

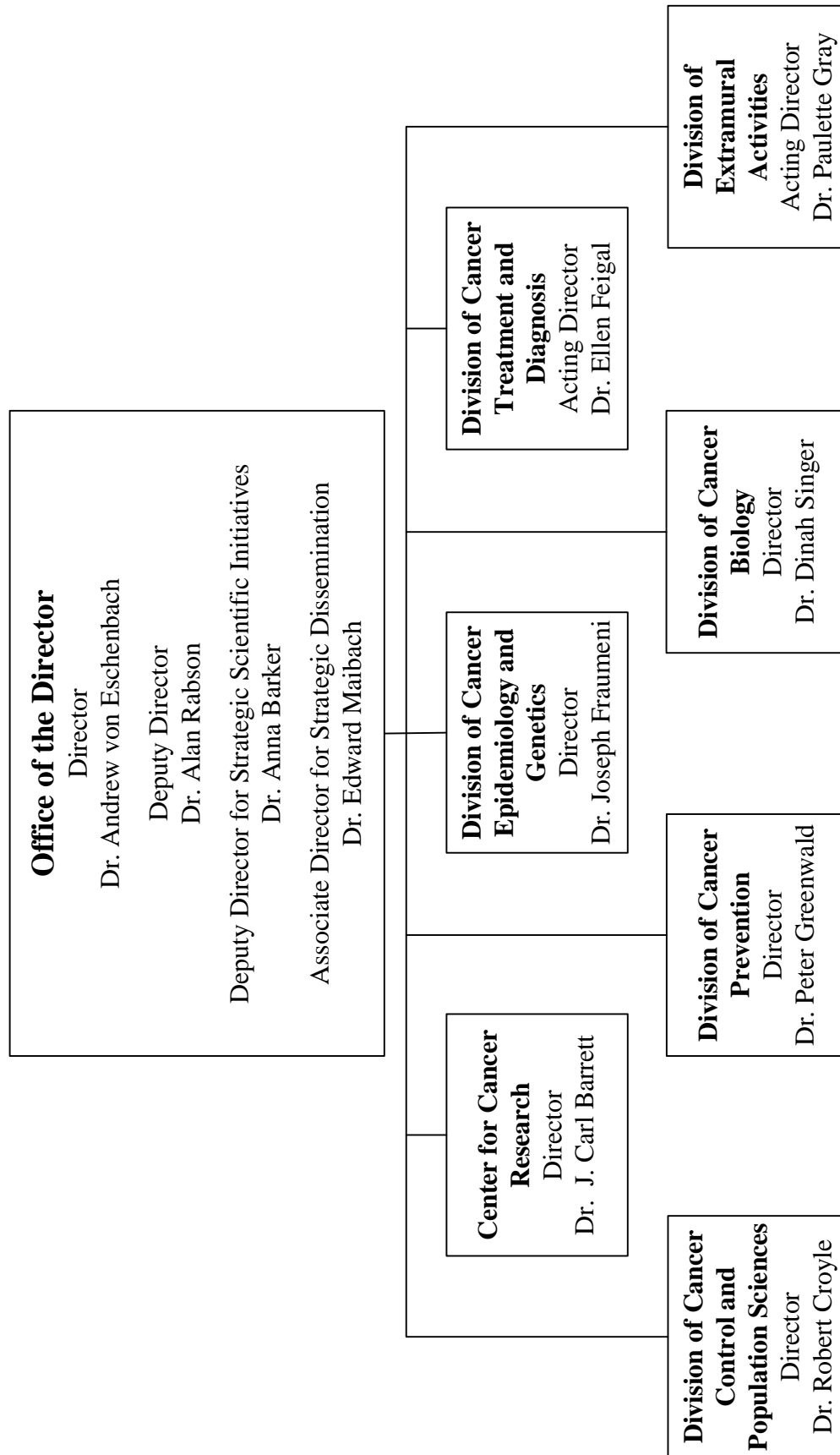
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

<u>FY 2005 Budget</u>	<u>Page No.</u>
Organization chart.....	2
Appropriation language.....	3
Amounts available for obligation .....	4
Justification narrative.....	5
Budget mechanism table.....	27
Budget authority by activity.....	28
Summary of changes.....	29
Budget authority by object.....	31
Salaries and expenses.....	32
Significant items in House, Senate and Conference Appropriation Committee Reports.....	33
Authorizing legislation.....	126
Appropriation history.....	127
Detail of full-time equivalent employment (FTE).....	128
Detail of positions.....	129

**NATIONAL INSTITUTES OF HEALTH**  
**National Cancer Institute**  
 Organization Chart



NATIONAL INSTITUTES OF HEALTH

National Cancer Institute

For carrying out Section 301 and title IV of the Public Health Service Act with respect to cancer, [\$4,770,519,000] \$4,870,025,000, of which up to \$8 million may be used for repairs and improvements at the NCI-Frederick Federally Funded Research and Development Center in Frederick, MD.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004]

*Language Analysis*

<i>..., of which up to \$8 million may be used for repairs and improvements at the NCI-Frederick Federally Funded Research and Development Center in Frederick, MD.</i>	<i>Language authorizes funds for NCI to undertake critical repairs and improvements to the buildings and facilities at the NCI-Frederick in Frederick, MD, consistent with the criteria that DHHS has established for the use of repair and improvement funds.</i>
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## Justification

### National Cancer Institute

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>
3,165	\$4,587,594,000	3,073	\$4,735,973,000	3,066	\$4,870,025,000	(7)	\$134,052,000

### INTRODUCTION

In 1971, the National Cancer Act proposed a goal to find the “cure” for cancer. Since then, scientists have developed a far greater understanding of how cancer develops and progresses within the human body. Now **we know that “cancer” is not one, but more than 100 distinct variations of disease.** We know that a cell becomes malignant as a result of changes to its genetic material and that accompanying biological characteristics of the cell also change. Advanced technology and biological research **is revealing characteristic genetic and other molecular differences among cancers that can be best targeted with tailored** preventive, diagnostic, and therapeutic interventions. **There will be no “magic bullet” to cure all cancer, but we can envision integrated strategies that will effectively prevent, eliminate, or modulate malignant disease.** We must act now to harness the recent exponential growth in knowledge of cancer as a disease process, growth that has been fueled by increasing levels of funding, scientific expertise, infrastructure, and enabling technologies. In 2001, the National Cancer Institute (NCI) issued to the nationwide cancer community a Challenge Goal: to eliminate the suffering and death due to cancer by 2015. While the ultimate goal of eliminating cancer continues to be our long-term commitment, the capacity to eliminate suffering and death will be achievable over the short-term. We must nurture our investment in infrastructure, scientific tools and technologies, and biomedical knowledge to power our ability to reach this Challenge Goal.

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

As the leader of the National Cancer Program, NCI provides vision and leadership to the nationwide community of researchers, public health workers, healthcare providers, patients, advocates, and policy makers working to defeat cancer. We strive to facilitate a seamless process for integrating discovery activities, accelerating the development of new interventions, and ensuring the delivery of new evidence-based interventions to all people in need. We must ensure that results of basic research are continuously evaluated for practical application and quickly moved into arenas of developmental research. Throughout all of our efforts in discovery and

development, we must have an eye toward the delivery of validated interventions to clinical practice and public health settings. Likewise, the impact of interventions on individual and public health can inform future research and development.

## STORY OF DISCOVERY

### ANTI-INFLAMMATORY THERAPEUTICS MAY PROVIDE SECONDARY BENEFITS FOR CANCER

Nearly 150 years ago, the German physician Rudolph Virchow first proposed a connection between inflammation and cancer. Noting that cancerous tissue also contains the cells and factors that are hallmark features of the body's inflammatory response, Virchow hypothesized that cancer begins at sites of chronic inflammation. At the time -- and for many years to follow -- the scientific community disavowed this idea because few could envision how the body's first line of defense against tissue injury and infection could also cause harm. Over the past decade, however, scientists have uncovered increasing evidence to support Virchow's claim. They have determined that the very factors recruited by the body to prevent infection and encourage healing at an injured site can misfire and produce damage. And, if the triggering bacteria, virus, or chemical irritant lingers in the body, a state of chronic inflammation can arise. Today, research indicates that chronic inflammation underpins a host of diseases, including cancer. Studies have shown that inflammatory cells promote tumor growth by producing a favorable growth environment, stimulating DNA instability and damage, enabling blood vessel development (angiogenesis), and facilitating the spread of cancer. About 15 percent of cancers throughout the world are linked to infectious agents that provoke chronic inflammation -- for example, the bacteria *Helicobacter pylori* is linked with gastric cancer and hepatitis B and C viruses with liver cancer. In addition, cancer may be associated with chronic inflammation caused by long standing exposure to chemicals such as those found in cigarettes or asbestos. But the most established and elucidated connection between chronic inflammation and cancer is with colorectal cancer, **a fact which has led to the application of anti-inflammatory drugs like aspirin as prevention agents.**

#### Drug Therapy Establishes the Link

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

#### The Search for a Common Thread

With a chemically diverse group of drugs like NSAIDs sharing the same therapeutic qualities and adverse side effects, it was assumed that they also share a common mode of action. The activity of these drugs was determined in 1971 when Dr. John Vane and his colleagues demonstrated that aspirin and all NSAIDs restrict inflammation by inhibiting the body's production of prostaglandins. Vane predicted that NSAIDs accomplish this outcome by blocking the activity of the cyclooxygenase (COX) enzyme, which catalyzes a key step in prostaglandin synthesis. Vane's Nobel Prize winning discovery paved the way for future studies confirming the role of COX enzymes in prostaglandin production, and ultimately for the development of drugs that treat inflammatory diseases by blocking the activity of the enzymes. At first, scientists knew of only one COX enzyme. In 1990, however, three research teams became interested in a protein produced by cells that were

becoming cancerous. Through further research, they found the gene responsible for producing this protein, and noted it was related to the COX enzyme. Naming the new protein COX-2, the scientists determined that it is activated only during inflammation, while the “original” COX-1 enzyme is present in cells at all times and functions to protect the lining of the stomach and intestines by stimulating mucous production.

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

### **Promising Therapies and Future Paths**

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

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

## **SCIENCES ADVANCES -- DISCOVERY, DEVELOPMENT, AND DELIVERY**

### ***Discovery***

*Drug Combination Enhances Induction of Tumor Cell Death by Apoptosis.* Researchers have been exploring the anti-cancer activity of the proteasome<sup>1</sup> inhibitor PS-341, a drug that may contribute to apoptosis<sup>2</sup> of cancerous cells. Recently, researchers devised a drug strategy combining PS-341 with a well known apoptosis inducer, tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). Researchers hypothesized that PS-341 would reduce cellular levels of the protein c-FLIP that normally inhibits the apoptotic activity of TRAIL,

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<sup>1</sup> Proteasomes are intracellular complexes responsible for breaking down proteins marked by the cell for destruction.

<sup>2</sup> Apoptosis is a type of cell death where the cell is “programmed” to “commit suicide” when it has been sufficiently damaged or is no longer needed.

allowing TRAIL to function. Investigators found that the combined action of PS-341 and TRAIL specifically destroyed lymphoma cells grown *in vitro*, while sparing normal bone marrow cells grown with the cancerous cells. To demonstrate the potential clinical value of this therapy, researchers used a mouse modeling technique that mimics autologous bone marrow transplantation, a procedure used in some cancer patients to restore their bone marrow after chemotherapy and/or radiation. In this model, researchers treated a mixture of tumor cells and normal bone marrow cells with the drug combination *in vitro*, and injected the treated cells into mice that had been irradiated to kill their own bone marrow cells. Mice receiving combination treated cells had a much higher tumor-free recovery and survival rate than mice receiving cells treated with either drug alone, presumably due to the superior ability of the combination therapy to eliminate the injected cancer cells. With further testing and validation, researchers hope these findings will lead to improved treatments for lymphomas, leukemias, multiple myeloma, and solid tumors.

*Individual Genetic Differences Influence Smoking Cessation Success.* Many smokers who attempt to quit are helped by the smoking cessation medication bupropion, while others do not seem to benefit from the drug. Scientists suspect genetic differences among individuals may be at the root of this variation. A research team composed of behavioral scientists, neuroscientists, pharmacologists, and geneticists, has generated the first empirical evidence that the *CYP2B6* gene, which is associated with nicotine metabolism in the brain, may influence the effectiveness of bupropion treatment. In this study of 426 smokers of European Caucasian ancestry<sup>3</sup>, participants received 10 weeks of either placebo or bupropion plus seven sessions of behavioral group counseling. Smokers who had variants of *CYP2B6*, which caused decreased gene activity, and therefore reduced nicotine metabolism, were less successful in quitting smoking. In women smokers, but not men, bupropion seemed to help overcome this genetic effect by decreasing withdrawal symptoms. While a great deal remains to be learned about the pharmacogenetics of smoking treatment, this study provides an important first step toward using genotype to identify smokers who are more vulnerable to relapse. Further studies could lead to novel therapeutics and tailoring of cessation treatments to individual smokers.

*Genetic Polymorphism<sup>4</sup> Provides Clues to Adult Brain Tumor Risk.* While researchers increasingly discover genetic and environmental risk factors for many types of cancers, the causes of brain tumors in adults remain poorly understood. Well established risk factors, such as high doses of radiation and certain rare genetic disorders, account for only a small number of brain tumors. In a recent study, investigators hypothesized that differences in the make-up of some genes -- those that code for proteins that help break down harmful chemicals such as solvents, pesticides, and ethanol -- may affect brain tumor risk. These researchers tested the blood of nearly 800 adult brain tumor patients, and a similar number of control patients, for polymorphisms in two such genes, *GST* and *CYP2*, that have been implicated in brain tumor risk. A number of the polymorphisms were indeed associated with the development of brain tumors. If these findings are validated in other studies of a similar scale, the next step would be to pool samples from multiple epidemiological studies and examine interactions of genotypes with

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<sup>3</sup> In this preliminary study, analyses were confined to Caucasians of European ancestry to reduce statistical bias due to racial admixture, a common statistical limitation of genetic analysis in small population studies.

<sup>4</sup> A polymorphism is a common variant or mutation in DNA, not always harmful.



specific occupational exposures. Defining the risk of brain tumor development by specific gene/environment interactions will help the cancer community to identify appropriate interventions and precautions for people at high risk.

*Pediatric Cancer Survivors Experience Long-Term Effects of Cancer and Its Treatment.* The impact of cancer and its therapy on the health status of long-term (five or more years) survivors of childhood cancer is not well understood. Investigators of the Childhood Cancer Survivor Study performed a retrospective cohort analysis to assess adult survivors of childhood cancer for general health, mental health, functional status, limitations of activity, and anxiety/fears as a result of the cancer or its treatment. Investigators found that while most adult survivors of childhood cancers in this study perceived their health as good, deficits in specific health domains were common. Poorer health was reported by females and by individuals with low income or low educational achievement. Survivors of CNS (central nervous system) tumors, bone tumors, and sarcomas reported greater functional impairment and/or limitations of activity, likely due to the aggressive nature of treatments for these diseases. Cancer-related anxieties or fears were most common in survivors of Hodgkin's disease, bone tumors, and sarcomas, possibly reflecting a greater awareness of potential adverse late effects. Research identifying attributes of cancer survivors at greatest risk for long-term health effects will help the cancer community to develop interventions to help people most in need of follow-up and care.

### ***Development***

*Molecularly Targeted Drug Shows Promise for Renal and Colorectal Cancer Treatment.* In 1999, NCI and the pharmaceutical company Genentech entered into a cooperative research and development agreement (CRADA) to test treatment of renal cell carcinoma (RCC) patients with the monoclonal antibody Avastin™ (bevacizumab). Avastin targets the protein vascular endothelial growth factor (VEGF), which is involved in the angiogenesis<sup>5</sup> that is required for renal cell tumor growth. In a Phase II study of 166 patients with advanced disease and no known treatment options, patients given standard interferon treatment plus Avastin showed no measurable tumor growth for about five months, compared to two months in patients given standard therapy plus placebo. These preliminary findings provide the basis for a larger trial to determine whether Avastin treatment can improve survival in RCC patients. NCI-supported clinical investigators and Genentech also conducted a Phase II study of patients with metastatic colorectal cancer, comparing standard frontline chemotherapy plus Avastin with standard chemotherapy alone. This trial showed improved survival (23 versus 14 months) as well as an improved response rate and lengthened time to progression. These findings have since been confirmed in a Phase III study. These studies are important first steps toward showing that recent laboratory advances in thwarting angiogenesis will work in patients. More than 20 additional clinical trials are currently underway to evaluate bevacizumab as a cancer treatment, including trials for breast, prostate, cervical, ovarian, pancreatic, and lung cancers; mesothelioma; and several types of leukemia.

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<sup>5</sup> Angiogenesis is the development and maintenance of new blood vessels.

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

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

*Researchers Develop Prognostic Factors for Survival in Pancreatic Surgery Patients.* Pancreatic cancer is a high-mortality disease with an overall 5-year survival rate for patients with adenocarcinoma, the most common form of this disease, at less than 5 percent. Only about 10 percent of adenocarcinoma patients are diagnosed while the cancer is confined to the pancreas. These patients are eligible for surgical resection, and their 5-year survival rate increases to about 20 percent. Recently, a team of investigators accessed data from NCI's Medicare-linked Surveillance, Epidemiology, and End Results (SEER) registries to examine the prognostic factors that influence survival in this group of patients. This retrospective cohort analysis of 396 adenocarcinoma surgical patients revealed that the strongest predictor of improved survival was postoperative adjuvant chemoradiation therapy. The investigators also found that a trend toward more patients being treated in teaching hospitals was leading to a gradual improvement in survival. Other predictors of improved survival included tumor size of less than 2 centimeters in diameter, absence of cancer in nearby lymph nodes, well-differentiated histology, and high

socioeconomic status. African Americans tended to have lower overall survival rates than other racial/ethnic groups. Of special note, socioeconomic status was shown to affect the likelihood of receiving adjuvant treatment, the most powerful predictor of survival. This finding warrants further investigation into a possible relationship between disparities in quality of care and survival outcomes for this disease.

## *Delivery*

*NCI-Supported Research Leads to Improved Survival in Two Childhood Cancers.* Progress made over the years has led to markedly improved survival outcomes for children with acute lymphoblastic leukemia (ALL). The number of young patients who survive 5 or more years has risen from less than 5 percent in the early 1960s to more recent rates of about 85 percent<sup>6</sup>. Prior to the present research, conventional therapy for childhood ALL included chemotherapy with mercaptopurine, accompanied by treatment with the steroid prednisone to help kill the cancer cells. Researchers have now discovered that replacing prednisone with a different steroid, dexamethasone, further improves survival. In a clinical trial of more than 1,000 standard-risk ALL patients younger than 10 years of age, 85 percent of those given dexamethasone survived at least 6 years without evidence of relapse, versus 77 percent of patients treated with prednisone. Future research must strive to continue improving survival outcomes in ALL patients.

In contrast to ALL, survival rates for children with Ewing's sarcoma has remained low despite dramatically improved patient outcomes following introduction in the 1970s of adjuvant chemotherapy regimens<sup>7</sup>. Recently, scientists tested use of the drugs isofamide and eposide, in addition to standard chemotherapy drugs, in newly diagnosed patients with Ewing's sarcoma or the closely related primitive neuroectodermal tumor of the bone. The added drugs significantly improved survival in patients with nonmetastatic disease. After 5 years, 69 percent of nonmetastatic patients who received the experimental drug regimen were disease free, compared to 54 percent of those treated with standard therapy. Overall 5-year survival was 72 percent in the experimental therapy group, compared with 61 percent in the group treated with standard therapy. Although patients receiving experimental therapy suffered more infections and spent more time in the hospital, overall toxicity levels were similar between the two groups. While further research is needed to continue improving survival rates, these findings hold promise for patients with nonmetastatic Ewing's sarcoma and primitive neuroectodermal tumor of the bone.

*Prevention Trial Shows Risk for Prostate Cancer Can be Reduced.* Prostate cancer is the most common cancer<sup>8</sup> and second leading cause of cancer death among men in the United States<sup>9</sup>. In June 2003, researchers reported findings from the Prostate Cancer Prevention Trial (PCPT) showing that prostate cancer can be prevented or delayed, at least in part, by drug intervention. The 10-year trial, involving nearly 19,000 participants nationwide, was originally scheduled to end in May 2004, but was ended a year early due to the conclusiveness of the data. Men in the

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<sup>6</sup> American Cancer Society Facts and Figures 2003.

<sup>7</sup> Holcombe, et. al. 2003. NEJM 348:694-701

<sup>8</sup> Aside from non-melanoma skin cancer.

<sup>9</sup> American Cancer Society Facts and Figures 2003

PCPT who took finasteride for 7 years were 25 percent less likely to develop prostate cancer than men taking a placebo. Most cancers were detected in early stages and were highly treatable. Sexual function side effects were more common in men taking finasteride, while urinary symptoms were found more often in men taking a placebo. Further research is needed to determine why men who developed prostate cancer while taking finasteride were more likely to have aggressive, high-grade tumors than those taking a placebo. However, these findings on prevention are a promising step in the effort to control the most common cancer among men in the United States.

*Combined Use of Pap Smear and HPV Testing May Improve Cervical Cancer Screening.*

Researchers have repeatedly shown the Pap smear, the standard for cervical cancer screening, to be effective for early detection of this disease. Although this test is limited in both sensitivity and reproducibility, due to the slow growing nature of cervical cancer the Pap smear is effective if women are screened on a regular basis. Because of the shortcomings of this test, health care providers in the United States favor annual over less frequent testing to ensure early detection. Scientists recently conducted a large clinical trial to investigate whether testing for Human Papillomavirus (HPV) infection, in addition to Pap smear testing, could safely lengthen the screening interval. Almost 21,000 women received a baseline Pap smear as well as a test for HPV and were monitored for up to 10 years. Women who were negative for both Pap smear and HPV testing at the onset of the study had a low risk of developing cervical cancer, whereas women who tested positive for either test had a much higher risk. This proof-of-principle research provides evidence that HPV testing in combination with Pap smear testing may safely permit longer screening intervals among patients who are negative for both measures. Positive results from either test would identify a small subgroup of women requiring more frequent surveillance.

*NCI Monograph Explores Socioeconomic Influences on Cancer Health Disparities.* NCI has released a monograph<sup>10</sup> that provides, for the first time, a comprehensive population-based analysis of the role of socioeconomic factors in U.S. cancer incidence, mortality, disease stage, treatment, and survival for all cancers combined and for six major cancers: lung, colorectal, breast, uterine, cervix, and melanoma of the skin. This monograph explores socioeconomic-related cancer disparities in the United States between 1975 and 1999, for the total population as well as for major racial and ethnic groups. Overall, poorer survival and smaller probabilities of both early detection and recommended treatment of cancers were associated with lower socioeconomic status (SES) for each racial/ethnic group. While socioeconomic inequalities in male lung and prostate cancer mortality have been widening, those in colorectal and breast cancer mortality narrowed over time and even appear to have reversed in the late 1990s. By identifying these and other cancer related health disparities, this monograph provides an important resource to public health researchers and policy makers who are working to reduce both the cancer burden and health disparities among various segments of the U.S. population.

*Recreational Activity Reduces Breast Cancer Risk in Postmenopausal Women.* Data from the Women's Health Initiative (WHI) Observational Study, a large prospective cohort study of

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<sup>10</sup> NCI Cancer Surveillance Monographs Series, Number 4.

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

## **WORKING TO ENSURE THAT NIH ROADMAP INITIATIVES ADVANCE NCI'S MISSION**

The NIH Roadmap focuses on new pathways to discovery, research teams of the future, and the re-engineering of the clinical research enterprise. These themes are in keeping with several major NCI initiatives and will accelerate the cancer-specific work and mission of NCI.

### ***New Pathways to Discovery***

New initiatives to more fully understand complex biological systems will complement major NCI priorities in integrative cancer biology, bioinformatics, molecular imaging, and nanotechnology applications for cancer.

### ***Integrative Cancer Biology and Bioinformatics***

As we are able to more fully understand complex biological networks, we will be able to develop and deliver novel, rationally designed ways to prevent, detect, diagnose, and treat cancer. One immediate objective, a clear interface between NCI and NIH-wide bioinformatics initiatives, is to generate *in silico*<sup>11</sup> cellular and microenvironment models. The relationships between cellular molecules, between individual cells, between cells and their microenvironment, and between the organism and its environment can all be recapitulated in these models. An understanding of the complex system of interactions between the cancer cell and its microenvironment will lead to the development of predictive and/or prognostic tools. An understanding of the environmental factors that may cause cancer -- e.g., chemical carcinogens, known viruses and bacteria, and novel infectious agents -- will lead to new cancer interventions.

### ***Molecular Imaging***

Molecular imaging resources developed through NIH initiatives will accelerate NCI's cancer-specific work in applying molecular or "functional" imaging to cancer prevention, detection, diagnosis, treatment, and monitoring. Molecular imaging of the physiological, cellular, and molecular processes in living tissue -- e.g., positron emission tomography (PET) -- increasingly allows physicians to monitor patient's progress and response to cancer therapy without the need

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<sup>13</sup> *In silico* analysis is performed using computers in conjunction with informatics capabilities.

for biopsies. Oncologic imaging guided intervention (OIGI) techniques allow precise delivery of various tumor-destroying approaches (chemicals, radiation, gene therapy, heat, and cold), which minimize trauma and damage to healthy tissue, shorten recovery times, and reduce healthcare costs. Better imaging of precancerous conditions will mean that more cancers can be diagnosed and treated before there is any evidence of anatomic change.

### *Nanomedicine*

One of the most promising and exciting areas of cancer research is the emerging field of nanoscience and nanotechnology. NCI envisions the potential for nanoscience to dramatically enhance our ability to effectively detect cancer, deliver targeted therapeutics, and monitor the effectiveness of cancer interventions. Nanoscience allows us to fashion devices small enough to enter human cells and organelles and interact with DNA, RNA, and proteins. For example, nanosensors have the capability of detecting proteins that may serve as markers for cancer early in the disease process, a step that is crucial to developing more effective treatment strategies. Nanosensors can also be "programmed" to seek out and enter cancer cells *in vivo*, enabling scientists to detect changes in the complex network of cellular components and functions. The development of *in vitro* nanoscience applications includes nanowires, nanotubes, and cantilevers used to study the molecular details of normal, precancerous, and cancerous tissue<sup>12</sup>. Eventually, nanoscience could enable the development of platforms to conduct multiple diagnostic tests and could be employed to target specific cancer cells, deliver therapeutic agents, and monitor treatment progress.

Results of recent research illustrates the promise of nanomedicine for improving cancer diagnosis. For example, a new type of nanoparticle has been found effective for diagnostic imaging of prostate cancer. Treatment options for prostate cancer patients depend in part on whether the disease has metastasized beyond the prostate gland. Men with localized disease are usually given the choice of treatment by radical prostatectomy, radiotherapy, or watchful waiting. However, the standard of care for men with lymph node metastasis is a more aggressive treatment with adjuvant androgen-deprivation therapy with radiation. The test procedure for detecting metastasis requires surgical removal of lymph nodes located near the prostate gland. No imaging technique has proven sufficiently sensitive to replace this invasive procedure. But recently, researchers tested a type of nanoparticle called lymphotropic superparamagnetic nanoparticles (LSNs) to enhance imaging of lymph nodes in prostate cancer patients. LSNs, which are small enough to enter individual cells, actively accumulate in lymph nodes in the body, and are sufficiently magnetic to be detected by magnetic resonance imaging (MRI). Animal studies have shown that MRI using LSNs can distinguish between normal and metastatic lymph nodes. Investigators recently used this technique to correctly identify lymph node metastasis in 100 percent of 33 patients known to have metastatic prostate cancer. This test also correctly classified 96 percent of patients with nonmetastatic cancer. Large prospective clinical trials are needed to determine the potential of this new procedure to routinely spare prostate cancer patients from lymph node biopsy.

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<sup>12</sup> For more information on these and other applications of nanotechnology, go to NCI's *Science Behind the News* Website, [press2.nci.nih.gov/sciencebehind/nanotech/nano00.htm](http://press2.nci.nih.gov/sciencebehind/nanotech/nano00.htm)

## ***Research Teams of the Future***

NCI's initiatives in building research teams span multiple scientific disciplines and engage partners from public, academic, and private settings.

### ***Interdisciplinary Team Science***

The interdisciplinary nature of today's cancer research requires new infrastructure that supports team science and enables the sharing of a multitude of resources. The centers, networks, and consortia, created and supported by NCI over the past 10 years, comprise a framework in which investigators can work effectively in interdisciplinary teams. NCI is now strategically expanding its centers, networks, and consortia by working with institutions in those states that have the capability to develop strong research and outreach programs. In addition, NCI is creating new Cancer Center models to serve states that do not have the institutional infrastructure to sustain a more traditional NCI Cancer Center. These innovative models will address geographic expansion, education and outreach activities, partnerships for research and delivery, and aids for underserved populations. NCI also maximizes the pace of investigator-initiated research by providing a broad range of flexible funding options and promoting collaborations and resource sharing wherever possible.

### ***Public-Private Partnerships***

NCI is increasingly looking beyond its institutional boundaries to engage in diverse partnerships with public, private, and academic sectors. NCI's partnership goals aim to eliminate bottlenecks and foster an "enabling culture" to accelerate progress against cancer, leverage funding to take advantage of expertise outside of the Institute, and build synergy within the cancer community. For examples of recent partnerships, see *Strategic Development of Cancer Interventions* below.

## ***Re-Engineering Clinical Research***

NIH initiatives for re-engineering clinical research support NCI's priority of ensuring that our clinical trials program is poised to address the most important medical and scientific questions in cancer care quickly and effectively. To streamline and integrate our cancer clinical trials programs, NCI has, for example:

- Enhanced collaborations between laboratory and clinical scientists.
- Simplified the administration of clinical trials. For example, the online Cancer Trials Support Unit (CTSU) Web site centralizes the common administrative, financial, and data collection activities of NCI's clinical trials cooperative groups.
- Expanded its role in public-private partnerships. Successful partnerships have led, e.g., to the delivery of Gleevec™ (imatinib mesylate) for treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors, Avastin™ (bevacizumab) for treatment of advanced colorectal cancer, and celecoxib to reduce the number of precancerous colon polyps in patients with familial adenomatous polyposis.

Continued efforts to re-engineer clinical research will address the full range of clinically relevant questions, produce effective screening and prevention strategies and treatment interventions,

ensure that trials are widely accessible to cancer patients and populations at risk for cancer and include a broad investigator community, and enable the delivery of new standards of care to target populations.

## **NEW AND EXPANDED NCI INITIATIVES**

### ***Centers for Integrative Cancer Biology***

The complexity of cancer together with increases in information concerning the cancer cell and its environment raises both challenges and opportunities in modern cancer biology. A comprehensive understanding of these genome-scale data sets depends on our ability to apply computational or mathematical modeling to them. To address this need, NCI plans on funding several centers in integrative cancer biology to promote the analysis of cancer as a complex biological system, with the ultimate goal of developing reliably predictive *in silico* models for development of cancer interventions.

These centers will facilitate the collaboration of scientists who bring new areas of expertise, particularly from the computational disciplines of mathematics, engineering, physics, and computer science. Researchers will work to develop models as a necessary framework for data analysis and validation. In turn, new data will help to refine model development. Multi-component, interactive processes at the sub-cellular, cellular, tissue, and organ levels should be amenable to modeling and simulation in ways previously limited by the lack of adequate data. This complex data modeling will require bioinformatics advances and the development of computer-based cancer biology hypotheses. Intra- and inter-cellular simulations will require mathematical expertise, as will the development of new theoretical frameworks. This initiative will encourage the emergence of integrative cancer biology as a distinct field. The application of new knowledge about the cancer cell and its interaction with the micro- and macroenvironments will fuel interventions that successfully prevent, detect, and treat cancer.

### ***Cancer Biomedical Informatics Grid (caBIG)***<sup>13</sup>

In cancer research today, thousands of scientists across myriad scientific disciplines are striving to understand the biology of cancer and apply their discoveries to the development of effective interventions for this complex disease. The potential power of the rich collections of data generated by these scientists can be fully realized by enabling individual investigators and research teams to combine and leverage their findings and expertise across the cancer research community. To move toward this vision, NCI and partners are developing the cancer Biomedical Informatics Grid (caBIG), an informatics platform that will integrate diverse data types and support analytic tools that can “talk” to one another. This platform will allow research groups to both tap into and contribute to the rich collection of emerging data that can support their individual investigations and allow for increased collaborations with other researchers.

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<sup>13</sup> For more information on caBIG, go to [caBIG.nci.nih.gov](http://caBIG.nci.nih.gov)



Because Cancer Centers provide the institutional framework around which much of cancer research is conducted, NCI is working with a representative sample of these Centers in the pilot phase of caBIG. CaBIG projects will be implemented initially at the funded pilot Centers and then more broadly across the Cancer Centers, Specialized Programs of Research Excellence, new NCI research initiatives, and intramural research programs. In the summer of 2003, NCI launched the initial phase of caBIG by sponsoring information seminars that engaged more than 100 participants from NCI Cancer Centers and by sending teams of scientists and information technology experts to 49 Cancer Centers to discuss their informatics strengths, needs, and potential contributions.

The caBIG pilot effort strives to:

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

### ***Optimizing Energy Balance to Reduce the Cancer Burden***

The term “energy balance” refers to the integrated effects of diet, physical activity, and genetics on growth and body weight over an individual’s lifetime. At a time when almost two-thirds of the U.S. population is considered overweight or obese, international teams of scientists have assembled compelling evidence that overweight and obesity, as well as low levels of physical activity, increase the risk of developing many cancers. A 2003 Institute of Medicine (IOM) report<sup>14</sup> on cancer prevention and control assigns top priority to the development of a national strategy to prevent obesity and sedentary behavior, second only to efforts to curtail tobacco use. However, because proven, evidence-based methods of preventing these unhealthful conditions are lacking, we must begin by learning more about energy balance through comprehensive and effective research.

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

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<sup>14</sup> *Fulfilling the Potential of Cancer Prevention and Early Detection*. National Academies Press, 2003.

## ***Strategic Development of Cancer Interventions***

At this time of rapid advances in knowledge of the molecular disease process of cancer, a fully-integrated national system is needed to ensure timely commercialization of new products that emerge from our research efforts. The potential for halting cancer has dramatically expanded in recent years through advances in genomics, proteomics, nanotechnology, molecular imaging, molecularly targeted therapy, radiation oncology, and other areas. However, only one to two new cancer drugs are approved each year and unfavorable market risk factors are limiting the development of important diagnostic tools. By looking beyond its institutional boundaries to the public, private, and academic sectors, NCI is uniquely positioned to accelerate the strategic development of cancer interventions.

NCI has recently engaged in a number of novel partnerships to expand collaborative research, leverage funding, promote technology transfer, and eliminate regulatory barriers. For example:

- Through an interagency agreement, NCI and the Food and Drug Administration (FDA) recently collaborated to share knowledge and resources to establish an improved regulatory process that facilitates the development of new cancer drugs and speeds their delivery to patients.
- NCI, FDA, and the bioinformatics company Correlogic Systems Inc. are collaborating to advance clinical proteomics studies to better understand protein structure and protein pattern changes involved in cancer development and progression and apply this knowledge to early detection, diagnosis, prognosis, treatment, toxicity monitoring, and follow-up surveillance. The partners are currently conducting clinical trials to test approaches for early detection of ovarian and prostate cancers based on protein pattern analysis of individual blood samples.
- The Academic Public Private Partnership Program (AP4) is supporting the discovery of new cancer agents and their rapid translation to human clinical trials. Through this program, NCI fosters collaborations among universities, pharmaceutical companies, biotech companies, and nonprofit organizations.

## ***Reducing Cancer-Related Health Disparities***

Overcoming health disparities is one of NCI's top priorities for reaching our Challenge Goal of eliminating suffering and death due to cancer. We know that complex interactions among genetic susceptibilities and the risks imparted by individual and group behaviors, age, and social and environmental circumstances determine health throughout an individual's life span. For example, African Americans and Alaskan Natives experience a higher incidence of colorectal, lung, and bronchus cancers than any other ethnic group. Statistics show that low socioeconomic status predisposes higher cancer death rates than higher socioeconomic status. In light of this and other evidence, the scientific community has a critical and unique role in addressing the moral and ethical dilemmas posed by the unequal burden of cancer in our society.

This an especially opportune time for NCI to commit additional resources to address cancer health disparities, in light of new technologies such as telemedicine<sup>15</sup>, which can bring screening

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<sup>15</sup> Telemedicine is the delivery of health services through remote telecommunications.

and diagnostic services to people where they live, and scientific advances in cancer prevention, treatment, and communications targeted to specific communities. New and expanded NCI efforts include the Centers for Population Health and Health Disparities (CPHHD) and the Minority-Based Community Clinical Oncology Program (CCOP):

- NCI, along with the National Institute of Environmental Health Sciences and the National Institute on Aging, recently provided support to establish CPHHDs. Interdisciplinary in focus, these centers provide environments conducive to collaborations among biomedical, social science, and environmental investigators working with communities serving low-income and racially diverse populations. The Centers will accelerate knowledge about factors that contribute to health disparities and the development of effective interventions to reduce them.
- Initiated in 1990, the Minority-Based CCOP provides minority cancer patients with access to state-of-the-art cancer treatment, prevention, and control technology in their own communities. The program has expanded to include 11 minority-based CCOPs grantees, more than 40 hospitals, and over 100 minority investigators.

### ***Building Capacity through Cohort Consortia***

Through cohort consortia, NCI is bringing together researchers across the United States and Europe who are studying the same disease site, to collaborate and pool exposure data and biospecimens. This type of data pooling is essential to conducting large cohort studies that employ advanced pattern-detecting genomic technologies. This research is needed to identify inherited susceptibility genes and gene-environment interactions in non-familial cancers. The cohort consortia approach accelerates the research process and allows scientists to perform subset analyses and confirmatory studies to examine gene-environment and gene-gene interactions. The unique epidemiologic infrastructure also provides an opportunity to partner with other NIH Institutes to investigate a series of complex diseases including diabetes, cardiovascular, and neurological diseases.

Cohort consortia represent a unique public-private partnership that currently includes 23 population cohorts. The Cohort Consortium for Breast and Prostate Cancer pioneered the approach and developed the Hormone-Related Gene Variants program to identify genes that may influence a person's susceptibility to hormone-related breast or prostate cancer and to develop methods of data sharing across genome and genotyping centers, removing a major obstacle to consortium research. This consortium is truly an interdisciplinary, coordinated research effort that includes formal collaborations with three major genome centers: the Whitehead/MIT Center for Genome Research, the Centre d'Etude du Polymorphisme Humain (CEPH) in Paris, and the NCI Core Genotyping Facility.

