DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

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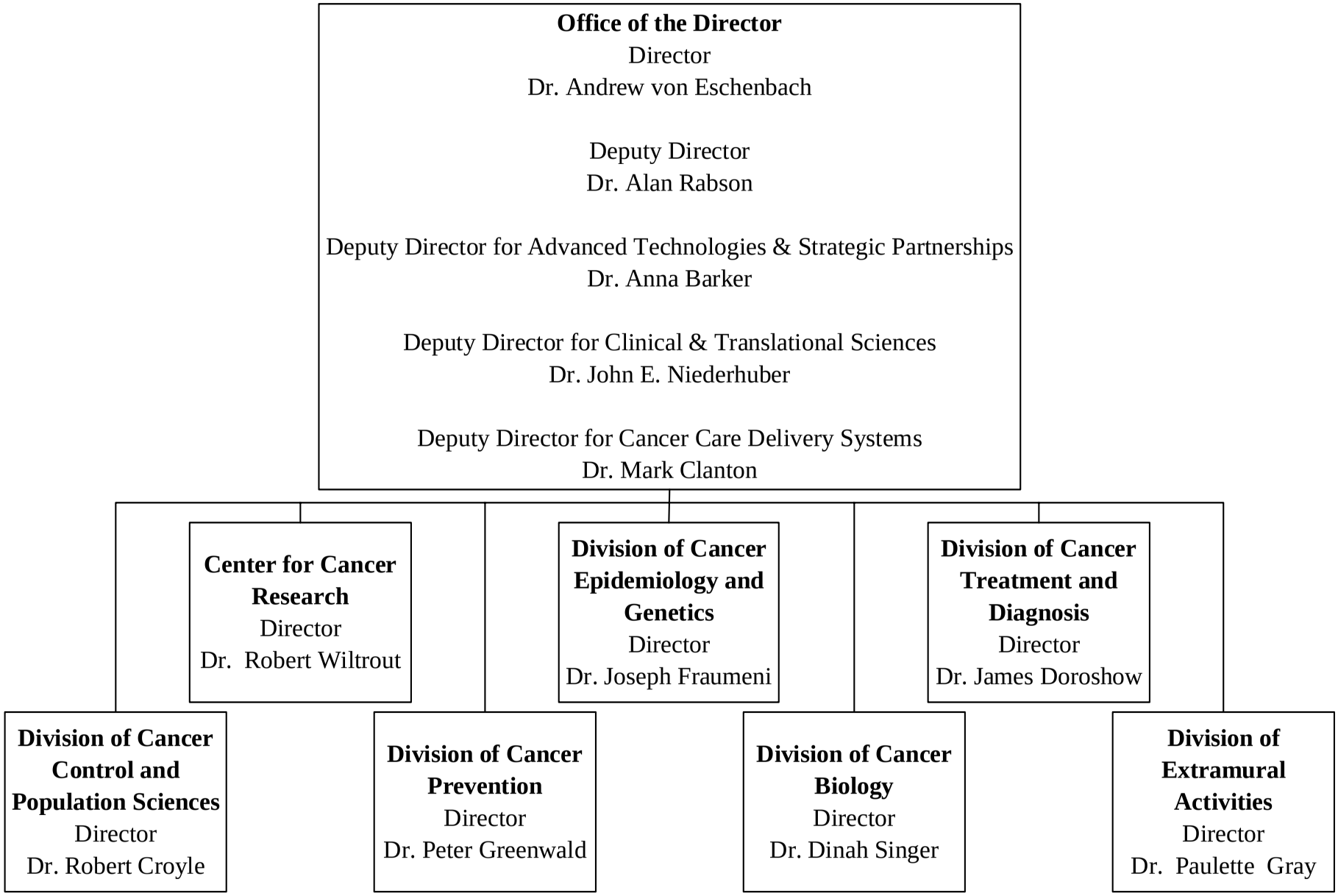
National Cancer Institute
Organization Chart



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, [$4,841,774,000] *$4,753,609,000,* of which up to $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 Health and Human Services Appropriations Act, 2006]

National Institutes of Health
National Cancer Institute

Amounts Available for Obligation 1/

Source of Funding	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Appropriation	$4,865,525,000	$4,841,774,000	$4,753,609,000
Enacted Rescissions	(40,267,000)	(48,418,000)	0
Subtotal, Adjusted Appropriation	4,825,258,000	4,793,356,000	4,753,609,000
Real transfer under NIH Director's one-percent transfer authority for Roadmap	(30,505,000)	(42,834,000)	0
Comparative transfer from OD for NIH Roadmap	30,505,000	42,834,000	0
Subtotal, adjusted budget authority	4,825,258,000	4,793,356,000	4,753,609,000
Unobligated Balance, start of year	10,317,000	0	0
Revenue from Breast Cancer Stamp	4,372,000	0	0
Unobligated Balance, end of year	(11,702,000)	0	0
Subtotal, adjusted budget authority	4,828,245,000	4,793,356,000	4,753,609,000
Unobligated balance lapsing	(9,000)	0	0
Total obligations	4,828,236,000	4,793,356,000	4,753,609,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2005 - $15,528,000 FY 2006 - $20,000,000 FY 2007 - $20,000,000
Excludes $30,000,000 in FY 2006 and $30,000,000 in FY 2007 for royalties.

Justification

National Cancer Institute

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended.

Budget Authority:

FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
2,854	$4,828,245,000	2,906	$4,793,356,000	2,920	$4,753,609,000	14	-$39,747,000

This document provides justification for the Fiscal Year 2007 activities of the National Cancer Institute, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2007 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)." Detailed information on the NIH Roadmap for Medical Research may be found in the Overview section.

INTRODUCTION

While the national investment in cancer research is making a difference in the lives of Americans every day, cancer remains one of our most urgent health concerns and the disease many fear most. This year, more than 1.3 million people will be diagnosed with cancer, and more than a half million people will succumb to the disease. Despite intensive efforts and success in gradually reducing the incidence and mortality rates of some cancers, we have made only marginal progress against the most intractable ones, including cancers of the pancreas, lung, and liver. For reasons not well understood, the incidence of certain malignancies — including adenocarcinoma of the esophagus, multiple myeloma, and kidney cancer — is rising. Research also demonstrates that some populations, most notably minorities and the poor, continue to bear a disproportionate cancer burden due to lack of insurance or a steady source of care and socio-demographic limitations that often result in lower use of screening services resulting in late diagnosis.[1]

NCI works to advance fundamental knowledge about cancer across a seamless and dynamic continuum of discovery, development, and delivery. The Institute provides vision and leadership for researchers across the United States and around the world and strives to ensure that the results of research are used in public health programs and clinical practice to reduce the burden of cancer for all people. Building on past discoveries and technological advances, NCI plans, conducts, and coordinates cutting-edge research and its application. The Institute supports the development of new technologies, encouraging creativity and innovation in all of our endeavors. The Institute provides research training and career development opportunities and maintains

[1] Data source is the NCI Surveillance, Epidemiology, and End Results (SEER) program.

collaborative environments to link scientists with their colleagues and with critical technological and information resources. As leader of the National Cancer Program, NCI also provides the public with scientifically sound cancer information using communication methods carefully designed to meet the needs of cancer patients, their families, and caregivers.

SCIENCE ADVANCES

NCI supports a broad range of research to expand our understanding of cancer and develop improvements in prevention and care. Some investigators conduct basic laboratory research on genes that may cause cancer. Others are studying the incidence of cancer in specific populations, such as people of low socioeconomic status and former smokers. Still other scientists focus on translational research such as developing tests to identify patients who carry genes that may make them susceptible to cancer or conducting early clinical trials to determine the readiness of new preventive agents, diagnostic tools, or treatment drugs for full clinical testing.

Understanding the Causes and Mechanisms of Cancer

New Insights into Angiogenesis May Lead to New Cancer Treatments

Preventing the formation of new blood vessels (angiogenesis) that support tumor growth has become a major focus for cancer treatment and prevention. Angiogenesis is tightly regulated by a balance of molecular mechanisms that promote or inhibit blood vessel growth. Scientists recently found that the nitric oxide (NO) molecule promotes angiogenesis. Nitric oxide is an important component of energy metabolism and is known to play a critical role in blood pressure control and wound healing. Ongoing studies at NCI have revealed that other molecules also play a key role in regulation of angiogenesis. One of these is the protein Thrombospondin-1 (TSP1), currently in clinical trials for cancer treatment as a potent inhibitor of angiogenesis. Ongoing collaborative studies have revealed an important "cross-talk" mechanism in angiogenesis that links TSP1 and NO. These researchers have shown that NO and TSP1 are involved in a feedback mechanism to control both wound healing and tumor growth. Researchers have also found specific peptides (small portions of protein) from the TSP1 protein that have powerful effects on NO-stimulated angiogenesis. This and other recent research also shows that substances that inhibit a protein called Nitric Oxide Synthase (NOS), which is involved in NO production, can increase the effects of radiation and chemotherapy. This new-found relationship between NO and TSP1 suggests that tumor growth can be partly controlled by proteins and peptides that target the regulation of angiogenesis by NO and reveals new molecular targets and potential treatment strategies for increasing cancer survival.

Genes Found to Predict Lung Metastasis of Breast Cancer

The primary cause of death from solid tumors is their spread (metastasis) to distant organs. Many cancers tend to metastasize to specific organs. For instance, breast cancers spread mostly to lung and bone. It is now accepted that the ability of a tumor to metastasize depends on the combined action of multiple genes. Cancer biologists have been testing the hypothesis that the organ site of metastasis is caused by specific genes that are activated, or expressed, in the primary tumor. In 2003, these researchers reported finding a specific gene expression pattern in breast cancer cells that preferentially spread to bone. Recent work shows that the genes that prompt breast tumors to spread to the lungs are very different from the genes that prompt metastasis to bone. Researchers examined the gene expression profiles, "or genetic

thumbprints," of 82 early-stage breast tumors. The ability of the tumors to metastasize to the lung matched up with certain gene expression profiles. Some of the lung-homing genes serve multiple functions that provide tumor growth advantages in the breast and in the lung. Other genes selectively contribute to aggressive growth in the lung. These findings provide one of the first clear demonstrations of organ-specific metastasis genes. The lung is one of the most frequent metastatic sites in human breast cancer and contributes significantly to morbidity and mortality. These results could provide novel prognostic markers to aid clinical oncologists in patient management and potential targets for new drug development. These findings also provide an ideal opportunity to study how breast and other tumors gain the ability to spread to specific organs. With further study, it may also be possible to develop novel diagnostic tests that use this genetic information.

Accelerating Progress in Cancer Prevention

Featured Science Advance

Vaccines to Prevent Cervical Cancer Prove Effective

The human papillomavirus (HPV) is transmitted sexually and causes almost all cases of cervical cancer. The disease kills about 288,000 women each year, including many in developing countries[2] . NCI is actively working in collaboration with industry on the development of vaccines that can prevent HPV infection and, by extension, cervical cancer. These test vaccines use virus-like particles (VLPs), produced through recombinant DNA technology, which consist of the major proteins that coat the outer shell of the virus. Vaccination causes the immune system to recognize and attack not just the VLPs, but also the virus itself, which the particles resemble. Two pharmaceutical companies, Merck and GlaxoSmithKline, have been licensed to use the vaccine technology from NIH and are developing versions that target the most common cancer-causing strains of HPV.

Researchers announced in October of 2005 that the experimental vaccine developed by Merck was found to be highly effective in women who participated in a two-year study. The vaccine, called Gardasil, protected against precancerous lesions caused by two strains of HPV. The vaccine targets HPV types 16 and 18, which cause about 70 percent of cervical cancers. The vaccine is not effective against about 30 percent of cervical cancers which are caused by other strains of HPV. When Gardasil was administered in three doses over six months, the protection was 100 percent for a period of 1.5 years against the lesions caused by the two strains in the vaccine. The study involved more than 10,000 women. Investigators at NCI are optimistic that a vaccine will be ready in the very near future. The long-term efficacy of the vaccine is still not known, and follow-up studies will be required to answer this question.

A Phase III clinical trial is also underway in collaboration with NCI and the government of Costa Rica to test an HPV 16/18 vaccine manufactured by GlaxoSmithKline. The investigators plan to enroll up to 7,000 women and follow them for at least four years. In this blinded study, either the experimental HPV vaccine or a hepatitis A vaccine is being given to all healthy young women who enroll in the trial. The women are then followed for four years for the development of HPV infection and cervical lesions, which are treated according to standard of care guidelines. Women in both arms of the study benefit from cervical cancer screening throughout the trial. At the end of the trial, the HPV vaccine or Hepatitis A vaccine will be offered to the women who did not receive one or the other during the trial, and vaccination against hepatitis B will be offered to all participants.

Because these vaccines are preventive, the most cost-effective time to give them would likely be before women become sexually active. In the United States, recommendations about when to give the vaccine would be made by the Advisory Committee on Immunization Practices at the Centers for Disease Control and Prevention. Researchers emphasize that women who get the vaccine should still follow guidelines for cervical cancer screening.

[2] World Health Organization estimate, see http://www.who.int/vaccine_research/diseases/hpv/en/.

Workers Exposed to Low Levels of Benzene Shown to Have Toxic Effects in Their Blood
Benzene is a clear, colorless and flammable liquid with a sweet odor. It is present at very low levels in air and water in our environment. Benzene makes up about 1 percent of every gallon of gasoline in the United States, and is released as a by-product of fuel combustion. Benzene is also produced in the burning of tobacco. People can be exposed to benzene through cigarette smoking, breathing second-hand smoke and polluted air, pumping gasoline, or even driving. Benzene is known to have toxic effects on the blood and bone marrow and has been linked to diseases such as leukemia and myeloid dysplastic syndromes[3] Past studies have also shown that people with certain inherited traits might be more sensitive to benzene exposure. The U.S. Occupational Safety and Health Administration requires that benzene levels in the workplace do not exceed 1 part per million (ppm). The health effects of occupational benzene exposures below this limit remains uncertain.

In this study, the white blood cell and platelet counts of 250 workers exposed to benzene, including exposures below 1 ppm in air but higher than normal background levels were significantly lower than those of 140 controls with exposure levels less than or equal to normal background exposure. Immature blood cells were more sensitive to the effects of benzene than were mature blood cells. This study also looked at the traits of three genes that influence the way benzene is processed when it gets into the body. Workers with genetic variants for two enzymes known to be involved in benzene metabolism were more susceptible to benzene exposures of 1 ppm or less and tended to have lower white blood cell counts than workers without these variants. These data provide evidence that benzene even at or below 1 ppm may adversely affect white blood cell counts, particularly in susceptible individuals. Other studies are needed to confirm these findings.

Prophylactic Mastectomy in BRCA1/2 Mutation Carriers Significantly Reduces Cancer Risk
Women with inherited BRCA1 or BRCA2 (BRCA1/2) gene mutations have a markedly increased risk of breast and ovarian cancers compared with the general population. These women sometimes elect bilateral prophylactic mastectomy to reduce their risk of breast cancer. However, data on risk reduction after bilateral prophylactic mastectomy in this high-risk group are limited. This study measured the incidence of breast cancer in 483 women known to have BRCA1/2 mutations, some of whom had elected prophylactic masectomy. The authors concluded that bilateral prophylactic mastectomy reduces risk of breast cancer in women with BRCA1/2 mutations by approximately 90 percent. Formal analyses have yet to be performed because of insufficient follow-up time and number of deaths in the sample, but it can be inferred that this risk reduction will be associated with a marked reduction in breast cancer mortality. The findings are consistent with earlier studies, but go further by addressing some of the limitations of those studies and providing stronger data on the magnitude of risk reduction. For those women who choose bilateral prophylactic mastectomy, this study provides evidence that they have chosen an effective prevention strategy.

Improving Early Detection and Diagnosis
Sentinel Nodes Predict Survival for Melanoma Patients
Melanoma is the most deadly of skin cancers, and it spreads to lymph nodes in about 20 percent

[3] The myelodysplastic syndromes (MDS) are a group of disorders characterized by one or more peripheral blood cytopenias secondary to bone marrow dysfunction.

of patients. In the early 1990s, researchers developed sentinel node biopsy (SNB), which detects melanoma cells present in lymph nodes near the tumor. However, several previous trials have failed to show a survival advantage resulting from the early detection and surgical removal of affected nodes. The Multicenter Selective Lymphadenectomy Trial (MSLT), enrolling 2,001 patients, was designed to compare overall survival between two groups of patients. One group was treated with wide excision of their melanoma and was followed with a "watch and wait" approach to detect and remove any developing lymph node tumors. The second group was treated with wide excision, SNB, and removal of lymph nodes that contained metastatic cancer cells. Results from this international trial show that patients treated with SNB were 26 percent less likely to have a recurrence of melanoma after five years than those treated with the "watch and wait" approach. This study shows that for some melanoma patients, detecting the cancer in the lymph nodes and removing the nodes early in treatment may reduce cancer recurrence and help patients live longer. Delay may allow the cancer to spread to more nodes and to distant organs. This study contributes to the rapidly changing standard of care for these patients. An international follow-up study, MSLT-II, will determine whether complete removal of the regional lymph nodes will benefit patients.

Developing Effective and Efficient Treatments

Addition of Trastuzumab to Chemotherapy for Breast Cancer Dramatically Improves Prognosis

Approximately 20 percent to 30 percent of breast cancer cells "overexpress" or make too much of a protein called HER-2. These tumors tend to grow faster and are generally more likely to recur than tumors that do not overproduce HER-2. Herceptin® (trastuzumab) was approved in 1998 for the treatment of advanced breast cancer patients with HER-2 positive cancer cells. Since then, two large randomized clinical trials have compared the use of trastuzumab given with chemotherapy to the use of chemotherapy alone to treat patients with early-stage, HER-2 positive breast cancer. Patients in these trials were randomly assigned to receive chemotherapy with doxorubicin and cyclophosphamide followed by paclitaxel, or doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab. Results were made public before the clinical trials were completed because the studies had clearly shown that trastuzumab treatment increased disease-free survival. Information from over 3,300 patients enrolled in these studies was used for analysis. Patients who received trastuzumab in combination with chemotherapy had a 52 percent decrease in disease recurrence and a significant improvement in overall survival, compared to patients treated with chemotherapy alone. Of about 22,200 women diagnosed with invasive breast cancer in the United States in 2005[4], about 30 percent have lymph node-positive breast cancer, and about 20 percent to 30 percent of these tumors overexpress the HER-2 protein[5]. For women with this type of aggressive breast cancer, the addition of trastuzumab to chemotherapy appears to virtually reverse prognosis from unfavorable to good.

Story of Discovery

New Genres of Mouse Modeling and Small Animal Imaging Technologies Promise More Efficient Cancer Drug Development

While researchers have been using mouse models since the 1960s to help identify cancer prevention and treatment

[4] American Cancer Society Facts and Figures 2005, http://www.cancer.org/downloads/STT/CAFF2005f4PWSecured.pdf.

[5] Cianfrocca M, and Goldstein LJ, 2004. Prognostic and predictive factors in early-stage breast cancer. Oncologist 9(6):606-16.

interventions, many agents shown to be effective against cancers in mouse models have failed in clinical testing. Although there are some differences between the biology of tumors in mouse models and in humans, the newest generation of cancer models can be used to identify drugs that will work in humans. Additionally, by applying advanced imaging techniques to the study of mouse models of human cancers, we will be able to dramatically accelerate the pace of cancer drug development. The idea is to improve the precision of preclinical research so that only drugs that are likely to be effective in humans are moved to early stage clinical trials. Our ability to integrate mouse models and imaging technologies in this way is possible today as a result of years of parallel development in the two technologies and recent work to merge them.

