

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

FY 2008 Budget for the National Institutes of Health:
A New Vision for Medical Research (Part II)

Witness appearing before the
Senate Subcommittee on Labor-HHS-Education Appropriations

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Mr. Chairman and Members of the Committee:

I appear before you today to present the President's budget request for the National Cancer Institute (NCI) of the National Institutes of Health (NIH). The Fiscal Year (FY) 2008 budget includes \$4,782,114,000.

INTRODUCTION

I am most pleased to be before you today to report on the Nation's progress in cancer research. While there has been a steady decline in the cancer mortality rate (the number of cancer deaths per 100,000 people) since 1991, we now have the excellent news that for the second year in a row there has been a decline in the absolute number of cancer deaths. In 2003, there were 369 fewer cancer deaths reported in the United States than in 2002. In 2004 (the most recent year reported) the decrease was almost ten times greater, at 3,014

[Figure 1]. This decline is even more significant when you consider that cancer is largely a disease of aging, and our population is not only growing in numbers, it is aging at an even greater rate. Progress is, indeed, heartening, but our work is not done. Too many of our citizens' patients and families alike continue to feel the pain and fear that come with the devastating news of a cancer diagnosis.

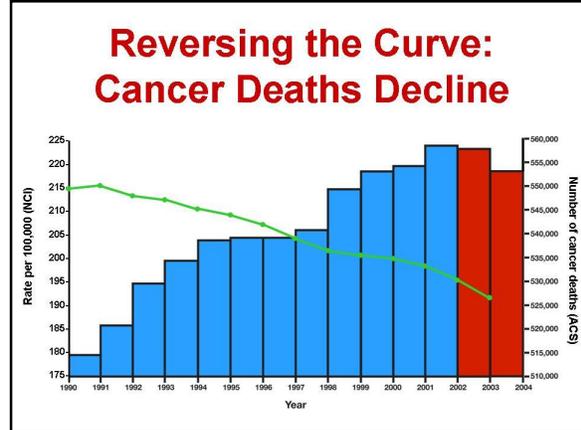


Figure 1: The green line represents the cancer mortality rate per 100,000 population. The bars represent the actual recorded number of cancer deaths in the United States.

While we measure our progress against cancer in terms of patients treated and lives saved, that effort also has a measurable economic impact. It has been projected that even a 1 percent decrease in cancer mortality will result in a \$500 billion benefit to the U.S. economy (Murphy, K. and Topel, R., *Journal of Political Economy*, 2006; 114(5),

871-904). In fact, such a benefit may ultimately be magnified many fold, because increasingly we recognize that cancer has become a model for developing our base of knowledge concerning many diseases. For example, the study of angiogenesis (blood vessel development) associated with tumor growth has been applied to greater understandings and treatment of macular degeneration, ischemic heart disease, diabetic wound healing, endometriosis and neurodegenerative illnesses. Furthermore, the unique capabilities of NCI's cancer researchers have been vital in other conditions. The identification of the AIDS virus and the development of assays to screen banked blood for the AIDS virus happened at the National Cancer Institute, where the current AIDS therapy regimen used around the world was also developed.

Today, the NCI is leading the way in identifying the genetic, molecular, and cellular mechanisms associated with cancer's research fronts that hold great potential to enhance research and research collaboration against other diseases, as well. Building upon the sequencing of the human genome and working in our newly developed "Center for Human Cancer Genomics," NCI is systematically identifying all the important inherited and acquired genetic alterations that contribute to cancer susceptibility. We are cataloguing genetic changes involved in the process of a normal cell becoming malignant, and we are applying this knowledge, in order to identify people at increased risk for developing cancer, prevent and detect cancer at its earliest, most treatable stages, and identify new targets for highly selective and specific therapeutic agents.

A RECORD OF REAL SUCCESS

The past year for cancer research and development has been one of substantial and heartening achievement. We are expanding both our knowledge and the technology tools to understand the mechanisms of cancer. Importantly, we are seeing scientific advances being rapidly applied to predict and preempt cancer.

- We reached an important public health milestone in June 2006, when the FDA approved a vaccine that prevents infection by the two types of the human papillomavirus (HPV) responsible for up to 70 percent of cervical cancer cases

worldwide. We can all take great pride in the fact that our Nation's strong commitment to and investment in cancer research at NCI led to this approval.