Other consortia supported by NCI include the InterLymph Consortium, developing a case-control study of the genetic and environmental basis of non-Hodgkin's lymphoma; the Health Maintenance Organization Cancer Research Network, developing the largest ever case-control study of pancreatic cancer; and a case-control consortium focusing on brain tumors. In addition, NCI is examining the feasibility of a cohort study in India to focus on nutrition and gene-diet interactions in cancer causation.

## *Exploring the Interface of Aging and Cancer*

The risk of developing cancer significantly increases with age and, as the population of older Americans expands in the next decade, unless preemptive measures are taken, the cancer burden will escalate. Close to 61 percent of all new cancers and 70 percent of deaths from cancer are in people older than 65<sup>16</sup>. We also know that current healthcare practices frequently fall short of providing the best available care for aging patients. And as cancer prevention and treatment strategies improve, the numbers of aging cancer survivors will also grow. This group will experience a greater risk of developing other health problems, disabling conditions, and recurrent cancers. NCI and the National Institute on Aging (NIA) have partnered to further invigorate the research community's focus on the intersection of aging and cancer. New initiatives will support seven areas of emphasis that emerged from the 2001 NCI/NIA Cancer Centers Workshop on Integrating Aging and Cancer Research, including:

- *Biology of Aging and Cancer.* Investigators will broaden understanding of genetics, molecular signatures, and age-related changes that contribute to mortality and vulnerability versus resilience in older patients.
- *Patterns of Care.* Studies will examine current cancer care practices and identify where changes are needed to improve the quality of care for older patients.
- *Treatment Efficacy and Tolerance.* Researchers will investigate radiation therapy, surgery, and standard technology; the pharmacology of anti-cancer drugs; limitations on admitting older patients to clinical trials; age-related treatment outcomes; and methods to prevent or offset unfavorable outcomes in older persons.
- *Effects of Comorbidity.* New studies will address the effective management of older cancer patients with pre-existing chronic conditions and concurrent diseases, including secondary cancers.
- *Prevention, Risk Assessment, and Screening.* Investigators will increase efforts to identify the impediments that prevent older people from receiving preventive, assessment, and screening services.
- *Psychosocial Issues and Medical Effects.* Investigators will examine treatment, quality cancer care, tumor recurrence, and multiple primary tumors in older patients.
- *Symptom Management and Palliative Care.* Research will include development of evidence-based interventions and guidelines that will support patients with cancer as well as families and caregivers.

NCI has also teamed with the National Institute of Aging and the National Library of Medicine (NLM)- to launch a Web site specifically aimed at providing to seniors a range of health information that is easy to understand and navigate (NIHSeniorHealth.gov). Through these initiatives the expertise and unique perspectives of scientists focused on the interface of aging and cancer will be applied to improve the quality of cancer care for older Americans.

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<sup>18</sup>Yancik R and Ries LA. *Hematol Oncol Clin North Am.* 14:17–23, 2000.

## **OTHER AREAS OF INTEREST**

### ***Addressing Obstacles to the Development of New Pediatric Cancer Treatments***

While effective treatment regimens for young cancer patients have brought about an impressive 47 percent decline in mortality rates since 1975<sup>17</sup>, more research is needed to further improve survival and to eliminate the long-term adverse effects of cancer treatments in the ever-growing population of childhood survivors. However, researchers face distinct obstacles to the development of newer treatments for cancer in children. Even cancers that are common in children are rare compared to most adult malignancies. Accumulating enough cases to test a new treatment requires collaboration among multiple research organizations. Drug development costs for developing agents that specifically target pediatric tumors can be prohibitive for the pharmaceutical industry given the relative rarity of childhood cancers. Twenty-first century anti-neoplastic drug development often focuses on agents that target specific molecular pathways in adult cancer cells. These same molecular pathways may also promote the growth and survival of childhood cancers. However, the drugs targeting these pathways need to be tested in the laboratory against pediatric cancer models to identify those drugs that might be effective for treating childhood cancers.

NCI is addressing these obstacles through a research strategy focused on the development of new treatments for pediatric cancers spanning the spectrum from preclinical drug discovery through Phase III studies aimed at obtaining FDA approval. For example:

- The newly established Pediatric Preclinical Testing Program aims to screen 10 to 15 new agents, or combinations of agents, annually against preclinical models for common pediatric tumors (e.g., mouse models).
- NCI's Pediatric Oncology Preclinical Protein-Tissue Array Project (POPP-TAP) and the Children's Oncology Group Phase I Consortium are characterizing the molecular features (RNA and protein expression) of pediatric tumors in children and in corresponding preclinical models.
- NCI -funded Cooperative Groups have successfully brought together pediatric oncologists worldwide to enroll children with cancer into clinical trials to effectively assess the safety and efficacy of experimental treatments.

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

### ***Improving Quality of Life for Cancer Patients and Their Caregivers***

Symptoms of cancer and side effects of related treatments can be severe in patients with advanced-stage disease, especially in those receiving aggressive and experimental therapies. Research has shown that symptoms affect patient's overall quality of life, including their ability

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<sup>17</sup> American Cancer Society Facts and Figures 2003

to do many of the things most people take for granted such as caring for themselves, doing household chores, sleeping, or going to work. Basic and clinical researchers are currently identifying symptoms according to tumor type and treatment choice, as well as methods for assessing symptoms. NCI is working to integrate symptom management and palliative care into the full spectrum of cancer quality improvement research and translation efforts, from initial treatment, through survivorship, and at the end of life. We are improving communication between patients and their healthcare teams and working with partners to research new interventions for symptoms and side effects such as lymphedema<sup>18</sup>, cachexia<sup>19</sup>, pain, and sleep disorders. In addition, basic and clinical researchers are currently:

- Determining which symptoms occur most frequently according to tumor type and treatment choice.
- Developing new methods for assessing symptoms.
- Developing and comparing strategies of symptom management.

Caregivers are a vital resource to the patient and are often responsible for accessing information, communicating with the patient's health care team, and providing hands-on care to alleviate symptoms. They are more likely to feel a greater sense of burden in their role when the patient has severe pain or fatigue. NCI is developing resources to better prepare caregivers to manage patients at home and ultimately improve caregivers' emotional and physical health as they continue to help their family members live with cancer.

### ***Advancing Radiation Oncology for Cancer Care***

Radiation oncologists are providing care for increasing numbers of cancer patients at some point during the course of their disease. Radiation is used in conjunction with image-guided, immune, traditional chemo-, and molecularly targeted therapies, as well as surgery. More patients are receiving specialized radiation therapies that kill tumor tissue while sparing healthy tissue. For example:

- Image-guided 3D-conformal therapy and intensity modulated radiation therapy deliver higher doses of radiation to the tissue while exposing normal tissue to reduced amounts.
- Brachytherapy, commonly used to treat prostate cancer, permits radiation sources to be placed within certain tumors.
- Proton particle beam therapy allows more precise administration of radiation to cancerous tissues.
- Radioimmunotherapy uses radioactive monoclonal antibodies to attack cancer cells throughout the body.

NCI's radiation oncology research embraces the goal of ensuring that highly effective cancer interventions are accessible to all who need them. NCI's intramural researchers collaborate with universities and industry to conduct multidisciplinary research aimed at understanding molecular processes affected by radiation, improve tumor control, and lessen injury of normal tissue.

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<sup>20</sup>Lymphedema is a condition in which excess fluid collects in tissue and causes swelling.

<sup>21</sup>Cachexia is the loss of body weight and muscle mass frequently seen in patients with cancer, AIDS, or other diseases.

Research in normal tissue radiation toxicity will also help the Nation to prevent and/or treat possible injury from radiological or nuclear terrorism.

Beyond development of radiation interventions, NCI has been a leader in radiation oncology quality assurance, pioneering the Patterns of Care studies over three decades ago to investigate adoption of recommended treatments for the most common cancers. NCI is now implementing shared quality assurance programs that will improve the technological sophistication of radiation oncology worldwide and create data sharing abilities via telemedicine. This improvement in technological resources is the backbone of the new cancer disparities research partnership program<sup>20</sup>, designed to enable research at institutions that serve primarily low-income, underserved, and ethnic and minority populations.

## **INNOVATIONS IN MANAGEMENT AND ADMINISTRATION**

### ***Diversity Grand Rounds***

The Office of Diversity and Employment Programs completed its first Diversity Grand Rounds Seminar Series November 13, 2003. Diversity Grand Rounds (DGR) is designed to provide the NCI community with tangible tools, resources, and information to manage and work productively in an increasingly diverse workforce. Also, the DGR series provides managers and supervisors a convenient way to fulfill their workforce diversity performance standards. The four seminars in the 2003 DGR series featured a variety of diversity topics including: the value of harnessing differences for more productive outcomes, the impact of unintentional intolerance and its ramifications in the workplace, understanding the compelling business case for diversity, and learning to manage the intergenerational dynamics in the workplace.

### ***NCI Management Information Systems Support Science and Resource Management***

In 2003, NCI's Office of Information Systems and Computer Services delivered to the NCI community innovative applications for science and resource management. For example:

- The Division of Cancer Epidemiology and Genetics Portfolio Management System is used to analyze costs of scientific studies and provide more efficient and accurate reporting to both NIH and NCI.
- The Grants Administration Branch Specialist Assignment System is used to manage grants processing workflow and balance workload among grants specialists.
- The Program Workbench (Workbench, Your Grants, Notifications) has integrated searching and presentation of grants data to program staff and notifies staff of the availability of new material.
- The Office of Space and Facilities Management Express Services System provides workflow and tracking system for small "handyman" projects.

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<sup>20</sup> Supported through the Cooperative Planning Grant for Cancer Disparities Research.

### ***Electronic Control Grants Checklists***

The Grants Administration Branch developed a comprehensive set of electronic documentation control checklists to be launched in FY 2004. These checklists will serve as a guide for NCI staff responsible for reviewing, in a uniform manner, a complex portfolio of grants that encompasses over 50 different funding mechanisms and 12,000 grant actions. The checklists, when accurately completed by appropriate NCI staff, will reasonably assure that these research grants and cooperative agreements are awarded in a timely and accurate manner consistent with existing policies and procedures. Having a set of standard checklists will help to ensure that our grantees are treated consistently and are being held to the standards appropriate for the type of award/funding mechanism being reviewed. It is important to note that the current set of questions contained in these checklists directs and focuses the review on the most important items of the grant file. At stake potentially are issues involving the safety of humans and/or animals that may be part of the research as well as the most effective use of considerable amounts of taxpayer dollars. Among the benefits of the electronic checklists are that they are expected to increase efficiency, improve customer service, avoid costs, facilitate workflow and foster collaborative work performance.

### ***Managing for Results in NCI's Business and Administrative Units***

In FY 2003, NCI's Office of Innovation and Evaluation continued efforts to fully implement and refine the strategic planning model it developed to assure that the business units in the NCI Office of Management are providing the products and services NCI scientists need to achieve the NCI mission. The strategic plans for the business units include goals for those President's Management Agenda initiatives that can be addressed at the Institute level. The NCI Office of Management components met--or substantively met--approximately 91 percent of the established Office of Management 2003 targets. Enhancements made in 2003 include linking business unit managers' performance contracts to unit business plans, synchronizing the schedules for developing business unit plans and managers' performance plans and for reporting progress against those plans, and formalizing the process for approval of business plans as they are revised and updated each year.

### ***NCI Property Management***

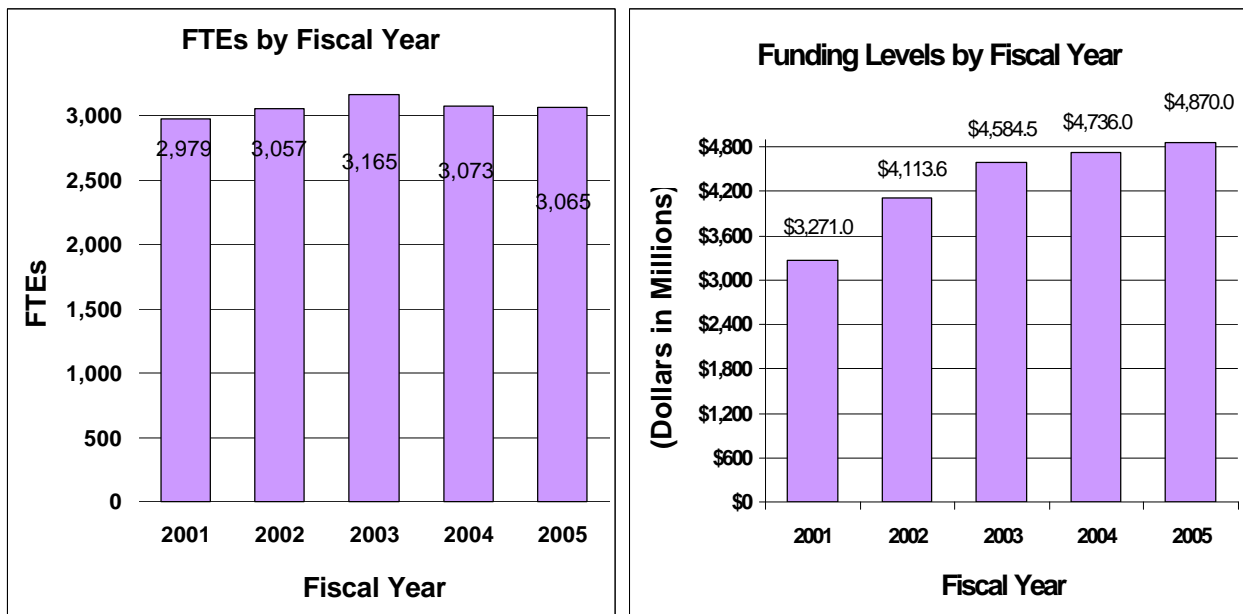
In 2003, the NCI Office of Space and Facilities Management significantly improved the quality of NCI property stewardship and inventory accountability. It established new procedures for handling NCI excess equipment from initial request by user to final acceptance by NIH Property; developed and implemented an NCI surplus request Web page; dedicated staff for removal of excess equipment prior to renovations and moves; and initiated quarterly inventory update reports and worked with property subcustodians to quickly identify problems related to property.



## Budget Policy

The Fiscal Year 2005 budget request for the NCI is \$4,870,025,000, an increase of \$134,052,000 and 2.8 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NCI's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NCI are shown in the graphs below. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.

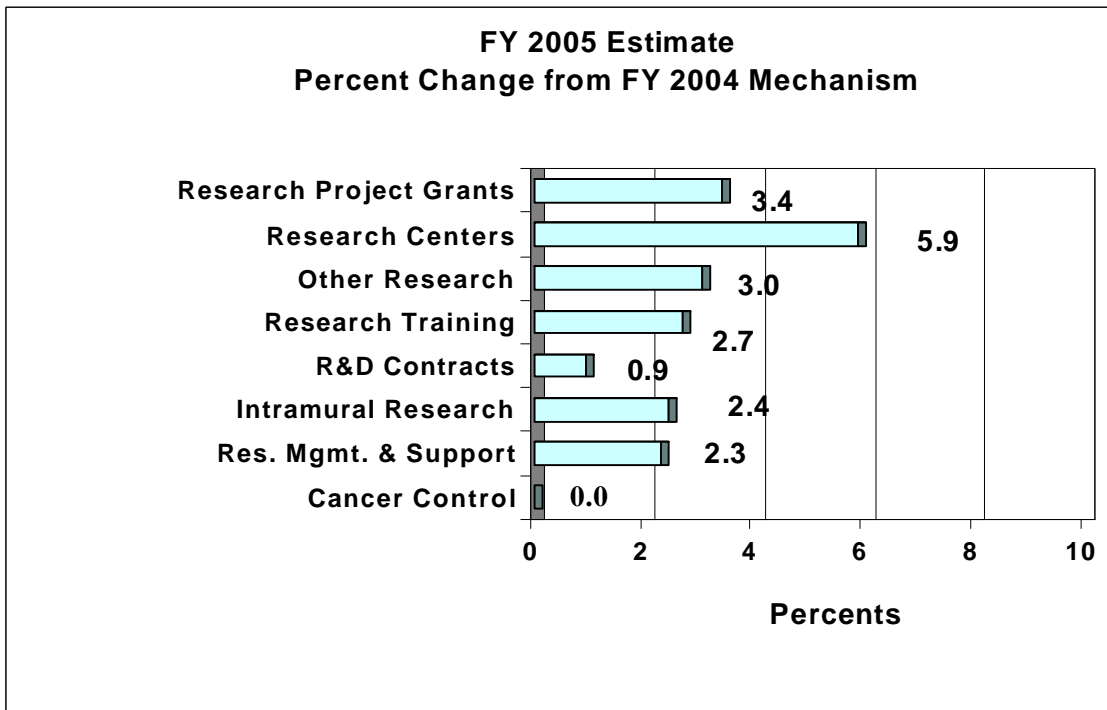
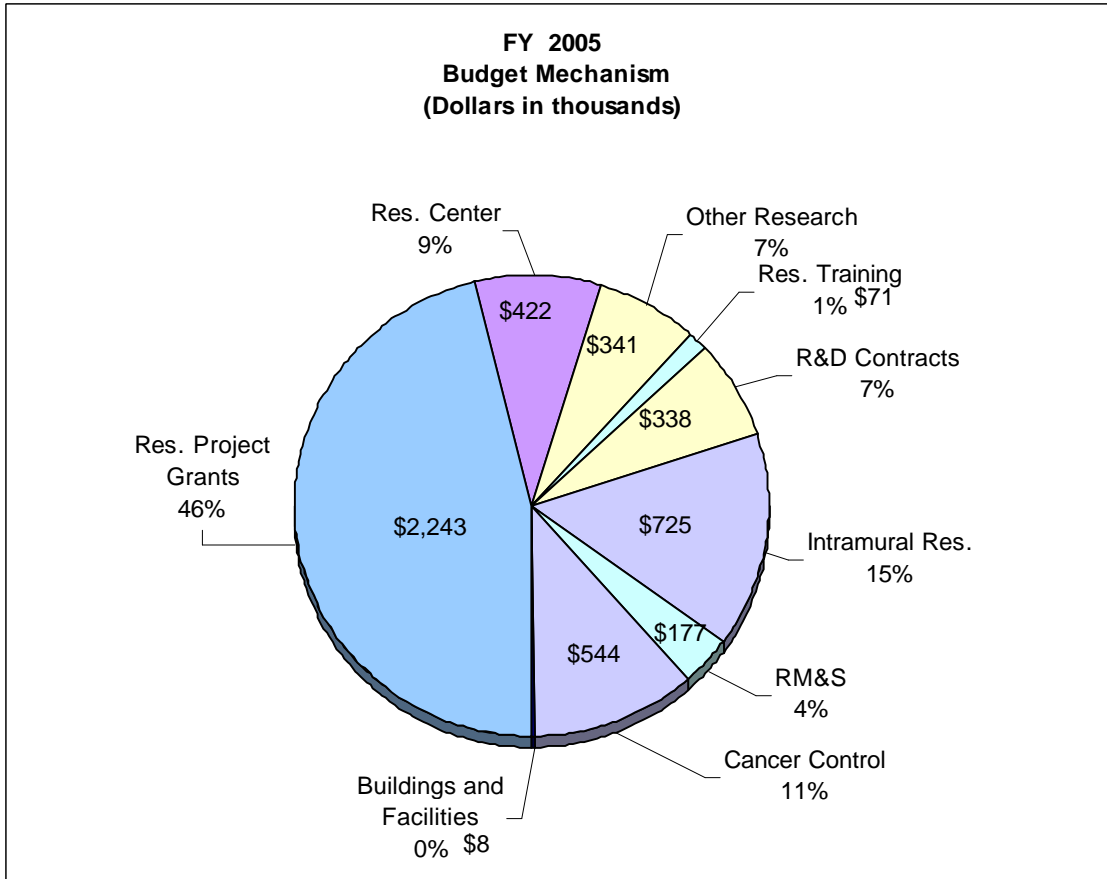


NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. The NIH is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NCI will support 1,583 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 140 research centers, 880 other research grants, including 526 clinical career awards, and 277 R&D contracts. Intramural Research and

Research Management and Support receive increases to support increased pay and estimated inflationary increases in FY 2005. This budget request includes funding of \$672,000 for a portion of the NIH obesity clinical research initiative. The mechanism distribution by dollars and percent change are displayed below:



**NATIONAL INSTITUTES OF HEALTH**  
National Cancer Institute

Budget Mechanism

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
	No.	Amount	No.	Amount	No.	Amount
<b>Research Grants:</b>						
<u>Research Projects:</u>						
Noncompeting	3,358	\$1,415,844,000	3,558	\$1,529,579,000	3,767	\$1,591,604,000
Administrative supplements	(285)	60,180,000	(296)	61,729,000	(298)	64,392,000
Competing:						
Full funded	20	2,825,000	24	3,724,000	24	3,761,000
Single year	1401	492,157,000	1421	472,351,000	1433	479,174,000
Renewal	395	173,411,000	361	174,148,000	361	174,148,000
New	1,001	317,409,000	1,054	295,128,000	1,066	301,951,000
Supplements	5	1,337,000	6	3,075,000	6	3,075,000
Subtotal, competing	1,421	494,982,000	1,445	476,075,000	1,457	482,935,000
Subtotal, RPGs	4,779	1,971,006,000	5,003	2,067,383,000	5,224	2,138,931,000
SBIR/STTR	356	90,857,000	398	101,210,000	409	103,773,000
Subtotal, RPGs	5,135	2,061,863,000	5,401	2,168,593,000	5,633	2,242,704,000
<u>Research Centers:</u>						
Specialized/comprehensive	122	378,079,000	129	396,500,000	133	418,915,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	0	5	2,034,000	7	3,090,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	122	378,079,000	134	398,534,000	140	422,005,000
<u>Other Research:</u>						
Research careers	486	71,845,000	499	74,238,000	526	76,812,000
Cancer education	102	30,041,000	104	31,206,000	106	32,006,000
Cooperative clinical research	78	158,714,000	80	162,330,000	80	167,330,000
Biomedical research support	0	3,842,000	0	4,016,000	0	4,037,000
Minority biomedical research support	0	3,853,000	0	3,853,000	0	3,853,000
Other	189	52,071,000	197	55,017,000	197	56,692,000
Subtotal, Other Research	855	320,366,000	880	330,660,000	909	340,730,000
<b>Total Research Grants</b>	<b>6,112</b>	<b>2,760,308,000</b>	<b>6,415</b>	<b>2,897,787,000</b>	<b>6,682</b>	<b>3,005,439,000</b>
<u>Research Training:</u>	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Individual awards	146	5,960,000	146	6,198,000	146	6,198,000
Institutional awards	1,374	59,890,000	1,403	62,789,000	1,437	64,662,000
Total, Training	1,520	65,850,000	1,549	68,987,000	1,583	70,860,000
Research & development contracts (SBIR/STTR)	291 (24)	364,962,000 (2,582,000)	277 (25)	335,097,000 (2,617,000)	277 (25)	338,268,000 (2,617,000)
Intramural research	<u>FTEs</u> 1,983	687,683,000	<u>FTEs</u> 1,952	708,011,000	<u>FTEs</u> 1,952	725,344,000
Research management and support	713	166,721,000	683	173,201,000	676	177,224,000
Cancer prevention & control	469	531,270,000	438	544,890,000	438	544,890,000
Construction		3,000,000		0		0
Buildings and Facilities		7,800,000		8,000,000		8,000,000
Total, NCI	3,165	4,587,594,000	3,073	4,735,973,000	3,066	4,870,025,000
(RoadMap Support)		(0)		(16,273,000)		(30,685,000)
(Clinical Trials)		(799,530,000)		(831,512,000)		(856,465,000)

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Budget Authority by Activity  
(dollars in thousands)**

ACTIVITY	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
<u>Research:</u>								
Cancer causation	968	\$1,190,653	950	\$1,220,205	948	\$1,248,343	(2)	\$28,138
Detection and diagnosis research	198	296,485	185	306,515	184	316,371	(1)	9,856
Treatment research	963	1,213,544	950	1,257,130	949	1,296,165	(1)	39,035
Cancer biology	495	769,356	481	798,311	480	822,350	(1)	24,039
Subtotal, Research	2,624	3,470,038	2,566	3,582,161	2,561	3,683,229	(5)	101,068
<u>Resource Development:</u>								
Cancer centers support	20	380,929	20	400,612	20	425,149	0	24,537
Research manpower development	40	174,880	37	179,209	37	187,038	0	7,829
Construction	2	11,615	2	8,880	2	8,931	0	51
Subtotal, Resource Development	62	567,424	59	588,701	59	621,118	0	32,417
Cancer prevention and control	479	550,132	448	565,111	446	565,678	(2)	567
<b>Total</b>	<b>3,165</b>	<b>4,587,594</b>	<b>3,073</b>	<b>4,735,973</b>	<b>3,066</b>	<b>4,870,025</b>	<b>(7)</b>	<b>134,052</b>

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Summary of Changes**

FY 2004 Final Conference		\$4,735,973,000	
FY 2005 Estimated Budget Authority		4,870,025,000	
Net change		134,052,000	
CHANGES	FY 2004 Budget Base		Change from Base
	FTEs	Budget Authority	FTEs Budget Authority
A. Built-in:			
1. Intramural research:			
a. Within grade increase		\$242,700,000	\$3,110,000
b. Annualization of January 2004 pay increase		242,700,000	2,478,000
c. January 2005 pay increase		242,700,000	2,720,000
d. One less day of pay		242,700,000	(938,000)
e. Payment for centrally furnished services		110,309,000	3,309,000
f. Increased cost of laboratory supplies, materials, and other expenses		355,002,000	5,151,000
Subtotal			15,830,000
2. Research Management and Support:			
a. Within grade increase		71,000,000	1,134,000
b. Annualization of January 2004 pay increase		71,000,000	725,000
c. January 2005 pay increase		71,000,000	796,000
d. One less day of pay		71,000,000	(275,000)
e. Payment for centrally furnished services		15,357,000	461,000
f. Increased cost of laboratory supplies, materials, and other expenses		86,844,000	1,260,000
Subtotal			4,101,000
2. Cancer Prevention and Control:			
a. Within grade increase		53,450,000	788,000
b. Annualization of January 2004 pay increase		53,450,000	546,000
c. January 2005 pay increase		53,450,000	599,000
d. One less day of pay		53,450,000	(207,000)
e. Payment for centrally furnished services		3,250,000	98,000
f. Increased cost of laboratory supplies, materials, and other expenses		97,655,000	1,417,000
Subtotal			3,241,000
Subtotal, Built-in			23,172,000

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Summary of Changes--continued**

CHANGES	FY 2004			
	Budget Base		Change from Base	
	No.	Amount	No.	Amount
<b>B. Program:</b>				
1. Research project grants:				
a. Noncompeting	3,558	\$1,591,308,000	209	\$64,688,000
b. Competing	1,445	476,075,000	12	6,860,000
c. SBIR/STTR	398	101,210,000	11	2,563,000
Total	5,401	2,168,593,000	232	74,111,000
2. Research centers	134	398,534,000	6	23,471,000
3. Other research	880	330,660,000	29	10,070,000
4. Research training	1,549	68,987,000	34	1,873,000
5. Research and development contracts	277	335,097,000	0	3,171,000
Subtotal, extramural				112,696,000
6. Intramural research	1,952	708,011,000	<u>FTEs</u> 0	1,503,000
7. Research management and support	683	173,201,000	(7)	(78,000)
8. Cancer prevention and control	438	544,890,000	0	(3,241,000)
9. Construction		0		0
10. Buildings and Facilities		8,000,000		0
Subtotal, program	3,073	4,735,973,000	(7)	110,880,000
Total changes			(7)	134,052,000

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Budget Authority by Object**

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease	Percent Change
<b>Total compensable workyears:</b>				
Full-time employment	3,073	3,066	(7)	-0.2
Full-time equivalent of overtime & holiday hours	10	10	0	0.0
Average ES salary	\$147,697	\$150,873	\$3,176	2.2
Average GM/GS grade	11.5	11.5	0.0	0.0
Average GM/GS salary	\$73,070	\$74,641	\$1,571	2.1
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	\$76,441	\$78,085	\$1,644	2.2
Average salary of ungraded positions	\$99,185	\$101,317	\$2,132	2.1
<b>OBJECT CLASSES</b>	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease	Percent Change
Personnel Compensation:				
11.1 Full-Time Permanent	\$153,724,000	\$158,598,000	\$4,874,000	3.2
11.3 Other than Full-Time Permanent	84,906,000	87,520,000	2,614,000	3.1
11.5 Other Personnel Compensation	7,765,000	8,010,000	245,000	3.2
11.7 Military Personnel	7,450,000	7,682,000	232,000	3.1
11.8 Special Personnel Services Payments	44,164,000	45,513,000	1,349,000	3.1
<b>Total, Personnel Compensation</b>	<b>298,009,000</b>	<b>307,323,000</b>	<b>9,314,000</b>	<b>3.1</b>
12.1 Civilian Personnel Benefits	63,811,000	65,808,000	1,997,000	3.1
12.2 Military Personnel Benefits	5,330,000	5,495,000	165,000	3.1
13.0 Benefits for Former Personnel	0	0	0	0.0
<b>Subtotal, Pay Costs</b>	<b>367,150,000</b>	<b>378,626,000</b>	<b>11,476,000</b>	<b>3.1</b>
21.0 Travel & Transportation of Persons	14,401,000	14,708,000	307,000	2.1
22.0 Transportation of Things	1,644,000	1,677,000	33,000	2.0
23.1 Rental Payments to GSA	3,000	3,000	0	0.0
23.2 Rental Payments to Others	2,253,000	2,300,000	47,000	2.1
23.3 Communications, Utilities & Miscellaneous Charges	7,790,000	7,983,000	193,000	2.5
24.0 Printing & Reproduction	4,051,000	4,137,000	86,000	2.1
25.1 Consulting Services	18,312,000	18,569,000	257,000	1.4
25.2 Other Services	190,322,000	194,055,000	3,733,000	2.0
25.3 Purchase of Goods & Services from Government Accounts	441,699,000	443,288,000	1,589,000	0.4
25.4 Operation & Maintenance of Facilities	126,620,000	124,280,000	(2,340,000)	-1.8
25.5 Research & Development Contracts	326,561,000	336,900,000	10,339,000	3.2
25.6 Medical Care	3,299,000	3,363,000	64,000	1.9
25.7 Operation & Maintenance of Equipment	14,701,000	14,969,000	268,000	1.8
25.8 Subsistence & Support of Persons	0	0	0	0.0
<b>25.0 Subtotal, Other Contractual Services</b>	<b>1,121,514,000</b>	<b>1,135,424,000</b>	<b>13,910,000</b>	<b>1.2</b>
26.0 Supplies & Materials	53,271,000	54,349,000	1,078,000	2.0
31.0 Equipment	31,366,000	32,004,000	638,000	2.0
32.0 Land and Structures	0	0	0	0.0
33.0 Investments & Loans	0	0	0	0.0
41.0 Grants, Subsidies & Contributions	3,132,521,000	3,238,805,000	106,284,000	3.4
42.0 Insurance Claims & Indemnities	0	0	0	0.0
43.0 Interest & Dividends	9,000	9,000	0	0.0
44.0 Refunds	0	0	0	0.0
<b>Subtotal, Non-Pay Costs</b>	<b>4,368,823,000</b>	<b>4,491,399,000</b>	<b>122,576,000</b>	<b>2.8</b>
<b>Total Budget Authority by Object</b>	<b>4,735,973,000</b>	<b>4,870,025,000</b>	<b>134,052,000</b>	<b>2.8</b>

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Salaries and Expenses**

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease	Percent Change
<b>Personnel Compensation:</b>				
Full-Time Permanent (11.1)	\$153,724,000	\$158,598,000	\$4,874,000	3.2
Other Than Full-Time Permanent (11.3)	84,906,000	87,520,000	2,614,000	3.1
Other Personnel Compensation (11.5)	7,765,000	8,010,000	245,000	3.2
Military Personnel (11.7)	7,450,000	7,682,000	232,000	3.1
Special Personnel Services Payments (11.8)	44,164,000	45,513,000	1,349,000	3.1
<b>Total Personnel Compensation (11.9)</b>	<b>298,009,000</b>	<b>307,323,000</b>	<b>9,314,000</b>	<b>3.1</b>
Civilian Personnel Benefits (12.1)	63,811,000	65,808,000	1,997,000	3.1
Military Personnel Benefits (12.2)	5,330,000	5,495,000	165,000	3.1
Benefits to Former Personnel (13.0)	0	0	0	0.0
<b>Subtotal, Pay Costs</b>	<b>367,150,000</b>	<b>378,626,000</b>	<b>11,476,000</b>	<b>3.1</b>
Travel (21.0)	14,401,000	14,708,000	307,000	2.1
Transportation of Things (22.0)	1,644,000	1,677,000	33,000	2.0
Rental Payments to Others (23.2)	2,253,000	2,300,000	47,000	2.1
Communications, Utilities and Miscellaneous Charges (23.3)	7,790,000	7,983,000	193,000	2.5
Printing and Reproduction (24.0)	4,051,000	4,137,000	86,000	2.1
<b>Other Contractual Services:</b>				
Advisory and Assistance Services (25.1)	17,098,000	17,388,000	290,000	1.7
Other Services (25.2)	190,322,000	194,055,000	3,733,000	2.0
Purchases from Govt. Accounts (25.3)	109,022,000	108,608,000	(414,000)	-0.4
Operation & Maintenance of Facilities (25.4)	22,289,000	22,766,000	477,000	2.1
Operation & Maintenance of Equipment (25.7)	14,701,000	14,969,000	268,000	1.8
Subsistence & Support of Persons (25.8)	0	0	0	0.0
<b>Subtotal Other Contractual Services</b>	<b>353,432,000</b>	<b>357,786,000</b>	<b>4,354,000</b>	<b>1.2</b>
Supplies and Materials (26.0)	51,639,000	52,693,000	1,054,000	2.0
<b>Subtotal, Non-Pay Costs</b>	<b>435,210,000</b>	<b>441,284,000</b>	<b>6,074,000</b>	<b>1.4</b>
<b>Total, Administrative Costs</b>	<b>802,360,000</b>	<b>819,910,000</b>	<b>17,550,000</b>	<b>2.2</b>



# NATIONAL INSTITUTES OF HEALTH

## National Cancer Institute

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

#### FY 2004 House Appropriations Committee Report language (H.Rpt 108-188)

##### Item

***Prostate Cancer***– . . . The Committee encourages NCI to place an increased priority on research through all available mechanisms, as appropriate, including clinical trials that result in earlier, more reliable detection methods and more effective and less disfiguring treatment regimes. The Committee encourages NCI to identify a budget strategy with specific prostate cancer funding opportunities and priority investments. (p. 56)

##### Action taken or to be taken

Prostate cancer is the most common type of cancer in men with the exception of skin cancers. In 2002, an estimated 189,000 men were diagnosed with the disease, and 30,200 died from it. No other cancer grows in both incidence and mortality with age as rapidly as prostate cancer. As the U.S. population ages, the impact of this cancer will increase. Furthermore, certain segments of the population are disproportionately affected. For example, African-American men are far more likely to develop prostate cancer than other Americans and more than twice as likely to die from it. Although significant progress has been made over the past several years to improve our understanding of prostate cancer, much remains to be learned about its causes, early detection, diagnosis, treatment, and prevention.

The NCI has prepared a prostate cancer research plan that will enable NCI and other NIH Institutes and Centers to respond to discoveries and opportunities while ensuring the best use of resources and a smooth flow between advances in knowledge and application. The plan outlines goals, objectives, and near-term milestones in seven different scientific areas that span the continuum of research. In focusing on these areas, it is critical to:

- Elucidate the molecular and cellular processes that lead to prostate cancer initiation, progression, and metastasis.
- Discover genetic, biochemical, environmental, and lifestyle factors and their interactions that define prostate cancer risk, play causal roles in prostate cancer initiation and progression, and inform the development of new strategies for prevention and early detection.
- Use knowledge gained about 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.
- Accelerate development and validation of optimal treatments that target the molecular and cellular characteristics of prostate cancer.

- Achieve a continuously improved understanding of the impact of prostate cancer and its care on individuals, families, and populations with special emphasis on survivorship, improving quality of care, and steadily reducing disparities in both care and outcomes.
- Develop and validate accurate prostate cancer models and ensure that they are integrated into research on the biology, prevention, early detection, and treatment of prostate cancer.
- Maximize the effectiveness and efficiency of prostate cancer scientists by providing them with essential resources and infrastructure for conducting their research.

### Biology, Progression, and Metastasis

In the last 5 years, significant progress has been made in understanding the functions of genes and proteins in normal and cancerous prostate tissues. This understanding can be used to develop new tools and agents for detection and diagnosis and for targeted destruction of cancerous cells. In addition, new models have been proposed to explain the transition from early to advanced disease, when clinical outcomes are typically poor. Further insight into prostate cancer progression has been gained from identifying and characterizing the factors that cause the growth of cells forming the prostate's structure and the proteins on their surfaces. This progress in prostate cancer biology research has fueled advancements in prevention, detection, diagnosis, and treatment.

For biological knowledge to translate into clinical practices that can reduce the burden of prostate cancer, research must continue to examine and understand the biology of the normal prostate, especially as it relates to the earliest stages of cancer initiation. Studies of cell-cell and cell-matrix communication will further the understanding of how cancer develops and lead to treatments targeting both the tumor and its microenvironment. The discovery of tumor markers, as well as markers of progression and of response to treatment, will allow for earlier diagnosis and targeted treatment of prostate cancer.

### *Recent Advances in Research*

*Initiation and Progression*— NCI-supported research has shown that hypermethylation (an early genetic change unique to some cancer cells) inactivates the glutathione-s-transferase-1 (GSTP1) gene in most prostate cancers, leaving cells vulnerable to damage and increasing the chances of additional genetic changes that could lead cells to become malignant. Researchers have also learned that hypermethylation is associated with loss of protein expression in men with prostate cancer, but not in men with certain benign diseases of the prostate. Other NCI-supported work has revealed the possibility of screening for alterations in the GSTP1 gene in urine.

*Development of Androgen-Independent Tumors*—Standard therapy for prostate cancer relies on blocking or removing androgens, hormones that are necessary for normal prostate growth. Most tumors respond to this therapy initially, but they all too often become resistant (refractory), resulting in disease progression. Investigators have identified many of the mechanisms behind the transformation of a tumor from androgen dependence to androgen independence. Recent NCI-sponsored research has revealed that:

- The androgen receptor (AR) plays a role in androgen-refractory prostate cancer.