The Refinement of Mouse Models of Human Cancers

Pioneers in the field of cancer modeling first created "xenograft" models in the 1960s, when investigators transplanted human cancer cells beneath the skin of immune suppressed mice. Xenograft models, still in use today, allow investigators to monitor the progression or remission of subcutaneous tumors, using calipers to measure tumor size. One drawback of xenograft models is that tumors are no longer located in the tissue microenvironment in which they developed. Because a tumor will behave differently depending on interaction with its microenvironment, preclinical research using xenograft models can be misleading. Many experimental cancer drugs that perform well in xenograft models are later found to be ineffective against the same cancers in humans.

Rapid advances in molecular biology and molecular genetics, beginning in the 1970s, later led to marked improvements in cancer mouse models. Researchers discovered tumor suppressor genes that help prevent cancer from developing and oncogenes that carry mutations that promote cancer initiation and progression. In the 1980s, researchers created transgenic mouse models by incorporating human oncogenes into the gene set of living mice. Researchers also created gene knockout models by eliminating certain tumor suppressor genes from live mice. Early transgenic and gene knockout mouse cancer models carried the genetic defect in every cell in the body and were highly susceptible to cancer development from an early age. These models still provide an excellent resource for examining the role of specific genes in cancer development and progression and for identifying potential targets of drug therapy. Because the presence of the cancer causing mutations in every cell of the body may alter the nature of the tumor microenvironment, these models are less useful for preclinical testing of prevention and treatment interventions.

Conditional transgenic and knockout mouse models, designed to reflect the nature of both the tumor and the microenvironment of human cancers, were introduced in the late 1990s. For example, in one form of this modeling system, researchers modify specific oncogenes or tumor suppressor genes *in vitro* to alter their expression except in the presence of a particular drug, often an antibiotic. Investigators then insert the modified gene into a specific tissue in living mice and add or remove the relevant drug to change the expression of the modified gene. With a conditional transgenic model for human breast cancer, for example, the investigator can choose when to activate an oncogene or inactivate a tumor suppressor which is present only in the mouse's breast tissue. Because the mouse tumor microenvironment closely resembles that in humans, conditional mouse models are well suited for use in preclinical research. In 1999, NCI established the Mouse Models of Human Cancers Consortium (NCI-MMHCC) to provide the leadership and resources to develop and validate these and other increasingly sophisticated mouse models of human cancer and to accelerate their dissemination to the research community.

The Interface of Imaging and Mouse Modeling

Preclinical investigators using transgenic or knockout mouse models of human cancer are faced with the challenge of assessing tumor growth that is occurring within the animal. In the current research paradigm for mouse cancer models, investigators typically sacrifice the animals at multiple time points before and after drug intervention and use histologic[6] techniques to study tumor attributes. This requires large numbers of animals and precludes longitudinal studies, a powerful research technique in which disease progression is monitored over time in the same animal.

To overcome some of these obstacles and add new dimensions to the research, NCI established the Small Animal Imaging Resource Program (SAIRP) in 1998 to facilitate the development of noninvasive imaging techniques to assess tumor properties in living animals. Through SAIRP, NCI-MMHCC, and investigator-initiated research, NCI has provided critical leadership and support to promote the miniaturization of imaging equipment originally

[6] Histology involves the use of microscopes and cell staining techniques to study cells and tissues.

designed for humans and development of equipment used only for animal models. This investment has been key to the use of sophisticated imaging techniques for assessing the effects of drug therapy on tumors growing within small animals. New small animal imaging systems are based on magnetic resonance imaging, computed tomography, positron emission tomography, ultrasound, single photon emission computed tomography[7], and other imaging technologies. Some of these imaging techniques provide incredibly detailed anatomical information and others permit molecular imaging of tumor biology. These advances in small animal imaging hold great promise for accelerating preclinical research using conditional mouse models of human cancer.

The Use of Optical Imaging and Reporter Probes to Image Drug Activity
Optical imaging techniques developed in the past several years by NCI-supported and other researchers are providing a powerful molecular imaging tool for preclinical research. Optical imaging uses highly sensitive detection systems that can sense low levels of light emanating from sources within the body. Although the body is relatively opaque, certain wavelengths of light will transmit weakly through the tissue. Mice are small enough to allow detectable levels of light transmission even from the body core. Cancer scientists have designed "reporter probes" for use with *in vivo* optical imaging techniques. These probes typically bind with high specificity to cancer cells and emit fluorescent or bioluminescent light in response to certain molecular events. Reporter probes incorporating the gene for luciferase are among the exciting new applications of optical imaging. Luciferase is the bioluminescent protein that produces the firefly's glow. Researchers have used optical imaging technology in a variety of mouse models to assess expression levels of cancer-causing genes, detect interactions of critical proteins, measure tumor burden, assess tumor response to therapy, and otherwise demonstrate the promise of this new technology in preclinical drug development research.

The Convergence of Science and Technology in Preclinical Research – The Next Step
This proof-of-principle research has brought us closer to a new research paradigm for accelerating the pace of cancer drug development. However, these approaches must be thoroughly validated before they can be routinely used for this purpose. NCI's initiative to support the use of leading edge small animal imaging technologies for preclinical drug evaluation is the next step in this process. NCI anticipates that preclinical studies using fully tested techniques for imaging mouse models will accurately identify which experimental agents will be effective in human patients and should be advanced to early stage clinical trials. We will no longer spend precious resources developing drugs destined to fail. Instead, teams of preclinical and clinical scientists will work together to advance effective treatment agents through the clinical trial system. This will ultimately lead to the increased availability of effective therapeutics for the cancer patients who need them.

Improving the Quality of Cancer Care

Prostate Cancer Outcomes Study Provides Insight into Treatment Options

The primary treatment choices for men with clinically localized prostate cancer are radical prostatectomy, external beam radiotherapy, radioactive seed implants, and conservative management. Although there are different treatment options, there are few direct comparisons of these treatments and as a result, there is continuing disagreement and uncertainty about the relative efficacy of these forms of disease management. The Prostate Cancer Outcomes Study (PCOS) was designed to address these limitations. Using survey data collected from more than 1,100 men enrolled in PCOS, researchers analyzed long-term side effects for men treated either with radical prostatectomy or external beam radiotherapy (EBRT). They found that at five years after baseline diagnosis, overall sexual function -- including libido, frequency, and potency -- declined to a similar level in both treatment groups. Erectile dysfunction and incontinence were reported more frequently in the radical prostatectomy group at five years, while bowel urgency and hemorrhoids were cited more often in the EBRT group. The authors note that because there is continuing uncertainty about the superiority of any single treatment strategy for clinically localized prostate cancers, patient preferences for outcomes among competing treatment strategies may be an important factor that drives treatment decisions. Although this study

[7] For more on these and other types of imaging, go to **imaging.cancer.gov/imaginginformation/cancerimaging**.

compared surgery with EBRT, the authors identified the need for additional prospective research using population-based samples comparing complications from all available treatments, including radioactive seed implants and hormone therapy.

Improving the Quality of Life for Cancer Survivors and Their Families

Study Identifies Employment Related Problems among Cancer Survivors

Approximately half of adult cancer survivors are under 65 years of age, and many of them face employment related consequences important both for themselves, their families and for our society. This study investigated employment and work-related disability in a cohort of adult cancer survivors who were employed at the time of diagnosis with a variety of cancers. Investigators studied employment from the time of diagnosis through the early years of survivorship, quantified self-reported effects of cancer survival on disability and employment, and identified risk factors associated with cancer-related disability and withdrawal from employment. The researchers found that 41 percent of the men and 39 percent of the women in this study stopped working during their cancer treatment. Projections from the data imply that 13 percent of survivors who were working at diagnosis quit for cancer-related reasons in the first four years of survivorship. The results of this study point to both short-term and long-term challenges for cancer survivors and the field of oncology. Survivors are at risk for disabilities and quitting work as a result of their cancer treatment. Employment outcomes can be improved with innovations in treatment and with clinical and supportive services aimed at better management of symptoms, rehabilitation, and accommodation of disabilities. The short-term challenge for oncology professionals is to identify survivors with employment problems at all stages of survivorship and help them with a comprehensive range of clinical and supportive services aimed at better management of symptoms, rehabilitation, and accommodation of disabilities. The long-term challenge for oncology is to devise new treatments that will cause fewer work-related disabilities.

Stress Management Increases Perceived Benefits of Cancer and Improved Immune Function

Many cancer patients and survivors have reported that the experience of having cancer has led to fortified personal resources and skills, stronger spirituality, closer relations with family and friends, a clearer sense of purpose, and changes in life priorities. With this information, researchers have begun examining the association between negative life challenges and the development of creative solutions that have a positive effect on people's lives, in terms of both physical and psychological manifestations. This study examined the effect of a cognitive-behavioral stress management (CBSM) intervention on emotional well being and immune function among women in the months following surgery for early-stage breast cancer. The CBSM intervention involves cognitive restructuring, reframing, and coping skills determined to be useful for women experiencing cancer. The researchers found that women who participated in the intervention reported perceiving greater benefit from having breast cancer than did the women in a comparison group. At three-month follow-up, women in the CBSM group also had improved lymphocyte proliferation. Researchers suggest that CBSM participants in the study, as a result of CBSM, now approach stressors in their life with a new sense of strength and confidence, a greater connection to others, or a different sense of priorities, all elements of the benefit finding scale used in this study. The changes in lymphocyte proliferation as a result of the intervention are important and could predate improved health (e.g., increased resistance to infection) or, perhaps, decreased rates of cancer recurrence. These results, however, must be

interpreted with caution. The researchers plan to monitor these women over the next five to ten years to determine if the psychologic or immunologic changes occurring after this intervention are related to health status or long-term disease free survival.

Overcoming Cancer Health Disparities

Studies Highlight Colon Cancer Disparities

Two new studies of colon cancer treatment add to a growing body of knowledge regarding racial disparities in cancer care. The first found that 11 percent fewer Black than White patients received adjuvant chemotherapy after surgery. The second concluded that non-English speaking patients were less satisfied with their care than English speaking patients. The first study examined Medicare records of 5,294 people diagnosed with stage III colon cancer between 1992 and 1996. By studying diagnosis and treatment codes, the researchers found that 70 percent of White patients received adjuvant chemotherapy, compared with 59 percent of Black patients. By integrating Medicare data with information from NCI's Surveillance, Epidemiology, and End Results database, the researchers were able to calculate the impact of many factors, including physician experience, hospital environment, and the socio-demographics of each patient's neighborhood. However, the study "showed no single or simple explanation." The second study involved a survey of 1,067 colorectal cancer patients where researchers found that non-White and non-English speaking patients reported significantly more problems with cancer care than White and English speaking patients. Only 52 percent of non-English speaking patients rated overall quality of cancer care as very good or excellent, compared with 81 percent of English-speaking patients. Much of the dissatisfaction among non-English speaking patients appeared to stem from concerns about coordination of care they encountered among the nurses, physicians, and other health care providers.

Randomized Trial Demonstrates Success of Dietary Interventions among Rural Residents

A low-fat, high-fiber diet plays a role in preventing many diseases including cancer. Unfortunately, current U. S. consumption of fat is high and fiber intake is less then recommended. The problem is often exacerbated in rural populations by lack of access to health care and low literacy rates among adults. This community-based randomized trial assessed the impact of a low-intensity, physician-endorsed, self help intervention that provided tailored dietary feedback. The trial was designed to promote improved dietary behavior in rural, low education/low literacy, partly minority populations, between 1999 and 2003. The intervention consisted of tailored feedback provided by physicians to their patients based on a baseline interview designed to personalize the problem, make it relevant to each participant, and intensify the interest in behavioral change. Researchers followed up with each participant through a brief telephone call that included minimal counseling, an offer of additional information, and an opportunity to answer questions. Each participant was then sent a theory-based, low-literacy nutritional education booklet written at or below a sixth grade reading level, along with a letter from the physician. Follow-up phone interviews were then conducted one, six, and twelve months after the materials were mailed. Participants reported significantly reduced dietary fat intake and increased dietary fiber consumption and/or expressed an intention to reduce dietary fat and eat more fiber, fruits, and vegetables. In many communities, residents view rural primary care providers as the only legitimate source of health information. However, many providers are overburdened with a large patient load. This study shows that a low-intensity dietary evaluation

and educational intervention may net significant changes, without increasing time constraints on physicians.

NIH ROADMAP FOR MEDICAL RESEARCH

NCI is actively participating in the NIH Roadmap for Medical Research, contributing approximately $30 million in FY 2005 and $43 million in FY 2006 in support and providing leadership and expertise to the many important research initiatives. The NIH Roadmap addresses major opportunities and gaps in biomedical research. The three Roadmap theme areas, New Pathways for Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise all complement NCI's strategic initiatives in Building Bridges to Link Science and Technology; Advancing Medical Informatics, and Reengineering Cancer Clinical Trials.

NCI is leading the development of the *Comprehensive Trans NIH Imaging Probe Database (MICAD),* an initiative within the NIH Roadmap Molecular Libraries and Imaging component supporting the New Pathways to Discovery theme. The MICAD contains text-based information, presented in a consistent summary format, on all *in vivo* imaging agents that have been reported in peer-reviewed literature. NCI contributed over 250,000 compounds that will be made available through MICAD. The imaging probe database will facilitate more rapid development of cancer imaging agents and provide oncologists with an efficient resource on all imaging agents relevant to cancer diagnosis and treatment. In addition, NCI-supported investigators are recipients of NIH Roadmap awards supporting Molecular Library Screening Center Networks (MLSCN). A nationwide consortium will produce innovative chemical tools for use in biological research, including cancer research, and projects supporting high-specificity/high-sensitivity molecular imaging probes.

The NCI Integrative Cancer Biology Program and development of multi-disciplinary computational models complement NIH Roadmap initiatives in Bioinformatics, Computational Bioinformatics and Nanomedicine. Seven National Centers for Bio-Computing (NCBCs) serve as hubs of a networked national effort to build the computational infrastructure for biomedical computing. NCI manages one of these centers to focus on multi-scale signaling in cancer. All NCBCs will educate and train researchers to engage in biomedical computing and provide necessary tools and resources.

NCI is complementing the NIH Nanomedicine initiative to increase fundamental understanding and investigate new approaches to nanotechnology. The NIH nanomedicine program has funded four centers to study the basic biological properties and design at the nano-scale. The NCI nanotech plan involves a much more focused approach closely linked to application. Together these two initiatives will benefit the cancer research community.

The NIH Roadmap effort for Reengineering the NIH Clinical Research Enterprise is addressing the need to build better integrated networks and academic centers linked to community-based health care providers. The NCI clinical trials system has been a model for many research institutions in clinical and translational research, and is complementing and contributing to the development of many of these Roadmap initiatives. NCI's caBIG™ program is setting standards

and providing models for bioinformatics, complementing the NIH Roadmap effort known as NECTAR (National Electronics Clinical Trials and Research). NCI's Rapid Access to Intervention Development (RAID) program has served as the infrastructure for the NIH Roadmap Translation Research Core Services, developing new small molecule therapeutic agents and reducing some of the common barriers between laboratory discoveries and clinical trials for new therapies.

Similarly, NCI contributes to Roadmap clinical research training initiatives through awards to institutions for broad multidisciplinary training. These include Cancer Centers programs that develop novel curricula for training residents and fellows in cancer clinical research.

NCI developed guidelines for the Clinical Translational Science Awards (CTSAs) and provided guidance on the Roadmap CTSA steering committee, based on experience gained from the NCI Cancer Centers Program. The CTSAs will provide professional education, training, resources and an academic home to investigators for clinical and translational research. The CTSAs have the potential to provide crucial support for NCI objectives focused on moving discoveries from the bench to bedside, benefiting cancer patients and the general population.

Several NCI grantees were recipients of the NIH Director Pioneer Award, one of the Roadmap theme initiatives for Research Teams of the Future. Pioneer Awards funded in 2004 and 2005 include support for advancing technologies in drug discovery and development, cell fate programming, and protein detection at the cellular level, each of which has great potential to impact research on cancer biology, diagnosis, and treatment.

FISCAL YEAR 2007 INITIATIVES

Excitement continues to build across the cancer community about the progress we are making toward our Challenge Goal to eliminate the suffering and death due to cancer by 2015! Past investments have made continued advances in high throughput computing, bioinformatics, imaging technology, nanotechnology, genomics, proteomics, and computational modeling possible, and these are paving the way for new discovery and accelerated intervention development and delivery. Collaborative efforts are streamlining the availability of tissue specimens, microarrays, image libraries, and epidemiological data. Newly established partnerships with other agencies within the Department of Health and Human Services, with other Federal and state agencies, and with the private sector are helping to leverage resources and build the kind of synergy that will ensure timely delivery of new cancer interventions to patients and people at risk. In Fiscal Year 2007, NCI will place special emphasis on expansion of the Cancer Centers program, the reengineering of cancer clinical trials, building bridges to link science and technology, advancing medical informatics, and integrating cancer science.

Cancer Centers — Driving Progress toward 2015

Cancer Centers are vital scientific and geographic hubs of progress for basic discovery. They are central platforms for the development of effective approaches to prevention, diagnosis, and therapy. They provide life saving interventions and other advances to patients, their families, and the public. Their research endeavors contribute to NCI's strategic efforts to understand the causes and mechanisms of cancer, accelerate progress in cancer prevention, and develop targeted

treatments and other interventions to lower the incidence of cancer and improve survival rates. NCI-designated Cancer Centers extend their reach into the community through networks that link the Centers with community hospitals and private oncology practices to provide patients with state-of-the-art care and access to clinical trials. They bring together the best of basic, translational, and population research to achieve improved cancer prevention, diagnosis, and treatment. Centers also link to their communities and regions through education and outreach networks, provide a locus for stable and integrated consortia and other partnerships, and are an important element of state cancer planning processes nationwide. Cancer Centers are also expected to be at the forefront of cancer prevention development and the dissemination of these interventions to their communities and regions.

NCI plans to expand the geographic coverage and impact of Cancer Center services by adding up to 15 new Cancer Centers over the next five years, increasing the number of Centers from 60 to as many as 75. This growth will establish Centers in states and in metropolitan areas where none currently exist and improve access to care for minority and other underserved populations. Vertical integration of programs and resources within individual Cancer Centers will strengthen outreach to the communities they serve. Horizontal integration to better link Cancer Centers to one another will be achieved by implementing progressive bioinformatics, communication, and related systems that will boost synergy, reduce redundancy, and leverage resources across the network of Cancer Centers. Moreover, by utilizing contemporary technologies, specialized services offered by Cancer Centers in the United States could be utilized anywhere in the world.

Reengineering Cancer Clinical Trials

Each year, NCI provides leadership, resources, and expertise for a clinical trials program that spans the entire spectrum of activity — from the discovery of novel molecules to the evaluation and application of new agents and interventions. NCI is seeking to develop a more robust infrastructure for cancer clinical trials that will strengthen scientific prioritization and coordination and improve the timeliness in which clinical trials are completed. Embracing this restructuring will ensure that life saving research advances make a substantive difference in reaching the NCI Challenge Goal.

To minimize duplication of effort and integrate a national cancer clinical trials network, NCI will support the development of a shared infrastructure of tools and procedures for trial design, data capture, data sharing, and administrative functions. This common clinical trials informatics platform will be overseen by, and made available to, the full range of investigators working within the cancer clinical trials system. The cancer Biomedical Informatics Grid™ will create a Web-based tool for clinical trial initiation and the development of standard case report forms in coordination with industry and the Food and Drug Administration. These new tools will also support the use of personal electronic health records to assist participants and their healthcare providers in coordinating their care during and following clinical trials. These efforts will respond to recommendations of the NCI Clinical Trials Working Group and are aligned with NIH Roadmap initiatives in clinical research.

Building Bridges to Link Science and Technology

More than ever before, biomedical science is dependent on the use of advanced technologies to maximize scientific discovery and the delivery of cancer interventions. Working together across

communities of scientists and technology experts is a new paradigm for cancer research and development. It increasingly requires new kinds of collaborations and a melding of cultures to achieve an environment friendly to the development, validation, and practical application of promising technologies. Technological advances in bioinformatics, imaging, nanotechnology, genomics, proteomics, metabolomics, and high throughput screening have set the stage for unprecedented progress in our efforts to reduce the burden of disease. These technologies will be instrumental in understanding the causes and mechanisms of cancer, facilitating the management of cancer risk, and helping to make "personalized" medicine a reality. Integrating technologies with cancer science promises to improve precision, reduce harmful side effects, and reduce costs of medical procedures.

