DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

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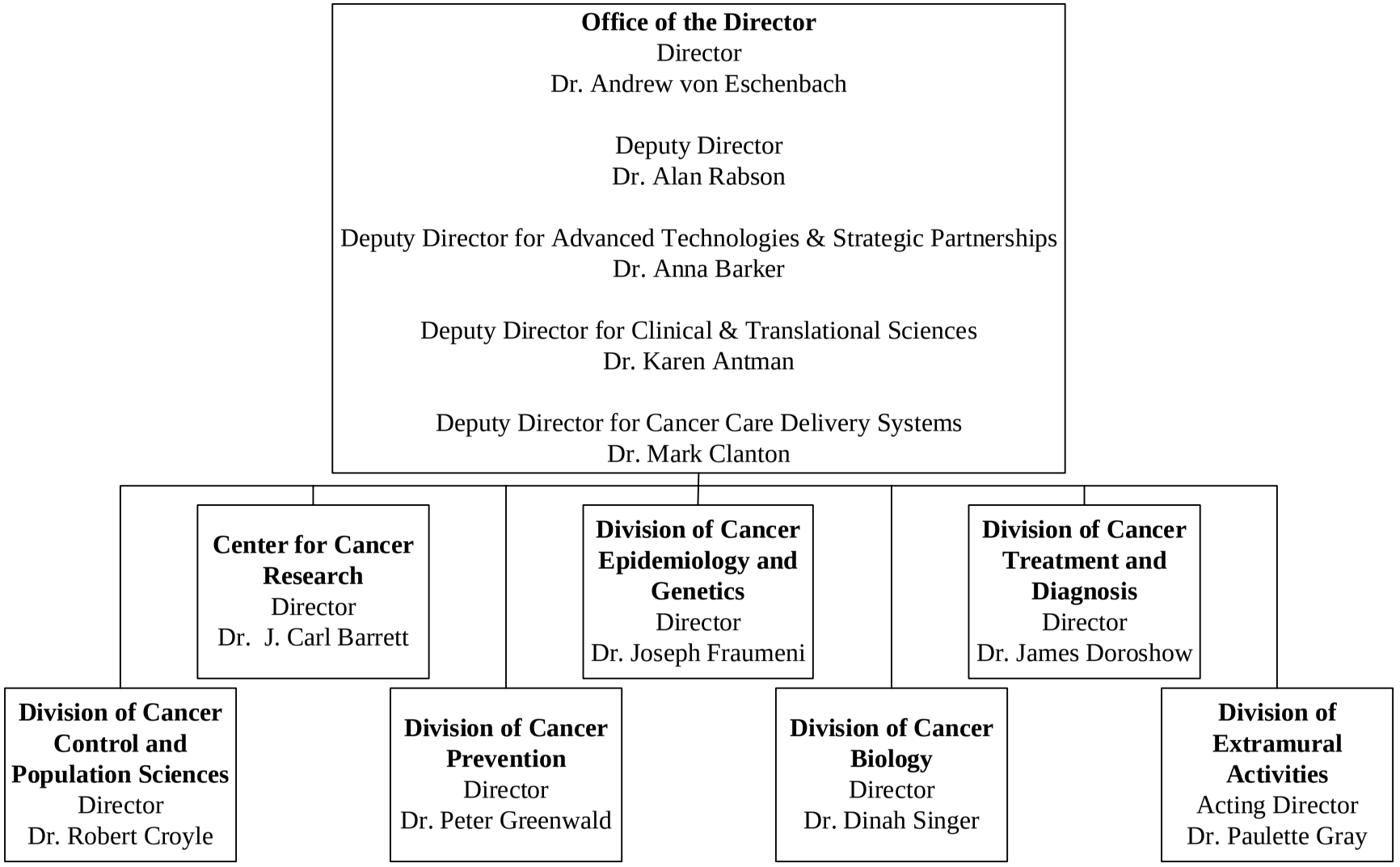
NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out Section 301 and title IV of the Public Health Service Act with respect to cancer, [$4,865,525,000] *$4,841,774,000*, of which up to [$8,000,000] $8,000,000 may be used for repairs and improvements at the NCI-Frederick Federally Funded Research and Development Center in Frederick, MD.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2005]

National Institutes of Health
National Cancer Institute

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$4,770,519,000	$4,865,525,000	$4,841,774,000
Enacted Rescissions	(31,264,000)	(40,267,000)	0
Subtotal, Adjusted Appropriation	4,739,255,000	4,825,258,000	4,841,774,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(15,357,000)	0	0
Comparative transfer to NIBIB for Radiology Program	(464,000)	0	0
Comparative transfer to Buildings and Facilities	(2,818,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	15,357,000	0	0
Subtotal, adjusted budget authority	4,735,973,000	4,825,258,000	4,841,774,000
Unobligated Balance, start of year	8,975,000	0	0
Revenue from Breast Cancer Stamp	4,814,000	0	0
Unobligated Balance, end of year	(10,317,000)	0	0
Subtotal, adjusted budget authority	4,739,445,000	4,825,258,000	4,841,774,000
Unobligated balance lapsing	(5,000)	0	0
Total obligations	4,739,440,000	4,825,258,000	4,841,774,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $12,512,000 FY 2005 - $15,000,000 FY 2006 - $15,056,000
Excludes $21,000,000 in FY 2005 and $31,000,000 in FY 2006 for royalties.

Justification

National Cancer Institute

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
2,981	$4,739,445,000	2,940	$4,825,258,000	2,940	$4,841,774,000	0	$16,516,000

This document provides justification for the Fiscal Year 2006 activities of the National Cancer Institute, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2006 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

Recent statistics show that cancer survival rates are improving while incidence and mortality decline. NCI monitors trends in cancer incidence, mortality, and related risk factors and uses this information to inform the direction of NCI's research priorities. *The Annual Report to the Nation on the Status of Cancer, 1975-2001*[1] was released in June 2004. Analysts found that 5-year survival rates had substantially improved during this time period for the most common 15 cancers in both men and women and ten cancers in children. In addition, overall observed cancer incidence rates dropped 0.5 percent per year from 1991 to 2001, while death rates from all cancers combined dropped 1.1 percent per year from 1993-2001. Death rates decreased for 11 of the 15 cancers in men and 8 of the 15 in women. Cancer incidence rates among men recently declined for 7 of the 15 most common cancer types: lung, colon, oral cavity, leukemia, stomach, pancreas, and larynx. And incidence rates among women decreased for 6 out of the 15 cancers: lung, colon, cervix, pancreas, ovary, and oral cavity. Of special note, lung cancer death rates among women recently leveled off for the first time and lung cancer incidence rates among women have shown a first ever decline.

Although these trends reflect progress in the prevention, early detection, and treatment of cancer, not all segments of the U.S. population have benefited equally. Reaching all segments of the population with high-quality services is essential to reducing cancer incidence and mortality even further, especially among underserved racial and ethnic populations as well as low-income and rural residents. It is critical that all partners with a stake in cancer control help to expedite the

[1] Prepared by NCI, the Centers for Disease Control and Prevention, the National Center for Health Statistics, the American Cancer Society, and the North American Association of Cancer Registries. seer.cancer.gov/report_to_nation/1975_2001/

translation of research discoveries to widespread and equitable delivery of preventive and clinical services.

Early in 2003, the Director of the National Cancer Institute took a bold step to move our national cancer agenda forward by announcing an NCI Challenge Goal to the Nation – to eliminate the suffering and death due to cancer by 2015. Since that time, NCI staff members have worked internally and with the national scientific, medical, and lay community to identify the critical elements required to reach this Goal. Through this process, seven priority areas have been identified as areas of strategic investment. These critical areas of research and development are *molecular epidemiology; integrative cancer biology; cancer prevention, early detection, and prediction; overcoming cancer health disparities; developing an integrated clinical trials system; strategic development of cancer interventions; and advanced technologies*. Each investment in these areas will accelerate the work and mission of NCI. All point to improved public health and patient care as our ultimate destination.

STORY OF DISCOVERY

Proteomics and the Early Detection of Cancer – Rich in History, Rich in Promise

Proteomics is the systematic study of proteins and their complex interactions in a cell, tissue, or organism. The word "proteomics" was coined just 10 years ago at a scientific meeting in Sienna, Italy, giving birth to this new field of study. In a very short length of time, proteomics research has dramatically extended our fundamental understanding of cancer and other diseases and is pointing to new methods for detection and treatment.

In one current undertaking, a team led by NCI's Dr. Lance Liotta and FDA's Dr. Emanuel Petricoin, has demonstrated the utility of proteomic profiling by mass spectrometry[2] for early detection of ovarian cancer. Success in this endeavor could drastically reduce mortality from this disease, which is usually detected in its later stages, when difficult to treat. In 2002, Drs. Liotta and Petricoin, along with scientists from Correlogic Systems, Inc. and colleagues in the extramural community, pioneered the use of mass spectrometry generated protein pattern analysis of blood samples to identify patterns, or "signatures," potentially associated with ovarian cancer. The team was able to reproduce, with remarkable accuracy, findings of protein signatures in blood samples previously collected for research purposes. This and other advances in proteomics follow a long history of scholarly learning about proteins and disease.

Discovering Proteins – "Standing in Front"
Focused study into the nature of proteins can be traced back to 1789. French chemist Antoine Fourcroy, while studying the composition of animal tissues, identified a type of substance which he named "albumin" or "Eiweisskörper." In 1838, Dutch physician and chemist, Gerrit Mulder, revealed that various types of "albumins" were found in plants as well as animals and proposed that these substances were a principle element of animal nutrition. Accordingly, Swedish colleague Jacob Berzelius suggested renaming these substances "protein" – Greek for "standing in front." During the nineteenth and twentieth centuries, scientists systematically characterized many properties that make proteins unique. They discovered that proteins were "macromolecules" (vastly larger than other molecules in the body), contained both positive and negative electrical charges on the same protein, and had varying shapes that were related to their function in the body. By 1936, the twenty amino acids, which are the "building blocks" of all proteins, had been identified.

Uncovering the Basic, but Versatile, Role of Proteins
Researchers soon began to see that proteins are crucial components of cellular machinery and are required for even the most basic functions of the cell. Scientists labored to identify new types of proteins, including enzymes that speed up chemical reactions, antibodies that recognize foreign substances in the body, structural proteins that form the walls of cells, and mechanical proteins such as those that enable muscles to contract. Scientists discovered that proteins transport oxygen, carry messages from one part of the body to another, and regulate body processes such as digestion, respiration, and the growth rate of cells. In the mid-twentieth century scientists learned that the DNA in genes form the code that the body uses to manufacture proteins. And since proteins must be of the correct size, shape, and electrical charge to perform their proper role in the cell, mutations in the genetic code can lead to the assembly of poorly functioning proteins. For example, cancer is caused by errors in proteins that regulate when and how fast cells replicate themselves, as well as the timing of cell death.

Using Protein Biomarkers to Detect Disease
Scientists also learned that a number of diseases characteristically disrupt the normal balance of protein concentrations in the body. Researchers generated hypotheses about using these changes in protein levels for disease diagnosis. The last century has seen the development of a limited number of protein tests that help identify whether a patient has a particular disease or assess how well a patient is responding to a treatment. Proteins used in this way are called "protein biomarkers."

Early protein biomarkers for cancer included prostatic acid phosphatase (PAP), discovered by Dr. Gutman and colleagues in the late 1930s and noted to be elevated in patients with metastatic prostate cancer. Carcinoembryonic

[2] A mass spectrometer identifies chemicals in a substance by their mass and electric charge.

antigen (CEA) was discovered by Drs. Gold and Freedman in 1965. CEA tends to be elevated in a number of cancers, especially gastrointestinal cancers. Although neither PAP nor CEA were effective for detecting early stage cancer, their discovery awakened a hope that scientists would soon discover biomarkers that could be used to accurately detect dangerous cancers early when they can be easily treated.

More recently, scientists have discovered prostate specific antigen (PSA), which aids in the early detection of many prostate cancers, and cancer antigen 125 (CA125), which helps to detect recurrences of ovarian cancer. However, PSA testing cannot be used in place of biopsy and CA125 tests are not sensitive enough to detect early stage ovarian cancers. Indeed, many scientists are concerned that cancer tests that rely on individual biomarkers will prove neither sensitive nor specific enough to conclusively diagnose early stage cancers.

Enter Proteomics – Analyzing Protein Patterns to Detect Cancer Early
Recent research has suggested that the types and amounts of proteins in the blood can be thought of as a record of the physiological and pathological condition of the body. This phenomenon exists because cells release protein into the blood as they perform their designated function. For example, cancer cells, because they behave differently than normal cells, release a different protein profile into the blood. Furthermore, scientists have discovered that cancer cells also influence the behavior of otherwise healthy cells in the tumor micoenvironment, which changes the type and amount of proteins these nearby cells release into the blood. Researchers are discovering that proteomic patterns, or signature profiles, may reflect the presence of early stage cancer far more reliably than tests for individual biomarkers.

NCI and FDA have founded the Clinical Proteomics Program (CPP) to translate this new knowledge into proteomic-based cancer interventions. As mentioned above, CPP researchers Lance Liotta, Emanuel Petricoin, and colleagues are developing a proteomic method to detect early stage ovarian cancer. This research team recently used artificial intelligence programs to analyze data from a special application of mass spectrometry technology. This system can detect the levels of thousands of proteins in a blood sample in a matter of seconds. In 2004, the CPP team, along with the Frederick Cancer Research Center Biomedical Proteomics Program, evaluated how well the method works by examining 68 women already diagnosed with ovarian cancer, as well as 43 women who were free of cancer. In this evaluation, the method worked correctly 100 percent of the time. Dr. Elise Kohn of the NCI will conduct a multi-institutional clinical trial to investigate the method's ability, when used in large numbers of patients and by multiple operators, to distinguish between blood samples from people with recurrent cancer and free from cancer.

Proteomic profiling tests are also in various stages of development for prostate, breast, lung, pancreatic, and colorectal cancer, holding hope for early detection interventions for these cancers. And, this historically rich area of investigation, with its promise for saving lives, can be said to have gotten its start in Dr. Fourcroy's laboratory in 1789, with the discovery of the most intriguing "Eiweisskörper."

SCIENCE ADVANCES

Scientists are Developing Better Prognostic Measures for Prostate Cancer. Many scientists believe that improvements in early detection and treatment of prostate cancer over the past decade have contributed to the decline in deaths due to this disease. However, the difficulty of predicting outcomes for individual prostate cancer patients remains a challenge. Only a subset of tumors identified by PSA screening and subsequent biopsy will pose a health threat and some of these tumors will be more aggressive than others. Another subset of tumors will grow so slowly as to be clinically unimportant. The three tools health care providers rely on for developing a prognosis – serum PSA levels, Gleason scoring[3], and clinical staging – have a limited ability to predict individual outcomes.

[3] Gleason scores are determined by microscopic examination of the prostate tumor. The closer the resemblance of the tumor to normal prostate tissue, the lower the Gleason score and the less aggressive the tumor is likely to be.

The Prostrate Cancer Prevention Trial (PCPT), a study that showed the drug finasteride to reduce a man's chances of getting prostate cancer by 25 percent, was also the first systematic study of men with PSA scores below the "normal" level of 4 ng/ml. Men in the control arm of the PCPT took a placebo for 7 years, were screened annually by PSA testing, and biopsied at the study's end. These biopsies found prostate cancer in 15 percent of 2,950 men who had consistently tested normal for PSA. The vast majority of these cancers were low and intermediate grade disease, which are often not clinically significant. Most of these men would not have been diagnosed if they were not participating in this study, since biopsies are not routinely performed in men with normal PSA levels. Performing biopsies at lower PSA levels would identify more cancers, but some men would undergo treatment needlessly. This research highlights the need for better ways to distinguish harmless, slow-growing cancers from higher risk disease to inform decisions about whether and how aggressively to treat individuals diagnosed with prostate cancer.

Investigators funded by the NCI Director's Challenge program are applying comprehensive molecular analysis strategies to this problem. One team of investigators recently analyzed prostate tumor biopsy samples from patients with known clinical outcomes to identify a gene expression molecular signature that can predict risk for relapse after treatment. This technique appears to improve predictive value when used in combination with conventional prognostic tools. These researchers also established a mouse model that can be used to study the biological processes underlining differences in gene expressions associated with risk of disease progression and/or relapse. This and other comprehensive molecular analysis research is leading to robust methods for identifying patients at risk of disease progression as well as identifying new potential targets for therapeutic intervention. These advances hold promise for more effective interventions for patients at risk of disease progression and reduced treatment related morbidity for low-risk patients.

Genetic Mutation Status Can Predict Lung Cancer Patient Response to Gefitnib.[4] About 10 percent of non-small-cell lung cancer (NSCLC) patients with advanced disease respond dramatically to the molecularly targeted drug, gefitinib. The other 90 percent do not respond to this drug at all. Gefitinib targets the epidermal growth factor receptor (EGFR) protein, which is often overexpressed in common solid tumors such as lung, breast, and colon. This protein helps to regulate cellular growth rate, and its overexpression in these patients leads to tumor formation. Scientists have been looking for genetic clues to explain the striking differences in the response of non-small-lung cancer patients to gefitinib. One NCI-supported team recently discovered that a subgroup of patients with NSCLC have specific mutations in the EGFR gene, which correlate with clinical responsiveness to gefitnib. These investigators also used *in vitro* experiments to show that the corresponding overactive mutant EGFR proteins caused increased cellular activity of a second protein, tyrosine kinase, a characteristic feature of cancerous cells. And, the cells expressing mutated EGFR protein were highly sensitive to the inhibiting effects of the drug gefitinib. This research demonstrates that specific genetic mutations confer sensitivity to gefitinib and suggests that mutational analysis of EGFR in tumors should identify a subgroup of patients likely to have a response to this agent and provide guidance about treatment. This study also paves the way for genetic identification of patients likely to respond to other drugs designed

[4] Trade name Iressa

to target specific molecular features of cancers.

Scientists Are Discovering New Approaches to Manipulating the AIDS Virus. The availability of more effective AIDS therapies would help reduce our Nation's cancer burden by preventing the development of AIDS-related malignancies. Current AIDS antiretroviral therapies suppress, but do not eliminate, the activity of this virus in the body. This virus is persistent, partly because Human Immunodeficiency Virus (HIV) is present in AIDS patients in two forms. Some HIV particles actively replicate, increasing their presence in the body. Other viral particles exist in latent form, residing in cells, but not replicating. AIDS retroviral therapies work by interfering with viral replication. This leaves a reservoir of latent virus which may later become active. Scientists are searching for drugs that are effective against the latent form of the virus.

Researchers at NCI have discovered characteristic differences in gene expression patterns among cells harboring latent HIV, those infected with replicating virus, and uninfected cells. They analyzed these differences to discover several genes that may provide targets for new treatment strategies that force latent virus to replicate, making the virus more vulnerable to antiretroviral therapy. For example, *egr1* is a gene that causes cell growth to slow down, which creates a more favorable environment for viral replication. These investigators were able to induce latent virus to replicate in this way *in vitro* by using a drug called resveratrol, which slows cell growth.

Although preliminary and a long way from clinical application, this research suggests that it may be possible to develop therapies that target cellular activity to help make HIV more vulnerable to treatment, perhaps eradicating it from the body. Scientists hypothesize that such therapies may be less susceptible to the development of drug resistance.

Artificial Neural Networks May Improve Prognosis of Neuroblastoma Patients. Neuroblastoma is a cancer of infants and young children, rarely found in children more than 10 years of age. Children with this disease are classified into risk groups according to the Children's Oncology Group risk stratification, which considers stage of disease, age of the child, and various prognostic markers. About 95 percent of low-risk and 80 percent of intermediate-risk children will survive 10 years or longer, compared to long-term survival rates of 25 percent for high-risk children.[5] This risk stratification helps guide treatment choices. Where low risk children usually only require surgery, high risk patients may receive intensive chemotherapy, stem cell transplant, surgery, and/or radiation. Researchers are working to develop improved prognostic models to predict which high risk patients are least likely to respond to conventional treatments, perhaps requiring alternate therapies.

Researchers at NCI have discovered a prognostic tool for neuroblastoma that appears to perform better than the current risk stratification system. These scientists used artificial neural networks (ANNs) to analyze gene expression patterns of primary tumors from 49 neuroblastoma patients whose clinical outcomes were known. ANNs are a type of pattern recognition artificial intelligence modeled after the human brain. The ANNs analyzed gene profiles consisting of over 25,000 genes to identify 19 genes that could predict, with a high level of accuracy, whether the patient had survived or succumbed to neuroblastoma. Moreover, based on the profiles of these

[5] American Cancer Society Website: Detailed Guide - Neuroblastoma (www.cancer.org/docroot/cri/cri_2_3x.asp?dt=31)

19 genes, the ANNs were able to predict which of the patients clinically classified as high risk, would not respond to conventional therapy. Although more study is needed to validate their findings, these researchers anticipate a future when ANNs can be used in clinical practice to distinguish a group of ultra-high risk neuroblastoma patients who will require alternate treatment strategies. Other patients who can be spared intensive therapy and its associated toxicity may also be identified.

New Treatment Improves Long-Term Outlook for Breast Cancer Survivors. Tamoxifen is widely used to prevent breast cancer recurrence in post-menopausal women. After about 5 years, however, tumors become resistant to the drug and tamoxifen loses its effectiveness. NCI partnered with the Canadian Cancer Society and the National Cancer Institute of Canada to conduct a randomized trial of the drug letrozole in postmenopausal women following 5 years of tamoxifen therapy for early stage breast cancer. Letrozole works by limiting the ability of an enzyme called aromatase to produce estrogen, a major growth stimulant in many breast cancers. In late 2003, these researchers reported that letrozole substantially increased women's chances of remaining cancer free. Overall, letrozole reduced the risk of recurrence by 43 percent, so that after 4 years of participating in the trial, 13 percent of the women taking the placebo, but only 7 percent of those taking letrozole, experienced cancer recurrence. Furthermore, 17 women taking the placebo died of breast cancer compared to 9 taking letrozole. Side effects of letrozole were similar to those experienced by women undergoing menopause and were generally mild. An updated analysis in June 2004 shows that letrozole improves overall survival by 39 percent in women with node-positive breast cancers.[6]

This research provides hope of substantially reducing the recurrence of breast cancers beyond the window of effective tamoxifen therapy. Follow up of women in this study will continue for another 10 to15 years. Further research is needed to determine the optimal timing for switching women from tamoxifen to letrozole or other aromatase inhibitors and how long these drugs should be administered.