- Amplifying the AR gene, which is rarely amplified in primary prostate tumors but is amplified in up to 30 percent of androgen-refractory tumors, may increase the sensitivity of tumor cells to the remaining androgens in the body.
- Mutations in the AR gene may make the AR more sensitive to androgens.
- Over expression of AR coactivators (proteins that enhance the function of AR) or reduced expression of AR corepressors (proteins that restrict AR function) could lead to activation of the AR by other hormones or even by anti-androgens.
- AR coactivators may stimulate the transcription of AR in the presence of low levels of androgens or other steroids, and activate pathways downstream of the AR.
- Tumor cells may bypass the AR pathway altogether in their transformation to androgen independence.

*Tumor Microenvironment*—Transforming growth factor (TGF)-beta proteins inhibit the growth of normal epithelial cells (which line the body’s internal and external surfaces) but can stimulate mesenchymal cells (which develop into connective tissue, blood vessels, and lymphatic tissue). In a human prostate cancer cell line, NCI-supported researchers showed that TGF-beta1 stimulated cells of stroma (connective tissue that supports organs) to develop characteristics indicative of reactive stroma, which occurs in many human cancers and appears to promote the development of tumors. When another group generated prostate tumors in the presence of reactive stroma and a TGF-beta1 inhibitor, these tumors had fewer blood vessels and were nearly half the size of control tumors. TGF-beta appears to have a major role in the two-way communication between stroma and epithelium that can lead to the generation of tumors and metastases.

*Bone Metastasis*—In recent years, efforts to discover the steps that lead tumors to metastasize to bone have identified that hyaluronan (or hyaluronic acid) may be necessary to promote metastasis to bone. NCI-sponsored researchers have found that hyaluronic acid levels are higher in prostate cancer cells than in normal prostate cells or cells from benign prostatic hyperplasia. An NCI-supported study showed that increased expression of hyaluronan synthase (HAS), the enzyme used to produce hyaluronan, by prostate tumor cells triggers adhesion of the tumor cells to bone marrow endothelial cells, allowing the tumor cells to spread to bone. When investigators inhibited HAS synthesis in prostate cancer cells injected into mice, the resulting tumors were smaller and had up to 80 percent less pathological formation of blood vessels than controls. Conversely, when the gene for HAS3 (one of three forms of the enzyme) was introduced into tumor cells, they grew more quickly in cell culture and formed larger tumors than control cells when injected into mice.

### Etiology and Prevention

By pursuing research on the direct causes and modulators of prostate cancer, the NCI has raised the possibility of prostate cancer prevention. Genetic, dietary, lifestyle, and environmental factors are being examined for their impact on prostate cancer risk. The biologic pathways leading to the development of a new prostate cancer or the progression of an otherwise indolent prostate cancer are being characterized. These endeavors have led to behavioral and drug-based strategies for reducing risk and blocking the cellular and molecular events that are required for tumor formation. NCI-sponsored investigators are also determining which risk factors are due to

racial differences and whether genetic, lifestyle, and/or environmental interactions modify risk. More information is also needed on the interactions of genetic predisposition and factors external to the body in prostate cancer susceptibility to design effective prevention strategies and to help develop methods for aggressively controlling disease progression and reducing mortality. As the biological origins of prostate cancer are continually refined, new targets for preventive interventions will need to be rapidly validated, and interventions will need to be prospectively examined in clinical trials.

#### *Recent Advances in Research*

##### *Androgen Receptor and Androgen Metabolism as Genetic and Biochemical Risk Factors—*

Deprivation of the hormone androgen leads to physiological changes in the prostate that can result in clinical responses in patients with prostate cancer. NCI-funded research in this area has revealed that higher risk genetic variations within the androgen receptor (AR) gene are found significantly more often in the higher risk African-American population than in lower risk Asian populations. AR regulates the PSA gene and a comparison of the AR and PSA genotypes demonstrated that men with the higher risk types of both genes had five times the risk for all prostate cancer and 10 times the risk for advanced prostate cancer than men with the lower risk types.

NCI-sponsored studies have also addressed the possibility that genes encoding androgen-metabolizing enzymes may be prostate cancer susceptibility genes. Variations in the enzymes of the 3-beta-hydroxysteroid dehydrogenase family of genes, for example, were found significantly more often in men with prostate cancer, especially those with a hereditary form of cancer, than men without cancer. A genetic variant of steroid 5-alpha reductase increased the risk of clinically significant prostate cancer in African-American men by 7-fold and in Hispanic men by 4-fold.

*Dietary Factors—*NCI-sponsored research has shown that prostate cancer risk is associated with total energy intake, and the risk for regional/distant prostate cancer is associated with dietary fat consumption. Genetic variants of the enzyme alpha-methylacyl-CoA-racemase, which metabolizes some of the fatty acids in red meat and dairy products, have been shown to be significantly associated with prostate cancer risk. NCI has also supported research associating genetic variants of the enzymes responsible for the metabolic inactivation of a byproduct of grilling meat and an apparent carcinogen of the rat prostate (2-amino-1-methyl-6-phenylimidazol[4,5-*b*]pyridine) with a significantly increased risk for prostate cancer.

*Environmental/Occupational Risk Factors—*Farming is the number one occupational risk factor for prostate cancer, and scientists have been seeking to clarify the potential risks associated with pesticide use. The NCI-sponsored Agricultural Health Study included more than 55,000 male pesticide applicators with no prior history of prostate cancer. Participants who reported occupational use of the fumigant methyl bromide had a slightly higher risk of developing prostate cancer than other men in the study. Also, exposure to several widely used insecticides increased the risk of prostate cancer, but only in men with a family history of the disease. Evidence also suggests that using chlorinated pesticides may be related to increased prostate cancer risk, especially in men over 50 years of age.

*Prevention Trials*—Almost 19,000 healthy men aged 55 and older participated in the NCI’s nationwide *Prostate Cancer Prevention Trial*, which investigated the prevention potential of seven years of treatment with the drug finasteride. The trial was concluded early when it revealed that finasteride results in a 25% reduction in the incidence of prostate cancer. The trial also showed that men taking finasteride had more advanced tumors than their placebo counterparts. NCI is conducting the *Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study* in collaboration with the National Public Health Institute of Finland. The study indicates that daily use of a modest dose of alpha-tocopherol (a form of Vitamin E) can lead to a striking reduction in prostate cancer incidence. A similar study revealed that long-term alpha-tocopherol supplementation decreased serum androgen concentrations thought to contribute to the incidence and mortality of prostate cancer. The NCI’s *Selenium and Vitamin E Cancer Prevention Trial (SELECT)* is an ongoing study that will definitively evaluate the potential of the dietary supplements selenium and vitamin E to prevent prostate cancer.

### Early Detection, Diagnosis, and Prognosis

Management of cancer begins with the early detection of disease. For men in whom cancer has been detected, the disease can be most successfully controlled when diagnostic and prognostic measures accurately predict the course of the disease and the most suitable treatments. Research in early detection, diagnosis, and prognosis is aimed at enhancing diagnostic accuracy with non-invasive techniques. New prostate cancer models and molecular technologies have been developed that could accelerate future research. These tools can facilitate the discovery of the natural history of prostate cancer, including all the biological steps from the initiation of a prostate cancer through advanced, metastatic disease. While early detection, particularly through the use of PSA screening, has led to an increase in the number of early-stage prostate cancer diagnoses, not all clinically significant tumors detected by PSA screening are life threatening. Many of the therapies for prostate cancer can have a significant impact on quality of life, so the identification of additional diagnostic and prognostic markers that can distinguish slow-growing from aggressive prostate carcinomas is of critical importance. Currently, the potential usefulness of several new markers needs to be validated in large clinical studies. Future studies are likely to focus on early disease detection, prognosis of disease course, prediction of response to treatment, risk of disease recurrence, and overall disease-free survival.

### *Recent Advances in Research*

- *Novel Biologic Markers*—NCI-supported investigators and NCI resources, such as the Cancer Genome Anatomy Project (CGAP), have utilized new technologies that have enabled the identification of new biomarkers and numerous genes unique to prostate cancer. Many of these genes are being further investigated to determine if they can be used as markers or therapeutic targets for prostate cancer. Several biologic markers that may be useful for early detection, prognosis, and targeted therapeutic interventions for prostate cancer were recently identified by NCI-sponsored research.

*Enhanced Imaging Technologies*—NCI has supported research to find noninvasive alternatives to removing lymph nodes surgically for examination, which is currently the only way to determine whether lymph nodes near the prostate gland have metastasis. One new technique may allow lymph node metastases to be detected with MRI. Lymphotropic superparamagnetic

nanoparticles are small enough to enter individual cells. They accumulate in lymph nodes when injected into the body, and are magnetic enough for detection by MRI. Investigators used these particles in conjunction with MRI to correctly identify lymph node metastasis in a group of patients known to have metastatic prostate cancer.

*Molecular Profiling*—Molecular profiling involves determining an individual tumor’s gene or protein expression patterns through such technologies as cDNA microarray and proteomic analysis, which were developed in the past decade and are still being optimized. In evaluating cells from normal prostate, benign prostatic hyperplasia, prostatic intraepithelial neoplasia (cells believed to precede the onset of cancer), and carcinoma, NCI-supported investigators detected cancer stage-specific gene expression patterns and identified previously characterized proteins and novel genes from these analyses. Patterns of multiple proteins detected by mass spectrometry have proven more selective and specific in identifying prostate cancers than the measurement of any single protein. Research has also shown the usefulness of the proteomics approach for prostate cancer screening using blood specimens collected from men. In the future, molecular profiles will be used to classify tumors and define subsets of patients so that treatment can be tailored for individuals.

### Treatment

NCI research leading to improved cancer treatment spans a spectrum of activities ranging from synthesis and discovery on the bench top, to preclinical testing of safety and efficacy in animal models, to, ultimately, phased clinical trials in increasing numbers of cancer patients. Much progress has been made in identifying genes that are expressed during the different stages of prostate cancer progression. These genes and their corresponding proteins can serve as novel targets for directing new therapeutics. However, limitations in the ability to accurately assess disease stage and treatment response can result in patients being “under-treated” for tumors that will ultimately advance or recur and “over-treated” for tumors that will continue to grow slowly. Additionally, while treatments for localized prostate cancer usually are effective, they are not always effective, nor are they free from side effects. Therefore, research is needed to develop optimal treatments for patients at different stages of prostate cancer.

### *Recent Advances in Research*

*Progress in Preclinical Models*—Recent advances in the development of complementary transgenic (incorporating human genes) and xenograft (implanted with human tissue) mouse models that display aspects of prostate cancer disease progression have led to changes in the way promising therapeutic agents are tested. Agents recently studied by NCI-sponsored investigators in transgenic mouse models include the vitamin D analogue EB 1089 and the nonsteroidal anti-inflammatory drug E-7869 (R-flurbiprofen). Current NCI projects are using transgenic models to explore stimulators of cell death, inhibitors of the formation of new blood vessels, and other novel agents.

*Hormone Therapy*—The results of a recent NCI-sponsored trial together with evidence from previous studies indicate that starting hormonal therapy early prolongs survival. In the randomized trial, men who had been treated with surgery for early-stage prostate cancer that was likely to recur due to lymph node metastases received immediate hormonal therapy or were

observed until the time of disease progression. Prostate cancer recurrence and death due to prostate cancer were significantly lower in men receiving the hormonal therapy than in the observational group after a median of 7.1 years following treatment.

*Prolonging Survival*—At autopsy, up to 85% of deceased men with prostate cancer show evidence of bone metastases. One team of NCI-supported investigators has revealed that treatment of bone metastases may prolong survival. Patients with symptomatic bone metastases who were responding to chemotherapy received additional chemotherapy, either alone or combined with radiostrontium ( $^{89}\text{Sr}$ ), a radioactive atom that concentrates in bone. The median survival of patients who received the  $^{89}\text{Sr}$  was approximately 65% longer than that of patients who received chemotherapy alone. This suggests that targeting the growth of bone metastases and/or altering their capacity to develop resistance to chemotherapy could provide symptomatic relief and prolonged survival. This finding is currently being followed up in a larger, national, randomized Phase III study to definitively determine whether the approach works and, if so, whether markers can be identified that predict development and progression of bone metastases.

*Bone Metastasis Treatment*—In February 2002, zoledronic acid (Zometa®) became the first bisphosphonate to be approved by the FDA for the treatment of bone metastases from prostate cancer that progress after treatment with androgen deprivation. The approval was based on the results of an NCI-sponsored randomized trial showing that significantly fewer men treated with zoledronic acid had a skeletal-related event at 15 months. A new national trial will follow up on this finding and determine whether earlier use of zoledronic acid can delay the development of bone metastases. Companion studies will try to identify predictive or prognostic markers for skeletal-related events.

*Cancer vaccines*—It has now been shown in clinical trials that cancer patients, when given the appropriate vaccine, can mount an immune response to antigens (proteins) associated with their own tumor. One of these antigens is the human prostate-specific antigen (PSA). NCI researchers have developed recombinant (genetically engineered) vaccines containing the human PSA gene and are currently conducting four clinical trials. Initial trials have shown that the vaccines appear to be safe, can generate an immune response in the majority of patients tested, can cause immune mediated killing of prostate cancer cells, and can be safely combined with either radiation or chemotherapy. In addition, some patients have shown significant decreases in PSA levels post-vaccination, which may well reflect disease stabilization and/or anti-tumor activity.

### Cancer Control, Survivorship and Outcomes

Most men who are diagnosed with prostate cancer can expect to live for many additional years, underscoring the importance of research on their long-term health and wellbeing. The NCI improves the lives of men who are at risk or who have already been diagnosed with prostate cancer by supporting research in the new areas of:

- Cancer control research in the behavioral, social, and population sciences to create or enhance interventions that reduce cancer risk, incidence, morbidity, and mortality.
- Survivorship research addressing the physical, psychosocial, and economic consequences of cancer diagnosis and treatment among survivors of cancer.

- Outcomes research that describes, interprets, and predicts the impact of various influences, especially interventions on endpoints that matter to patients, providers, private payers, government agencies, accrediting organizations, or society at large.

Currently, it is also important to know the extent to which PSA screening benefits the many U.S. men who opt for the test. Moreover, results are needed from randomized controlled trials of screening and treatment to understand the reasons for the observed population trends in mortality and survival. We also need to know the extent to which the over-diagnosed are being over-treated. In addition, with new knowledge that the long-term side effects of prostate cancer therapy are more common than originally thought, research must determine whether recently adopted practice changes and supportive care measures help prevent or alleviate these effects.

#### *Recent Advances in Research*

*Complications of Prostate Cancer Treatment*—NCI-sponsored studies have used patient surveys and claims data to examine the long-term complications of prostate cancer treatment, particularly urinary, sexual, and bowel dysfunction. Recent results from the large Prostate Cancer Outcomes Study (PCOS) have shown significantly higher complication rates for the common initial prostate cancer treatment modalities, external beam radiation and prostatectomy, than were observed in previous studies involving small numbers of patients. NCI-supported researchers have also assessed the effects of androgen deprivation therapy, whose use has increased rapidly, on sexual function and other quality of life measures.

*New Survey Tool*—A new 50-item questionnaire, the Expanded Prostate Cancer Index Composite (EPIC), is currently being used in a number of multi-institutional trials funded by the NCI and other organizations. EPIC may be adopted as a standard approach for measuring urinary, sexual, bowel, and hormonal symptoms following prostate cancer therapy.

*Assessing Trends in Prostate Cancer Incidence and Mortality*—NCI-sponsored work has assessed trends in prostate cancer incidence and mortality rates. Some of this research indicates that PSA screening might be an important contributory factor to the mortality decline that began in the mid-1990s. Ongoing screening trials indicate that the mortality decline may also be due to changes in treatment patterns (such as the increasing use of hormonal therapy) and cause of death misclassification.

*Racial Disparities*—Recent NCI-sponsored studies have explored differences between whites, African-Americans, and other racial/ethnic groups in screening, stage at diagnosis, treatment, treatment complications, and survival. These studies showed that African-American men are diagnosed at more advanced stages of disease and have poorer survival rates and duration. These studies also indicated that African-American men who are diagnosed with localized disease are just as likely as non-Hispanic white or Hispanic men to receive aggressive therapy; however, for men diagnosed with more advanced disease, African-American men are less likely than non-Hispanic white men to receive aggressive therapy.

*Quality of Life*—Using findings from the Prostate Cancer Outcomes Study, researchers have learned that the majority of men (about 60 percent) who received treatment for prostate cancer



were satisfied with their treatment decisions. The types of treatment chosen did not affect their perceptions of health-related quality of life 2 years later. But Hispanic men who chose radical prostatectomy or androgen deprivation therapy were less satisfied than non-Hispanic white men. In all population groups, the men who were most satisfied were those who perceived themselves as cancer-free, maintained social relationships, and had good urinary and bowel control, normal erectile function, and good general health.

### Laboratory and Preclinical Models

The NCI supports the use of various cell, organ, animal, and mathematical models for studying mechanisms of prostate cancer development and progression and testing prevention and treatment strategies. The NCI emphasizes the use of models to study specific genes and pathways that are thought to play a role in prostate cancer development and progression and in interventions directed at these genes and their gene products. But although a variety of models mimic one or more aspects of prostate cancer in humans, no single model replicates the full spectrum of human disease development and progression. Furthermore, our limited understanding of prostate cancer etiology, progression, and metastasis complicates the validation of existing models and the development of new models. It is important to determine the extent to which scientific model systems are similar to and different from the human disease state, and to understand the significance of these similarities and differences for preclinical assessment of diagnostic tools and preventive and therapeutic interventions.

### *Recent Advances in Research*

*Transgenic Animal Models*—The transgenic adenocarcinoma of the mouse prostate (TRAMP) model was recently used for preclinical testing of therapeutic strategies and chemopreventive agents and for studying the events that lead to androgen independence at the molecular level. This model incorporates human genes not normally present in the mouse and these mice consistently display pathological changes leading to high-grade prostatic intraepithelial neoplasia (PIN, believed to precede the onset of cancer), adenocarcinoma, and metastasis. NCI-supported studies have shown that the prostate tumors that spontaneously develop in TRAMP mice progress to androgen independence and that one or more mutations can be found in the androgen receptor gene sequences of each mouse that has become androgen independent. Variants of the TRAMP mouse model have recently been developed that progress to distinct precancer or cancer stages, yet do not proceed to metastasis.

*Xenografted Animal Models*—Numerous human prostate cancer cell lines derived from different sources ranging from primary tumors to distant site metastases have been implanted into mice that are unable to develop a normal immune response. The cells from these mouse models display different genetic backgrounds, androgen sensitivities, and metastatic potential. The site of implantation also influences the behavior of the cells; PC-3 cells lead to metastases following orthotopic placement (in natural position) in the prostate but not following subcutaneous implantation (just beneath the skin). Xenografted animals have recently been used to study inducers of cell death and other therapeutic interventions. They have also been employed in microarray analysis of gene expression in normal versus diseased prostate.

*Knockout Animal Models*—Knockout mouse models, in which a specific gene has been inactivated, have been developed for studying the involvement of specific gene products and regulator sequences in prostate cancer development and progression. These models provide a tailored environment for testing targeted gene therapies and other therapies based on gene product replacement. Knockout models based on the tumor suppressor Nkx3.1 and/or Pten genes have been found to display prostatic abnormalities such as hyperplasia, PIN, and possible progression to adenocarcinoma. A recent study has shown that the high-grade PIN lesions removed from Nkx3.1/Pten compound knockout mice resulted in adenocarcinoma and lymph node metastases following transplantation into immunodeficient animals.

### Resource and Capacity Building

The NCI coordinates, conducts, and supports research, training, health information dissemination, and other programs addressing the cause, diagnosis, prevention, and treatment of cancer and the continuing care of patients with cancer and their families. As the principal federal sponsor of cancer research and research training, the NCI primarily funds biomedical research through investigator-initiated research, allowing researchers to ask critical questions, remain creative in exploring research topics of professional scientific interest, develop innovative technologies, and make discoveries that expand the scientific knowledge base. Limitations of investigator-initiated research can include underrepresented research in some priority areas and the prohibitive cost of individually maintained resources and advanced technologies. The NCI has expanded ongoing initiatives and introduced new initiatives that target high-priority research topics, support core services, and support the training of the next generation of prostate cancer researchers.

### *Ongoing Initiatives That Support Resource and Capacity Building*

*Specialized Programs of Research Excellence (SPOREs)*—NCI has expanded the Prostate Cancer SPOREs for translational research from 4 in 2000 to 11 in 2003. The programs provide valuable infrastructure for translational research to develop new scientific approaches in early detection, diagnosis, treatment, and prognosis. An expanded network of prostate SPOREs is scheduled to bring about innovative inter-SPORE pilot and early-phase clinical interventions.

*Centers of Excellence in Cancer Communications Research*—The Centers foster the advancement of cancer communication science by examining the processes and mechanisms through which communication plays a role in cancer control. The NCI funded four Centers in July 2003 to carry out a variety of projects. These projects include facilitating information seeking related to prostate, breast, and colorectal cancers; promoting fruit and vegetable intake among African-Americans; examining media coverage of cancer-related issues in African-American newspapers; and developing and evaluating new interactive health communication systems.

*Early Detection Research Network (EDRN)*—Scientists in this network have applied advances in genomics (the study of genes and their function) and proteomics (the study of proteins and their function) to discover a variety of promising biomarkers, including protein patterns predictive of prostate cancer. The network enables the collaborative development and testing of promising biomarkers or technologies, with rapid dissemination of results. This consortium currently

includes 18 biomarkers development laboratories, with 3 that address prostate cancer; 3 biomarkers validation laboratories; 9 clinical and epidemiologic centers, with 2 that address prostate cancer; and a single data management and coordinating center.

*In Vivo Cellular and Molecular Imaging Centers (ICMICs)*—Each ICMIC brings together experts from diverse scientific and technological backgrounds to conduct multidisciplinary research on cellular and molecular imaging in cancer. These centers narrow the gap between the discovery of new cancer genes and intracellular pathways, and the translation of these discoveries into clinically useful, minimally invasive imaging approaches to gaining a greater understanding of cancer. ICMIC projects have included non-invasive imaging of gene expression in prostate cancers and combining metabolic PET imaging with molecular pathology to assess disease progression and response to treatment in patients with prostate cancer.

*Clinical Proteomics Program (CPP)*—Proteomics, the comprehensive study of proteins and their functions, is an important complement to studies of the genetic changes associated with cancer. Scientists at the NCI and FDA are working together through the CPP to explore complex protein patterns and define protein profiles that can be used for early detection, diagnosis, prognosis, and treatment monitoring. CPP investigators are examining serum protein patterns that may help determine whether men with mildly elevated PSA levels have prostate cancer or need no further diagnostic analysis and treatment. Such a test could save many men from having to undergo biopsy and help them make more informed decisions about treatment.

*Addressing the Needs of Minority Populations*— The *Minority Institution/Cancer Center Partnership Program* links Minority-Serving Institutions with NCI Cancer Centers to 1) increase the number of minority students involved in cancer research, including prostate cancer research, 2) strengthen the research capabilities of minority institutions, and 3) reduce incidence and mortality in minority populations. All major U.S. minority institutions with medical schools now participate in the program. NCI has also collaborated with Minority-Serving Institutions to increase access to and involvement in clinical trials by underrepresented populations, minority researchers, and patients and physicians. These efforts are especially critical for prostate cancer because of the high incidence and mortality rates among certain minority populations. The NCI's *Special Populations Networks* for Cancer Awareness Research and Training are building relationships between minority communities, NCI Cancer Centers, and NCI Cooperative Groups to address cancer health disparities in specific populations.

#### Item

**Cancer Centers** — The Committee is pleased with the substantial progress in cancer research and the many opportunities that have been created by the sustained investment in biomedical research and technology. One of the most successful investments by the NCI is the Cancer Centers program, which has the potential to accelerate progress further by linking its state-of-the-art resources with the broader cancer community. In order to speed progress and promote greater collaboration among scientists, the Committee requests that NCI explore innovative and creative ways to share information throughout the cancer community, utilizing the infrastructure of the national cancer centers program. Given that minority populations suffer disproportionately from virtually every form of cancer, the Committee encourages NCI to give consideration to the

establishment of a comprehensive center at a minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities. (p. 56-7)

Action taken or to be taken:

NCI-designated cancer centers are a major strategic element of the NCI's challenge goal to eliminate death and suffering due to cancer by the year 2015. This will require a serious reexamination and expansion of the role of cancer centers in the future in becoming more aggressive as platforms for effecting the Discovery, Development, Delivery continuum that forms the basis for the 2015 goal. A reformed cancer centers program will improve the vertical relationship of centers to the NCI in implementing national priorities and focus extensively on the horizontal relationships between (i.e., networking) centers in the conduct of research, education, and outreach activities that move these priorities to completion as rapidly and efficiently as possible. Sharing information and utilizing infrastructure between centers will be at the heart of the NCI's strategies.

As a first step, last year the NCI formed a P30/P50 Working Group that was charged with recommending the changes and steps that must be taken to effect the most efficient implementation of the Discovery, Development, Delivery continuum. Specifically, the Working Group was asked to consider strategies for balancing the breadth and depth of the centers program, maximizing translation of research discoveries, developing the objectives of a national cancer agenda focused on reducing the cancer burden, and facilitating partnerships with other government, private, philanthropic, and industrial entities. This group of leaders in cancer research consisted of cancer center directors who hold center grants and the principal investigators for NCI's Specialized Programs of Research Excellence (SPOREs). Their recommendations will form the basis of a roadmap for reforming the cancer centers program and other programs in the NCI. Some of the key recommendations are:

- Consolidate the infrastructure of cancer centers to create greater economies of scale;
- Include cancer centers on a regular basis in the NCI strategic planning process;
- Utilize centers to develop infrastructure and test novel methods for disseminating knowledge in clinical, cancer control, and early detection research;
- Encourage greater geographic distribution of cancer centers by creating programs for institutions that cannot currently meet all of the NCI's requirements to link with existing cancer centers;
- Provide the means for cancer centers to actively establish strategic, programmatic links with state health departments, other state agencies, local governments, and critical Federal agencies such the Center for Disease Control; and
- Adopt as a top priority a nationally integrated clinical research informatics system that unifies the NCI, centers, and industry.

While the NCI is currently forming an implementation plan to address these recommendations, one area has already been initiated because of its critical strategic importance. The NCI has launched a new initiative coordinated through its Center for Bioinformatics to create a virtual web or grid to connect the NCI-designated Cancer Center community. The primary objective is to provide the enabling infrastructure to facilitate the sharing of tools and data that meet common

needs and leverage the combined strengths of Centers and investigators. This initiative is called the Cancer Biomedical Informatics Grid (CaBIG) and is in the pilot-testing phase. When completed, CaBIG will help redefine how research is conducted, care is provided, and patients and participants interact with the biomedical research enterprise.

The NCI is working with several minority institutions that have the potential to become NCI-designated Comprehensive Cancer Centers. There are three ongoing strategic efforts to encourage widespread involvement of minority institutions and minority communities in cancer research, training, education, and outreach:

- The NCI has a very aggressive ongoing effort to establish cancer centers in geographic areas of the country with large minority populations that suffer disproportionate cancer incidence and mortality rates compared to national averages. This has resulted in encouraging the development of consortium cancer centers when no one institution has the strengths to satisfy the stringent requirements of the NCI's cancer centers program. Examples of states that the NCI believes have a high potential to develop successful cancer centers in the very near future are Louisiana, Georgia, and South Carolina.
- Through the NCI Minority Institution/Cancer Center Partnership Program, the NCI has engaged all of the minority institutions with medical schools in the cancer research and outreach effort, as well as another 30 institutions that have had no relationship with the NCI in the past. These partnerships are designed to enhance the research capability of minority institutions and increase the research and outreach activities of NCI-designated cancer centers focused on disproportionate incidence and mortality in minority and underserved populations.
- In the last five years the Special Populations Networks (SPN) sponsored by the NCI's Center to Reduce Cancer Health Disparities has developed effective community networks that can be linked to the cancer research enterprise and participate in cancer education and information dissemination. More than 300 formal partnerships have been established with community-based organizations, over 2000 community/lay health workers have been trained in cancer awareness and 200 pilot projects have been funded. The SPN has been renamed Community Networks to Reduce Cancer Disparities (CNRD), which is a truer reflection of how their mission has evolved.

Additionally, as part of the "Cooperative Planning Grant for Cancer Disparities Research Partnership Program," (CDRP) the NCI provided funding for a Patient Navigator Program to be implemented at CDRP funded sites. While CDRP provides resources for the cooperative planning, development and conduct of radiation oncology clinical research trials in institutions that care for a disproportionate number of medically underserved, low income, ethnic and minority populations, the Patient Navigator Program provides a means to diminish cancer incidence and mortality by providing personal one-on-one assistance to patients with abnormal findings or cancer.

A Cancer Patient Navigator is a trained, culturally competent individual who assists the cancer patient facing a bewildering and complex program of medical care. Patient Navigator Programs vary according to the needs of each community, but are designed specifically to provide individualized education about cancer, the need for treatment, and the types of tests and medical services required to treat the disease. In addition, the patient navigator coordinates and tracks appointments for medical tests, treatments, and other follow-up medical appointments.

The CDRP sites are in the preliminary stages of developing and implementing their Patient Navigator Programs. Once established, the programs can participate in cancer education and information dissemination. Two sites, Rapid City Regional Hospital and Laredo Medical Center, have active programs. Four sites, Daniel Freeman Memorial Hospital, New Hanover Regional Medical Center, UPMC McKeesport Hospital and The Regional Cancer Center at Singing River Hospital will implement their programs this year.

#### Item

*Neurofibromatosis (NF)*– The Committee is pleased that NCI is conducting phase II clinical trials of NF1 patients with plexiform neurofibromas. The Committee is concerned about recent declines in funding for NF research, recognizing NF’s connection to many of the most common forms of human cancer. The Committee encourages NCI to substantially increase its efforts in NF research in further development of animal models, natural history studies, therapeutic experimentation, and clinical trials. (p. 57)

#### Action taken or to be taken

Neurofibromatosis type 1 (NF1) is a common inherited disorder, which affects 1 out of every 3,000 people (>80,000 persons affected in the United States). NF1 is characterized by a number of progressive changes of the skin, nervous system, and skeleton. Patients with NF1 have an increased risk of developing benign and malignant tumors of the nervous system.

NF is studied by several Branches and Programs at the NCI, including the Pediatric Oncology Branch (POB), the Neuro-oncology Branch, the Mouse Cancer Genetics Program, and the Division of Cancer Epidemiology and Genetics. In addition, NCI supports pediatric clinical trials cooperative groups that specifically include children with cancers associated with NF1.

#### *Pediatric Oncology Branch*

Plexiform neurofibromas are tumors, which arise from the outer layer of nerves and occur in approximately 25% of patients with NF1. They grow along the length of nerves within the skin or deep inside the body and involve multiple branches of a nerve. Plexiform neurofibromas are a major source of pain, disfigurement, and impairment of nerve function. In some cases, they may develop into malignant tumors. Plexiform neurofibromas that cause significant problems are treated by surgical removal. However, most of the tumors cannot be removed completely, and up to 44% of tumors regrow after the first surgery. There is no other standard treatment for patients with NF1 and progressive plexiform neurofibromas.

The POB has a long-standing interest in the development of new treatments for patients with treatment refractory cancers, and has recognized the need to extend these treatments to patients

with NF1. The underlying cause of NF1 is a defective gene. The function of this gene is to produce a protein called neurofibromin. In patients with NF1, neurofibromin is decreased, and the decrease in neurofibromin is felt to contribute directly to tumor formation. Neurofibromin helps control the activity of another protein called *ras*. *Ras* can be thought of as an "on/off" switch for cell growth. When *ras* is "on", cells divide. When *ras* is "off", the cells do not divide. Neurofibromin helps to keep *ras* turned "off". Decreased levels of neurofibromin therefore may allow for uncontrolled cell division and tumor formation. Drugs that inactivate *ras* are being studied as a new way to treat cancer. These drugs may also provide a logical means of controlling the tumors in patients with NF1.

R115777 is a new experimental drug that interferes with the function of the *ras* protein and other proteins in cells by blocking a step in the formation of these proteins. R115777 can block the growth of cancer cells and of tumor cells derived from patients with NF1 in test tubes and in animals. This experimental drug has completed evaluation in early clinical trials for adults. At tolerable doses of R115777, a 30% response rate was observed in adult patients with treatment refractory leukemias, and responses were observed in adults with solid tumors.

After completion of a phase I trial of R115777 for children with NF1 and plexiform neurofibromas to determine the optimal dose of R115777, the NCI POB is now coordinating a phase II clinical trial of R115777 for children and young adults with NF1 and progressive plexiform neurofibromas. The main purpose of this research study is to determine if R115777 can increase the time to disease progression of plexiform neurofibromas in patients with NF1. Patients 3-25 years of age and younger with measurable, growing plexiform neurofibromas that cannot be completely surgically resected are eligible for this trial.

Unlike cancers, the growth of plexiform neurofibromas is unpredictable, and can include periods of rapid growth or long periods of quiescence. Some plexiform neurofibromas remain static indefinitely after a period of active growth. This erratic behavior can make it difficult to measure the effectiveness of R115777 as a treatment for plexiform neurofibromas. In order to find out if R115777 will be helpful for patients with plexiform neurofibromas, the effects of the drug are therefore compared to a placebo in each patient who is treated on the study. Patients are followed closely with magnetic resonance imaging (MRI) studies for signs of increase of the neurofibroma. If the plexiform neurofibromas are increasing in size, the patient is switched to the other treatment (from placebo to R115777 or vice versa). Should the tumor be stable or decrease in size, the patient continues to receive the same treatment for as long as it is well tolerated and appears to be of benefit. The design of this study is complicated, but will hopefully offer the best chance of determining if R115777 is of benefit for progressive plexiform neurofibromas.

In collaboration with the Children's National Medical Center in Washington, DC and the Mayo Clinic in Rochester, Minnesota, the NCI POB is coordinating a phase I trial of pirfenidone for children and young adults with NF1 and plexiform neurofibromas to determine the optimal dose, toxicities, and pharmacokinetics of pirfenidone. Overall pirfenidone has been well tolerated with nausea, vomiting, or diarrhea as dose-limiting toxicities. A phase II trial of pirfenidone for

children with NF1 and progressive plexiform neurofibromas to assess the potential benefit of pirfenidone in this population is in preparation.

The NCI POB is also participating in an ongoing multi-institutional study to assess the natural history of patients with NF1 and plexiform neurofibromas. The primary goals are to study the natural history of plexiform neurofibromas and to evaluate the usefulness of volumetric tumor measurements in this disease. Other goals of the Natural History Protocol are to establish a tissue bank, in which tissue samples obtained on the protocol will be made available to investigators after appropriate review.

The NCI is interested in the development of a phase I trial of BAY 43-9006 for patients with refractory solid tumors and NF1 and plexiform neurofibromas. BAY 43-9006 is an inhibitor of Raf1 kinase, a downstream target of Ras, and has completed evaluation in early clinical trials for adults with solid tumors. Upon completion of the phase I trial the plan would be to develop a phase II trial for patients with NF1 and progressive plexiform neurofibromas. Should new treatment modalities be promising, these agents will be evaluated for the treatment of other disease manifestations of NF1 such as optic nerve tumors or dermal neurofibromas.

NCI also presented at a recent workshop organized by the National Institute of Neurological Disorders and Stroke (NINDS) with the goal to develop new therapies for neurofibromatosis, which was attended by scientists from multiple NIH Institutes, as well as extramural scientists.

#### *Children's Oncology Group*

NCI also supports clinical trials through the pediatric clinical trials cooperative group that specifically include children with cancers associated with NF1. Of special relevance are the brain tumors associated with NF1 and in particular the low-grade gliomas that develop in children with NF1. The Children's Oncology Group continues accrual to its clinical trial for children younger than 10 years of age with progressive low-grade astrocytoma. Over 300 children have now been entered into this study, including 89 children known to have NF1. At current rates of accrual, the study should complete patient enrollment in approximately one year.

The primary objective of the study is to compare event-free-survival in children who are treated either with a regimen of carboplatin and vincristine (CV) or with a regimen of 6-thioguanine (6TG), procarbazine, CCNU, and vincristine (TPCV). Accrual is limited to children with disease that is progressive after surgery or those whose risk of neurologic impairment with progression is high enough to require immediate treatment.

#### *Mouse Cancer Genetics Program*

The NCI Mouse Cancer Genetics Program uses mouse models to increase the understanding of the biology and genetics of certain tumors associated with NF1, with the ultimate goal to use this model to develop new therapies.

Astrocytoma is one of the most common forms of brain cancer, accounting for close to 40% of all primary brain tumors. Due to its diffusely infiltrative nature, malignant astrocytoma is essentially incurable, because complete surgical resection is not possible and current therapies cannot be localized to the tumor cells without damaging normal brain tissue. Patients with NF1



are at an increased risk for developing astrocytoma, and this demonstrates that the neurofibromin and p53 tumor suppressor pathways are important in preventing astrocytoma. A mouse model of malignant astrocytoma was developed by combining mutations in Nf1 and p53. This model recapitulates the stages of progression and diffuse infiltration seen in astrocytoma patients and is used to gain insight into the biology of astrocytoma and to better understand the genetic influences on susceptibility to cancer.

NF1 is characterized by clinical heterogeneity, whereby one family member may have a severe form of the disease while another may have a mild form. Studies on families of patients have shown that genes other than the NF1 gene affect the number of non-cancer tumors that form. Data from mouse models in NF1 show that these genes also affect the cancer tumors associated with NF1 (astrocytoma and malignant peripheral nerve sheath tumors, for example). The NCI mouse cancer genetics program uses mouse models to identify genes affecting resistance to astrocytomas and malignant peripheral nerve sheath tumors and to study the biology of these tumors. The end goal of this research is to improve current treatments for these tumors through a better understanding of tumor biology.

In addition to identifying new molecular targets for rational drug design, this mouse model is being developed for testing new therapies. As a part of this effort, NCI is collaborating with the NIH MRI Research Facility (NMRF) and NINDS on an initiative to optimize brain imaging of a mouse model of NF1. Different methods of imaging and quantification of tumor burden will be evaluated, and multiple mice will be imaged simultaneously to increase the throughput for testing experimental therapeutics. The development of astrocytoma will be followed in this model and the efficacy of various therapeutics tested using MRI.

#### *Division of Cancer Epidemiology and Genetics*

NCI scientists began studies of NF2 in 1987 and collaborated on the clinical components of these studies with investigators from NINDS, NEI, and the NIH Clinical Center. NF2 is characterized by the development of bilateral vestibular schwannomas (VS), which cause hearing loss and vestibular symptoms in early adulthood. Meningiomas and other benign central and peripheral nervous system tumors are also common. Although NF2 is relatively rare, unilateral VS and meningiomas comprise 30% of all brain tumors in adults. The study population has consisted of two major groups: members of multi-generation NF2 families and sporadic cases whose parents were unaffected. Patients with NF2 and their at-risk relatives underwent a detailed clinical evaluation that included gadolinium-enhanced MRI of the brain, ophthalmologic and audiologic examinations, a physical examination that included evaluation of cranial and spinal nerve function, and molecular genetic studies of blood samples. In collaboration with scientists from Massachusetts General Hospital, DNA from the studied families was used to clone the NF2 gene and to determine the spectrum of mutations that occurred within the families.