- Researchers have begun to survey the human genome for DNA variants, to identify genes that predict risk for common cancers. Capitalizing on new knowledge of

human genetic variation and technical advances in whole-genome scanning, The Cancer Genetic Markers of Susceptibility (CGEMS) project is currently targeting genes that increase the risk of prostate and breast cancer [Figure 2]. Work is beginning on a similar study for pancreatic cancer. These studies of large numbers of patients will be

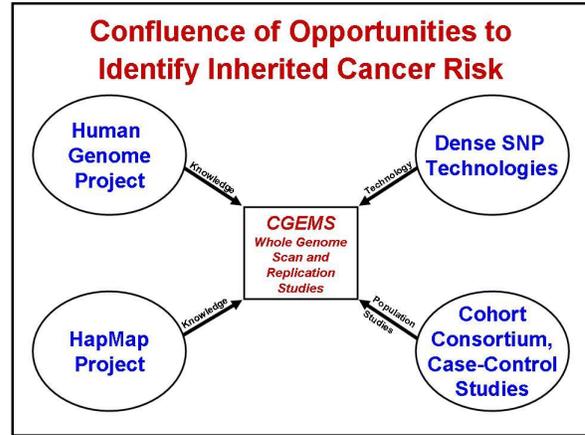


Figure 2: Previously developed technologies are used to analyze DNA specimens from large patient cohorts.

useful both for understanding causal pathways and for developing preventive interventions. DNA variants found to be associated with cancer risk will rapidly be made available publicly to the scientific community through the NCI cancer Biomedical Informatics Grid (caBIG™) database.

- Genomic technology is already being applied to explain why some patients with diffuse large B-cell lymphomas (DLBCL) live longer and respond better to therapy than others [Figure 3]. Under the

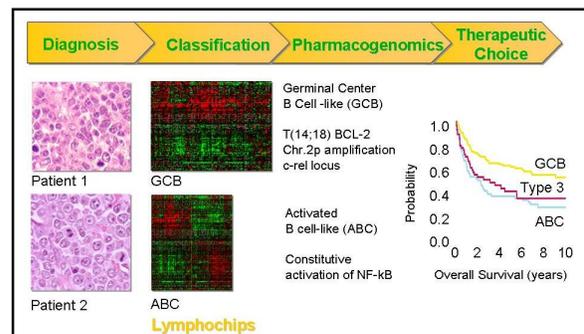


Figure 3: Previously developed technologies are used to analyze DNA specimens from large patient cohorts.

microscope, the DLBCL cancer cells from every patient look the same, but genetic differences have been shown to predict good versus poor prognosis. As a result of this research, it may be possible to determine which patients are most

likely to respond to a specific treatment, thus sparing those patients unlikely to see a significant benefit the side effects of a failed treatment.

DELVING DEEPLY INTO THE CANCER CELL ENVIRONMENT

Building on the success of the CGEMS project in identifying inherited genetic risks, the NCI and the National Human Genome Research Institute have launched a pilot phase of The Cancer Genome Atlas (TCGA), a collaboration designed to determine the feasibility of using large-scale genome analysis technology to identify important genetic changes involved in cancer. TCGA is currently studying lung, brain (glioblastoma), and ovarian cancers which collectively account for more than 210,000 cancer cases each year in the United States.

Other initiatives are expanding our study of the cancer cell and the networks and the cellular microenvironment that also appear to be significantly involved in tumor development and metastasis. These studies of molecular carcinogenesis are being conducted at the single-cell or the subcellular level, using high-resolution, three-dimensional electron microscopy. These technologies allow us to look within the nucleus to study differences in chromosome movement and location during stages of abnormal cell growth.

On another front, there is increasing evidence that cancer stem cells or cancer initiator cells are both the driving force behind many cancers and the basis for long-term risk. The presence of such cells, first demonstrated in acute myeloid leukemia patients, provides a different and exciting model with which to further explore cancer biology. NCI is establishing a group of scientists across the National Institutes of Health interested in embryogenesis and cancer stem cell biology, in order to advance the study of the underlying mechanisms in these processes.

ADVANCED TECHNOLOGIES ACCELERATE PROGRESS

It is clear that the area of advanced technologies development is absolutely essential and critical in creating tools for speeding up and enabling the discovery process. In

addition to the genomic technology projects (CGEMS and TCGA), NCI is investing in the development of critical technology platforms in a number of other strategic areas, such as nanobiology, proteomics and computational biology.

Recognizing the key role of biospecimens in all of biomedical research, not just cancer research, NCI has led a pioneering effort to provide the first guidelines that standardize and enhance specimen collection and biorepositories. These guidelines have made it possible for NCI to develop a common biorepository infrastructure that promotes resource-sharing and enables data comparison among research laboratories, while also ensuring patient protection and ethical integrity.

We also believe that advanced imaging technologies will play a significant role in the prevention and preemption of cancer, as well as in making go or no-go decisions for early oncologic drug development. The NCI is working now in the aforementioned subcellular space, to be able to view in real time the interactions between drugs and cells and the resulting secondary functional changes. The NCI is developing new targeted and non-targeted molecular imaging agents for use as lymphatic markers, angiogenic markers, and surrogate markers for drugs that enhance quantitative methods to measure early, real-time tumor response. These technologies are further examples of NCI initiatives that produce benefits that will be realized across multiple areas of biomedical research.

