evidence-based review of effective strategies to facilitate dissemination of cancer-related interventions. We will communicate the results through the World Wide Web, print, and other channels. And, in partnership with the Centers for Medicare and Medicaid Services, we are helping to support a national demonstration to test a new Medicare smoking cessation benefit for older smokers, including dissemination of an evidence-based smoking cessation guide for smokers ages 50 and older and a guide for Spanish speaking Medicare beneficiaries.

# Planning National Agendas for Disease-Specific Research

*When I entered the clinical trial, my doctor said to me, “You are not going to die right away.” This was a big surprise! I felt so bad and had been told that I could expect to live only a few more months. I just assumed I was at the end of the road. After several tries that failed, they finally found a treatment regimen that seems to have turned my cancer around — at least for now. This kind of thing is very unusual for pancreatic cancer. I have been so blessed and want others to know that there is hope.*

- CHRISTINE, CLINICAL TRIAL PATIENT

Each of the 1,268,000 Americans who will be diagnosed with cancer this year will battle a very specific, very personal disease. While the hundred-plus distinct diseases we call “cancer” have several essential attributes in common, each type of cancer has its own unique characteristics that affect how it arises, how it progresses, and how it can be most effectively treated. And while we have learned much that is broadly applicable to all types of cancer through our core research programs and the initiatives of the Extraordinary Opportunities, we must be equally alert to the specific tendencies and behaviors of each cancer type. This is why NCI plans, promotes, and carries out an ambitious program of *disease-specific research*.

NCI charts the course for its disease-specific efforts primarily through advice from expert Progress Review Groups (PRGs). The PRGs are panels of 20 to 30 prominent members of the scientific, medical, and advocacy communities that assess the state of the science for a single type of cancer or a group of closely related cancers and make recommendations for future research. Over a nine-month period, each PRG identifies gaps in our understanding of the disease under study, barriers to progress, and key research priorities. The process culminates in the wide release of PRG findings and priorities in a comprehensive report. All PRG reports become road maps that guide NCI and the scientific community in their efforts to make

progress against specific types of cancer. To date, six PRG reports have been issued. Six more PRGs are in progress or planned. (See schedule, page 97.)

NCI’s extensive slate of PRGs includes breast, prostate, lung, and other common types of cancer as well as less common diseases like pancreatic cancer, multiple myeloma, and brain tumors. By addressing these more unusual types of cancer through the PRGs, NCI hopes to raise awareness of the scientific opportunities afforded by each disease and to stimulate much-needed research.

## RESPONSE AND COMMUNICATION

The NCI responds rapidly and enthusiastically to PRG recommendations. For each PRG, NCI staff:

- Form an internal working group of disease-specific experts to spearhead the Institute’s response to the recommendations, identify gaps in our understanding, and propose new programs and initiatives where needed.
- Thoroughly analyze the recommendations to determine the extent to which they are being addressed — or could be addressed — through existing programs or efforts.
- Reconvene the PRG to discuss what we learn through this analysis and to clarify what gaps remain.

- Develop strategies to implement the recommendations, particularly in gap areas.
- Communicate our decisions to the scientific community and enlist their active participation in the implementation process.
- Ensure that effective mechanisms are in place to implement decisions.
- Follow up to ensure that the recommendations continue to be addressed.
- Report on our results.

To ensure that researcher and advocacy communities are aware of NCI's disease-specific priorities, NCI is developing a comprehensive, systematic plan for disseminating and promoting the PRG reports. PRG-related information is distributed at major medical meetings, in journals and newsletters, and on the World Wide Web. NCI has also partnered with several advocacy groups to promote the priorities identified by various PRGs.