Many patients with NF2 develop a variety of ocular abnormalities in addition to central and peripheral nervous system tumors. NCI collaborated with investigators from NEI, NICHD, NINDS, and Washington University School of Medicine on a study that demonstrated that retinal and optic nerve lesions in NF2 patients result from loss of function of this gene. Specifically, these lesions in NF2 patients had lost the normal NF2 allele, but retained the mutant allele. This

same mechanism is also associated with the development of nervous system tumors in NF2 patients.

Individuals with a disorder caused by mutations in a single gene often differ in the extent to which the disorder affects them. The difference in clinical manifestations may be caused by chance, by modifying genes at other locations in the genome, by environmental exposures, or by some combination of these factors. A large collaborative study involving investigators from NCI, the University of British Columbia and McGill University, Canada, St. Mary's Hospital, England, and Klinikum Nord Ochsensoll, Germany, has shown that relatives with NF2 have specific clinical features that are more similar to one another than to unrelated individuals with NF2. These correlations may be due to effects of the specific mutation in each family, shared modifying genes, or environmental exposures. However, the investigators observed similar and even greater intrafamilial correlations for each clinical feature when they compared subgroups of NF2 patients with the same general type of mutation. These results cannot differentiate between the role of specific NF2 mutations or the effects of modifying genes. To provide more insight into the causes of clinical variability, other statistical methodologies are needed that can assess the role of both genetic and environmental factors at the same time.

#### Item

***Lymphoma***– The Committee recommends that NCI increase its efforts to examine the issue of environmental and viral links to lymphoma. Although many studies have suggested an increased risk of lymphoma associated with environmental factors such as chemicals, pesticides and herbicides, other investigations have reported inconsistent results. However, many of these studies are weakened by limited sample sizes, flaws in study design, and imprecision in the measurement of environmental carcinogen exposures. The Committee recommends that NCI work to develop a well-constructed prospective study, using a multidisciplinary approach to examine environmental links to lymphoma. In a recent report, the Institute of Medicine concluded that there is moderate to strong biological evidence supporting a role of Simian Virus 40 in human cancer. Recent reports suggest that more than 40% of lymphomas tested were positive for this virus. Additional research studies have also found an association between other viruses, such as human herpes virus 8 and hepatitis C, and lymphoma. As a result of these studies, it is possible that more than half of all lymphomas may be attributed to viruses. The Committee encourages NCI to increase its efforts to examine the viral etiology of lymphoma. (p. 57)

#### Action taken or to be taken:

During the past 30 years, the reported incidence and death rate due to lymphomas have increased strikingly, nearly doubling since 1970. Lymphomas have gone from being relatively rare to being the fifth most common cancer in the United States. In 2002, the most recent year for which data are available, approximately 60,000 new cases of lymphomas were diagnosed. Of those, 53,900 were non-Hodgkin's lymphomas and 7,000 cases were Hodgkin's disease. From those incidence rates, it was estimated that 25,800 people would die that year of non-Hodgkin's lymphoma and 1,400 of Hodgkin's disease.

The reasons for the increase in incidence of NHL over the past twenty years are poorly understood. In addition to incidence rates that have risen 3 percent per year in the United States for four decades, mortality from NHL has also risen 1.6 percent, compared with 0.2 percent for all cancers combined. Only a small portion of the increase is attributable to changes in diagnostic practices, AIDS-related cases, and other known causes. An analysis of trends in both sexes and around the world suggests that an etiologic agent has become increasingly prevalent in the general environment.

Clinical investigations have shown that prognosis of NHL varies according to histology. These findings have led NCI scientists to assess the demographic patterns and trends in population-based rates of different histologic subgroups of NHL. Overall, the broad categories of small lymphocytic, follicular, diffuse, high-grade, and peripheral T-cell NHL appear to be distinct entities with specific age, sex, racial, temporal, and geographic variations in rates.

### Role of Environment

The NCI is organizing a workshop on the association of environmental factors with lymphoma that is tentatively planned for early summer 2004. This workshop will bring together an international, multidisciplinary group of scientific experts in the field of lymphoma to discuss and assess the state of the research and our current understanding of this disease, and to identify new areas for future research relating to this topic.

Epidemiologic research into the etiology of NHL has examined the role of pesticide use, along with a wide range of other possible risk factors. In a case-control study of NHL in the U.S., NCI scientists are measuring pesticide residues in household dusts, serum samples, and tap water, and collecting questionnaire data on the history of residential pesticide use. Early results indicate that most of the household dust samples collected from participants' homes contained residential insecticides, polycyclic aromatic hydrocarbons (PAHs), and polychlorinated biphenyl (PCB) as a result of being tracked inside. Farmers exposed to certain pesticides have been shown to have an increased risk for developing NHL. The Agricultural Health Study is a major effort designed to evaluate the relationship between pesticides and other agricultural factors and the risk of cancer and other diseases. Enrollment in this cohort includes about 90,000 men and women from Iowa and North Carolina. Initial findings suggest an association with the use of the pesticide, alachlor, and lymphoma risk. This association will be followed up again in the next few years to determine if the association holds or strengthens.

The limitations of available epidemiological studies of NHL include small sample size, inability to investigate specific lymphoma subtypes and lack of information on genetic factors. Recently, a new generation of large-scale molecular epidemiology studies have been initiated in North America, Europe, and Australia, led by both intramural and extramural scientists. These case-control studies are large in size, including a detailed review of the pathological and genetic characteristics of the cases of NHL and state-of-the-art assessment of exposure to environmental and endogenous risk factors. DNA is collected from cases and controls, allowing the study of genetic susceptibility factors. The InterLymph consortium has been established between the principal investigators leading these studies to share data and biological samples in order to explore etiologic and mechanistic hypotheses that cannot be adequately addressed in the

individual studies. InterLymph represents a model to overcome the limitations of molecular cancer epidemiology, namely, the lack of power for the analysis of gene-environment interactions and the study of subtypes of malignancies defined according to molecular criteria. Among the hypotheses that will be initially addressed are: individual susceptibility from variation in genes involved in immunological response; and the potential role of viruses, including HTLV-I, HHV-6, KSHV, SV-40, EBV, and hepatitis C; along with immune-related medical conditions and treatments, sunlight exposures, dietary factors, hair dye use and other hypothesized risk factors, for NHL.

### The Role of Viral Infections

In the mid-1980s, the University of West Indies, Jamaica and two referral hospitals in Trinidad and Tobago established parallel registries of hematologic malignancies that were used to identify cases for a hospital-based case-control study of NHL. A type of NHL, called T-cell leukemia/lymphoma, is endemic in this area and is caused by HTLV-1 infection. Up to 60-70% of NHL cases in the Caribbean have been estimated to be attributable to HTLV-I. Further characterization of adult T-cell leukemia (ATL) was also performed using case data from these registries.

A cohort of 48,420 individuals in California was studied by NCI scientists to determine whether hepatitis C virus (HCV) infection preceded the development of NHL and other B-cell lymphoproliferative disorders. Stored sera from 95 subjects with either NHL, multiple myeloma, or Hodgkin's disease diagnosed a mean of 21 years after phlebotomy were screened for antibodies to HCV as well as viral RNA, based on previous reports of antibody-negative viremia. Sera from 4 cases and 1 of 95 age-, sex-, and race-matched controls were repeatedly reactive by enzyme immunoassay, but none were confirmed by recombinant immunoblot assay; none of the case sera had HCV RNA by reverse transcription polymerase chain reaction. These prospective data do not support previous reports of a substantial role of chronic HCV infection in the etiology of B-cell neoplasia.

The incidence of Kaposi's sarcoma (KS) and NHL in the general population has markedly increased since the onset of the AIDS epidemic in 1981. NCI scientists examined the effect of changes in infection rates and introduction of treatments on the incidence of these two cancers. Age-standardized incidences for KS and NHL from 1973 through 1998 were obtained from nine registries in the Surveillance, Epidemiology, and End Results (SEER) program. During the mid-1990's, KS incidence declined sharply in all nine registries. Decreases were most evident in San Francisco, where KS rates among white men had risen from 0.5 per 100,000 persons per year in 1973 to between 31.1 and 33.3 from 1987 through 1991, then declined to 2.8 in 1998. In San Francisco, NHL rates among white men rose from 10.7 per 100,000 persons per year in 1973 to a peak of 31.4 in 1995, and then declined to 21.6 in 1998. NHL types that were AIDS-associated declined most steeply, whereas the incidence of NHL types not associated with AIDS were either stable or increasing.

Using the AIDS-Cancer Match Registry study, NCI scientists have also examined the spectrum of tumors related to KSHV infection risk by looking at second cancer risk in persons with KS. Compared with other persons with AIDS, those persons with AIDS-associated KS had higher

risk for certain types of NHL. This relationship appears specific, since no association was found between KS and various other hematologic or solid malignancies.

NCI scientists used AIDS and cancer registries to identify cases of non-Hodgkin's lymphoma among 304,439 U.S. adults with AIDS. In a total of 10,510 cases of NHL, 4 pleural lymphomas and 10 peritoneal lymphomas were identified, representing 0.13 percent of the total NHL cases. Pleural/peritoneal lymphoma cases tended to have a higher prevalence of prior KS, but were otherwise similar to other NHL types in age, race, and HIV transmission category. Twice as many cases of pleural/peritoneal lymphoma had immunoblastic cell types than did other NHL types. Median CD4 counts for pleural/peritoneal lymphomas were also much higher than for other NHL, but post-NHL survival was similar. Pleural and peritoneal lymphomas represent a rare subtype of AIDS-associated NHL and the increased frequency among persons with prior KS suggests a common etiology, presumably infection with KS-associated herpes virus (KSHV), as found in primary effusion lymphoma.

NCI scientists studied the relationship between cancer risk and AIDS-related immunosuppression among 82,217 adults who had a CD4 count measured at AIDS onset and had survived into the follow-up period. Data were obtained using linked records from AIDS and cancer registries in 11 U.S. regions. The risks of developing AIDS-defining KS, NHL, and cervical cancer were elevated 258-fold, 78-fold, and 8.8-fold, respectively. The risk of KS and NHL rose as immunosuppression (decreasing CD4 counts) increased. Among NHL subtypes, the association with lower CD4 counts was strongest for immunoblastic lymphoma and central nervous system lymphoma. The risk of cervical cancer did not vary with CD4 count. For non-AIDS-defining cancers, neither the combined risk nor the risk of specific types were associated with declining CD4 counts.

Epstein-Barr virus (EBV), which causes infectious mononucleosis, and human herpesvirus 8 (HHV-8) are both associated with lymphomas and other lymphoproliferative diseases in immuno-suppressed individuals. However, these viruses are often absent in many cases of non-Hodgkin's lymphoma in the normal population. Recently, there have been several reports indicating that other viruses such as simian virus 40 (SV40) may also be involved with lymphomas in both HIV and non-HIV-infected populations. Two independent studies have found both SV40 DNA and large T antigen sequences in over 40% of non-Hodgkin's lymphomas. However, there are also other studies that have failed to detect SV40 in lymphoma patients or tumor specimens. Therefore, the validity of these recent studies remains to be determined.

Additional research is needed on the etiologic role of infectious agents in lymphoma. The NCI is currently planning a new research initiative to investigate, explore, and correlate new etiologic roles for already known cancer viruses, for previously unknown viruses, and for other known or hitherto unknown microbial agents that may be associated with human cancer. This endeavor will foster and promote collaborative arrangements in which scientists with expertise in virology, epidemiology, immunology, pathology, clinical aspects of chronic diseases, molecular biology, computational biology, and genomic technology will work together to apply innovative approaches for identifying the infectious agents involved in human cancers such as lymphoma.

Additionally, this initiative will enhance our understanding of the role of the macro-environment (extrinsic factors) in cancer initiation and progression, especially the role of microbial agents in the etiology of cancer, both through direct interactions with the target cell and through modification of the micro-environment.

#### Item

***Hodgkin's and Non-Hodgkin's lymphoma*** – The Committee encourages NCI to increase its investment in clinical research on lymphoma and strengthen its collaboration with industry to improve the efficiency and timeliness of the lymphoma drug development process. The Committee recommends that, in addition to initiatives to improve the lymphoma drug development process, NCI increase its investment in several other areas of research, including research on nonablative transplants, immunomodulatory regimens, central nervous system lymphoma, the late and long-term effects of current lymphoma treatments, and lymphoma etiology and prevention. The Committee also encourages NCI to cooperate with private organizations in the development of a comprehensive lymphoma tissue bank. (p. 58)

#### Action taken or to be taken

During the past 30 years, the reported incidence and death rates due to lymphomas have increased strikingly, nearly doubling since 1970. Lymphomas have gone from being relatively rare to being the fifth most common cancer in the United States. In 2002, the most recent year for which data are available, approximately 60,000 new cases of lymphomas were diagnosed. Of those, 53,900 were non-Hodgkin's lymphomas (NHL) and 7,000 cases were Hodgkin's disease (HD). From those incidence rates, it was estimated that 25,800 people would die that year of NHL and 1,400 of HD.

#### *Lymphoma: Non-myeloablative BMT and Immunomodulatory Treatments*

In patients with NHL, white blood cells called B cells ignore normal signals to stop growing. More than 50,000 patients are diagnosed with the low-grade (follicular) form of this disease each year. Most patients achieve remission with initial chemotherapy, but a continuous pattern of relapse develops, resulting in progressively shorter lymphoma-free periods. Current treatments include radiation therapy for localized disease, chemotherapy, monoclonal antibodies, and bone marrow transplantation. Additional treatments are needed to increase survival in patients with disease that has relapsed or is refractory (resistant) to treatment.

Treatment with Rituximab, a monoclonal antibody to the cell surface protein CD20, eliminates both normal and tumor B cells. This effect lasts for more than 3 months and has been effective in patients with both fast and slow growing tumors, including previously untreated patients with small tumors. Although Rituximab is becoming accepted as a standard therapy for low grade NHL, most patients eventually relapse or develop resistant disease.

Another standard treatment is high dose chemotherapy followed by autologous (auto) blood or marrow transplantation (BMT). Although response rates are better than with conventional chemotherapy, auto BMT has not lead to an overall improvement in survival because patients continue to relapse. Studies showed that the presence of lymphoma cells in the blood or marrow graft prior to performing the transplant procedure was the best predictor of relapse for auto BMT

patients. As a result, studies are underway looking at the use of rituximab to remove tumor cells before, during, and/or after auto BMT.

An alternative to using the patient's cells for transplant is to use cells from a matched donor. In addition to eliminating the problem of tumor cells in the graft, cells from another person (called an allo transplant) have been shown to have anti-tumor activity. Relapse rates using cells from a matched donor are lower compared to auto-transplants. Unfortunately, this lower relapse rate has been offset by serious (and sometimes fatal) transplant-related side effects. This led to the development of less toxic transplant regimens, called non-myeloablative. This kind of regimen contains just enough chemotherapy to allow the donor cells to grow in the patient, but not enough to kill either the patient's normal blood cells or tumor cells. This approach relies on the natural ability of the donor cells to kill the lymphoma cells. Because the patient's blood cells are minimally affected, the toxicity compared to a standard allo transplant is reduced (but not eliminated).

To test the merits of these two approaches (auto transplant with rituximab and non-myeloablative allo transplant), the Blood and Marrow Transplant Clinical Trials Network, which is co-funded by NCI and NHLBI, has just launched a phase II/III multi-center study. Approximately 350 patients will be enrolled at more than 20 transplant centers in this six-year study. Patients with a matched sibling donor will receive a non-myeloablative allo transplant. Patients without a matched donor will receive an auto transplant followed by maintenance therapy with rituximab.

There are several other approaches to immunomodulatory therapy being tested by NCI-funded centers. For example, investigators have coupled rituximab to radioactive metal ions. This turns rituximab into a sort of smart bomb for lymphoma cells. A crossfire effect kills not only the CD20-positive cells rituximab binds to, but also nearby tumor and blood vessel cells that don't bear the CD20 protein.

In addition to antibodies against CD20, therapeutic vaccines targeting the tumor-specific antibody (called an idiotypic) have demonstrated promising results against lymphomas in phase I/II studies and are currently being evaluated in phase III randomized trials. Additional vaccine therapies being developed include those based on dendritic cells, idiotypic proteins engineered to produce a stronger immune response, DNA, heat shock proteins, and gene-modified tumor cells. It is hoped that these immunotherapeutic agents, used alone or in combination, may someday allow effective treatment of lymphoid malignancies and delay or even replace the need for conventional cytotoxic therapies.

### *Primary CNS Lymphoma*

Primary CNS lymphomas (PCNSL) are relatively rare but generally are difficult to treat with modest responses to standard therapy. Patients have been faced with significant neurological toxicity based upon the CNS radiation therapy that has been used to control this disease. Research into the treatment of CNS lymphoma has revolved around two primary goals – intensifying therapy to improve disease control and manipulation of treatment regimens to minimize the long-term toxicity. These two goals combine into approaches that intensify chemotherapy to the CNS tissues and eliminate the need for brain radiation. These efforts must

be tested in clinical trials that evaluate the outcome for patients treated with new approaches. A major hurdle to research in this disease has been the paucity of patients available to enter these clinical trials.

The NCI has funded a consortium that is dedicated to the study of innovative therapies for CNS malignancies, including Primary CNS Lymphoma. This consortium is titled, "New Approaches to Brain Tumor Therapy Consortium," or NABTT. Participants include investigators with specific expertise in CNS malignancy and access to relatively large numbers of patients who can be entered into clinical research. This consortium is currently performing a series of phase II studies designed to evaluate newer treatment regimens. Current regimens under study explore the use of dose intensified methotrexate and thiotepa without brain radiation, and include the use of immunotherapy with rituximab, an antibody that targets a specific lymphocyte marker on the malignant cells. In addition to these consortium studies, the NCI is sponsoring multiple ongoing phase I studies that are testing novel agents and will also include patients with primary CNS lymphoma. If these initial experiences suggest that these new agents have activity against CNS lymphoma then more extensive studies will be done.

Several of the NCI funded cooperative groups, such as the Radiation Therapy Oncology Group (RTOG) and the North Central Cancer Therapy Group (NCCTG), are actively engaged in developing therapeutic interventions that reduce neurotoxicity in PCNSL. In separate programs, the NCI and the National Institute for Neurologic Disease and Stroke (NINDS) actively support research into blood-brain barrier disruption which can allow systemic therapies to obtain better access to brain malignancies. These multiple directed efforts are intended to collaboratively achieve better treatment for patients with these diseases.

#### *Lymphoma Treatment Targets and Novel Agents*

The proliferation of potential treatment targets and identification of novel agents directed at those targets facilitates NCI's development of novel treatments for patients with lymphomas. These trials include novel agents of many kinds, including molecularly-targeted small molecules, monoclonal antibodies, and anti-sense oligonucleotides. Agents already in development or in the planning stages include the following: Hu1D10 antibody, Campath-1H antibody, rituximab, IDEC-Y2B8 (anti-CD20 radioimmunoconjugate), LMB-2 antibody, triapine (small molecule ribonucleotide reductase inhibitor), GTI-2040 (antisense ribonucleotide reductase oligonucleotide), flavopiridol (CDK inhibitor), MLN 518 (tyrosine kinase inhibitor), BMS-247550 (epothilone B analogue), CCI-779 (rapamycin analogue), UCN-01 (CDK inhibitor), bryostatins (CDK inhibitor), arsenic trioxide, bortezomib (proteasome inhibitor), tipifarnib (FTI inhibitor), interleukin-12, oxaliplatin, 506U78 (AraG prodrug), thalidomide, depsispeptide, (histone deacetylase inhibitor), SAHA (histone deacetylase inhibitor), HeFi-1 (anti-CD30 antibody), G3139 (antisense Bcl-2 oligonucleotide).

#### *Cooperative Efforts with Industry*

The NCI cooperates on the development of novel anticancer therapies with commercial as well as institutional entities ranging from fresh start-ups to the multinational biopharmaceutical firms.



In July 2003, the “Academic-Public-Private Partnership Program (AP4)” request for application (RFA) was released. AP4 will support the discovery of new cancer agents and their rapid translation to human clinical trials. With this program, the NCI promotes collaborations between universities, pharmaceutical companies, biotech companies, and non-profit organizations. AP4 represents a new paradigm in drug discovery, development, and delivery for the NCI. This was developed out of a request by the Leukemia, Lymphoma, and Myeloma Progress Review Group to foster partnerships between many players to expedite drug development and availability of therapies and was NCI’s response to the request to create a Cancer Translational Research Allied Consortium.

### *SPOREs*

The NCI has funded two Lymphoma Specialized Programs of Research Excellence (SPOREs). One particular SPORE project seeks to design predictive and therapeutic tools based on the association of a virus (EBV) with HD. In the effort to develop new predictive markers, specimen collection protocols are being incorporated into the intermediate risk Children’s Oncology Group HD protocol. Analyses of specimen are ongoing and a new investigation is focused on the size of DNA fragments in plasma, a potential marker for viral activity. The second part of the study explores therapeutic strategies using vaccination or cellular immunotherapy, respectively, with the use of two viral proteins known to be targeted by the immune system. The ultimate goal is to conduct early phase clinical trials to establish safety and efficacy for this approach.

Another project focuses on the epidemiology of NHL in HIV-infected populations. Fast progress in these studies led to several findings: a) elevated levels of B-cell stimulatory factors were observed prior to the appearance of B-cell lymphoma; and b) DNA-modifying activities associated with B-cell activation are now believed to contribute to the genesis of the forms of AIDS-lymphoma that are not associated with oncogenic virus (EBV, HHV8) infection. Thus serum levels of the above markers are being measured in a longitudinal nested case-control study.

### *Recent NCI Supported Clinical Developments in Lymphoma Research*

Rituximab plus chemotherapy for aggressive NHL – Results of an intergroup study exploring the use of rituximab and CHOP chemotherapy in older patients with aggressive lymphoma have been reported. The study was a collaboration by several of the NCI sponsored cooperative groups and was designed to further explore the benefit provided by this new combination regimen. The findings suggested that more doses of the new drug, rituximab, may provide benefit beyond chemotherapy, and that continuing treatment with rituximab after completion of chemotherapy can delay the time to relapse, perhaps preventing it.

More intensive chemotherapy for aggressive NHL - The hypothesis that more intensive chemotherapy of aggressive lymphoma could be safely given and might improve outcome was studied in a study from the Southwest Oncology Group (SWOG). Treatment with dose intensified CHOP was safely administered and resulted in improved survival. Estimated overall survival at 5 years was 14% better than that of patients treated with standard-dose CHOP in an earlier SWOG study. This more intensive chemotherapy regimen is being tested in a phase III randomized clinical trial, and combinations with novel drugs are being evaluated.

Defining Standard of Care for first treatment of Hodgkin's Disease - While Hodgkin's Disease is curable in the majority of patients, a significant number still succumb to the disease and the chemotherapy and radiation necessary for treatment cause significant side effects. Research continues to identify more effective and less toxic therapies, and to determine what current treatment regimens offer the best balance of activity and toxicity. A large NCI sponsored randomized phase III study compared two frequently used chemotherapy regimens (ABVD and MOPP/ABV hybrid). It showed that the two regimens were very similar in their ability to control the disease, but also showed that the more intensive regimen caused more toxicity. These results established ABVD as the standard of care in this country, showing it to be a preferable first line regimen for patients, providing good clinical effects for most patients with a better safety profile.

Chemotherapy plus radioimmunotherapy for indolent NHL - Advanced follicular lymphoma is incurable with conventional chemotherapy and radiotherapy. A Phase II trial tested a novel regimen of six cycles of CHOP chemotherapy followed 4-8 weeks later by a radioactive lymphoma targeted antibody in 90 patients. Treatment was well tolerated. This study has established the feasibility, tolerability, and activity of this regimen for patients with advanced follicular lymphoma. This novel treatment appears promising compared to SWOG's historical experience using CHOP alone and is currently being compared to CHOP plus rituximab in a randomized Phase III trial.

#### *Ongoing Clinical Activity in Lymphoma*

There are currently 101 clinical trials for patients with lymphoma using agents under NCI IND, including 14 phase I trials, 55 phase II trials, 8 phase I/II trials, and 17 phase III trials. The NCI continues to identify novel agents that might offer therapeutic benefit to patients with lymphoma and will establish collaborative arrangements to participate in the evaluation of those agents where appropriate. Some examples of ongoing efforts:

- The NCI directly manages a large phase III study testing the use of idiotype vaccination added to standard chemotherapy for indolent lymphoma. It is hoped that the vaccine will focus the immune system against the lymphoma cells and eliminate residual disease following chemotherapy.
- The NCI Intramural Research Program (IRP) has developed a novel treatment regimen for aggressive lymphoma, EPOCH-R, which has shown very promising activity in phase II studies. NCI scientists have developed the Lymphochip technology that is able to evaluate the gene expression in lymphomas tissues. It has been shown that different types of lymphoma can be classified based upon their genetic profile, and this profile may allow clinicians to better predict those patients who would be better served by more or less aggressive treatments. Working with the Cancer and Leukemia Group-B, an NCI sponsored cooperative group, the NCI IRP will perform a definitive study that will determine whether the NCI developed EPOCH-R regimen can provide better cure rates in aggressive lymphoma, and will hopefully validate lymphochip analysis as a method to accurately characterize lymphoma types and their individual responses to therapy.

### *Long-Term Treatment Toxicity*

With current interventions, physicians are able to cure a significant number of patients with lymphoma. NCI is committed to advancing more effective treatments. The therapies necessary to achieve these cures consist of cytotoxic chemotherapy and radiation, both bringing significant short- and long-term toxicity. Multiple studies have documented that cumulative dosing of both drugs and radiation increase the risk of secondary cancers that develop over time. Radiation therapy is clearly associated with a risk of local solid tumors and leukemias in up to 5% of cured patients and, when it is necessary to use radiation to treat the Central Nervous System (brain and spinal cord), significant decreases in functioning can follow. Progressively over time, NCI funded research has concentrated on the use of alternate treatments in modified doses to prevent these complications. Recent advances include:

- Laparotomy and splenectomy for staging of lymphoma is a procedure that involves a major surgery opening the abdomen and removing lymph nodes and spleen. Beyond the acute costs, risks, and discomfort, there are long-term consequences of immune suppression and susceptibility to opportunistic infections. Cooperative group studies performed over the past 2 decades have now shown that this procedure is very rarely necessary for treatment decisions and as a result the procedure is very rarely used.
- Radiation therapy is very effective against lymphoid malignancies and has been a mainstay of treatment for lymphoma. As newer systemic therapies have been tested, Cooperative Group studies have shown that there is no need for radiation therapy in the majority of patients. Additionally, research from the Radiation Therapy Oncology Group (RTOG) investigators has improved the techniques used to give radiation therapy to limit exposure of normal tissues to radiation. These combined efforts have markedly decreased patients' exposure and will result in fewer neurologic complications and secondary malignancies.
- Cognizant of the risks of leukemia and lymphoma associated with certain chemotherapies, recently developed treatment regimens have minimized the use of these drugs. Agents with few long-term toxicities are becoming predominant, replacing those higher risk agents. While it will take a decade to exactly quantify the reduction in secondary malignancies from the newer treatments, it is expected that their incidence will drop dramatically.
- Vincristine is an important drug in the treatment of lymphoma, but is associated with progressive nerve toxicity that can lead to significant numbness and weakness. To avoid these toxicities, the doses of vincristine are often reduced, likely compromising the activity of the chemotherapy regimens. The NCI intramural program has spearheaded the use of infusional vincristine, where the drug is given by slow infusion over several days, and has found that much more vincristine can be given this way with fewer side effects. These regimens will now be tested in large multicenter trials to determine whether the long-term neurologic toxicities will be attenuated while maintaining disease control.
- Other chemotherapy drugs can cause heart damage (doxorubicin) and often cause sterility. A regimen exploring short course intensive chemotherapy with multiple different agents for Hodgkin's Disease has been developed at Stanford. This regimen appeared very promising in phase II studies with very impressive rates of long-term disease control, as well as a very reasonable toxicity profile with no cardiac toxicity and very little evidence of sterility in the patients who were interested in having families. Based on these early results, the regimen is currently being tested in a large phase III trial within all the US

cooperative groups, headed by the Eastern Cooperative Oncology Group (ECOG). Results of this study are expected to be available within the next 5 years.

### *Lymphoma Tissue Bank*

The NCI currently supports several human tissue resources, including the Cooperative Human Tissue Network, Clinical Trials Cooperative Groups, Cancer Family Registries, and tissue banks located at individual SPOREs. The National Dialogue on Cancer's Research Team has collaborated with the NCI and over 100 experts from various sectors to develop the *National Biospecimen Network (NBN) Blueprint* that proposes to standardize most of the key aspects of tissue collection, processing, annotation, access, and distribution that will allow comparison of genomic and proteomic data from biospecimens collected at different institutions. This blueprint describes best practices for all aspects of biospecimen management. The report recommends that some pilot projects be initiated to test the new concept.

### Item

***Myelodysplasia and myeloproliferative disorders*** — The Committee is pleased with NCI's efforts to address the lack of basic knowledge about myelodysplasia and myeloproliferative disorders, two very different types of chronic diseases of bone marrow cells that can develop into acute leukemia. The Committee encourages NCI to carry out the recommendations of its recent conference of experts on these diseases and to advance new research initiatives into developing effective treatments. (p. 58)

### Action taken or to be taken

Myelodysplastic Syndrome (MDS) and Myeloproliferative Disease (MPD) are similar in that both are premalignant blood stem cell diseases, they affect relatively small numbers of patients, the severe forms of the disease are often fatal, and there are no standard curative treatments. Because of the premalignant nature of these diseases, and the fact that patients are seen at many centers across the country, they have often not been included in NCI supported research.

However, NCI recognizes the importance of studying myelodysplasia (MDS) and myeloproliferative disorders (MPD) in understanding normal and malignant blood cell formation. This recognition is exemplified by a series of meetings sponsored by the NCI:

- Per previous Congressional request, NCI and National Heart, Lung, and Blood Institute (NHLBI) cosponsored a State of the Science (SOTS) Implementation Working Group Meeting for Myeloproliferative, Myelodysplastic and Marrow Failure Syndromes on March 2, 2003. The final report is available at <http://www.webtie.org/sots/Meetings/Leukemia/FnlRep703.pdf>.
- Two State of the Science (SOTS) meetings: (1) SOTS Meeting on Myelodysplastic Syndromes, October 30-31, 2000, <http://www.webtie.org/sots/Meetings/Leukemia/10-30-2000/Default.htm>; and (2) SOTS Meeting on Myeloproliferative Disorders and Mastocytosis, April 29, 2002, <http://www.webtie.org/sots/Meetings/Leukemia/04-29-2002/lectures.htm>; and

- The Leukemia, Lymphoma and Multiple Myeloma Progress Review Group Meetings, which addressed issues related to myelodysplasia and stem cell biology. See: Report of the Leukemia, Lymphoma and Myeloma Progress Review Group, May 2001 <http://prg.nci.nih.gov/llm/finalreport.html>, and NCI Strategic Plan to Address Recommendations of the Leukemia, Lymphoma, and Myeloma PRG, October 2002 <http://prg.nci.nih.gov/llm/llm.pdf>.

The March 2003 working group included a broad group of investigators. The recommendations of that meeting form the foundation of a comprehensive strategy to understand these two groups of diseases. The recommendations from the March 2003 meeting included:

- Endorse the importance of basic and clinical research on both MDS and MPD by giving priority to applications in these area
- Make funds available for basic research initiatives for MDS and MPD

In response to the second recommendation, NCI and NHLBI staff held subsequent meetings to coordinate activities between the two institutes. Two concepts for initiatives (Request for Applications) to stimulate innovative research in myelodysplasia and myeloproliferative disorders have been approved by the NHLBI Board of Extramural Advisors and are under review by the NCI.

In response to research priorities in this area, the NCI is working with several hematology research groups interested in developing investigator-initiated grant and program project grant applications. Discussions initiated at the March 2003 Working Group Meeting resulted in the submission of three Program Project (P01) grant applications to the NCI, two related to MDS and one about MPD. These applications are undergoing peer review. The MPD application proposes an International Consortium on MPD involving many of the researchers of the Polycythemia Vera Study Group, which was previously funded by NCI.

The NCI already supports a range of studies addressing the treatment of MDS and MPD. More than 20 novel agents are being tested in clinical trials. These include molecularly-targeted agents, monoclonal antibodies, and anti-sense oligonucleotides. Inside cells, drugs target cell growth, proliferation and cell death pathways, DNA transcription and replication, signaling molecules, and metabolic functions. Targets outside of the cell include growth signaling receptors, immune effector mechanisms, and blood vessels. A partial list of drugs, biologics, and vaccines in development include: Campath-1H antibody, MLN 518, bortezomib, thalidomide, CC-5013, Revimid, flavopiridol, UCN-01, Gleevec, bryostatins, arsenic trioxide, tipifarnib, triapine, depsipeptide, SAHA, Gemtuzumab ozogamycin, G3139, MDX-010, phenylbutyrate, Azacitidine, Atrovastatin, a TRAIL receptor agonist, 17-AAG, DN-101, Anti-Thymocyte Globulin, radiolabeled anti-CD45 and anti-CD33 monoclonal antibodies, and myeloid antigen peptide (PR-1) vaccines.

Hematopoietic stem cell transplantation is currently the only treatment with curative potential for MDS and MPD. Approximately 10 studies exploring variations of allogeneic bone marrow transplantation are ongoing at multiple centers. Current data show that among patients with less

advanced MDS, 3-year survival rates of 65% to 75% are achieved with HLA-identical related and unrelated donors. The probability of relapse is less than 5%. Among patients with advanced MDS, about 35% to 45% who receive transplants from related donors and 25% to 30% who receive transplants from unrelated donors are in remission beyond 3 years. The incidence of post-transplant relapse is 10% to 30%. Transplantation is successful in 50% to 80% of patients with MPD if performed before leukemic transformation.

Examples of relevant ongoing protocols include: Allogeneic Marrow and Peripheral Blood Stem Cell Transplantation for Treatment of Myelodysplasia and Myeloproliferative Disorders; Allogeneic or Syngeneic Marrow or Peripheral Blood Stem Cell Transplantation for Agnogenic Myeloid Metaplasia with Myelofibrosis; Allogeneic Peripheral Blood Stem Cell (PBSC) Transplantation for the Treatment of “Less Advanced” Myelodysplasia; A Pilot Study on Allogeneic Bone Marrow Transplantation as Primary Therapy for Patients with MDS and MPD; Autologous Stem Cell Transplantation for Myelodysplasia in First Remission; Matched Unrelated or Related Bone Marrow Transplantation for Hematologic Malignancies and Bone Marrow Failure; and Treatment of Advanced AML and MDS with Targeted Radiotherapy by Iodine-131-labeled anti-CD45 antibody followed by non-myeloablative allogeneic hematopoietic stem cell transplant.

#### Item

***Cancer genomics***– The Committee commends NCI for its commitment to understanding the role of genomics and genetics in the progression of cancer. Considerable effort must now be directed toward applying those findings to tumor classification and therapeutic choice, with a focus on breast, colorectal and lung cancer, as well as leukemia and lymphoma. An important component of this effort will be to build a public database of whole genome expression profiles from various tumor types, which includes clinical outcome information. The Committee encourages NCI to ensure that this data is available to health professionals to assist physicians and patients in choosing the best treatment options. (p. 58-9)

#### Action taken or to be taken

As the committee notes, a public database of whole genome expression profiles from various tumor types is a very important tool. The Cancer Genome Anatomy Project (CGAP) has been generating these data for the research community. It has 3 major components: 1) the determination of transcription in human tumors as well as normal cells and 2) the determination of transcription in mouse cells and tumors (a new component); 3) polymorphism identification and analysis in genes that have been shown to be involved in some aspect of tumorigenesis or protection thereof. The transcriptome definition in the various cell types is important in research designed to uncover the tumor-causing genes, markers for tumor types, metastasis genes, metastasis markers and outcome markers. All the data generated can be found on the Web site [CGAP.NCI.NIH.GOV](http://CGAP.NCI.NIH.GOV), together with information on how to use them. Recently, NCI prepared a CD-based tutorial to help investigators to use the tools. In addition, NCI is working to integrate new data generated using genome chips to the CGAP data. These novel chip experiments clearly point to a greater diversity in transcription than has been realized to date. It will be very important in the field of cancer genetics that the old and new data are merged as it will point to new diagnostic, clinical, and prevention targets.

The CGAP database has transcription information on a number of normal and cancerous breast tissues, normal and cancerous colon tissues, normal and cancerous lung tissues, and white blood cells, both leukemia and those that are lymphoma samples. These data facilitate molecular oncology research and are important material for the discovery and development of interventions.

Furthermore, through the NCI's Director's Challenge Program, the Specialized Programs of Research Excellence (SPOREs), and through investigator initiated research grants, the NCI is encouraging and supporting the development of genomic-based molecular profiles that will aid in tumor classification and aid in more effective management of cancer patients. The Director's Challenge Program supports twenty-two projects with the goal of developing molecular profiles that improve tumor classification. The NCI Center for Bioinformatics has collaborated with the Director's Challenge investigators to develop a public database of gene expression data. The Director's Challenge investigators are currently submitting their profiling data to the database. Efforts are underway to annotate the molecular profile data with the important clinical data associated with the specimens analyzed. The availability of the clinical annotation of the molecular data will significantly increase the value of this public resource.

The NCI Center for Bioinformatics is developing the Cancer Biomedical Informatics Grid (CaBIG), a comprehensive cancer bioinformatics system to serve the cancer research community. Gene expression data is submitted to the database through the Gene Expression Data Portal. Any investigator may submit gene expression data to the database. It is also being populated by data from Director's Challenge investigators, NCI intramural investigators, and other academic investigators. This public gene expression database is anticipated to become a significant resource for the cancer research community and will help in developing and testing strategies for using genomic data to help make decisions about patient management.

NCI is supporting programs to evaluate the application of genomic profiles to problems in the management of cancer patients. Through the NCI Program for the Assessment of Clinical Cancer Tests (PACCT), the NCI, NCI-supported clinical cooperative groups, and a biotechnology company are developing a clinical trial to test the ability of a molecular profile to identify women with node negative breast cancer who are cured by their initial surgery and do not need to be subjected to toxic chemotherapy. The breast cancer trial was proposed by a breast cancer working group convened by PACCT. The trial, which is expected to accrue approximately 8000 patients, will be carried out by the clinical cooperative groups with the molecular profiles of the patients determined by the biotechnology company. The trial is expected to begin accrual by summer/fall of 2004. Successful completion of this trial may result in a large percentage of women with early stage breast cancer being spared from the effects of chemotherapy.