In Fiscal Year 2007, NCI will accelerate work in nanotechnology, imaging, and computational modeling. Linking nanotechnology into cancer applications has the potential to dramatically reduce the adverse effects of cancer with multifunctional, targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents in high concentrations directly to cancer cells and tissues while sparing healthy tissue. Innovations in cancer imaging will move the field more rapidly beyond anatomical imaging to methods that detect and monitor the molecular features of cancer. Imaging technologies in combination with nanotechnology, proteomics, and high throughput screening will be optimized for data sharing; biomarker identification; minimally invasive image-guided prevention, early detection, treatment, and palliative therapies; and assessment of therapeutic effectiveness. Computational modeling is a central feature of integrative cancer biology studies aimed at generating predictive and testable models of cancer.

Advancing Medical Informatics

The NCI Surveillance, Epidemiology, and End Results (SEER) database contains information on more than six million *in situ*[8] and invasive cancer cases with approximately 360,000 new cases accessioned each year. The SEER registries routinely collect data on patient demographics, primary tumor site, morphology, histology, extent of disease, stage at diagnosis, first course of treatment, and follow up. Medical information systems will provide access to data important for all aspects of cancer research. The cancer Bioinformatics Grid (caBIG™) will continue to provide a foundation for leveraging data, research tools, scientists, and organizations in an open environment with common standards and shared tools. NCI will provide continued technical expertise and models to support data exchange for use in both research and medical practice. Cancer researchers will be able to locate de-identified data on patients with common diagnoses, conditions, or treatments and use it to determine patterns of disease, successful treatments, and outcomes. Using electronic data sharing, researchers across the country will be able, for example, to access data on the molecular characteristics of patients with a particular type of cancer who are being treated with a specific drug. CaBIG™ will also provide a foundation that will allow the Cancer Research Network and regional networks developed by Cancer Centers to enhance patient care.

Integrating Cancer Science

Cancer science is currently at a crossroad where input and approaches from a breadth of disciplines are necessary to understand and appreciate its complexities. Scientists are recognizing the need for study designs with the power to uncover the environmental, lifestyle,

[8] *In situ* means confined to the site of origin.

genetic, and molecular determinants and pathways involved in cancer initiation, promotion, and progression. Cancer research of the future will be energized as people from the various disciplines combine forces. Epidemiologists, geneticists, behavioral scientists, and biologists will be working alongside statisticians, engineers, physicists, bioinformaticians and computer scientists, sociologists, psychologists, communication specialists, and educators to improve the quality of cancer care, and health outcomes for diverse populations. Large-scale consortial efforts involving population cohorts will systematically evaluate and identify molecular and biochemical biomarkers of susceptibility, gene-environment interactions, causal pathways and intermediate outcomes, and early-stage lesions amenable to early detection and treatment. New paradigms of collaboration will mean new ways of thinking about how we do science.

New funding mechanisms will accelerate development of infrastructures for cutting-edge interdisciplinary research at the intersection of basic, clinical, and population sciences. Integrated review of grant applications will take into account the melding of various disciplines, support large-scale team-based consortia to foster the inclusion of genomics and other emerging technologies into epidemiologic study designs, and use other less formal ways to encourage interdisciplinary teams to evolve in both directed and serendipitous ways. Investments in integrative science will uncover the many factors influencing cancer initiation, promotion, and progression and thereby hasten the development of cancer interventions. Disparate perspectives and approaches will build the kind of synergy required to facilitate the flow of information from basic research to application.

OTHER AREAS OF INTEREST

Understanding the Factors that Influence Cancer Outcomes

Annual Report Provides Updates on the Progress against Cancer

First issued in 1998, *The Annual Report to the Nation on the Status of Cancer*[9] is the product of collaboration among NCI, the American Cancer Society, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries. It provides updated information on cancer rates and trends in the United States. The latest report, issued in 2005, cites a decrease of 1.1 percent per year, from 1993 to 2002, in observed death rates from all cancers combined. Declines in death rates reflect progress in prevention, early detection, and treatment. However, not all segments of the U.S. population benefited equally from advances. In men, death rates from all cancers combined declined 1.5 percent per year, from 1993 to 2002, compared to a 0.8 percent decline in women from 1992 to 2002. Death rates decreased for 12 of the top 15 cancers in men, and nine of the top 15 cancers in women. Lung cancer is the leading cause of cancer deaths in both men and women. The 2005 report highlights patterns of care for cancer patients and strategies for improving cancer survival by ensuring that evidence-based treatment services are available and accessible. The authors also examine racial and ethnic disparities in cancer. From 1992 to 2002, prostate, lung, and colon/rectum cancers in men, and breast, colon/rectum, and lung cancers in women continue to be the leading sites for incidence and mortality for each racial and ethnic population. The authors emphasize that reaching all segments of the population with high-quality prevention, early detection, and treatment services could reduce cancer incidence and mortality even further. Additionally, monitoring the

[9] *The Annual Report to the Nation on the Status of Cancer*. Go to **seer.cancer.gov**. Click on the icon "1975-2002 Report to the Nation."

dissemination of cancer treatment advances is an important aspect of ensuring uniformly high standards of care. The report concludes that substantial geographical variations in treatment patterns exist but that much of contemporary cancer treatment is consistent with evidence-based NIH Consensus Development Statements, which are considered a 'gold standard' for care recommendations.

Energetics Research

New NCI-supported Transdisciplinary Research on Energetics and Cancer centers will support a diverse team of scientists from across the United States to conduct research on the relationship between obesity and cancer. The centers will examine diet, weight, and physical activity and their effects on cancer and serve as focal points for the study of energy balance and energetics (the study of the flow and transformation of energy through living systems). The centers will also provide training opportunities for new and established scientists to conduct research that answers critical questions to help guide our nation's public health efforts. These studies will range from the biology and genetics of energy balance to the behavioral, sociocultural, and environmental influences on nutrition, physical activity, weight, and energy balance. NCI will strive to help avoid an increase in cancer deaths in the 21st century due to obesity like the one caused by tobacco in the 20th century.

Overcoming Cancer Health Disparities

Our Nation cannot reach the Challenge Goal set forth by NCI without addressing the cancer health disparities dilemma. Gender, ethnicity, and socioeconomic status are among the major factors that influence disparate rates of cancer incidence, morbidity, and mortality. Areas in which cancer health disparities are particularly evident include reduced access to cancer screening and diagnostic services, treatment disparities, lack of awareness about cancer risk and prevention, lack of access to clinical trials, and differential exposures to cancer causing agents. NCI efforts focus on improving the status of economic, social, cultural, psychological, behavioral, and biological factors that contribute to cancer health disparities. Research in NCI's biology, etiology, prevention, detection, and treatment portfolios addresses many of these issues. Resources and infrastructure necessary for disparities research include informatics, specimen resources, clinical trial groups, statistical methodology, drug and reagent resources, centers, consortia, and education and training of people prepared to work in careers focused on cancer health disparities.

HIV/AIDS-Related Research

Working through a new Office of AIDS Malignancy, NCI continues its commitment to meeting the needs of people infected with the human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) who are often more susceptible to some types of cancer. While the numbers of deaths per year in the United States due to AIDS has decreased in the era of highly active antiretroviral therapy, the number of people living with the disease has increased. AIDS-defining malignancies include non-Hodgkin's lymphoma, cervical cancer, anal cancer, and Kaposi's sarcoma.

The NCI Intramural Research Program is an internationally recognized center for research on HIV and AIDS. The Program integrates studies across multiple areas including epidemiology, correlative science, and treatment research. Some intramural scientists assess changes in the

cancer burden among HIV/AIDS patients whose lives have been extended as a result of improved treatments. Others focus on the development of novel targeted treatments and prevention interventions and on drug resistance for cancers in HIV infected individuals. Still others work to combine their expertise in cancer with that of retroviral vaccines to promote integrative science, cross fertilization, and progress in both areas. The HIV Drug Resistance program continues to make important contributions to AIDS-related research. Core NCI laboratories support epidemiologic, prevention, and treatment investigations.

The NCI Extramural Research Program supports vital investigator driven HIV/AIDS research as well as the AIDS Malignancy Consortium (AMC), which is the only clinical trials group aimed at improving the treatment and prevention of cancer in the context of HIV infection. The AMC works closely with the National Institute of Allergy and Infectious Disease (NIAID) to manage AIDS associated co-morbidities. NCI co-funds the Center for AIDS research with NIAID, supplies tissue resources for use in HIV/AIDS studies, and supports collaborative initiatives that leverage other NIH long-term cohorts. Cohort studies bring together researchers across geographic areas to collaborate and pool data and biospecimens for the purpose of studying the longitudinal patterns of disease. NCI also partners with others to address the critical needs of people affected by the global AIDS epidemic. These initiatives include collaboration with AMC and the Fogarty International Center programs at NIH to disseminate information on AIDS associated malignancies and to support an annual international forum.

Training and Career Development

NCI uses multiple strategies for preparing the next generation of cancer researchers to face challenges that are increasingly multidisciplinary and span basic, clinical, behavioral, and applied research. Each year, we provide cancer research training and career development opportunities to more than 2,000 graduate students, postdoctoral fellows, and oncologists. Collaborations with other NIH institutes and government agencies and partnerships with academic centers all promote innovative training programs.

NCI intramural divisions train a large portion of the world's future cancer researchers. For example, to address the increasing demand for basic and clinical scientists with experience in translational research, the NCI Center for Cancer Research has developed several interdisciplinary training programs. Translational research demands that investigators be capable of integrating molecular mechanisms of disease within the complexity of whole living biosystems designed and validated as predictive models of human disease. Innovative courses provide an overview of the general principles of cancer biology and treatment, epidemiology, mechanisms of resistance, metastasis, use of preclinical models, and identification of novel molecular targets. Participants have an unprecedented opportunity to learn new information, glimpse into future developments of translational research in clinical oncology, meet leaders in cancer research, and interview cancer survivors. NCI also manages a Cancer Research Interns in Residence Program to encourage qualified minorities and persons with disadvantaged backgrounds to consider a career in scientific research.

Innovations in Scientific Review

NCI has established several innovative structures for improving the quality and breadth of scientific review processes.

Intramural Scientific Review Processes Recognize Team Science

Decades ago, the most innovative science was done by the single scientist or small groups of scientists. Today, the most innovative science is often done by large teams of interdisciplinary researchers. Because of this, the scientific review process within the Center for Cancer Research has been revised to recognize team science. Within their review, principal investigators are encouraged to collaborate with intramural and extramural colleagues and to participate in scientifically meritorious multidisciplinary and interdisciplinary projects. Appropriate credit is now given for distinct collaborative contributions for which leadership, significant scientific contributions, or training and mentoring are evident even if those do not lead to first or last authorship in publications. This is a major innovation in the Intramural review process that encourages innovative team science and will often lead to more successful translational research.

Interdisciplinary Approaches to Peer Review Engage Scientists across the Institute

In 2005, NCI expanded the use of new models for coordinating review of large initiatives such as the Centers for Cancer Nanotechnology Excellence (CCNE), Multidisciplinary Career Development in Cancer Nanotechnology Research, and the Cancer Nanotechnology Platform Partnerships. Review teams were formed with representatives from multiple branches and programs to coordinate the identification and recruitment of reviewers. The tools and models developed for these initiatives were featured at a recent NIH retreat for Scientific Review Administrators.

NCI also evaluated a new approach for the review of program project grant applications in 2005. Panels of reviewers consider applications in clusters of two to four applications according to scientific research areas and approaches. The evaluation demonstrated the success of the cluster review approach with a significant reduction in the number of reviewers, improved scoring consistency and priority score spread across review panels, and reduction in costs and overall time for reviewers and NCI staff.

Advocates Enhance the Quality of Peer Review for Clinical Research

The NCI Division of Extramural Activities collaborated with the Consumer Advocates in Research and Related Activities (CARRA) Program in the NCI Office of Liaison Activities to train CARRA members in peer review and facilitate their participation in review of applications to support clinical research projects. The CARRA office held three 2 1/2 day training sessions during FY 05, with approximately 25 CARRA members at each session. The training provided orientation to peer review including the format and review criteria of various types of grant applications, NIH requirements for protection of human subjects, and how to prepare a critique. DEA review and referral staff participated in refining the curriculum, prepared the mock review materials, and lead sessions in the training. The NCI CARRA office is sponsoring a trans-NIH working group composed of review representatives and public liaison officers of several NIH

Institutes and Centers to promote inclusion of consumer advocates in peer review more widely across NIH.

Electronic Tools to Enhance 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.

Electronic Grants Management Is Fully in Place
The NCI transition from paper based to electronic grants management is 100 percent complete. To date, five other NIH Institutes/centers have adopted NCI's Electronic Grant File Web-based database. NCI is more effectively tracking and analyzing its research portfolio through electronic coding, indexing, and analysis of over 12,000 grant applications and awards each year. That information is provided to the public through the NCI Research Portfolio Website (researchportfolio.cancer.gov). A newly developed Web-based application of electronic document control forms has been fully implemented and is improving the efficiency of grants administration and stewardship.

Resources for Researchers
NCI efforts continue to support innovation in providing the many resources needed by cancer researchers.

Web-Based Collaboration Portals Facilitate Large Studies
The NCI Division of Cancer Epidemiology and Genetics (DCEG) conducts large population-based studies to identify environmental and genetic determinants of cancer. These studies, which may be national or international in scope, are multi-disciplinary, multi-center and involve the participation of several investigators and study coordinators. Studies may involve several thousand participants who are monitored over a period of many years. To assure effective collaboration among study sites, study coordinators, investigators, and study participants and to avoid study delays, DCEG has launched password protected Web-based collaboration study portals. The portals promote sharing of information where appropriate, but also preserve sections on the site that provide a higher level of security. These portals provide all team members ready access to timely information and promote the effective use of collective knowledge and experience. Regardless of study location, the portals facilitate smarter, faster decision making and the efficient management of studies.

Trans-NCI Team Develops Plans for Managing Biospecimen Resources
The increased emphasis on molecular and genetic approaches to translational and clinical cancer research has enhanced the focus on our need for high quality medical biospecimen resources and biorepository practices. In 2004, in response to a National Cancer Advisory Board (NCAB) recommendation, NCI formed a Biospecimen Coordinating Committee (BCC) to examine current practices and make recommendations for enhancing research practices and management of resources. Following the formulation and acceptance by the NCAB of their recommendations, the BCC is now equipped to put into place effective management tools and practices to optimize these very important resources and information for cancer research.

Intramural Centers of Excellence
The NCI Intramural Program has established new cross-administrative and innovative Centers of Excellence to serve as umbrella structures that bring together a critical mass and unique mix of basic, translational, and clinical scientists to work in multidisciplinary teams to aggressively pursue new approaches for the prevention and treatment of cancer. The Center of Excellence in Immunology (CEI), the most established Center to date, is a community of scientists who integrate discovery with the development of novel, immune-based treatments for cancer and AIDS. CEI members stand at the forefront of immunotherapy with their combined research resulting in more than 4,700 publications in peer-reviewed scientific journals since 1990 and many of the treatment approaches in use today.

Management Tools and Support Systems
NCI leaders are able to make decisions with better and more easily accessible information with new tools and support systems.

Dashboard Provides Front End Interface for Accessing Data
The NCI Dashboard is an innovative software front end designed to provide timely access to consistent enterprise-wide data using existing databases. It will provide a valuable interface and management tool for NCI leadership and others to use in quickly accessing information on trends and the current status of our research portfolio, conducting various kinds of analyses, and responding to queries. The Dashboard provides multiple drill-down capabilities such as four-year funding trends that can be examined separately in detail by NCI division, specific types of cancer, or broad areas of research.

Workforce Management Tools for Managers
The NCI Office of Workforce Development (OWD) provides managers with information, resources, and tools to recruit and retain, manage for results, and optimize performance. OWD offers numerous workforce management tools such as customized training plans, organizational development services to help managers create and maintain efficient environments, coaching around conflict and tangible resources for supervisors. OWD also offers human capital management tools such as fellowship programs and is currently leading the process in developing a strategic human capital plan and leadership programs.

Automated Salaries Cost and FTE Forecasting
NCI released into production an automated personal services forecasting tool for both salary cost and full time equivalent (FTE) usage projection. This system draws financial data and information about personnel actions from the existing source systems, and combines it with information provided by staff about planned accessions and separations. It then applies a sophisticated set of calculations and assumptions to arrive at an accurate prediction of the salaries and FTE for two out years. This system provides a much needed tool to more finely manage finances and staff resources.

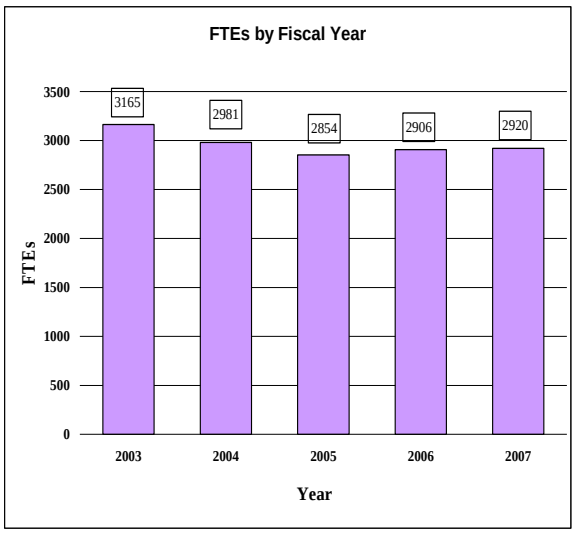
Reinventing the NCI Small Business Innovative Research Program
NCI has initiated a process to optimize its Small Business Innovation Research/Small Business Technology Transfer Research (SBIR/STTR)programs. The process will yield a plan for the program that defines the strategies, metrics, and milestones required to enable a successful SBIR

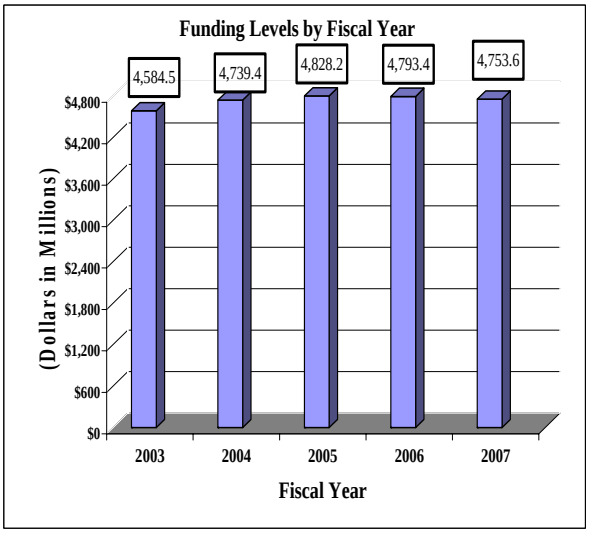
program. Several teams are working to produce different components of the plan, focusing on Metrics, Strategic Marketing and Business Development, Internal Communications and Training, the Review Process, and Facilitating Success for Awardees. The Metrics team will develop a plan and methodology for tracking how successful the NCI SBIR program is in stimulating technological innovation; meeting NCI R&D needs; and commercializing innovations. The Strategic Marketing and Business Development team will develop a comprehensive marketing strategy for ensuring that NCI is attracting the most promising small businesses to the SBIR and STTR programs. The Facilitating Success for Awardees team will develop strategies to assist SBIR companies in moving their technologies toward commercial development and clinical application.