Even with all these efforts in place, we recognize that the ultimate success of the PRG process depends on researchers' ability and willingness to undertake research projects in disease-specific areas of critical need. NCI encourages the scientific community to respond to its disease-specific priorities by treating the PRG reports as broad Program Announcements that indicate the most pressing needs and opportunities, and notifies the community about current fund-

ing opportunities that address the PRGs' recommendations through its Cancer Research Initiatives Web site ([cri.cancer.gov](http://cri.cancer.gov)). Grant applications that reference a PRG report receive special consideration in the funding exceptions process.

Consumer advocates also play a key role in the PRGs and their follow-up. Advocates are involved throughout the PRG process, serving as PRG members and keeping their communities informed about the PRG and its recommendations and mobilizing in support of PRG priorities. They may also help raise awareness of the priorities among researchers and clinicians.

## HIGHLIGHTS OF PRG RECOMMENDATIONS

Based on review and analysis of the recommendations of the first six PRGs, it is clear that many of the recommendations are, or could potentially be, addressed by programs that are already in place. In some cases modification or supplementation of an existing program is sufficient to get the research on track. The PRGs have also pointed to obvious gaps in NCI's disease-specific programs. For example:

- The **Breast Cancer PRG** noted that our lack of understanding of the biology and developmental

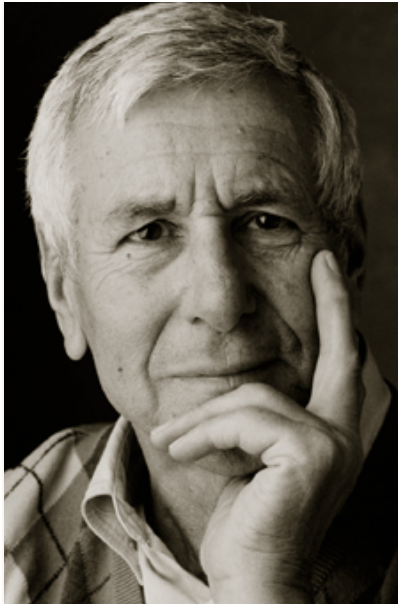


### Multiple myeloma incidence is on the rise.

**My doctor said I had multiple myeloma, and I said, "What's that?" When she said it was cancer, I was stunned. I had never even heard of this disease.**

Multiple myeloma is a cancer of blood plasma cells that grow out of control and form tumors, usually in the bone marrow. These tumors interfere with the blood-forming functions of the marrow and the abnormal plasma cells cease producing infection-fighting antibodies. Multiple myeloma is one of the blood system cancers that are rising in incidence – new cases are increasing by nearly one percent per year. An estimated 14,400 new cases will be diagnosed in 2001.

Deaths from this disease also are increasing, and the average patient survives only three years from diagnosis. Typically a disease of the elderly, myeloma is now striking people as young as their twenties and thirties. Multiple myeloma was one focus of NCI's Leukemia, Lymphoma, and Myeloma (LLM) PRG, whose report was released in May 2001; the PRG group recommended a large case-control study to investigate the etiology of the three diseases, as well as the development of an infrastructure and methodologies to better understand the interaction among immune function, infectious agents, environmental toxins, and lifestyle factors that can lead to the diseases' development.



## Pancreatic cancer continues to affect thousands.

**My father died from pancreatic cancer. My brother and I wonder if we've inherited a high risk for this awful disease. Are scientists working on ways to prevent this cancer and find out who's at risk?**

Pancreatic cancer is a particularly devastating disease because it spreads quickly, seldom causes clear symptoms until it is advanced, and is almost universally fatal. In 2001, an estimated 29,200 new cases will be diag-

nosed, with most patients living six months or less after diagnosis. Severe wasting and pain are tragic hallmarks of pancreatic cancer. Recognizing the urgent need for improved detection, treatment, and symptom management of this disease, NCI convened a Pancreatic Cancer PRG in 2000. The PRG stressed the need to better understand how the normal pancreas develops and functions — an essential foundation for research on how pancreatic cancers arise and the environmental and other factors that may influence their growth and spread.

genetics of the normal breast was a significant barrier to progress against the disease. The NCI responded by joining several other NIH Institutes to release a Program Announcement (PA) seeking applications for research on normal breast development, as well as on changes in the breast throughout the development of early and advanced cancer. This PA has generated eight new research projects.