A second PACCT working group is evaluating how molecular and genomic markers can address important clinical issues in colon cancer. A critical clinical issue is the identification of Stage II colon cancer patients who are at high risk of disease progression. These patients are not routinely treated but may benefit from chemotherapy following surgery. Four projects in the Director's Challenge program are developing molecular profiles in colon cancer. These include

profiles that identify high-risk stage II patients. As these profiles are identified, NCI is ready to move them rapidly toward clinical application.

A large study of lung adenocarcinomas is being initiated to confirm gene expression profiles identified by Director's Challenge investigators. These profiles classify early stage lung adenocarcinomas into good and bad prognostic groups. The study is a collaboration between Director's Challenge investigators, investigators from lung SPOREs, and investigators from the clinical comparative groups. This collaboration will ensure the availability of the 600 frozen, high-quality lung adenocarcinomas with clinical annotation needed for the study. Analysis of specimens will be carried out at four independent sites using standardized protocols. The large study has been preceded by a data comparability study to insure that the data from the four analytical sites can be combined for analysis. The data comparability study was carried out in collaboration with two commercial partners in addition to the academic investigators at the analytical sites. The large lung adenocarcinoma study is currently being initiated. It is anticipated that the confirmation study will identify patients with early stage adenocarcinomas of the lung who are cured by resection and need no further therapy. Importantly, patients at risk for cancer progression who may benefit from aggressive, or eventually targeted, therapeutic intervention will also be identified. These high-risk patients can be entered onto clinical trials to evaluate new therapeutic interventions. The profiles may also identify targets for development of new therapeutics.

The Leukemia, Lymphoma Molecular Profiling Project (LLMPP) is a collaboration between NCI intramural investigators, Director's Challenge investigators, investigators from the clinical cooperative groups, and international investigators. This important collaboration was organized to provide access to frozen lymphoma specimens with associated clinical data. These rare specimens are not available from any single institution. The LLMPP has facilitated a comprehensive molecular analysis of all of the most important subtypes of lymphoma. The LLMPP has developed molecular profiles that identify a high-risk subset of diffuse large B-cell lymphomas and a profile associated with risk of disease progression in mantle cell lymphoma. The LLMPP is developing diagnostic signatures in most of the other lymphoma subtypes and is working closely with a biotechnology company to develop a diagnostic microarray for all lymphomas. The LLMPP is also developing a strategy for a clinical trial that will assess molecular profiles of diffuse large B-cell lymphomas being treated with alternative therapies. The molecular status of the patients will be correlated with the response to these specific therapies. Molecular profiling projects in adult and pediatric leukemias are being carried out by both Director's Challenge investigators and other academic investigators. These profiles are not as mature as the molecular profiles developed in lymphomas; however it is anticipated that significant effort will be made to move these profiles toward clinical application in the coming year.

A new initiative entitled "Strategic Partnering to Evaluate Cancer Signatures" is intended to provide support to large collaborative projects proposing to move molecular signatures toward clinical application. The investigators applying to this initiative will already have identified molecular profiles that may have clinical utility. This initiative will provide the resources to confirm and refine the profiles and resources to develop the assays that will allow assessment of



the profiles in the clinical setting. Successful completion of these projects will result in molecular profiles that are ready to be validated in clinical trials. It is anticipated that the initiative will be made available to the cancer research community shortly.

#### Item

***Bone metastases***– The Committee urges NCI to continue its emphasis on studying the bone microenvironment and bone metastasis related to prostate cancer, breast cancer and multiple myeloma and to support research to delineate the mechanisms of reciprocal interactions between tumor cells and bone. NCI is also encouraged to establish a repository of human bone metastases for the scientific community and support research to generate three-dimensional in vitro and/or in vivo models that yield bone metastasis. (p. 59)

#### Action taken or to be taken

The major cause of death in cancer patients occurs when the primary tumor spreads (metastasis) to distant but vital organs of the body. Although it is difficult to determine how frequently tumors metastasize to the bone, it is known that a high percentage of patients with prostate cancer, breast cancer, and multiple myeloma develop bone metastasis. Bone metastases are also frequently seen in patients with lung cancer, renal cancer and melanoma. There are approximately 350,000 deaths per year in the United States from cancer patients with bone metastasis.

Bone metastases are associated with frequent intractable bone pain, bone fragility and deformity, bone fractures, hypercalcemia, nerve compression syndromes such as spinal cord depression, and death. There are two types of bone metastasis, osteolytic and osteoblastic. In osteolytic lesions, factors such as parathyroid related protein and interleukins are released by tumor cells in the bone microenvironment. These factors act on bone cells, which in turn, produce factors that stimulate osteolytic (bone resorption) or osteoblastic (new bone formation) activities. It is also evident that reciprocal interaction between tumor cells and the bone marrow microenvironment is critical in tumor cell survival and growth which eventually leads to the formation of bone metastases. Both osteoblastic and osteolytic lesions are seen in patients with bone metastasis.

The relationship between prostate cancer and bone metastasis is unique among cancers. Approximately 90% of the advanced prostate cancer patients develop bone metastasis and are characteristically osteoblastic. One third of the patients with prostate specific antigen (PSA) greater than 20 at the time of diagnosis have radiologic evidence of bone metastasis. In addition, bone marrow samples of patients thought to have localized disease have frequently been shown to have elevated PSA at the time of prostatectomy, suggesting that bone marrow metastasis may be an early event, even prior to clinical symptoms and nuclear radiographic positivity. Similarly, of the more than 44,000 deaths due to breast cancer in the U.S. in 2002, more than 80% of the breast cancer patients showed evidence of bone metastasis.

Multiple myeloma (MM), which represents 13% of all lymphoid cancers in the white population and 31% in the black population, is a severely debilitating as well as incurable cancer. The major source of morbidity and mortality associated with MM are osteolytic lesions that occur only in the area adjacent to the myeloma cells. New bone formation that normally occurs at the

sites of bone destruction is also absent. These results suggest that locally active factors produced by myeloma cells induce extensive bone destruction and block new bone formation.

In order to improve therapy and ultimately prevent bone metastasis, the NCI is using a multi-pronged approach to increase our understanding of the unique role the bone microenvironment plays in metastasis of cancer to the bone with the hope that the resulting information will help (a) to improve clinical trials using bisphosphonates, and (b) to stimulate basic research which will lead to a precise understanding of the pathophysiology of bone metastasis.

Bone metastases are a major source of morbidity in breast and prostate cancer, leading to pain, pathologic fractures, spinal cord compression, and hypercalcemia. Hormonal therapy such as aromatase inhibitors for breast cancer and androgen deprivation for prostate cancer can induce osteopenia, a condition that further predisposes patients with bone metastases to complications. Although several members of the class of bisphosphonates are FDA-approved to delay skeletal-related events in prostate, breast, or myeloma, it is not yet known whether initiating treatment earlier in the course of disease could have a greater impact on preventing bone complications and prolonging life by altering the microenvironment of the bone marrow. The following phase III studies are studying ways to optimize the potential benefit from bisphosphonates.

**Prostate Cancer:** Zometa® (zoledronic acid) is the only bisphosphonate approved for patients with prostate cancer. The pivotal trial was conducted in men with metastases to bone who had progressed after treatment with at least one hormonal therapy. In a collaborative effort with industry, NCI is supporting a large national trial that will evaluate whether starting zoledronic acid at the time of initiation of hormone therapy will be beneficial. Laboratory correlates to the clinical trials include markers of bone turnover and bone density, as well as predictors of bone recurrence.

Another relevant phase III trial, led by MD Anderson Cancer Center, and sponsored by the GU Specialized Program of Excellence (SPORE) is a randomized trial of standard chemotherapy for metastatic prostate cancer, docetaxel, plus or minus gefitinib, and EGFR inhibitor. There is preclinical evidence that the combination may be beneficial in men with prostate cancer that has metastasized to the bone.

**Breast Cancer:** Three published randomized trials in women with curable breast cancer have yielded conflicting results regarding effect on disease-free and overall survival when bisphosphonates are given in the adjuvant setting. It is unclear whether bisphosphonates simply decrease skeletal complications or whether they can alter the function of osteoclasts so that the microenvironment of the bone marrow is no longer a good “soil” for tumor “seeds.” A trial nearing completion through the National Surgical Adjuvant Breast and Bowel Project (NSABP) is designed to provide a definitive answer to the question by randomizing 2,400 women with early stage breast cancer to receive the bisphosphonate clodronate or placebo in addition to their standard adjuvant therapy.

Another phase III trial that will attempt to extend results from the NSABP trial is in development. S0307 will test whether the type of bisphosphonate and the length of treatment

make a difference in terms of benefit in disease-free and overall survival. Both studies are open to all qualified physicians through the NCI's Clinical Trials Support Unit and both studies will collect specimens to analyze for predictive and prognostic markers.

**Renal Cell Carcinoma:** The development and progression of clear cell renal carcinoma is related to loss of function of the tumor suppressor gene called von Hippel-Lindau (VHL). In the absence of normal function, vascular endothelial growth factor (VEGF) accumulates and is believed to play a key role in the development of vascular tumors such as clear cell renal cancer.

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody. Recently, a large definitive trial in metastatic colorectal cancer conducted through the NCI-sponsored cooperative groups demonstrated a significant improvement in overall survival when bevacizumab was added to standard chemotherapy. A small trial conducted in patients with metastatic renal cell carcinoma by NCI intramural scientists demonstrated a significant improvement in time to progression in patients who received bevacizumab, suggesting that blocking angiogenesis in renal cancer may also be effective in this disease. A definitive trial to test this hypothesis has just opened.

Bisphosphonates and endothelin receptor antagonists are novel treatment approaches that may be useful in the management of bone metastasis and cancer associated bone pain. Preclinical trials in pet dogs have been designed to study the role of these agents alone and in combination with conventional chemotherapeutic agents for the treatment of bone cancers and bone metastasis. Through the addition of biological endpoints into these trials we expect new information on the use of these agents in future human trials to be better understood. Although earlier in development, the NCI is actively involved in the development of novel therapeutics that may target bone cancers and bone metastasis. These agents are currently moving towards murine preclinical studies. The use of pet animals in pre-clinical trials may facilitate the translation of these new agents towards the treatment of bone metastases in human patients.

The current understanding of the molecular underpinnings of bone metastasis is now beginning to emerge. Several recent developments suggest that bone metastasis is a research area of great opportunities for the following reasons: 1) the availability of a number of experimental models, obtained by intracardiac or orthotopic injections, to study bone metastasis in prostate and breast cancer and in multiple myeloma; 2) the availability of microarray and related technologies and the laser capture micro-dissection technology permit evaluation of complex interactions, such as those involved in tumor-bone microenvironment interactions; 3) significant advances in basic bone biology research, with development of a repertoire of critical reagents, have provided a large cohort of basic biologists who could enter the field of bone metastasis; and 4) the identification of the molecular interactions between tumor and bone cells has progressed to the next stage where gene array technology may be applied to identify new targets for therapy. Tumor growth does not appear to be a major point of regulation of bone metastases, although growth is the most common parameter assayed in vitro. Researchers are therefore encouraged to use microarray and proteomics technologies to compare metastatic versus non-metastatic cells and design an efficient system for validating the physiological significance of identified candidate genes/proteins in vivo using animal models. Further, the role played by malignant tumor cells (e.g., breast and prostate cancer) on bone turnover also needs to be delineated.

The NCI issued an initiative in May 2002, entitled "Molecular Interactions between Tumor Cells and Bone." The purpose of this Request for Application is to solicit grant applications from researchers interested in understanding the pathophysiology of bone metastasis, especially as it relates to tumor cell-bone stroma interactions. This will lead to a better understanding of the unique features of the bone and its microenvironment that renders it an attractive site for tumor cells. This multi-institutional initiative was co-sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS).

One hundred and eight applications were received, 18 applications (\$4.5 million) were funded. NCI funded eight applications (\$2 million), eight grants were funded by NIDDK (\$2 million), and two by NIAMS (\$500,000). The NCI funded studies are all directed at either identifying or characterizing the various biological factors that tumor cells produce that give them the ability to metastasize to the bone. This will allow the generation of novel therapeutic reagents that will specifically target these critical traits that the tumors acquire in order to permit bone metastases.

The NCI has identified the study of cancer microenvironment as an area of Extraordinary Opportunity in its Bypass Budget proposal. The main focus under this theme is to: 1) define the molecular signatures of cells in the cancer microenvironment at various points during initiation and progression of cancer; 2) identify factors used by cancer cells to activate cells in the tumor microenvironment, which in turn support tumor growth and progression; 3) identify the origin of cells and factors that comprise the tumor microenvironment; 4) establish a repository for antibodies, cell lines, animal models, and tissues that relate to cells in the microenvironment; and 5) apply knowledge derived from molecular analysis studies exploring tumor-host interactions to create targeted interventions. Research under this Extraordinary Opportunity will also address issues related to bone metastasis observed in several human malignancies including, prostate and breast cancer and multiple myeloma.

The NCI has initiated or is participating in a number of Trans-NIH wide initiatives to address research issues that are relevant to tumor metastasis, including bone, and to cover a number of human cancers such as those of the prostate, breast, multiple lung and myeloma.

A Program Announcement, entitled "Bone Anabolic Hormones, their Receptors and Signal Transduction Studies," solicits applications that focus on systemic hormones, local growth factors and bone-active cytokines with potential bone anabolic effects. Although the primary focus is on basic research, the long-term objective is to identify potential targets of therapeutic value in the treatment of tumor metastasis to bone.

A Program Announcement, entitled "Complex Formation in Hormonal Regulation of Gene Expression," that is designed to exploit and expand upon advances made in the area of hormonal regulation of gene expression, especially the role of novel factor(s) associated with steroid hormones in breast and prostate cancer. An area of great interest in cancer biology is that bone metastases in these tumors often progress to a stage where they become estrogen- independent or androgen-independent.

Since 2002, the NCI has organized or co-sponsored several workshops or international symposia related to tumor microenvironment with special emphasis on bone metastasis.

- In April 2002, NCI co-sponsored the “Third North American Symposium on Skeletal Complications of Malignancy.” This symposium focused on (a) bone marrow microenvironment and animal models of bone metastasis, (b) biology and clinical aspects of bone metastasis in prostate cancer, (c) biology and clinical aspects of bone metastasis in breast cancer, (d) biology and clinical aspects of bone metastasis in multiple myeloma, (e) preclinical and clinical studies on bone metastasis: future directions, and (f) current and future status of adjuvant therapy of bone metastasis.
- In December 2003, NCI co-sponsored the “Fourth International Conference on Cancer-Induced Bone Diseases.” The conference provided clinicians and basic researchers, including biologists, urologists, oncologists and endocrinologists, with a comprehensive program on the most recent advances made in the pathophysiology and management of patients with cancers that involve the bone. The conference covered a spectrum of bone metastases caused by breast cancer, prostate cancer, and osteolytic lesions. Discussions involved the skeleton and specific cancers with possibility for bone metastases, including breast and prostate cancers, and multiple myeloma. Unraveling the molecular basis for cancer metastasis to the skeleton will improve understanding not only of the most common cancers, but also provide new insights into normal and abnormal bone remodeling. Segments of this symposium were also devoted to the clinical management of patients with these complications of malignancy and included the latest pharmacologic and surgical treatments.
- In April 2004, NCI will sponsor a workshop on “Lymphangiogenesis and Cancer: Research Directions and Therapeutic Opportunities.” It is well known that solid tumors metastasize predominantly through the lymphatics while hematologic malignancies spread via the vascular system. While considerable progress has been made in the last 15 years on angiogenesis, lymphangiogenesis is a relatively poorly studied area of science. This workshop will bring together experts in the area of lymphangiogenesis, cancer biologists, clinical oncologists, vascular biologists, imaging and animal model experts, and investigators from pharma to provide a state-of-the-art understanding of this field, identify promising research avenues, and therapeutic opportunities.

The NCI is part of two federal working groups related to bone metastasis. The first, the “Federal Working Group on Bone Diseases,” has members from many institutes at the NIH as well as representation from other federal agencies. The second more recently established group is focused on promoting research in the area of lymphatics, and has members representing various institutes of the NIH as well as members from the Lymphatic Research Association. Lymphangiogenesis, or the formation of new lymph vessels, is important in the dissemination of tumor cells to different sites, especially in solid tumors. Since many solid tumors, including breast, prostate, lung, renal and melanoma, metastasize to bone, research in lymphangiogenesis will help to better understand the process of tumor metastasis, including bone metastasis.

A major contribution to our understanding of the process of bone metastasis has been the demonstration that the bone microenvironment critically influences the behavior of cancer cells that metastasize to bone. The bone microenvironment alters the phenotype of metastatic tumor cells in a manner that changes tumor behavior. Furthermore, some of the molecular mechanisms responsible for the bi-directional interaction between bone and tumor cells in vivo have been recently identified.

#### Item

***Tobacco harm reduction***— The Committee is aware that NCI has established the Tobacco Control Research Branch, which is designed to reduce cancer incidence and mortality caused by tobacco use through a comprehensive research program, and applauds the establishment of a collaborative research effort between the NCI and the CDC related to the analysis of tobacco products and harm reduction. The Committee is aware of a 2001 report from the Institute of Medicine entitled “Clearing the Smoke, Assessing the Science Base for Tobacco Harm Reduction.” This report notes that despite overwhelming evidence and widespread recognition that tobacco use poses a serious risk to health, some tobacco users cannot or will not quit, and raises the question of whether or not addicted tobacco users who do not quit could reduce the health risks of tobacco products. NCI should be prepared to report to the Committee during the fiscal year 2005 budget hearings regarding the findings of this collaboration with regard to the effectiveness of harm reduction for those tobacco users who are unable to quit. (p. 59)

#### Action taken or to be taken

NCI greatly appreciates the Committee’s recognition of the Tobacco Control Research Branch (TCRB) and its collaborations with CDC. NCI is also committed to expanding and enhancing collaboration with CDC to maximize the effectiveness and efficiency of both agencies' tobacco control activities. In this regard, TCRB and the CDC's Office on Smoking and Health (OSH) have completed a memorandum of agreement outlining plans for a broad range of collaborative activities to be undertaken over a 5-year period.

The problem of tobacco use remains a significant public health reality. Currently, there are 46 million adult smokers in the U.S., representing approximately 23% of the population. The prevalence of smoking has decreased considerably since the early 1960s; during the 1990s prevalence decreased by approximately 1% per year. Despite these advances, tobacco remains the leading cause of preventable, premature death in the U.S. Every year, approximately 440,000 Americans die from tobacco-caused illness. Fully half of all long-term smokers, approximately 90% of whom began smoking in their teenage years, will die prematurely from tobacco use and one in four smokers will die in middle age (35-69 years) losing, on average, 20-25 years of normal life expectancy. Reflecting the fact that tobacco use is the cause of approximately one-third of all cancer deaths, research on tobacco and tobacco-related cancers is identified as a scientific priority. Through this research, NCI seeks to understand the causes of tobacco use, addiction, and tobacco-related diseases and apply the knowledge acquired to their prevention and treatment.

To date, the only proven way to reduce the enormous burden of disease and death due to tobacco use is to prevent youth from beginning to smoke, and to help smokers, both youth and adults, to quit. Accelerating cessation, through individually based treatment and through population-based strategies, will have the greatest immediate impact on population health. We have much to offer people who smoke and want to quit, including effective behavioral treatments and medications, and the evidence strongly suggests that people who keep trying to quit do succeed, although many will require numerous attempts before being successful.

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

NCI appreciates the Committee's attention to *Clearing the Smoke: Assessing the Science Base of Tobacco Harm Reduction* (Institute of Medicine, 2001). This report examines the challenges in evaluating whether or not tobacco products purported to reduce harm actually reduce the health risks of tobacco use. The report looks at the types of products that could reduce harm, both tobacco industry and pharmaceutical, and reviews the available evidence for their impact on various forms of cancer and other major diseases. It recommends approaches to monitoring and regulating these products and tracking their public health effects. It also calls for research to fill knowledge gaps and inform policies, regulations, and programs.

#### Tobacco Harm Reduction Activities

NCI is engaged in a number of research activities that relate to new tobacco products and harm reduction, including:

- The NCI is funding investigator-initiated grants on tobacco products and their impact on individual and population health. These studies are investigating the use of pharmaceuticals in reducing tobacco harm, testing some of the potential reduced exposure products, the effects of the use of potential reduced exposure tobacco products on smoking cessation, and the impact of current smokers switching to new tobacco products on exposure to tobacco toxins (as determined by biomarkers).
- NCI has implemented the Health Information National Trends Survey (HINTS), which is a national health communications survey that collects data every two years to assess the public's need for, access to, and use of cancer-related information. This survey contains questions about tobacco product use and perceptions of the health risks associated with the use of different types of tobacco products, including those claiming to reduce harm.
- NCI collaborates with researchers at CDC's Air Toxicants Laboratory at the National Center for Environmental Health. This laboratory is investigating how chemical additives, constituents, and design affect the toxicity, carcinogenicity, and addictiveness of tobacco use. The findings from research conducted at this laboratory are intended to further the

scientific understanding of how chemical makeup and product design influence the health consequences of tobacco products.

- NCI has recently established a tobacco harm reduction network. This independent authoritative group of scientists is charged with developing a comprehensive strategy for assessing the impact of potential reduced exposure products and prioritizing areas for future tobacco harm reduction research. The group also aims to coordinate the development of mechanisms for sharing data and providing guidance on conducting transdisciplinary tobacco harm reduction science, as well as informing tobacco policies and regulation.
- The Scientific Advisory Committee on Tobacco Product Regulation (SACTob) was established by the World Health Organization and held its first meeting in October 2000. The committee is composed of national and international scientific experts on product regulation, smoking cessation and laboratory analysis and includes representatives from NCI and CDC. SACTob provides scientific recommendations to WHO that address the most effective and evidence-based means to achieve a coordinated regulatory framework for tobacco products. One of the recommendations resulting from this group pertains to new tobacco products that are promoted to reduce harm.
- In May 2001, NCI, CDC, the National Institute on Drug Abuse (NIDA), the Robert Wood Johnson Foundation (RWJF), and the American Legacy Foundation, convened the Reducing Tobacco Harm Conference to develop research recommendations aimed at addressing the knowledge gaps identified in the IOM report. The major research recommendations of the Conference were in the areas of: a) products and methods for reduced tobacco toxin exposure and harm reduction; b) exposure and toxicity assessment for reducing tobacco harm; and c) public health impact (communication, surveillance, and regulation).
- In February 2002, NCI, in collaboration with CDC and other partners, convened the First Conference on Menthol Cigarettes. This conference sought to evaluate the state of the science regarding the health implications of adding menthol to cigarettes and to set research priorities for further investigation into the health effects of menthol cigarettes. An article about the proceedings of the conference is scheduled to appear in a supplemental issue of *Nicotine & Tobacco Research* in February 2004.
- In September 2002, NCI, together with CDC and the Swedish Centre for Tobacco Prevention convened the *3rd International Conference on Smokeless Tobacco: Advancing Science & Protecting Public Health* in Stockholm, Sweden. This conference examined the use, health effects, chemistry and constituents, and global health impact of smokeless tobacco. The conference included discussion of smokeless tobacco being promoted as a potentially less harmful product than cigarettes.
- The NCI, the American Legacy Foundation, and the California Tobacco Related Disease Research Program led a one-day meeting in February 2003 to address the ethics of tobacco industry funding of research. This conference included independent scientists, tobacco control advocates, ethicists, lawyers, and even several tobacco company representatives. A goal was to assess whether there is a mechanism whereby tobacco companies could provide funds for research in a way that would be considered acceptable to the scientific and tobacco control advocacy groups. The general perspective is that it may be possible to



accomplish that goal. A summary of that meeting is being written to guide future endeavors in this area.

- NCI plans to convene about 30 government and non-government scientists to participate in a Methods and Markers Conference scheduled for February 26-27, 2004 in Bethesda, MD. The goal of this meeting is to identify methods and biomarkers for exposure and disease risk that can be used to assess potential reduced exposure/reduced risk products, both medications and tobacco products. As a result of this conference, there will be a publication intended to educate the scientific and public health communities, and regulatory agencies, about the strategies that should be employed in assessing pharmaceutical products and new tobacco products within the framework of tobacco harm reduction.

#### Other Tobacco-Related Activities

- The CDC and the WHO, with funding from NCI and other national and international organizations, developed the Global Youth Tobacco Survey (GYTS), which is currently administered to youth in approximately 95 countries. This survey is school-based and employs a common methodology and core questionnaire to track tobacco use among youth across countries.
- The Tobacco Use Supplement to the Current Population Survey, which collects information from a large, nationally representative sample of the U.S. population, is a key source of national and state-level data on tobacco use in U.S. households. This data is used to conduct tobacco-related research, to monitor the overall control of tobacco use and to evaluate state tobacco control programs.
- The CDC's Guide to Community Preventive Services: Tobacco Prevention and Control addresses a variety of health topics relevant to communities, public health agencies, and health care systems. It summarizes what is known about the effectiveness of community-based tobacco control interventions designed to prevent tobacco use initiation, promote tobacco use cessation and reduce exposure to environmental tobacco smoke (ETS).
- NCI, in collaboration with CDC and the American Cancer Society, has created a Web site, [www.smokefree.gov](http://www.smokefree.gov), which offers science-driven tools, information, and support that have been effective in helping smokers quit. The Web site features links to the NCI's Cancer Information Service (CIS) telephone-based quitline, 1-877-44U-QUIT, and to the CIS instant messaging service, "LiveHelp," where smokers can connect to a trained smoking cessation counselor for individualized quitting assistance.
- The Public Health Service Clinical Practice Guidelines: *Treating Tobacco Use and Dependence*, was created by a 30-member expert panel, charged with identifying effective, validated, tobacco dependence treatments and practices. NCI and CDC scientists served as members of the panel.
- The Cancer Control PLANET (Plan, Act, Network with Evidence-based Tools) Web portal is a collaborative effort by NCI, CDC, and other federal and non-government partners aimed at providing access to data and resources that can help cancer control planners, health educators, program staff, and researchers design, implement, and evaluate evidence-based cancer control programs. One of the goals for PLANET is to help bridge the gap between the discovery of effective interventions and their incorporation into effective programs and policies at the local and state level.

- NCI, together with CDC and other partners, recently convened two national meetings: the National Conference on Tobacco and Health Disparities (December, 2002) and Women, Tobacco, and Cancer (February, 2003). Both meetings brought together researchers and public health practitioners to formulate recommendations for research and dissemination. Anticipated products include meeting reports and publications in peer-reviewed journals.
- NCI's newly formed Tobacco Intervention Research Clinic (TIRC) is a state-of-the-science research entity with a mission to interact and collaborate with the broader scientific community, including other government organizations, academia, and private industry, to design and conduct cutting-edge original research on treatment for tobacco dependence. Both behavioral treatments and new pharmacotherapies will be considered for study at the TIRC. The TIRC's first study is a proof-of-concept trial to determine the feasibility of a previously untested, comprehensive, multi-component, smoking cessation treatment designed to treat smokers who are having exceptional difficulty quitting (i.e., cancer survivors who continue to smoke). The study is designed to explore the potential of developing a potent smoking cessation intervention for cancer survivors by enhancing currently available treatments with contingency management, a promising behavioral technique that rewards patients for not smoking. This study is intended to generate pilot data to assist in designing a larger study of smoking cessation in cancer survivors. Future studies under consideration include evaluation of a new drug to enhance smoking cessation and prevent weight gain, studying the effects of dosing schedule on the effectiveness of nicotine replacement therapy, and investigating a novel behavioral approach to cessation, modeled after evidence-based treatments for phobias.

Tobacco remains the nation's leading cause of premature, preventable death. Sustained commitment, collaboration, and investment in tobacco control will ensure the steady decrease in the prevalence of all types of tobacco use, and consequently, tobacco-related cancers. There is much to be learned about tobacco products that purport to reduce harm and/or to assist smokers to quit. NCI plans to continue to collaborate with partners to develop and implement a framework for the independent and objective scientific research, review, and interpretation of data on tobacco products and their use. In addition, we will work to ensure that the science is synthesized and disseminated to scientists, health care providers, policymakers, and the public.

FY 2004 Senate Appropriations Committee Report language (S. Rpt 108-81)

Item

**Blood Cancers** – The Committee urges the NCI to continue to implement the research priorities for leukemia, lymphoma, and multiple myeloma included in the May 2001 Progress Review Group Report. (p. 102)

Action taken or to be taken

Following the publication of the Leukemia, Lymphoma and Myeloma (LLM) Progress Review Group (PRG) report, the NCI followed up with an extensive portfolio review, concentrating on the areas that the LLM PRG indicated were of highest priority. Based on this portfolio review, a working group of NCI staff developed strategies that would fill the gaps in our current portfolio and that would address the PRG recommendations. In November 2002, the NCI published the

“Strategic Plan to Address the Recommendations of the Leukemia, Lymphoma, and Myeloma Progress Review Group”. Some of the items reported here are from programs that were ongoing at the time of the PRG report and some were developed based on the Strategic Plan. This list is illustrative of the progress that NCI has made in leukemia, lymphoma, and myeloma.

#### *Etiology and Pathobiology*

The PRG recommended molecularly characterizing hematological malignancies and identifying molecular targets. The NCI had an ongoing project from the Director’s Challenge: Toward a Molecular Classification of Tumors that investigated the gene expression patterns of different lymphomas and showed clinical outcomes that are linked to specific patterns. Diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, and follicular lymphoma are just some of the malignancies that have been molecularly characterized by this assay. The future holds promise for using gene profile signatures to assist physicians in diagnosis and, eventually, treatment decisions. Currently, intramural scientists are working together with members of the Cancer and Leukemia Group B (CALGB) cooperative group on a clinical trial that will incorporate tumor microarray analysis in all patients to identify molecular mechanisms of drug resistance, develop molecular prognostic models, and assess microarray tissue diagnosis. The results of this study will have important implications for future treatment of DLBCL.

The NCI has also re-issued the request for “Correlative Studies using Specimens from Multi-Institutional Prevention and Treatment Trials”. This initiative currently has many projects examining different types of leukemia. This initiative addressed the PRG’s recommendation to provide molecular characterization of hematological malignancies.

To respond to the PRG’s recommendation that effort be focused on the understanding of the interactions among genotype and a host of factors that can lead to hematopoietic malignancy, the LLM working group proposed expanding the Cohort Consortium, a multiple-cohort consortium designed to facilitate the conduct of large-scale, powerful studies of gene-environment interactions, to include these malignancies in the study. In an upcoming 2004 meeting, the Cohort Consortium will consider expanding its studies to include leukemia and lymphoma.

The Mouse Models of Human Cancer Consortium has developed six models to study hematologic malignancies. These models will be useful in addressing the PRG recommendation to identify the basic mechanisms responsible for genome instability and other mutations in hematological malignancy, as well as looking into the relationship with the host biological environment.

#### *Drug development and therapeutics*

In March 2003, the NCI and NHLBI co-hosted a State of the Science “Implementation Working Group Meeting for Myeloproliferative (MPD), Myelodysplastic (MDS), and Marrow Failure Syndromes”. This responded to the PRG’s recommendation that NCI foster partnerships between various stakeholders. In addition to informing this research community to ongoing programs that could enhance their research, this open forum allowed discussion of issues and the ability of the participants to assign themselves to planning committees to address four areas relevant to MPD/MPS research and treatment: 1) patient availability; 2) diagnosis of these

diseases; 3) cellular and molecular diagnosis; 4) software and database monitoring. The NCI and NHLBI are preparing Request for Applications (RFAs) in this area.

In July 2003, the RFA “Academic-Public-Private Partnership Program (AP4)” was released. This RFA responded to the recommendation by the LLM PRG to foster partnerships between multiple experts to expedite drug development and availability of therapies and was NCI’s response to the request to create a Cancer Translational Research Allied Consortium. AP4 will support the discovery of new cancer agents and their rapid translation to human clinical trials. With this program, the NCI promotes collaborations between universities, pharmaceutical companies, biotech companies, and non-profit organizations. AP4 represents a new paradigm in drug discovery, development, and delivery for the NCI.

The CLL (Chronic Lymphocytic Leukemia) Research Consortium (CRC) continues to make significant progress on the genetics, biochemistry, immunobiology, pharmacology and clinical treatment of this disease. The NCI has expanded the activities of the CRC by funding a supplemental application. This supplement was used (1) to add a familial CLL component to the program project, (2) to further expand activities using the transgenic CLL mouse model developed in the initial grant to perform preclinical evaluation of novel therapeutics in vivo and (3) to further fortify the clinical trial infrastructure of the CRC. This responds to the recommendation that the NCI foster partnerships between various stakeholders to expedite the availability of therapies.

In fulfilling the PRG request for development of resources to translate lead structures into therapeutic agents, RAID (Rapid Access to Intervention Development-preclinical) and R\*A\*N\*D (Rapid Access to NCI Discovery Resources) have approved 3 meritorious applications. The first agent, from the RAID program, is for treatment of advanced acute myelogenous leukemia and MDS to decrease relapse following hematopoietic stem cell transplant. This targeted radiotherapy uses an antibody to a panhematopoietic antigen. The next two funded proposals are both from the R\*A\*N\*D program. The first is a proposal to identify small molecules that compete for the interaction of the relevant pathway proteins regulated by the BCR/ABL oncoprotein. The second proposal is in the development of intervention strategies for leukemia and lymphomas that involve subnanoparticles of elemental selenium that will be used as anti-tumor agents.

The Community Clinical Oncology Program (CCOP) now has two prevention and control trials, one for ALL (“Difference in parental caregiving demands in childhood ALL by length of infusion therapy”) and one for multiple myeloma (“Oral antibiotic prophylaxis of early infection in multiple myeloma”). CCOP responds to the PRG recommendation to increase the development of the required resources to translate “lead” structures and molecules into effective therapeutic agents.

The Cancer Therapy Evaluation Program (CTEP) continues to make strides in the planning, assessment, and evaluation of clinical trials. This broad activity responds to the PRG’s recommendation that NCI have a priority of drug development for the hematologic malignancies.

The proliferation of potential treatment targets and identification of novel agents directed at those targets facilitates CTEP's development of novel treatments for patients with lymphomas. There are currently 101 clinical trials for patients with lymphoma using agents under NCI IND, including 14 phase I trials, 55 phase II trials, 8 phase I/II trials, and 17 phase III trials.

Recently, NCI funded a Specialized Program of Research Excellence (SPORE) to promote innovative translational research in all aspects of leukemia. This includes research in the epigenetics of drug resistance, therapy (including targeting of specific transcription factors for therapy), and molecular epidemiology. This satisfies the recommendations to develop more therapeutics for hematologic malignancies.

#### *Education, Communication, and Survivorship Research*

The InterLymph consortium has been established between the principal investigators leading studies in this area of research to share data and biological samples in order to explore etiological and mechanistic hypotheses that cannot be adequately addressed in the individual studies. This responds to the LLM PRG's request to identify and target individuals and populations at high risk for adverse long-term outcomes and also to study the interaction between genotype and other factors that can lead to hematopoietic malignancy. InterLymph represents a model to overcome the limitations of molecular cancer epidemiology; namely, the lack of power for the analysis of gene-environment interactions and the study of subtypes of malignancies defined according to molecular and genetic criteria. Among the hypotheses that will be initially addressed are: individual susceptibility from variation in genes involved in immunological response; role of *Borrelia* infection in lymphomagenesis; familial aggregation in NHL and related malignancies' risk factors for rare NHL types; and UV exposure and NHL risk.

NCI has funded the Multiple Myeloma Prevention Study, a Phase IIB, double blind, placebo-controlled study of an NSAID (non-steroidal anti-inflammatory drug—non-selective or selective agent) administered for the modulation of biomarkers associated with MGUS/smoldering myeloma. This responds to the PRG request to identify and target individuals and populations at high risk for adverse long-term outcomes.

#### Item

***Bone Metastasis*** – The Committee encourages NCI to continue its emphasis on studying the bone microenvironment and bone metastasis related to prostate cancer, breast cancer and multiple myeloma and to support research to delineate the mechanisms of reciprocal interactions between tumor cells and bone. To provide an infrastructure for this research, NCI is encouraged to establish a repository of human bone metastases for the scientific community and support research to generate three-dimensional in vitro and/or in vivo models that yield bone metastases. (p. 102)

#### Action taken or to be taken

Please refer to pages NCI-66 through NCI-71 of this document for NCI's response to this significant item regarding Bone Metastasis.

### Item

***Brain Tumor*** – In November 2000, the NCI and NINDS convened a panel of experts to review the field of brain tumor research and make recommendations to enhance it. The Committee is pleased that the Institutes followed that meeting by establishing the Neuro-Oncology Branch, an inter-institutional initiative aimed at bringing a multidisciplinary approach to brain tumor research. The Committee now urges the NCI and NINDS to establish a coordinated and multi-institutional tissue bank that would gather not only tissue but also blood and cerebrospinal fluid from patients with all varieties of brain tumors. The system should also be linked to a comprehensive database of relevant clinical, demographic, pathologic, biologic, and therapeutic information on all patients whose tissue is banked. The Committee further strongly urges the NCI to increase funding and the number of Specialized Programs of Research Excellence in Brain Tumors [SPORE] grants in the upcoming fiscal year, with particular emphasis on those proposals that include both basic research and clinical treatment applications. (p. 102)

### Action taken or to be taken

In FY 2003, the intramural Neuro-Oncology Branch (NOB), which is supported jointly by NCI and NINDS, initiated a major tissue banking protocol in collaboration with two NCI-funded clinical trials consortia, the North American Brain Tumor Consortium (NABTC) and the New Approaches to Brain Tumor Therapy CNS Consortium (NABTT). Together these two clinical trials consortia comprise more than 20 cancer centers and major medical centers located across the United States. Their mission is to enroll adult patients in early phase trials of the most promising new therapeutic strategies for brain tumors. Beginning this year tumor and blood specimens from patients on NABTC and NABTT trials are now banked at NOB, along with specimens from brain tumor patients being treated on protocols at the NIH Clinical Center. Samples of cerebrospinal fluid are not part of this banking effort, but they continue to be collected on individual research protocols.

The tumor specimens consist of frozen tissue suitable for molecular analysis of DNA, RNA, and protein. The prospective collection of specimens according to a strict protocol ensures that the samples are handled in a consistent and appropriate manner so that they can be used to generate reproducible results in the laboratory.

A major advantage of this collaborative arrangement is that through the data management centers of the clinical trials consortia the banked specimens are annotated with highly reliable data regarding patient demographics, tumor diagnosis, treatment history, and disease outcome. Additional quality control is provided by a team of three highly-qualified neuropathologists who review and confirm the diagnosis ascribed to each of the banked tumor specimens before it is used for research. This information is gathered into the Glioma Marker Network Initiative database housed at NOB.