New Method to Identify Blood Proteins May Spur Novel Disease Marker Discoveries. Research in the relatively new field of proteomics[7] has suggested that the types and amounts of proteins in the blood can be thought of as a record of the physiological and pathological condition of the body. Scientists have begun developing proteomic technologies to diagnose cancer earlier than is now possible, develop individualized patient therapies, determine toxic and beneficial effects of treatment before administering them to patients, and discover potential molecular targets for new cancer treatments. One challenge facing scientists is the difficulty of detecting proteins that exist in trace amounts in a blood sample but that contain a wealth of diagnostic information. Efforts to identify these proteins have been impaired mainly because the separation steps meant to reduce amounts of large, highly abundant proteins cause a simultaneous loss of smaller, low-abundance proteins.

One team of NCI-supported researchers has applied conventional technologies to improve detection of these low abundance proteins in serum (a blood sample with red blood cells and clotting factors removed). These researchers crafted a multi-step procedure to separate proteins

[6] Node-positive means that the breast cancer had spread to the lymph nodes at the time of diagnosis.
[7] Proteomics is the systematic study of the proteins in a cell, tissue, or organism.

from a tiny volume of serum, about four one-hundredths of a teaspoon, based on size, electrical charge, and other chemical properties. Using mass spectrometry detection equipment, they were able to identify 1,444 diverse proteins. This number is well over and minimally overlapping with the 490 identified in previous research. This research emphasizes the scope and complexity of the human serum proteome, which has been estimated to contain more than 10,000 proteins. These researchers created a publicly available database[8] of the human serum proteome to serve as a resource for other investigators.

Researchers Identify Patients' Risk Factors for Death from Breast Cancer. The Center for Disease Control and Prevention (CDC) and NCI have reported that there are 9.8 million cancer survivors living in the United States today. Breast cancer survivors represent about 22 percent of this number, or about 2.6 million individuals.[9] Scientists are seeking to better understand risk factors that influence whether a woman diagnosed with breast cancer will ultimately die of this disease or from another cause. NCI researchers analyzed data from NCI's Surveillance, Epidemiology, and End Results (SEER) Program for more than 400,000 breast cancer patients diagnosed between 1973 and 2000. Women diagnosed at a younger age were more likely to die of breast cancer, as were women diagnosed with later stage disease and/or with larger tumors. Women with estrogen receptor negative tumors were more likely to die of their cancer than those with estrogen receptor positive tumors. Black women were more likely to die of their breast cancer than White women, even after accounting for other risk factors. The investigators suggest that this disparity may be caused in part by differences in treatment and a higher prevalence of obesity and obesity-related health conditions in Black patients. This and other research to determine the factors that increase a patient's risk of dying from their cancer will help healthcare workers and patients choose the best treatment option for each individual.

Researchers Investigate Causes of Tobacco Use and Relapses during Smoking Cessation. The 2004 Surgeon General's report, *The Health Consequences of Smoking*, [10] estimates that smoking causes 159,600 cancer deaths each year including cancers of the lung, mouth, stomach, bladder, pancreas, esophagus, and larynx. Recent research at NCI-supported Transdisciplinary Tobacco Use Research Centers (TTURCs) sheds light on the causes of tobacco use and relapse during smoking cessation attempts and suggests interventions to help people quit smoking.

- Weight gain is a side-effect, experienced when individuals quit smoking, which often leads to relapse. Smokers with a particular variant of the dopamine[11] receptor gene are more likely to experience a greater sense of food reward and weight gain after quitting smoking. However, the smoking cessation drug, bupropion, helped to prevent post-smoking cessation weight gain in these individuals.
- The U.S. Public Health Service recommends that smoking cessation treatment be made available to all smokers. A recent survey of state employers shows that only 29 of 45 states surveyed require smoking cessation treatment to be included in health insurance plans of state employees. Only 17 of these 45 states provided the complete range of coverage for smoking cessation recommended by the U.S. Public Health Service. This

[8] http://bpp.nci.nih.gov
[9] June 25 issue of CDC's *Morbidity and Mortality Weekly Report*, "Cancer Survivorship - United States, 1971 - 2001."
[10] surgeongeneral.gov/library/smokingconsequences
[11] Dopamine is a natural substance that can produce feelings of pleasure when it binds to dopamine receptor proteins in the brain.

research shows that states are lagging in adopting this promising avenue for reducing smoking rates among their employees.

- Physicians have a unique opportunity to talk to their teenage patients about tobacco use. However, according to a recent audit of the Wisconsin Medicaid medical records, physicians asked only 55 percent of adolescent patients about their smoking status during a 2-year period. The greater the age of the patient, the more likely the physicians were to record smoking status. Pregnant teenagers were also more likely to be questioned about smoking. Previous studies based on physician self report may have overestimated smoking interventions with adolescents.
- A better understanding of why people smoke will lead to more individualized cessation treatments. A new questionnaire, the Wisconsin Inventory of Smoking Dependence Motives (WSDM-68), has helped researchers to answer this question. Developed by Transdisciplinary Tobacco Use Research Center investigators, the questionnaire asks 68 questions to identify motivations including emotional attachment to smoking, response to other smokers, smoking to relieve stress, smoking for mental stimulation, and smoking automatically. These researchers found that individuals who smoked automatically, to enhance mental activity, to alleviate distress, or because they were in a smoking environment were most likely to relapse while quitting.

NIH ROADMAP INITIATIVES ADVANCE NCI'S MISSION

Increasingly, scientists must be able to work in interdisciplinary teams to understand and fully explore the interplay among environmental, lifestyle, genetic, and molecular variables contributing to cancer and take advantage of the technological resources available to help them do this. NIH Roadmap initiatives for building *Research Teams of the Future* are designed to foster team science by making it easier for scientists to work across disciplines and organizations. New funding mechanisms will grant principal investigator status to all key members of a research team, provide research funding to multiple institutions, require integrated reviews of grant applications that take into account the melding of the various disciplines, and encourage interdisciplinary teams to evolve in both directed and serendipitous ways.

These mechanisms will have a tremendous impact on NCI's ability to support the collaborative research critical to cancer studies in such fields as molecular epidemiology and integrative cancer biology where partnerships among scientists are essential to accelerating our understanding of the causes, risk factors, initiation, and progression of cancer. Epidemiologists must partner with one another and with genomicists and other investigators from the clinical, basic, and population sciences for large-scale studies that have the efficiency and power to characterize the interplay among various genetic, environmental, and life style factors that influence the initiation and development of cancer. Studies in integrative cancer biology need the synergism of working across multiple disciplines to build, characterize, and validate computational models. New mechanisms for supporting research in cancer biology will also enhance continued interdisciplinary research to address vital questions related to cancer and the immune system, the interface of aging and cancer, and the role of microbial agents in the etiology of human cancers.

In addition, continued development of technologies to enhance bioinformatics, advance the use of cancer imaging, build proteomic and metabolomic technologies, and explore nanoscience and its application to cancer prevention, early detection, diagnosis, and treatment all rely heavily on team science approaches. These teams bring together the expertise of the most innovative biomedical scientists, clinicians, physical scientists, mathematicians, engineers, and others linked in cutting-edge collaborations for technology development.

NEW AND EXPANDED INITIATIVES

The NCI initiatives described below span the spectrum of scientific research, technology leadership, application in public health and patient care, and communication and transfer of results.

Scientific Research

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

Cancer Vaccine Research

Prevention vaccines that can suppress the carcinogenic process either at its inception or in pre-invasive stages are currently in development. A promising example is a new vaccine strategy that targets the infectious agent human papilloma virus (HPV), the cause of virtually all cases of cervical cancer. Versions of this vaccine are now in Phase III clinical testing and are anticipated to be available in the near term to women at risk. If made available to healthcare communities around the world, a successful cervical cancer prevention vaccine could save hundreds of thousands of lives every year.[12] Researchers are also developing strategies that use vaccines in combination with chemoprevention agents. Until recently, scientists harbored considerable doubt about the feasibility of effectively combining a potent anti-inflammatory agent with vaccination, because of the opposing nature of their activity. Anti-inflammatory drugs work by partially suppressing immune function and vaccination promotes immune activity. NCI-supported researchers recently used a mouse model to show that the anti-inflammatory celecoxib can indeed work synergistically with vaccination. Research is ongoing to validate this and other strategies that combine chemoprevention with vaccination.

NCI is also increasing efforts to develop treatment vaccines that target cancers from early to advanced stages, often in combination with conventional therapies. NCI's interdisciplinary translational research consortium for development of treatment vaccines focuses on recombinant vector-based vaccines[13] to treat a range of human carcinomas. Researchers are evaluating eight different vaccines in patients with colorectal, lung, breast, and prostate cancers. A Phase III

[12] Based on World Health Organization estimates of about 510,000 reported cases of cervical cancer each year, with nearly 80 percent in developing countries, and 288,000 deaths from cervical cancer yearly. (http://www.who.int/vaccine_research/diseases/hpv/en/)

[13] Recombinant technologies combine pieces of DNA from more than one source. A vector is the vehicle (e.g. a virus) used to deliver the vaccine.

clinical trial will test several vaccine strategies against advanced drug-resistant pancreatic cancer. And, three clinical trials are testing combination therapy with recombinant viral vaccines and local radiation of tumors in patients with prostate, lung, and colorectal cancer.

Computational Modeling for Integrative Cancer Biology
Computational modeling is a central feature of the Integrative Cancer Biology Program (ICBP), aimed at generating predictive and testable models of cancer. Computational biologists are developing computer programs that use complex, interactive calculations to analyze massive amounts of data about cancer cells and their micro- and macroenvironments. These modeling programs, similar to those used by meteorologists to help predict the weather, use combinations of simple statistical tests, data mining applications, and higher-order mathematical equations. Computational models might be used to study the interaction of molecules in the cell or the response of a cancer patient's immune system to a developing tumor. Once refined and validated, computational models will not only yield insights and knowledge about cancer, but will also be used to help diagnose cancer patients and to plan and monitor treatment strategies.

NCI will establish nine centers of integrative cancer biology to provide the nucleus for the design and validation of computational and mathematical cancer models that will simulate complex processes at all stages of cancer, from the basic cellular level through tumor growth and metastasis. These centers will assemble teams of cancer biologists and scientists from fields such as mathematics, physics, information technology, imaging sciences, and computer science and will forge interactions between clinical and basic researchers with the more theoretically oriented computational programmers and mathematical modelers. Seamless integration of these teams will allow the computational models to be quickly verified and tested with experimental biological or clinical observations. Researchers will also rely on the Mouse Models of Human Cancer Consortium[14] to supply animal models that mimic the development of cancer in humans. Training and educational efforts will be critical to the dissemination and acceptance of computational models and the education of the next generation of integrative cancer biologists. NCI's cancer Biomedical Information Grid (caBIG) will be of central importance to the success of this initiative.

Biomarker Discovery
Biomarkers are substances such as DNA or proteins that may be expressed differently in precancerous or cancerous patients than in cancer free individuals. Biomarkers in cancer research hold promise for making "personalized" medicine a reality. They have many potential applications including early diagnostic tests, monitoring response to treatment, detecting metastatic disease, and building "designer" therapies. When more fully validated, they will enable scientists to more rationally discover and develop drugs and quickly identify patients, who will respond to specific therapeutic interventions. One of the most promising areas of biomarker research is the field of proteomics. Recent breakthroughs are enabling scientists to identify patterns of protein markers associated with cancer initiation and progression and with particular cancers.

NCI's Early Detection Research Network (EDRN) is at the forefront of biomarker research and has helped lay the groundwork for proteomic biomarker technologies.  systematic discovery of

[14] emice.nci.nih.gov

new biomarkers for clinical use will require a major coordinated initiative. A highly organized approach to the discovery of biomarkers through the study of protein patterns found in the body fluids of cancer patients is needed. Researchers will need technologies that can detect proteins of all sizes, present even in minute quantities, with a high degree of specificity and sensitivity. With increased resources in Fiscal Year 2006, NCI will establish a new Clinical Proteomics and Biomarker Discovery Program designed to evaluate and develop needed technologies, systematically create required reagents and resources, and establish clinical proteomics programs to translate discoveries to patients at the earliest possible time. Achieving this level of resolution will also require the use of a sophisticated bioinformatics platform that will enable teams of investigators to share, aggregate, and compare standardized data.

Preclinical Development for Cancer Drugs

Often the most difficult phase of drug development for cancer prevention and treatment is the preparation and presentation of the preclinical information required by the FDA to file an investigational new drug (IND) application. Experimental diagnostic devices undergo similar FDA scrutiny before they can be tested on humans. NCI has designed a number of programs to provide preclinical research resources to academic and academically-affiliated investigators who typically have limited resources. Programs include Rapid Access to Intervention Development, Rapid Access to Prevention Intervention Development, the Developmental Therapeutics Program, and the Mouse Models of Human Cancers Consortium. The newer Comparative Oncology Program is developing a national and international resource for investigators interested in the study of cancer biology and therapy through research of naturally occurring cancers in pet animals.

The recently accelerated pace of scientific and technological advancement has made the need for accessible, affordable preclinical resources even more critical. Preclinical development of prospective drugs and diagnostic technologies will require enhanced infrastructure including more accurate, predictive, efficacy models; rational processes for selection of lead candidates; and new NCI capabilities for process scale-up. An integrated preclinical development program that places significant emphasis on new approaches is required in order to define the pharmacology, toxicology, distribution, and other significant parameters associated with the administration of small molecules and biologics. New technologies such as pharmacogenomics[15] and metabolomics[16] will be part of a new approach to preclinical development, and should be available to the community.

Studies of Highly Lethal Cancers

In 2004, about 31,860 people in the United States will be diagnosed with pancreatic cancer. There will be about 14,250 new cases of esophageal cancer, and an expected 18,920 people will be told they have liver cancer.[17] These are highly lethal diseases. One obstacle facing scientists is that the relative rarity and high lethality of these cancers make it difficult to conduct large studies on common risk factors, such as chronic inflammation and the roles of genetic, environmental, and lifestyle factors in the initiation and progression of these diseases. It is not

[15] Pharmacogenomics examines the inherited variations in genes that dictate drug response and explores the ways these variations can be used to predict how a patient will respond to a drug.

[16] Metabolomics involves the study of the metabolome, the total of all metabolites expressed in a cell, tissue or organism during its lifetime. A metabolite is any substance that is produced by metabolism.

[17] American Cancer Society Website: Cancer Reference Information (www.cancer.org/docroot/CRI/CRI_0.asp)

unusual, for example, for population studies of breast or prostate cancer to enroll tens of thousands of participants. In contrast, the relatively low numbers of patients with highly lethal cancers demand significant cooperation and coordination to assemble enough patients to conduct even one study. NCI is proposing to address this obstacle by developing a consortium of investigators to conduct epidemiological studies of highly lethal cancers. This consortium approach will pool the resources of multiple institutions. Through the collection, storage, management, and sharing of data for a large numbers of cases, investigators will be able to amass enough knowledge to evaluate the possible combinations of genetic, environmental, and lifestyle factors – from molecular to behavioral – that are causing these cancers. This unparalleled collection of data will provide an ideal resource for exploring new hypotheses emerging from basic and clinical research, and provide hope for those individuals who suffer from highly lethal cancer.

Technology Leadership

NCI leads the Nation in using innovative approaches for harnessing the full potential of cancer research and development. Recent advances in bioinformatics, cancer imaging, proteomics, and nanotechnology are dramatically accelerating the rate with which cancer interventions can be developed, tested, and integrated into medical practice.

Bioinformatics

The cancer Biomedical Informatics Grid (caBIG), first announced in July 2003 and now in its pilot phase, will provide the informatics infrastructure that will revolutionize the biomedical research enterprise. Until now, bioinformatics resources have been developed in organizational isolation, with tremendous variability in rules, processes, vocabularies, data content, and analytical tools. This lack of common standards and unifying architecture has limited the ability of researchers across the country and worldwide to rapidly analyze and share diverse research data. The caBIG will facilitate the collection, storing, searching, analysis, classification, management, and archiving and retrieval of research data. It will ultimately provide a voluntary virtual network linking researchers, institutions, and organizations worldwide to enable the integration of diverse data types and the sharing of interoperable analytic tools – a "World Wide Web" of cancer research.

Specific biomedical research tools that are being developed as part of caBIG activities include clinical trial management systems, tissue banks and pathology tools, and a rich collection of integrative cancer research applications. Over 50 NCI-designated Cancer Centers have partnered with the NCI to identify common needs and develop the vision, structure, and approach of the caBIG. Participating Centers have initiated research projects that rely on pilot caBIG infrastructure. Stakeholders from other Federal agencies, private industry, and patient advocacy groups are also actively involved in caBIG activities. The NCI envisions that caBIG will evolve into a large community of voluntary participants from national and international biomedical research fields. Ultimately, caBIG will support a range of other applications, including patient-centric tools such as Web-based clinical trials matching programs and personal health records, which will irrevocably benefit cancer patients and the public at large.

Cancer Imaging

Access to sophisticated imaging equipment and methodologies is a basic necessity of cancer research, from the adoption of new image-guided techniques in clinical care settings to the investigation of molecular interactions in cancer cells. NCI develops infrastructure to facilitate the use and testing of imaging technologies in clinical trials through programs such as the Network for Translational Research in Optical Imaging and the Ultrasound Research Interface. We support development of imaging not only for detecting cancer and monitoring treatment but also to help identify patients who are most likely to respond to a particular drug or combination therapy. New molecular imaging and biosensing technologies are providing clinicians with telling details about the environs of patients' tissues, opening doors to faster, more accurate detection and diagnosis, facilitating more precise image-guided therapies, and making it easier to monitor treatment outcomes. NCI supports preclinical investigators by developing and making available new small animal and molecular imaging technologies. With support from two NCI programs, the Mouse Models of Human Cancers Consortium (MMHCC) and the Small Animal Imaging Resource Programs (SAIRP), researchers are imaging mouse models to study all stages of cancer initiation, progression, and metastasis in cancer-prone animals. NCI's *In Vivo* Cellular and Molecular Imaging Centers bring together experts from diverse scientific and technological backgrounds to conduct research on cellular and molecular imaging in cancer.

With new resources in 2006, NCI will increase support to develop methods to image the interaction between the immune system and cancer and to clarify the underlying biological relationship between anti-tumor immune responses and autoimmune responses to normal cells and other tissues in humans undergoing cancer immunotherapy.

Proteomics

Scientists are taking new steps to identify profiles, or signatures, of proteins and peptides (fragments of proteins) that are found in tumors and often in the circulating blood that signal early phases of cancer development. Mass spectroscopy, a favored approach involving high energy lasers, high powered electronic sensing, and computing, is used to identify specific proteins and their fragments based on their size and electrical charge. Another avenue is to use DNA and antibodies to capture proteins and measure their quantity on electronic chips. Patients in the near future may well have small samples of their blood analyzed using these and other technologies that will, within minutes, identify abnormal proteins that indicate early, very treatable cancers.

The NCI Biomedical Proteomics Program (BPP) supports state-of-the-art facilities that provide researchers with the expertise and technology required to accelerate basic proteomic research, from protein discovery to studies of protein expression and characterization. Scientists at the BPP work closely with colleagues from the NCI/Food and Drug Administration (FDA) Clinical Proteomics Program (CPP). This program seeks to apply the discoveries of basic proteomics research directly to patient diagnosis, toxicity monitoring, and therapeutic intervention. For example, CPP researchers are developing a proteomic method to detect early stage ovarian cancer with a diagnostic blood test.

Researchers are also working to overcome technical challenges to improve the power of proteomic profiling. Many diagnostically informative proteins are found in minute quantities in

blood samples that contain hundreds of thousands of proteins. The net effect will require us to refine the technology so that it can find "a needle in the haystack" with unprecedented reliability. In 2006, NCI will expand support for the development of advanced technology platforms for overcoming protein detection and other barriers to preparing diagnostic methods for clinical testing.

Nanotechnology

Nanotechnology is the creation of useful materials, devices, and systems through the manipulation of material with at least one dimension less than 100 nanometers, where a nanometer is one billionth of a meter. Nanotechnology offers an unprecedented and paradigm changing opportunity to study and interact with normal and cancer cells at molecular and cellular scales, in real time and during the earliest stages of the cancer process. For example, one team of NCI-supported scientists is crafting a nano-sized construct to identify areas of new blood vessel growth, or angiogenesis, which is characteristic of growing tumors. Imaging agents and diagnostics will allow clinicians to detect cancer in its earliest, most treatable, pre-symptomatic stage. Therapeutic agents will be delivered directly to cancer cells and those tissues in the microenvironment that play a critical role in the growth and metastasis of cancer. Other nanotechnologies will enable investigators to quickly identify new targets for clinical development and predict drug resistance, monitor predictive molecular changes and prevent precancerous cells from becoming malignant, provide real-time assessments of therapeutic and surgical efficacy, and aid in the management of symptoms of cancer that adversely impact quality of life.

NCI's Board of Scientific Advisors has recently approved the NCI Alliance for Nanotechnology in Cancer, a set of three new initiatives to further progress in nanotechnology. With adequate resources, the first initiative will establish the Centers for Cancer Nanotechnology Excellence, which will enable integration of nanotechnology platforms into basic and applied research to facilitate clinical application. The second initiative funds Multidisciplinary Career Development Awards to train researchers to apply nanotechnology expertise to cancer research and clinical oncology questions. The third investment area, Nanotechnology Platforms for Cancer Research, will be the primary mechanism to support projects by individual investigators to develop and deploy nanomaterials and nanoscale devices to the cancer research community and to accelerate movement of those platforms with the greatest promise into clinical use.

Application in Public Health and Patient Care

NCI is working with other agencies and organizations to bridge the gap between the promise of research and its application for people. We work to ensure that newly developed interventions move through well designed, well run clinical trials and work with others to ensure that those found effective and safe are made available to cancer patients everywhere.