- The Prostate Cancer PRG told us that the lack of validated animal models of prostate cancer was severely impeding progress. Since then, four separate research teams have begun work on models of prostate cancer through NCI's Mouse Models of Human Cancers Consortium.
- The Leukemia, Lymphoma, and Myeloma PRG found that the infrastructure for developing new treatments of hematologic malignancies, particularly those exploiting molecular targets, is inadequate. They called for the development of consortia that would bring together experts across multiple disciplines and institutions to participate in the rapid discovery and development of cancer therapies. The ultimate goal of the program would be to shorten drug development time of five to ten years to about two years through an alliance among academia, industry, government, and patients. NCI is currently investigating ways to create and support these novel consortia.

## New drugs provide hope for prostate cancer patients with bone metastases.

When prostate cancer spreads, it often invades the bones, where it causes severe, debilitating pain. However, several drugs currently under study may combat bone metastases, slowing the spread of the cancer and improving the patient's quality of life. For example, the class of drugs known as bisphosphonates has already been established as effective against breast cancer and multiple myeloma, but these drugs have not been considered particularly effective against prostate cancer — until now. Clodronate, a bisphosphonate, has shown activity against prostate cancer metastasis, opening the door for further studies involving more potent bisphosphonates, or higher doses of the drug. A second drug, Atrasentan, targets the protein endothelin-1, which promotes cell growth in bone and which is overactive in prostate cancer cells. Finally, a combination of chemotherapy and a bone-targeted radiation drug, strontium-89 (Sr-89), may prolong the lives of men with prostate cancer that has spread to the bones. Sr-89 is a radioactive substance used to relieve bone pain caused by metastatic prostate cancer. When injected by vein, Sr-89 moves into bones and delivers radiation directly to cancer that has spread there. Metastasis was a key topic of interest for the Prostate Cancer PRG, whose report is found at [planning.cancer.gov/PRGReports/PPRGReport/toc.htm](http://planning.cancer.gov/PRGReports/PPRGReport/toc.htm).



## New imaging technology improves early detection for lung cancer.

Spiral CT is a promising new technique that can be used to detect lung cancer at a very early stage, before it has had a chance to spread. This technique uses X-rays to scan the entire chest quickly, in 15 to 20 seconds, during a single breath-hold. It is safe — the amount of radiation during a spiral CT scan is about the same as that absorbed during a mammogram — and simple. But will detecting these early tumors reduce the likelihood of dying from lung cancer? The NCI is working to find out. The year-long Lung Screening Study (LSS), began in the fall of 2000 to gauge the feasibility of a larger, more definitive study down the road. Through the LSS, we will learn, first and foremost, whether smokers will be willing to be randomized to receive something other than a spiral CT scan in a comparative study. The LSS will also provide important information about the medical follow-up of people who have the scans, as well as the costs involved. The Lung PRG, whose report was released in August 2001, discussed the topic of screening extensively, calling for the rapid evaluation of spiral CT as a means of detecting cancer early and ultimately reducing deaths from lung cancer.

Furthermore, NCI is taking steps to address a number of broad scientific needs noted by several PRGs, such as the need for research training and the development of biomarkers of disease. For example:

- NCI is currently expanding the Specialized Programs of Research Excellence (SPOREs) program to cover a number of the cancers addressed by the PRGs, including gynecologic cancers, brain tumors, leukemia, lymphoma, and myeloma. SPOREs are described in detail on page 26-28.
- Several PRGs have recognized a need for the identification of biomarkers of disease. The Early Detection Research Network (EDRN) is dedicated to meeting this need. Projects specifically related to prostate, lung, and ovarian cancers are among those well under way, with others planned. For more on EDRN, see page 75.
- Several PRGs discussed the importance of more accurate diagnosis and staging of cancer. Research conducted through the The Director's Challenge: Toward a Molecular Classification of Tumors will facilitate diagnosis at the molecular level, enabling greater precision in diagnosis and treatment. To date, the Director's Challenge has stimulated some 22 supported projects covering a diverse array of cancers including breast, prostate, lung, brain, ovary, colon, and leukemia and lymphoma. See page 75 for more information on the Director's Challenge initiative.



