

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2013 Budget Request

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

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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) 2013 NCI budget of \$5,068,864,000 includes an increase of \$2,717,000 over the comparable FY 2012 level of \$5,066,147,000.

As many of you will read upon its release later today, the 2012 Annual Report to the Nation on the Status of Cancer offers a generally encouraging view of cancer trends. The Report documents that death rates from all cancers combined for men, women, and children in the United States continued to decline between 2004 and 2008, the latest year for which we have complete analysis. Age-adjusted mortality rates for 11 of the 18 most common cancers among men and for 14 of the 16 most common cancers in women have declined. The overall rate of new cancer diagnoses, also known as incidence, among both men and women also declined over similar periods, although for women the decline leveled off from 2006-2008.

These continued declines in death rates for most cancers, as well as the overall drop in incidence, are powerful evidence that our nation's investment in many fields of cancer research produces life-saving approaches to cancer control. The breadth of the nation's cancer portfolio and our ability to pursue many different approaches to cancer research must match the heterogeneity of cancer itself, which we now understand to be literally hundreds of genetically distinct diseases with many avenues to prevention, screening, diagnosis, and treatment.

BASIC SCIENCE

A large part of the NCI basic research portfolio uses molecular biology and genetics to deepen our knowledge about the origins and behavior of cancers and to develop drugs and understand drug resistance. For example, decades of basic research culminated in development of the molecularly targeted drug Gleevec (imatinib). Since FDA approved the drug in 2001, it has been the treatment of choice – and a very effective one – for CML, or chronic myelogenous leukemia, as well as a few other cancers. Targeted drugs usually inhibit enzymes – in this case, kinases – that are essential to the survival of cancer cells, rather than broadly killing all rapidly dividing cells in the body. In CML, the target is the abnormal protein made by fused genes, BCR-ABL, in cancerous blood cells, where in its activated or “on” state the mutant enzyme pushes white blood cells into overdrive, causing disease. Gleevec blocks the mutant enzyme, kills cancer cells, and returns the blood system and the patient to a normal state.

But despite Gleevec’s generally powerful effects, some CML patients relapse when new mutations make the BCR-ABL protein resistant to Gleevec, allowing the abnormal enzyme to drive white blood cell growth again despite treatment. This phenomenon, drug resistance, is now being encountered with the several other targeted therapies more recently introduced for lung cancer, melanoma, and other cancers. So it is encouraging to report that NCI-supported research has identified a number of drugs targeting BCR-ABL proteins even after they acquire mutations that confer resistance to Gleevec. Two of these, approved a few years ago, did not overcome one relatively common resistance mutation. But a third generation of drugs is able to do that, in an

interesting new way, by freezing the target protein in an inactive conformation, so that its enzyme cannot work. This example illustrates another important point. Many different research streams – from genetics to structural biology to pharmacology – were required for these advances in treatment. The need to bring together multidisciplinary teams to focus on key questions like drug resistance in cancers increasingly defines modern biomedical research.

To strengthen NCI's ability to drive similar discoveries, NCI this year consolidated a number of its genomics initiatives – including the flagship program TCGA (The Cancer Genome Atlas) – into a single Center for Cancer Genomics. TCGA's aim is to characterize comprehensively the genomic alterations in hundreds of samples of about 20 known tumor types. With the project nearing completion on schedule, the vast influx of data promises to dramatically alter our knowledge of the genetic changes that drive cancer development. The new Center will work with other components of NCI to ensure that the findings are applied to developing new diagnostics and therapeutics and are integrated swiftly into medical practice.

SCREENING AND PREVENTION

Early detection of cancer can enhance therapy. Last year I briefed this Subcommittee on the recently concluded National Lung Screening Trial, which had demonstrated that current and former smokers who were screened with low-dose helical computed tomography were 20 percent less likely to die of lung cancer compared to others who received standard chest x-rays.