Clinical Trials Integration

NCI supports clinical trials at the NIH Clinical Center and at close to 3,000 other sites across the United States. As we look to the future, NCI is reengineering its clinical trials system to be even more integrated and robust, to anticipate scientific and technological advancements, and enhance partnerships and collaborations with an interdisciplinary and translational focus. A highly

interactive and optimally coordinated cancer clinical trials system will facilitate the effective conduct of Phase I clinical trials, better prioritize and coordinate large Phase II and III trials,[18] and directly address regulatory and other issues that affect the timeliness with which clinical trials can be completed and their findings translated into practice. NCI will continue to enhance its working relationship with the Food and Drug Administration (FDA) and the Office of Human Research Protections (OHRP) to develop more streamlined policies and procedures for the conduct of clinical trials and to accelerate the approval of new interventions through the regulatory process. An effective infrastructure will include cross-disciplinary and patient advocate input.

Partnership with CMS

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

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

New Tobacco Interventions

Tobacco use remains the single most preventable cause of death in the United States, accounting for approximately 440,000 deaths in the United States each year. About 46 million people in our country, or 23 percent of the population, currently smoke. Cigarette smoking contributes to nearly one-third of all cancer deaths[19]. Tobacco use is a major risk factor for lung cancer as well as cancers of the esophagus, larynx, kidney, and pancreas.

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[18] **Phase I trials** are studies involving small numbers of patients to evaluate how new drugs should be given (by mouth, injected into the blood, or injected into the muscle), how often, and at what dose level. **Phase II trials** continue to test the safety and efficacy of drugs, usually focusing on how effective they are for specific types of cancer. **Phase III trials** test new drugs, new combinations of drugs, or new surgical procedures in comparison to the current standard. Phase III trials generally enroll larger numbers of people and are frequently conducted at multiple sites – e.g., doctors' offices, clinics, and cancer centers.

[19] American Cancer Society Website: Cancer and Early Detection – Tobacco and Cancer (www.cancer.org/docroot/PED/ped_10.asp)

NCI, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism support the Transdisciplinary Tobacco Use Research Centers (TTURCs) to conduct tobacco use, control, and addiction research. The research spans a broad range of disciplines, including molecular biology, genetics, neuroscience, epidemiology, imaging, primary care, behavioral science, communication, health policy, biostatistics, economics, and marketing. Scientists at seven TTURCs collaborate to explore the complex and interactive factors that lead to tobacco use and its consequences.

Recently, a number of new tobacco products with claims purported to reduce health risk have entered the market. Unlike smoking cessation products, tobacco products do not undergo rigorous, objective scrutiny either for their constituents or for the accuracy of their health claims. A greater science base is required before we will know if any of these new products create benefit or harm at the individual and population levels. NCI has awarded a contract to create a Tobacco Harm Reduction Network, which will facilitate collaboration and communication among government and non-government scientists and organizations. The Tobacco Harm Reduction Network will focus on issues pertaining to both tobacco products purported to reduce harm and pharmaceutical products that could be marketed to reduce tobacco use and associated harm. NCI also plans to fund multidisciplinary research to generate comprehensive scientific information on the chemical composition, exposure, addictive properties, differential toxicity, and public health impact of potential reduced-exposure tobacco products. The key research question to be addressed is whether or not new, reduced-exposure tobacco products provide a truly less harmful alternative to conventional cigarettes. NCI will also support research on laboratory assessment of new tobacco products promoted with harm reduction claims and associated behaviors and exposure conditions of users. The results of this research will enable NCI to provide guidance to the Federal Trade Commission on a new cigarette testing method. It also will enable the evaluation of new and existing testing methods and provide information regarding their strengths and weaknesses, taking into account their relevance for actual human smoking behavior.

In a related initiative, NCI and the Centers for Disease Control and Prevention (CDC) are implementing a National Network of Tobacco Cessation Quitlines to provide smokers with access to support and the most up-to-date information they need to quit. States that currently have quitlines will receive funding to enhance their services and states that do not have them will receive grants to establish quitlines as well as to access services. An easy-to-remember, toll-free telephone number, 1-800-QUIT-NOW, will serve as a single access point to the national network of quitlines.

New Energetics Research Centers

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

energy balance, and the relationship between energy balance and cancer using pre-existing biological specimens from ongoing case control or cohort studies. We continue to support research on improving the assessment of diet and physical activity, ranging from studies of biological measures of energy intake and expenditure to a conference on the use of e-technologies to assess and modify physical activity, diet, and energy balance in real time.

The centers for Transdisciplinary Research in Energetics[21] and Cancer (TREC) are the result of a new cutting-edge initiative for fostering collaborations and training opportunities to explore genetic, behavioral, socio-cultural, and environmental influences on nutrition, physical activity, weight, energy balance, and energetics. Modeled after the successful Transdisciplinary Tobacco Use Research Centers (TTURCs), TREC centers will focus on two great challenges that require integration across diverse disciplines:

- Enhancing our understanding of the mechanisms linking energy balance and cancer.
- Developing innovative obesity prevention approaches at the social-environmental and policy levels that will have a broad impact on populations. Researchers will give particular attention to prevention approaches targeting children, as well as adults, at critical time periods when weight gain is likely to occur, such as during smoking cessation, cancer treatment, and major life transitions.

Communication and Transfer of Results

NCI provides Web-based information on cancer and clinical trials, toll-free telephone service in all regions of the country, and printed brochures and educational packages distributed directly to cancer patients and their families as well as to oncology practices and patient advocacy organizations. The NCI Cancer Research Portfolio and the International Cancer Research Portfolio Web sites provide invaluable resources to investigators desiring to locate research information or find collaborators in areas of interest.

Patient Navigator Pilot Projects

There are too many people who receive a cancer diagnosis either late for effective early treatment or with limited personal resources to take advantage of the quality cancer care that is available today. NCI is piloting an innovative program for placing patients in contact with "patient navigators" who help individuals and their families work with an often complex healthcare system. Patient navigators are experienced advocates from local communities – e.g., lay people, social workers, and nurses – who are able to communicate credibly with patients. They work with vulnerable or disadvantaged people to help them obtain accurate information on diagnosis and treatment procedures, access to hospitals and clinics, guidance on financial assistance, and help with tracking their records and obtaining prescriptions. In some cases they also arrange for language translation, travel, social support, or religious counseling.

Newly piloted Patient Navigator Programs in Rapid City, South Dakota, and Laredo, Texas, are supplemented with funds from NCI to serve large Native American and Hispanic communities, respectively, each with high poverty rates.[22] Evaluations of these programs will help to identify

[21] Energetics is the study of the flow and transformation of energy through living systems.
[22] crchd.nci.nih.gov/initiatives/#Navigator

successful elements, attract collaborators, and model other services and programs to reduce the devastation of cancer among older, minority, and other medically underserved populations.

Cancer Information Service
The National Cancer Institute's (NCI) Cancer Information Service (CIS) Partnership works with over 450 public and private organizations nationwide to support data driven, outcome-focused education and public health projects, especially for minority and medically underserved populations. The Cancer Information Service (CIS) helps people become active participants in their health care by providing the latest scientific cancer information in understandable language. CIS and partners also provide technical assistance to build capacity in the areas of clinical trials, breast and cervical cancer screening, general cancer awareness, and tobacco education. The CIS offers smoking cessation assistance, cancer-related publications, and recorded information about cancer 24 hours a day, 7 days a week. CIS serves the entire United States, Puerto Rico, the U.S. Virgin Islands, and the Pacific Islands.

CIS is conducting a 2-year demonstration pilot, initiated in 2003, to reduce cancer health disparities among women, rarely or never screened for cervical and breast cancer, in partnership with the United States Department of Agriculture (USDA), the Centers for Disease Control and Prevention (CDC), and the American Cancer Society (ACS). This public-private partnership is working with regional and local public health practitioners and stakeholders from eight Appalachian states with the highest cervical and breast cancer morbidity and the lowest screening rates for these cancers.

INNOVATIONS IN MANAGEMENT AND ADMINISTRATION

Electronic Tools to Enhance NCI's Grants Administration and Portfolio Management
NCI continues to improve its grants administration and portfolio management, provide information on its research portfolio, and better coordinate activities with other parts of NIH. For example:

- The NCI transition from paper-based to electronic grants processes is 75 percent complete. Two other NIH Institutes/Centers are using NCI's Electronic Grant File Web-based database and several others will begin using it during the coming Fiscal Year.
- The electronic coding, indexing, and analysis of over 12,000 grant applications and awards in 2004 is providing NCI staff with more effective and efficient ways to track and analyze its research portfolio and provide that information to the public through the NCI Research Portfolio Web site (researchportfolio.cancer.gov). All coding is now electronic – no paper copies are used by staff. NCI is also supporting the trans-NIH Knowledge Management for Disease Coding pilot project. The goal of that project is to improve the quality, consistency, and transparency of the NIH budgetary process and the overall reporting of research activities.
- Several standard procedures and standard terms and conditions developed by NCI for use in NIH grant awards have been adopted for NIH-wide use.
- A newly developed Web-based application of electronic document control forms is improving the efficiency of grants administration and stewardship oversight.

Successful New Approaches to Peer Review
In February 2004, NCI began a pilot project for reviewing Program Project (PO1) grant applications. The approach involves having panels of reviewers consider applications in groups of two to four according to scientific research areas and general technical approaches. This clustered review process has improved the consistency of review practices, reporting, and scoring; significantly reduced the number of reviewers and overall reviewer time and effort; and reduced costs by eliminating site visit reviews for PO1 grants. The success or failure of an application depends first and foremost on how well the application text conveys the intent, merit, and impact of the proposed research.

In 2004, NCI also began using new models for reviewing large initiatives such as the Integrative Cancer Biology Program and the National Cooperative Drug Discovery Group. The approach uses teams with representatives from multiple programs to complete various review assignments. This approach has received special recognition from program staff and reviewers and will be expanded.

earch Training and Career Development Programs Focused on Team Science
Scientists trying to span the divide between different research disciplines and work collaboratively often find themselves frustrated by roadblocks such as difficulties in securing funding or lack of basic infrastructure to support a project that requires diverse expertise. NCI is engaged in a number of activities to help researchers stay current with the changing culture of medical research and various scientific and technological developments. The NCI Training Commission assesses current training and career development activities in extramural and intramural programs to inform strategic program planning. NCI helped to create a new NIH business model for recognizing multiple principal investigators and other key contributors to research projects to better reflect the team approach used in modern science. The Multidisciplinary Career Development in Cancer Nanotechnology Research initiative was launched in December of 2004 to support career development of individuals from the basic, biomedical, clinical, and information sciences and engineering who are pursuing the application of nanotechnology to cancer research.

ruitment and Retention of Scientists from Underrepresented Populations
The Introduction to Cancer Research Centers (ICRS) is a pilot program that identifies, trains, and mentors talented postdoctoral fellows and summer students from populations underrepresented in science and individuals from disadvantaged backgrounds. Other NCI programs that recruit individuals from underrepresented groups include the Research Supplements for Underrepresented Minorities Program, the Continuing Umbrella of Research Experiences (CURE) Supplement to Cancer Center Core Grants, the CURE Supplement to Institutional Training Grants, the Minority Predoctoral Fellowship Program, the Career Development Program, the Minority Institution/Cancer Center Partnership Program, and Minority Biomedical Research Support (MBRS) Grants to Minority Serving Institutions.

New Office of Workforce Development
The new NCI Office of Workforce Development (OWD) addresses training, recognition, and advancement issues in a strategic and facilitated manner. In 2004, OWD launched its *Building a Model Culture* initiative by conducting a survey to assess the existing culture at NCI and to predict the impact of culture on performance. NCI will use the survey results to focus action planning on aligning NCI culture with its mission. The OWD has also designed the NCI

Training Warehouse to provide desktop access to up-to-date training information for NCI employees. Two OWD-designed training topics, *Knowledge Management: a Mentoring Program* and *Coaching for Conflict Management,* are examples of new opportunities available to NCI employees.

Helping Employees Prepare for Transition

NCI developed and conducted a series of four Employee Support Workshops for employees affected by the Fiscal Year 2003 A-76 Extramural Activities Support Services study. The workshops were designed to help employees prepare for possible transition by assessing skills and interests, writing resumes, and honing interviewing skills. A change agent workshop helped provide managers and supervisors with tools and techniques needed to coach and advise their employees.

king Electronic Health Information in the Research and Practice Settings

A new collaboration between NCI and the HHS Office of the National Coordinator for Health Information Technology was established in 2004 to examine the potential for linking electronic health records with the electronic clinical research infrastructure in order to facilitate the exchange of information between the care and research settings. This initiative holds promise for making clinical research more effective and efficient and has broad implications for individualized long-term care management.

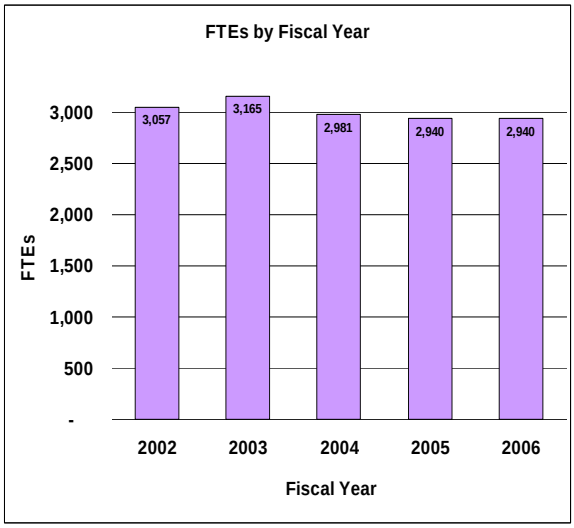
roactive Small Business Program

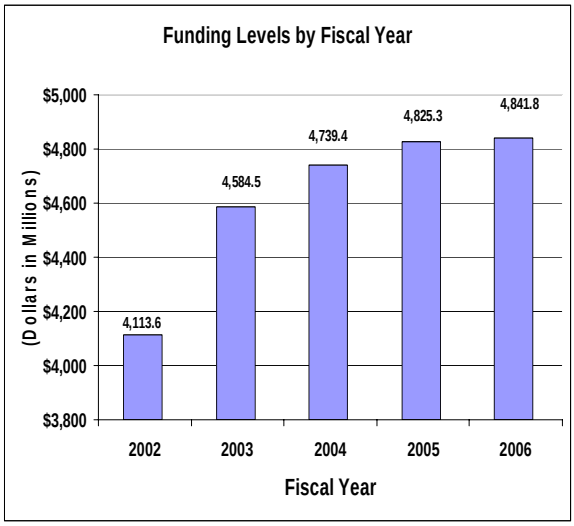
NCI's Small Business Program has modified a number of HHS forms to make them easier to complete. In particular, the sub-contract award reporting on SF 294 forms has been praised by HHS. The NCI Program also initiated an outreach activity for Historically Black Colleges and Universities and Minority Institutions (HBCU/MIs) that includes conducting several workshops on NCI research opportunities. Information gathered from these workshops resulted in a number of successful teaming efforts by HBCU/MIs on various NCI requirements.

Budget Policy

The Fiscal Year 2006 budget request for the NCI is $4,841,774,000, an increase of $16,516,000 and 0.3 percent over the FY 2005 Appropriation. Also included in the FY 2006 request is NCI's support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NCI are shown in the graphs below.





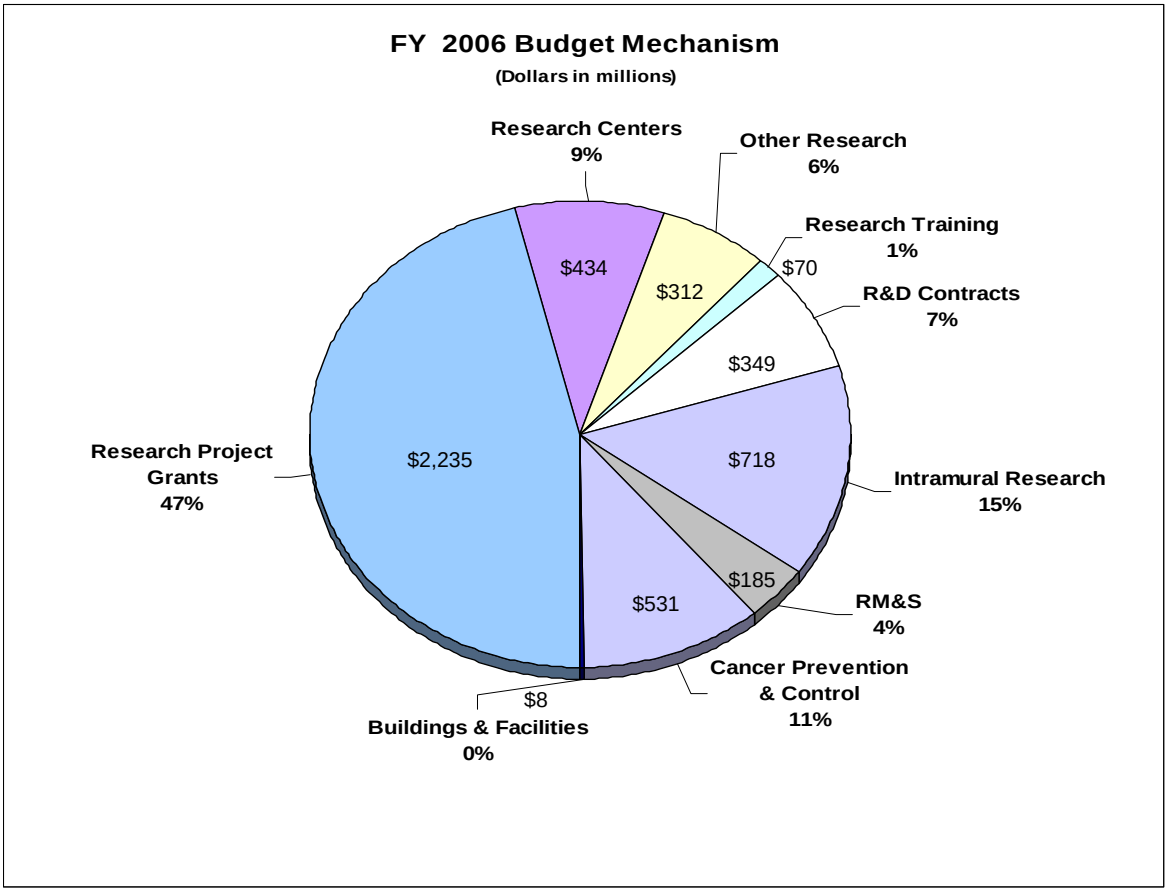
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. The average cost of competing RPGs will be held at the FY2005 level. There will be no inflationary increases for direct, recurring costs in Noncompeting continuation RPGs.

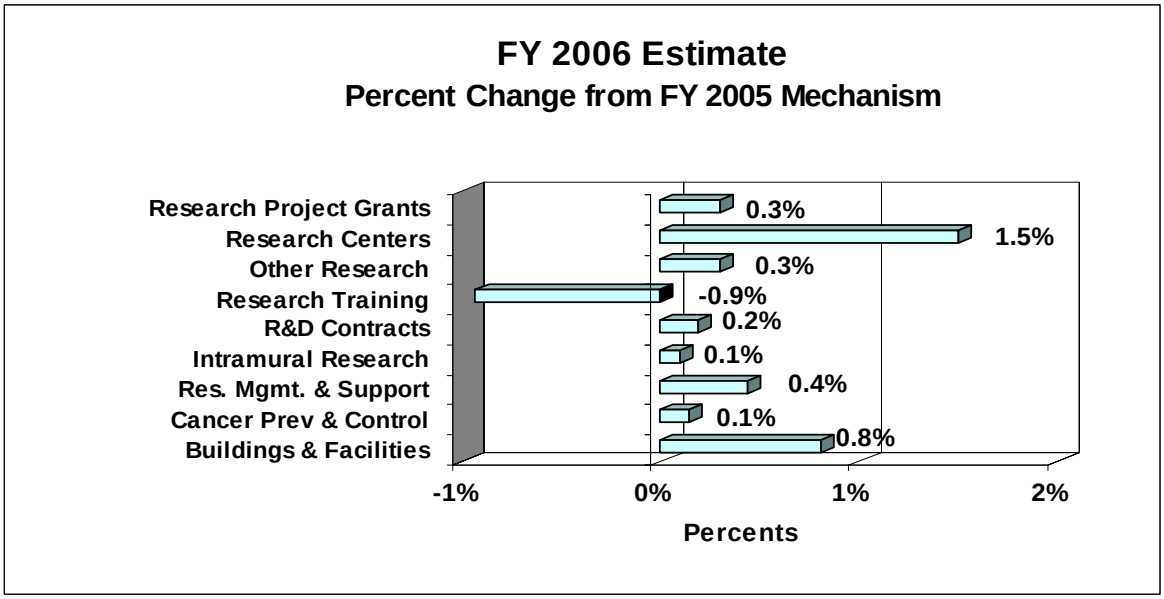
Advancement in medical research is dependent on attracting the best and the brightest to pursue careers in biomedical research. In the Fiscal Year 2006 request, stipend levels for post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will increase by 4.0% for those with 1-2 years of experience, with all other stipends remaining at the FY2005 levels. NIH will also provide an increase of $500 per post-doctoral fellow, for increased health insurance costs. This increase in stipends and health benefits is financed within the FY2006 request by reducing the number of Full-Time Training Positions by 29. NCI will support 1,546 pre- and postdoctoral trainees in full-time training positions.

The Fiscal Year 2006 request includes funding for 160 research centers, 907 other research grants, including 535 clinical career awards, and 312 R&D contracts. Intramural

Research and Research Management and Support receive increases of 0.1 percent and 0.4 percent respectively.