## Brain tumors pose unique challenges for researchers and patients.

**We have to carefully weigh the potential benefit of every brain tumor surgery, chemotherapy, or radiation treatment against the risk of mental and functional damage. And with children, we worry about future learning or developmental problems.**

Many cancers have one or more subtypes, but brain and central nervous system (CNS) tumors are extraordinary in this regard — more than 125 types are known to exist, and their symptoms, aggressiveness, treatment, and outcome vary greatly. Because brain tumors affect the organ that is the essence of the

“self,” surgical approaches for treating most other cancers — removing the tumor and a border of normal tissue if not the entire affected organ — often cannot be used without damaging vital mental processes or brain functions. Moreover, many brain and CNS tumors are highly resistant to radiation and chemotherapy. The Brain Tumor PRG convened by NCI noted these special challenges in its report, published in 2000, and called for the development of novel treatment agents and approaches, including new chemotherapies, treatments that target the immune system, gene therapy, antiangiogenesis agents, and viral agents.



## ASSESSING THE IMPACT OF THE PRGs

It is too early to fully assess this, but the early signs are encouraging. NCI has recently begun the critical task of assessing the impact of the PRG effort within the research community. As part of a system for evaluating the PRG process and outcomes, the Institute will analyze changes in grant applications, funding levels, and types of research funded that occur after the completion of a PRG. Starting with the Breast and Prostate PRGs, NCI will issue a status report two to three years after each PRG, and the groups will reconvene to discuss the status of the recommendations and NCI's response and to consider further action. This process will provide valuable information and insight about our directions in disease-specific planning.

While the process may be refined over time, it is clear that the combined perspectives of PRG members, NCI staff, researchers, and cancer advocates will continue to influence the future direction of both broad-based and disease-specific research. By working together, we can ensure the most effective use of resources focused on both needs and opportunities for advances against all cancers.

## New initiatives aim to improve breast cancer treatment.

The findings of clinical trials in breast cancer over the last ten years have provided physicians and their patients with a wealth of new information to guide their treatment choices – but at the same time, have also complicated their decision making. To help oncologists and patients choose between radiation therapy, chemotherapy, or hormone therapy to try to eliminate cancer cells left behind after surgery, NCI co-sponsored a consensus conference at the end of 2000 to synthesize the information from recent research and make recommendations for routine cancer care. The breast cancer experts participating in the conference provided advice on the factors that should guide the choice of adjuvant therapy, as these follow-up treatments are known, and made recommendations about which patients should consider hormonal, chemotherapy, or radiation therapy. In addition, consensus conference participants also considered the side effects and quality of life experienced by patients undergoing the various forms of adjuvant therapy and promising new directions for this research. In other research, NCI is sponsoring clinical trials to compare the effects of removing only one or a few lymph nodes during breast cancer surgery to the standard, more invasive practice of removing more lymph nodes.