INTERAGENCY COLLABORATIONS

Addressing cancer requires work across institutional and sector boundaries, so members of the Department of Health and Human Services (DHHS) family of agencies, other federal offices, and the private sector can share knowledge and partner in the development of systems-based solutions. NCI has long been at the forefront of research and development of biomarkers for use in diagnosis and treatment for cancer. Now, a Biomarkers Consortium launched last year includes participants from the Foundation for the NIH, NIH, FDA, CMS, and private industry with the goal of validating biological markers for a variety of diseases, including cancer. The first

project approved by the Consortium is the evaluation of an imaging agent that detects an increase in cell metabolism characteristic of tumor growth. NCI is conducting trials in lung cancer and non-Hodgkin's lymphoma that use this ability to view cellular metabolism to monitor tumor masses for increased activity (cell growth) or decreased activity (cell death) during the early stages of anticancer treatment.

The joint NCI-FDA Interagency Oncology Task Force (IOTF), established in 2003 to enhance and accelerate the overall process of developing new cancer interventions, released two new guidance documents and a final rule intended to streamline the early clinical development of new drugs and biologics for cancer and other diseases. This has enabled the first-in-human "Phase 0" trial (a step before the classic Phase 1 level of drug study) that measures the activity of a new drug in a limited number of patients using a single, small dose of the study agent, prior to the traditional dose-escalation, safety and tolerance studies. Phase 0 will substantially compress drug development time.

TRAINING THE NEXT GENERATION OF CANCER RESEARCHERS

Cancer is one of the most exciting and innovative areas of medical research. It takes a superbly trained, highly effective workforce to make discoveries, to translate them into new interventions, and to put the improved knowledge base and cutting-edge tools to work for patients. NCI will continue to play an important role in developing the cancer research workforce in the United States and in other countries. We stand firmly by the Institute's commitment to provide unparalleled training opportunities for talented researchers from a wide variety of disciplines to advance their careers. In fact, many of the current programs at NIH had their origins in the NCI.

Of special significance are minority training programs, such as the Continuing Umbrella of Research Experiences (CURE), which begins with talented minority high-school students and continues progressively and selectively through long-term funding to qualified minority students interested in scientific, cancer research-related careers.

REACHING THE PATIENT AND COMMUNITY

NCI must continue to make progress for each cancer patient. Yet, the recent report on cancer deaths that showed a decrease in deaths nationally also confirms a troubling fact: Minority and low-income populations shoulder a disproportionate cancer burden and are not benefiting equally from important advances. We must bring the best science to patients, 85 percent of whom are treated in the communities where they live. With that obligation in mind, NCI is launching a pilot of the Community Cancer Centers Program (NCCCP). This pilot project will study how best to provide easily accessible, state-of-the-art, multi-specialty cancer care and earliest phase clinical trials research to patients in their communities. Through this program we will also learn best how to educate patients concerning risk, healthier living, screening practices, clinical trial participation, survivorship, and end-of-life issues.

This program is about bringing the newest science to patients where they live—a challenge that is more critical now than at any time in our history. Our nation's healthcare system faces many looming stresses, particularly in light of the fact that the first wave of baby boomers turns 65 in 2011. With the graying of a generation comes the need for a new way to confront the diseases of aging—and especially to anticipate what will be a marked increase in cancer incidence. That makes even more important our efforts to develop advanced technologies that will eventually lead to the genomic and proteomic breakthroughs essential to enable us to preempt disease at earlier stages.

There is great cause for optimism, but an optimism that should be tempered by an understanding of the very real hurdles to progress we still face. These are challenges that we must address as a community. In doing so, the encouraging trends of decreasing death rates from cancer will become the rule, not the exception. We will learn how to deliver the best of our science to everyone—not just a few.

John E. Niederhuber, M.D.
Director, National Cancer Institute

John E. Niederhuber, M.D. became Director of the National Cancer Institute (NCI) in September 2006. Prior to that he had been the Institute's Acting Director, from June 2006. He was formerly the Wattawa Professor-Bascom in Cancer Research, Professor of Surgery and Oncology at the University of Wisconsin School of Medicine. Dr. Niederhuber served the University of Wisconsin as the Director of the University of Wisconsin Comprehensive Cancer Center from July 1997 until October 2002. He came to the University of Wisconsin in 1997 from Stanford University where he had served as Chair of the Department of Surgery. In June 2002, President George W. Bush appointed Dr. Niederhuber Chair of the National Cancer Advisory Board, a position he held until resigning to become the Deputy Director at NCI in 2005.