The mechanism distribution by dollars and percent change are displayed below:





NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

Budget Mechanism

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,588	$1,516,635,000	4,041	$1,624,338,000	3,898	$1,626,196,000
Administrative supplements	(312)	54,576,000	(313)	55,551,000	(310)	54,861,000
Competing:						
Renewal	399	188,786,000	361	174,148,000	361	174,148,000
New	1,088	304,856,000	974	274,218,000	991	279,840,000
Supplements	7	2,196,000	6	3,075,000	6	3,075,000
Subtotal, competing	1,494	495,838,000	1,341	451,441,000	1,358	457,063,000
Subtotal, RPGs	5,082	2,067,049,000	5,382	2,131,330,000	5,256	2,138,120,000
SBIR/STTR	397	99,579,000	375	96,800,000	375	96,800,000
Subtotal, RPGs	5,479	2,166,628,000	5,757	2,228,130,000	5,631	2,234,920,000
Research Centers:						
Specialized/comprehensive	149	411,625,000	151	424,895,000	152	430,173,000
Clinical research	0	0	0	0	0	0
Biotechnology	5	1,976,000	7	3,089,000	8	4,249,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	154	413,601,000	158	427,984,000	160	434,422,000
Other Research:						
Research careers	506	75,089,000	526	77,457,000	535	79,334,000
Cancer education	101	32,214,000	101	32,536,000	101	32,536,000
Cooperative clinical research	65	154,357,000	65	154,357,000	65	154,357,000
Biomedical research support	1	89,000	1	112,000	1	130,000
Minority biomedical research support	0	3,853,000	0	3,853,000	0	3,853,000
Other	202	42,286,000	203	43,018,000	205	42,055,000
Subtotal, Other Research	875	307,888,000	896	311,333,000	907	312,265,000
Total Research Grants	6,508	2,888,117,000	6,811	2,967,447,000	6,698	2,981,607,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	161	6,546,000	155	6,598,000	185	7,950,000
Institutional awards	1,347	61,036,000	1,412	63,928,000	1,361	61,919,000
Total, Training	1,508	67,582,000	1,567	70,526,000	1,546	69,869,000
Research & development contracts	321	355,431,000	312	347,851,000	312	348,509,000
(SBIR/STTR)	(17)	(3,321,000)	(40)	(8,600,000)	(40)	(8,600,000)
	FTEs		FTEs		FTEs	
Intramural research	1971	708,314,000	1944	717,220,000	1944	717,948,000
Research management and support	592	182,021,000	584	184,298,000	584	185,111,000
Cancer prevention & control	418	529,980,000	412	529,980,000	412	530,730,000
Construction		0		0		0
Buildings and Facilities		8,000,000		7,936,000		8,000,000
Total, NCI	2981	4,739,445,000	2940	4,825,258,000	2940	4,841,774,000
(RoadMap Support)		(16,276,000)		(30,505,000)		(43,263,000)
(Clinical Trials)		(799,955,000)		(815,859,000)		(815,859,000)

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual FTEs	FY 2004 Actual Amount	FY 2005 Appropriation FTEs	FY 2005 Appropriation Amount	FY 2006 Estimate FTEs	FY 2006 Estimate Amount	Change FTEs	Change Amount
Research:								
Cancer causation	950	$1,205,150	925	$1,210,876	925	$1,213,481	0	$2,605
Detection and diagnosis research	148	347,048	144	353,772	144	354,522	0	750
Treatment research	1,019	1,239,861	996	1,205,807	996	1,208,487	0	2,680
Cancer biology	326	792,761	318	862,066	318	863,781	0	1,715
Subtotal, research	2,443	3,584,820	2,383	3,632,521	2,383	3,640,271	0	7,750
Resource development:								
Cancer centers support	18	418,224	12	431,181	12	437,698	0	6,517
Research manpower development	32	183,702	70	202,476	70	203,398	0	922
Construction	0	0	0	0	0	0	0	0
Buildings & Facilities	0	0	2	9,105	2	9,109	0	4
Subtotal, resource development	50	601,926	84	642,762	84	650,205	0	7,443
Cancer Control & Prevention	488	552,699	473	549,975	473	551,298	0	1,323
Total	2,981	4,739,445	2,940	4,825,258	2,940	4,841,774	0	16,516

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes

FY 2005 Estimate				$4,825,258,000
FY 2006 Estimated Budget Authority				4,841,774,000
Net change				16,516,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$250,203,000		$3,247,000
b. Annualization of January 2005 pay increase		250,203,000		2,306,000
c. January 2006 pay increase		250,203,000		4,299,000
d. One less day of pay		250,203,000		(971,000)
e. Payment for centrally furnished services		106,886,000		534,000
f. Increased cost of laboratory supplies, materials, and other expenses		360,131,000		6,993,000
Subtotal				16,408,000
2. Research Management and Support:				
a. Within grade increase		71,635,000		1,166,000
b. Annualization of January 2005 pay increase		71,635,000		660,000
c. January 2006 pay increase		71,635,000		1,231,000
d. One less day of pay		71,635,000		(279,000)
e. Payment for centrally furnished services		20,000,000		100,000
f. Increased cost of laboratory supplies, materials, and other expenses		92,663,000		1,799,000
Subtotal				4,677,000
3. Cancer Prevention and Control:				
a. Within grade increase		57,220,000		860,000
b. Annualization of January 2005 pay increase		57,220,000		527,000
c. January 2006 pay increase		57,220,000		983,000
d. One less day of pay		57,220,000		(223,000)
e. Payment for centrally furnished services		15,000,000		75,000
f. Increased cost of laboratory supplies, materials, and other expenses		87,012,000		1,690,000
Subtotal				3,912,000
Subtotal, Built-in				24,997,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	4,041	$1,679,889,000	(143)	$1,168,000
b. Competing	1,341	451,441,000	17	5,622,000
c. SBIR/STTR	375	96,800,000	0	0
Total	5,757	2,228,130,000	(126)	6,790,000
2. Research centers	158	427,984,000	2	6,438,000
3. Other research	896	311,333,000	11	932,000
4. Research training	1,567	70,526,000	(21)	(657,000)
5. Research and development contracts	312	347,851,000	0	658,000
Subtotal, extramural				14,161,000
	FTEs		FTEs	
6. Intramural research	1,944	717,220,000	0	(15,680,000)
7. Research management and support	584	184,298,000	0	(3,864,000)
8. Cancer control and prevention	412	529,980,000	0	(3,162,000)
9. Construction		0		0
10. Building and Facilities		7,936,000		64,000
Subtotal, program	2,940	4,825,258,000	0	(8,481,000)
Total changes			0	16,516,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	2,940	2,940	0
Full-time equivalent of overtime & holiday hours	8	8	0
Average ES salary	$146,186	$149,036	$2,850
Average GM/GS grade	11.7	11.7	0.0
Average GM/GS salary	$78,284	$79,811	$1,527
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$78,716	$80,251	$1,535
Average salary of ungraded positions	$106,100	$108,169	2,069

OBJECT CLASSES		FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$155,538,000	$161,720,000	$6,182,000
11.3	Other than Full-Time Permanent	90,761,000	94,300,000	3,539,000
11.5	Other Personnel Compensation	6,946,000	7,015,000	69,000
11.7	Military Personnel	7,273,000	7,557,000	284,000
11.8	Special Personnel Services Payments	46,729,000	47,663,000	934,000
	Total, Personnel Compensation	307,247,000	318,255,000	11,008,000
12.0	Personnel Benefits	66,820,000	69,426,000	2,606,000
12.1	Military Personnel Benefits	4,909,000	5,101,000	192,000
13.0	Benefits for Former Personnel	82,000	82,000	0
	Subtotal, Pay Costs	**379,058,000**	**392,864,000**	**13,806,000**
21.0	Travel & Transportation of Persons	16,211,000	16,050,000	(161,000)
22.0	Transportation of Things	1,217,000	1,223,000	6,000
23.1	Rental Payments to GSA	10,000	10,000	0
23.2	Rental Payments to Others	1,701,000	1,709,000	8,000
23.3	Communications, Utilities & Miscellaneous Charges	7,513,000	7,551,000	38,000
24.0	Printing & Reproduction	5,927,000	5,945,000	18,000
25.1	Consulting Services	14,531,000	14,250,000	(281,000)
25.2	Other Services	197,141,000	187,467,000	(9,674,000)
25.3	Purchase of Goods & Services from Government Accounts	499,178,000	501,488,000	2,310,000
25.4	Operation & Maintenance of Facilities	77,394,000	75,846,000	(1,548,000)
25.5	Research & Development Contracts	346,607,000	345,295,000	(1,312,000)
25.6	Medical Care	5,008,000	5,008,000	0
25.7	Operation & Maintenance of Equipment	12,602,000	12,602,000	0
25.8	Subsistence & Support of Persons	161,000	161,000	0
25.0	**Subtotal, Other Contractual Services**	**1,152,622,000**	**1,142,117,000**	**(10,505,000)**
26.0	Supplies & Materials	44,560,000	44,782,000	222,000
31.0	Equipment	20,990,000	20,571,000	(419,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	3,195,449,000	3,208,952,000	13,503,000
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	0	0	0
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**4,446,200,000**	**4,448,910,000**	**2,710,000**
	Total Budget Authority by Object	**4,825,258,000**	**4,841,774,000**	**16,516,000**

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$155,538,000	$161,720,000	$6,182,000
Other Than Full-Time Permanent (11.3)	90,761,000	94,300,000	3,539,000
Other Personnel Compensation (11.5)	6,946,000	7,015,000	69,000
Military Personnel (11.7)	7,273,000	7,557,000	284,000
Special Personnel Services Payments (11.8)	46,729,000	47,663,000	934,000
Total Personnel Compensation (11.9)	**307,247,000**	**318,255,000**	**11,008,000**
Civilian Personnel Benefits (12.1)	66,820,000	69,426,000	2,606,000
Military Personnel Benefits (12.2)	4,909,000	5,101,000	
Benefits to Former Personnel (13.0)	82,000	82,000	0
Subtotal, Pay Costs	**379,058,000**	**392,864,000**	**13,806,000**
Travel (21.0)	16,211,000	16,050,000	(161,000)
Transportation of Things (22.0)	1,217,000	1,223,000	6,000
Rental Payments to Others (23.2)	1,701,000	1,709,000	8,000
Communications, Utilities and Miscellaneous Charges (23.3)	7,513,000	7,551,000	38,000
Printing and Reproduction (24.0)	5,927,000	5,945,000	18,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	14,059,000	13,778,000	(281,000)
Other Services (25.2)	197,141,000	187,467,000	(9,674,000)
Purchases from Govt. Accounts (25.3)	327,036,000	329,133,000	2,097,000
Operation & Maintenance of Facilities (25.4)	8,551,000	8,380,000	(171,000)
Operation & Maintenance of Equipment (25.7)	12,602,000	12,602,000	0
Subsistence & Support of Persons (25.8)	161,000	161,000	0
Subtotal Other Contractual Services	**559,550,000**	**551,521,000**	**(8,029,000)**
Supplies and Materials (26.0)	44,300,000	44,522,000	222,000
Subtotal, Non-Pay Costs	636,419,000	628,521,000	(7,898,000)
Total, Administrative Costs	**1,015,477,000**	**1,021,385,000**	**5,908,000**

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2005 House Appropriations Committee Report language (H. Rpt 108-636)

Item

Pediatric cancer — To expedite the progress and further improvements in outcomes for children with cancer, the conferees encourage NCI to increase its support of dedicated translational research to accelerate the pace of pediatric cancer clinical trials. The conferees also urge NCI to place a significant focus on genomic and proteomic approaches to identifying and validating potential molecular targets for therapeutic exploitation and evaluation in a controlled clinical trial setting. The existing, NCI-supported national clinical trials infrastructure and network, the Children's Oncology Group, should be the dominant participant in this accelerated effort. (p. 63)

Action taken or to be taken

NCI continues its long-standing support for childhood cancer clinical research through the pediatric Cooperative Group program, as currently embodied by the Children's Oncology Group (COG). NCI also supports pediatric oncology clinical and translational research through its intramural research program in the Pediatric Oncology Branch (POB) and through the Pediatric Brain Tumor Consortium, the COG Phase 1 Consortium, multiple Program Project grants, and other investigator-initiated research projects.

COG has made substantial progress in the past year in efficiently opening clinical trials in a timely manner. COG activated 19 clinical trials for children with cancer in FY2004, which was more than the combined number of trials activated in the two preceding fiscal years. As a result, phase III clinical trials will be open in FY2005 for virtually all of the major types of cancer that occur in children.

Many of COG's phase III clinical trials have tissue collection and translational research projects incorporated into them, thereby contributing to the goal of identifying potential molecular targets for therapeutic exploitation. The collection of tumor tissue and normal tissue from children enrolled on these trials makes COG an extraordinary resource for translational research.

The COG Phase I Consortium and the Pediatric Brain Tumor Consortium are conducting clinical trials of a number of molecularly targeted agents. Like COG, the Phase 1 Consortium activated more clinical trials in FY2004 than in the two preceding fiscal years combined. The Phase 1 Consortium currently has 14 clinical trials open for patient enrollment. The Pediatric Brain Tumor Consortium currently has 10 active clinical trials.

The NCI POB is another important resource for childhood cancer translational research. Its clinical research program emphasizes protocols for high risk sarcoma and leukemia patients and new drug development studies for pediatric cancer patients.

Current clinical research efforts in high risk sarcoma patients include development of effective immunotherapeutic strategies and utilization of allogeneic bone marrow transplant to generate graft-vs.-tumor effects. Similar strategies are being used for recurrent leukemia patients. The POB also conducts clinical trials of molecularly targeted agents for children and young adults with neurofibromatosis 1.

Item

Pancreatic cancer – The Committee is concerned that there are too few scientists researching pancreatic cancer, which is the country's fourth leading cause of cancer deaths. Tragically, 99 percent of people diagnosed with this disease die within six months. The Committee compliments the NCI's past efforts for increasing the research field through its program of a 50 percent formalized extended payline for grants that were 100 percent relevant to pancreatic cancer, an initiative that was an important method for attracting both young and experienced investigators to develop careers in pancreatic cancer. The Committee understands that NCI is adjusting this policy for the current year and looks forward to learning whether this revised approach is even more successful in increasing the number of prostate cancer grants. (p. 63)

Action taken or to be taken

NCI recognizes the need to encourage young and experienced researchers to take up the challenges pancreatic cancer presents and NCI is committed to finding creative ways to increase the number of investigators and attract new researchers in this field. The pancreatic grant funding policy initiated by the Institute in FY 2004 reflects NCI's determination to fund more and better research in this area. The current policy resulted in the funding of the same investigators who would have been funded under the previous extended payline policy – but it also resulted in better proposals being funded. This policy affords NCI more latitude in funding researchers in pancreatic cancer and encourages NCI staff to bring meritorious research grants to the attention of NCI's Executive Committee regardless of priority score.

The current funding policy seeks to improve the chances of pancreatic-related research grants which will help fuel investigator interest in this field. The mediocre success under the previous extended payline policy was inadequate. In order to bring more researchers into this area, NCI has adopted a more flexible strategy that will fund those grants that were eligible under the previous extended payline while opening the door to investigators who do important work in pancreatic-related research but still did not meet the 100 percent threshold.

In FY 2004, there were three R01 applications that NCI considered to be 100 percent focused on pancreatic cancer that fell within 10 points (50 percent) of the R01 payline. One received funding as an exception from the third review round; one revised application received a better review score and received funding early from the September review round; and the other revised application received a better review score and was offered early funding, but asked to defer funding until December (in FY 2005).

In FY 2004, no R01 application with 50% or greater (but less than 100%) relevance to pancreatic cancer research was within 10 points of the R01 payline. We hope that NCI will receive more pancreatic relevant applications in FY 2005, but historically the number of relevant applications under 100 percent has been very small every year.

The revised policy of FY 2004 had a positive impact on the quality of the pancreatic R01 exceptions funded. In prior years, those two applications which were revised and received better review scores would have been paid to conduct work under the weaker applications initially proposed. The delay of the appropriation in FY 2004 had the consequence of encouraging the investigators to revise and strengthen their proposals in response to the recommendations of the prior peer review. The result was that NCI funded demonstrably better research with the same investigators who would have been funded under the extended payline policy.

The Institute believes this positive impact shows the new policy should be left in place for further evaluation at the end of FY 2005. The Institute's Executive Committee will review the actual awards made for pancreatic exceptions in July 2005 to assure that the new policy results in at least the same number of investigators being funded as would be the case if the extended payline policy were still in effect.

NCI has also released a Program Announcement (PA) to invite innovative R01 applications to determine how the dietary intake of energy and bioactive food components influence pancreatic cancer development and prevention. This PA seeks to encourage collaboration between nutritional scientists and cancer biologists/oncologists and gastroenterologists to jointly examine key mechanisms in the pancreatic cancer process in order to begin to establish links between the quantity and form of energy consumed and/or bioactive food component intakes with pancreatic tumor incidence and behavior.

Item

Neurofibromatosis (NF) — The Committee is pleased that NCI is conducting phase II clinical trials of NF1 patients with plexiform neurofibromas. Recognizing NF's connection to many of the most common forms of human cancer, the Committee encourages NCI to increase its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation, and clinical trials. The Committee hopes that NCI will aggressively pursue clinical and translational research while still maintaining a solid basic research portfolio. (p. 64)

Action taken or to be taken

NF research is conducted by several Branches and Programs at the NCI, including the Pediatric Oncology Branch (POB) and the Mouse Cancer Genetics Program. NCI also supports pediatric clinical trial cooperative groups that are tailored to include children with cancers associated with NF1. NCI estimates a funding increase of 3% for NF research since FY 2003.

NCI has a long-standing interest in the development of new treatments for patients with treatment refractory cancers, and has recognized the need to extend these treatments to patients with NF1. The underlying cause of NF1 is a defective gene that contains instructions for making a protein called neurofibromin which helps control tissue growth. The decreased levels of neurofibromin found in NF1 patients contribute to tumor formation. Neurofibromin helps control the activity of another protein called *ras*. *Ras* can be thought of as the "on/off" switch for cell growth. When *ras* is "on," cells divide. When *ras* is "off," cells do not divide. Neurofibromin helps to keep *ras* turned "off." Decreased levels of neurofibromin therefore may allow for uncontrolled cell division and tumor formation. Therefore, drugs that inactivate *ras* are being studied as a new way to treat cancer.

One such drug, R115777, is an experimental drug that interferes with the function of the *ras* protein. Based on the results of a phase I clinical trial of R115777 for children with NF1 and plexiform neurofibromas, the NCI POB is now coordinating a multi-institutional phase II trial of R115777 for children that is open for patient accrual. This study will determine whether R115777 can slow the time to disease progression for patients with progressive plexiform neurofibromas and will determine whether R115777 can make plexiform neurofibromas decrease in size.

In collaboration with the Children's National Medical Center in Washington, DC and the Mayo Clinic in Rochester, Minnesota, the NCI completed accrual on a phase I trial of pirfenidone for children with NF1 and plexiform neurofibromas. This trial will determine the optimal dose, toxicities, and pharmacokinetics of pirfenidone, an agent that acts to inhibit the overexpression of growth factors in present in patients with NF1.

NCI is also developing a tissue microarray for pediatric solid tumors and NF1 associated tumors with the goal of analyzing these tumors for the presence of targets for new molecularly targeted agents. The data obtained from the tissue microarrays will be used to make rational decisions in the development of drugs for pediatric cancers and NF1.

NCI also supports clinical trials through the Children's Oncology Group. Approximately 400 children have now been entered into a clinical trial for children younger than 10 years of age with progressive low-grade astrocytoma. For children with NF1, the primary objective of the study is to determine their event-free-survival and overall survival following treatment with a regimen of carboplatin and vincristine (CV).

The NCI Mouse Cancer Genetics Program uses mouse models to increase the understanding of the biology and genetics of certain tumors associated with NF1, with the ultimate goal is to use this model to improve current treatments, as well as to design and test new therapies.

Item

Liver cancer —The Committee notes with concern the number of people who develop and die from liver cancer. As the symptoms of liver cancer often do not appear until the disease is advanced, only a small number of liver cancer cases are found in the early stages of the disease when they can be easily treated. The Committee is aware that NCI,

in collaboration with NIDDK, convened an Experts Conference in April, 2004 to help define the most pressing areas requiring additional research, professional education and public awareness initiatives. The Committee encourages NCI to pursue the research initiatives that result from the Conference. (p. 64)

Action taken or to be taken

The NCI continues to collaborate with NIDDK and the other NIH Institutes and Cancer Centers to sponsor research activities to prevent, diagnose, and treat liver cancer and to promote scientific conferences to exchange information about liver cancer. Over 90 percent of primary carcinomas of the liver are hepatocellular carcinomas (HCC). While HCC is a common cause of cancer and cancer-related mortality worldwide, until recently it has been considered a rare cancer in the United States. New studies demonstrate that liver cancer is the most rapidly rising cancer in the United States, resulting in at least 14,000 deaths annually and ranking as the eighth most common cause of cancer death in men. The recent upsurge in HCC in the United States may be attributable to chronic infection with hepatitis C virus (HCV), which is found in more than half of patients diagnosed with HCC.

This rise in the incidence of HCC has not been accompanied by improvements in early detection or treatment that might lead to improved patient survival. Liver cancer remains a highly fatal disease with average survival rates after the onset of symptoms of less than one year. The rising incidence of liver cancer, its continued high mortality rate, and the lack of effective treatments underlie the need for research into the origins of HCC which is critical to the development of early detection methods and interventions that might counteract these trends.

To help define the most urgent areas requiring additional research, the NCI co-sponsored an Experts Conference with NIDDK on liver cancer. This Conference, "Hepatocellular Carcinoma: Screening, Diagnosis, and Management," was held in April 2004 at the NIH. The key topics and summary recommendations from the conference were published in a special supplement to the November 2004 issue of *Gastroenterology* (Reference: *Gastroenterology* November 2004; 127(5): Suppl 1: S1-S323).

The summary recommendations focused on the promotion of research in four main areas: surveillance, prevention, early detection, and treatment. Based on the recommendations from this conference, NCI and NIDDK are discussing the potential development of a Request for Applications specifically designed to address the main areas of research outlined above.

These activities will complement and expand on ongoing basic research that focuses on the etiology and molecular pathogenesis of HCC and molecular profiling and diagnosis, clinical trials of new therapeutic agents, and prevention research.