## Schedule of Completed and Planned Progress

### Review Groups

Completed August 1988	Breast Cancer
Completed August 1988	Prostate Cancer
June 1999-November 2000	Colorectal Cancer
November 1999-February 2001	Brain Tumors
February 2000-May 2001	Pancreatic Cancer
April 2000-August 2001	Leukemia-Lymphoma-Myeloma
August 2000-November 2001	Lung Cancer
December 2000-February 2002	Gynecologic Cancers
March 2001-May 2002	Kidney/Bladder Cancer
June 2001-August 2002	Stomach/ Esophageal Cancer
September 2001-November 2002	Liver/Bile Duct Cancer
December 2001-February 2003	Skin Cancers

*I've been treating children with leukemia for over thirty years now. We're actually able to cure the majority of the children we see now, and that's nothing short of a miracle, in my book. Still, there's a lot to be done — too many children suffer needlessly during their illness, and too many children suffer devastating aftereffects of their treatment. And even today, far too many children die. I think we're making progress, though. I look forward to the day when we have leukemia (and all cancers!) under control — and I think we may even see it in my lifetime.*

- DAVID, ONCOLOGIST

### Hope and Promise Are Becoming More Real

Dr. Alan Rabson has seen it unfold.

Alan S. Rabson, M.D., began his career at the National Cancer Institute as a resident in pathological anatomy in 1955. After serving as Deputy Chief for Laboratory Pathology and Division Chief for Cancer Biology, Diagnosis, and Centers, he became NCI's Deputy Director in 1995. Recently, he talked about NCI's accomplishments since the passage of the National Cancer Act in 1971 and about the future of cancer research and care.

*In 1971, when the National Cancer Act was signed, the goal was to cure cancer within five years. Thirty years later, we still haven't cured cancer. Why is this?*

Well, 30 years later we do cure more than half of all cancers. For example, nearly half of all high-grade lymphomas are cured. The overwhelming majority of all testicular cancers are cured. We're curing more breast cancer and ovarian cancer now than ever before, and most all of this has come about since 1971.

We're also much more attuned to the importance of detecting cancer early and the possibilities for preventing its development. For example, when the National Cancer Act was signed, screening mammography was not standard medical practice as it is today. In addition to regular mammography, women at high risk for breast cancer now have the option of taking drugs, such as tamoxifen, that may prevent the disease altogether.

But also, our goal now is to stabilize patients so that while they still may have cancer, they can have the longest period possible of high quality life. The treatments we're developing now are making this

possible for more and more people. For instance, treatment with the drug gemcitabine prolongs the lives of people with pancreatic cancer, and it's possible that new drugs we're developing may prolong these people's lives further. And the development of Taxol™ in the 90s greatly improved and revolutionized the treatment of ovarian cancer.

*After the Act was passed, a group of experts was convened to figure out how we should plan and conduct cancer research. What impact did that group have on how we do science today?*

We convened several large groups out at a retreat facility in Virginia. We brought in around a hundred people at a time — all the top experts in cancer research in the world. We asked them, "If you had infinite resources, what would you do?" It was a wonderful experience, but many of the goals we came up with depended on things we had no technology for. For example, we talked about genes, and what we could do if we could sequence or clone them. We had the right ideas, but we were waiting for molecular biology to catch up. Now we can do things we never dreamed possible.

*What has been the most exciting thing that has happened during your tenure at NCI?*

In my 46 years here, everything has been exciting! But if I had to choose one thing, it would be the advances in molecular biology and genetics that have changed the world of cancer research and opened doors for so many new opportunities to explore. As we've come to understand the molecular signatures of cancer cells, we can classify tumors

according to their genetic characteristics. And the future promises to be even more exciting, as we discover new, targeted, and effective means of cancer treatment and prevention. One of the best examples of this is the development of a new, targeted treatment for chronic myelogenous leukemia and potentially other forms of cancer. And breast cancer patients whose tumors have certain molecular characteristics have benefited tremendously from the introduction of Herceptin™, another targeted treatment. In addition, public support for basic biomedical research has become much stronger, in large part because of the growth of the advocacy commu-

nity. We've also enjoyed tremendous political support, which is a reflection of the popular support.

*What can we expect from cancer-related science in the next 5-10 years, and what will it mean for patients?*

More patients will be cured, but more than that, more people will live with a stabilized disease. Will we ever cure all cancers? No. But we will learn to manage most of them and patients will be able to maintain a high quality of life — just as people with heart disease can live well for many years after their diagnosis.