Budget Policy

The Fiscal Year 2007 budget request for the NCI is $4,753,609,000, a decrease of $39,747,000 and 0.8 percent under the FY 2006 Appropriation. Included in the FY 2007 request is NCI's support for the trans-NIH Roadmap initiatives, estimated at 1.2% of the FY 2007 budget request. 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. Note that as the result of several administrative restructurings in recent years, FTE data is non-comparable.





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. We estimate that the average cost of competing RPGs will be $340,000 in FY 2007. While no inflationary increases are provided for direct recurring costs in noncompeting RPGs, where the NCI has committed to a programmatic increase for an award, such increases will be provided.

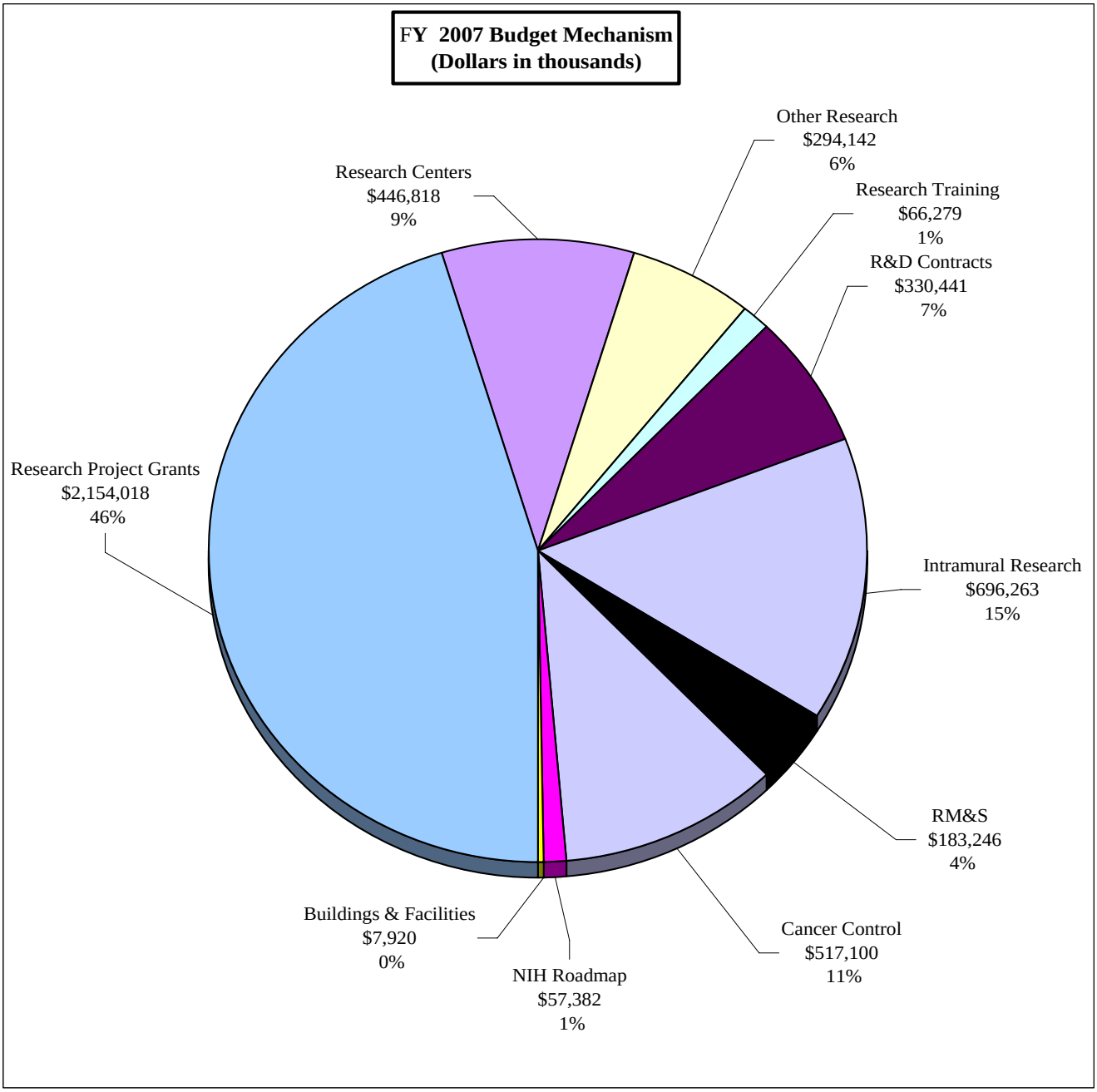
NIH must nurture a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills. In the FY 2007 budget request for NCI, $1.8 million will be used to support 20 awards for the new K/R "Pathway to Independence" program.

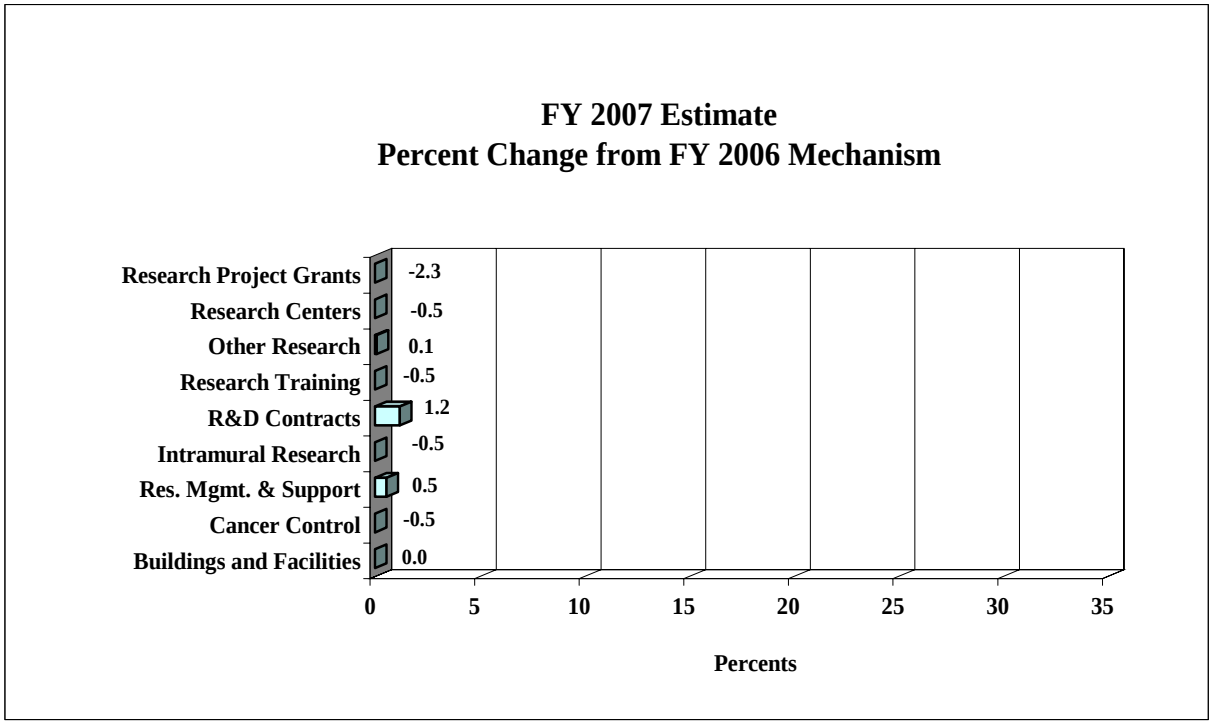
NCI will also support the Genes, Environment, and Health Initiative (GEHI) to: 1) accelerate discovery of the major genetic factors associated with diseases that have a substantial public health impact; and 2) accelerate the development of innovative technologies and tools to measure dietary intake, physical activity, and environmental exposures, and to determine an individual's biological response to those influences. The FY 2007 request includes $7.8 million to support this project.

In the FY 2007 request, stipend levels for trainees supported through the Ruth L. Kirschstein National Research Service Awards will remain at the FY 2006 levels.

The FY 2007 request includes funding for 151 research centers, 871 other research grants and 285 R&D contracts. Intramural Research decreases by 0.5 percent. Research Management and Support increases by .5 percent.

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




FY 2007 Estimate
Percent Change from FY 2006 Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural Research
Res. Mgmt. & Support
Cancer Control
Buildings and Facilities
-2.3
-0.5
0.1
-0.5
1.2
-0.5
0.5
-0.5
0.0
0
5
10
15
20
25
30
35
Percents

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Mechanism

MECHANISM	FY 2005 Actual		FY 2006 Appropriation		FY 2007 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,862	$1,603,571,000	3,885	$1,614,009,000	3,876	$1,594,683,000
Administrative supplements	(292)	50,655,000	(292)	50,655,000	(280)	48,655,000
Competing:						
Renewal	297	143,425,000	280	143,148,000	280	143,148,000
New	988	295,260,000	1,019	298,082,000	939	270,722,000
Supplements	7	1,185,000	6	3,075,000	6	3,075,000
Subtotal, competing	1,292	439,870,000	1,305	444,305,000	1,225	416,945,000
Subtotal, RPGs	5,154	2,094,096,000	5,190	2,108,969,000	5,101	2,060,283,000
SBIR/STTR	265	97,775,000	263	95,735,000	259	93,735,000
Subtotal, RPGs	5,419	2,191,871,000	5,453	2,204,704,000	5,360	2,154,018,000
Research Centers:						
Specialized/comprehensive	152	454,252,000	152	449,168,000	151	446,818,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	0	0	0	0
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	152	454,252,000	152	449,168,000	151	446,818,000
Other Research:						
Research careers	531	76,652,000	525	75,357,000	541	76,657,000
Cancer education	101	34,581,000	99	33,966,000	99	33,806,000
Cooperative clinical research	63	142,847,000	63	139,802,000	63	139,302,000
Biomedical research support	0	0	0	0	0	0
Minority biomedical research support	0	3,367,000	0	3,316,000	0	3,116,000
Other	179	42,904,000	179	41,451,000	168	41,261,000
Subtotal, Other Research	874	300,351,000	866	293,892,000	871	294,142,000
Total Research Grants	6,445	2,946,474,000	6,471	2,947,764,000	6,382	2,894,978,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	198	8,409,000	183	8,357,000	182	8,317,000
Institutional awards	1,271	58,890,000	1,274	58,262,000	1,267	57,962,000
Total, Training	1,469	67,299,000	1,457	66,619,000	1,449	66,279,000
Research & development contracts	318	351,065,000	285	326,560,000	285	330,441,000
(SBIR/STTR)	(32)	(6,721,000)	(40)	(8,600,000)	(40)	(8,600,000)
	FTEs		FTEs		FTEs	
Intramural research	1,832	711,009,000	1,864	699,763,000	1,878	696,263,000
Research management and support	612	182,323,000	623	182,246,000	623	183,246,000
Cancer prevention & control	410	531,634,000	417	519,650,000	417	517,100,000
Construction		0	0	0		0
Buildings and Facilities		7,936,000	0	7,920,000		7,920,000
NIH Roadmap for Medical Research	0	30,505,000	2	42,834,000	2	57,382,000
Total, NCI	2,854	4,828,245,000	2,906	4,793,356,000	2,920	4,753,609,000
(Clinical Trials)		(781,808,000)		(764,874,000)		(755,189,000)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2005 Actual FTEs	FY 2005 Actual Amount	FY 2006 Appropriation FTEs	FY 2006 Appropriation Amount	FY 2007 Estimate FTEs	FY 2007 Estimate Amount	Change FTEs	Change Amount
Research:								
Cancer Causation	888	$1,199,071	891	$1,141,221	898	$1,135,002	7	($6,219)
Detection and Diagnosis Research	124	363,648	123	379,903	124	379,835	1	(68)
Treatment Research	926	1,217,624	938	1,199,488	942	1,196,014	4	(3,474)
Cancer Biology	388	800,199	388	835,168	390	794,328	2	(40,840)
Subtotal, Research	2,326	3,580,542	2,340	3,555,780	2,354	3,505,179	14	(50,601)
Resource Development:								
Cancer Centers Support	17	463,810	12	451,998	12	449,671	0	(2,327)
Research Manpower Development	30	189,929	72	194,283	72	195,388	0	1,105
Construction	0	0	0	0	0	0	0	0
Buildings & Facilities	1	9,036	1	8,149	1	8,149	0	0
Subtotal, Resource Development	48	662,775	85	654,430	85	653,208	0	(1,222)
Cancer Control & Prevention	480	554,423	479	540,312	479	537,840	0	(2,472)
NIH Roadmap for Medical Research	0	30,505	2	42,834	2	57,382	0	14,548
Total	2,854	4,828,245	2,906	4,793,356	2,920	4,753,609	14	(39,747)

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes

FY 2006 Estimate				$4,793,356,000
FY 2007 Estimated Budget Authority				4,753,609,000
Net change				(39,747,000)
	FY 2006 Appropriation		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$262,510,000		$3,401,000
b. Annualization of January 2006 pay increase		262,510,000		2,061,000
c. January 2007 pay increase		262,510,000		4,387,000
d. Payment for centrally furnished services		112,618,000		1,689,000
e. Increased cost of laboratory supplies, materials, and other expenses		324,635,000		7,067,000
Subtotal				18,605,000
2. Research Management and Support:				
a. Within grade increase		75,601,000		1,222,000
b. Annualization of January 2006 pay increase		75,601,000		595,000
c. January 2007 pay increase		75,601,000		1,268,000
d. Payment for centrally furnished services		27,199,000		408,000
e. Increased cost of laboratory supplies, materials, and other expenses		79,446,000		1,730,000
Subtotal				5,223,000
3. Cancer Control:				
a. Within grade increase		56,904,000		866,000
b. Annualization of January 2006 pay increase		56,904,000		448,000
c. January 2007 pay increase		56,904,000		953,000
d. Payment for centrally furnished services		7,976,000		120,000
e. Increased cost of laboratory supplies, materials, and other expenses		87,408,000		1,903,000
Subtotal				4,290,000
Subtotal, Built-in				28,118,000

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Summary of Changes--continued

CHANGES	FY 2006 Appropriation		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,885	$1,664,664,000	(9)	($21,326,000)
b. Competing	1,305	444,305,000	(80)	(27,360,000)
c. SBIR/STTR	263	95,735,000	(4)	(2,000,000)
Total	5,453	2,204,704,000	(93)	(50,686,000)
2. Research centers	152	449,168,000	(1)	(2,350,000)
3. Other research	866	293,892,000	5	250,000
4. Research training	1,457	66,619,000	(8)	(340,000)
5. Research and development contracts	285	326,560,000	0	3,881,000
Subtotal, extramural				(49,245,000)
	FTEs		FTEs	
6. Intramural research	1,864	699,763,000	14	(22,105,000)
7. Research management and support	623	182,246,000	0	(4,223,000)
8. Cancer control and prevention	417	519,650,000	0	(6,840,000)
9. Construction		0		0
10. Buildings and Facilities		7,920,000		0
11. NIH Roadmap for Medical Research	2	42,834,000	0	14,548,000
Subtotal, program		4,793,356,000		(67,865,000)
Total changes			14	(39,747,000)

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Budget Authority by Object

	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	2,906	2,920	14
Full-time equivalent of overtime & holiday hours	7	7	0
Average ES salary	$156,618	$160,064	$3,446
Average GM/GS grade	11.9	11.9	0.0
Average GM/GS salary	$82,841	$84,663	$1,822
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$80,543	$82,275	$1,732
Average salary of ungraded positions	$115,508	$118,309	$2,801

OBJECT CLASSES		FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$162,185,000	$167,194,000	$5,009,000
11.3	Other than Full-Time Permanent	94,214,000	96,602,000	2,388,000
11.5	Other Personnel Compensation	7,282,000	7,355,000	73,000
11.7	Military Personnel	6,412,000	6,604,000	192,000
11.8	Special Personnel Services Payments	48,991,000	48,011,000	(980,000)
	Total, Personnel Compensation	319,084,000	325,766,000	6,682,000
12.0	Personnel Benefits	71,268,000	72,760,000	1,492,000
12.2	Military Personnel Benefits	4,606,000	4,745,000	139,000
13.0	Benefits for Former Personnel	57,000	57,000	0
	Subtotal, Pay Costs	**395,015,000**	**403,328,000**	**8,313,000**
21.0	Travel & Transportation of Persons	13,754,000	13,616,000	(138,000)
22.0	Transportation of Things	1,170,000	1,175,000	5,000
23.1	Rental Payments to GSA	11,000	10,000	(1,000)
23.2	Rental Payments to Others	590,000	593,000	3,000
23.3	Communications, Utilities & Miscellaneous Charges	6,133,000	6,164,000	31,000
24.0	Printing & Reproduction	3,194,000	3,196,000	2,000
25.1	Consulting Services	21,461,000	21,040,000	(421,000)
25.2	Other Services	146,626,000	138,271,000	(8,355,000)
25.3	Purchase of Goods & Services from Government Accounts	506,143,000	507,151,000	1,008,000
25.4	Operation & Maintenance of Facilities	85,938,000	84,219,000	(1,719,000)
25.5	Research & Development Contracts	308,356,000	309,633,000	1,277,000
25.6	Medical Care	5,583,000	5,583,000	0
25.7	Operation & Maintenance of Equipment	13,395,000	13,395,000	0
25.8	Subsistence & Support of Persons	179,000	179,000	0
25.0	**Subtotal, Other Contractual Services**	**1,087,681,000**	**1,079,471,000**	**(8,210,000)**
26.0	Supplies & Materials	42,025,000	42,245,000	220,000
31.0	Equipment	18,892,000	18,514,000	(378,000)
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	3,182,041,000	3,127,915,000	(54,126,000)
42.0	Insurance Claims & Indemnities	0	0	0
43.0	Interest & Dividends	16,000	0	(16,000)
44.0	Refunds	0	0	0
	Subtotal, Non-Pay Costs	**4,355,507,000**	**4,292,899,000**	**(62,608,000)**
	NIH Roadmap for Medical Research	**42,834,000**	**57,382,000**	**57,382,000**
	Total Budget Authority by Object	**4,793,356,000**	**4,753,609,000**	**3,087,000**

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Salaries and Expenses

OBJECT CLASSES	FY 2006 Appropriation	FY 2007 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$162,185,000	$167,194,000	$5,009,000
Other Than Full-Time Permanent (11.3)	94,214,000	96,602,000	2,388,000
Other Personnel Compensation (11.5)	7,282,000	7,355,000	73,000
Military Personnel (11.7)	6,412,000	6,604,000	192,000
Special Personnel Services Payments (11.8)	48,991,000	48,011,000	(980,000)
Total Personnel Compensation (11.9)	**319,084,000**	**325,766,000**	**6,682,000**
Civilian Personnel Benefits (12.1)	71,268,000	72,760,000	1,492,000
Military Personnel Benefits (12.2)	4,606,000	4,745,000	
Benefits to Former Personnel (13.0)	57,000	57,000	0
Subtotal, Pay Costs	**395,015,000**	**403,328,000**	**8,313,000**
Travel (21.0)	13,754,000	13,616,000	(138,000)
Transportation of Things (22.0)	1,170,000	1,175,000	5,000
Rental Payments to Others (23.2)	590,000	593,000	3,000
Communications, Utilities and Miscellaneous Charges (23.3)	6,133,000	6,164,000	31,000
Printing and Reproduction (24.0)	3,194,000	3,196,000	2,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	21,011,000	20,590,000	(421,000)
Other Services (25.2)	146,626,000	138,271,000	(8,355,000)
Purchases from Govt. Accounts (25.3)	350,845,000	351,214,000	369,000
Operation & Maintenance of Facilities (25.4)	39,405,000	38,617,000	(788,000)
Operation & Maintenance of Equipment (25.7)	13,395,000	13,395,000	0
Subsistence & Support of Persons (25.8)	179,000	179,000	0
Subtotal Other Contractual Services	**571,461,000**	**562,266,000**	**(9,195,000)**
Supplies and Materials (26.0)	41,686,000	41,895,000	209,000
Subtotal, Non-Pay Costs	637,988,000	628,905,000	(9,083,000)
Total, Administrative Costs	**1,033,003,000**	**1,032,233,000**	**(770,000)**

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute
SIGNIFICANT ITEMS IN HOUSE, SENATE, AND CONFERENCE APPROPRIATIONS COMMITTEE REPORTS

FY 2006 House Appropriations Committee Report Language (H. Rpt. 109-143)

Item

Breast cancer **-** The Committee remains concerned about missed opportunities in breast cancer screening, detection, prevention, control, early diagnosis, and mammogram detection, reading and analysis. The Committee encourages NCI to further accelerate advances in breast cancer screening technology and to capitalize on existing and create new technologies that improve early diagnosis, health outcomes, and survival. (p. 57)

Action taken or to be taken

Early detection and diagnosis of cancer is a fundamental aspect of successful cancer treatment. The NCI continues to support the development and refinement of new and existing breast cancer screening tools in order to get women the appropriate treatment faster. The Digital Mammographic Imaging Screening Trial (DMIST) compared the diagnostic performance of digital mammography and screen-film mammography in 49,500 women and used all four digital mammography machine types. Results (www.cancer.gov/dmist) revealed that the screening accuracy of digital and screen-film mammography was similar and demonstrated that several subsets of women would benefit from digital screening: women under age 50; women of any age with dense or heterogeneously dense breasts; and pre- or perimenopausal women of any age.