The long-standing brain tumor bank maintained by the Glioma Marker Network and its associated Neuro-Oncology Informatics System consists of tissue samples collected over more than fifteen years that have been carefully annotated by consensus pathology review, which makes them useful for many types of retrospective studies. The Glioma Marker Network

Initiative database is designed to contain not only clinical information about the specimens but also the results of molecular analyses performed on the samples at the NOB laboratories and at collaborating institutions around the country. This database will extend and enhance the information already provided in the publicly available Web-based databases for the NCI's Cancer Genome Anatomy Project and Cancer Molecular Analysis Project. Earlier this year two meetings were convened by NCI and NINDS to seek advice from extramural investigators on how these resources can continue to be developed in ways that provide the greatest utility to the clinical and basic research communities.

The NCI Cooperative Human Tissue Network continues to procure and distribute large numbers of brain and other neurological tissue specimens with associated demographic and histopathologic data to researchers nationwide for basic and developmental studies in cancer research. More than 1500 adult and pediatric brain specimens were provided in calendar year 2002.

For pediatric brain tumor patients, a protocol for the prospective collection, banking, and annotation of tumor and blood specimens has been submitted to the NCI by the Children's Oncology Group (COG). The COG is the major NCI-supported consortium organizing clinical trials for children with cancer, and it pursues an active program of translational research conducted by both COG investigators and outside collaborators. This protocol will provide for the collection of frozen tumor specimens and blood samples from patients enrolled on trials at the many institutions that participate in the COG.

More recent tissue banking efforts are underway at the Brain Tumor Specialized Programs of Research Excellence (SPOREs). Finally, the NCI's support of infrastructures such as the Shared Pathology Informatics Network, the Specimen Resource Locator, and the Tissue Expediter helps to increase the access of the research community to appropriate tissue specimens for many different kinds of research projects.

In FY 2003, NCI supported four SPOREs devoted to brain tumor research. A SPORE represents teams of basic and clinical or applied investigators focused on translational research in the respective cancer. One of the Brain Tumor SPOREs was co-funded by NINDS.

Over the short funding period, these Brain Tumor SPOREs have developed into a very dynamic collaborative group, with intensive links between individual SPOREs and with ongoing collaborations with other NCI-based programs (e.g. the Mouse Models in Human Cancer Consortium). The interactions were highly visible at three inter-SPORE meetings organized by the NCI.

Besides the intensive work on their projects, two of the SPOREs propose to extend their program by supplemental funding in preclinical research in low grade brain tumors as well as in a Phase I clinical trial using a combination of radiation therapy with a biological agent that inhibits the growth of vessels in newly diagnosed brain tumors. Both studies developed from, and are directly related to, existing research projects within SPOREs.

A new solicitation for Brain Tumor SPOREs attracted five new applications that will be reviewed in 2004. From this round, NCI and NINDS plan to co-fund in the same year at least one new Brain Tumor SPORE.

One important requirement for each SPORE is to develop and maintain a high quality tissue banking activity. All current Brain Tumor SPOREs are active in this area and thus may be ready to join the effort to create a nationwide brain tumor-related tissue bank linked to a comprehensive database containing clinical, biological, pathological, demographic, and therapeutic information.

It is clear that development of further targeted cancer interventions will require broad access to uniformly collected and stored biospecimens, along with a bioinformatics platform that will facilitate the comparison of data. For these purposes a blueprint for establishment of a National Biospecimen Network (NBN) was recently developed through a collaborative effort of the NCI and the National Dialogue on Cancer. The blueprint is a visionary model that offers the opportunity to overcome the critical barrier of tissue access to facilitate genomic and proteomic research. It will allow for the development of a system that will increase access to important tissue samples while at the same time streamlining the collection and analysis of these samples from existing resources, while ensuring patient privacy.

#### Item

***Cancer and minorities*** – The Committee remains concerned that cancer rates for Native Hawaiians and other Native American Pacific Islanders are disproportionately high. The Committee encourages the NCI to expand its research in this area. (p. 103)

#### Action taken or to be taken

The unequal burden of cancer in our society is more than a scientific and medical challenge. Certain populations experience the negative consequences of significant disparities in cancer incidence, the care they receive, and the outcomes of their disease. These differences have been recognized for some time but are now being documented with increasing frequency and clarity.

In August 2002, the NCI Director visited the University of Hawaii at Manoa and the Cancer Research Center of Hawaii. The Director had the opportunity to meet local oncologists and to hear the challenges Native Hawaiians and Pacific Islanders face regarding culturally competent and cutting-edge cancer care.

In FY 2003, led by NCI's Center to Reduce Cancer Health Disparities (CRCHD) and the NIH National Center of Minority Health and Health Disparities (NCMHD), a team of health care experts from the Pacific Basin community, supported through the NCI's Special Populations Network (SPN) Papa Ola Lokahi in Hawaii, worked to develop a needs assessment tool and administer this tool to community leaders and health professionals in six jurisdictions throughout the Pacific Basin: the Republic of the Marshall Islands, Republic of Palau, Federated States of Micronesia, Commonwealth of the Northern Marianas, Guam, and American Samoa. The team examined a number of issues including health infrastructure capabilities, socio-economic factors,



current sources of health services, quality of care from health care providers, as well as the knowledge, attitudes, and behaviors of the Pacific Basin Islanders to cancer care.

### *Community Outreach*

The ʻImi Hale Native Hawaiian Cancer Awareness Research and Training Network located in Honolulu (one of 18 SPNs) recently completed its fourth year of a five-year cooperative agreement. This project is housed within Papa Ola Lokahi, a consortium of Native Hawaiian non-profit organizations and public agencies with the single purpose of improving the health and wellness of Native Hawaiians. ʻImi Hale provides the cancer awareness and research infrastructure for Native Hawaiians in the state through memoranda of agreement with community organizations and key institutions including the Cancer Research Center of Hawaii, the Cancer Information Service (Hawaii), Kamehameha Schools, and the Native Hawaiian Center of Excellence (University of Hawaii School of Medicine).

The ʻImi Hale works collaboratively with key partners at the community, state, and national levels to provide support systems and expertise to achieve 5 main objectives:

1) development and implementation of programs to increase cancer awareness among Native Hawaiians; 2) develop mechanisms to increase education about clinical trials in Native Hawaiians; 3) create programs to increase number of Native Hawaiian researchers 4) develop programs to increase number of research grants addressing cancer in Native Hawaiians; and 5) establish a culturally appropriate, participatory research process to support scientifically rigorous research that is respectful of Native Hawaiian cultural beliefs, practices, and customs.

ʻImi Hale Native Hawaiian Cancer Research & Training Network project is examining existing tumor registry data for patients diagnosed between 1995 and 1997, and is comparing differences among the Hawaii's five major ethnic groups – Native Hawaiian, Caucasian, Chinese, Filipino, and Japanese. This project is the first project to request access to archived breast cancer tissue in a newly formed tissue bank repository of the Cancer Research Center of Hawaii.

In addition, in FY 2003, two pilot projects were competitively awarded:

- Feasibility of an After-School Program to Reduce Obesity in Hawaiian Youth
- Nasal Ciliary Function in Hawaiians to examine variation in nasal mucociliary function in healthy Hawaiian and Caucasian males in order to explain ethnic differences in susceptibility to recurrent lung disease.

The ʻPacific Islander Cancer Control Networkʼ located at the University of California, Irvine, the Chao Family Comprehensive Cancer Center (a designated NCI Cancer Center), and the Center for Health Policy and Research, in collaboration with the National Office of Samoan Affairs and eight community-based organizations, are coordinating programs for cancer prevention education, research, and training among four subgroups of Pacific Islanders in the US. The aim of this SPN is to improve cancer awareness, enhance recruitment to clinical trials, and increase the number of cancer control investigators among American Samoans, Native Hawaiians, Tongans, and Chimorras-Guamanians in the United States.

In FY 2003, the following pilot projects were competitively awarded:

- Breast Cancer knowledge, attitudes, and practices among Chamorro Women in San Diego
- Cultural Meaning and Cancer Among Tongans which seeks to improve cancer awareness and increase use of cancer prevention services
- Evaluation of Clinical Trials Educational Material to determine how clinical trial education materials, emphasizing low-literacy, may be improved to more effectively communicate and educate the Pacific Islander community
- Fa 'aSamoa and Cancer Screening (PICCN), which addresses the relationship between fa 'aSamoa and cultural beliefs about cancer screening and early detection.
- Social Support Use Among Chamorros With Breast Cancer, which examines the resources that breast cancer survivors access during the treatment and healing process.

### *Cancer Control*

The NCI Cancer Information Service (CIS) is collaborating with the Intercultural Cancer Council and the Centers for Disease Control and Prevention (CDC) to organize and implement a Comprehensive Cancer Control Planning Institute in the Pacific Islands. They will augment these activities with the composition and dissemination of a quarterly newsletter to Pacific Island partners that provides information on cancer control planning in the Pacific Islands and consolidates information on federally funded cancer control projects and partner organizations in the Pacific Island jurisdictions.

The Social and Behavioral Sciences Program (SBSP) at the Cancer Research Center of Hawaii was formally established in July of 2001. The SBSP unites a multidisciplinary team of investigators and staff to conduct innovative, socially relevant research to prevent and control cancer and other major chronic diseases. The NCI, along with the National Human Genome Research Institute (NHGRI), the CDC, and state agencies including the Hawaii Department of Health and the Office of Youth Services, serve as key funding organizations for the SBSP.

The emphasis of research at SBSP is on modifiable risk behaviors, early detection, social and health policy, and the use of new health communication technologies for disease prevention. General research interests lie in advancing the understanding of individual and communities' behaviors for cancer prevention and control, and in developing, implementing, and evaluating interventions to reduce cancer incidence, morbidity, and mortality. These interests have led to a research program based on five interrelated themes:

- Cancer prevention and detection among children, youth, and families;
- An emphasis on persons at high-risk for cancer and risk communication strategies to reach these persons;
- Ethnic factors, especially in Hawaii's diverse cultural groups;
- Social policy relevant to cancer prevention and control; and
- Use of innovative communication technologies to build healthy individuals, families, and communities.

These research themes are being applied to cancer prevention and control in the areas of sun protection and avoidance, tobacco control, healthy nutrition, colorectal cancer screening and genetic testing, and limiting alcohol consumption. The program emphasizes community-based

research that involves strong collaborative relationships with individuals and groups in Hawaii and elsewhere.

### *Cancer Surveillance and Trends*

The NCI Surveillance, Epidemiology, and End Results (SEER) Program collects and publishes cancer incidence and survival data from population-based cancer registries and supplemental registries. SEER was recently expanded to increase coverage from 14 to 26 percent of the U.S. population (from about 39 million to nearly 74 million). With the expanded reporting beginning in 2003 (for 2000 data), this coverage will include 23 percent of African Americans, 40 percent of Hispanics (32 percent of non-Mexican Hispanics), 45 percent of American Indians and Alaska Natives, 53 percent of Asians, and 70 percent of Native Hawaiians and Pacific Islanders.

Age-specific cancer death rates for all sites combined for American Indian/Alaskan Native, Asian/Pacific Islander, and Hispanic populations were lower than for white and black populations. Asian/Pacific Islander women had the lowest age-specific death rates except for women under age 50. In the 2000 U.S. Census, the Asian/Pacific Islander (API) population makes up a higher proportion of the U.S. population compared to the 1990s. Within the API category, the composition of recent immigrants (by country of origin) is different from second generation APIs. These changes will have implications not only for the cancer burden as these populations grow and age, but also on a greater need for culturally appropriate prevention, early detection, and treatment programs.

The California Health Interview Survey (CHIS) is designed to provide detailed information on the physical and mental health status of California adults and children. Specifically, it looks at prevalence and management of chronic diseases, diet and exercise patterns, and use of cancer screening services. CHIS has taken advantage of California's rich racial, ethnic, and linguistic diversity by fielding the survey in six languages. It is a valuable source of information on racial/ethnic groups not well covered by other surveys, including Asian-Americans, Pacific-Islanders, and American Indians.

NCI is funding a study to determine cancer-related knowledge and attitudes among American Samoans, a population seldom studied by cancer researchers. Specially trained personnel conducted face-to-face interviews with randomly selected respondents in the US Territory of American Samoa; Oahu, HI; and Los Angeles, CA, using a survey based on the National Health Interview Survey and focus group findings. The survey included questions concerning knowledge of risk factors for cancers, family resources (health insurance coverage, employment status, and family income), and demographic characteristics. Participants could complete the survey in English or Samoan. The results from respondents indicated that residents of American Samoa or Hawaii would rather not know that they had cancer; that they believe cancer is a punishment from God; and that they believe cancer can be cured by *fofo*, traditional Samoan healers. This study documented cancer-related knowledge and attitudes among American Samoans and set the stage for culturally sensitive interventions aimed at improving cancer control in this population.

### *Scientific Discovery*

The University of Guam (UOG) is the only four-year institution of higher learning in the Western Pacific serving the U.S. territories of Guam and the Commonwealth of the Northern Mariana Islands, as well as all of Micronesia. The student population consists of approximately 50% Pacific Islanders, 32% Filipino, 9% Caucasians, 8% Asians, and 1% other minorities. The Cancer Research Center of Hawaii is an NCI-designated cancer center at the University of Hawaii. There are four research programs established at the CRCH, along with a large clinical trials unit and the Hawaii Tumor Registry. These two institutions have formed a Minority Institution/Cancer Center Partnership with the following objectives: a) to increase the cancer research capabilities in a variety of different disciplines at the UOG, b) to increase the number of minority scientists of Pacific Islander ancestry engaged in cancer research or other cancer related activities by providing pertinent undergraduate, graduate, and postgraduate training opportunities, c) to provide career development for cancer investigators at the UOG in order to develop and sustain independently funded cancer research programs at the UOG, d) to further strengthen the focus of research, training, and outreach activities at the CRCH on the disproportionate incidence, mortality, and morbidity in minority populations, e) to expand the geographic region of the U.S. served by CRCH to the Territory of Guam, and f) to ultimately reduce the impact of cancer on the population in the Territory of Guam (and possibly other U.S. island territories in the Pacific) by enhancing the awareness of cancer prevention opportunities and improving the quality of care for cancer patients.

### *Clinical Trials*

NCI has begun a Minority Accrual Initiative, whose goals include increasing the number of minority investigators and minority patients in cancer research. The University of Hawaii has received additional funding to foster minority accrual to clinical trials through this initiative. Historically, the University of Hawaii and its affiliated hospitals have accrued large numbers of minority patients, both Asian-Americans and Native Hawaiians, to prevention and treatment trials.

### *Education and Training*

The NCI Comprehensive Minority Biomedical Branch (CMBB) administers the CURE program (Continuing Umbrella of Research Experience). The goal of this program is to increase the pool of trained researchers including persons having origins in any of the original peoples of the Hawaiian Islands or the Pacific Islands. Included in this group are: Guamanians, Samoans, Fijians, Polynesians, Tongans, Micronesians, Tahitians, Marshallese, Melanesians, Other Pacific Islanders, and Native Hawaiians.

NCI is funding the Asian American Pacific Islander (AAPI) Educational Outreach Project, a unique public private partnership with the Centers for Medicare and Medicaid Services (CMS) and the National Asian Women's Health Organization (NAWHO). Under the project, an AAPI mammography print was adapted, tested, and nationally disseminated. Developed for Chinese, Vietnamese, and Pacific Islander women in their 40s and older, this breast health screening brochure was adapted from CMS funded intervention research conducted by the CMRI, a California based quality improvement organization. NCI collaborated with five AAPI community organizations for consumer testing of this educational resource.

Item

***Cancer Genomics*** --The Committee commends NCI for its commitment to understanding the role of genomics and genetics in the progression of cancer. Considerable effort must now be directed toward applying those findings to tumor classification and therapeutic choice, with a focus on breast, colorectal and lung cancer, as well as leukemia and lymphoma. An important component of this effort will be to build a public database of whole genome expression profiles from various tumor types, which includes clinical outcome information. The Committee encourages NCI to ensure that this data is available to health professionals to assist physicians and patients in choosing the best treatment options. (p. 103)

Action taken or to be taken

Please refer to pages NCI-63 through NCI-66 of this document for NCI's response to this significant item regarding Cancer Genomics.

Item

***Cancer Survivorship*** – With the advances that have resulted from the ongoing commitment and investment in biomedical research, and the resultant advances in cancer treatment, cancer for many has become a chronic illness. Currently, there are over 9 million cancer survivors in the Nation, and this number is expected to grow dramatically. More must be done to improve the understanding of the growing cancer survivorship population, including determinations of physiological and psychological late effects, prevalence of secondary cancers, as well as further development of effective survivorship interventions. The Committee supports an aggressive expansion of the NCI Office of Cancer Survivorship activities and urges the NCI to continue its work to expand the Office of Cancer Survivorship within NCI, as well as advance and increase opportunities in cancer survivorship. The Committee was pleased to see NCI include cancer survivorship in the cancer bypass budget and urges NCI to provide increased funding for cancer survivorship research. (p. 103)

Action taken or to be taken

NCI's challenge goal of eliminating the suffering and death due to cancer is squarely aligned with the interests of the 9.6 million cancer survivors in the United States today. The population of cancer survivors continues to grow, a testament to NCI's many successes in preventing cancer from progressing to its later and more virulent stages. These successes include important progress in delivery and use of cancer screening, enhancement of early detection technologies, discovery and use of more effective and often multimodal therapies, provision of a broadening array of supportive care and rehabilitative options, and increasingly wider adoption of active screening behaviors and healthier lifestyles by those at risk for cancer, as well as by those with a history of the disease. While the ultimate goal of eliminating cancer continues to be our long-term commitment, the capacity to dramatically reduce the suffering caused by cancer is within our immediate grasp.

NCI leads the nation in championing research on the health and functioning of our growing population of cancer survivors. The number of research grants that seek to evaluate and improve the post-treatment experience of cancer survivors has increased almost 30 percent in FY 2003, and includes a significant focus on interventions that improve psychosocial and health-related

outcomes. Additionally, the NCI has been successful in attracting new scientists to the field of cancer survivorship research. In FY 2002, 25% of grants in the survivorship research portfolio were awarded to junior scientists or senior researchers new to the field of cancer survivorship. Many of these awards support the development of pilot data that will serve as the basis for more sophisticated and clinically significant future research efforts. The highlights below represent significant milestones in the continued expansion of the Office of Cancer Survivorship.

### *Research*

Research findings continue to improve our understanding of the growing cancer survivorship population, including determinations of physiological and psychological late effects, prevalence of secondary cancers, and further development of effective survivorship interventions.

Recent research has begun to reveal some of the potential benefits for cancer survivors and their families that are likely to result from the expansion of our understanding of genetic risk. For example, the e4 allele of the *Apolipoprotein E (apoE)* gene has been identified as a potential genetic marker for increased risk of neuro-cognitive deficits among adult survivors of cancer (breast and lymphoma) who have undergone chemotherapy. NCI is funding research to investigate mechanisms of risk for these late effects using noninvasive techniques such as morphometric magnetic resonance imaging (MRI), functional MRI, diffusion tensor imaging, MR spectroscopy, and positron emission tomography.

In 2003, NCI introduced the Common Terminology Criteria for Adverse Events. This new measure represents the first comprehensive system for reporting the incidence of both acute and late effects of cancer treatment, as well as their duration. Educational tools will be made available to the scientific community. This new scoring system will enable investigators to:

- Compare newer treatments for all cancers with the current regimens;
- Investigate molecular mechanisms for late tissue damage based on the severity of effects experienced by patients;
- Facilitate the development of interventions for use in clinical trials to prevent, reduce, or possibly reverse late effects of cancer treatment; and
- Standardize reporting of adverse events and compare outcomes between trials and institutions.

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

In FY 2003, NCI continued its commitment to expand cancer survivorship research by reissuing the Long-Term Cancer Survivors Research Initiative. The growing commitment to, and interest in, the field of cancer survivorship research is demonstrated by the 58% increase in the number of grant applications received in response to the re-issuance of this Request for Application (RFA).

### *Tools*

In an effort to expand cancer survivorship tools and resources, the NCI has created several products that enable more effective communication with diverse audiences.

- The OCS Prevalence Statistics Web site provides updated information about cancer survivors in the United States. The site will soon be expanded to track minorities and to provide information on survivors' second malignancies, quality of life, and prevalence data by state.
- The Facing Forward series for cancer survivors, family members, and medical professionals is designed to educate and empower cancer survivors as they face the challenges associated with life after cancer treatment. NCI is partnering with the American Cancer Society to distribute Life after Cancer Treatment, which provides information about, and resources for, managing recovery. A second volume, Ways You Can Make a Difference in Cancer, describes the benefits of, and strategies for, giving back to the community. NCI is partnering with over 50 local and national organizations to disseminate and evaluate these materials. The series will expand to include booklets for family members and healthcare providers.
- In partnership with Cancer Care, the Intercultural Cancer Council, the Lance Armstrong Foundation (LAF), and Living beyond Breast Cancer, NCI created a three-part teleconference series to provide survivors and their loved ones with a better understanding of what to expect after treatment ends. Funding for the program was made possible by an educational grant from the LAF.

### *Meetings*

The President's Cancer Panel (PCP) recognizes the nearly 10 million cancer survivors alive today as a visible measure of the success of the national cancer program. However, the PCP also equates post-treatment medical, physical, emotional, and social issues faced by cancer survivors as barriers still to be overcome. To address these issues, identify additional barriers, and to develop recommendations for further research, post-treatment follow-up, and interventions to promote better quality of life, the PCP has embarked on a series of five meetings to elicit input from survivors, caregivers, providers, insurers and employers, to identify specific cancer survivor needs and ways of responding to them. Members of government agencies in the U.S. and Europe have provided testimony and interacted with members of the general public, academic, research and medical communities, representatives of the insurance and provider communities, and others at these events. This testimony will be analyzed, synthesized and formulated in a report to the President in 2004.

Survivors of childhood cancer are a true testament to the success of the war on cancer. It is currently estimated that there may be as many as 250,000 childhood cancer survivors in the

United States alone. Today, almost 78% of those diagnosed with cancer under the age of 14 can expect to be alive at 5 years, and 10-year survival is above 70%. Research on the late and long-term effects of cancer and its treatment conducted in this population is growing rapidly and serves as the foundation for studies regarding the potential challenges and issues faced by survivors who are diagnosed with cancer as adults. Data from research studies have shown that cancer survivors may face a range of debilitating and even life-threatening sequelae of cancer or its treatment. These include neuro-cognitive problems, premature menopause, cardiac dysfunction, sexual impairment, chronic fatigue and pain syndromes, and second malignancies. The true long-term burden of a cancer history on these individuals and their families has yet to be determined.

The recent release of the IOM report on "Childhood Cancer Survivorship: Improving Care and Quality of Life," has stimulated enormous interest in the medical community to the needs of this unique population. In response to this report, and to compelling testimony on the cancer survivorship experience of childhood cancer survivors gathered recently by the President's Cancer Panel, there has been increased demand by the advocacy community for attention to care guidelines. In response to this, and to the recommendations of the IOM, the NCI is moving to convene a group of experts in the area of childhood cancer care to help advance efforts to establish guidelines for appropriate follow-up care of childhood cancer survivors.

In June 2004, the NCI and the American Cancer Society will co-sponsor the second biennial cancer survivorship research conference in Washington DC. The title for the conference is "*Cancer Survivorship: Pathways to Health After Treatment.*" Leaders at the forefront of cancer survivorship research will be invited to present their current findings on the long-term and late effects of cancer and its treatment; the identification of populations at greatest risk for these effects; and interventions, behaviors, and surveillance efforts designed to improve health outcomes for cancer survivors and their family members. Strategies and resources needed to support and implement change at the research, clinical, and policy level will be discussed. The 2004 scientific conference will also profile a Survivor-Researcher Mentor program. The purpose of this program is to enhance the conference experience for cancer survivors and consumer advocates by providing opportunities for small group discussions and question and answer sessions with cancer researchers. Participants in the mentoring program will be charged with helping to disseminate conference findings to a broader audience of cancer survivors and their families through their affiliations with national cancer organizations (e.g. newsletters, Web sites).

#### Item

***Chronic Lymphocytic Leukemia (CLL)*** – The Committee strongly encourages the NCI to increase the level of research aimed at determining the underlying cause and optimum therapies for CLL, the most common form of adult leukemia in the United States. The Committee is encouraged by the NCI's willingness to consider a supplementary application for research funding for the CLL Research Consortium. The Committee further urges the NCI to expand funding for the Consortium to speed up the progress in funding significant scientific breakthroughs. (p. 103)



Action taken or to be taken:

The CLL Research Consortium (CRC) continues to make significant progress on the genetics, biochemistry, immunobiology, pharmacology, and clinical treatment of this disease. The NCI expanded the activities of the CRC (1) to add a familial CLL component to the project, (2) to further expand activities using the transgenic CLL mouse model developed in the initial project to perform preclinical evaluation of novel therapeutics in vivo, and (3) to further fortify the clinical trials infrastructure of the CRC.

For the past 30 years, families with two or more living cases of CLL have been enrolled within the NCI Familial Cancer Registry. Medical records and biological specimens have been collected for these subjects. Based on these data, NCI intramural researchers have found that age of onset in familial cases is approximately 10 years earlier than in sporadic cases, and that there is often a higher percentage of second primary tumors in these patients. These families provide an ideal opportunity to conduct whole genome searches, to study candidate genes, and to evaluate other biomarkers in investigating the etiology of this disease. Efforts to recruit new families in order to expand the search for a susceptibility gene are continuing through a newsletter posted on the CLL Family Registry News Web site at:

<http://dceg.cancer.gov/hgp/geb/CLL/CLLnewsletter.html>.

In order to expand these studies, NCI intramural investigators formed an international consortium of investigators with an interest in familial CLL to collaborate and share data. The consortium will enrich ongoing scientific investigations by bringing together clinical investigators with genetic epidemiologists to pursue linkage studies and candidate gene approaches in order to determine the genetic underpinnings of CLL. The CRC is collaborating with NCI intramural investigators on this familial CLL project with funds obtained via a competitive supplement. The CRC is contributing clinical data and bio-specimens on families with multiple cases of CLL. An analysis of the CRC database has shown that individuals with familial CLL do not differ from those with sporadic CLL. The CRC is actively recruiting families and has obtained specimens from 14 families with two CLL cases. These families and others accrued will be combined with those recruited by the NCI intramural investigators and other groups in order to conduct new whole genome mapping and candidate gene studies to identify genetic causes of CLL.

Multiple efforts are underway to develop new therapies for CLL including gene therapy and novel agents. T cells in CLL patients are known to be defective and are immune-incompetent. Gene therapy for CLL has been developed whereby neoplastic B cells are infected with Ad-CD154 ex vivo rendering these transduced B CLL cells to function as proficient antigen presenting cells. When these transduced cells are administered to the patients via intravenous injection, an immune response against CLL cells is induced. Functional T cells are observed in these CLL patients. Data from a phase I study involving repeated injections of these transduced cells demonstrated that these injections sometimes resulted in the resolution of cervical adenopathy. A phase II clinical trial is underway to assess the biologic activity and safety of repeated doses of Ad-CD154 transduced leukemia B cells. To date, seven patients have received repeated injections of transduced cells with little or no toxicity.

Studies are also underway concerning the biochemical resistance of leukemia cells to apoptosis. Several novel regulators of apoptosis have been identified. The compound, Etodolac, a non-steroidal anti-inflammatory agent, has been shown to modify the resistance of CLL cells to apoptosis.

An NCI research group recently identified a method to readily distinguish two types of CLL that have very different clinical courses. Current methods to distinguish these two CLL types, one of which is a clinically aggressive disease with a median survival of six to seven years while the other is an indolent disease with a median survival of greater than 12 years, are based on DNA sequencing of immunoglobulin genes, making them impractical to do in a clinical diagnostics laboratory and, therefore, unavailable to most CLL patients. However, using DNA microarrays consisting of over 10,000 genes identified by the Human Genome Project, the NCI group readily diagnosed two distinct forms of CLL. The finding should be of direct clinical benefit in that a distinction can be made between those patients that should be managed conservatively versus patients with the aggressive form of CLL.

#### Item

***Chronic Myeloproliferative Disorders*** – Polycythemia vera, idiopathic myelofibrosis and essential thrombocytosis are malignant diseases of the bone marrow that are underserved with respect to research funding, considering the number of people they strike. These disorders are chronic and can transform into acute leukemia. They offer great research promise with respect to insights into the behavior of blood cells, since the cells that they affect appear normal but behave abnormally. The major obstacle to research into the causes and the treatment of these disorders has been the lack of Federal funds designated for this purpose. The Committee strongly believes that the NCI should expand research into these disorders, and be prepared to report to the Committee during the fiscal 2005 budget hearing about existing efforts, as well as planned future efforts to better understand these disorders. (p. 103-4)

#### Action taken or to be taken

Chronic myeloproliferative disorders, which include polycythemia vera, idiopathic myelofibrosis, essential thrombocytosis, eosinophil and mast cell proliferative diseases, and myelomonocytic leukemia, are malignant or premalignant diseases of the bone marrow. They are relatively rare compared to leukemia, and are often excluded from treatment studies in favor of patient homogeneity. As a result, definitive studies of the myeloproliferative disorders themselves are only possible in a collaborative setting.

Imatinib mesylate is a selective tyrosine kinase inhibitor of c-abl, bcr/abl, c-kit, and platelet-derived growth factor-receptor (PDGF-R) that revolutionized the treatment of chronic myelogenous leukemia. c-kit is expressed on normal and abnormal blood stem cells. PDGF has been implicated in the pathogenesis of myeloproliferative disorders (MPD). Other agents with potential significant activity are hypomethylating agents, antiangiogenic agents, farnesyltransferase inhibitors, and topoisomerase I inhibitors.

Preliminary data on treatment of polycythemia vera with imatinib are promising and need further investigation. Patients with juvenile myelomonocytic leukemia (JMML), chronic

myelomonocytic leukemia (CMML), idiopathic hypereosinophilic syndrome and mastocytosis also showed a positive response to imatinib. Responses among myelofibrosis patients were less promising. A combination treatment regimen including imatinib may be more effective for them.

Recent biologic findings relevant to myeloproliferative diseases include the importance of angiogenesis in CMML with a possible autocrine role for vascular endothelial growth factor, and the further understanding of the role of tyrosine kinase fusion genes and activation in some patients. Therapeutic discoveries have been hampered by the paucity of studies looking at individual diseases. The Children's Oncology Group has launched a study of farnesyl transferase in patients with JMML.

In March 2003, NCI, in collaboration with the National Heart, Lung, and Blood Institute (NHLBI), brought together investigators to implement the recommendations of the 2002 State of the Science meeting on myeloproliferative and myelodysplastic disorders. Participants reviewed existing resources and recommended new approaches to enhance study of chronic myeloproliferative and other blood disorders. This meeting indicated the need for a comprehensive strategy to increase the number of clinical trials investigating the chronic myeloproliferative diseases. Patient samples need to be made available to investigators performing correlative studies. This strategy should include a tissue bank, genomic libraries through NCI's Cancer Genome Anatomy Project (CGAP), common definitions and diagnostic criteria, and increased priority for research studies of these diseases. As a result of this meeting, NCI and NHLBI are developing a joint initiative to provide funds for individual research studies. The NCI Quick Trials Program is also a potential source of investigator-initiated funds.

NCI is committed to assist investigators to develop common definitions, update diagnostic requirements, identify tissue needs, and define endpoints for treatment studies. This will lead to a standardized approach to classification of disease subtypes and lay the groundwork for phase I, II, and III clinical trials. At the meeting, it was noted that platelet-lowering agents in low risk essential thrombocytosis patients with high platelet counts and anagrelide in low risk polycythemia vera patients with thrombocytosis are ready for randomized trials. There are promising agents such as thalidomide, interferon, or Enbrel(c) which should be tested in phase I and II studies for myelofibrosis.

Another result of the March 2003 meeting is the submission of a Program Project Grant (P01) application by the attendees. The application is a focused collaboration of clinical investigators with access to patients, who are willing to share clinical data, and blood and marrow samples. This International Consortium on MPD involves many of the researchers of the Polycythemia Vera Study Group, which was funded by NCI from 1965 - 1988. This application is currently undergoing peer review.

NCI will give special consideration to studies of myeloproliferative diseases. Currently funded collaborative groups will be encouraged to develop studies of myeloproliferative diseases. For example, the Blood and Marrow Transplant Clinical Trials Network (cofunded with NHLBI) has been asked to review existing transplant data on these patients and develop a multi-center reduced-intensity transplant trial. Transplantation is successful in 50% to 80% of patients with

MPD if performed before leukemic transformation, and is the only cure for severe disease. However, the side effects of the standard transplant regimen prevent many patients from considering this option.

#### Item

***Complementary and Alternative Cancer Therapies*** – The Committee expects the NCI to expand its work and its collaborative efforts with NCCAM to support research on promising complementary and alternative cancer therapies as well as on their integration with traditional therapies. (p. 104)

#### Action taken or to be taken

The NCI Office of Cancer Complementary and Alternative Medicine (OCCAM) acts as a coordinating office by collaborating with NCI intramural and extramural offices/divisions to increase NCI's growing research agenda in CAM-related cancer prevention, treatment, symptom management, and rehabilitation. OCCAM is dedicated to the scientific evaluation of CAM approaches, the expansion of relevant research, and the production of information resources on CAM topics.

NCI's largest CAM or CAM-related project is the Selenium and Vitamin E Cancer Prevention Trial (SELECT). SELECT is the largest-ever prostate cancer prevention trial. Results of previous studies suggested that selenium and vitamin E may reduce the risk of developing prostate cancer by 60 percent and 30 percent, respectively, but only a large clinical trial such as SELECT can confirm those initial findings. Patient enrollment on the study began August 22, 2001 with the goal being to enroll 32,400 men over a five-year period. As of August 2003, SELECT had enrolled 24,639 men, or 76 percent of the targeted goal.

NCI is sponsoring a supplemental project to the [California Health Interview Survey \(CHIS\)](#) to examine the use of CAM in preventing and treating cancer and other chronic illnesses. This study is a collaborative effort of NCI and the [University of California at Los Angeles \(UCLA\) Center for Health Policy Research](#). It will be the largest population-based survey conducted to date to document use of complementary and alternative medicine services by cancer survivors. The study will allow researchers to compare use of complementary and alternative services by respondents who report a cancer diagnosis, those who report other chronic diseases, and healthy adults. California's population includes many Asians and Latin Americans, so the study will benefit from large samples of these groups, who are generally thought to incorporate CAM services into their regular medical care.

NCI also supports the Surveillance, Epidemiology, and End Results (SEER) program. SEER is an authoritative source of information on cancer incidence and survival in the United States. Through a research contract with investigators from Wayne State University in Detroit, Michigan, a study is being initiated to examine the effect of CAM use by head and neck cancer patients on their compliance with recommendations for conventional therapy.

New wording has been added to the recently re-released program announcement titled "Quick-Trials for Novel Cancer Therapies" to encourage the submission of studies of CAM

interventions. This announcement is the source of the great majority of grant applications that the NCI receives for pilot clinical studies.

Among the NCI-designated comprehensive cancer centers, there are several clinical trials being implemented including:

- Phase I Study of Huanglian (Chinese Herb) in Patients with Advanced Solid Tumors (*Memorial Sloan Kettering Cancer Center*)
- Phase II Randomized Study of the Effects of a Low Fat, High Fiber Diet or Androgen Deprivation Therapy of Serum Factors in Patients with Prostate Cancer (*UCLA Comprehensive Cancer Center*)

#### The Research Development and Support Program

This program facilitates research programs and workshops to encourage high quality CAM research and the bridging of practice and research communities to form research partnerships. Examples of Program Activities include the following:

##### *International Center of Traditional Chinese Medicine (TCM) For Cancer*

The NCI has funded its first planning grant to support the development of an international center for research in TCM for cancer. This funding supports a partnership between a leading NCI-designated Cancer Center and a major cancer hospital in China. This cross-cultural collaboration of investigators will study TCM in appropriate clinical and laboratory environments.

##### *Supplements to Cooperative Groups for CAM Clinical Trials*

OCCAM collaborates with the NCI's Cancer Therapy Evaluation Program and the NCI's Division of Cancer Prevention to provide supplementary funds to support CAM-related clinical trials, performed by the NCI's Cooperative Groups and Community Clinical Oncology Programs. This includes studies of herbs such as St. John's Wort, Ginkgo biloba, Valerian, Black Cohosh; other dietary supplements such as glutamine, zinc, coenzyme Q10, soy protein and soy isoflavones, ginger, lycopene, flaxseed; and approaches derived from non-Western traditional healing systems such as acupuncture and mindfulness relaxation. NCI is also sponsoring a study of lycopene, a bioactive compound derived from tomatoes, in patients with metastatic prostate cancer.

##### *Technical Assistance Workshop*

OCCAM sponsored a two-day Technical Assistance Workshop in March 2003 for investigators interested in cancer CAM research. This two-day workshop was designed to assist researchers in the development of competitive applications for cancer CAM research funding from NIH.

##### *Invited Speakers Series*

OCCAM is devoted to bringing the latest cancer CAM research data to the NIH community to encourage intramural CAM cancer research and collaboration and to increase awareness among the extramural program staff. To further this mission, a seminar series was initiated in January 2002. Presentation topics included:

- Acupuncture Research: Examples of the State of the Science from Bench to Bedside (January 2002)

- Melatonin, Chronobiology, and Cancer (February 2003)
- The State of Complementary and Alternative Medicine in United Kingdom Cancer Care: Advances in Research, Practice, and Delivery (April 2003)

#### *NCI Director's Support*

Over the past year, the NCI Director has delivered keynote remarks and participated in panel discussions on the subject of complementary medicine and spirituality in cancer care in an effort to raise awareness of NCI programs in CAM and other related areas. These presentations include:

- Keynote Remarks, Jung Educational Center Annual Spring Benefit, Houston, Texas, April 10, 2003.
- Keynote Remarks, "Charting the Unknown: Where Science and the Spirit Intersect," Symposium for Health Care Chaplains, Texas Children's Hospital, October 16, 2003.
- Keynote remarks, 1<sup>st</sup> Annual Meeting of the American Psychosocial Oncology Society, Orlando, Florida, January 30, 2004.

Other upcoming events include:

- Keynote remarks, Conference on Cancer & The Human Spirit, June 2004.
- Production of a NCI Cancer Patient Education Network video on the evaluation of physicians & patients on CAM or integrative therapies.

#### Practice Assessment Program

This program provides a unique opportunity for direct interaction between the NCI and the community of CAM practitioners who treat cancer patients. Two components of the Practice Assessment Program are the Best Case Series program and the Prospective Outcomes, Monitoring, and Evaluation (POMES) program.

