DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

FY 2008 BUDGET REQUEST

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

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March 6, 2007

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Mr. Chairman and Members of the Committee:

I am pleased 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, a decrease of $9,094,000 below the FY 2007 annualized continuing resolution of $4,791,208,000, comparable for transfers proposed in the President's request.

INTRODUCTION

I am most pleased to be before you today to report on the Nation's progress on cancer research. While there has been a steady decline in the cancer mortality rate since 1991, we now have the excellent news that for the second year in a row, there was a decline in the absolute number of cancer deaths. This notable decline in actual deaths due to cancer is more significant considering the aging of our population and the increasing number of citizens. The remarkable findings were highlighted by President Bush during his visit to the National Institutes of Health (NIH) campus in January which for the first time focused on the impact of cancer research. But we are not done—many citizens continue to feel the pain of the devastating news of a diagnosis of cancer or the loss of a loved one.

While the declining rate of deaths due to cancer is tremendous news, this change in cancer mortality also has a significant economic impact. It has been projected that even just a 1% decrease in cancer mortality will result in a $500 billion impact on the U.S. economy (Murphy, K. and Topel, R., Journal of Political Economy, 2006; 114(5), 871-904). What is not as evident to the citizens of our country is the impact of cancer research on our understanding of many other diseases. Cancer continues to be a model system for other diseases. For example, the study of angiogenesis (blood vessel

development) associated with tumor growth has been applied to a greater understanding and treatment of macular degeneration, ischemic heart disease, diabetic wound healing, endometriosis and neurodegenerative illnesses. Advances in cancer accelerate progress in other diseases. The identification of the AIDs virus, the development of assays to screen banked blood for the AIDs virus and the current therapy was developed at the National Cancer Institute (NCI).

The NCI is leading the way on a number of fronts to identify the genetic, molecular, and cellular mechanisms associated with cancer. Building upon the sequencing of the human genome, working in our newly developed "Center for Human Cancer Genomics" NCI is systematically identifying all the important genetic alterations that are inherited or acquired that contribute to cancer susceptibility. We are not just cataloguing the genetic changes and other factors involved in a normal cell becoming malignant, but applying this knowledge to identify people at increased risk for developing cancer, to be able to prevent cancer and/or to detect cancer at its earliest stage of development when there is the best hope for effective therapy, and to identify new targets for highly selective and specific therapeutic agents.

We are already seeing the result of gene profiling applied to patient care. An example is in non-Hodgkins lymphoma, where tumors that look the same under the microscope actually have very different characteristics when their DNA is analyzed. These genetic differences have been shown to correspond to good versus poor prognosis for the patients. Using these genetic signatures, treatments are now tailored to a particular patient and his/her tumor.

NCI must continue to make progress for the cancer patient. We must bring the best science to the patients, the vast majority (85%) of whom is treated in community-based, private practice oncology settings. With that in mind, NCI is launching the Community Cancer Centers Program (NCCCP) pilot. This pilot project will study how best to provide easily accessible, state-of-the-art, multispecialty cancer care and earliest phase clinical trials research to patients in the communities where they live. Through this

program we will learn best how to educate patients concerning risk, healthier living, screening practices, clinical trial participation, and survivorship issues.

A RECORD OF REAL SUCCESS

The past year in cancer research and development shows a record of substantial and heartening achievement. We are expanding our knowledge and the technology tools to understand the mechanisms of cancer. Importantly, we are seeing these advances rapidly applied to patient care.

- An important public health milestone was reached last June when 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. Our Nation's strong commitment and investment in cancer research at NCI led to this approval, something in which we all can take great pride.
- NCI opened the first-in-human "Phase 0" clinical trials program in July 2006. The Phase 0 trial, a step before the classic Phase I level of drug study, measures the activity of a new drug in a small number of patients using a single, small dose of the study agent prior to the traditional dose escalation, safety and tolerance studies. The purpose is to get data upon which to design protocols based upon observed activity in a patient; for example, determining the concentration of drug that gets into the blood or actually seeing if an agent is getting to the specific target in the tumor using imaging technology. This new step in speeding up the process of drug development and approval is linked to our transition from highly toxic chemotherapies to the new era of highly characterized tumors and specific, less toxic molecularly targeted agents. This new paradigm in early phase clinical testing will substantially compress the drug development time.
- NCI has long been at the forefront of research and development of biomarkers for use in diagnosis and treatment for cancer. A Biomarkers Consortium was launched this year which 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).