The NCI supports several clinical trials seeking to improve the use of magnetic resonance imaging (MRI) for detecting and diagnosing breast cancer. More than 1,000 participants at 22 sites in the U.S. will participate in a trial to assess the performance and usefulness of high resolution breast MRI in women with a current breast cancer diagnosis to detect disease that is often difficult to find with standard clinical and mammographic methods in the breast opposite the one with known disease. Accrual is complete in this three-year trial and follow up continues. Another group of more than 240 participants with locally-advanced breast cancer are being recruited at six institutions across the nation to identify molecular and imaging characteristics that may be used to identify patients who are likely to respond to novel therapeutic agents that could then be tested prior to or with standard therapeutic agents. These trials will use contrast-enhanced breast MRI and enable the investigators to gather sufficient preliminary data to estimate sample size for trials of novel therapeutics in this setting for patients who fail to respond to standard chemotherapy regimens.

The ongoing NCI-supported trial, Screening Breast Ultrasound in High-Risk Women**,** is designed to assess the diagnostic yield of whole breast bilateral screening sonography combined with mammography compared to mammography alone in the detection of breast cancer in high-risk women with dense breasts. About 2,000 participants are being enrolled at 20 sites across the U.S. in this three-year, phase III trial. Results will provide guidance to patients and practitioners on the role, if any, of screening breast ultrasound and the associated risk of an unnecessary biopsy.

In the area of characterizing women who may be at higher risk of breast cancer in whom more intensive screening can be targeted, NCI scientists have confirmed other reports, mostly from Europe, that approximately 1 in every 200 U.S. women carries the mutation 1100delC in the CHEK2 gene, and they are about twice as likely to develop breast cancer as women without this mutation. This information increases our understanding of specific patient genotypes that can lead to higher breast cancer risk.

The NCI continues to leverage and expand research in all aspects of breast cancer surveillance. The NCI-supported Breast Cancer Surveillance Consortium (BCSC) is a collaborative network of seven mammography registries with linkages to pathology and/or tumor registries. The BCSC is an ongoing effort to improve understanding of breast cancer screening practices in the U.S. and their relation to changes in stage at diagnosis, survival, or breast cancer mortality and has facilitated tracking the patterns of use of digital mammography as it has entered community practice. The BCSC report, "Evaluating Screening Performance in Practice," is available online at http://breastscreening.cancer.gov/espp.pdf

Item

Ovarian cancer **-** The Committee remains concerned that survival rates associated with ovarian cancer have improved only slightly over the past 20 years. . . . . The Committee encourages NCI to sustain and strengthen its commitment to and investment in ovarian cancer and maintain the specialized programs of research excellence (SPORE) initiatives directed toward ovarian cancer in fiscal year 2006. (p.58)

Action taken or to be taken

A key component of the NCI's overall research portfolio on ovarian cancer is the transdisciplinary research conducted in the Ovarian Cancer SPORE program, initiated in 1999 with the funding of four sites and recently expanded to five sites. The five Ovarian SPOREs are involved in a number of activities to identify an effective early detection screening tool for both high-risk and average-risk populations. Four of the Ovarian SPOREs have collaborated with the Cancer Genetics Network to test the effectiveness of quarterly CA125 (a biomarker that may suggest the presence of cancer) screens and annual transvaginal ultrasounds for detecting ovarian cancer in high risk women.

The Ovarian SPOREs are also involved in developing a prospective repository of specimens (blood and urine) from women with advanced ovarian cancer. This repository will be utilized to test promising new biomarkers for ovarian cancer recurrence, including those developed through proteomics applications. This NCI-led study was announced in September 2005. More information is on the web:
http://www.cancer.gov/newscenter/pressreleases/OvarianMultiInstituteTrial.

The NCI remains strongly committed to investing in ovarian cancer research and maintaining its Ovarian SPOREs. Funding for NCI ovarian cancer research has increased from $76.9 million in FY 2001 to $100 million in FY 2005. Three of the five Ovarian SPOREs were initially funded at a level of $2.3 at the end of FY 2004 and a fourth SPORE was awarded in FY 2005. The fifth Ovarian SPORE is in a no cost extension period through the end of FY 2006.

Item

Liver Cancer **-** The Committee remains concerned with the increasing incidence of primary liver cancer, which is in sharp contrast to many other forms of cancer where the incidence is declining and the treatment options are rapidly increasing. The Committee is aware that NCI, working with NIDDK, has convened an Experts Conference and is moving ahead with plans to increase resources dedicated to this disease. The Committee urges NCI to make a strong commitment to research on primary liver cancer with particular focus on the development of drugs that target the cancer without killing healthy cells by interfering with the cellular pathways of the disease. The Committee further urges NCI to continue to support the NIDDK sponsored HALT-C clinical trial which has particular relevance to the NCI mission. (p. 58)

Action taken or to be taken

The NCI remains dedicated to the development of drugs targeting liver cancer, with particular emphasis on the evaluation of new biologic agents that interfere with the cellular pathways of the disease. Over 90 percent of primary carcinomas of the liver are hepatocellular carcinomas (HCC). While HCC, also called primary liver cancer, is a common cause of cancer and cancer-related mortality worldwide, until recently it has been rare in the U.S. New studies demonstrate that liver cancer is the most rapidly increasing incidence of cancer in the U.S., resulting in at least 14,000 deaths annually. The recent upsurge in HCC in the U.S. may be attributable to chronic infection with hepatitis C virus (HCV), found in more than half of patients diagnosed with HCC.

The 2004 Conference, "Hepatocellular Carcinoma: Screening, Diagnosis, and Management," co-sponsored by the NCI and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), set out summary recommendations for HCC that were published in a special supplement to the November 2004 issue of Gastroenterology. The 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 continue to discuss the potential development of a Request for Applications specifically designed to address these main areas of research. For treatment, the recommendations supported development and evaluation of innovative local ablative therapies, cytotoxic agents, and molecularly targeted therapies along with basic research to define key molecular pathways that contribute to the malignant transformation of liver cells.

Regarding the HALT-C project with the NIDDK, the NCI met its obligation to fund the project for two years. In FY 2005, however, the NCI decided it could no longer earmark funds for the project. The NCI's decision was not the result of any concerns regarding the HALT-C project, but a necessary fiscal reprioritization to meet its other important cancer research initiatives.

The NCI is currently sponsoring development of 17 new agents in 29 phase I and phase II clinical trials for patients with liver and hepatobiliary cancer (cancer of the bile ducts and biliary tract). Twenty-three of these trials are for patients with HCC. In addition, the NCI is funding phase II trials evaluating radiofrequency ablation (i.e., the use of electrical current passed through electrodes placed directly into a tumor to destroy it with heat) and chemoembolization (i.e., a procedure in which the blood supply to a tumor is blocked surgically or mechanically and

anticancer drugs are administered directly into the tumor) in patients with HCC. During FY 2006, an NCI-funded trial will begin to test an investigational agent for the chemoprevention of HCC in patients chronically infected with HCV. The NCI recently issued two program announcements soliciting research grant applications in etiology, prevention, and treatment of HCC.

Item

Pancreatic cancer **-** Pancreatic cancer is the country's fourth leading cause of cancer death. Most patients present with advanced disease at diagnosis and the median overall survival rate for people diagnosed with metastatic disease is only about six months. The Committee is concerned that there are too few scientists researching pancreatic cancer and 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. The Committee considers this an important method for attracting both young and experienced investigators to develop careers in pancreatic cancer. In 2004, the NCI established a new policy for awarding additional grants in pancreatic cancer research and extended this initiative to research that is 50 percent relevant to pancreatic cancer. The Committee requests NCI to report in February, 2006 on how the two changes in policy have affected the pancreatic cancer portfolio, including the percentage relevancy of each grant to pancreatic cancer, and urges NCI to continue its commitment to fertilize the pancreatic cancer field. (p. 58)

Action taken or to be taken

The NCI continues to be strongly committed to expanding funding for high quality research project grants addressing the difficult problem of pancreatic cancer and for increasing the number of investigators working on the complex issues associated with pancreatic cancer research.

Following a recommendation of the 2001 Pancreatic Cancer Progress Review Group, in FY 2002 and 2003, NCI experimented with a special exception process for R01 research grant applications – effectively extending the standard R01 payline by 50 percent to automatically fund applications that were 100 percent relevant to pancreatic cancer and received scientific merit scores in peer review within 11 and 10 percentile points of the paylines in those years.

In FY 2004 and 2005, NCI modified that policy, expanding the eligible research to be considered for funding to include applications that were at least 50 percent relevant to pancreatic cancer and making the selection process dependent on approval by the relevant Division Director with oversight of the full NCI Executive Committee rather than providing funding automatically based on the review score.

The change to permit consideration of applications with at least 50 percent relevance to pancreatic cancer had no effect on the number of grants selected for funding. The applications submitted to NCI with less than 100 percent but at least 50 percent relevance to pancreatic cancer were not of sufficient scientific merit to warrant selection for funding. Similarly, the change in the selection process from an automatic extended payline award process to a process overseen by the NCI extramural Division Directors had no effect on the number of exception grants selected

for funding. However, it has resulted in an improvement in the scientific merit of the grants which have been awarded to conduct pancreatic cancer research.

The improvement in scientific merit has occurred because investigators with scores within the former extended payline range have been encouraged to revise and resubmit applications based on the comments that were received in the critique of peer review. Although this delayed the start of several research projects, the revision and resubmission in response to the peer review critique resulted in better science being funded.

Specifically in FY 2005, automatic payment for relevant R01s, which fell within an eight point range of the R01 payline, was tempered with careful consideration of the flaws identified in peer review and the opportunity that the applicant had to remedy those flaws by revising and improving the application. The number of pancreatic R01 exceptions funded in FY 2005 (four) compares favorably to the numbers funded in prior years. There were three identified in FY 2004 and ultimately funded; four were funded in FY 2003; and three funded in FY 2002. All the grants funded have been coded 100 percent pancreatic cancer research.

To address the larger question of whether NCI's efforts to expand research in pancreatic cancer has been successful in recent years, it might be informative to note that in FY 2001, NCI had a portfolio of 16 R01s coded 100 percent relevant to pancreatic cancer research for a total of $5.3 million in funding. In comparison, NCI funded 55 R01s coded 100 percent relevant to pancreatic cancer research in FY 2005 for a total of $19.7 million. Overall, the number of R01 grants coded 100 percent relevant to pancreatic cancer in NCI's portfolio has increased 240 percent since FY 2001.

Item

Neurofibromatosis (NF) - . . . . The Committee recognizes that basic research has successfully brought NF into the clinical era and encourages NCI to create, fund, and implement NF clinical trial infrastructures including NF centers, patient data bases, and tissue banks. The Committee further encourages NCI to apply existing cancer drugs to NF patients in clinical trials and to develop new drugs for NF which could then apply to the general population because of NF's connection to many forms of human cancer. The Committee is aware of significant new advances in NF research in the past few years in the area of tumor suppression and encourages NCI to continue to coordinate its efforts with other NIH institutes and government agencies. (p.59)

Action taken or to be taken

Patients with neurofibromatosis type 1 (NF-1) have mutations in the NF-1 tumor suppressor gene. These patients have a propensity to develop benign and malignant tumors. Children with NF-1 are predisposed to develop juvenile myelomonocytic leukemia (JMML), characterized by myeloid cell over production and infiltration of non-blood-cell-forming organs. The NF-1 gene product participates in signaling pathways involved in growth and differentiation. However, our understanding of exactly what role NF-1 plays in regulating cell proliferation is incomplete. NCI is funding several grants to investigate how NF-1 protein dysregulation alters cell proliferation and differentiation in JMML, and one grant to investigate the relationship of a tyrosine

phosphatase to the function of NF-1 gene product in JMML. Mutations in this phosphatase may be related to the development of JMML and other myeloid malignancies.

In collaboration with National Institute of Neurological Disorders and Stroke (NINDS), NCI provided funding to the National Neurofibromatosis Foundation to support the meeting entitled "The National Neurofibromatosis Foundation International Consortium for the Molecular and Cell Biology of NF1 and NF2 and Schwannomatosis" in Aspen, Colorado, in June 2005. This meeting brought together scientists and clinicians to share their latest research findings and experiences and to form new collaborative ventures. Critical gaps in knowledge relating to NF1 and NF2 and schwannomatosis, a rare form of NF, were discussed and strategies to address them were suggested. These discussions will play an essential role in developing improved therapies for the complications of these disorders with broad implications to the fields of developmental neurobiology and cancer research.

Item

American Russian Cancer Alliance (ARCA) **-** The Committee encourages NCI to continue and enhance its support for the research programs of ARCA, recognizing both the scientific opportunities within the partnership and the national interest in fostering the international effort to develop new, productive avenues for the use of nuclear stockpiles previously earmarked for weapons development. (p. 60)

Action taken or to be taken

In the past year, interaction between NCI and the American Russian Cancer Alliance (ARCA) has been significantly enhanced. Most notably, NCI has provided funding to Fox Chase Cancer Center (FCCC) to support the infrastructure of ARCA. NCI also approved additional funding to FCCC to work on tobacco research in conjunction with the ARCA partners at the N.N. Blokhin Cancer Center in Moscow. In March 2006, along with its ARCA partners, FCCC and the University of Maryland Greenebaum Cancer Center (UMGCC), NCI will be sponsoring a conference at the N.N. Blokhin Cancer Center in Moscow entitled, "Prevention and Treatment of Tobacco-Related Cancers." Several NCI scientists will be participating.

NCI participation in ARCA continues to highlight the scientific opportunity and cooperative relationship between U.S. and Russian cancer researchers created by this partnership. An NCI representative along with representatives of the U.S. ARCA partners, and the ARCA Executive Director participated in a briefing to the U.S. Department of State on the NCI-ARCA activities. At the invitation of ARCA, an NCI representative also attended a briefing in Austria on NCI-ARCA collaborations for several U.S. Congressional Members and staff, the Speaker of the Russian Duma, and other additional members of the Duma and their staff.

NCI sponsored three staff members of the N.N. Blokhin Cancer Center on a trip to the U.S. spanning 14 days aimed at showcasing best practices in cancer communication. In addition to visiting the NCI itself, the trip included visits to FCCC and UMGCC, as well as the M.D. Anderson Cancer Center, the Susan Komen Foundation, the American Cancer Society, and the Centers for Disease Control and Prevention. By all accounts, this was a very successful endeavor with valuable contacts made between the U.S. and Russian participants.

NCI also supported the visit of Russian scientists to visit UMGCC for a week to confer and work on the Radioisotopes in Cancer Therapy project. Another Russian researcher is being sponsored by NCI to work on this project in Baltimore, Maryland, for a period of six months, starting in January 2006. This work is directly related to the development of new uses for Russian nuclear stockpiles. It is anticipated that in 2006, NCI will partner with ARCA to conduct a scientific conference in Bethesda, Maryland, that will focus on the use of radioisotopes in imaging for cancer detection and diagnosis, cancer treatment, and palliative care for cancer patients.

Item

Cancer Metastasis - The NCI is encouraged to develop an interdisciplinary and integrated approach to study bone metastasis, by combining the expertise of oncologists, bone biologists and metastasis experts. Key issues to address include the generation of novel organ-like or mouse models which closely mimic tumor bone interactions that will pave the way for delineating novel mechanisms of how tumor cells go to the bone; designing novel targets for better prognosis; and effective therapeutic targeting. The Committee encourages NCI to continue supporting research that furthers the understanding of the causes and consequences of sarcoma. The Committee also recommends that NCI support research on osteosarcoma to improve survival and quality of life and to prevent metastatic osteosarcoma in children and teenagers who develop this cancer. (p. 60)

Action taken or to be taken

The NCI continues to promote research and clinical trials in bone metastasis. In addition to several NCI/NIH initiatives, NCI is an active participant in the Federal Working Group on Bone Diseases, and has actively participated and supported meetings on bone metastasis.

Novel experimental models closely mimicking human bone metastasis has led to considerable progress in the understanding of the biology of the bone microenvironment and the factors that make it an attractive target for metastasis for many human cancers. NCI investigators have identified a number of novel proteins or growth factors that enable tumor metastasis to the bone. They have also shown that the inhibition of a well-characterized pathway involving two proteins decreases the ability of prostate cancer cells to grow in the bone, as well as demonstrating that zoledronic acid has dual effects--inhibiting bone destruction and stopping bone growth activity of prostate cancer cells. NCI investigators have used proteasome inhibitors to successfully target not only multiple myeloma cells but also the bone microenvironment.

The NCI is developing treatments for cancers known to have a tendency to bone metastases, such as prostate cancer. Building on the recent discovery that the drug docetaxel can prolong survival in hormone refractory prostate cancer, two multi-institutional phase III trials are examining whether addition of either an agent that stops new blood vessel growth (bevacizumab) or an agent that blocks the action of a bone metastasis promoting protein, endothelin-1 (atrasentan) is able to improve survival. The NCI is collaborating with the private sector to develop a novel inhibitor against an enzyme that is highly expressed on osteoclasts (cells that initiate bone loss) and involved in promoting tumor invasion. Another promising area of targeting bone metastasis is by preventing the adhesion and attachment of tumor cells to bone cells via proteins called integrins. Tumor cell attachment to bone cells is crucial for tumor cell survival. To test the

efficacy of cell adhesion inhibitors, phase II trials with integrin inhibitors in several malignancies with bone metastases are under way.

Recent novel findings in osteosarcoma research include the identification of a new gene, ezrin, and the isolation of a new protein, CReMM. Ezrin is necessary for osteosarcoma metastasis in mouse models of osteosarcoma and is also present and relevant in children with osteosarcoma. NCI is evaluating Ezrin's potential as a target for therapeutic intervention. Tumor biopsies from adolescent patients have shown abnormalities in the gene suggesting that CReMM could be a novel protein marker of this disease.

NCI has launched a new program focused on the study of naturally occurring cancers in pet animals as models of human disease. Dogs develop osteosarcomas that share strong similarities to human disease, and they have shown to be better models than conventional laboratory animal models. Recent efforts include development of a reagent kit for the study of dog cancers and development of a multi-center clinical trial network, which will offer the pharmaceutical industry and the broader academic community access to dogs as models for drug development.

The NCI-supported Children's Oncology Group (COG) is collaborating with several European clinical cooperative groups to conduct a new, large, phase III clinical trial that will include children, adolescents, and young adults with newly diagnosed surgically removeable osteosarcoma. The COG is also conducting a study in children and adolescents with newly diagnosed metastatic osteosarcoma to determine whether herceptin can improve the outcome for these poor prognosis patients.