Item

Lymphoma—Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL) represent a serious health burden, because of their persistent high incidence and the inadequate

improvement in survival rates. The Committee encourages NCI to strengthen its support for translational and clinical lymphoma research which can utilize laboratory discoveries in lymphoma biology specifically to develop new approaches in the clinic for patients. The Committee recommends that NCI evaluate its current investment in lymphoma clinical research and expand or initiate programs that would ensure support for translational and clinical research efforts.

The Committee encourages NCI to enhance and expand its commitment to investigation of the etiology and prevention of lymphoma. In the past decade there has been a dramatic and unexplained increase in the incidence of the disease; this epidemic is particularly evident in young and middle-aged persons. Evidence suggests that these cancers develop from genetic damage caused by environmental factors such as chemicals, toxins and ultraviolet light, and infectious organisms such as hepatitis C, as well as immune dysfunction. (p. 64)

Action taken or to be taken

The causes for the significant increase in incidence of NHL over the past twenty years continue to be poorly understood. Only a small portion of the increase is attributable to changes in diagnostic practices, AIDS-related cases, and other known causes. An analysis of trends in both sexes and around the world suggests that an etiologic agent has become increasingly prevalent in the general environment. Associations with environmental agents and viruses have been noted, but are not consistently found within lymphoma in general, or within individual types of lymphoma, so that no primary or dominant etiologic agent has been identified.

Recent lymphoma research shows evidence is gaining for a role of polychlorinated biphenyls (PCBs) and organochlorines. Sera from four different serum banks are being analyzed to identify these and other exposures that may precede the onset of NHL by many years. The NCI-SEER study has shown an increased risk of NHL in people infected with Hepatitis C virus. The study also suggested a beneficial effect of consumption of fruits and vegetables.

Clinical investigations have shown that prognosis of NHL varies according to histology and genetic profile. The translation of histologic and genotypic findings into potential clinical markers has led NCI scientists to assess the demographic patterns and trends in population-based rates of different cellular subgroups of NHL. Overall, the broad categories of small lymphocytic, follicular, diffuse, high-grade, and peripheral T-cell NHL appear to be distinct entities with specific age, sex, racial, temporal, and geographic variations in rates. Better classification systems, more relevant preclinical models, and better drug targeting are all needed to improve our ability to treat this disease.

Lymphoma continues to be an area of specific interest in both the laboratory and the clinic, with increasing emphasis on translating preclinical data into clinical testing. NCI-funded research covers a broad spectrum of efforts.

NCI is supporting the evaluation of over 20 agents for effect in lymphoma and lymphoma-related targets. Over 80 studies specific to patients with lymphoma are directly sponsored by the NCI, with more studies that include lymphoma along with other diseases.

Depsipeptide is a novel drug with a new mechanism of activity currently under study at the NCI. It has shown dramatic and durable effects in as many as 50% of patients with cutaneous T-cell lymphomas. Preliminary results suggest it will also be effective in some patients with peripheral T-cell lymphoma, a cancer with a high mortality rate.

Biologic-based therapies are also showing promise. Zevalin is the first FDA-approved radiolabeled monoclonal antibody used in treating non-Hodgkin's lymphoma and is licensed from the NIH for this use.

NCI intramural and extramural investigators have joined forces in a coordinated series of ongoing case-control studies focused on NHL. The NHL collaboration, known as InterLymph, represents a new generation of large-scale molecular epidemiology studies, with investigators pooling data from North America, Europe, and Australia to identify reasons for the increasing incidence of this tumor around the world. Each case-control study includes a detailed review of the pathological and genetic characteristics of the NHL cases. The investigators are sharing data in order to test for genetic and environmental causes that cannot be addressed in individual studies with smaller sample sizes. Because the consortium involves essentially all major on-going epidemiologic studies of NHL, it represents a model for the study of other malignancies.

Item

Blood cancers— The Committee is pleased that important new therapies have been developed for the blood cancers--leukemia, lymphoma, and multiple myeloma. Despite the introduction of these new therapies--including monoclonal antibody, radioimmunotherapies, and a proteasome inhibitor--far too many Americans still die from the blood cancers. The Leukemia, Lymphoma, and Myeloma Progress Review Group, a blue ribbon advisory panel of the National Cancer Institute (NCI), recommended in May 2001 the establishment of new multi-disciplinary and multi-institutional structures to shorten the timeline for new blood cancer drug development. The Committee encourages NCI to develop new strategies to accelerate the development of new blood cancer therapies, which might include, among other options, public-private partnerships, multi-disciplinary collaborations, and multi-institutional initiatives. NCI should consider flexible uses of current funding mechanisms in order to respond to the key recommendation of the blood cancer Progress Review Group, which was to reduce dramatically the time required to develop new therapies. (p. 65)

Action taken or to be taken

Supporting Academic/Public/Private Partnership Programs

At the suggestion of the Leukemia, Lymphoma, and Myeloma Progress Review Group (LLM PRG), NCI is supporting the formation of partnerships among academia, industry, nonprofit institutions, and government entities. These Academic Public Private

Partnership Programs (AP4s) will research novel cancer therapeutic, prevention, diagnostic, and imaging interventions. The overall goal of the partnerships will be to speed the translation of newly discovered cancer interventions to clinical trials. NCI is assisting the formation of these partnerships by funding 1-year planning grants.

The principal investigators and institutions are recognized leaders in the field of anticancer intervention, discovery, and development and have assembled excellent teams to plan and organize the AP4 centers. The AP4 centers will afford NCI an optimal opportunity to fund top-caliber, results-oriented research. Of the 14 potential partnerships currently being planned, two are focused on blood cancers.

One potential AP4 center plans to concentrate on developing new therapeutics and technologies for the treatment, diagnosis, and imaging of a range of orphan cancers such as acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), and ovarian cancer. Another proposed AP4 center focuses on the development of improved diagnostics and therapeutics for two rare and generally fatal malignancies, pancreatic cancer and multiple myeloma.

Research Consortia

In addition, NCI program staff has interacted with the American Society of Hematology and the Aplastic Anemia and MDS International Foundation to develop research consortia for specific diseases or treatment modalities. These include chronic lymphocytic leukemia (CLL), myelodysplastic disease (MDS) and myeloproliferative disease (MPD), and blood and marrow transplantation. In collaboration with the National Heart, Lung, and Blood Institute (NHLBI), NCI funds the Blood and Marrow Transplant Clinical Trials Network. Currently four phase III clinical trials are actively accruing patients with six additional phase II or III clinical trials at various stages of the approval process.

Initiatives

NCI has re-issued two Program Announcements entitled “Quick Trials for Novel Cancer Therapies: Exploratory Grants” and “Clinical Cancer Therapy and Prevention Research.” These initiatives currently support many projects related to blood cancers and address the LLM PRG’s recommendations to provide for molecular characterization of hematological malignancies, and new and novel treatment and prevention strategies. With the NHLBI, NCI has also cosponsored a Request for Applications entitled “Cellular and Genetic Discovery toward Curative Therapy in Myeloproliferative Disorders.”

The Rapid Access to Intervention Development (RAID) and Rapid Access to NCI Discovery Resources (R*A*N*D*) programs were initiated to fulfill the recommendation of the LLM PRG to develop resources to rapidly translate lead-structures into therapeutic agents. Numerous applications have been reviewed and approved including those for compounds in development for the treatment of MDS, leukemia, lymphoma and multiple myeloma.

Item

Myelodysplasia and myeloproliferative disorders research— The Committee recognizes NCI's support for a new research initiative in myeloproliferative disorders, which are chronic diseases of bone marrow cells that can develop into acute leukemia. The Committee encourages NCI and NHLBI to bring together scientific and clinical experts in these fields to explore collaborative and crosscutting research mechanisms to further this research agenda. The Committee also urges NCI to utilize the Surveillance, Epidemiology, and End Results (SEER) program to collect data on the incidence and distribution of these diseases. (p. 65)

Action taken or to be taken

NCI continues to support research into Myeloproliferative Disorders (MPDs) and Myelodysplasia (MDS) and will help fund NHLBI's recently released Request for Applications (RFA) entitled "Cellular and Genetic Discovery toward Curative Therapy in Myeloproliferative Disorders (MPD)." NCI is participating in this RFA by providing funds to support up to 12 new grants in response to this RFA in FY 2005.

NCI staff has also been working with investigators and research groups in MDS and MPD to develop research consortia in these disease areas. Three program project grants were submitted and reviewed, two on MDS and one on MPD. However, none of them received fundable priority scores. Two amended applications were subsequently received, one on MDS and one on MPD. In September 2004, these applications were reviewed. The applications are currently awaiting scoring by the parent review committee and the second level of review by the National Cancer Advisory Board.

Ongoing clinical research into therapeutic interventions for MDS/MPD include evaluation of the promising drugs bortezomib (Velcade), tipifarnib (Zarnestra), bevacizumab, imatinib (Gleevec), flavopiridol, Campath-1H, bryostatin, MS-275, epithilone-B, triapine, CCI-779, thalidomide, revlimid, phenylbutyrate and gemtuzumab ozogamycin.

In the U.S., and in most areas of the world, the determination of what is collected as cancer in cancer registries is based on definitions set forth in the International Classification of Diseases for Oncology (ICD-O), published by the World Health Organization. NCI's Surveillance, Epidemiology, and End Results (SEER) Program uses this same international standard and collects data according to these ICD-O definitions and categorizations. Periodically, the WHO convenes a panel of experts to revise and update the ICD-O according to advancing scientific understandings and standards. Such a panel reviews scientific studies to determine which diseases should be considered malignant cancer. In previous editions of the ICD-O, myeloproliferative and lymphoproliferative disorders and myelodysplastic syndromes were classified with a behavior code indicating uncertainty about whether they were benign or malignant, and therefore information about them was not collected by most cancer registries, including the SEER Program. With the coding classification change for these disease areas from unknown to malignant in the third edition of the ICD-O published in 2000, data is now

becoming available for cases newly diagnosed in 2001 and data for 2002 diagnosed cases will be available in April 2005.

With the most recent revision of the ICD-O, the following MPDs- and MDS-relevant conditions became reportable in the U.S. for cancer diagnosed in 2001 and forward:

For the 2001 year of diagnosis, myelodysplastic syndromes:

- Refractory anemia
- Refractory anemia with sideroblasts
- Refractory anemia with excess blasts
- Refractory anemia with excess blasts in transformation
- Refractory cytopenia with multilineage dysplasia
- Myelodysplastic syndrome with 5Q deletion (5q-) syndrome
- Therapy-related myelodysplastic syndrome, not otherwise specified (NOS)
- Myelodysplastic syndrome, NOS

Under Chronic myeloproliferative disorders for 2001:

- Polycythemia vera
- Chronic myeloproliferative disease, NOS
- Myelosclerosis with myeloid metaplasia
- Essential thrombocythemia
- Chronic neutrophilic leukemia
- Hypereosinophilic syndrome

Item

Chronic lymphocytic leukemia (CLL)— This incurable disease is the most common form of adult leukemia in the U.S. The Committee encourages NCI to strengthen research efforts into CLL, including improved therapies and their rapid movement from the laboratory to the bedside. The Committee is pleased to learn that the unique multidisciplinary and multi-institutional research consortium funded by the Institute for the past five years is proceeding with a competing renewal of its initial grant to permit continued study of CLL at the cellular and clinical levels. The Committee encourages NCI to consider enhancing the scope of research activities funded through the CLL Research Consortium as it works to defeat this devastating blood disorder. (p. 65)

Action taken or to be taken

Since its initial funding in 1999, the CLL Research Consortium has made substantial progress in research on the genetics, biochemistry and immunology of CLL and has identified promising candidate therapies for this disease. There have been many accomplishments over the past period of funding:

1. identification of new genetic lesions involved in pathogenesis
2. new mouse model for CLL
3. identification of novel mechanisms regulating cell death in CLL
4. identification of small molecules that enhance cancer cell killing
5. improved understanding of factors associated with disease heterogeneity

6. identification of cells associated with leukemia initiation and progression processes
7. identification of leukemia-cell clearance mechanisms involved in cellular and immune gene therapies
8. identification of Leukemia-Associated Antigens
9. improved understanding of the state of T cell death in CLL
10. identification of novel pharmacologic and biologic agents for CLL
11. improved algorithms for assessing disease progression risk and response to therapy
12. development of infrastructure that facilitates bench-to-bedside and bedside-to-bench research
13. development of a web-based biomedical informatics system
14. development of a National Tissue Bank

Investigators of the CLL Consortium continue to interact with the NCI intramural investigators in familial CLL studies. They are accruing families with two or more living cases of CLL (http://dceg.cancer.gov/fam-cllsi.html). These families provide material for genetic studies and for studies to characterize B-cell abnormalities that may be pre-cursor states for CLL. Studies at NCI and elsewhere have found that first degree relatives of CLL cases from high-risk families have a higher probability of developing monoclonal B-cell lymphocytosis than do individuals from the population at large. Members of the international familial CLL consortium have submitted a paper proposing standards and criteria for B-cell findings that can be applied to both population and high risk family studies.

NCI investigators are collaborating with investigators at some of the CLL Research Consortium centers to standardize familial CLL studies. Developing a standardized approach for detecting markers on the surface of CLL cells, designing a risk factor questionnaire to be used by all participating groups, and planning for enhanced family accrual and biospecimen collections will pave the way so that new genome-wide scans can be conducted on CLL family samples pooled from multiple centers. Standardizing the methodology will enhance early detection of initial disease and relapse, as well as help determine the very early molecular changes that characterize this leukemia.

The CLL Research Consortium's competitive renewal grant application was reviewed in October 2004 and is awaiting second level of review by the National Cancer Advisory Board. Cytogenetic studies that take advantage of newly discovered genetic lesions of CLL and enhanced drug discovery studies based on molecular pathways in the pathogenesis of CLL are highlights of this competitive renewal application.

Item

Tuberous sclerosis complex— Tuberous sclerosis complex (TSC) is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the brain, heart, kidneys, lungs, liver, eyes or skin. In light of its similarities to the uncontrolled growth of cancer cells, many scientists believe that determining the cause of tumor growth in TSC could open the way for cures and treatments for cancer as well.

The Committee encourages NCI to support programs examining the molecular and cellular basis of TSC, and the role of TSC in tumor development. (p. 65)

Action taken or to be taken

Tuberous sclerosis complex is named for one of the most common features of the disease, tuber-like brain growths that calcify and become sclerotic with age. These abnormal growths are thought to cause the epileptic seizures that are the most common presenting feature of TSC. In addition to growths in the brain, lesions of the kidney and lungs are especially problematic for TSC patients. NCI recognizes TSC as an important area of investigation for the purpose of alleviating patient suffering and for deciphering the mechanisms of growth control that have gone awry in this disease. Recent discoveries have shown that these growth control mechanisms are also perturbed in sporadic cancers and in other hereditary predispositions to cancer, such that studies of TSC synergize with those of many cancers.

In 2003, NCI joined a trans-NIH initiative to coordinate TSC-related activities. Led by the National Institute of Neurological Disorders and Stroke (NINDS), the coordinating committee published a research plan for TSC in 2003 and met in 2004 to assess progress on the plan. The plan's major areas of emphasis are:

- Determine the molecular and cellular basis of TSC
- Understand and treat the symptoms of TSC
- Understand the expression of TSC symptoms across life span
- Develop resources that facilitate and accelerate TSC research

NCI has contributed to each of these areas and plans to expand its contributions in FY 2005.

Determine the molecular and cellular basis of TSC

TSC is caused by mutation of one of two genes, TSC1 or TSC2, which leads to unregulated cell growth. It is this growth that is thought to contribute to tumor formation. In support of this idea, many of the molecules that transmit the pro-growth signals that inhibit the TSC proteins and stimulate protein synthesis are abnormal in sporadic cancers and hereditary predispositions to cancer.

Two years ago, three NIH-sponsored research groups reported that the TSC proteins inhibit an enzyme which controls protein synthesis. Very rapidly, this basic discovery led to the first clinical trials for TSC. More recently, basic research supported by the NCI has led to several discoveries that provide potential new targets for therapy.

Understand and treat the symptoms of TSC

Currently, NCI is supporting a non-randomized clinical trial testing whether rapamycin treatment can reduce or eliminate renal angiomyolipomas (AML) associated with either TSC or sporadic lymphangioleiomyomatosis (LAM). NCI plans to fund a multicenter clinical trial testing rapamycin against TSC-associated AML. This Phase II trial will unite clinicians and patients at six medical centers, providing a greater opportunity for TSC patients to receive treatment. Recognizing that more clinical trials will be

necessary, NCI is participating with the trans-NIH coordinating committee to develop an NIH-wide call for proposals for clinical trials specifically for TSC.

Understand the expression of TSC symptoms across life span
Natural history studies of TSC patients are being conducted by the NCI, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI). NHLBI has enrolled a number of TSC patients in a clinical study of LAM, and some of these patients also develop kidney lesions including renal cysts, AML, and renal cancers. NCI researchers are studying these patients to develop criteria for differentiating non-fatty AML from renal cancers in an effort to identify useful therapeutic markers, mechanisms of tumorigenesis, and potential targets for therapies.

Develop resources that facilitate and accelerate TSC research.
A genetically engineered line of mice lacking the TSC1 protein is maintained and distributed free of charge by the NCI-sponsored Repository of the Mouse Models of Human Cancer Consortium.

Item
American Russian Cancer Alliance—The Committee recognizes the contribution of the American Russian Cancer Alliance (ARCA) in its pursuit of novel research activities that ultimately benefit cancer patients worldwide. The Alliance has brought together the scientific strengths, expertise, and particular resources of both nations for the benefit of humankind through its effort to diagnose, treat and prevent cancer. The Committee notes in particular the unique ARCA projects in molecular imaging and radionuclide therapy that capitalize on the exceptional scientific expertise and technical capabilities of the leading Russian nuclear research centers and American cancer centers. The Committee encourages NCI to establish a mechanism to support the continued development of this collaboration between the United States and Russian cancer researchers and to develop a plan to support the necessary infrastructure at U.S. institutions for the Alliance and its activities. (p. 66)

Action taken or to be taken
The NCI Office of International Affairs (NCI/OIA) has been working closely with the American-Russian Cancer Alliance (ARCA), which started nearly 3 years ago and involves the University of Maryland Greenebaum Cancer Center in Baltimore, the Fox Chase Cancer Center in Philadelphia, the N.N. Blokhin National Cancer Research Center in Moscow (the largest cancer treatment center in Russia), and the Kurchatov Institute (the premier Russian nuclear research center). The U.S. ARCA partners are supported by cancer center grants from NCI and numerous NCI grants to individual investigators.

Representatives of NCI, including the NCI Director and the Director of NCI/OIA, met with representatives of ARCA in Moscow in June 2004. In August 2004, NCI/OIA supported participation in NCI's Summer Courses on Cancer Prevention of six Russian participants nominated by the Blokhin Cancer Research Center. Subsequently, NCI/OIA and ARCA leadership have planned two joint activities for the coming year. The first activity planned for early in 2005 will be a joint cancer communications activity that will

allow personnel from both countries' institutions to interact and to facilitate the building of cancer communication infrastructure at the Blockhin Center. In addition to the NCI Office of Communication in the U.S., the activity will involve communications personnel from the Centers for Disease Control and Prevention and several U.S. nongovernmental entities with extensive cancer communications activities. A second collaborative activity being planned for 2005 focuses on building infrastructure and capacity in the area of cancer prevention. NCI/OIA will continue to interact with ARCA seeking additional avenues of collaboration.

Item

Bone metastasis study—The Committee encourages NCI to develop an integrated approach to study bone metastasis, leveraging the expertise of cancer and bone biologists, clinical oncologists and metastasis experts and representatives from pharmaceutical industry. Key issues to address include the generation of novel models which mimic tumor/bone interaction and which delineate mechanisms to determine why tumor cells prefer bone for metastasis. The Committee also urges NCI to expand research on osteosarcoma to improve survival and quality of life and to prevent metastatic osteosarcoma for children and teenagers who develop this cancer. (p. 66)

Action taken or to be taken

The major cause of death in cancer patients occurs when the primary tumor spreads (metastasis) to distant but vital organs of the body. It is known that a high percentage of patients with prostate cancer, breast cancer, and multiple myeloma develop bone metastasis. Bone metastases are also frequently seen in patients with lung cancer, renal cancer, and melanoma. It is estimated that there are about 350,000 deaths per year in the United States from cancer patients with bone metastasis. It is evident that reciprocal interaction between tumor cells and the bone marrow microenvironment is critical in tumor cell survival and growth which eventually leads to the formation of bone metastases.

In order to improve therapy and ultimately prevent bone metastasis, the NCI is using a multi-pronged approach to increase our understanding of the unique role the bone microenvironment plays in metastasis of cancer to the bone.

Basic Studies in bone metastasis

NCI supports studies to: (a) define the molecular signatures of cells in the cancer microenvironment at various points during initiation, progression, and cancer metastasis; b) identify factors used by cancer cells to activate cells in the tumor microenvironment, which in turn support tumor growth and progression; c) identify the origin of cells and factors that comprise the tumor microenvironment; d) establish a repository for antibodies, cell lines, animal models, and tissues that relate to cells in the microenvironment; and e) apply knowledge derived from molecular analysis studies exploring tumor-host interactions to create targeted interventions.

- Recent findings have shown that the extracellular calcium released from the bone resorption process provides a feedback mechanism resulting in increased PTHrP

production by breast cancer cells with calcium-sensing receptors. This finding provides a new potential target for the development of novel therapeutics.

- New results indicate that osteoprotegerin inhibits the establishment and progression of human prostate cancer tumors injected into human adult bone. Treatment with zoledronic acid also reduced human prostate tumor burden in bone in a mouse model. The implication of these studies is that the inhibition of the primary bone resorptive stage may be sufficient to stop tumor establishment and growth.

- One example of proteins produced by cancer cells that metastasize to bone is uPA –a protein that is normally expressed on bone cells and its effects result in normal bone turnover. To nullify the effects of uPA produced by prostate cancer cells, investigators are making attempts to target a uPA inhibitor, Maspin, to interfere with bone metastasis in prostate cancer models.