## How It All Comes Together

When the National Cancer Act was adopted in 1971, there was widespread hope that the additional resources and responsibilities that it would bring to the NCI would soon lead to a “magic bullet” cure for cancer. Instead, as a result of research over the last thirty years, we now know that cancer is a complex set of diseases, for which there is no single cure.

An examination of what we have learned in the major fields of cancer research shows how far we have come and why implementing the plans described in this document is essential for continuing the remarkable progress of the last three decades.

■ **Cancer Biology** – Scientists have learned that cancer is a disease resulting from multiple genetic changes and have identified numerous hereditary, environmental, life style, and infectious agents that initiate the genetic changes that lead to cancer. NCI research initiatives related to the Signatures of Cancer Cells and Genes and the

Environment focus further exploration into the inner workings of cells and the processes that contribute to cancer development and progression.

■ **Prevention and Control** – We have come to recognize the roles of tobacco, diet, and exercise in cancer development and have identified numerous environmental carcinogens. We also know that some individuals are more susceptible to these exposures than others. Better understanding the many causes of cancer has opened multiple avenues to prevention, including chemoprevention. Numerous evidence-based interventions have been employed to better control cancer. Continued research on Genes and the Environment, Tobacco and Tobacco-Related Cancers, Molecular Targets, and Cancer Communications will lead to further improvements in the future.

- **Early Detection and Diagnosis** – Thirty years ago, cancer was often detected only when it was so far advanced that it was next to impossible to treat it effectively. Today, physicians are armed with a variety of non-invasive screening and detection tools including mammography, colonoscopy, ultrasound, and CT imaging as well as tests of body fluids or tissue such as the PSA for prostate, HPV for cervical, and CA-125 for ovarian cancer. In some cases, they also can use genetic testing to determine predisposition to a specific type of cancer. We will continue to make progress in early detection and diagnosis through research and development on the Signatures of Cancer Cells and Cancer Imaging.
- **Treatment** – Today, treatment is more targeted and less debilitating: physicians use image-guided surgery and radiation therapy and surgical techniques such as lumpectomy instead of mastectomy. And we are beginning to develop drugs such as Herceptin™ for breast cancer and Gleevec™ for chronic myelogenous leukemia that target the specific genetic characteristics of cancer. Many more promising treatments are on the horizon based on the discoveries and advances of the past 30 years. Our continued efforts in Molecular Target research and development and acceleration of NCI's National Clinical Trials Program are critical to making these treatments a reality.
- **Surviving Cancer and End-of-Life Issues** – At the time the National Cancer Act was passed, many people did not survive cancer at all. Today in the U.S. there are over eight million cancer survivors who need care and support to make the most of their lives. For those who lose the struggle with cancer, we have learned much in the last thirty years about easing their pain at the end of life. We are committed to improving our performance in addressing survivorship and end-of-life issues through continued research on the Quality of Cancer Care and initiatives in Cancer Communications.

Continuing progress in cancer research will depend on our ability to maintain a research system that allows the scientific community to apply new insights and emerging technologies, pursue innovative ideas, and facilitate collaboration among experts from a range of scientific disciplines. Cross-cutting to all of these are our NCI Challenge efforts for Enhancing Investigator-Initiated Research; building Centers, Networks, and Consortia; Studying Emerging Trends in Cancer; Reducing Cancer-Related Health Disparities; building and maintaining Informatics and Information Flow systems; and preparing future cancer scientists through Cancer Research Training and Career Development programs.

Go to [cra.nci.nih.gov/2\\_accomplishments/index.htm](http://cra.nci.nih.gov/2_accomplishments/index.htm) for more information on the National Cancer Act and the past 100 years of advances against cancer.