Dr. Niederhuber's research at the NCI focuses on the study of tissue stem cells as the cell-of-origin for cancer. His lab is working to identify, characterize fully and isolate this population of cells with the hypothesis that such cells might be the required therapeutic target. Under investigation, are the conditions that would make it possible to grow cancer stem cells in culture, such as hypoxia. Post transcriptional profiles of stem cells compared to other tumor cells and cells of the tumor microenvironment are being used to determine differences and potential drugable targets in cancer stem cells. Small interfering RNA (siRNA) technology is being used to reduce or block candidate gene expression. Tyrosine kinases and other cellular pathways, such as Hedgehog, in subpopulations of cancer stem cells compared to non-stem cells are used to further define unique targets. His lab is also studying the viral cancer vector HPV, to identify the binding site theorized to be a stem cell epithelial receptor.

The complex relationship between tumor cells and the microenvironment is another component of Dr. Niederhuber's research program. Studies will focus on how normal stroma is changed during tumor progression with the goal of developing strategies to prevent the development of tumors based upon an understanding of the alterations in the microenvironment. He holds a clinical appointment on the NIH Clinical Center Medical Staff.

Dr. Niederhuber is a nationally recognized cancer surgeon with a special clinical emphasis in gastrointestinal cancer, hepatobiliary cancer and breast cancer. He is recognized for his pioneering work in hepatic artery infusion chemotherapy and was the first to demonstrate the feasibility of totally implantable vascular access devices. The *Blk*-proto-oncogene was a novel discovery in Dr. Niederhuber's laboratory while he was a member of the faculty at The Johns Hopkins Medical School and is of interest because of its unique expression in B-cells and its participation in both proliferative and apoptotic pathways during B-cell differentiation.

Dr. Niederhuber has been a member of the Society of Surgical Oncology since 1978 and served as SSO President (2001-02). He also served as President of the American Association of Cancer Institutes (AACI) (2001-03). Dr. Niederhuber was one of the founding members and served on the executive committee of the American College of Surgeons Oncology Cooperative Group.

He served as a member of the NCI Cancer Centers Review Committee (1984-86) and the NCI Division of Cancer Treatment Board of Scientific Counselors (1986-1991). He was Chairman of the Board from 1987-1991. He was a member of the NCAB Subcommittee to Evaluate the National Cancer Program (Committee to Assess Measures of Progress Against Cancer), chairing the Molecular Medicine Panel (1993-95). Dr. Niederhuber has served on the General Motors Cancer Research Foundation Kettering Prize Selection Committee (1988-89) and twice served on the GMCRF Awards Assembly (1988-92), (1998-02). He chaired the ASCO Surgical Oncology Task Force for the 2001-02 strategic planning process and the ASCO Public Policy and Practice Committee (2002-2003). He was a member of the Burroughs-Wellcome Foundation Translational Research Advisory Committee (1999-06).

Dr. Niederhuber is a graduate of Bethany College, Bethany, West Virginia and the Ohio State University School of Medicine. He was an NIH Academic Trainee in Surgery at the University of Michigan (1969-70) and a Visiting Fellow, Division of Immunology, The Karolinska Institute, Stockholm, Sweden (1970-71). He completed his training in surgery at the University of Michigan in 1973. He was a member of the faculty of the University of Michigan from 1973 to 1987, being promoted to Professor of Microbiology/Immunology and Professor of Surgery in 1980. During 1986-87, he was Visiting Professor in the Department of Molecular Biology and Genetics, The Johns Hopkins University School of Medicine.

Dr. Niederhuber joined the faculty at The Johns Hopkins School of Medicine in 1987 as Professor of Surgery, Oncology, and Molecular Biology and Genetics. In 1991, He was appointed Emile Holman Professor of Surgery, Professor of Microbiology and Immunology and Chair of the Department of Surgery, Stanford University. He left Stanford in 1997 to become the Director of the University of Wisconsin Comprehensive Cancer Center where he guided the consolidation of the University's two distinguished NCI supported cancer centers.

Dr. Niederhuber was recipient of a U.S. Public Health Service Career Development Award from NIAID (1974-79). In 1978 he received the Distinguished Faculty Service Award from the University of Michigan. He has also been recognized with the Alumni Achievement Award from The Ohio State University College of Medicine in 1989 and the Distinguished Alumni Award in Medicine from Bethany College (1995). He was elected to *Who's Who in America* in 1998 and *Who's Who in Medicine and Health Care* (1997). In addition, he has received numerous honorary professorships and is currently serving on the editorial board of ten scientific journals. He was a member of the editorial board of the *Journal of Clinical Oncology* (1993-95). He has authored and coauthored more than 180 publications and edited four books, including, with distinguished colleagues, the highly regarded reference text *Clinical Oncology* which is currently in its third edition.