- NCI-supported investigators have identified a unique protein from human bone marrow samples of prostate cancer patients which is able to stimulate new bone formation. This protein is absent in the bone marrow of normal individuals or patients who show no evidence of bone metastasis and provides important clues as to how prostate tumor cells interact with bone cells to produce the clinical effects typical of advanced prostate cancer.

<u>Basic studies in Osteosarcoma</u>

- Intramural investigators have conducted studies that suggest that MMP-7, which is broadly expressed in Ewing's sarcoma cells and tissue, may be a potential therapeutic target because its inactivation may enhance the efficacy of conventional chemotherapy in Ewing's sarcoma.

- Work on the role of insulin-like growth factors (IGFs) in pediatric sarcomas focuses on potential therapeutic approaches. NCI-supported investigators are collaborating with Immunogen to test a new humanized monoclonal antibody directed against an IGF receptor.

- Microarray studies have shown that turning off ezrin, a gene found to be upregulated in highly metastatic osteosarcoma cells, can reverse the metastatic phenotype of osteosarcoma cells. Reduction of ezrin leads to dramatically decreased metastatic behavior. Ezrin is also now linked to activation of mTOR, and investigators are exploring mTOR inhibitors as potential anti-metastatic agents.

- Investigators at NCI have recently developed mouse models of metastatic osteosarcoma and identified novel proteins that appear to play a major role in metastatic behavior in this model. Current research is trying to determine the signaling pathways that mediate these effects on metastatic behavior with the hope that novel therapeutic interventions can be identified and tested in patients with metastatic osteosarcoma.

Clinical studies in Bone Metastasis

- Two studies supported by NCI through the initiative, "Correlative Studies Using Specimens from Multi-Institutional Treatment Trials" are using novel imaging and molecular methods for the detection of occult bone metastases.

- Data from two phase III trials with docetaxel (taxotere®) demonstrated prolonged survival in hormone refractory prostate cancer. Building on this discovery, two concepts for phase III trials have been approved, to determine if an antiangiogenic agent (bevacizumab, avastin®) or atrasentan can delay progression and/or improve survival.

- A new randomized phase II trial will test whether combined bone-targeted therapy with strontium-89 and a bisphosphonate can delay progression and improve survival in prostate cancer patients when added to therapy for androgen sensitive disease.

- NSABP B34 has successfully completed its enrollment of more than 3,000 women. This trial will hopefully resolve the conflicting views about whether bisphosphonates simply decrease skeletal complications or whether they can improve breast cancer survival by altering the function of osteoclasts.

Clinical studies in Osteosarcoma

- The Children's Oncology Group (COG) is conducting a phase II study for patients with newly diagnosed metastatic osteosarcoma that investigates the use of cisplatin/adriamycin/methotrexate and ifosfamide/etoposide in a prospective manner in this patient population. The COG will also soon open a randomized phase III treatment study in localized or limited metastatic osteosarcoma.

- Institutional Review Board (IRB) approval was recently received for a new salvage therapy for recurrent osteosarcoma and Ewing's sarcoma using a combination of sequential gemcitabine/docetaxel.

Item

Tobacco Harm Reduction – The Committee continues to encourage research about tobacco products intended to reduce the harm caused by cigarette smoking and encourages NCI to expedite its research and review of existing literature regarding tobacco harm reduction. The Committee is particularly interested in what can be done from a public policy perspective to reduce tobacco related mortality and morbidity in that ten to fifteen percent of the adult population who cannot or will not quit smoking. The Committee encourages NCI to focus on the difference in harm caused by cigarettes versus potential reduced exposure tobacco products and how effective these products are or could be in smoking cessation efforts. NCI should consider exploring why Sweden has been so successful in reducing smoking and smoking related disease and what has been the impact of non-combustion products on smoking cessation in Sweden. (p. 66)

Action taken or to be taken

Forty years after the Surgeon General's first report on smoking and health, the nation has made enormous progress toward reducing tobacco use. Overall, adult smoking prevalence has decreased by nearly half from 42.4 percent in 1965 to 22.5 percent in 2002. Among some subgroups, progress has been even greater. For example, the prevalence of smoking among adults with an undergraduate degree has decreased to 12.1% and among adults with a graduate degree to 7.2%.

Nonetheless, tobacco use remains the nation's leading cause of preventable, premature death. During the period 1995-1999, more than 440,000 people died annually from diseases caused by smoking, of which cancer was the leading cause. While some population subgroups have met or exceeded the Healthy People 2010 goal of reducing smoking prevalence to 12% or lower, overall prevalence is nearly double this figure.

Education to better inform the public on smoking and health issues is a crucial component of tobacco control and prevention efforts. It is vital that the public understand that the only proven way to reduce the enormous burden of disease and death caused by tobacco is to prevent youth from beginning to smoke, to help youth and adult smokers to quit, and to eliminate public exposure to Environmental Tobacco Smoke (ETS). Today, we have much to offer people who smoke and want to quit, including effective behavioral treatments and medications. The evidence strongly suggests that people who keep trying to quit do succeed, although many will require numerous attempts before being successful.

Recently, a number of new tobacco products with claims of reducing exposure or harm have entered the market. Unlike smoking cessation products, tobacco products do not undergo rigorous, objective scrutiny, either for their constituents or for the accuracy of their health claims. A greater evidence base is required before we will know if the new products create benefit or harm at the individual and population levels. The main messages that NCI communicates to the public on this subject are that: 1) all tobacco use causes cancer and many other serious diseases; 2) the impact of potential reduced-exposure/reduced-harm products must be evaluated at both the individual and population level; and 3) more research is needed to determine whether any tobacco products purported to reduce exposure or harm actually do so.

The body of data currently available on potential reduced-exposure tobacco products is extremely limited. Little is known about smoking behavior among users of these products or the potential impact of these products on public health, including their potential impact on smoking prevention and cessation efforts. There is an urgent need for scientific guidance regarding methods for evaluating exposures to users of these products under actual smoking conditions and their subsequent public health impact. Two independent multidisciplinary scientific committees have outlined research needs and priorities related to tobacco harm reduction. A 2001 Institute of Medicine report provided specific recommendations for research to fill knowledge gaps and inform policies, regulations, and programs on the methods and products purported to reduce exposure and, potentially, harm. Additionally, a May 2001 conference convened by the

NCI, the National Institute on Drug Abuse (NIDA), the Centers for Disease Control and Prevention (CDC), the Robert Wood Johnson Foundation (RWJF), and the American Legacy Foundation developed research recommendations related to human smoking behavior and exposure and toxicity assessment for tobacco products purported to reduce harm.

To contribute to the body of data on new potential reduced-exposure tobacco products, NCI is currently pursuing two new research initiatives. The first is a program announcement that was released to the scientific community in May 2004. Through this solicitation, NCI will fund multidisciplinary research to generate comprehensive scientific information on the chemical composition, exposure, addictive properties, differential toxicity, and public health impact of potential reduced-exposure tobacco products. These products have been engineered, manufactured, marketed, and promoted by the tobacco industry as less hazardous and/or potential smoking cessation tools because they purportedly deliver lower amounts of toxic, carcinogenic, and addictive substances to the user, compared with conventional brands. However, to date, there is no science-based evidence to support the notion that tobacco products that are advertised with implied harm-reduction claims will actually reduce tobacco-related disease burden.

The second initiative aims to understand tobacco use behavior and exposure to toxins among users of new tobacco products promoted to reduce harm. The purpose of this initiative is to conduct research on the behavior and use of new tobacco products promoted with harm reduction claims to better understand their impact on individual and public health. In particular, research will focus on measuring human smoking behavior and exposures to toxins from tobacco products under actual conditions of use. The initiative also enables the application of validated tests to new potential reduced-exposure tobacco products to generate data that will inform the scientific community and regulatory agencies about the properties and potential impact of these products, compared with conventional products.

NCI is engaged in a number of other research activities related to new tobacco products and harm reduction. Most recently, NCI participated in the International Agency for Research on Cancer (IARC) Working Group on Smokeless Tobacco and some Related Nitrosamines. Publication of an IARC Monograph based on the Working Group meeting will follow at some future time.

In September 2004, NCI announced new funding for the Transdisciplinary Tobacco Use Research Centers (TTURC) initiative, which originally awarded grants to seven research centers in 1999. This new investment, totaling almost $12 million, will be funded over the next five years by the National Institute on Drug Abuse (NIDA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and NCI. The centers will study a wide range of topics, including genetic and psychosocial factors that influence tobacco use and addiction; effective smoking cessation treatments; exploration of molecules or genes that could affect tobacco exposure and disease risk; and the public health impact of regional and national tobacco control policies. The University of Minnesota TTURC

includes a focus on studying potential reduced-exposure tobacco products, using biomarkers to more effectively assess actual human exposure.

In partnership with CDC, NCI is committed to delivering evidence-based smoking cessation interventions to all Americans. Our work includes collaborating on the National Quitline Network and developing www.smokefree.gov. NCI will establish the new toll-free telephone number to serve as a single access point to the National Quitline Network. This telephone support, along with Web-based support on www.smokfree.gov, will provide the highest level of assistance to smokers who want to quit. Using one easy to remember number, smokers in every state will have access to the information and support they need to quit smoking. Individual, proactive smoking cessation counseling is the essential component of quitline effort.

NCI and CDC are collaborating with NIDA, and the World Health Organization (WHO) to plan a Global Tobacco Products Testing Laboratory Network. This Network will bring together scientists engaged in laboratory-based study of tobacco products and tobacco product constituents.

In February 2004, NCI, NIDA, NIAAA, and CDC held a meeting to discuss the state-of-the-science on methods and biomarkers used to assess the degree of tobacco toxin exposure. This 2-day meeting focused on developing best practice recommendations, given the current knowledge base, for methods and biomarkers used to assess potential reduced-exposure products - both tobacco industry and pharmaceutical products.

NCI has awarded a contract to create a Tobacco Harm Reduction Network, which will facilitate collaboration and communication among government and non-government scientists and organizations. The Tobacco Harm Reduction Network will focus on issues pertaining to both tobacco products purported to reduce harm and pharmaceutical products that could be marketed to reduce tobacco use and harm. The group aims to coordinate the development of mechanisms for sharing data and providing guidance on conducting transdisciplinary tobacco harm reduction science, as well as informing tobacco policies and regulation.

NCI and other scientific agencies have long been interested in the health hazards of smokeless tobacco products. In 2002, the NCI, CDC and the (Swedish) Centre for Tobacco Prevention hosted the 3rd International Conference on Smokeless Tobacco in Stockholm, Sweden. The mission of the conference was to update the available information on the science of smokeless tobacco prevention and control. A Summary Report of the meeting is available online at http://cancercontrol.cancer.gov/tcrb/smokeless_conf.html.

There is much to be learned about tobacco products that purport to reduce harm and/or to assist smokers to quit. We will continue to collaborate with our partners to develop and implement a framework for independent and objective scientific research, review, and interpretation of data on tobacco products and their use. In addition, we will work to

ensure that research is synthesized and disseminated to scientists, health care professionals, policymakers, and the general public. Sustained commitment, collaboration, and investment in tobacco control research will help continue the nation's steady progress towards reducing the prevalence of tobacco use, and consequently, cancers caused by tobacco.

FY 2005 Senate Appropriations Committee Report language (S. Rpt 108-345)

Item

Anticancer compounds—The Committee encourages the National Cancer Institute to increase research in the area of anticancer compounds. Sources of these compounds include marine invertebrates, terrestrial plants, and microorganisms that may be used to develop small molecule anticancer drugs. The Committee further understands that little research is conducted in this area and therefore urges the Institute to conduct appropriate research in this area. (p. 97)

Action taken or to be taken

Over 60% of currently available anticancer drugs and over 70% of anti-infectious agents originate in one way or another from natural sources. With an estimated 5-15% of plant resources pharmacologically studied thus far, the marine environment barely explored, and less than 1% of the micro-organisms as yet cultured, natural resources remain a vast untapped resource for the discovery of novel lead compounds for development into potential new drugs for the treatment of cancer and other serious human diseases.

NCI has been at the forefront of investigating natural products as a source of potential anticancer agents for over 40 years, and has played a major role in the development of most of the anti-cancer drugs currently available. While some of the drugs show efficacy as single agents, most are used in combination therapy with other active agents.

Since 1960, NCI has had an extensive program aimed at the discovery and development of novel anticancer agents from natural sources with samples coming from over 25 mainly developing countries worldwide. These samples are distributed to over 40 investigators worldwide for research aimed at the discovery of novel agents for the treatment of cancer and all other human diseases. Distribution is subject to the signing of Material Transfer Agreements ensuring the protection of source country rights. The following agents illustrate the impact this program has had over the years and several agents listed below are currently in either preclinical or clinical development for the treatment of cancer and/or AIDS.

- Plant Sources. Over 95,000 plant samples representing approximately 13,000 species were collected primarily from temperate regions through an interagency agreement with the USDA. Over 114,000 extracts were tested, and led to the discovery and development of: Paclitaxel (taxol®), effective in the treatment of breast, ovarian and forms of lung cancer, and Kaposi sarcoma; topotecan and irinotecan, effective against small cell lung and colorectal cancers; and homoharringtonine, effective against various leukemias. NCI also assisted in the

development of vinblastine and vincristine, effective against childhood leukemias, and etoposide, effective against lymphomas and bronchial and testicular cancers. Calanolides A and B are in clinical trials in the U.S. and Southeast Asia for the treatment of AIDS, while prostratin is in preclinical development.

- Microbial Sources**.** Over 180,000 microbial-derived extracts, mainly provided by pharmaceutical company partners, were tested. Among the drugs developed were: doxorubicin (adriamycin), effective against breast cancer, leukemias and lymphomas; the bleomycins, effective against lymphomas, testicular, and head and neck cancers; actinomycin, effective against choriocarcinomas, testicular cancer, and Wilm's tumor; and mitomycin C, which has shown some effect against breast, head and neck, and non small cell lung cancers. The anti-HIV microbocide, cyanovirin, is in preclinical development.

- Marine Sources. 10,000 marine invertebrates (sponges, tunicates, etc.) were collected by investigators mainly funded though NCI grants, and some 16,000 extracts have been tested. Although no commercial drug has yet been realized, several drugs are currently in clinical trials. These include bryostatin, as well as dolastatin 10 and dolastatin 15 and their synthetic derivatives, cematodin and synthatodin. Also, ET7389, synthetically derived from halichondrin B isolated from a sponge, is in early clinical trials, while the salicylihalimides, chondropsins, and diazonamides, also isolated from sponges, are in preclinical development.

Item

Bladder and Renal Cancer- The Committee is concerned about the poor implementation of the 2002 Progress Review Group Report on Bladder and Renal Cancers. The incidence and mortality of renal cancer has been steadily increasing over the past several decades. Renal cancers are silent killers; for many, renal cancers are not recognized until late in the disease, when cancer has already spread beyond the kidney. NCI is urged to expand studies to improve detection and diagnosis of renal cancer. For patients with metastatic renal cancer, survival is only 9 percent with a median survival time of 12 months. There are very few effective treatments. Metastatic bladder cancer also responds poorly to treatment. The Committee urges NCI to develop a novel treatment network to rapidly identify and test for new therapies for renal and bladder cancer in human patients and to expand studies on mechanisms of metastasis in these patients. (p. 98)

Action taken or to be taken

Molecular genetic evidence has shown that kidney cancer is not a single disease, but is made up of a number of different types of cancer, each with a different histology, different clinical course, and different gene mutations. Discovery of this molecular complexity in kidney cancer made it necessary to radically altered how research was to be conducted going forward. Cooperation and data sharing among scientific teams became critical to the acceleration of progress. Aware of the need for a culture shift from individual research to team science, NCI scientists linked over 80 scientists/physicians

from 22 labs and branches from 7 Institutes/Centers at the NIH to refine, share, and apply their understanding of the genetic basis of kidney cancer.

With this infrastructure in place, NCI has systematically incorporated the thirteen priorities identified by the Kidney/Bladder Cancers Progress Review Group (PRG) as key elements in the areas of Discovery, Translational Research and Treatment, Cancer Control and Quality of Life.

Discovery

Much progress is being made in understanding the biological mechanisms and risk factors for kidney cancer. NCI has identified genetic, epigenetic, RNA expression, and proteomic alterations in tumors and can now place many alterations in specific biological pathways for certain subtypes of kidney cancer. Science continues to add to the list of discoveries and the following truncated list of advances illustrates NCI's progress in this area:

- Discovered the Von Hippel-Lindau (VHL) kidney cancer tumor suppressor gene on chromosome 3.
- Showed that the VHL gene was the gene for hereditary and sporadic clear cell kidney cancer.
- Described the VHL cancer gene pathway.
- Discovered Hereditary Papillary Renal Carcinoma (HPRC) on chromosome 7.
- Described the hereditary form of chromophobe and oncocytic renal carcinoma in the Birt Hogg Dubé (BHD) syndrome.
- Described the fumarate hydratase mutations in type 2 papillary renal cancer families associated with Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC).
- Described the biochemical pathway of the FH gene in type 2 papillary kidney cancer.

NCI has generated and is characterizing mouse models of bladder and kidney cancers. These models will allow identification and validation of prognostic, preventive, and therapeutic targets, and their inhibiting agents.

Translational Research and Treatment

NCI-funded research in kidney and bladder cancer has benefited greatly from the move toward translational research. Often research from a different cancer type becomes relevant to kidney or bladder cancer. Such was the case for papillary renal cell carcinoma (PRCC), a disease that strikes children.

Several years ago researchers discovered that a specific family of growth-linked genes made good markers in blood tests for melanoma. NCI-funded scientists have recently found several cases of PPRC carcinoma in which one gene was fused abnormally to a variety of different genes. The error causes this gene to function abnormally and implicates it in the development of PPRC. Investigators now hope to devise treatments capable of blocking some of the downstream targets of this particular gene.

NCI is using new minimally invasive techniques to image and assess the biological and clinical effects of targeted therapeutics. While laboratory techniques can provide detailed

histologic or chemical information, location in the body or organ is lost when tissue or fluids are removed from the body. NCI can now use functional imaging to assess the biological and clinical effects of targeted therapeutics and to monitor changes over time. Imaging will have great impact on renal and bladder cancer research.

NCI sponsored research has resulted in the development of a number of rationally designed agents to combat kidney cancer. In addition, NCI is developing new genomics and proteomics-based tests to detect kidney cancer and assess bladder cancer recurrence. These tests are based on unique molecular factors, such as p53 alterations. Other detection tools in development include non-invasive detection methods such as MSP-Based Detection of Renal Cancer and Microsatellite DNA Analysis, as well as a new agent, Levulan PD, to enhance the detection of bladder cancer.

Cancer Control/Quality of Life Priority

NCI programs to reduce the number of smokers in the U.S. remains a key intervention to eliminate both bladder and kidney cancer. Cigarette smoking is the primary risk factor for kidney/renal pelvis cancer; smoking approximately doubles the risk of renal cell cancer and quadruples the risk of renal pelvis cancer. It has been estimated that smoking cessation would reduce renal pelvis cancer incidence by half, renal cell cancer by one third, and bladder cancer by 50 percent in men and 30 percent in women. An NCI-funded project will measure the association between the news media's coverage of tobacco and cancer-related risks and issues and public perceptions of the need for personal behavior changes.

NCI continues to find ways to close the gaps between and barriers to standards of practice and care that currently result in disparate outcomes for kidney and bladder cancer patients. In an effort to close the gap in health disparities and cancer mortality among medically underserved African Americans, NCI is funding a series of regional cancer prevention and early detection training programs for nurse educators from the nation's historically Black colleges and universities and minority institutions. An NCI-funded partnership between the University of Pittsburgh Cancer Institute (UPCI) and Hampton University (HU) will combine the strengths of both institutions to establish cancer biology teaching and laboratory work in the HU curriculum, expose HU students to UPCI faculty and programs, and develop core faculty expertise in cancer biology at HU while giving UPCI access to minority populations.

Item

Blood Cancers— The Committee is pleased that important new therapies have been developed for the blood cancers--leukemia, lymphoma, and multiple myeloma. It has been brought to the Committee's attention that the Leukemia, Lymphoma, and Myeloma Progress Review Group, a blue ribbon advisory panel of NCI recommended in May 2001 the establishment of new multi-disciplinary and multi-institutional structures to shorten the timeline for new blood cancer drug development. The Committee encourages the NCI to develop new strategies to accelerate the development of new blood cancer therapies, which might include, among other options, public-private partnerships, multi-disciplinary collaborations, and multi-institutional initiatives. The Committee further

urges the NCI to consider flexible uses of current funding mechanisms in order to respond to the key recommendation of the blood cancer Progress Review Group. (p. 98)

Action taken or to be taken
Please refer to pages NCI-46 through NCI-49 of this document for NCI's response to this significant item regarding Blood Cancers.

Item
Bone Metastasis—The NCI is encouraged to develop an integrated approach to study bone metastasis, leveraging the expertise of cancer and bone biologists, clinical oncologists and metastasis experts and representatives of the pharmaceutical industry. Key issues to address include the generation of novel models which mimic tumor/bone interaction and which delineate mechanisms to determine why tumor cells prefer bone for metastasis. It is clinically relevant to learn how to use information to change the bone microenvironment so that it is hostile to the invading tumor cells. The Committee also urges NCI to expand research on osteosarcoma to improve survival and quality of life and to prevent metastatic osteosarcoma in children and teenagers who develop this cancer. (p. 98)

Action taken or to be taken
Please refer to pages NCI-47 through NCI-49 of this document for NCI's response to this significant item regarding Bone Metastasis Study.

Item
Brain Tumors-- The Committee is concerned that insufficient attention is being given by NCI and NINDS to brain tumor research. The Committee encourages NCI to fund at least five Specialized Programs of Research Excellence in Brain Tumors [SPORE] grants in the upcoming fiscal year, with particular emphasis on those proposals which include both basic research and clinical treatment applications. (p. 98)

Action taken or to be taken
Each year, more than 100,000 new brain tumor cases are diagnosed, including tumors that arise in the brain and tumors that spread to the brain from other cancers such as breast and lung. Cancer is the second leading cause of death in children, and brain tumors are the second most common childhood cancer. The causes of brain tumors remain largely unknown, and there are virtually no means of prevention. Scientists have begun to develop better and less toxic treatments for brain tumors, which will produce longer survival and higher quality of life.