DELVING DEEPLY INTO THE CANCER CELL ENVIRONMENT

At the NCI, we have pioneered efforts to identify all the genetic alterations that are inherited and that predispose a person to be at increased risk for developing cancer. The Cancer Genetic Markers of Susceptibility (CGEMS) project is identifying the common genetic changes that contribute to prostate and breast cancer risk using single nucleotide polymorphism (SNP) analysis or small genetic regions showing changes associated with malignancy. A similar analysis for pancreatic cancer is just beginning. The ability to identify at risk patients or to detect the disease at its earliest stage of development has been proven to provide the best hope for effective therapy and high quality of life.

Similarly, NCI and the National Human Genome Research Institute have launched The Cancer Genome Atlas (TCGA) to determine the feasibility of using large-scale genome analysis technology to identify important genetic changes involved in cancer. A TCGA Pilot Project is 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 not only the cancer cell but 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 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.

There is increasing evidence that cancer “stem cells” or “cancer initiator” cells are the driving force behind many cancers and are 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 trans-NIH group of scientists interested in embryogenesis and cancer stem cell biology to advance the study of the underlying mechanisms in these processes.

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 these discoveries, to translate them into new interventions, and to put the improved knowledge base and these 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 origin in the NCI.

Of special significance, are minority training programs which encompass the continuum from talented high school minority students through programs, including the Continuing Umbrella of Research Experiences (CURE), that direct long-term funding to qualified minority students interested in scientific, cancer research-related careers.

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) already mentioned,

NCI is investing in the development of critical technology platforms in a number of other strategic areas—such as nanobiology, proteomics and computational biology.

The NCI, in recognition of the key role of biospecimens in all of biomedical research as well as cancer research, has led a pioneering effort to provide the first guidelines that standardize and enhance specimen collection and biorepositories. Using these guidelines, NCI has developed a common biorepository infrastructure that promotes resource sharing and enables data comparison among research laboratories while 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 subcellular space to be able to view in real time drug-cellular target interaction and functional change secondary to such interactions. 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.

INTERAGENCY COLLABORATIONS

Addressing the cancer problem requires that NCI work across institutional and sector boundaries, share knowledge, and bring together the diverse members of the Department of Health and Human Services (DHHS) family of agencies, as well as other federal offices, and the private sector, in partnerships that can help develop systems-based solutions to the cancer problem. Last year marked the launch of an unprecedented public-private research partnership in the Biomarkers Consortium that was described previously.

The joint NCI-FDA Interagency Oncology Task Force (IOTF), which was 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 Phase 0 trial described previously.

REACHING THE PATIENT AND COMMUNITY

The advances being made in these and many other areas offer real hope for continuous progress. However, even the new progress report based on NCI-SEER data from the American Cancer Society (ACS) confirms that minority and low-income populations shoulder a disproportionate cancer burden and aren't benefiting equally from these important advances. One way NCI is attempting to address this problem is by bringing the results of genomic and proteomic science to patients where they live through the NCI Community Cancer Centers Program (NCCCP) pilot, with the hope of broadening access to clinical trials and to cutting-edge prevention, diagnosis, and treatment interventions.

Through partnerships with NCI-designated Cancer Centers, the NCCCP's goals are to expand access to cancer prevention, screening, treatment, survivorship follow-up, and end-of-life care, as well as increasing participation in early phase clinical trials and reducing healthcare disparities in community hospital-based settings where 85% of our patients actually receive their treatment.

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, such encouraging trends will become the rule, not the exception.

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 had 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 Center's 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 is 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 has 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.