Item

Tobacco harm reduction **-** In a recent study funded by NCI, a panel of leading tobacco experts was asked to review scientific literature for the comparative mortality risks of low-nitrosamine smokeless tobacco products and conventional cigarettes. The panel of experts concluded that, based on published scientific literature, low-nitrosamine smokeless tobacco products pose a substantially lower risk to the user than conventional cigarettes. Given this important conclusion, the Committee urges NCI to continue its research into harm reduction strategies for cigarette smokers, and consider the role low-nitrosamine smokeless tobacco products may play in the overall effort to reduce the incidence of cigarette smoking in the U.S. (p. 60)

Action taken or to be taken

Tobacco use, particularly cigarette smoking, is the single most preventable cause of death in the United States; an estimated 440,000 Americans die prematurely from smoking each year. Cigarette smoking alone is directly responsible for approximately 30 percent of all cancer deaths annually in the U.S. NCI's research efforts in the prevention and control of tobacco use are premised on three fundamental facts: all tobacco products are hazardous; there is no safe level of tobacco use or environmental tobacco smoke exposure; and the only proven way to reduce the burden of disease and death due to tobacco products is to prevent their use and to assist those who use tobacco products to quit.

In light of the proliferation of new tobacco products on the market, NCI has begun two efforts to increase our knowledge of their health effects. In May 2004, NCI announced a new program

announcement entitled, “Testing Tobacco Products Promoted to Reduce Harm,” to stimulate multidisciplinary research on the properties, patterns of use, and health effects of potential reduced-exposure tobacco products. Additionally, NCI technical experts are currently reviewing proposals in response to a contract solicitation entitled, “Laboratory Assessment of Tobacco Use Behavior and Exposure to Toxins Among Users of New Tobacco Products Promoted to Reduce Harm.” The purpose of this contract is to research and develop new methods to study the characteristics and use of new tobacco products promoted with harm reduction claims so we can better understand their impact on individual and public health. NCI anticipates funding this contract in fiscal year 2006.

NCI is also funding the development of a Tobacco Harm Reduction Network, whose primary goals include the establishment of an independent scientific group to provide expertise and advice on tobacco harm reduction, the development of a comprehensive research strategy and infrastructure for scientific collaboration and communication, and the advancement of mechanisms for sharing data and research methods. A series of preliminary planning meetings have already been held to determine the structure and operation of the Network.

Lastly, in June 2006, NIH will convene a State-of-the-Science conference titled, “Tobacco: Prevention, Cessation and Control,” co-sponsored by NCI and numerous other DHHS agencies. The conference will provide an unbiased, independent, evidence-based assessment of several key questions in the field of tobacco prevention, cessation, and control research. Among the five questions to be evaluated by the conference panel is: “What is the effect of smokeless tobacco product marketing and use on population harm from tobacco use?” The conference will be an important opportunity to synthesize and evaluate the most current information in this area.

NCI will continue to collaborate with scientific partners from government and non-governmental organizations around the world to develop and implement a framework to permit independent and objective research, as well as data synthesis related to tobacco products that are purported to reduce harm. Our efforts will focus on how these products are used by the consumer, and their impact on health at the individual and population-based level. We are confident that we will continue to make progress towards reducing the enormous burden of death and disease which results from tobacco use.

Item

Advanced technologies - The Committee commends NCI for its goal of eliminating the suffering and death caused by cancer by the year 2015. The Committee encourages NCI to pursue the use of advanced technologies such as nanotechnology, proteomics, and imaging, to rapidly translate basic research discoveries into targeted interventions to ultimately achieve the 2015 goal. (p. 61)

Action taken or to be taken

NCI is committed to facilitating the convergence of scientific disciplines and enabling the integration of advanced technologies so progress can be accelerated in the discovery, development, and delivery of interventions that will eliminate the burden of cancer. The National Advanced Technology Initiative for cancer (NATIc) is an NCI-funded initiative that would link the National Cancer Program and R&D initiatives being developed in selected National Laboratories and advanced technology facilities in more than 40 states and regions.

Connected in real time via a bioinformatics grid as a "network of networks" of science, technology, and treatment, NATIc will help accelerate the emerging discipline of molecular oncology to create a pipeline of new, personalized cancer diagnostics and therapeutics from laboratory concept to clinical reality and out into community. This initiative would:

- Accelerate the implementation of a nationwide high-end information technology grid for bioinformatics that could be uniquely adapted for real time data sharing. NCI's pilot version, called caBIG, is currently being implemented among 50 cancer centers, the Food and Drug Administration (FDA), and other organizations.
- Develop a comprehensive biomarker discovery and validation program.
- Foster the application of emerging technologies, such as nanotechnology, and integrate molecular agents with advanced imaging devices.
- Accelerate a nationwide "real time" medical information electronic system for research and medical data sharing using technologies and devices currently employed by the banking industry and large-scale commercial enterprises.
- Enhance the discovery and validation of new targets of genes and proteins critical to cancer development.

In addition, NCI is working toward the deployment of an advanced and integrated infrastructure for cancer clinical trials. This clinical research infrastructure will:

- Strengthen collaborations with industry, FDA, Centers for Medicare and Medicaid Services, and other public, private, academic, and patient advocacy organizations to oversee the conduct of cancer clinical trials.
- Develop new infrastructure and procedures to standardize, coordinate, and track clinical trials development and accrual across all NCI-supported clinical trials.
- Increase utilization of imaging tools in screening and therapy trials, evaluate new imaging probes and methodologies, enable access to the imaging data from trials in an electronic format, and facilitate evaluation of image-guided interventions.
- Expand access and improve the timeliness for completion of the highest priority clinical studies.
- Foster the development of a cadre of established clinical investigators who could work between bench and bedside.
- Pilot new approaches and develop prototypes for clinical trials networks that could improve the efficiency, coordination, and integration of our national efforts.
- Develop a common clinical trials informatics platform that could be made available to the full range of investigators working within the cancer clinical trials system.

NCI is dedicated to reducing and eliminating the suffering and death due to cancer and recognizes the potential advanced technologies such as nanotechnology, proteomics, and imaging have to rapidly translate basic research discoveries into targeted interventions. NCI will continue to work on the cutting edge of technology and science in our battle with this terrible disease.

Item

Informatics grid - The Committee is pleased with NCI's development of the cancer Biomedical Informatics Grid (caBIG) as a network to facilitate the integration of diverse data types and the sharing of interoperable analytic tools. NCI is encouraged to work with the Office of the National Coordinator for Health Information Technology to use CaBIG as a prototype for an interoperable clinical data network. (p. 61)

Action taken or to be taken

There has been significant progress in the development of the cancer Biomedical Informatics Grid™ (caBIG™) [http://cabig.nci.nih.gov]. Representatives from 50 NCI-designated Cancer Centers and 30 other organizations -- over 600 people in all -- have collaborated in building infrastructure and interoperable tools that enable data sharing across domains to speed the discovery of new knowledge and its application to cancer prevention, treatment, and cure. caBIG™ applications cover a wide area, from basic research (e.g., microarray and molecular analysis) to clinical trials (e.g., clinical trials management, adverse event reporting). The foundational infrastructure, caGrid, makes possible the integration of diverse databases of cancer specific biological information to the internet.

The NCI uses multiple approaches to ensure that caBIG™'s interoperable research network contributes to national health information technology efforts. Senior NCI officials meet regularly with their counterparts in the Department of Health and Human Services (HHS) Secretary's Office and with the National Coordinator for Health Information Technology (ONCHIT) and his staff to discuss opportunities for integrating the clinical research infrastructure into the National Health Information Network (NHIN). The NCI co-chaired one of the ONCHIT workgroups that reviewed responses to the ONCHIT Request for Information on the NHIN, and NCI personnel play leadership roles in the ONCHIT Federal Health Architecture and Consolidated Health Informatics activities. NCI staffs the Workgroup on the National Health Information Infrastructure of the HHS National Committee on Vital and Health Statistics, a leading advisory committee on health information technology. The NCI plays key roles in the development of health information technology standards through these collaborations.

The NCI also works closely with other U.S. federal agencies, its counterparts overseas and industry in the advancement of health information technology. The Food and Drug Administration, for example, is a partner in developing an electronic infrastructure for regulatory reporting of new drug development. Informatics researchers from other NIH initiatives, such as the NIH Roadmap, and from abroad, such as the U.K.'s National Cancer Research Institute, are exploring ways to link to caBIG™. caBIG™ is engaging new participants from the broader cancer community and industry, including biomedical R&D and informatics companies.

FY 2006 Senate Appropriations Committee Report Language (S. Rpt. 109-103)

Item

Blood Cancers - The Committee acknowledges some notable advances in the treatment of blood cancers, including leukemia, lymphoma, and multiple myeloma. These include several new drugs that have been approved and introduced to the market in the last 3 years, products of a strong public-private partnership. Despite new treatments, these cancers represent a serious

health crisis. Almost 115,000 Americans will be diagnosed with these cancers in 2005, and nearly 55,000 will die from them. Moreover, the 5-year survival rates for these cancers lag behind the 64 percent 5-year survival rate for all cancers; the rate for multiple myeloma is only 32 percent, and for non-Hodgkin's lymphoma it stands at 59 percent. The Committee encourages the Institute to strengthen its support for translational and clinical blood cancer research. The blood cancers strike individuals of all ages, races, and each gender, and serve as valuable prototypes for the development of therapies for all types of malignant disorders. The Committee urges the institute to explore all mechanisms to support blood cancer research to improve treatment options and rapidly move discoveries from the laboratory bench to the patient's bedside. (p. 90)

Action taken or to be taken

During the past year, approximately 3,400 patients with leukemia and myelodysplastic syndrome (MDS) were enrolled onto NCI extramural clinical trials and 25 new NCI-sponsored clinical trials on blood cancers were activated. Five new extramural pediatric leukemia trials also began in FY 2005, including a new phase III trial for 1,500 children with standard risk acute lymphoblastic leukemia (ALL). NCI-funded studies were also used for an FDA submission for approval of the drug nelarabine for children and adults with recurrent or refractory T-cell ALL.

Recent NCI actions will strengthen clinical blood cancer research. The NCI undertook a comprehensive review of cancer clinical trials through the Clinical Trials Working Group. The group's report is available online at http://integratedtrials.nci.nih.gov/ict/CTWG_report_June2005.pdf. The report makes specific recommendations for better coordinating activities across funding mechanisms and leveraging of resources across all of NCI which will speed up blood cancer clinical trials.

The NCI has five Specialized Programs of Research Excellence (SPOREs) in blood cancers: three for lymphoma; one for leukemia; and one for myeloma. The SPOREs conduct high quality translational research primarily aimed at the development of new therapies, including targeted therapy, immunotherapy, radiotherapy, and chemotherapy. Significant advances were achieved in the development of treatment of multiple myeloma, acute myeloid leukemia, and in early detection of lymphoma, amongst others.

NCI intramural investigators have made significant progress against blood cancers, including studies showing that BL22, a recombinant immunotoxin, has a high complete remission rate in hairy cell leukemia patients and that FK228, a histone deacetylase (HDAC) inhibitor, is effective against peripheral and cutaneous T-cell lymphoma.

Ongoing NCI studies include:

- Pediatric Phase I Trial of BL22 for Refractory CD22-Positive Leukemias and Lymphomas
- Pediatric Phase I Trial of LMB2 for Refractory CD25-Positive Leukemias and Lymphomas
- Phase II Study of UCN-01 In Relapsed or Refractory Systemic Anaplastic Large Cell And Mature T-Cell Lymphomas

- Phase II Short-Course EPOCH-Rituximab for Untreated CD-20+ HIV-Associated Lymphomas
- Pilot Study of Non-myeloablative, HLA-matched Allogenic Stem Cell Transplantation for Pediatric Hematopoietic Malignancies

Item

Bone Marrow Failure Diseases - The Committee encourages NCI to expand its research efforts into bone marrow failure diseases, including aplastic anemia, myelodysplastic disorders [MDS], and paroxysmal nocturnal hemoglobinuria [PNH]. Each year, between 20,000 and 30,000 Americans are diagnosed with these diseases. In some cases, MDS, the most prevalent of these diseases, can progress over time to become acute leukemia. More research is critically needed to understand the causes of these diseases, develop effective treatments and cures, and prevent the progression of certain cases into leukemia. Furthermore, cancer patients who undergo chemotherapy often develop bone marrow failure diseases. The Committee encourages NCI to gain a better understanding of the link between chemotherapy and these diseases, and to explore the development of alternatives means of treating cancer without causing the subsequent development of bone marrow failure diseases. (p. 90)

Action taken or to be taken

To treat patients with aplastic anemia (AA), clinicians need to know if the disease is caused by "classic" autoimmune disease, or some other mechanism (for example, a hereditary lack of blood stem cells.) Investigators recently found that careful measurement of bone marrow-derived blood cell precursors (called CD34+ cells) could separate these two kinds of patients and predict whether the patients go on to develop leukemia. Predicting the course of disease earlier in treatment will lead to more aggressive treatment for patients who need it. The investigators have also made progress identifying auto-reactive T cells that attack CD34+ cells. This technique aids in the diagnosis of "classic" AA. It could also lead to treatments against the specific class of T cells that cause AA. The NCI is initiating clinical trials to build on these findings.

Paroxysmal Nocturnal Hemoglobinuria (PNH) results when one of the protein building blocks of blood stem cells is defective in an environment where blood cell development is abnormal. The resulting red blood cells are more likely to burst because of a process called complement activation, which is a normal part of fighting infections. Blood stem cells of affected patients have a gene mutation called PIG-A. Originally, the PIG-A mutation was thought to indicate disease but more recent studies show the same mutation in blood progenitor cells of normal individuals. Investigators are trying to determine the role of PIG-A in the disease. It appears that the underlying marrow failure in these patients, and not the presence of the PIG-A mutation per se, is what leads to the development of leukemia.

Patients with MDS cannot make red blood cells and also have trouble making platelets and white blood cells. The bone marrow continues to produce more and more precursors (blasts), but they do not develop into mature cells. Patients can be divided into early and advanced disease groups based on the kinds of cell deficits (red cells, white cells, platelets, or a combination), chromosomal mutations, and percent of blasts. Investigators have found a new way to classify patients based on the amount of methylation in several relevant genes. (Methylation turns genes

on and off.) Since MDS treatment depends on patient prognosis, this finding has clinical importance.

NCI scientists have developed a mouse model for MDS that recapitulates all of the key findings of the human disease, including transformation to acute leukemia. They are using drugs known to be effective in humans in the mice to determine if this model will be useful in screening drugs for MDS. NCI investigators are also studying two transcription factors known as inhibitor of DNA binding protein 1 (Id1) and C/EBP as therapeutic targets for bone marrow diseases. One NCI laboratory has identified a novel class of adult, inactive pluripotent stem cells that may represent a unique reservoir of stem cells for bone marrow transplantation and the treatment of leukemia.

The NCI, along with the NIH Office of Rare Diseases and the National Heart, Lung and Blood Institute (NHLBI), funded the "Bone Marrow Failure Scientific Symposium," which was organized by the Aplastic Anemia and MDS International Foundation, Inc., and held in October 2005. This meeting brought together intramural scientists from NHLBI and NCI and extramural investigators funded by the NIH in these diseases to review the current state of science in these diseases and offered an opportunity to develop new collaborations and relationships among these investigators, scientists, and clinicians.

Item

Breast cancer **-** Breast cancer's toll continues to threaten the lives and the quality of life of thousands of women across all walks of life. In addition to ongoing research activities underway at the National Cancer Institute, the Committee strongly urges the NCI to give increased attention to areas of research that focus on helping women to more fully restore and improve their quality of life after treatment, including further breast cancer research on lymphedema, stress, nutrition, exercise, weight, and the environment. (p. 91)

Action taken or to be taken

There are 10.1 million cancer survivors alive today in the United States. Of these, the largest constituent group is survivors of breast cancer who represent 22 percent of the prevalent population. For many, cancer has become a chronic illness, and it is a disease that affects family, community, and society.

In the nearly 10 years since its inception, NCI's Office of Cancer Survivorship (OCS) has developed funding opportunities, initiatives, and partnerships with outside agencies. The NCI's OCS now manages over 110 research grants addressing issues facing survivors who have completed their cancer therapy and seek to return to full and productive lives. A large portion of NCI's survivorship research portfolio focuses on intervention research. These grants focus on strategies that prevent or diminish adverse physical and psychosocial effects of cancer and its treatment.

In a recently funded study, a research team is evaluating the use of strength training as a potential means to prevent one of the more troubling adverse effects of breast cancer treatment, lymphedema, the accumulation of lymphatic fluid that causes swelling. The research team hopes that this practical intervention will reduce the occurrence and control the negative effects of arm

swelling among long-term survivors. In a second important study, investigators are assessing a population-based sample of 600 breast cancer survivors to: 1) describe risk factors for, and the time course of, developing lymphedema; 2) systematically study progression, regression, or fluctuations of lymphedema; 3) assess changes in measures of quality of life as they relate to the diagnosis of lymphedema and its changes over time; 4) test specific hypotheses about subgroups at particular risk of progression or exacerbation of this condition. Knowledge gained from both of these studies will enable us to better understand the causes of lymphedema in breast cancer patients, and inform recommendations about who may be at risk for this complication and the role that exercise may have in promoting the physical function and overall health of breast cancer survivors.

To advance our knowledge about the growing population of long-term cancer survivors, NCI reissued the Long Term Cancer Survivors Research Initiative. In 2005, 17 grants were awarded and research proposals addressed the full range of domains affected by cancer and its treatment (physical, psychosocial, behavioral, and economic) in long-term survivors with a focus on understudied areas and gaps in current research.

In 2006, the NCI, along with the Lance Armstrong Foundation, will provide support for the fourth year of their collaboration with CancerCare, the Intercultural Cancer Council, Living Beyond Breast Cancer, and the National Coalition for Cancer Survivorship to produce a three-part educational teleconference series on "Living With, Through and Beyond Cancer." Each year, special topics relevant to long-term recovery are addressed, such as dealing with fear of recurrence, managing fatigue and 'chemo brain' (diminished cognitive function), understanding follow up medical care, and records. The calls have involved as many as 1,800 listeners for a given program and are literally heard around the world.

In October 2005, the NCI announced the Transdisciplinary Research on Energetics and Cancer (TREC) initiative that will support a diverse team of scientists from across the United States. This unique initiative aims to integrate the study of diet, weight, and physical activity, and their effects on cancer by supporting research centers that focus on energy balance and energetics (the study of the flow and transformation of energy through living systems). Under the initiative, the centers will provide training opportunities for new and established scientists to conduct research on energy balance and cancer, including breast cancer.

Item

Breast cancer **-** The Committee remains concerned about missed opportunities in breast cancer screening, detection, prevention, control, and early diagnosis including those in mammogram detection, reading and analysis. The Committee strongly urges the NCI to further accelerate advances in breast cancer screening technology and to capitalize on existing and create new technologies that improve early diagnosis, health outcomes, and survival. (p. 91)

Action taken or to be taken

Please refer to page NCI-34 of this document for NCI's response to this significant item regarding breast cancer screening.

Item

Cancer Metastasis - the NCI is encouraged to develop an interdisciplinary and integrated approach to study bone metastasis, by combining the expertise of oncologists, bone biologists and metastasis experts. Key issues to address include the generation of novel organ-like or mouse models which closely mimic tumor bone interactions that will pave the way for delineating novel mechanisms of how tumor cells go to the bone; the development of novel targets for better prognosis; and effective therapeutic targeting. Designing new strategies to make the bone microenvironment hostile to invading tumor cells is of high clinical relevance. 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. 91)

Action taken or to be taken

Please refer to page NCI-40 of this document for NCI's response to this significant item regarding cancer metastasis.