Brain Tumor SPOREs

There are currently four Brain Tumor SPOREs. One Brain Tumor SPORE, awarded to Duke University, was co-funded by the National Institute of Neurological Disorder and Stroke (NINDS). As a whole, the Brain Tumor SPOREs focus on clinical treatment applications. As a group, they have recently initiated discussions about performing collaborative studies on pediatric patients. By combining the pediatric brain tumor patient base at all four sites, there is the potential to perform significant studies on this

subpopulation of patients. Two of the Brain Tumor SPOREs have been successful in obtaining administrative supplement funds, one for a minority investigator and the other for a combination Phase I clinical trial for glioblastoma multiforme with ABT-510 (an agent that inhibits blood vessel formation) and radiation. At this point, there have been a number of discussions about the focus of a collaborative Inter-SPORE trial. Eight to nine different interventions have been discussed, including the expansion of an epidemiological SPORE project concentrated on identifying genetic and brain tumor risk factors. The next Brain SPORE solicitation for applications is scheduled for June 1, 2006.

NCI also supports pediatric brain tumor clinical trials through the Children's Oncology Group. Approximately 400 children have now been entered into a study for children younger than 10 years of age with progressive low-grade astrocytoma, including 115 children known to have NF1. For children with NF1, the primary objective of the study is to determine their event-free-survival and overall survival following treatment with a regimen of carboplatin and vincristine.

NCI has established an integrated clinical, translational, and basic research program that engages the strengths and resources of both NCI and NINDS for the purpose of developing novel experimental therapeutics for children and adults with tumors of the central nervous system. Toward this end, the NCI has a growing laboratory effort devoted to developing new strategies for utilizing genetic vectors to explore basic biologic questions and develop novel therapeutic approaches that can be brought into the clinic. In addition, the NCI has closely aligned its efforts with the NIH-sponsored extramural effort in brain tumor basic and clinical research. In particular, NCI hopes to establish close working collaborations with other NCI-sponsored collaborative clinical trials groups that have an interest in brain tumors for the purpose of synergizing the strengths of these groups with some of the unique capabilities of the NIH intramural program. Through this alliance of basic and applied science, closely linked to individuals capable of conducting solid clinical investigation, a new generation of therapeutic breakthroughs is being realized.

NCI is committed to cancer treatment research and has created a preclinical and clinical drug development pipeline for the identification and evaluation of new agents for the treatment of primary brain tumors. This includes the creation of an Animal Brain Tumor Therapeutics Core for the in vitro and in vivo evaluation of new compounds using a moderately high throughput approach. The most promising of these agents are rapidly moved into early phase or phase I clinical trials and then moved forward into either expanded phase II trials at the NIH Clinical Center or through one of the three NCI-sponsored extramural early phase brain tumor consortia. Agents that look promising in these expanded phase II trials are then brought to the large NCI-sponsored extramural cooperative clinical trials groups for definitive phase III evaluation. This preclinical/clinical drug development pipeline has proven successful, and NCI has partnered with significant numbers of academic investigators and biotechnology/pharmaceutical companies to develop a large number of new agents for the treatment of primary brain tumors.

Furthermore, through its Radiation Oncology Branch, NCI supports ongoing combined modality clinical trials in the area of brain tumors. In the Pediatric Oncology Branch at NCI, systemically administered drugs that penetrate the blood-brain barrier are identified and targeted for studies in patients with brain tumors. NCI's Mouse Cancer Genetics Program (MCGP) has developed a mouse model of malignant astrocytoma, one of the most common forms of brain cancer and one that accounts for close to 40% of all primary brain tumors. NCI is using this model to gain insight into the biology of astrocytoma and to better understand the genetic influences on susceptibility to cancer.

Item

Cancer Centers and Minorities— The Committee commends NCI on the success of its cancer centers program. Given that minority populations suffer disproportionately from virtually every form of cancer, the Committee encourages NCI to support the establishment of a comprehensive center at a minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities. (p. 98)

Action taken or to be taken

The NCI is committed to addressing the disproportionate burden of cancer in minority populations through the development of NCI-designated cancer centers in minority institutions, as well as to a number of additional strategies:

- The ***Minority Institution/Cancer Center Partnership Programs (MI/CCP),*** which partners Minority-Serving Institutions (MSIs) with existing NCI-designated Cancer Centers, was established in 2000 to take maximum advantage of their respective expertise and experience. The program fosters development of independent cancer research programs and minority career scientists in MSIs and improves minority-focused outreach and training efforts in NCI-designated Cancer Centers. MSIs are then better positioned either to compete for independent NCI designation or to form equal and permanent research alliances with existing NCI-designated Cancer Centers. The NCI-designated Cancer Centers participating in these partnerships, on the other hand, can realize substantial progress in their efforts to implement effective research, outreach, and education programs that truly have an impact on minority populations.

- ***Cancer Center Planning Grants*** provide support for institutional planning activities that will position cancer centers to compete for NCI designation. One of the seven current awardees, the Howard University Cancer Center (HUCC), is also an MSI collaborating with Johns Hopkins University. Five other awardees are located in states with significant minority populations, including South Carolina, Georgia, Texas, New Mexico, Kentucky, and Oklahoma.

- ***Affiliations and consortia:*** Realizing that many institutions serving minorities may not have the research capability or the desire to apply for NCI designation independently, NCI recently revised the cancer center guidelines to encourage the development of affiliations and consortia. We specifically encourage consideration

of partnerships that address cancer in minority and other underserved populations. In at least one state, such a consortium has received legislative support and funding.

Through NCI's "Discovery, Development, Delivery " continuum, links between existing Cancer Centers, their affiliates and partners in research, and the state, municipal, and private organizations within their community will continue to develop. NCI is actively seeking mechanisms to foster both the vertical integration (i.e. from the cancer centers through the community layers they serve) and the horizontal integration (i.e. across cancer centers and a nationwide network of public and private partners) of the benefits of cancer research. This integration, once firmly established, will provide a more unified approach to the conquest of cancer, and a more uniform delivery of the benefits of cancer research into all communities.

Item

Cancer and Native Hawaiians—The Committee remains concerned about the high incidence of breast, colon, and lung cancer among the native Hawaiian population. The Committee anticipates an update on the Director's task force to explore the continuing unique needs of the people of Hawaii and the Pacific Basin region. (p. 99)

Action taken or to be taken

Significant progress toward understanding and addressing the needs of the Hawaiian and Pacific Basin populations is being achieved through a 5-year cooperative agreement with Papa Ola Lokahi, a Native Hawaiian owned-and-operated community-based health organization. Through this agreement, the NCI continues to fund a variety of culturally competent cancer awareness, research, and training activities.

Via an administrative supplement to the Papa Ola Lokahi cooperative agreement, NCI helped establish the Cancer Council of the Pacific Islands (CCPI), a group of native physicians and other health professionals representing the six U.S.-associated jurisdictions of the Pacific region organized to address the cancer health needs within each of these jurisdictions. The CCPI has proven more effective in collecting and achieving results than an outside task force. Through the CCPI's efforts, data collection and subsequent recommendation implementation is much further ahead in a shorter time frame than would otherwise be possible working through a task force comprised of non-indigenous members or "outsiders." CCPI accomplishments are also significant in that, for the first time, island leaders are provided a controlling voice in the design, development, and implementation of their own survey instrument and subsequent activities. With the assistance of selected professors and students from the University of Hawaii, a comprehensive cancer assessment was administered in Kosarae, Chuuk, Pohnpei, Yap, Belau, Marshall Islands (Ebeye, Majuro), Northern Mariannas, American Samoa, and Guam. NCI is now implementing the prioritized listings of health needs identified as a result of those assessments, including addressing nursing training needs and initiating cervical cancer screening activities.

Item

Chronic Lymphocytic Leukemia [CLL]— This incurable disease is the most common form of adult leukemia in the United States. The Committee once again urges the NCI to

increase research into CLL, including improved therapies and their rapid movement from the laboratory to the bedside. The Committee is pleased to learn that the unique multidisciplinary and multi-institutional research consortium funded by the NCI for the past 5 years is proceeding with a competing renewal of its initial grant to permit coordinated continued study of CLL at the cellular and clinical levels. The Committee strongly urges the NCI to give favorable consideration to continuing and expanding the scope of research activities funded through the CLL Research Consortium as it works to defeat this devastating blood disorder. (p. 99)

Action taken or to be taken
Please refer to pages NCI-43 through NCI-44 of this document for NCI's response to this significant item regarding Chronic Lymphocytic Leukemia (CLL).

Item
Complementary and Alternative Cancer Therapies—The Committee expects the NCI to expand its work and its collaborative efforts with NCCAM to support research on promising complementary and alternative cancer therapies as well as on their integration with traditional therapies. (p. 99)

Action taken or to be taken
NCI is the only institute or center within the NIH, other than the National Center for Complementary and Alternative Medicine, with an office dedicated to the scientific evaluation of CAM approaches, the expansion of relevant research, and the production of information resources on CAM topics. NCI's Office of Cancer Complementary and Alternative Medicine (OCCAM) acts as a coordinating office by collaborating with NCI intramural and extramural offices/divisions to increase NCI's growing research agenda in CAM-related cancer prevention, treatment, symptom management, and rehabilitation. NCI's activities relevant to CAM continue to increase with NCI recently supporting approximately 400 projects in CAM and CAM-related research.

Currently 28 of the 84 open clinical trials within the NCI Clinical Community Oncology Program (CCOP) networks throughout the country are examining the use of CAM or CAM-related interventions. Included among them are studies of herbs such as St. John's Wort, Ginkgo biloba, Valerian, Black Cohosh; other dietary supplements such as l-carnitine, alpha-lipoic acid, zinc, coenzyme Q10, soy protein and soy isoflavones, ginger, lycopene, flaxseed; mind-body interventions such as stress management training and approaches derived from non-Western traditional healing systems such as acupressure and mindfulness relaxation. One important trial initiated in the past year is a study of a homeopathic product for prevention of oral pain and inflammation (mucositis) in children undergoing bone marrow transplantation. This is the first large scale, multicenter clinical trial of a homeopathic product in cancer patients in the U.S.

Data acquisition has been completed on the CAM sub-study of the California Health Interview Survey (CHIS) and preliminary findings were presented at the November 2004 meeting of the American Public Health Association. This study was a collaborative effort of NCI and the University of California at Los Angeles (UCLA) Center for Health

Policy Research and is the largest population-based survey conducted to date to document use of complementary and alternative medicine services by cancer survivors.

NCI collaborated with the United Kingdom's National Cancer Research Institute (NCRI) to implement a seminar designed to bring together experts in cancer CAM research and practice to: 1) provide an overview of the current scenario relating to complementary therapies in the UK, 2) provide an opportunity to discuss issues relating to research into complementary therapies in cancer care, 3) help to inform the work of the newly established NCRI Complementary Therapies Clinical Studies Development Group, 4) help inform NCI and the US research communities of research issues and activities in the UK, 5) provide an opportunity to hear the views of, and network with, leading international researchers and clinicians, and 6) identify the next steps to ensure that research progress is made in this area. NCI presented information about the OCCAM and the activities of its Research Development and Support Program to serve as an example, as well as provide consultation for the development of NCRI's own programs. NCI is supporting the development of an official proceedings document, as well as publication of some materials in peer-reviewed journal(s).

NCI's Practice Outcomes Monitoring and Evaluation System (POMES) has been created to review data of cancer patients treated in a CAM practice. POMES projects are designed to independently verify the findings of the best case series, to document and record the frequency with which positive outcomes occur, and to document the details of the therapy given. This information is helpful for determining if a clinical trial is merited and feasible and, if so, supplies detail necessary to design such a study. The current POMES initiative focuses on an NCI-sponsored data gathering project at a homeopathic clinic in Calcutta, India.

Through its OCCAM Web site (http://cancer.gov/cam), NCI provides a link for the general public, the research and practice communities, and other governmental agencies who are seeking updated information about NCI's CAM activities, as well as other information on CAM and cancer. The site contains updates of the status of current and planned NCI CAM projects; funding opportunities; clinical trials; links to CAM information; information about the Best Case Series Program; and assistance on how to write NIH-sponsored grants.

The NCI and the National Center for Complementary and Alternative Medicine (NCCAM) continue to collaborate on various initiatives and individual projects, including some of those discussed above. In FY 2004, these activities expanded further in the areas of information and communications. Some examples of joint projects include:

- A prospective collaborative clinical trial at the Columbia Presbyterian Medical Center examining the effect of the Kelley-Gonzalez regimen (a nutritional program with oral pancreatic enzymes and a "detoxification" regimen) on survival rate and quality of life among patients with Stage II, III, or IV pancreatic cancer.

- A study through the M.D. Anderson Community Clinical Oncology Program (CCOP) of a liquid shark cartilage product as an adjunctive treatment in patients receiving conventional chemotherapy and radiotherapy for advanced stage non-small cell lung cancer.

- Development of a new plain language CAM brochure designed for cancer patients and caregivers. Key messages in the brochure are based on the findings from the patient focus groups qualitative research project.

Item

Gynecologic Cancers— In the last 5 years, approximately 130,000 women in the United States have lost their lives to gynecologic cancer. The Committee commends the NCI for creating a cervical cancer and endometrial cancer SPORE, bringing the total number of gynecologic cancers SPORES to six, and expects that the NCI will expand the number of centers in the future. Unfortunately, 70 percent of ovarian cancer patients continue to be diagnosed in advanced stages when 5-year survival rates remain less then 25 percent. The Committee encourages continued research by the four ovarian SPORES that will lead to a better understanding of prevention and the development of a screening tool offering women earlier diagnosis when this cancer is more curable. The Committee also supports the expansion of NCI's collaboration with the NICHD for faculty development of gynecologic oncologists. (p. 99)

Action taken or to be taken:

NCI has a variety of projects underway focused on ovarian cancer early detection and prevention. In addition, NCI has sponsored training for researchers focused on gynecologic cancer through partnership with the National Institute of Child Health and Human Development (NICHD), the NIH Office of Research on Women's Health, and through the NCI's training programs, as well as through the Ovarian and Gynecologic SPORE programs.

Early Detection and Prevention

The Ovarian Cancer SPOREs are poised to make significant contributions to the early detection and prevention of ovarian cancer. During the past 5 years, these groups of investigators have developed an effective infrastructure which enables them to collaborate closely and freely with each other. The following four activities represent high priorities:

- Completion of the collaborative screening study on women at high risk for ovarian cancer. This study is designed to test the effectiveness of the CA-125 biomarker in a high risk population and determine if an exponential rise in this biomarker can detect ovarian cancer at an early stage. About 2000 participants are enrolled across the U.S.; 40% of the participants are enrolled at SPORE sites.

- Completion of the Avon-NCI Progress for Patients breast biomarker study. This study is designed to validate the effectiveness of a panel of biomarkers used in conjunction with mammography for the early detection of breast cancer.

Ultimately, the goal is to provide high risk women with additional clinical options which address their increased risks for both breast and ovarian cancers.

- Development of a biomarker panel for the early detection of ovarian cancer. Two Ovarian SPOREs have recently identified candidate biomarkers for early detection. Validation of a panel of early detection markers for ovarian cancer was ranked as a high priority activity by the SPORE Biomarkers Working Group.

- Performance of an Inter-SPORE prevention trial on high risk women with a COX-2 inhibitor (Celecoxib). COX-2 inhibitors have been found to inhibit the growth of ovarian tumor cells in vitro and are also potent inhibitors of ovulation. A pilot study with 20 participants was the first completed prevention study for ovarian cancer in the Nation. Preliminary results suggest that vascular endothelial growth factor (VEGF) may be a useful molecular biomarker to track in future trials involving Celecoxib or other nonsteroidal anti-inflammatory drugs. A decrease in VEGF expression may also have a biological significance in inhibiting angiogenesis during tumor formation or growth. A multi-site (Inter-SPORE) clinical protocol has been written and circulated, but is currently under re-evaluation given current concerns regarding the agent's cardiovascular effects.

Through the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), NCI seeks to determine whether certain cancer screening tests reduce deaths from prostate, lung, colorectal and ovarian cancer. Screening to detect early-stage ovarian cancer is theoretically appealing, because this malignancy is typically heralded by vague, non-specific symptoms and is characterized by advanced stage at diagnosis. In the PLCO Cancer Screening Trial, participants in the intervention arm are screened annually for 6 years with a CA-125 blood test and concurrently for 4 years with a transvaginal ultrasound (TVU). Although the trial and follow up will continue for many years, interim results are published as warranted. A list of publications and presentations associated with the PLCO Cancer Screening Trial can be found at http://www3.cancer.gov/prevention/plco/updates.html.

NCI, in collaboration with the Gynecological Oncology Group and the Cancer Genetics Network, is funding a new, 5-year prospective study to identify ways to lower the risk of developing ovarian cancer, as well as to improve the ability to detect this cancer at an earlier, more readily curable stage. The Ovarian Cancer Prevention and Early Detection Study targets women at elevated risk of developing ovarian cancer, either because they have a strong family history of breast and/or ovarian cancer or because they have tested positive for changes in genes which increase the risk of developing ovarian cancer. This study is evaluating two interventions: (1) risk-reducing removal of the ovaries and fallopian tubes; and (2) a novel ovarian cancer screening strategy.

NCI's intramural program has been the leader in applying proteomic technology to cancer diagnosis and monitoring. The proteomics program was initiated with the hypothesis that circulating blood contained peptides (small protein fragments) and proteins that could yield a signature pattern for the presence of small volume and/or organ-confined cancer. Ovarian cancer

was chosen as the proof of concept for this hypothesis because having a blood test to identify the presence of ovarian cancer in small volume and/or when organ-confined could make a significant public health impact. Since project initiation, NCI and its collaborators have demonstrated that state-of-the-art tandem mass spectrometry coupled with advanced bioinformatics data mining tools can yield protein signature models that have high sensitivity and high specificity for the presence of ovarian cancer in retrospective datasets. This concept has been confirmed recently by other NCI-sponsored investigators. NCI investigators have also identified important quality control and quality assurance steps for sample acquisition, storage, and mass spectrometry interface. This progress has markedly improved the reliability, reproducibility, and accuracy of mass spectrometry proteomic signatures. NCI has now embarked upon a multi-institutional protocol for the collection of blood samples from women with ovarian cancer in first clinical remission.

Training

For the past 5 years, NCI has supported the development of gynecologic oncologists through the NICHD Women's Reproductive Health Research Career Centers. The Centers support the research career development of obstetrician-gynecologists, designated Women's Reproductive Health Research (WRHR) Scholars, who have recently completed postgraduate clinical training, and who are commencing basic, translational and/or clinical research relevant to women's health. The goal of this initiative is to promote the performance of research and transfer of findings that will benefit women's health. In addition, for the past 5 years, NCI has funded the University of North Carolina, one of 10 sites designated for Building Interdisciplinary Careers in Women's Health, a program coordinated by the NIH Office of Research on Women's Health and NICHD.

In addition, the SPOREs support the career development of senior level postdoctoral or clinical fellows through the SPOREs' Career Development Program (CDP). In FY 2003, approximately $225,000 went to OB/GYN training and career development through the relevant SPOREs.

Also, awards were made for research training in gynecologic oncology under several other mechanisms. Approximately $3 million was awarded to the following training programs combined: individual career awards, Institutional Ruth L. Kirschstein National Research Service Awards, Individual Post Doctoral Fellowships, Pre Doctoral Fellowships and the Institutional Clinical Oncology Research Career Development Program**.**

Item

Liver Cancer—The Committee notes that in contrast to many other cancers, the number of people who develop and die from liver cancer has increased 24 percent since the year 2000. As the symptoms of liver cancer often do not appear until the disease is advanced, only a small number of liver cancer cases are found in the early stages of the disease, when it can be easily treated. The Committee is aware that the NCI, in collaboration with NIDDK, convened an Experts Conference that will help define the most urgent areas requiring additional research, professional education and public awareness initiatives.

The Committee urges NCI to issue a Request for Applications based on the findings of this conference. (p. 100)

Action taken or to be taken
Please refer to pages NCI-37 through NCI-38 of this document for NCI's response to this significant item regarding Liver Cancer.

Item
Lung Cancer – Lung cancer remains a major public health issue and is the leading cause of cancer death among women and minority populations. The death rate is expected to escalate as the population ages. Treatment and research now require an interdisciplinary approach and thoracic surgeons play an important role in both. The Committee encourages the Institute to work with the thoracic surgical community to identify priority areas for new clinical and translational studies and to ensure their participation in any interdisciplinary research efforts. Thoracic surgeons should be included in all relevant review and advisory committees and councils. (p. 100)

Action taken or to be taken
Lung cancer remains the leading cause of lung cancer death in the United States, with an estimated 174,000 new cases and 160,500 deaths in 2004. Multidisciplinary approaches to the diagnosis and treatment of lung cancer are critical, with involvement of medical oncologists, thoracic surgical oncologists, radiation oncologists, pulmonologists, radiologists, and pathologists as indispensable members of the team. Since the mainstay of treatment for early stage disease is surgery, thoracic surgeons are essential thought leaders in the idea generation, review, development, conduct, and successful completion of important scientific and clinical studies in this disease. NCI recognizes that their participation in interdisciplinary research efforts is absolutely vital. NCI has and will continue to work with the thoracic surgical community to facilitate this effort. To that end, thoracic surgeons are currently and will continue to be an integral part of review and advisory activities including:

- Chairing/co-chairing and/or participating as members of all lung cancer committees of NCI's Cooperative Groups.
- Participating in scientific review and advisory committees reviewing scientific and clinical trials proposals.
- Participating as members of the Lung Cancer Progress Review Group.

NCI has a close relationship with the thoracic surgical community, and NCI staff has met with and continue to meet and confer with the major thoracic surgical societies and the thoracic surgical oncology investigators on a regular basis.