# Acknowledgments

Each year the National Cancer Institute calls upon countless people at NCI and in research, professional, and advocacy organizations around the country to provide their insights, perspectives, and expertise to help us develop *The Nation's Investment in Cancer Research Plan and Budget Proposal*. We express our gratitude to all who contributed to this effort for the Fiscal Year 2003 Plan.

Several NCI staff deserve special recognition for their contributions to the development of this document. *Cherie Nichols*, Director of the Office of Science Planning and Assessment, served as overall advisor for the project. *Kathie Reed*, Branch Chief for Science Planning, provided leadership and guidance for each step of the process from conceptualization to production. *Kathy Gallagher*, *Jane Lockmuller*, *Kate Nagy*, *Jennifer Sutton*, and *Anne Tatem* worked tirelessly alongside the Champions from around the Institute to conceptualize, write, and ensure the accuracy of the material. Several other staff in the Office of Science Planning and Assessment played significant supporting roles including *Buddy Clark*, *Marilyn Duncan*, *Kevin Callahan*, *Jim Corrigan*, *Bernard Glassman*, *D. J. Joya*, and *Anna Levy*. *John Hartinger* and *Ngan Nguyen* in the NCI Financial Management Branch ensured the integrity and accuracy of the budget information with diligence and dedication. *Paul LaMasters* in the Office of Communications ensured the quality and timeliness of document printing.

## **Extraordinary Opportunity and NCI Challenge Champions**

NCI Director *Dr. Richard Klausner* served as Editor-in-Chief with support from *Dr. Alan Rabson* and *Dr. Robert Wittes*. The NCI staff members listed below served as Champions for the Extraordinary Opportunity and NCI Challenge areas.

## **Extraordinary Opportunity Champions**

Genes and the Environment – *Dr. Robert Hiatt*, *Dr. Robert Hoover*  
Cancer Imaging – *Dr. Ellen Feigal*,  
*Dr. Daniel Sullivan*  
Defining the Signatures of Cancer Cells –  
*Dr. Robert Strausberg*

Molecular Targets of Prevention and Treatment – *Dr. Robert Wittes*,  
*Dr. Edward Sausville*, *Dr. J. Carl Barrett*  
Research on Tobacco and Tobacco-Related Cancers – *Dr. Robert Croyle*,  
*Dr. Neil Caporaso*, *Dr. Scott Leischow*  
Cancer Communications – *Dr. Barbara Rimer*,  
*Dr. Susan Sieber*, *Ms. Mary McCabe*

## **NCI Challenge Champions**

Investigator-Initiated Research – *Dr. Marvin Kalt*, *Dr. Dinah Singer*  
Centers, Networks, and Consortia – *Dr. Ellen Feigal*, *Dr. Brian Kimes*  
National Clinical Trials Program – *Dr. Robert Wittes*, *Dr. Michael Christian*  
Studying Emerging Trends in Cancer –  
*Dr. Rachel Ballard-Barbash*, *Dr. Brenda Edwards*  
Quality of Cancer Care – *Dr. Joseph Lipscomb*, *Dr. Martin Brown*  
Reducing Cancer-Related Health Disparities –  
*Dr. Robert Hiatt*, *Dr. Jon Kerner*,  
*Dr. Harold Freeman*  
Informatics and Information Flow –  
*Dr. Kenneth Buetow*, *Ms. MaryAnn Guerra*  
Cancer Research Training and Career Development – *Dr. Brian Kimes*

In addition to these Champions, *Dan Grauman*, *Susan Greenhut*, *Jill Johnson*, *Cheryl Marks*, *Tracy Thompson*, *Stacey Vandor*, and *Paula Zeller* made significant contributions to the content and accuracy of this document.