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 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. 91-2)

Action taken or to be taken

The CLL Research Consortium (CRC) funded by NCI has made tremendous progress since its initial funding in 1999. Over 165 papers have been published in outstanding journals, including *Blood*, *Proceedings of National Academy of Sciences*, *New England Journal of Medicine*, *Nature Medicine*, and *Journal of Clinical Oncology*. Seminal accomplishments include:

- The characterization of genetic lesions and patterns of specific gene expression in CLL that have brought new opportunities for distinguishing patients who might have different tendencies for disease progression or response rates to a given therapy. For example, the Consortium was first to demonstrate that microRNA genes, a family of highly conserved non-coding genes, are found on a region of chromosome 13 that is deleted in more than half of CLL cases. These genes are involved in temporal and tissue-specific gene regulation and differences in their expression can be associated with differences in the clinical behavior of CLL as well as other cancers. Another gene identified on chromosome 13 is a novel tumor suppressor gene (ARLTS1) associated with development of familial CLL and familial solid-tissue cancers. Again, this information would enable physicians to categorize CLL patients into familial or sporadic origin. Finally, the over expression of ZAP-70, a specific type of tyrosine kinase enzyme, is a risk factor for aggressive disease and may help identify patients in need of more aggressive treatment.

- The development of the first transgenic mouse model for CLL that enables investigators to study disease pathogenesis and perform preclinical evaluation of novel therapeutic agents in vivo.
- The identification and development of novel pharmacologic and biologic agents for CLL. These include molecules with novel mechanisms of action, small molecule inhibitors of proteins that block programmed cell death as well as biologic agents such as monoclonal antibodies and gene therapy reagents. The Consortium completed the first gene therapy phase I trial in CLL using an adenovirus-CD154 construct. The Consortium also rescued a novel compound, flavopiridol, from the junk pile of drug development. Adventis-Sanofi had discontined the development of this compound until investigators in the Consortium developed a new dosing schedule that resulted in tremendous activity against CLL in patients. The patients developed tumor lysis syndrome, a condition that is rare in cancer drug development thus indicating the drug was efficacious and very potent against CLL. Adventis-Sanofi has resurrected the development of flavopiridol and will attempt to obtain fast track approval from the FDA.
- The improvement of algorithms to assess disease progression risk and response to therapy.
- The development of infrastructure that facilitates bench-to-bedside and bedside-to-bench research via the establishment of a national tissue bank, a CRC biomedical informatics system, and a familial CLL cohort.

The NCI also supports CLL research activities through the Quick Trials mechanism, cooperative agreements, contracts, and the intramural research program. On average over the last five years, 13 cooperative group CLL protocols and 17 phase I/II protocols were actively accruing patients at approximately 177 patients per year. In addition, there are at minimum 15 phase I/II CLL protocols that are ongoing. NCI scientists have discovered that patients treated for relapsed and refractory CLL with hematopoietic (blood-cell forming) stem cell transplantation from another individual develop a strong internal antibody response against as yet unknown molecular targets on the surface of CLL tumor cells. The researchers envision that the identification of these molecular targets may lead to the development of new monoclonal antibody drugs for the therapy of CLL. Three other phase I trials involving immunotoxins are underway. NCI scientists are also working with international investigators to identify susceptibility genes in families with multiple cases of CLL.

Item

DES **-** The Committee continues to support increased efforts to study and educate the public and health professionals about the impact of exposure to the synthetic hormone diethylstilbestrol [DES]. The Committee expects NCI to continue to consult with organizations representing individuals impacted by DES as it carries out DES research and education efforts. (p.92)

Action taken or to be taken

The NCI has partnered with the Centers for Disease Control and Prevention (CDC), the Department of Health and Human Services' Office on Women's Health, and advocacy and health care provider organizations to lead the development and implementation of a national campaign to inform consumers and health professionals about the potential health effects associated with exposure to DES. The drug was prescribed for pregnant women between 1938

and 1971, when the Food and Drug Administration advised physicians to stop prescribing DES because it was linked to a rare form of vaginal cancer. In the United States, an estimated 5 to 10 million persons, including pregnant women and their children, were exposed to DES during those years, and research has confirmed health risks associated with DES exposure. Consumer materials are available in print and online, and include a comprehensive set of fact sheets on DES history, research, resources, and health effects. The CDC website (http://www.cdc.gov/des/) provides information for consumers, including women who were prescribed DES during their pregnancies, as well as their sons and daughters; provides information for health care providers; and offers tools to help share information from the DES Update website, including promotional materials, a website linking kit, fact sheets, and newsletter articles. The information can be downloaded and printed from the website, or free print materials are available by calling 1-800-CDC-INFO.

NCI's website (http://www.cancer.gov/cancerinfo/persons-exposed-to-des) provides reference material to help clinicians identify individuals who may have been DES-exposed. Separate fact sheets are available concerning women who were prescribed DES and for DES-exposed daughters and sons that describe confirmed health effects, provide information on screening and treatment, and list DES resources for clinicians and patients.

Additionally, the NCI continues to follow up on research that conclusively linked DES to increased risk of a rare vaginal cancer in young women. In the NCI DES Follow-Up Study, begun in 1992, research focuses on the long-term health effects of DES exposure. Three phases of questionnaire mailings and national death searches have been conducted to follow approximately 20,000 mothers, daughters, and sons in 1994, 1997, and 2001. Analysis of data from the 2001 questionnaire revealed no excess risk of cancer overall in DES-exposed daughters or sons compared with the general population using Surveillance Epidemiology and End Result data. The association of in utero exposure to DES and risk of adult breast cancer was assessed in the daughters' follow-up cohort. The age-adjusted invasive breast cancer incidence in DES-exposed daughters was 40% higher than in unexposed daughters, and almost twice as high among women 40 years of age and older, but not among those younger than 40. While an earlier analysis of data through 1997 suggested that the association of DES exposure and breast cancer in women of all ages combined was restricted to estrogen receptor-positive tumors, a subsequent analysis including data through 2001 did not confirm this finding. Further follow-up with additional breast cancer cases will help confirm the finding of increased breast cancer risk. A questionnaire that will be sent to DES sons and daughters and unexposed subjects in the spring of 2006 is under development.

The Third Generation Study has also enrolled adult daughters of exposed and unexposed women who participated in the DES daughters' study to address concerns about possible multi-generational effects of DES exposure. Preliminary analyses of the approximately 800 (88 percent) responses began in 2004 and show no effects of DES on the age of the onset of menstruation or menstrual irregularity, although there is a suggestion that prevalence of infertility is elevated. Follow-up of this cohort through a mailed questionnaire is planned for 2009, and data analysis will continue.

A newsletter with summaries of results from the study and other information of interest to study participants was mailed in the spring of 2005 and also made available online at the study's website (www.desfollowupstudy.org).

Item

Health Cognition **-** The Committee encourages NCI's Division of Cancer Control and Population Sciences to continue to build innovative collaborations such as the Health Cognition Group. The activities of this group of researchers are designed to plumb knowledge from basic research on how people process and use health information and synthesize it with the development and evaluation of theory-based interventions to promote healthy behavior. Although these efforts are directed primarily to behaviors relevant to cancer, they will also serve the broader goal of developing theoretical frameworks that can be applied across a range of behavioral domains and conditions. (p. 92)

Action taken or to be taken

One of NCI's top priorities as identified in the Institute's strategic plan is to ensure the successful application of evidence-based interventions for preempting cancer, which depends heavily on our ability to move effective interventions into practice. The NCI builds innovative collaborations to increase the positive impact our efforts have on healthy behavior. The Health Cognition Group illustrates NCI's commitment to develop research collaborations that can increase our understanding of cancer, its causes, and the aftereffects of treatment from a variety of perspectives.

Physical activity is an example of a behavioral domain that can be important in preventing weight gain and decreasing weight and is relevant to multiple disease areas, including cancer. However, few adults or children actually achieve the recommended 30 minutes of moderate physical activity on most days of the week. To change these trends, it is essential to understand how physical activity behavior may be modified. Accordingly, the NCI recently released an initiative seeking to understand the mechanisms of physical activity behavior change in order to increase the knowledge base necessary to develop effective physical activity interventions. Specifically, funded investigators seek to elucidate the psychosocial, environmental, and physiological factors involved in the mechanisms of physical activity behavior change to better understand the factors involved in the causal pathways that lead to physical activity behavior change. Other partners in this initiative are the National Institute of Diabetes and Digestive and Kidney Diseases, the NIH Office of Disease Prevention, the NIH Office of Research on Women's Health, and the NIH Office of Behavioral and Social Sciences.

Recently, the NCI funded a new initiative that will expand its efforts to understand the relationship between obesity and cancer. The Transdisciplinary Research on Energetics and Cancer (TREC) initiative will support a diverse team of scientists from across the United States. This unique initiative aims to integrate the study of diet, weight, and physical activity, and their effects on cancer by supporting research centers that focus on energy balance and energetics (the study of the flow and transformation of energy through living systems). Under the initiative, the centers will provide training opportunities for new and established scientists to conduct research on energy balance and cancer.

The NCI has also initiated a program, the Advanced Training Institute on Health Behavior Theory (ATI), to enable attendees to extend their knowledge of, and experience with, the conceptual, methodological, and statistical underpinnings of health behavior theories. The ATI is a seven-day intensive learning course for new or early investigators. It is designed to offer in-depth instruction on the use, development, and evaluation of health behavior theory.

In order to meet the NCI challenge goal of eliminating the suffering and death due to cancer, innovations across the cancer control continuum must be delivered and adopted into public health, primary care, and oncology specialty care practice as efficiently and expeditiously as possible. The innovative collaborations of the Health Cognition Group and other efforts described here are designed to lead to theory-based interventions to promote healthy behavior. Many of these activities are developing theoretical frameworks that can be applied across a range of behavioral domains and conditions.

Item

Imaging Systems Technologies **-** The Committee is encouraged by progress made by the NCI following its August 1999 conference on biomedical imaging, and it urges the NCI to continue to take a leadership role with the Centers for Medicare and Medicaid Services and the Food and Drug Administration to avoid duplicative reviews of new imaging technologies which may prevent their benefits from reaching patients on a timely basis. The Committee is aware of the great potential for improved patient care and disease management represented by molecular imaging technologies, especially positron emission tomography [PET] through its ability to image the biology of many kinds of cancer and other diseases. The Committee continues to support the NCI's increased emphasis on examining the molecular basis of disease through imaging technologies such as PET and MicroPET. The Committee also continues to encourage the large-scale testing of women for breast cancer and men for prostate cancer to demonstrate and quantify the increased diagnostic and staging capabilities of PET relative to conventional diagnostic and staging technologies, including mammography. (p. 93)

Action taken or to be taken

The NCI continues to organize an annual National Forum on Biomedical Imaging in Oncology, which brings together industry, the FDA, the CMS and the NCI to discuss issues related to facilitating the process of getting new imaging technologies to patients. The most recent Forum was held April 7 and 8, 2005, in Bethesda, Maryland. The NCI also coordinates periodic Inter-agency Councils on Biomedical Imaging in Oncology (ICBIO), where industry can have a closed meeting with the FDA and CMS together, moderated by NCI, to discuss a proprietary product.

At present, drug development trials rely on conventional diagnostic and staging technologies, such as computed tomography (CT) and magnetic resonance imaging (MRI) to determine patient eligibility for the drug trial and to monitor response. However, functional imaging tests, such as fluorodeoxyglucose-positron emission tomography (FDG-PET) can give an earlier, and perhaps more biologically relevant, indication of whether a drug is effective or whether the dose used is appropriate. This allows early elimination of ineffective drugs and will accelerate development of promising drugs. The NCI is currently working closely with the FDA through its Interagency Oncology Task Force (IOTF) to define the scientific evidence required for the use of FDG-PET as a clinically meaningful endpoint in various cancer clinical trial settings. Several ongoing

projects, including trials in lung and head and neck cancer, will validate imaging as an endpoint for evaluation of oncologic treatments. This will lead to either a reduction in the number of subjects needed in a clinical trial or a reduction in the length of time to carry out the trial, or both.

The Digital Mammographic Screening Trial (DMIST) study compared the diagnostic performance of digital and film mammography in 49,500 women with no signs or symptoms of breast cancer. The study included women age 40 and older. DMIST showed that, for the entire population of women studied, digital and film mammography had very similar screening accuracy. However, three groups of women will benefit more from digital than film mammography: those under age 50; those of any age with heterogeneously (very dense) or extremely dense breasts; and those of any age who are pre- or peri-menopausal.

The National Lung Screening Trial (NLST) is designed to determine if lung cancer screening using spiral computerized tomography reduces lung cancer mortality in a high-risk population of 53,419 former smokers. All participants receive an initial screen and two subsequent yearly screens. Some sites are contributing to a tissue bank for future biomarker research and evaluating quality of life issues, cost-effectiveness assessments, and the impact of screening on smoking cessation.

Numerous practical applications of nanoparticles as a platform technology for imaging have also been defined, including imaging of tumor vasculature, lymph nodes, lymphatic vessels especially in breast cancer, and the whole body vasculature. Nanoparticles afford a higher density of imaging beacons (MRI, optical, PET), resulting in an increased sensitivity of detection of cancer or precancerous lesions.

Other developments in imaging technology include:

- New PET Agents for Cancer Monitoring. F-L-Thymidine (FLT) is a new PET contrast agent that measures tumor proliferation rates. NCI scientists have begun producing and quality control testing of FLT for human use. Subsequently, FLT will be tested in patients with brain, breast or prostate cancer.
- New microPET and microSPECT Cameras. NCI scientists are designing and constructing the next generation of microPET and microSPECT cameras for animal research using new flat-panel detector technology. This will allow higher sensitivity and higher resolution imaging than has ever been possible.
- NCI scientists have successfully used a novel micro-MRI contrast reagent (G6) in mouse imaging studies to detect early-stage lymph node metastasis. This work has been the basis of a U.S. Patent Office application.

Item

Liver Cancer **-** The Committee remains concerned with the increasing incidence of primary liver cancer, which is in sharp contrast to many other forms of cancer where the incidence is declining and the treatment options are rapidly increasing. The Committee is aware that NCI, working with NIDDK, has convened an Experts Conference and is moving ahead with plans to increase resources dedicated to this disease. The Committee urges NCI to make a substantial

commitment to research on primary liver cancer with particular focus on the development of drugs that target the cancer without killing healthy cells by interfering with the cellular pathways of the disease. The Committee further urges NCI to continue to support the NIDDK sponsored HALT-C clinical trial which has particular relevance to the NCI mission. (p. 93)

Action taken or to be taken
Please refer to page NCI-36 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. The Committee is encouraged by the success of new targeted drug therapies demonstrated in recent clinical trials in stage 4 patients. The Committee encourages the NCI to work with the thoracic surgical community to initiate new clinical trials that involve patients at an early stage of the disease when surgery is a treatment option. The trials should test the effectiveness of these new drugs as adjuvant therapy to improve the outcome of established thoracic surgical therapy for lung cancer. (p.93)

Action taken or to be taken
Surgery to remove primary solid lung tumors reduces cancer burden in patients. In addition, this approach also may remove or reduce tumor signals that are thought to interfere with a patient's immune response to residual tumors. Increasing a patient's ability to mount an immune response against lung tumors may be an important factor in treatment strategies.

For example, the post-operative setting provides an optimal window for employing anti-tumor vaccine strategies. NCI is funding a novel vaccine clinical trial for non-small cell lung cancer (NSCLC) through the Quick Trial initiative. This Phase I clinical trial aims to induce an anti-tumor immune response in patients with NSCLC by loading the patient's immune cells, known as dendritic cells (DC), with certain proteins from the patient's own irradiated (killed) tumor cells. These loaded cells are then combined with various human immune system stimulants to induce anti-tumor immunity. The Phase I clinical trial evaluates the safety and tolerability of administering this form of DC vaccine to a selected group of postoperative patients with NSCLC. A total of 12 to 15 patients will be treated in two cohorts with different doses of vaccine and will be followed for a total of one year for responses to the vaccine. Scientists will also monitor patients for possible changes in serum proteins that help regulate the activities of the immune system (cytokines) that may be related to tumor immunity and suppression. Evidence that the vaccine is safe, the manufacturing process is feasible, and the vaccine induced immune responses will provide the information required to support subsequent clinical trials focused on clinical outcomes and survival for this deadly disease.

This year, an NCI-funded study showed that the addition of bevacizumab to standard chemotherapy in patients with NSCLC (non-squamous) provides a statistically and clinically significant survival advantage with tolerable toxicity. This represents a new treatment standard in this population of patients with metastatic non-squamous non-small cell lung cancer.

In FY 2005, NCI announced an integrated effort to eliminate the suffering and death due to lung cancer by 2015. As part of this integrated implementation plan, three critical strategies will be targeted: reducing the risk for lung cancer by achieving more effective tobacco control; improving the likelihood of a cure through earlier detection and treatment of lung cancer and pre-cancer; and introducing novel targeted therapies through cohesive partnerships with ongoing or planned biology initiatives. The NCI's I-2 team, or Integration Implementation Team, specifically recommended focusing on improving smoking cessation, advancing early detection, and increasing new drug development and response to therapy.

The NCI continues to work with the thoracic surgical community to develop new grant applications that support surgical clinical trials. All lung cancer clinical trials performed by the clinical trials cooperative groups are led or co-led by thoracic surgeons, and NCI's Cancer Therapy Evaluation Program staff is intimately involved with the thoracic surgical community to develop new clinical trials.

Item

Lymphoma **-** The Committee strongly urges that the NCI take bold action to address lymphoma as a public health problem and to capitalize on important research advances to date. While new treatments have become available for patients, more and improved treatment options are needed. The Committee strongly encourages the NCI to boost its investment in translational and clinical lymphoma research. The Committee commends the NCI and the NIEHS for convening a workshop on the viral and environmental links to lymphoma and recommends that steps be taken to strengthen the NCI investment in this area. The Committee encourages the NCI to direct resources to: (1) studies of adequate scope to assure the identification of environmental risk factors for specific subtypes of lymphoma; (2) small studies designed to improve detection and quantification of historically difficult-to-measure environmental factors; (3) studies that are directed toward enhancing the understanding of the role of the immune system in the initiation and progression of lymphoma; and (4) studies that examine the simultaneous presence of a wide profile of infectious agents among individuals with lymphoma. The Committee also encourages that resources be used for research related to long-term survivors of both non-Hodgkin's lymphoma and Hodgkin's lymphoma. The Committee strongly supports the recommendation of the Leukemia, Lymphoma, and Myeloma Progress Review Group [LLM PRG] that resources be invested in identifying the populations of patients that are at high risk of adverse outcomes from their treatment for lymphoma. (p. 93-4)

Action taken or to be taken

The NCI is aggressively pursing answers to the factors that contribute to lymphomas. Since 1998, NCI intramural investigators have been conducting the largest U.S. case-control study of environmental risk factors for non-Hodgkin's lymphoma (NHL). The study has found increased risk for NHL to be associated with exposure to hepatitis C virus, polychlorinated biphenyls, dioxins and furans, and chlordane in termite treatments. NCI scientists are collaborating with CDC investigators to improve assays of environmental exposure and develop methods using smaller blood samples.

The NCI also organized an international consortium of lymphoma case-control studies known as InterLymph http://epi.grants.cancer.gov/InterLymph. This international collaboration fosters

investigations into the molecular epidemiology of NHL, allowing investigators to pool their data to study the effects of susceptibility genes and specific types of lymphomas. Results to date demonstrate that common genetic variations in immune pathways influence the risk of diffuse large B-cell lymphoma and, to a lesser extent, follicular lymphoma.

By understanding different immune system components of lymphomas, the NCI is creating the foundation for targeted therapy**.** Histone deacetylase (HDAC) inhibitors are promising anti-tumor agents. These drugs alter the structure of the histone proteins associated with DNA and contribute to regulating gene expression. Although not well-studied in B-cell lymphoma, NCI-supported research has found that the drugs repressed lymphoma cell proliferation and promoted cell death in these cells, providing new rationale for using HDAC inhibitors in the treatment of B-cell lymphoma.