Additionally, in fall 2003, NCI and the Thoracic Surgery Foundation for Research and Education (TSFRE) announced a jointly sponsored program for career development of thoracic surgeons in the early stages of their careers in cancer research. The joint program involves shared salary support for thoracic surgeons on the NIH Mentored Clinical Scientist Development Award and Mentored Patient Oriented Research Career

Development Award. The Clinical Scientist award will support the development of outstanding research scientists who are committed to a career in laboratory or field-based research and the Patient Oriented Career award will support clinically trained professionals who have made a commitment to focus on patient-oriented research. Each of these awards supports a 5 year period of supervised research experience that integrates didactic studies with laboratory or clinically-based research.

Item

Molecular Cancer Diagnostics – The Committee understands that the NCI is aware of the potential for molecular cancer diagnostics using circulating nucleic acids, including in particular extracellular RNA in plasma. The Committee believes that this technology could have enormous potential for the early detection, monitoring and selection of more effective treatment of a broad array of cancers and therefore encourages the NCI to explore the use and clinical application of this technology. (p. 101)

Action taken or to be taken

The NCI has undertaken several initiatives to use a range of post-genomic technologies (such as genomics, proteomics, molecular imaging, and nanotechnology) to develop biomarkers for a range of diagnostic, prognostic, and predictive purposes. For many types of cancer, accurate methods for early detection, diagnosis, prevention, and treatment can have a substantially beneficial impact on patient outcomes.

The NCI is actively pursuing programs that support the development of new molecular diagnostics using circulating DNA, RNA, and protein in plasma and serum. Although the exact mechanism of how tumor nucleic acids are released is unknown, several studies have demonstrated that patients with malignant disease have increased amounts of proteins and extracellular nucleic acids in their serum and plasma. Recent advances in molecular biology have improved the ability of scientists to specifically detect changes in nucleic acids that may serve as signatures of cancer, including cancer-causing gene mutations, loss of heterozygosity, and microsatellite instability.

The NCI manages several programs involved in developing technologies to create molecular diagnostics using circulating DNA, RNA, and protein such as the Innovative Technologies for the Molecular Analysis of Cancer awards and the Director's Challenge Program. Furthermore, the NCI is funding many studies to identify particular patterns of circulating nucleic acids and proteins that could be used to develop molecular diagnostics such as the Exploratory Studies in Cancer Detection, Prognosis and Prediction and Correlative Studies using Specimens from Multi-Institutional Prevention and Treatment Trials and the Phased Application Awards in Cancer Prognosis and Prediction.

The NCI Early Detection Research Network (EDRN), a consortium of more than 300 investigators which functions as an integrated network of biomarker discovery and validation laboratories, is identifying proteomic profiles to aid in diagnosis and prognosis of cancer patients. The network is supporting a number of studies utilizing plasma DNA and circulating nucleotides in cancer detection and diagnosis. The methylation of plasma DNA—where a methyl group compound is joined to DNA—is being investigated as

potential biomarkers for prostate, lung, and esophageal cancer, a rapidly rising cancer in terms of numbers and lethality.

Recently, the NCI's Cancer Biomarkers Research Group has issued a program announcement (PA) and a Small Business Innovation Research (SBIR) Request for Application (RFA) to study circulating exfoliated cells and other macromolecules, such as DNA, RNA, and proteins, in bodily fluids, such as serum, urine, sputum in molecular cancer diagnostics.

Recent work by NCI-funded investigators revealed that loss of heterozygosity in nine microsatellite markers in serum from patients whose cancer has spread was significantly correlated with response to therapy. These results suggest that circulating DNA markers in serum could help predict individual patient response to therapy.

Another research program monitored K-RAS mutations in pre-treatment and post-treatment plasma specimens from patients enrolled in phase I trial for non-small cell lung carcinoma. This study found that several patients that began the study with K-RAS plasma mutations lost these mutations after responding to the clinical trial therapy. These results are suggestive that the analysis K-RAS mutations in plasma could be used to monitor patient response to therapy.

Intramural activities such as the FDA/NCI Clinical Proteomics program have identified proteomic patterns in human serum using SELDI technology to distinguish normal individuals from cancer patients with high sensitivity and specificity. Finally, the NCI has undertaken a program to optimize and accelerate the discovery and development of protein cancer biomarkers across the cancer research community by providing common reagents and technology platforms to NCI-supported investigators. The NCI believes that post-genomics molecular diagnostics hold significant promise to detect cancer early, especially for patients with diseases such as ovarian, pancreatic, and lung cancer, where there are few therapeutic options during the later stages of disease.

Item

Multidisciplinary Research— NCI is commended for its innovative support of multidisciplinary training programs to enhance the scientific workforce. The Committee encourages NCI to explore new opportunities with the Office of Behavioral and Social Sciences Research to increase the number of scientists who can bridge the realms of behavioral and social science research and public health or biomedical research. (p. 101)

Action taken or to be taken

Seven years ago, NCI had a small portfolio of behavioral research projects, largely focused on smoking, fruit and vegetable consumption, and mammography utilization. With the establishment of the Behavioral Research Program at NCI, the Institute undertook a major effort to evaluate, strengthen, and expand both the breadth of the research program and the expertise of the scientists who lead it. In addition to the traditionally supported areas of research, NCI expanded its support of interdisciplinary

sciences in areas such as risk communication, decision-making, socio-cultural research, consumer health informatics, policy analysis, neuroscience, and behavioral genetics.

In line with its mission, NCI makes a special effort to coordinate its work with colleagues at the Centers for Disease Control and Prevention (CDC), the NIH Office of Behavioral and Social Sciences Research (OBSSR), and other NIH institutes with major behavioral science programs. NCI and OBSSR are strong partners in behavioral and social science research and training. NCI participates on, and contributes financially to, many exciting research initiatives that are fostered by OBSSR on behalf of the NIH. For example, NCI is an integral part of a new OBSSR initiative to Strengthen Behavioral and Social Science in medical schools. In response to growing recognition of the role played by behavioral and social factors in health and disease, the OBSSR and the Robert Wood Johnson Foundation asked the Institute of Medicine (IOM) to conduct a study of medical school education in the behavioral and social sciences. This IOM report, *Improving Medical Education: Enhancing the Behavioral and Social Science Content of Medical School Curricula,* is completed and recently published. Based upon the recommendations of this IOM report, the OBSSR has developed a special initiative, soon to be published, with the primary purpose of funding the development of innovative courses, curricula, and educational approaches designed to increase knowledge and skills in the behavioral and social sciences among medical students. There are specific domains noted in the IOM report that will provide a focus for such training. These domains are aligned with NCI Strategic Priorities and include patient behavior, physician-patient interaction, social and cultural issues in health care, health policy and economics, physician role and behavior, and mind-body interactions in health and disease. NCI will provide scientific guidance and management for the funded grants. Additionally, in FY 2004, NCI funded two grants under the OBSSR Request For Applications (RFA) entitled *Research on Mind-Body Interactions and Health.* The two funded grants will investigate how various mind-body/psychosocial factors affect stress-related hormones and patients' immune function.

Item

Myelodysplasia and Myeloproliferative Disorders- The Committee recognizes NCI's support for a new research initiative in Myeloproliferative Disorders [MPDs), which evolved from a recent conference involving the Institute and NHLBI. MPDs and Myelodysplasia [MDS] are chronic diseases of bone marrow cells that can develop into acute leukemia. The Committee encourages NCI and NHLBI to bring together scientific and clinical experts in these fields to explore collaborative and crosscutting research mechanisms to further this research agenda. The Committee also urges NCI to utilize the Surveillance, Epidemiology, and End Results [SEER] Program to collect data on the incidence and distribution of these diseases. (p. 101)

Action taken or to be taken

Please refer to pages NCI-42 through NCI-43 of this document for NCI's response to this significant item regarding Myelodysplasia and Myeloproliferative Disorders Resarch.

Item

Nanosystems Biology -- The Committee encourages NCI to support a collaborative effort to bring nanotechnology, systems biology and molecular imaging together to examine the molecular basis of cancer. Initial efforts have shown that cancers such as breast cancer are not a single disease, but may encompass many different diseases, when examined at the molecular level. Many clinical trials of new drugs are now considered to fail if only 10 percent of patients benefit, yet the 10 percent may represent a specific type of the disease, where the drug may be 100 percent effective. Bringing these three disciplines together may allow researchers to identify specific sub-types of cancer and to better target new interventions. Successful results of such an effort could lead to a molecular classification of many types of cancer and to targeted molecular treatments for molecular-specific diseases. (p. 106)

Action taken or to be taken

Nanotechnology, systems biology, and molecular imaging have all played significant roles in studying the molecular basis of cancer and identifying possible pathways and targets for treatment. NCI is working to synergize the efforts in these disciplines to accelerate understanding and therapeutic applications. Recently, NCI developed a Cancer Nanotechnology Plan (http://nano.cancer.gov) to guide technology development for cancer diagnosis and therapy. New initiatives in 2004 focused on centers for nanotechnology development, multidisciplinary career development, and individual research projects established as part of the NCI Alliance for Nanotechnology in Cancer. In 2004, NCI established a nanotechnology characterization laboratory in partnership with the National Institutes of Standards and Technology that will perform physico-chemical and biological characterization of nanomaterials. This effort will help investigators accelerate the development of nanoscale diagnostic and therapy platforms for clinical application.

Knowledge of molecular changes in cancer cells and their environment helps define their nature and predict pathologic behavior of cancer, as well as responsiveness to treatment. It also assists helps identify new targets and approaches for more effective interventions. Understanding the profile of molecular changes in a cancer makes it possible to correlate the resulting phenotype of that cancer with molecular events and use those correlations to develop more effective strategies of detection, diagnosis, treatment, and prevention.

The Innovative Molecular Analysis Technologies (IMAT) program supports research projects to develop and carry out pilot applications of novel technologies that will enable the molecular analysis of cancers and their host environment in support of basic, clinical, and epidemiological research. Technologies supported through the IMAT program include those that: detect changes in DNA; measure the expression of genes and their products; detect and analyze gene and cellular products and determine function of specific proteins; identify infectious agents outside the body that play a role in cancer; or analyze major signaling networks involved in cancer.

NCI created the Unconventional Innovations Program (UIP) to spur development of daring technologic improvements in cancer treatment and detection. This program seeks

to stimulate development of new technology platforms in cancer that can transform what is now impossible into the realm of the possible for detecting, diagnosing, and intervening in cancer at its earliest stages of development. Begun in 1999, the program is targeted to invest $50 million over a 10-year period through a new management approach to the development of technologies that target quantum improvements in existing technologies or entirely new approaches, rather than incremental improvements to the state of the art. The program attracts the involvement of investigators from disciplines that have not traditionally received support from NCI in taking on the defined technology challenge.

The UIP has been largely productive in nanotechnology and molecular beacon development, including nanoparticle-based diagnostics, therapeutics, and imaging agents. Nanotechnology is improving imaging instrumentation and leading to better design of imaging probes. The confluence of nanotechnology with molecular imaging technology, guided by a systems biology approach, represents a significant step forward in our understanding of—as well as our ability to diagnose and treat—cancer at the genetic and cellular level.

A specific example of a nanoparticle-based diagnostic that was developed in the UIP program is an agent from Washington University (http://otir.nci.nih.gov/tech/uip_awards.html#lanza) for MRI detection of new blood vessel growth with an alphaVbeta3-nanoparticle. The nanoparticles are loaded with a compound resulting in the ability to be detected by MRI. The particles are designed to bind to tumor blood vessels expressing a specific receptor over-expressed in tumor vasculature. This particular agent has now been submitted to the NCI's Development of Clinical Imaging Drugs and Enhancers Program (DCIDE) (http://www3.cancer.gov/bip/dcide.htm) for further development. Through the DCIDE program, the nanoparticle will be further evaluated to obtain animal toxicity, pharmacology, and safety data to allow the investigators to file an Investigational New Drug (IND) application. This nanoparticle will have the capability to provide important molecular imaging information and also eventually be loaded with drugs for targeted therapeutic intervention.

NCI is committed to investing in the application of new technologies emerging from the study of nanoscience that promise to give biomedical researchers and healthcare providers even more options for detecting and monitoring the widely varying biologic events in cancer. Researchers are designing molecular biosensors to be injected into the bloodstream to seek out and destroy cancer cells. These biosensors will also allow physicians to image the cancer and follow the patient's response to therapy, with minimal side effects and little disruption of healthy tissue.

In FY 2004, NCI introduced a new Integrative Cancer Biology (ICB) program. The goal of the ICB program is to understand the complex networks within cancer cells, and between cancer cells and their environment to discover new leads for cancer prevention, detection, diagnosis, and/or treatment. The program will work to:

- Support collaborative research groups, consisting of biologists, chemists, physicists, mathematicians, and/or engineers to develop a biological model that recapitulates cellular interactions and interactions between cells and their microenvironment;
- Recruit and train interdisciplinary scientists in the areas of molecular and cellular cancer biology, bioinformatics, computational biology, physics, chemistry, and/or engineering to build and characterize models;
- Develop a consortium to define the molecular signatures of cancer cells and cells in the microenvironment;
- Develop targeted interventions based on the derived knowledge of the cellular interactions with the microenvironment; and
- Define the dynamic communication among cancer cells, surrounding cells, and immune cells that control or promote tumor growth, and characterize the interaction between the innate/inflammatory and adaptive immune system and the cancer cell during cancer initiation and progression.

The ICB program will work in conjunction with NCI's ongoing technology programs to expand micro- and nanotechnology tool development to enable cancer signature detection, targeting, and treatment and enable detection of molecular signatures of cancer cells.

NCI has achieved accomplishments in 2004 related to Nanosystems Biology as it specifically relates to imaging. The Cancer Imaging Program has filed an IND for the imaging agent ferumoxytol. This particle can be used as an agent to image lymph node metastases and brain tumor margins and vasculature. Using the resources of the DCIDE program, two small exploratory trials have been executed to assess the ability of ferumoxytol to better delineate brain tumor margins and neovasculature and to preliminarily assess the agent for metastatic lymph node detection in prostate and breast cancer.

Item

Neurofibromatosis – The Committee commends NCI for conducting phase II clinical trials of NF1 patients with plexiform neurofibromas. The Committee is concerned about recent large drops in funding for NF research, and recognizing NF's connection to many of the most common forms of human cancer, the Committee encourages NCI to substantially increase its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation, and clinical trials. The Committee is mindful of NF's rapid movement toward clinical research and encourages NCI to aggressively pursue clinical/translational research while still maintaining a solid basic research portfolio. (p. 101)

Action taken or to be taken

Please refer to pages NCI-36 through NCI-37 of this document for NCI's response to this significant item regarding Neurofibromatosis.

Item

Pancreatic Cancer – The Committee remains concerned about the lack of scientists researching pancreatic cancer, the Nation's fourth-leading cause of cancer death. The NCI's recent policy of offering a 50 percent extended payline for grants that are 100 percent related to pancreatic cancer was viewed as a critically important effort to encourage both young and experienced investigators to develop careers in this research field. Thus, the Committee is disappointed that the NCI plans to weaken that policy and adopt a new strategy consisting of identifying grants that are 50 percent directed to pancreatic cancer and then bringing them to the attention of the NCI Executive Committee. The Committee notes that this special consideration will not necessarily result in actual funding. Therefore, the Committee urges the NCI to maintain the 50 percent extended payline for 100 percent relevant pancreatic cancer research grants as the best way to attract a critical mass of scientists to this field. (p. 102)

Action taken or to be taken

Please refer to pages NCI-35 through NCI-36 of this document for NCI's response to this significant item regarding Pancreatic Cancer.

Item

Radio Waves— It has been brought to the Committee's attention that radio waves may prove promising in reducing cancerous tumors. While current radio frequency ablation requires placing electrodes directly into the tumor, this new non-invasive technique would target only the cancer cells while avoiding healthy tissue. The Committee urges the NCI to support research using this non-invasive cancer-targeting technique. (p. 102)

Action taken or to be taken

Minimally invasive and non-invasive cancer therapies are logical steps along the path to NCI's ultimate goal of eliminating the suffering and death due to cancer. Increasingly, radiofrequency (radio wave)-mediated thermal destruction of tumors (RF ablation) is being applied to treat a variety of cancers. Real-time image guidance underpins this precision therapy, which is designed to ablate tumors while sparing surrounding normal tissues. Much work is still needed to validate the methods, refine the techniques, delineate the scope of application, continue translation to humans, and determine long-term results. In the planning stages now are three multi-center clinical trials, including the following:

- RF Ablation of early stage lung cancer in patients whose medical conditions preclude surgical removal, the treatment that is ordinarily curative in this group. Such studies that systematically test alternatives to open surgery and lung removal will prove increasingly important as detection by screening raises the proportion of early stage cases among all newly diagnosed lung cancers.

- RF Ablation of primary liver cancer. There is an increasing incidence and prevalence of viral hepatitis C infection in the United States, post-necrotic cirrhosis and primary liver cancer are on the rise. Partial surgical removal of the liver can be effective, but liver transplantation is considered the only definitive

cure. These treatments carry significant risk of morbidity and mortality. In the planned study, RF ablation will be assessed for its safety and its ability to control or eliminate tumor, prevent or impede progression, preserve quality of life, and serve as a bridge therapy to transplantation.

- RF Ablation of painful bone metastases. This will be a study of the safety and efficacy of RF ablation in the management of painful bone metastases, as well as its impact on quality of life.

In addition to RF ablation, other forms of ablative treatment which must be administered through a needle puncture or surgical incision to achieve precision include cryotherapy (freezing) and microwave therapy. Some clinical experience has already been gained with cryotherapy in primary and metastatic liver cancers and in prostate cancers.

A new and completely noninvasive method of inducing precise thermal destruction is high-intensity focused ultrasound (HIFU). The focused ultrasound beam targets tumor with one-millimeter accuracy. As with the minimally invasive therapies, HIFU is guided by imaging, most often magnetic resonance (MR). HIFU offers the potential of completely noninvasive treatment of cancers of the prostate, breast, liver, and kidney, as well as intraoperative application in brain tumors. Currently planned or in progress are validation studies of MR-guided HIFU in patients with symptomatic benign tumors of the uterus.

Importantly, since these minimally-invasive and noninvasive therapies are new, the regulatory pathways are, to a large extent, developmental. An active dialogue on this matter between NCI and the FDA has begun to yield a general framework for safety testing, treatment validation and optimization, and the conduct of larger clinical trials.

Item
Tuberous Sclerosis Complex — Tuberous sclerosis complex, or TSC, is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the brain, heart, kidneys, lungs, liver, eyes or skin. In light of its similarities to the uncontrolled growth of cancer cells, many scientists believe that determining the cause of tumor growth in TSC could open the way for cures and treatments for cancer as well. To those ends, the Committee strongly encourages NCI to support programs examining the molecular and cellular basis of TSC, and the role of TSC in tumor development. (p. 102)

Action taken or to be taken
Please refer to pages NCI-44 through NCI-46 of this document for NCI's response to this significant item regarding Tuberous Sclerosis Complex.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
National Cancer Institute	Section 41B	42§285b	Indefinite	$4,754,732,000	Indefinite	$4,771,905,000
National Research Service Awards	Section 487(d)	42§288	a/	70,526,000	b/	69,869,000
Total, Budget Authority				4,825,258,000		4,841,774,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997 2/	2,060,392,000 2/	2,385,741,000	2,102,949,000 2/	2,381,399,000 3/
1998 2/	2,217,482,000 2/	2,513,020,000	2,558,377,000	2,547,314,000
1999	2,528,760,000 2/5/	2,787,830,000	2,927,187,000	2,927,187,000
Rescission				(1,940,000)
2000	2,732,795,000 2/	3,163,417,000	3,286,859,000	3,332,317,000
Rescission				(17,763,000)
2001	3,249,730,000 2/	3,505,072,000	3,804,084,000	3,754,456,000 4/
Rescission				(2,005,000)
2002	4,177,203,000	4,146,291,000	4,258,516,000	4,190,405,000
Rescission				(9,172,000)
2003	4,673,510,000	4,673,510,000	4,642,394,000	4,622,394,000
Rescission				(30,046,000)
2004	4,770,519,000	4,770,519,000	4,770,519,000	4,770,519,000
Rescission				(31,264,000)
2005	4,870,025,000	4,870,025,000	4,894,900,000	4,865,525,000
Rescission				(40,267,000)
2006	4,841,774,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Excludes enacted administrative reductions of $1,095,000 and $38,000.
4/ Excludes enacted administrative reductions of $781,000.
5/ Reflects a decrease of $7,301,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	687	693	693
Center for Cancer Research	1,658	1,574	1,574
Division of Cancer Biology	39	42	42
Division of Extramural Activities	81	86	86
Division of Cancer Treatment and Diagnosis	174	190	190
Division of Cancer Prevention	86	86	86
Division of Cancer Control and Population Sciences	119	129	129
Division of Cancer Epidemiology and Genetics	137	140	140
Total	2,981	2,940	2,940
FTEs supported by funds from Cooperative Research and Development Agreements	(7)	(7)	(7)

FISCAL YEAR	Average GM/GS Grade
2002	11.4
2003	11.5
2004	11.7
2005	11.7
2006	11.7

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	8	8	8
Total - ES Salary	$1,130,757	$1,169,485	$1,192,290
GM/GS-15	228	225	225
GM/GS-14	345	340	340
GM/GS-13	304	310	310
GS-12	481	485	484
GS-11	208	220	217
GS-10	25	30	30
GS-9	152	155	155
GS-8	75	78	76
GS-7	84	88	85
GS-6	16	16	16
GS-5	13	13	13
GS-4	5	5	5
GS-3	0	0	0
GS-2	2	2	2
GS-1	0	0	0
Subtotal	1,938	1,967	1,958
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	44	44	44
Senior Grade	19	19	19
Full Grade	12	12	12
Senior Assistant Grade	5	5	5
Assistant Grade	1	1	1
Subtotal	82	82	82
Ungraded	918	905	905
Total permanent positions	2,141	2,062	2,053
Total positions, end of year	2,946	2,962	2,953
Total full-time equivalent (FTE) employment, end of year	2,981	2,940	2,940
Average ES salary	$141,345	$146,186	$149,036
Average GM/GS grade	11.7	11.7	11.7
Average GM/GS salary	$75,692	$78,284	$79,811