Recent findings from another long-term study also point to screening as an effective way to cut deaths from another common cancer – colorectal adenocarcinoma, which kills about 49,000 Americans every year. Clinical studies, several funded by NCI, have consistently demonstrated that tests for fecal blood and direct observation of the colon with endoscopy can effectively reduce the mortality rates associated with colorectal cancer – by up to 50 percent, according to one recent estimate. NCI also is investing in studies to understand behavioral and economic barriers to screening to increase screening rates, especially among minority populations.

DIAGNOSIS AND TREATMENT

One of the most critical aspects of cancer is its remarkable heterogeneity – cancer is actually a collection of hundreds of genetically distinct diseases, each with its unique vulnerabilities. Lung adenocarcinomas, for instance, develop through a variety of genetic changes, and each pattern of changes requires a different therapeutic approach. Just a few years ago, it was recognized that up to 7 percent of lung adenocarcinomas contain a fused chromosome that activates the protein made by a gene called *ALK* to cause cancerous growth. FDA last fall approved crizotinib to treat patients with the abnormal *ALK* gene. Crizotinib blocks the activity of the enzyme, again a kinase, produced by the fused *ALK* gene, similar to the action of Gleevec in CML. This oral drug has been approved by the FDA and must be used with a companion molecular test to make sure it is used to treat only tumors with the abnormal *ALK* gene.

Another potential treatment recently emerged from academic research laboratories, this one for metastatic prostate cancer. MDV-3100 is a so-called anti-androgen therapy that prevents male hormones from stimulating the growth of prostate cancer cells through androgen receptors – preventing testosterone from binding to androgen receptors and preventing the androgen receptor from initiating the production of proteins that induce tumor growth. Current anti-androgen drugs suppress the growth of prostate cancer cells temporarily, but in most patients the cancer ultimately develops resistance to these drugs by increasing the amount of receptors. MDV-3100, by contrast, binds so tightly to the androgen receptors that it prevents them from functioning even when the receptor numbers are very high. The new drug performed so well that the clinical trials were halted early, and the drug now awaits approval at FDA.

PROVOCATIVE QUESTIONS

During the past 14 months, NCI has brought together researchers to propose, craft, and debate what they consider to be the critical questions in cancer research that may fall outside our current sphere of focus, but that could lead to important discoveries about the causes and behaviors of cancers. NCI convened 17 workshops across the country that identified some 24 Provocative Questions, and NCI has set aside an initial \$15 million from its FY 2012 budget to fund some of the more than 750 applications received under this program. While this initiative does not replace the NCI's longtime and essential emphasis on funding investigator-initiated research, it represents a useful new approach to making the greatest impact with our research dollars.

Congress' past investments in cancer research are the reason we are able to report promising scientific findings each year, and why the Report to the Nation continues to show steady progress against a wide range of cancers. We are now able to define genetic changes that cause cancer, use them to control cancer with more precise tools, and thereby reduce the Nation's cancer burden. The President's budget for 2013 for the National Cancer Institute will provide the support for discoveries in basic science, cancer control and prevention, for early detection and diagnosis, and for methods to prevent, treat, and in some instances cure, cancers.

Harold Varmus, M.D.

Director, National Cancer Institute

Harold Varmus, co-recipient of a Nobel Prize for studies of the genetic basis of cancer in 1989, became Director of the National Cancer Institute on July 12, 2010, after 10 years as President of Memorial Sloan-Kettering Cancer Center, following six years as Director of the National Institutes of Health. He is a member of the U.S. National Academy of Sciences and the Institute of Medicine and is involved in initiatives to promote science in developing countries. The author of over 350 scientific papers and five books, including a recent memoir titled *The Art and Politics of Science*, he was a co-chair of President Obama's Council of Advisors on Science and Technology, a co-founder and Chairman of the Board of the Public Library of Science, and chair of the Scientific Board of the Gates Foundation Grand Challenges in Global Health. In 2001, he received the National Medal of Science.