#### *Best Case Series Program*

This program affords opportunities for CAM practitioners to have an independent assessment of the documentation case studies of cancer patients treated with alternative interventions. Medical records, diagnostic imaging, operative, and pathology reports are submitted to the OCCAM which evaluates and summarizes each case study, arranges the review of the original radiology and pathology slides, and plans for the presentation of data before the Cancer Advisory Panel for CAM (CAPCAM). The program's goal is to identify CAM interventions in practice that warrant prospective research.

#### *Practice Outcomes, Monitoring, and Evaluation Systems (POMES)*

One of the NCI-initiated prospective research steps that can be taken as the result of a best case series review is a practice outcomes monitoring and evaluation system (POMES) project. Such projects are designed to independently verify the findings of the best case series, to document and record the frequency with which positive outcomes occur, and to document the details of the therapy given. This information is helpful for determining if a clinical trial is feasible and, if so, provides important detail necessary to design such a study. The current POMES initiative focuses on an NCI-sponsored data gathering project at a homeopathic clinic in Calcutta, India. Presently,

a memorandum of understanding between the OCCAM and this clinic is signed and a protocol describing the study is near completion.

### Communications Program

The OCCAM Web site (<http://cancer.gov/cam>) provides a link for the general public, the research and practice communities, and other governmental agencies that are seeking updated information about NCI's CAM activities, as well as other information on CAM and cancer.

### *Conference Support and Participation*

NCI provided funding to the Center for Mind-Body Medicine of Washington, D.C. to support the 5<sup>th</sup> Comprehensive Cancer Care Conference held in April 2003. Staff from the OCCAM presented at this conference discussing how to perform a best case series, opportunities for funding of CAM cancer research, symptom management, and how patients can most effectively assess quality, evidence-based CAM information.

On April 1-3, 2003, NCI supported the "Integrating Research on Spirituality and Health and Well-Being into Service Delivery: A Research Conference" via a grant to the International Center for the Integration of Health and Spirituality. More than 500 physicians, psychologists, nurses, clergy, social workers, researchers, epidemiologists, students, and others interested in health and spirituality attended the conference to discuss ways in which research on health and spirituality can be integrated into the delivery of clinical care and social services.

### *Survey Project*

OCCAM, with the assistance of the NCI Office of Communications, implemented two surveys targeting CAM practitioners and conventional cancer researchers in December 2003. These surveys are designed to assess the opinions, interests, and experiences of the respondents on issues relevant to cancer CAM practice and research. Results from the surveys will be used to inform the content of new and existing projects for the provision of technical assistance to grant applicants, the solicitation of grant applications, and the documentation of the outcomes of CAM therapies currently in practice. The results will also serve as a discussion base for developing and improving existing programs that will bridge the CAM practice community and the conventional cancer research community.

### Collaborations with the NIH National Center for Complementary and Alternative Medicine (NCCAM)

The NCI and NCCAM continue to collaborate on various initiatives and individual projects, including some of those discussed above. In FY 2003, these activities expanded further in the areas of information and communications. Some examples of joint projects follow:

### *Research Collaborations*

The OCCAM, in collaboration with NCCAM, released a call for applications for developmental grants in cancer complementary and alternative medicine. This announcement invites research grant applications from interested investigators to conduct innovative developmental pilot research investigating CAM in cancer. The intent of this initiative is to encourage and support the development of basic and clinical CAM cancer research and to provide the basis for more

extended research projects by establishing the methodological feasibility and strengthening the scientific rationale for these projects. This announcement is the first NCI-initiated call for grants in the field of CAM and the response from the research community has been very encouraging. In the three rounds of application and review in FY 2003, over 200 applications were received. Over 40 grants received in response to this announcement have been funded since the first submission date in October 2001.

#### *Projects with NCI-Designated Cancer Centers*

The NCI and NCCAM have jointly funded a three-year program to support innovative, high-quality developmental CAM research at six NCI-designated Cancer Centers. The long-term goal of the program is to increase the number of successful R01 CAM cancer applications submitted to, and funded by, the NCI and NCCAM. Forty-nine projects have been funded through this program.

#### *Collaborative Clinical Trials*

NCI and NCCAM continue to jointly support the prospective trial at the Columbia Presbyterian Medical Center examining the effect of the Kelley-Gonzalez regimen (a nutritional program with oral pancreatic enzymes and a “detoxification” regimen) on survival rate and quality of life among patients with Stage II, III, or IV pancreatic cancer. Both organizations also support a study through the M.D. Anderson Community Clinical Oncology Program of a liquid shark cartilage product as an adjunctive treatment in patients receiving conventional chemotherapy and radiotherapy for advanced stage non-small cell lung cancer. Patient accrual is continuing for each of these trials.

#### Information and Communication Collaborations

##### *Summaries of CAM Literature*

NCI's OCCAM and the Office of Communications, in conjunction with NCCAM, are continuing to produce fact sheets on CAM topics. These documents are based on information contained in the NCI Physicians Data Query CAM summaries and can be accessed via OCCAM and NCCAM Web sites and the NCI Cancer Information Service.

##### *CAM Cancer Patient Focus Groups*

In February 2003, NCI and NCCAM completed the planning and implementation of patient/caregiver telephone focus groups that assisted in assessing the CAM educational needs of this population. The information gathered from this process will help guide the development of educational pieces focusing on CAM and incorporating key messages about CAM use, including risks and benefits, into existing patient education material produced by both institutes.

#### Item

**DES** – The Committee continues to strongly 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 the NCI to continue its support of research in this area, and to continue to consult with organizations representing individuals impacted by DES as they carry out DES research and education efforts. (p. 104)



### Action taken or to be taken

Originally prescribed for pregnant women between 1938 and 1971 to prevent miscarriages, DES, a synthetic estrogen, is now linked to increased risks of cancer, genital abnormalities, and/or compromised fertility. An estimated 5 to 10 million individuals are at risk; this includes women who took the drug while pregnant, as well as their children. Several lines of evidence suggest that hormonal exposures early in life, including in utero, may influence risk of breast and other hormonally-related tumors in adults. To assess this hypothesis, NCI researchers have worked closely with five collaborating centers to reassemble and combine the U.S.-based cohorts of DES-exposed daughters, sons, and mothers that were studied in the 1970s and 1980s.

The NCI DES Follow-Up Study will continue to focus on the long-term health effects of DES exposure. The study, which began in 1992, has sent questionnaires to more than 15,000 women and men in 1994 and 1997. The 1997 questionnaire, which was distributed to over 6,500 daughters and 3,600 sons who were exposed to DES in utero as well as to unexposed individuals, had a greater than 90% response rate. The third questionnaire was similar in length and in the types of questions that were asked, and was mailed to almost 8,700 exposed and unexposed daughters and sons in the summer of 2001 with a response rate over 90%. Standardization of the questionnaire over time allows NCI researchers to compare any changes in the health habits and experiences of the respondents over time. Analysis of the 2001 data will begin in spring 2004. NCI scientists evaluated the association of in utero exposure to DES and risk of adult breast cancer among the follow-up cohort of 4,821 exposed and 2,095 unexposed women. Breast cancer incidence in DES-exposed daughters was compared with incidence in unexposed daughters, adjusting for birth year, age at menarche, age at first birth, and number of births. There was a 40% increased risk of the incidence of invasive breast cancer in exposed versus unexposed women. DES exposure was associated with a 2.5- fold increased breast cancer risk among women aged 40 and older, but not among those younger than 40. DES exposure was modestly associated with estrogen receptor-positive tumors. This analysis will be updated with approximately 40 additional breast cancer cases identified in the 2001 round of follow-up, for whom hormone receptor status is known.

In addition, in response to concerns about possible multi-generational effects of DES exposure in humans, a new NCI initiative is underway to systematically follow the granddaughters of women who took DES during pregnancy. The Third Generation Study, which was launched in August 2000, has enrolled adult daughters of women who participated in the DES daughters' study. The study will compare the two groups of third-generation women, those whose mothers were exposed to DES and those whose mothers were not exposed, with respect to various health outcomes. Over 900 young women from all five U.S. research centers were approached to participate in the study and almost 800 (88%) agreed to participate. Study participants were asked to complete a mailed questionnaire describing their medical, gynecological, and reproductive histories. Of 153 women who reported certain breast or gynecological diagnoses, 125 provided permission to obtain their medical records to confirm the diagnoses, and records were obtained for 95. Analysis of these baseline data will begin in the fall of 2003.

NCI has also partnered with the Centers for Disease Control and Prevention (CDC) to lead the development and implementation of a national campaign to inform both consumers and health professionals about the potential health effects associated with diethylstilbestrol (DES) exposure.

Since the initial campaign planning meeting held at NIH in 1999, NCI, CDC, the HHS Office on Women's Health, and representatives of advocacy and health care provider organizations have worked together to plan and implement the campaign. The development and implementation phases of the campaign are complete. The dissemination phase began in January 2003 and will be complete by spring 2004.

After formative research to assess target audiences' knowledge of DES-related health risks and health monitoring, target audiences were identified, appropriate dissemination channels identified, draft materials for each audience were developed and pre-tested, and the campaign was renamed, "CDC's DES Update." The target audiences include a broad range of health care providers and consumers, including known-exposed individuals and those who may have been exposed but are unaware of their exposure status. Earlier DES education programs had targeted physicians only.

In 2001, materials were developed and pre-tested to meet the information needs for each target audience. Materials for health care providers in a variety of formats were developed in collaboration with medical and nursing school faculty at DHHS Centers for Excellence in Women's Health at Wake Forest University, University of Illinois at Chicago, Drexel University, University of California at Los Angeles, and the University of Wisconsin. These materials were designed to be presented by clinicians and medical and nursing faculty in various medical education settings.

Materials developed for consumers are now available in print and online, and include a comprehensive set of fact sheets on DES history, research, resources, and health effects. In addition, the materials include instructions on how to interpret DES research, tips for talking with health care providers, and ways to track personal DES health history for known-exposed individuals and those unaware of their DES exposure. The consumer materials and Web-based DES reference material for clinicians were developed in collaboration with the DES Working Group, including CDC and NCI staff, as well as representatives of advocacy and health care provider organizations. The consumer materials were cleared through the DHHS in Fall 2002.

The implementation phase began in 2002 with DES exhibits at 10 major national conferences of health care professional societies. The exhibits were designed to alert providers to the upcoming dissemination of DES materials to the public, explain DES-related health risks, and describe the new materials and DES resources for health care providers.

The distribution of materials phase of the campaign began in early 2003. CDC and/or their partners have attended over 30 national, state and, local health care professional conferences, provided Grand Rounds lecture series and symposium presentations. CDC's DES Update also includes a Web site (<http://www.cdc.gov/des/>) from which information can be downloaded and printed, and a toll-free number (1-888-232-6789) to call for free print materials. The Web-based

DES reference for clinicians will soon be available through the NCI and CDC Web sites. The addition of continuing education unit (medical and nursing) credit available through the CDC is currently under review and is expected to be approved by early 2004. Through the course of this reporting period, CDC has worked with over 26 national consumer groups and 37 health care provider organizations serving target populations, as well as developing new partnerships with other health related organizations, and regional and state health care provider organizations in order to disseminate DES materials to consumers and providers. A number of medical and health professionals=academic programs have requested DES information to embed into their curriculum. To date, 11 nurse practitioner programs, 6 nurse midwife programs and 23 physician assistant programs have requested curriculum information.

A series of five teleconferences for the public, designed to meet information needs of known-exposed audiences has been completed. DES researchers have discussed the latest research on 1) Breast Cancer Risks Associated with DES Exposure, 2) Latest Research on DES Sons, 3) Clear Cell Cancer Risks for DES Daughters, 4) Research on Reproductive Health Risks for DES Daughters, and 5) DES Animal Research.

CDC's DES Update is being evaluated at several points in time to assess change in knowledge, penetration of materials, and learning outcomes for target populations of consumers and health care professionals. A pre-campaign evaluation of DES knowledge, attitudes and behavior has been completed. Process evaluation measures include: web statistics analysis, public inquires via email, public inquires to the toll-free line, media placements, conference attendee rates, and learning outcomes post-testing through Indiana University Centers of Excellence in Women's Health (CoE).

#### Item

***Diet and Nutrition*** – The evidence is mounting that diet and nutrition play a key role in causing cancer and preventing it. For example, studies show that a diet with little fiber may be a contributing factor in colon cancer, while lycopene found in tomatoes may be useful in preventing prostate cancer. Likewise, diet can play a major role in treating a variety of cancers. The Committee encourages the National Cancer Institute to dedicate more funding to research and education programs focused on diet and nutrition. (p. 104)

#### Action taken or to be taken

The National Cancer Institute (NCI) is dedicated to funding research and education programs focused on diet and nutrition. To reinforce this commitment to Congress, research partners, the scientific community, advocates, and the public, NCI has included Energy Balance as a new scientific priority in its 2005 Bypass Budget. The term "energy balance" refers to the integrated effects of diet, physical activity, and genetics on growth and body weight over an individual's lifetime. Scientists are increasingly aware of the importance of understanding the effects of energy balance on the development and progression of cancer and on cancer patients' quality of life after treatment. The goal of NCI's priority in this area is to understand the causes of adverse patterns of weight, physical activity, and diet; define their contributions to cancer; and apply this knowledge to cancer prevention and control.

The prevalence of obesity has changed dramatically over the last 40 years. It was relatively stable at approximately 10% for men and 15% for women during the early 1960s to the late 1970s. During the late 1980s and early 1990s rates of obesity increased, and the most current estimates from the 1999-2000 National Health and Nutrition Examination Survey (NHANES) indicate that the prevalence of obesity has increased to 27.5% for men and 33.4% for women. Of particular concern are increases in rates of overweight among children and adolescents. Prevalence rates, which were approximately 5% during the 1960s, have tripled to over 15% in 1999-2000 among school-aged children and adolescents. These national health surveillance data provide a strong rationale for a research focus on innovative approaches to improving energy balance, weight control, and the prevention of overweight and obesity.

At a time when almost two-thirds of the U.S. population is considered overweight or obese, international teams of scientists have assembled compelling evidence that as weight and obesity increase, and physical activity decreases, the risk of developing many cancers rises. A comprehensive 2002 international review by the International Agency for Research on Cancer (IARC) summarized, for the first time, the compelling evidence that prevention of obesity reduces risk for many of the most common cancers such as colon, postmenopausal breast, uterine, and renal cell cancers and that physical activity reduces risk for colon and breast cancers. With the rapid rise of obesity and sedentary lifestyles among children and youth, research must focus particular attention on this vulnerable population. NCI efforts in this area will complement and extend existing efforts by NIH and other Federal and private partners. A brief description of ongoing and planned activities related to diet and nutrition follows.

#### *Diet, Nutrition and Physical Activity – Ongoing Research*

NCI continues to provide funding for research and education programs related to diet and nutrition, including epidemiologic studies; improving diet and physical activity measures and monitoring; diet behavior; and increased consumption of fruits and vegetables.

NCI supports human population and clinical-related research that investigates the etiology and development of cancer by delineating, characterizing, and analyzing factors of risk and individual susceptibility, and by applying population and molecular genetic methods in genetic epidemiology. This includes the effects of diet and nutrition, physical activity, energy balance, alcohol, and other lifestyle and environmental exposures on cancer risk. Examples of NCI-funded large cohort studies with a primary emphasis on diet and nutrition are the *Seventh Day Adventist Cohort Study*, the *Black Women's Cohort*, the *Multiethnic/Minority Cohort Study*, the *Nurses Health Study*, and the *VITAL Vitamins and Lifestyle Study: a Cohort Study of Dietary Supplements and Cancer Risk*.

NCI and its partners are improving needed diet and physical activity measures, including both self-reported and objective measures. The Observing Protein and Energy Nutrition (OPEN) study, the largest of its kind, used biomarkers of dietary intake to assess the accuracy of dietary assessment methods commonly used in epidemiology, intervention, and surveillance research. The investigators found that self-reported intake measures used in many studies are not sufficiently accurate. Further research will examine whether these findings are true for diverse populations, for other dietary-report or physical activity instruments, and across varying nutrients

and food groups, as well as how the measurement inaccuracies may affect ongoing prospective cohort studies.

NCI also supports major innovations in dietary and physical activity assessment within the NHANES to improve its capacity for monitoring diet, weight control and physical activity, all key factors in cancer control. This survey is the major U.S. national survey for monitoring these health characteristics.

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

As a first step in the development of energy balance interventions, NCI is researching key determinants of behavior change. Although much is known about how dietary and physical activity behaviors can be changed, attempts to develop behavioral interventions to effectively increase physical activity are relatively new. Toward this end, NCI is sponsoring an NIH-wide effort to accelerate research on the mechanisms of physical activity behavior change. In addition, NCI has worked with groups such as the Agency for Healthcare Research and Quality and the National Academy of Sciences to conduct research reviews, providing information to aid evidence-based intervention development for dietary and physical activity behaviors.

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

NCI has been collaborating closely with USDA’s Food, Nutrition and Consumer Services. The current focus is on two environmental change initiatives to increase children’s fruit and vegetable consumption and to encourage them to adopt healthy eating habits that will reduce their risk of being overweight and/or obese. The first project is the 4-State Pilot Fruit & Vegetable Program. It provides 106 schools with funding to provide free fruits and vegetables as snacks to students throughout the day. The pilot was very successful – children ate more fruits and vegetables and ate less high calorie, high fat vending options. The second project, Fruits and Vegetables Galore: Helping Kids Eat More is a how-to-kit which will be made available to 100,000 schools in early 2004. This kit focuses on implementing school salad bars and other effective ways to increase fruits and vegetables in school meals. USDA, NCI, and other 5 A Day partners will work

together to train school food service managers to implement salad bars and change vending options.

### *Diet and Cancer Prevention*

There are many reports linking diet, dietary components, energy balance, and obesity with several cancer sites, including breast, colon, and prostate. The NCI has numerous programs that are focusing on these particular cancers, their etiology, mechanism of susceptibility, and prevention strategies.

Compelling evidence from preclinical studies and observational studies in humans suggest that dietary components, including compounds found in fruits, vegetables, and grains, are likely to alter cancer susceptibility. Dietary constituents have been found to modify many of the pathways involved in carcinogenesis, including apoptosis, cell cycle control, differentiation, inflammation, angiogenesis, DNA repair, and carcinogen metabolism. Some of the most consistent evidence for a relationship between diet and cancer prevention concerns the dietary trace element selenium. The NCI SELECT (Selenium and Vitamin E Cancer Prevention Trial) is testing the hypothesis that selenium may offer some protection against cancer of the prostate. Although selenium has been shown to modify several aspects of the cancer process, the pathways and targets that are most critical for bringing about a phenotypic change remain to be revealed.

The observed variation in cancer incidence among and within populations with similar dietary patterns may also reflect interactions with genetic factors. Understanding the dynamic interactions between gene polymorphisms and/or dietary influences on gene expression, as well as on DNA methylation and other epigenetic events and on post-translational modification of proteins is needed. These processes may assist in explaining the role of diet under a variety of physiological conditions including obesity. Additionally, interactions among numerous dietary components may influence absorption, metabolism, and/or the site of action of individual bioactive food components, making their study a more complex undertaking. Unraveling the effects of diet on genes and their encoded proteins, as well as identifying genetic influences on these bioactive food components, is essential for identifying those who will and will not benefit from intervention strategies.

Recent NCI grant awards are aimed at enhancing a multidisciplinary approach to understanding the role of nutrients as modifiers of pathways involved with cancer. Some important but heretofore under investigated areas in nutrition and cancer prevention include: 1) exfoliated cells as surrogate samples for the action of bioactive food components in target tissues, 2) examination of in utero dietary exposures and cancer risk in adulthood, 3) nutritional linkages to pancreatic cancer, 4) dietary thiol regulation and cancer, 4) connections between diet and inflammatory response in cancer, 5) diet, insulin resistance and colon cancer risk, and 6) free radical and antioxidant relationships to cancer prevention and treatment.

### *Energy Balance – Future Initiatives*

For fiscal year 2005, NCI is developing a Request for Application to establish centers for transdisciplinary research on energetics and cancer. These centers will involve scientists from multiple disciplines and encompass projects spanning the biology and genetics of energy balance

to behavioral, socio-cultural, and environmental influences upon nutrition, physical activity, weight, energy balance, and energetics. The primary goal of the centers will be to foster collaboration among transdisciplinary teams of scientists to accelerate progress toward reducing cancer incidence, morbidity, and mortality associated with obesity, low levels of physical activity, and poor diet.

Other initiatives that are planned as part of the new scientific priority are listed below.

- Support research in collaboration with other NIH institutes in innovative technologies, such as electronic handheld monitoring devices and Internet surveys, in the assessment of diet, weight control, and physical activity behaviors.
- Improve the ability to capture information on diet, weight, and physical activity behaviors across diverse cultural populations.
- Support research on interventions that focus on weight control through diet and physical activity in cancer patients and in populations at high risk for cancer.
- Develop effective approaches to improving and targeting health messages in the areas of dietary guidance, physical activity recommendations, and food labeling by supporting health communication research in partnership with other NIH institutes.
- Evaluate public comprehension of health recommendations on physical activity and nutrition through the NCI Health Information National Trends Survey (HINTS).
- Establish surveys of healthcare providers to evaluate knowledge, attitudes, and practice related to weight control in clinical practice.
- Initiate innovative research on economic factors related to diet, physical activity, and energy balance in at-risk populations, in collaboration with Federal partners, including the U.S. Department of Agriculture.

#### Item

***Gynecologic Cancers***- The Committee is encouraged by the success of the Gynecological Cancer SPORE program but believes an increased investment is needed as the survival rate for ovarian cancer remains disappointingly low--14,300 women are expected to die this year while 25,400 will be diagnosed during that same time. The Committee believes the CanCOR program should be expanded to help identify barriers to receiving optimal care among women with newly diagnosed gynecological cancer. The NCI should also develop prophylactic and therapeutic HPV vaccines to prevent cervical cancer and strengthen research in the biology of endometrial cancer in order to improve prevention and treatment, thus sparing women the need to undergo hysterectomy and other cancer therapy. The Committee also believes that the NCI should be partnering with the NICHD Reproductive Sciences Program to investigate gynecological cancer. (p. 104)

#### Action taken or to be taken:

NCI has an ongoing multi-pronged multi-disciplinary effort in molecular etiology and treatment of gynecologic cancers. Substantial advances have been made intramurally in the NCI Center for Cancer Research (CCR), and through collaborations with extramural colleagues through participation in the Specialized Programs of Research Excellence (SPOREs) network, the Cancer Genetic Network (CGN), the Gynecologic Oncology Group (GOG) clinical trials cooperative group and its association with the international Gynecologic Cancer International Clinical Trials

Group, and public/private partnerships with industry. The continuing advances of the NCI/FDA Clinical Proteomics Program have led to development, quality control, and now clinical trial application of several novel proteomics technologies for diagnosis and assessment of molecular targeted treatments of ovarian cancer. In addition to these important advances, NCI investigators are active participants in community education and interaction with the advocacy communities for gynecologic cancers. A Gynecologic Malignancies Faculty of intramural investigators has been developed to provide opportunities for clinical and scientific education and training, clinical and scientific resources for the community, and to advance and cross-fertilize within the intramural and extramural oncology and gynecology communities.

### Ovarian Cancer

Ovarian cancer remains the most deadly of the gynecologic cancers. Potential reasons for this continuing poor outcome include the nonspecific and late clinical presentation of this cancer and the lack of reliable and cost efficient methods of early detection. Early detection alone without changes in current standards of treatment can have a substantial impact on public health.

NCI CCR investigators have had a lead role in the NCI Director's Challenge to advance our understanding of the molecular etiology of ovarian cancer. Recent studies have identified gene expression patterns that can be used to segregate different histologies of ovarian cancer. The potential clinical translations of this approach is as a diagnostic adjunct for cases of carcinoma of unknown primary and the triage of those patients to the best possible therapeutic intervention, and for identification of novel diagnostic and molecular therapeutic targets.

The NCI/FDA Clinical Proteomics Program has previously reported the development of a novel protein pattern signature with potential to be developed as a diagnostic tool. A clinical reference laboratory was created in FY 2003 and has just completed quality control and quality assurance assessments. The priority clinical applications of the reference laboratory are: a) to evaluate serum samples, received collaboratively from SPORE and Early Detection Research Network (EDRN) sites, from women without ovarian cancer or risk and those with diagnosed ovarian cancer in order to further validate the serum proteomic signatures; b) to continue the ongoing collaboration with the prospective CGN trial of women at high risk for breast and/or ovarian cancer; c) to evaluate serum samples being collected prospectively in GOG clinical trials for newly diagnosed women; and d) to provide laboratory support for the prospective ongoing remission monitoring clinical trial of the NCI CCR.

This remission monitoring study is accruing women who are in first remission after treatment for advanced stage ovarian cancer. Serial serum samples, measurement of CA125 biomarker, clinical examinations, and imaging studies are done during the remission period through documentation of recurrence. The serum samples will be subjected to proteomic pattern analysis and the results of the changes in the protein signatures will be compared to the changes in CA125 for sensitivity and specificity and positive predictive value for recurrence prediction. This is a high priority study that is being expanded to incorporate multiple extramural partners to assure rapid completion. Partners solicited include SPORE and EDRN sites where the institution has an ongoing effort in ovarian cancer research.



Proteomic technologies have also been applied to clinical trials of molecularly targeted therapeutics in ovarian cancer. Two clinical trials, in partnership with the Cancer Therapeutics Evaluation Program (CTEP) and industry, are ongoing. Imatinib mesylate (Gleevec) and ZD1839 (Iressa) are being tested in phase II clinical trials in the NCI CCR. Women participating undergo minimally invasive biopsy of tumor prior to initiation of treatment and then again after one month of therapy. These biopsies are subjected to laser capture microdissection, a process invented within the NCI CCR, of both tumor cells and local support stromal cells. The proteins from these cell collections are arrayed into tissue lysate arrays, an approach developed within the NCI CCR, and then evaluated for expression and modulation of expression of key signaling proteins known or hypothesized to be involved in the biochemical function of imatinib or ZD1839, respectively. This approach will vet the putative molecular target within the tumor and stroma and allow assessment as to whether or not modulation of the target or related targets is associated with clinical behavior. This is an important advance to understanding how these agents in particular, and the class of agents in general, may work and can lead to more rapid improvements in our approach to therapeutic regulation of ovarian cancer. This technology and biopsy-intense approach is difficult to do in other academic centers due to pressures of reimbursement and other nonclinical issues and is an ideal use of the specialized clinical research center of the NIH.

NCI investigators have also identified several putative biomarkers associated with ovarian cancer development and progression. One such example is the granulins-epithelin precursor (GEP). This gene was identified as differentially expressed in gene libraries constructed from tissues that were subjected to laser capture microdissection. Differential protein expression was confirmed and ongoing work has shown this protein to be important in survival, as well as invasion and proliferation of ovarian cancer in vitro and in animal models. A biotechnology industry Cooperative Research and Development Agreement (CRADA) was developed for preclinical and subsequent clinical development of a monoclonal neutralizing antibody molecular therapeutic against GEP.

Through the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, the NCI is carrying out a major evaluation of selected screening procedures for early cancer detection. Questionnaire data and biologic samples are collected in this population for use in studies on the etiology of breast cancers and for the evaluation of early markers of cancer development. Because of the prospective design, screening exams, and sequential pre-diagnostic blood sample collections, it will be possible to relate genetic, hormonal and other biomarkers to subsequent development of cancer.

Another important clinical issue is whether women who carry mutations in the BRCA1/2 genes and women who have a family history of ovarian cancer also benefit from the risk reduction associated with certain gynecologic surgeries, such as hysterectomy, tubal ligation, and oophorectomy. However, most of the studies to date on this topic involved women identified from high-risk genetic clinics, and women who attend these clinics may be more likely to develop ovarian cancer than other high-risk women. To assess this issue, NCI investigators studied women who carried BRCA1/2 mutations but who were not identified from high-risk clinics. In a case-control study of Israeli women, ovarian cancer risk was reduced after surgery in

mutation carriers and in non-mutation carriers, which reinforced the view that gynecologic surgeries may reduce risk in all high-risk women.

Among the many pressing clinical issues in the management of women who carry mutations in BRCA1/2 is determining the appropriate role of oophorectomy as a risk reduction strategy for women at increased risk of ovarian cancer. NCI investigators, in collaboration with investigators from the Gynecologic Oncology Group (GOG) and the Cancer Genetics Network (CGN), have designed a national, prospective follow up study of genetically at risk women who elect to undergo risk-reducing oophorectomy. The following issues are being addressed: (a) what is the prevalence of clinically occult ovarian cancer at the time of risk-reducing oophorectomy? (b) are there identifiable precursor lesions in the ovaries of genetically at risk women? (c) what is the incidence of primary peritoneal carcinomatosis and breast cancer subsequent to this operation? and (d) how does this surgical procedure affect the quality of life for the women who elect it?

NCI investigators studying hereditary breast and ovarian cancer families (HBOC) will make clinical predictive genetic testing for BRCA1/2 mutations available to interested family members who have been participating in long-term research studies. All families have been notified of their mutation status, and the process of bringing interested family members to the NIH Clinical Center for genetic risk assessment, counseling, genetic testing and results disclosure is now underway. HBOC is the prototype inherited cancer disorder when it comes to translating the findings of laboratory research in cancer genetics into more effective modes of clinical practice.

NCI scientists have also analyzed breast cancer family history as a risk factor for ovarian cancer among women in the prospective NCI Breast Cancer Detection Demonstration Project (BCDDP) Follow-up Cohort. Among ovarian cancer patients, associations were consistent with hereditary breast/ovarian cancer, suggesting that a carefully studied family history may permit identifying ovarian cancer patients who warrant more formal genetic risk assessment.

Another BCDDP investigation explored whether aspirin, acetaminophen, or other medications might decrease ovarian cancer risk. Some recent studies had suggested that risk was reduced in long-term medication users, but a prospective analysis showed that women who used these medications did not experience reduced risks.

### Cervical Cancer

Cervical cancer is one of the most common cancers among women worldwide. Over 400,000 new cases are diagnosed each year, resulting in about 200,000 deaths. The frequency of advanced or recurrent cervix cancer has diminished in the United States with the continuing education and application of early detection through pelvic examinations and cervical smears. However, advanced cervix cancer is still observed and has a poor prognosis. Furthermore, infection with one of approximately 15 oncogenic human papillomavirus (HPV) types is now known to be the cause of nearly all cervical tumors. Although cytological screening programs have been in place for several decades, these programs have not been effective at controlling cervical cancer in developing countries, where the vast majority of cervical cancer cases are diagnosed. In developed countries such as the United States, where screening programs have been successful, the costs associated with screening and subsequent colposcopic evaluation and

treatment are very high. Therefore, better preventive strategies against cervical cancer based on our new knowledge of the central role of HPV infection are needed. NCI has taken several steps to increase our understanding of HPV and give it clinical applications through better screening techniques and potential vaccinations.

NCI investigators have developed novel vaccine approaches now in clinical trial in the NCI CCR, and through NCI investigators, in clinical trials in the GOG clinical cooperative group. In addition, a multiplex ribozyme is under development and shows promise for clinical translation. Application of proteomics technologies to understand the molecular etiology of preneoplastic progression of cervix cancer has been initiated and clinical trials are under development from which to glean samples to allow advancement of this important molecular analysis.

Other pre-clinical studies have convincingly demonstrated the potential prophylactic efficacy of virus-like particle (VLP) based on the HPV vaccines developed at the NCI. Based on promising findings in phase I and II trials, NCI investigators, in collaboration with GlaxoSmithKline (GSK), plan to conduct a phase III trial in Costa Rica to evaluate the prophylactic efficacy of the HPV16/18 L1 VLP-based vaccine manufactured by GSK. The investigators will invite approximately 20,000 women ages 18-25 to participate. Each participant will be followed with yearly clinic visits and pelvic exams for four years to obtain information on long-term adverse events and to determine whether vaccination protects against the development of incident, histologically confirmed precancers associated with HPV16 or HPV18 infections.

NCI investigators have begun to use our understanding of HPV to increase the effectiveness of cervical cancer screening. Researchers have repeatedly shown the Pap test, the standard for cervical cancer screening, to be effective for early detection of cervical cancer. Despite limitations in both sensitivity (ability to detect disease) and reproducibility, the Pap smear is effective if women are screened on a regular basis, due to the slow-growing nature of cervical cancer. Testing for HPV DNA, however, has demonstrated extremely high sensitivity for identifying cancer. NCI scientists recently conducted a large study to investigate whether testing for HPV infection in addition to Pap smear testing could safely lengthen the interval between cervical cancer screenings. Almost 21,000 women received a baseline Pap smear as well as a test for HPV. Investigators monitored the women for development of cervical cancer for up to 10 years. Women who were negative for both Pap smear and HPV testing at the onset of the study had an extremely low risk of developing cervical cancer, largely because a negative HPV test had such a high negative predictive value. Women who tested positive for either test had a much higher risk. This research provides evidence that HPV testing in combination with Pap smear testing may safely permit longer screening intervals among patients with negative results for both measures. Positive results from either test identify a small subgroup of women requiring more frequent surveillance. These results were incorporated into recent FDA licensure of HPV DNA testing as an adjunct for Pap smear screening.

NCI investigators also conducted a three-country comparison using 188 Pap tests to explore how HPV DNA may help standardize equivocal cervical cytologic interpretations internationally. The Pap tests, collected in a study of 20,000 women in Portland, Oregon, had been interpreted independently by five U.S. cytopathologists and classified as “squamous atypia.” For

comparison, one British and two Scandinavian pathologists reviewed the slides. All eight reviewers' classifications of negative, equivocal, or abnormal Pap smears were compared using the kappa statistic. Cytologic interpretations were then compared with HPV DNA testing. Oncogenic HPV DNA detection was significantly associated with increasingly abnormal interpretations for each reader. The British reader tended to rate tests as more abnormal than the American pathologists, while the Scandinavians tended to rate tests as more normal. Reference to the HPV DNA standard clarified the tendency of readers to render systematically more or less severe interpretations. International research on cytopathology, particularly on the possible uses of HPV DNA testing, will require calibration of local cytologic definitions.

Previous studies from NCI investigators have suggested that among HPV-infected women important determinants of cervical cancer disease development include host immune response to HPV, smoking, parity, long-term oral contraceptive use, chronic inflammation, aspects of nutrition, and infection with sexually transmitted agents other than HPV. To further define the factors related to progression to CIN 2-3 among HPV infected women, large cohort studies are being conducted in Costa Rica and in the United States. The Costa Rica cohort is a population-based study of 10,000 women. As part of this study, women with evidence of HPV infection, with or without abnormal Pap tests, have been followed for seven years with repeat cytological screening, biological specimen collection, and assessment of risk factor profiles. Specific factors being evaluated include mucosal immune response, HLA alleles, chromosomal alterations, contraceptive and reproductive practices, diet, cigarette smoking, and infection with sexually transmitted agents other than HPV.

The U.S.-based study, in which women were seen at four clinical centers, was aimed at investigating specific immune responses to viral infection and risk of subsequent persistence and/or progression of lesions. In this study, women diagnosed with Pap smear changes indicative of HPV infection were followed with repeat Pap smears, specimen collection, and risk factor assessment every six months for a period of two years. Biological samples are being tested for cellular and humoral responses to HPV to assess various immunological markers that may correlate with disease status over time.

NCI investigators have examined HPV genotypes and sexual and reproductive risk factors among women with adenocarcinoma, squamous cell carcinoma, and control subjects. HPV 18 was most strongly associated with adenocarcinoma, and HPV 16 was most strongly associated with squamous cell carcinoma. More than three lifetime sexual partners was a risk factor for both adenocarcinoma and squamous cell carcinoma. Ever being pregnant was inversely associated with adenocarcinoma, while having five or more pregnancies was associated with squamous cell carcinoma. The relative importance of HPV genotypes 16 and 18 and the differences in reproductive cofactors suggest distinct causes for cervical adenocarcinoma and squamous cell carcinoma.

Hormonal factors may play a more prominent role in cervical adenocarcinoma than squamous cell carcinoma. NCI investigators evaluated whether obesity, which can influence hormone levels, was associated with adenocarcinoma and squamous cell carcinoma. In a case-control study, participants completed interviews and provided cervicovaginal samples for HPV testing.

Height, weight, BMI, and Waist to Hip Ratio (WHR) were positively associated with adenocarcinoma. Neither height nor weight was found to be associated with squamous cell carcinoma, and associations for BMI and WHR were weaker and not statistically significant. Analyses using only HPV positive controls showed similar associations. Obesity and body fat distribution were associated more strongly with adenocarcinoma than with squamous cell carcinoma. Although questions about screening remain, obesity may have a particular influence on the risk of glandular cervical carcinoma.

NCI investigators have also launched the first systematic clinical/genetic/epidemiologic study of the Inherited Bone Marrow Failure Syndromes of childhood. These disorders are well-known causes of bone marrow failure and acute leukemia in childhood. It has recently been recognized that, as affected children increasingly survive these early life illnesses, they are also at risk of a number of unusual solid cancers as young adults. Cancers of the uterine cervix, labia and anogenital region represent an important subset of these malignancies. Female members of families being studied at the NIH Clinical Center undergo a comprehensive gynecologic evaluation aimed at detecting pre-cancerous lesions and at investigating the role of HPV and other exposures in the pathogenesis of these cancers in genetically susceptible individuals.

#### Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer in the United States, though not the most lethal. Epidemiologic data indicate that endometrial cancer is a cancer where incidence and mortality are most affected by having a high body mass index (BMI). These data suggest that maintaining a normal body weight could prevent about one half of endometrial cancers. However, the alarming trends of increasing BMI in the United States suggest that endometrial cancer may become more common. Gene expression arrays are being used to examine the biologic differences in cancers from women of normal and high BMI. It is hypothesized that gene patterns will uncover different signaling events that may lead to novel approaches to design and implement effective preventive strategies. Gene expression profiling of 140 endometrial cancers is nearing completion and ready for analysis. Initial results have been reported describing global gene expression differences between different histologic types of endometrial cancer. Work is ongoing to identify a gene expression profile specific to those individuals who possess lymph node metastasis at first presentation. These profiles could be used to identify and refer those individuals who will most benefit from specialized care to a gynecologic oncologist. The goal of these efforts is to elucidate differences in the underlying biology of risk of endometrial cancer and type and presentation from which to design and implement preventive and therapeutic strategies.