## **Fiscal Year 2003 Planning Committee**

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

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Deputy Director, NCI

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Deputy Director, Extramural Science and Director, Division of Cancer Treatment and Diagnosis

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Director, Center for Cancer Research

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*Dr. Peter Greenwald*  
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*Ms. Susan Waldrop*  
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Board of Scientific Advisors

*Dr. Michael Kastan*, Co-Chair  
*Dr. Craig Thompson*, Co-Chair  
Board of Scientific Counselors

*Ms. Paula Kim*, Member  
Director's Consumer Liaison Group

*Dr. Phillip Sharp*, Chair  
*Ms. Ellen Stovall*, Member  
National Cancer Advisory Board

## Valuable World Wide Web Locations

National Cancer Institute (NCI) [cancer.gov](http://cancer.gov)  
National Institutes of Health [www.nih.gov](http://www.nih.gov)  
Department of Health and Human Services [hhs.gov](http://hhs.gov)

This document online [plan.cancer.gov](http://plan.cancer.gov)

*Provides links to:*

- *NCI Initiatives* – Details of initiatives related to the Extraordinary Opportunities including program links
- *NCI Research Resources* – Over 100 research services and tools for cancer researchers
- *Funding Opportunities* – Research funding and training opportunities available through NCI
- *CancerNet* – Information for patients and physicians, links to Physician Data Query (PDQ®) and CANCERLIT®
- *cancerTrials* – Clinical trials information for patients, physicians, and investigators
- *NCI NewsCenter* – Recent major press releases from NCI
- *Specialized Programs of Research Excellence* – Information about NCI's SPORE program
- *Atlas of Cancer Mortality* – Customized viewing of geographic cancer trends in the U.S.

NCI Science Planning and Assessment [planning.cancer.gov](http://planning.cancer.gov)

*Provides links to:*

- *Cancer Research Portfolio* – A comprehensive database of NCI-supported research
- *Progress Review Group Reports* – Reviews of NCI's programs for specific cancer types
- *Research Initiatives by Type of Cancer* – Current NCI initiatives, many with funding opportunities

## Ordering This Document

By email [cisocc@pop.nci.nih.gov](mailto:cisocc@pop.nci.nih.gov)  
By Internet [cancer.gov/publications](http://cancer.gov/publications)  
By phone 1-800-4-CANCER  
By fax 1-301-330-7968

*Cancer Research Training* [cancertraining.nci.nih.gov](http://cancertraining.nci.nih.gov)

Research training, career development, and educational opportunities available through the NCI

*Cancer Centers* [cancer.gov/cancercenters](http://cancer.gov/cancercenters)

Information on the Cancer Centers Program with links to NCI's national network of Cancer Centers

*SEER* [seer.cancer.gov](http://seer.cancer.gov)

Cancer surveillance data for the United States from the NCI Surveillance, Epidemiology, and End Results Program

*NCI Science Behind the News* [newscenter.cancer.gov/sciencebehind](http://newscenter.cancer.gov/sciencebehind)

Straightforward tutorials of basic concepts in cancer and cancer research

*Cancer Information Service* [cis.nci.nih.gov](http://cis.nci.nih.gov)

The latest, most accurate cancer information and *LiveHelp*, online instant messaging service available Monday through Friday from 9:00 a.m. to 4:30 p.m. Eastern Time

## Other Ways to Obtain Information

### Patients

Call the Cancer Information Service (CIS) at **1-800-4-CANCER** (1-800-422-6237) Monday through Friday from 9:00 a.m. to 4:30 p.m. your local time from anywhere in the U.S. to receive a personalized response to your specific questions about cancer. Deaf and hard of hearing callers with TTY equipment may call **1-800-332-8615**.

Send an email to [cancermail@cips.nci.nih.gov](mailto:cancermail@cips.nci.nih.gov) with the one-word message "Help" to receive a contents list and ordering instructions for receiving NCI information via email.

### Physicians

Call **1-800-345-3300** or email [cancermail@cips.nci.nih.gov](mailto:cancermail@cips.nci.nih.gov) to request CancerNet Search Services to obtain PDQ® and CANCERLIT® information.