The NCI is also supporting studies of proteins that alter gene expression in T-cell lymphoma. The proteins that regulate gene expression can also be affected by the addition or subtraction of methyl groups by DNA methyltransfersases (DNMTs). New experiments from these studies suggest that DNMTs can form complexes with HDACs and alter the expression of proteins specifically required for T-cell lymphomas to become malignant. Drugs designed to inhibit HDACs or DNMTs or combinations of these inhibitors are attractive candidates for novel anticancer therapies in T-cell lymphoma.

The NCI has promoted studies that examine the simultaneous presence of infectious agents among individuals with lymphoma, specifically in the context of HIV infection. For example, the NCI supports the AIDS Malignancy Consortium (AMC), which conducts clinical trials on AIDS-associated lymphoma. The AMC has shown that combination chemotherapy can be safely administered along with Highly Active Anti-Retroviral Therapy (HAART) to patients with AIDS-associated lymphoma. Another AMC study showed that the addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy results in improved clinical outcome for individuals with AIDS-associated lymphoma. However, these patients are at an increased risk for death from infection-related complications of therapy, and the higher infectious death rate may be compounded by the deficient immunity of these individuals.

In order to research outcomes for long-term survivors of both Hodgkin's lymphoma and NHL, the NCI has supported the Childhood Cancer Survivor Study (CCSS) for the past 13 years. The CCSS has expanded the cohorts to be followed so that long-term effects of the newer cancer regimens can be determined. Hodgkin's and NHL patients are well represented in CCSS cohorts.

The NCI also supports clinical trial protocols aimed at treating lymphoma. The Blood and Marrow Transplant Clinical Trials Network (BMT CTN), cosponsored by the NCI and the National Heart, Lung and Blood Institute, has two active phase III lymphoma protocols. One compares two transplant strategies in relapsed follicular NHL patients to determine whether one type of stem cell transplant is better than the other in improving long-term progression-free survival. The other, focused on chemotherapy-sensitive diffuse large B-cell lymphoma,

compares progression-free survival after a specific type of transplant (autologous hematopoietic stem cell transplantation) using two different types of pre-transplant conditioning.

Item

Native Hawaiians **-** The Committee remains concerned about the high incidence of breast, colon, and lung cancer among the Native Hawaiian population. The Committee commends the NCI for its progress toward understanding and addressing the needs of the Hawaiian and Pacific Basin populations through its cooperative agreement with Papa Ola Lokahi and looks forward to a report of the prioritized health needs identified by those assessments. (p. 94)

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 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.

Through the Papa Ola Lokahi agreement, the NCI helped establish the Cancer Council of the Pacific Islands (CCPI), a group of native physicians and other health professionals representing U.S.-associated jurisdictions of the Pacific region, to address the cancer health needs of these populations. In 2003, the CCPI conducted a comprehensive cancer needs assessments in nine locales: American Samoa, Guam, the Commonwealth of Northern Mariana Islands, the Republic of Belau (Palau), Republic of the Marshall Islands, and the four states of the Federated States of Micronesia. The researchers compiled cancer-related data, assessed the existing programs, and identified gaps in the delivery of cancer care, including a lack of ability to measure and track cancer data, a lack of cancer screening, diagnostic and treatment facilities, and a lack of cancer education and training.

In September 2004, the results of those assessments were reported in Public Health Dialogue Volume 11, Number 2 and outlined the needs and priorities of each locale. NCI implemented the prioritized listings of health needs identified as a result of those assessments, including addressing nursing training needs and initiating cervical cancer screening activities. An update of the cancer health needs and cancer prevention and control barriers of each locale is expected to be published in early 2006 and will aid in further prioritizing cancer health needs.

Item

Neurofibromatosis - The Committee commends NCI for conducting clinical trials of NF1 patients. 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 recognizes that basic research has successfully brought NF into the clinical era and encourages NCI to create, fund, and implement NF clinical trials infrastructures including NF centers, patient data bases, and tissue banks. The Committee further encourages NCI to apply existing cancer drugs to NF patients in clinical trials both extramurally and intramurally, and to develop new drugs for NF which could then apply to the general

population because of NF's connection to most forms of human cancer. The Committee is aware of significant new advances in NF research in the past few years in the area of tumor suppression, and encourages NCI to continue to coordinate its efforts with other NIH institutes and government agencies. (p. 95)

Action taken or to be taken
Please refer to page NCI-38 of this document for NCI's response to this significant item regarding neurofibromatosis.

Item
Ovarian Cancer **-** Congress remains concerned that mortality rates associated with ovarian cancer have not seen the decreases that other cancer sites have experienced in the past 5 years. As the deadliest of all gynecologic cancers, ovarian cancer takes the lives of three-quarters of all women diagnosed with it within 5 years. Congress commends the National Cancer Institute for its recognition of the importance of studying this deadly women's disease and appreciates the NCI's recent investment that is helping to increase the understanding of the unique molecular pathways associated with ovarian cancer through its Specialized Programs of Research Excellence [SPOREs] program. As such, Congress strongly encourages NCI to sustain and strengthen its commitment to and investment in ovarian cancer and maintain the SPOREs initiatives directed toward ovarian cancer in fiscal year 2006. (p. 95)

Action taken or to be taken
Please refer to page NCI-35 of this document for NCI's response to this significant item regarding ovarian cancer.

Item
Prostate Cancer **-** The Committee commends the NCI for the considerable investment in prostate cancer, the leading cause of non-cutaneous cancer death among men, and encourages NCI to continue to support research to improve the accuracy of screening and early detection of prostate cancer. (p. 96)

Action taken or to be taken
The NCI is committed to using knowledge of the molecular and cellular biology of prostate cancer to develop improved methods for detecting and diagnosing pre-malignant and malignant lesions and for better predicting disease progression and response to therapy. NCI-sponsored researchers are assessing the value of using prostate-specific antigen (PSA) as a biomarker for detection and have compared outcomes in men with higher and lower PSA velocities (rate of change in PSA levels). NCI-sponsored research results include:

- Men with higher PSA velocities in the year before treatment for localized prostate cancer are more likely to have their prostate cancer recur and are likely to die sooner than men with lower PSA velocities.
- Early data from the prostate cancer screening arm of the Prostate, Lung, Coloretal, and Ovarian (PLCO) cancer screening trial show that men with a PSA test result of 7 ng/ml or greater are more likely to have a subsequent prostate biopsy than men with lower but still

abnormal test results. Men with a positive digital rectal exam without a positive PSA test were less likely to receive a biopsy than men with a positive PSA test.

- Researchers analyzed data from 8,575 healthy men to determine the relative sensitivity (percentage of true positive results) and specificity (percentage of true negative results) of PSA screening. They found that sensitivities and specificities varied widely and concluded that a man's risk of developing prostate cancer cannot be determined solely from his PSA level.
- Researchers recently created a reliable method to calibrate instruments in different laboratories to detect potential cancer biomarker proteins with the same accuracy. The method uses surface-enhanced laser desorption (SELDI) mass spectrometry (MS) to help clinicians detect protein biomarkers for prostate cancer. NCI is now testing whether the technique correctly classifies prostate cancers and controls from different institutions.
- A study of 2,779 men without prostate cancer showed that about one-third of those who were obese and overweight had lower levels of PSA, which may help explain why obesity appears to increase the risk of aggressive forms of prostate cancer. Because of this, PSA screening in overweight and obese men could produce false-negative results and delay the diagnosis of prostate cancer.

New and continued initiatives include:

- The Correlative Studies with Specimens from Multi-Site Trials initiative fosters collaborations and interactions between basic researchers, scientists working in private industry, and clinical investigators to perform clinical translational research on promising predictive and prognostic markers.
- A task force is planning the Prostate Specialized Program of Research Excellence (SPORE) National Biospecimen Network Pilot. This pilot project will provide an ongoing platform for the prostate cancer SPOREs to test and validate prostate cancer biomarkers.
- Prostate cancer diagnosis is the target for one of the recently awarded NCI Centers of Nanotechnology Excellence. The focus for the development of this novel platform will be a nanofluidics platform capable of measuring a large number of genetic changes in prostate cancer.

The NCI continues to support clinical trials related to early detection, diagnosis, and prognosis of prostate cancer to evaluate technologies and detection methods, such as CT scans using CT-on-rails, positron emission tomography using carbon-11 acetate, and contrast-enhanced magnetic resonance imaging to help locate and diagnose tumors in patients with prostate cancer.

Item

Social Work **-** The Committee encourages NCI to coordinate with the Centers for Disease Control and Prevention to conduct further research on the outcome of social work interventions to meet patient and family psychosocial needs in hospitals and cancer treatment centers. (p. 96)

Action taken or to be taken

The prolongation of life for people with cancer has focused attention on the need for psychosocial support to improve the quality of life for those living with chronic illness. Key to

developing effective psychosocial interventions in cancer is having a basic understanding of the nature and extent of cancer and treatment-related aftereffects and their risk factors. Symptom management and palliative care research have been a growing part of the cancer research program at the NCI. A vital focus is on the development and application of interventions that will prevent or reduce the adverse aftereffects of cancer and its treatment on survivors' physical, psychological, and social functioning.

A number of the NCI-funded intervention studies among survivors, both in active treatment and post-treatment, are being designed and tested for delivery by oncology social workers. In one study, women completing adjuvant breast cancer therapy are being counseled by specially trained oncology social workers on what to expect during the post-treatment recovery period, on how to identify and apply active coping strategies, and on healthy lifestyle behaviors and choices. In response to a request for applications addressing the barriers cancer patients face to receiving optimal palliative care and symptom management, NCI is funding research to test models that rely on social workers to deliver the planned intervention. These studies, with others like them, promise to provide the evidence base needed to understand how best to use social workers to deliver effective interventions with the potential to improve both quality of care and quality of life outcomes for patients diagnosed and treated for cancer, and their family members.

The NCI has been an active participant in the development of the NIH Social Work Research Plan and the associated program announcement (PA) entitled Research on Social Work Practice and Concepts in Health. The goal of this PA is to encourage innovative empirical research on social work practice, concepts, and theory to improve health outcomes for persons with medical and behavioral disorders.

Several partnership activities to expand research on the outcome of social work interventions to meet patient and family psychosocial needs are ongoing. The NCI is working closely with colleagues at the Centers for Disease Control and Prevention (CDC) to define and develop strategies to address the gap areas identified in the CDC's National Action Plan for Cancer Survivorship. NCI staff has also worked closely with colleagues in the NIH Office of Behavioral and Social Sciences Research on a recently awarded contract with the Institute of Medicine to provide detailed information on the nature, breadth, and models used to provide psychosocial services to cancer patients and families in the community. Finally, in partnership with CancerCare, a non-profit community service agency that uses social workers to provide counseling services and educational programs to thousands of cancer patients and their family members across the country, the NCI is working to deliver an annual series of evidence-based educational teleconference programs to provide post-treatment survivors and their healthcare providers with information and tools to adapt to the chronic and late effects of cancer.

Item

SPORE Program **-** The Specialized Programs of Research Excellence [SPORE] Program at the NCI was established to support efforts to move laboratory findings into clinical practice to benefit patients in the near term. The Committee understands that the program has resulted in the translation of some exciting research into cancer clinical trials for vaccines, chemoprevention and dietary interventions. The results to date from SPORE funding include multi-center clinical trials, biomarker studies, prevention studies, genetic registries, data sharing, and tissue banking

projects, all with critical patient focus. The Committee strongly encourages the NCI to continue to keep this translational goal at its forefront. The Committee further understands that the SPORE program has been extremely successful in rapidly moving science to practices that benefit patients; funded research that requires a team approach to cancer; supports collaboration across basic science, population science and clinical investigation; and provides a rapid translation from the laboratory to patient care. The Committee further urges that the translational research momentum, developed under the SPORE program, be maintained by the NCI. (p. 96)

Action taken or to be taken

The SPORE Program remained a key in NCI's translational program in FY 2005. With 60 programs across the country, more than 120 active clinical trials, and a vast range of collaborative activities, the SPORE program continues in its main mission to move basic discoveries in cancer into clinical practice. The growth stabilization of the program in recent years has allowed NCI to direct attention to continuing and increasing the quality of translational research. This is done by working to overcome the barriers that hamper movement of laboratory findings into clinics and, importantly, by nurturing collaborations among SPORE investigators and between SPOREs and other NCI programs. SPOREs have become an important element in many of the priorities pursued by NCI.

Prostate SPOREs are conducting a pilot study for the National Biospecimen Network, a large scale effort to develop a systematic nationwide collection of human tissue samples to accelerate cancer research in this area. The Breast Cancer SPOREs, in collaboration with the American College of Radiology Imaging Network and the Cancer and Leukemia Group B, will conclude in the near future a major Phase III clinical trial using advances in imaging, genomic, and proteomic analyses to measure tumor responses to pre-treatment therapy. Breast Cancer SPOREs are also active in a special NCI partnership with the Avon Foundation and NCI designated Cancer Centers, conducting 16 early phase clinical interventions in breast cancer. Over the past two years the Lung Cancer SPOREs have made critical paradigm shifting discoveries in the area of therapy targeting the Epidermal Growth Factor Receptor (EGFR). Discoveries made by SPORE investigators launched an ongoing multi-center multifaceted collaboration resulting in new strategies of treatment and the development of clinical tests that would distinguish lung cancer patients with the highest benefit from targeted therapies at hand. Other areas of significant progress include proteomics, combined chemotherapy and targeted therapy, gene therapy, genetic predisposition to lung cancer and its relevance to smoking, and epigenetics. More information on recent scientific advances is available on NCI's SPORE website: http://spores.nci.nih.gov/public/index_public.html#sci_adv.

To maintain translation research momentum and to facilitate vigorous scientific exchange and collaborations, NCI organizes numerous meetings through the SPORE Program. The Annual SPORE Investigators' Workshop represents a culmination of these efforts, and more than 1,000 participants from the SPORE program, government, industry, and patient advocacy groups attended the meeting in 2005. During these meetings, SPORE investigators discuss collaborations and present results and interact with shareholders across the spectrum of translational cancer research. In July 2006, NCI will sponsor the 14th Annual SPORE Investigators' Workshop.

NCI leadership recently launched an initiative to evaluate the current status of NCI's investment in translational research and envision its future in an inclusive, representative, and transparent manner. The initiative will be led by NCI's Translational Research Working Group (TRWG). The analysis and recommendations of TRWG will help shape the future of translational research sponsored by the NCI, including the SPORE Program.

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. The Committee is encouraged that NCI is participating in a Trans-NIH Tuberous Sclerosis Coordinating Committee, and urges NCI's continued involvement in this process. The Committee also urges NCI to collaborate with NIDDK on a conference on nutrient sensing and insulin-signaling in cells with inclusion of TSC research. (p. 96)

Action taken or to be taken

Both the intramural and extramural research components of the NCI made major contributions to our understanding of TSC in the past year. NCI-sponsored research revealed that exposure during development to the synthetic hormone diethylstilbestrol increases the incidence of uterine tumors in rats carrying one mutation in the TSC2 gene, but not in wild-type rats. This work indicates that the fetal environment may influence the proportion and severity of TSC phenotypes in people, and could help explain the wide variation in presentation among people with identical mutations in their TSC genes. In addition, NCI-funded researchers continued to make critical advances in understanding the molecular interactions that transmit the function of TSC1 and 2 by identifying new components of the pathways through which they signal.

NCI continues to fund a clinical trial testing the utility of drug rapamycin as a treatment for renal angiomyolipoma (AML), a condition which develops in many TSC patients. In addition, NCI is funding the first multi-center phase II clinical trial on rapamycin for treatment of lymphangioleiomyomatosis (LAM), also associated with TSC. For this trial, patients are being actively recruited for treatment at six centers in the United States.

The NCI has been working with the Trans-NIH Tuberous Sclerosis Coordinating Committee, led by the National Institute of Neurological Disorders and Stroke (NINDS), to promote research into TSC. Along with three other NIH institutes and the Tuberous Sclerosis Alliance, NCI has joined with NINDS to offer a Program Announcement with set-aside funds on TSC, which seeks grant applications on a broad range of issues central to understanding TSC. Areas of interest to the NCI include the development of cell culture and animal models of TSC, identification of downstream targets of tuberin and hamartin proteins, and investigation of the roles of TSC1 and 2 in renal cell carcinogenesis. The NIH plans to fund a number of new grants through this initiative by April 2006.

NCI is working with the National Institute on Diabetes and Digestive and Kidney Disease (NIDDK) to organize a scientific meeting, "Nutrient Stress, Insulin Signaling, and Hamartoma

Syndromes," in May 2006. The meeting is expected to attract approximately 100 participants, many of whom do not yet work on TSC. One of the major goals of the meeting is to promote cross-fertilization between investigators in insulin signaling and researchers in TSC. Sessions will be devoted to clinical aspects of hamartoma (noncancerous growth) syndromes, insulin signaling, and nutrient sensing.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2006 Amount Authorized	FY 2006 Appropriation	2007 Amount Authorized	FY 2007 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$4,726,737,000	Indefinite	$4,687,330,000
National Cancer Institute	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	66,619,000		66,279,000
Total, Budget Authority				4,793,356,000		4,753,609,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1998	2,217,482,000 2/	2,513,020,000	2,558,377,000	2,547,314,000
1999	2,528,760,000 2/4/	2,787,830,000	2,927,187,000	2,927,187,000
Rescission	0	0	0	(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 3/
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	4,841,774,000	4,960,828,000	4,841,774,000
Rescission				(48,418,000)
2007	4,753,609,000			

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 $781,000.
4/ 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 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Office of the Director	684	689	690
Center for Cancer Research	1,519	1,545	1,550
Division of Cancer Biology	44	46	47
Division of Extramural Activities	81	84	85
Division of Cancer Treatment and Diagnosis	177	180	183
Division of Cancer Prevention	87	91	92
Division of Cancer Control and Population Sciences	123	128	129
Division of Cancer Epidemiology and Genetics	139	143	144
Total	2,854	2,906	2,920
Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research			
FTEs supported by funds from Cooperative Research and Development Agreements	(3)	(3)	(3)

FISCAL YEAR	Average GM/GS Grade
2003	11.5
2004	11.7
2005	11.9
2006	11.9
2007	11.9

NATIONAL INSTITUTES OF HEALTH
National Cancer Institute

Detail of Positions

GRADE	FY 2005 Actual	FY 2006 Appropriation	FY 2007 Estimate
Total - ES Positions	5	8	8
Total - ES Salary	$759,545	$1,252,945	$1,280,510
GM/GS-15	210	210	210
GM/GS-14	356	356	356
GM/GS-13	318	328	328
GS-12	445	460	460
GS-11	205	215	224
GS-10	18	18	18
GS-9	156	156	156
GS-8	83	83	83
GS-7	90	90	90
GS-6	21	21	21
GS-5	13	13	13
GS-4	5	5	5
GS-3	2	2	2
GS-2	2	2	2
GS-1	0	0	0
Subtotal	1,924	1,959	1,968
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	39	39	39
Senior Grade	17	17	17
Full Grade	9	9	9
Senior Assistant Grade	6	6	6
Assistant Grade	1	1	1
Subtotal	73	73	73
Ungraded	839	854	858
Total permanent positions	2,017	2,054	2,064
Total positions, end of year	2,841	2,893	2,907
Total full-time equivalent (FTE) employment,end of year	2,854	2,906	2,920
Total ES level	5	8	8
Average ES salary	$151,909	$156,618	$160,064
Average GM/GS grade	11.9	11.9	11.9
Average GM/GS salary	$80,350	$82,841	$84,663

Includes FTEs which are reimbursed from the NIH Roadmap for Medical Research

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New Positions Requested

	FY 2007		
	Grade	Number	Annual Salary
Research Assistant	AD/401/0	4	$66,000
Staff Scientist	AD/401/0	5	$92,000
Senior Investigator	AD/602/0	1	$165,000
Senior Clinician	AD/602/0	2	$190,000
Health Science Administrator	GS 14	2	$102,000
Total Requested		14	