Using a follow-up cohort from the Breast Cancer Detection Demonstration Project (BCDDP), NCI investigators conducted a study among 37,583 women to investigate whether a family history of breast cancer is associated with endometrial cancer risk. During the follow-up period, 648 women with endometrial cancer were identified. Controlling for age, menopausal status, race, BMI, breast cancer diagnosis, and family size, the presence of breast cancer in a first-degree or second-degree relative did not affect the risk of endometrial cancer. Risk did not vary with a relative's age at breast cancer diagnosis or the number of affected relatives with breast cancer. A non-significant increase in risk, however, was observed among women with a first-degree

relative who had bilateral but not unilateral cancer. Women with a personal history of breast cancer were more likely to develop endometrial cancer during the course of follow-up, but even in this subgroup family history of breast cancer did not enhance endometrial cancer risk.

We also know that menopausal estrogen therapy (ET) increases endometrial cancer risk, but certain key aspects of this association are unknown, including whether risk disappears after ET cessation and whether risk is higher in women with higher BMI or in smokers. NCI investigators analyzed the association of these factors on the risk of endometrial cancer in a BCDDP Follow-up Study. Results indicate that endometrial cancer risk decreased with increasing time since last ET use, but remained significantly elevated even 10 years after last use. Higher BMI and current smoking may exacerbate risk associated with ET, but significantly increased risks were not limited to these groups.

Within the BCDDP cohort, NCI investigators also examined the relationship of physical activity and endometrial cancer risk. Past-year physical activity of all types was assessed in 23,369 women who returned the baseline questionnaire and had no prior hysterectomy and/or endometrial cancer. There were no dose-response relationships with either total or vigorous physical activity; however, compared to the lowest total activity quartile, the higher four quartiles had a non-significantly lower risk. The study suggests that recent physical activity is not strongly related to the risk of endometrial cancer, and that prolonged exposure and longer follow-up may be necessary.

Using retrospective data and archived endometrial biopsy specimens from a large managed health care group in the U.S., NCI investigators have begun to explore the natural history of endometrial cancer. A study has been launched to assess the risk of developing endometrial cancer among women who are diagnosed with endometrial hyperplasia, which is a suspected precursor to endometrial cancer. The study will compare women who developed endometrial cancer at least one year after being diagnosed with hyperplasia to similar women who were diagnosed with hyperplasia but did not go on to develop cancer. This study has the potential to clarify some of the confusing issues associated with predicting which women with hyperplasia are at high risk of subsequent cancer, and could shed light on some of the mechanisms involved in the natural history of endometrial cancer.

In addition to the NCI activities already described, the Gynecologic Cancers Progress Review Group identified a number of high-priority scientific opportunities to be pursued in order to hasten our progress against cervical, endometrial, and ovarian cancers. Among these was the need: a) to develop preclinical models that mimic human endometrial cancer, and b) to understand hormone interactions, especially estrogen and progesterone, in endometrial cancer. In the fiscal year 2003, NCI funded four grants that were responsive to these recommendations. Tumor suppressor genes play an important role in the normal function of cells. Three of the recently funded NCI grants focus on examining how the loss of these suppressor genes results in endometrial cancer. These studies have generated two animal models. The fourth funded NCI grant focuses on hormonal interactions associated with breast and endometrial cancer risk.

The NCI continues to make a concerted effort to promote research in endometrial cancer. In 2002, a multidisciplinary group of about 35 researchers including clinicians, basic biologists, and researchers interested in making animal models were brought together for a NCI-sponsored workshop on Endometrial Cancer Biology. The goal of this workshop was to define and discuss current concepts, identify areas to pursue and encourage collaborative projects that would advance research in endometrial cancer. To promote research in basic cancer biology, NCI released an initiative in 2003, entitled, “High Impact Pilot Studies in Cancer Biology” to support novel pilot projects in basic cancer biology that could have a major impact on our understanding of cancer mechanisms. One of the grants described above was successfully funded by this mechanism.

A major approach in NCI epidemiology studies has been to attempt to clarify the effects of environmental factors influencing cancer through examining effects within subgroups defined by genetic markers. These include various cancer-susceptibility genes known to affect either hormone or carcinogen metabolism. A large case-control study in Poland of breast, endometrial and ovarian cancers is currently underway to evaluate the interrelationship of genetic and environmental factors. This study has special components to assess the relationship to cancer risk of occupational exposures (given that a large proportion of Polish women work outside their homes, often in industrialized settings) and of physical activity (women are being asked to wear accelerometers to provide more objective evidence of their recreational, occupational and household levels of physical activity). This study also has an extensive pathology component in order to allow precise classification of tumors and to assess the influence of various tumor markers, including some of which are being assessed by newly developed tissue microarray techniques.

### CanCORS

The Cancer Care Outcomes Research and Surveillance Consortium (CanCORS ) research initiative is a collaborative research consortium that examines the effects of health care practices and interventions in newly diagnosed cohorts of lung and colorectal cancer patients. These prospective studies collect information about medical care practices used to manage patients over the course of their disease, various outcomes associated with these practices, and information about patient and provider behaviors and perceptions. This is the first major step by NCI to develop a system for obtaining details about cancer care beyond the initial surgical and radiation treatment that is now routinely collected in high quality cancer registries.

CanCORS is now in its third year of funding. The seven teams of investigators from around the U.S. have agreed to conduct an evaluation of progress. Specifically, they will assess collaborative efforts among investigators, and track progress against the original research goals. They will also develop a conceptual framework for longer-term evaluation efforts that will be based on outcome goals and markers including collaboration, integration, publications, policy implications, and health outcomes. The evaluation results will inform discussions about whether to expand CanCORS in the future and possibly broaden the initiative to other cancers including gynecologic.

## SPOREs

The Specialized Programs of Research Excellence (SPOREs) solicits both Ovarian and Gynecological (GYN) Cancer SPORE applications. Ovarian SPOREs are restricted to research focused on ovarian cancer, while the GYN SPOREs can focus on either endometrial or cervical cancer or a combination of the two. In FY2003, NCI funded two GYN SPOREs: one at Johns Hopkins University focused on cervical cancer, and the other at MD Anderson Cancer Center focused on endometrial cancer. The next GYN solicitation for applications is scheduled for October 1, 2004. The four ongoing Ovarian SPOREs recently submitted re-competing grant applications and funding decisions will be made soon.

One of the objectives of the SPORE program is to promote Inter-SPORE collaborations focused on driving a particular SPORE activity towards a clinical endpoint or in providing support for a unique opportunity viewed to be of high translational merit. These activities are supported by short-term (2-3 year) administrative supplements to parental SPORE awards. During the past two years, the four Ovarian SPOREs have collaborated on three funded Inter-SPORE activities. One involves a collaborative effort with the NCI supported Cancer Genetics Network (CGN) on a high risk screening trial for ovarian cancer. Participants in this trial are at high risk for ovarian cancer and are screened quarterly for CA-125 levels and annually by trans-vaginal ultrasound. Investigators hope to determine if these relatively non-invasive procedures can detect ovarian cancer at an early stage in these women.

Another Inter-SPORE activity is aimed at identifying genetic changes in pre-cancerous lesions in ovaries obtained from women at high risk for ovarian cancer. The goal of this study is to determine if an early genetic change(s) can be used as a risk/early detection biomarker or as a potential target for therapeutic intervention. This study has the added potential to increase our understanding of the early stages of ovarian cancer development.

The collective goal of all of these early phase clinical studies is to ultimately provide more options and better-integrated care to (initially) high risk, then average risk, ovarian cancer patients. There are immediate goals to add a prevention option to the high risk screening trial and incorporate in measures that address breast cancer risk. It is the intent of the NCI to continue to foster these types of interactions and to maintain or increase the number of Ovarian Cancer SPOREs.

As mentioned above, the two GYN SPOREs represent a new organ site and were funded in September 2003. Four of the six projects proposed on the Cervical Cancer SPORE are focused on the development and testing of four different HPV vaccines. These vaccines are being developed for both therapeutic, as well as prophylactic, means. The Endometrial Cancer SPORE includes four projects aimed at treatment, prevention, and the development of risk and predictive biomarkers for endometrial cancer.

NCI also supports career development of OB/GYN Oncologists and Basic Scientists in translational research with career development funds made available through the SPOREs program. Currently, the four NCI funded Ovarian SPOREs support the career development of eight OB/GYN cancer researchers while the two NCI funded GYN SPOREs support four



gynecologic cancer researchers. Trainees include both MDs and PhDs. The planned GYN SPORC for FY 2004 will add two additional trainees in GYN cancer research. In addition, the NCI currently funds two OB/GYNs and two gynecologic cancer researchers through K23 patient oriented research career awards and a gynecologic oncologist through a K08 basic research career award. The NCI plans to pay one additional K08 to a gynecologic oncologist, bringing the funding success rate for OB/GYN and GYN cancer researchers to 100%. The NCI has also begun a dialogue with Society for Gynecologic Investigation and will work with them to foster training and career development opportunities in the area of gynecologic cancer research.

#### Item

***Health Communications*** – The Committee is pleased at the growth of this program of research, since health communications is such a vital contributor to the public health and health care generally. Understanding and improving communication between health providers and patients, improving communication with low literacy populations, and understanding what aids and hinders public health messages is critically important for building a healthier Nation. The Committee particularly encourages NCI to provide additional information about the HINTS survey that will commence this year. This will be the first national health communications survey, involving some 8,000 adults. (p. 104)

#### Action taken or to be taken

NCI appreciates the Committee's recognition of health communication as a vital contributor to the public health and health care generally. From primary prevention to survivorship or end-of-life care, and all points between, communication plays a vital role in reducing the burden of cancer. Communication can motivate people and communities to take actions that reduce their cancer risk. It can be used to encourage healthy diets, regular exercise, smoking cessation, and the utilization of age-appropriate cancer screening. In every cancer diagnosis, communication plays a key role in helping patients and physicians make informed decisions about treatment options and the associated risks and benefits. Importantly, cancer survivors are more likely to experience a better quality of life when they have access to useful, appropriate information and support. Culturally appropriate communication facilitates decisions that are compatible with people's values and beliefs, which in turn promote satisfaction with their decisions. In short, effective communication across the cancer control continuum is a critical element in the NCI's challenge goal of the elimination of the suffering and death due to cancer by 2015.

NCI is committed to helping Americans better understand news about cancer – whether the news comes in the form of a diagnosis, media report, or Web site. A better understanding of cancer encourages appropriate responses and minimizes inappropriate ones. It also helps improve communications between patients and health care professionals in order to facilitate more informed decision-making by patients. To achieve these important aims, the Institute's communication and education activities span the cancer control continuum. For example, in the realm of prevention and detection, NCI's communication activities provide the information, tools, and encouragement people need to embrace actions known to reduce cancer risk (including refraining from tobacco use, wearing sunscreen, eating at least 5 to 9 servings of fruits and vegetables each day, and being physically active) and utilize age-appropriate cancer screening

and early detection tests (including mammograms, Pap tests, and colorectal cancer screening tests). NCI's communication activities in the areas of diagnosis, treatment, and survivorship include empowering people who have cancer to make informed decisions about treatment, disease management, palliative care, and end-of-life options.

The Health Information National Trends Survey (HINTS) is the first and only national health communications survey that collects data every two years to assess the public's need for, access to, and use of cancer-related information. HINTS is a telephone interview with a representative national sample of American adults, with over-sampling of the largest ethnic minority populations. The survey provides a unique set of data that enables both extramural and NCI investigators to examine the relationship between health communication and cancer-related knowledge, attitudes, and behaviors. The survey:

- Provides updates on changing patterns, needs, and information opportunities;
- Identifies changing communications trends and practices;
- Assesses cancer information access and usage; and
- Provides information about how cancer risks are perceived.

NCI communication scientists are currently analyzing the survey data. Extramural investigators will have the opportunity to do so in 2004.

The Centers of Excellence in Cancer Communication Research (CCECRs) are the centerpiece of NCI's Communications initiative. The Centers are expected to contribute to the fundamental advancement of cancer communication science by examining the processes and mechanisms through which communication plays a role in cancer control. Four Centers were funded in July 2003 to carry out a variety of projects such as information-seeking related to prostate, breast, and colorectal cancer; decision aids concerning tamoxifen use among women at high risk for breast cancer; promotion of fruit and vegetable intake among African-Americans; examination of media coverage of cancer-related issues in African-American newspapers; and development and evaluation of new interactive health communication systems, among others. The range of projects will cover the discovery-development-delivery continuum and all the Centers will train future cancer communication scientists.

One of NCI's most powerful delivery arms is the Cancer Information Service (CIS). The CIS helps people become active participants in their health care by providing the latest scientific cancer information in understandable language. Through a network of 14 regional offices located at cancer centers or major medical centers throughout the country, the CIS serves the entire United States, Puerto Rico, the U.S. Virgin Islands, and the U.S. Territories. In 2002, the CIS handled over 1.4 million requests for service from patients, their families, the general public, and health professionals through multiple channels. The CIS offers a variety of services to the public including smoking cessation services (1-877-44U-QUIT), publications, and recorded information about cancer 24 hours a day, seven days a week. In addition, through its Partnership Program, CIS collaborates with national, state, and regional organizations to develop appropriate cancer education programs for minority and medically underserved populations. The Partnership Program brings cancer information to people who do not traditionally seek health information or who may have difficulties doing so because of educational, financial, or language barriers.

Furthermore, NCI has created the Center for Strategic Dissemination (CSD) within the NCI Office of the Director. The goal of dissemination at NCI is to turn knowledge into applications that benefit people. Therefore, the mission of the new center is to collaborate with staff throughout the Institute, and with NCI's external partners, to facilitate the development of "customer-centric" applications across the cancer control continuum (from basic to clinical research, and from prevention to survivorship).

Congress, NIH, and NCI have long been attuned to the need to disseminate the results of NCI's research. In 1937, when NCI was first authorized, Congress mandated that "NCI promote the useful application of research results." In 1971, the National Cancer Act requires NCI "to ensure more rapid and effective communication of research results to medical practitioners and, as appropriate, to the general public..." In 1976, NIH Director Don Fredrickson, addressed "the need to accelerate the transfer of new technology across the interface between the biomedical community and the health care community." The creation of NCI's CSD at this time is a natural extension of those mandates, and is also a product of our 2015 challenge goal – first articulated in February, 2003 – to eliminate suffering and death due to cancer.

Over the past several years, our Division of Cancer Control and Population Sciences (DCCPS) has developed an innovative cancer control dissemination program that features knowledge synthesis, grant support, and partnership approaches (e.g., Cancer Control PLANET) to facilitate dissemination. The CSD is working closely with DCCPS, as well as with the Office of Communication, the Office of Liaison Activities, the Office of Science Planning and Assessment, the Center to Reduce Cancer Health Disparities, and will soon be working with all NCI Divisions and Centers, to coordinate and facilitate a strategic dissemination process focused on achieving our 2015 challenge goal.

To "turn knowledge into applications that benefit people," and to accomplish our 2015 challenge goal, we must relentlessly focus on three processes: discovering the knowledge, developing the applications that have the most value to people and organizations in diverse real-world settings, and delivering these applications to the people and organizations who can benefit from them.

NCI's objectives for dissemination therefore are:

- To harmonize and better integrate the various aspects of dissemination at NCI.
- To better understand the perceived needs of people (i.e., priority audiences) and organizations, and to use these insights to shape NCI's program development efforts and dissemination strategies.
- To make people and organizations aware of NCI's information and applications that have value for them.
- To enable people and organizations to make informed cancer-related decisions.
- To persuade and enable people and organizations to adopt evidence-based approaches that will help reduce the risk and burden of cancer.

The CSD will coordinate and facilitate NCI's pursuit of these objectives. The strategies to be employed by CSD and its internal partners include: using extramural and in-house research and

active collaboration with NCI program staff, grantees and contract holders, to facilitate customer-centric approaches to program design; identifying evidence-based applications or, as necessary, developing “best practice” applications, and distributing them as appropriate; actively cultivating partnerships to expand our distribution channels and leverage our impact; and promoting our applications aggressively through mass media and targeted channels.

An overarching consideration for NCI is that the dissemination activities must work to *decrease* cancer disparities. Unless the reduction of cancer disparities is a prominent consideration in dissemination planning, a common unintended consequence is an *increase* in disparities.

#### Item

***Kidney Cancer*** – . . . . kidney cancer is often not diagnosed until it has spread to other parts of the body, decreasing chances of long-term survival from the disease. The Committee is concerned that treatment options are very limited, particularly for late-stage kidney cancer patients. Therefore, the Committee strongly urges the NCI to place a greater emphasis on and dedicate expanded resources to research on kidney cancer. The Committee requests the NCI to convene an expert conference by December 2003 to develop a short- and long-term research agenda and action plan for improving the diagnosis and treatment of kidney cancer. The Committee recommends that the conference include patient advocates. (p. 105)

#### Action taken or to be taken

The National Cancer Institute conducted the Kidney/Bladder Cancers Progress Review Group (PRG) in November 2001. The PRG provided outside experts the opportunity to review progress, determine the current state of the science, and identify areas of research that NCI could support to advance progress against kidney and bladder cancers. From this information, approximately 125 experts and patient advocates from various disciplines made recommendations for kidney and bladder cancer research. A number of these recommendations addressed kidney cancer diagnosis and treatment. As a whole, they constitute a short- and long-term research agenda for improving the diagnosis and treatment of kidney cancer.

In response to the PRG recommendations, NCI created the Kidney/Bladder Cancers Working Group to review the NCI research portfolio, identify gaps, and develop strategies for filling the most important of these gaps. The Working Group, together with the NCI Director, presented its analysis and proposals to the Kidney/Bladder Cancers PRG in February 2003. The PRG and Working Group discussed the Institute’s response to the PRG’s recommendations at length – and then began developing an action plan for advancing progress against kidney and bladder cancers.

The NCI’s investment in kidney cancer research increased from \$16 million in fiscal year 1997 to \$25.6 million in fiscal year 2002. Since risk factors for, and causes of, kidney cancer are still not clear, just over half of NCI-funded research projects in fiscal year 2001 focused on identifying the molecular and etiological underpinnings of kidney cancer. Findings in these areas will catalyze advances in the diagnosis and treatment of kidney cancer. The following information describes NCI’s recent actions to improve kidney cancer diagnosis and treatment.

### *Identification of the molecular and etiological underpinnings of kidney cancer*

More rapid increases in the incidence and mortality rates for renal cell cancer have been noted among African Americans than Caucasians. However, the reasons behind the upward trend and the ethnic differences remain unclear. In April 2002, NCI scientists launched the "Case-control Study of Renal Cell Cancer Among Caucasians and African Americans in the U.S." This population-based study will strive to identify environmental and genetic determinants that underlie the demographic patterns. In particular, the investigators hope to clarify the role of smoking, obesity, hypertension, medications, susceptibility genes, and other factors in the etiology of renal cancer. The investigators plan to recruit 1,400 Caucasian and 700 African American cases and 2,800 controls from the Detroit and Chicago metropolitan regions over a four-year period.

NCI is also recruiting individuals at high risk of kidney cancer through its Cancer Genetics Network (CGN). The CGN, a network of eight U.S. centers that have joined forces to make possible research that a single institution may not be able to accomplish because of insufficient numbers of participants, or the time needed to recruit them, is supporting investigations into the genetic basis of cancer susceptibility. The CGN's kidney cancer study aims to recruit sufficient families with a history of kidney cancer to enable the identification of genetic mutations involved in the genesis of kidney cancer.

### *Development of approaches for risk assessment of localized and advanced kidney cancer to direct therapy*

NCI's Cancer Treatment Evaluation Program is sponsoring a number of phase II clinical trials in kidney and bladder cancer which investigate in an exploratory fashion whether a novel agent can induce changes in the target of interest and whether this appears to correlate with clinical outcome. One phase III study in patients with transitional cell carcinoma uses P53 status to randomize patients to MVAC or observation. Patients will be followed for relapse-free survival and overall survival.

Identification and prioritization of agents—alone or in combination—that target known kidney cancer growth and progression pathways, and the development of innovative therapeutic strategies that will eradicate kidney cancer, preserve kidney function, and maintain quality of life is critical. Advances in our molecular understanding of kidney cancer have created one of the most fertile areas in which to test targeted therapies, anti-angiogenic strategies, and immunotherapeutic approaches. Recent research advances have created a great opportunity for research to translate these advances into meaningful outcomes for patients.

NCI's Clinical Cancer Therapy Research Program is supporting the translation of basic and preclinical discoveries into therapies for kidney cancer. Four kidney cancer projects are pursuing Interferon-alpha therapy, RNA-transfected cell immunotherapy, and modulation of retinoic acid action.

### *Other promising research initiatives*

Finally, because important scientific discoveries are sometimes impossible to predict and plan, the NCI is funding a significant number of investigator-initiated research projects focusing on the

kidney but not directly on kidney cancer diagnosis and treatment. Included in this portfolio are grants funded by the Pilot and Feasibility Program in Urology, a joint initiative with the National Institute of Diabetes, Digestive, and Kidney Diseases. The aim of this initiative is to foster high-risk pilot and feasibility research by investigators developing a new line of research in urologic diseases. NCI also is supporting a number of studies on the role of the extracellular matrix of the kidney in organ and tumor development. These studies will inform the identification of new or better diagnostics and treatments for kidney cancer. Lastly, NCI's Cooperative Human Tissue Network has procured thousands of normal and cancerous kidney tissue samples for investigators pursuing a wide variety of kidney cancer-related studies.

Additionally, for the past 20 years, members of NCI's Urologic Oncology Branch and Laboratory of Immunobiology have worked together to identify the genes that predispose to the development of renal cancer. Rare families with very strong inherited tendencies to develop kidney cancer were studied. As a result of these studies, four genes that predispose to kidney cancer were identified, and DNA diagnostic tests were developed to identify carriers of disease-causing mutations. In FY 2003, NCI identified the gene responsible for a rare inherited form of kidney cancer, the Birt-Hogg-Dube' syndrome. NCI also confirmed reports by an international group that a specific gene was responsible for another rare inherited form of kidney cancer - hereditary leiomyoma renal cell carcinoma. The identification of these kidney cancer genes has provided a powerful tool to understand the specific biochemical changes that occur during kidney cancer formation. Understanding these specific biochemical changes had led to several new initiatives for kidney cancer treatment performed in NCI's Surgery Branch, and at the Dana Farber Cancer Institute.

#### Item

***Lymphoma--*** The Committee recommends that NCI increase its efforts to examine the issue of environmental and viral links to lymphoma. Although many studies have suggested an increased risk of lymphoma associated with environmental factors such as chemicals, pesticides and herbicides, other investigations have reported inconsistent results. However, many of these studies are weakened by limited sample sizes, flaws in study design, and imprecision in the measurement of environmental carcinogen exposures. The Committee recommends that NCI work to develop a well-constructed prospective study, using a multidisciplinary approach to examine environmental links to lymphoma.

In a recent report (October 2002) the Institute of Medicine concluded that there is moderate to strong biological evidence supporting a role of Simian Virus 40 in human cancer. Recent reports suggest that more than 40% of lymphomas tested were positive for this virus. Additional research studies have also found an association between other viruses, such as human herpes virus 8 and hepatitis C, and lymphoma. As a result of these studies, it is possible that more than half of all lymphomas may be attributed to viruses. The Committee encourages NCI to increase its efforts to examine the viral etiology of lymphoma.

More than 61,000 Americans will be diagnosed with Hodgkin's lymphoma and non-Hodgkin's lymphoma [NHL] in 2003. The Committee notes that there have been significant advances in the treatment of Hodgkin's lymphoma over the last 30 years and some improvements in the

treatment of NHL. However, NHL treatments are not adequate, and treatment improvements are absolutely critical for this group of cancer patients. Although industry has recently developed several new NHL therapies, the involvement of the National Cancer Institute in lymphoma research is still critical. The Committee urges that NCI increase its investment in clinical research on lymphoma and strengthen its collaboration with industry to improve the efficiency and timeliness of the lymphoma drug development process. (p. 105-6)

Action taken or to be taken

Please refer to pages NCI-51 through NCI-61 of this document for NCI's response to this significant item regarding Lymphoma.

Item

***Myelodysplasia and Myeloproliferative Disorders*** – The Committee is pleased with NCI's efforts to address the lack of basic knowledge about myelodysplasia and myeloproliferative disorders, two very different types of chronic diseases of bone marrow cells that can develop into acute leukemia. The Committee urges NCI to carry out the recommendations of its recent conference of experts on these diseases and advance new research initiatives into developing effective treatments. (p. 106)

Action taken or to be taken

Please refer to pages NCI-61 through NCI-63 of this document for NCI's response to this significant item regarding Myelodysplasia and Myeloproliferative Disorders.

Item

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

Action taken or to be taken

Nanotechnology, systems biology, and molecular imaging have all played significant roles in studying the molecular basis of cancer and identifying possible pathways and targets for treatment. NCI is working to synergize the efforts in these disciplines to accelerate such understanding and therapeutic applications. Currently, NCI has a strategic planning process for cancer nanotechnology research underway. Several working groups have been assembled and are identifying research opportunities to integrate nanotechnology into basic and translational cancer research programs.

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

The Innovative Molecular Analysis Technologies (IMAT) program supports research projects to develop and carry out pilot applications of novel technologies that will enable the molecular analysis of cancers and their host environment in support of basic, clinical, and epidemiological research. Technologies supported through the IMAT program include those that: detect alterations and instabilities of genomic DNA; measure the expression of genes and gene products; analyze and detect gene and/or cellular products including post-translational modification and function of proteins; identify and characterize exogenous infectious agents in cancer; or assay the function of major signal transduction networks involved in cancer.

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

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

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

NCI will hold a workshop on building the interface between nanotechnology and imaging technology to identify new and improve existing clinical detection, diagnostic, and disease monitoring technologies. This meeting brings engineers from nanotechnology laboratories into



discussions with researchers developing contrast agents needed in identifying cancerous cells and tissues.

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

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

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

Many areas of modern biomedical research and, in particular, translations of complex discoveries into useful clinical applications increasingly require multi-disciplinary and inter-disciplinary teams. The past decade presented us with identification of the human genome, steady progress in systems biology, and advances in technology and computational sciences that offer unprecedented opportunities for benefits to human health. Much innovation and progress will still spring from and depend on creative individual investigators, but collaborative synergy will be necessary to realize many of the promises of "molecular medicine." NCI is working with the scientific community to foster team science approaches to accelerate the pace of discovery, development, and delivery to accomplish the goal of eliminating death and suffering from cancer by 2015.

#### Item

***Neurofibromatosis*** – Neurofibromatosis [NF] research has significant potential for cancer patients since NF genes have been implicated in the signaling processes that determine cell growth and cell differentiation. It will contribute to the development of new technologies and enhance understanding of the fundamental processes of both cancer and NF. The Committee encourages NCI to intensify and expand its NF research portfolio in such areas as molecular biology, development of animal models, natural history studies, malignant transformation in

tumors, therapeutic intervention, and clinical trials. It recommends that NCI use all available mechanisms, including requests for applications, program announcements, and the national cooperative drug discovery group program to achieve this end. The Committee expects NCI to coordinate its efforts with other Institutes where appropriate and to be prepared to report on its progress at the fiscal year 2005 appropriations hearings. The Committee thanks NCI for conducting phase II clinical trials of NF1 patients with plexiform neurofibromas. Finally the Committee encourages NCI to increase its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation, and clinical trials. (p. 107)

Action taken or to be taken

Please refer to pages NCI-47 through NCI-51 of this document for NCI's response to this significant item regarding Neurofibromatosis.

Item

**Prostate Cancer**—The Committee is aware of the considerable investment that has been made in prostate cancer, the leading cause of cancer death among men, and encourages NCI to continue to support research to improve the accuracy of screening and early detection of prostate cancer. Emphasis should also be placed on the development of new, more effective therapies for cancer that was not detected early enough and is no longer confined to the prostate capsule.

The Institute has worked with the urologic scientific community to identify research needs in other urologic oncology, including bladder, kidney and testis cancers. The Committee expects the Institute to increase the research resources directed to these other urologic cancers, which affect thousands of men and women annually.

The success in treating prostate, and other cancers, means that there are many individuals in society who are cancer survivors. There are a series of distinct physical and emotional issues facing these individuals, and the Committee encourages NCI to develop programs that address these problems. (p. 108)

Action taken or to be taken

Please refer to pages NCI-34 through NCI-44 of this document for NCI's response to this significant item regarding Prostate Cancer and NCI-117 through NCI-119 regarding Kidney and Bladder Cancer.

In addition, the following information relates to NCI efforts in testicular cancer.

Testicular cancers (TC), are rare but are important to study because they are the most common cancer in young males between the age of 15-35 years and the incidence has increased over the last 50 years. NCI currently funds a number of projects related to TC, in areas that include basic research as well as clinical studies. The overall goal is to better understand the molecular mechanisms that govern these cells and their behavior, in order to make better versions of the current drugs, which will more specifically target the tumor cells.

Identification of TC susceptibility genes is important in order to dissect the biology of the germ cell's transformation. Case Western Reserve University is discovering susceptibility genes in a mouse model and will use them to evaluate inherited risk for TCs in humans. Another type of genetic study being done at Fred Hutchinson Cancer Research Center examines whether the risk of TC associated with environmental contaminants is modified by genetic polymorphisms in oxidative stress systems.

Another area of great interest is drug discovery and development. Researchers at Massachusetts Institute of Technology are studying the leading drug used against TC, cisplatin. They hope to uncover the mechanisms by which the cells respond to cisplatin, thereby better understanding the toxicity of this agent, in order to design less toxic versions of these metal complexes. Drugs that more specifically target the tumor cells will cause less damage to surrounding normal tissue.

There are studies being done on TC survivors, several of them with the goal of developing interventions to modify risk behaviors. For example, those patients who were treated with cisplatin-based chemotherapy have an increased risk for cardiovascular disease, which is the focus of a project at University of Pennsylvania. Another behavior research project is being done at the University of Hawaii, identifying issues and concerns of survivors that may vary according to ethnicity.

FY 2004 Conference Committee Report language (H. Rpt 108-401)

Item

***Pediatric cancer clinical trials*** - To increase the likelihood of a cure for every child with cancer, the conferees urge NCI to increase its support of translational research to accelerate the pace of pediatric cancer clinical trials. The existing NCI-supported national infrastructure of a clinical trials network should be the dominant component of this accelerated effort. (p.769)

Action taken or to be taken

The Children's Oncology Group (COG) is a National Cancer Institute (NCI)-supported clinical trials cooperative group devoted exclusively to childhood and adolescent cancer research. Through the COG, NCI supports clinical trials that reliably identify whether new treatments are of benefit to children with cancer. This pediatric cooperative group program has a history of successfully conducting translational research projects in association with large, phase III clinical trials.

Recently, an NCI-supported study presented at the Plenary Session of the 2003 American Society of Hematology Meeting described gene expression microarray studies using leukemia cells from hundreds of children enrolled in pediatric cooperative group studies. This work has led to the identification of a new prognostic marker that can robustly distinguish between children with acute lymphoblastic leukemia (ALL) likely to relapse versus those likely to be cured with currently available therapy. This observation has major implications for how treatment can best be tailored to meet the needs of each child with ALL. NCI recognizes that COG clinical trials are essential if progress in increasing cure rates for children with cancer is to continue into the future.

In this age of molecularly targeted therapy, translational research relating tumor cell biology to clinical outcome is critical for future progress. NCI directly supports enrollment of patients onto COG's clinical trials, the collection of tumor samples for biology studies, and selected translational research studies. NCI offers a variety of additional funding opportunities for which COG researchers can compete to accomplish additional translational research. NCI staff work with COG researchers to make sure that they are aware of these opportunities and to advise them as appropriate in the grants submission process.

An important new NCI initiative is the establishment of a Pediatric Preclinical Testing Program to annually screen 10 to 15 new agents, or combinations of agents, against a panel of preclinical models for common pediatric tumors (e.g., mouse models). These preclinical models will allow researchers to screen cancer drugs developed for adults for their potential applicability to pediatric tumors. A second initiative is the NCI's Pediatric Oncology Preclinical Protein-Tissue Array Project (POPP-TAP). This Program, which is being sponsored in collaboration with the COG Phase I Consortium, is characterizing the molecular features in mouse models of childhood cancers and comparing these expression patterns to those observed in children with the same cancers. Molecular characterization of preclinical tumor models may point to critical signaling pathways that can be targeted by specific anti-cancer agents. A better molecular characterization of the tumor models may also suggest translational research studies that can be applied to clinical specimens obtained from COG studies.

In addition, patients with neuroblastoma (NB) are carefully risk-stratified in order to determine appropriate therapy. Despite this, patients with high-risk NB have a less than 30% probability of survival, and it is not possible to predict which patients will respond to therapy and which will die of disease. Investigators in NCI's Pediatric Oncology Branch have utilized gene expression profiling and artificial neural networks (ANNs) to develop an accurate predictor of survival. ANN-based algorithms identified 34 genes that correctly predicted outcome for 98% of these patients. Moreover, these predictor genes were able to further partition COG stratified high-risk patients into two subgroups according to their survival status. These findings provide evidence of a gene expression signature that can predict prognosis independent of currently known risk factors.

The New Approaches to Neuroblastoma Therapy Consortium (NANT) (<http://www.nant.org>) is a consortium of university and children's hospitals funded by the NCI to test promising new therapies for neuroblastoma. NANT members constitute a group of closely collaborating investigators linked with laboratory programs where novel therapies for high-risk neuroblastoma are being developed. The group conducts early trials to test new drugs and new combinations of drugs so that promising therapies can be tested nationally.

Another important initiative is the Pediatric Brain Tumor Consortium (PBTC) (<http://www.pbtc.org>). The primary objective of the PBTC is to rapidly conduct phase I and II clinical evaluations of new therapeutic drugs, intrathecal agents (agents injected into the cerebrospinal fluid), delivery technologies, biological therapies, and radiation treatment strategies in children up to 21 years of age with primary central nervous system tumors. The PBTC

includes nine leading academic institutions with extensive experience in the design and conduct of clinical trials for children with brain tumors. Another objective of the PBTC is to develop and coordinate innovative neuro-imaging techniques. Results from PBTC studies are made available to large international collaborative groups for confirmatory phase II and multi-agent phase III clinical trials.

Finally, NCI has as part of the Cancer.gov website a home page for childhood cancers (<http://www.cancer.gov/cancerinformation/cancertype/childhood/>). This page provides a consolidated view of childhood cancer information on one, easy-to-navigate page that is easily accessible on the Cancer.gov Web site.

Item

***Needs of Hawaiians*** – The conferees encourage the Director of NCI to establish a task force to explore the continuing unique needs of the peoples of Hawaii and the Pacific Basin region. (p. 769)

Action taken or to be taken

Please refer to pages NCI-81 through NCI-86 of this document for NCI's response to this significant item regarding the Needs of Hawaiians.

Item

***Tobacco Harm Reduction*** – The conferees concur with language in the House report regarding the importance of the collaboration between NCI and CDC regarding tobacco harm reduction. In addition, the conferees urge the NCI to examine what additional scientific research is needed to determine the relative risks of different tobacco products. (p. 770)

Action taken or to be taken

Please refer to pages NCI-71 through NCI-75 of this document for NCI's response to this significant item regarding Tobacco Harm Reduction.

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Authorizing Legislation**

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	\$4,666,986,000	Indefinite	\$4,799,165,000
National Cancer Institute	Section 411	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	<u>a/</u>	68,987,000	<u>b/</u>	70,860,000
<b>Total, Budget Authority</b>				<b>4,735,973,000</b>		<b>4,870,025,000</b>

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

b/ Reauthorizing legislation will be submitted.

**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Appropriations History**

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation <sup>1/</sup>
1996 <sup>2/</sup>	\$1,994,007,000 <sup>2/</sup>	\$2,251,084,000	\$2,184,467,000 <sup>2/</sup>	\$2,251,084,000
Rescission				(2,654,000)
1997 <sup>2/</sup>	2,060,392,000 <sup>2/</sup>	2,385,741,000	2,102,949,000 <sup>2/</sup>	2,381,399,000 <sup>3/</sup>
1998 <sup>2/</sup>	2,217,482,000 <sup>2/</sup>	2,513,020,000	2,558,377,000	2,547,314,000
1999	2,528,760,000 <sup>2/5/</sup>	2,787,830,000	2,927,187,000	2,927,187,000
Rescission				(1,940,000)
2000	2,732,795,000 <sup>2/</sup>	3,163,417,000	3,286,859,000	3,332,317,000
Rescission				(17,763,000)
2001	3,249,730,000 <sup>2/</sup>	3,505,072,000	3,804,084,000	3,754,456,000 <sup>4/</sup>
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			

<sup>1/</sup> Reflects enacted supplementals, rescissions, and reappropriations.

<sup>2/</sup> Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

<sup>3/</sup> Excludes enacted administrative reductions of \$1,095,000 and \$38,000.

<sup>4/</sup> Excludes enacted administrative reductions of \$781,000.

<sup>5/</sup> 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 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	749	748	746
Center for Cancer Research	1,656	1,574	1,569
Division of Cancer Biology	51	51	51
Division of Extramural Activities	109	110	110
Division of Cancer Treatment and Diagnosis	208	205	205
Division of Cancer Prevention	102	99	99
Division of Cancer Control and Population Sciences	148	145	145
Division of Cancer Epidemiology and Genetics	142	141	141
Total	3,165	3,073	3,066
FTEs supported by funds from Cooperative Research and Development Agreements			
	(9)	(9)	(9)
FISCAL YEAR	Average GM/GS Grade		
2001	11.3		
2002	11.4		
2003	11.5		
2004	11.5		
2005	11.5		



**NATIONAL INSTITUTES OF HEALTH  
National Cancer Institute**

**Detail of Positions**

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6	1	1	1
ES-5	3	3	3
ES-4	3	3	3
ES-3	0	0	0
ES-2	1	1	1
ES-1	0	0	0
Subtotal	8	8	8
Total - ES Salary	\$1,135,043	\$1,181,580	\$1,206,984
GM/GS-15	226	220	219
GM/GS-14	323	320	318
GM/GS-13	308	300	298
GS-12	498	484	483
GS-11	249	240	240
GS-10	26	24	24
GS-9	193	187	187
GS-8	139	134	134
GS-7	145	140	140
GS-6	34	30	30
GS-5	22	20	20
GS-4	14	14	14
GS-3	3	3	3
GS-2	5	5	5
GS-1	0	0	0
Subtotal	2,185	2,121	2,115
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General	1	1	1
Director Grade	51	51	51
Senior Grade	21	21	21
Full Grade	9	9	9
Senior Assistant Grade	7	7	7
Assistant Grade	2	2	2
Subtotal	91	91	91
Ungraded	981	952	950
Total permanent positions	2,193	2,129	2,124
Total positions, end of year	3,265	3,172	3,164
Total full-time equivalent (FTE) employment, end of year	3,165	3,073	3,066
Average ES level	ES-4.37	ES-4.37	ES-4.37
Average ES salary	\$141,880	\$147,697	\$150,873
Average GM/GS grade	11.5	11.5	11.5
Average GM/GS salary	\$70,192	\$73,070	\$74,641