

Testimony

Before the

Subcommittee on Labor, Health and Human Services, Education, and Related Agencies

Committee on Appropriations

United States Senate

Fiscal Year 2014 Budget Request

Statement of

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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) 2014 NCI budget of \$5,125,951,000 includes an increase of \$63,189,000 over the comparable FY 2013 (FY2012) level of \$5,062,762,000.

Cancer Deaths Continue to Decline

The 2013 Report to the Nation on the Status of Cancer shows that overall cancer death rates continued to decline in the United States among both men and women, among all major racial and ethnic groups, and for all of the most common cancer sites, including lung, colon and rectum, female breast, and prostate. However, death rates continued to increase for melanoma of the skin (among men) and for cancers of the liver, pancreas, and uterus. The Report also emphasizes the importance of human papilloma virus (HPV) infection as a cause of the growing number of cancers, and shows that incidence rates are increasing for HPV-associated oropharyngeal and anal cancers. Also noted was that HPV vaccination coverage remains

disappointingly low, falling short of the U.S. Government's Healthy People 2020 target, and much lower than vaccination rates reported in several other countries.

The continued decline in death rates for most cancers shows that our nation's investment in cancer research produces life-saving approaches to cancer control. However, there is still work to do, for example in reducing tobacco exposure and obesity. Taken together, adverse health effects from cigarette smoking – including heart disease, stroke, and cancer - account for an estimated 443,000 deaths every year in the U.S. – nearly 1 in 5 deaths that could have been prevented. Smoking is responsible for about 30% of all cancer deaths in the U.S., which in 2013 will translate to 174,000 preventable cancer deaths. Accordingly, NCI supports research into tobacco cessation, behavioral modification, and, on a policy level, the effectiveness of the state and community tobacco control efforts. Obesity, another significant cause of disease and preventable death, is associated with heart disease, stroke, type 2 diabetes and at least 8 types of cancers. NCI funds research on the molecular mechanisms of obesity and cancer, and has developed new initiatives that explore ways to prevent and control obesity as a cancer risk factor.

NCI-Supported Research Advances

The past year has yielded significant advances across the spectrum of cancer research, including studies of cancer mechanisms, prevention, detection, and therapy. One cancer detection study showed that the protein fibulin-3 may be able to identify patients with mesothelioma, suggesting that it may be a promising biomarker for high-risk populations exposed to asbestos. Another study found a way to target mesothelin, a cell surface protein that is present in normal tissues but overexpressed in more than 90% of pancreatic cancers and mesotheliomas, as well as in lung and ovarian cancers. Currently, the NCI intramural program is conducting a Phase I study of SS1P, an immunotoxin that targets mesothelin and destroys cancer cells, with plans for a Phase II study underway.

NCI is supporting research to identify the genetic drivers of cancer and to advance adoption of precise tumor diagnosis and the development of targeted therapies. The two major genomics initiatives, involving hundreds of investigators nation-wide, are The Cancer Genome Atlas (TCGA) and the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative, focused on adult and pediatric cancers respectively. TCGA recently completed a study of lung squamous cell carcinoma that identified several potential therapeutic targets related to the initiation and progression of that disease. Another study examined nearly 400 endometrial (uterine) cancers and identified four new subtypes with several possible therapeutic targets. This study also found genomic similarities between endometrial and other cancers, including breast, ovarian, and colorectal. A TARGET study identified a subclass of acute lymphoblastic leukemia with high risk of recurrence associated with novel chromosomal translocations; these translocations represent exploitable therapeutic targets. Another TARGET study found few recurrent mutations among 240 cases of high-risk neuroblastoma, suggesting a limited number of targets for this pediatric disease.

In 2011, one of the noteworthy achievements was FDA approval of a new class of drug, vemurafenib, for the treatment of metastatic melanoma. The drug targets mutant forms of the BRAF protein, which is mutated in about 60% of these patients, leading to inhibition of a key growth pathway in the tumor cell, the MAPK pathway. Although the drug can increase the lifespan of these patients, almost all patients eventually develop drug resistance and relapse.

Recent observations from several research groups have indicated that drug resistance can arise by any of several mechanisms. Some resistance is attributable to activation of the MAPK pathway, which can result from further mutation of BRAF itself or changes in other genes in the MAPK pathway. In other cases, resistance seems to result from activation of parallel pathways. These findings are now leading to clinical trials testing the hypothesis that combining the BRAF inhibitor with drugs that have been shown in preclinical models to reduce development of these resistance mechanisms will lead to longer therapeutic responses.

A potentially exciting therapeutic advance has come from immunotherapy research for B cell lymphoma being conducted at several institutions. The approach is to use genetic engineering to construct a chimeric antigen receptor (CAR) by combining parts from two different receptors, each with key immune functions, into one receptor that is then expressed by the patient's own normal T cells. Early phase clinical trials with a receptor called anti-CD19 CAR, which works by directing T cells to the malignant B cells of the tumor, have resulted in several dramatic long-term responses in patients with advanced stage lymphoma.

Precision Medicine – Approaches to Cancer

Incorporation of genomics into cancer research and clinical trials constitutes a growing portion of the institute's research portfolio. In the years ahead, NCI and the entire cancer research enterprise, will extend studies of the pathogenetic roles for specific genomic changes in tumors and test more interventions that are based on genetic profiles of tumors. There are several ways in which NCI is expanding its pursuit of these goals, most notably by mandating that all NCI-sponsored clinical trials include tissue collection and genomic analysis. NCI is also developing new approaches that explore the relationship between a cancer patient's genomic data (genotype) and the behavior of each patient's tumor (phenotype). One such study is the Exceptional Responders initiative, which will begin with phenotypes –asking why a small number of patients respond very well to a particular regimen, while the same treatment fails in almost all others with the same cancer type. To probe this phenomenon, researchers will explore the genomic data (genotype) to look for clues as to why some patients enrolled in clinical trials respond to agents that do not benefit most patients in the same study. Some recently reported cases provide dramatic evidence for how a combination of molecular factors can explain why patients responded so well to therapy while comparable patients did not.

An approach from the opposite perspective (genotype to phenotype) is the “NCI MATCH” study, which aims to screen about 3,000 patients with advanced cancers in an effort to find approximately 1,000 such cancers with genetic mutations for which new therapies, including some not yet approved for use, are made available by the pharmaceutical industry through collaborative arrangements. This approach will provide a level of genomic data far beyond what would typically be available when genotyping is limited to one or more mutations known to be associated with a particular cancer type. There is a great opportunity for investigator-initiated research to build on information that emerges from this kind of novel trial, leading to yet greater therapeutic insight.

Targeting RAS

The Frederick National Laboratory for Cancer Research (FNLRCR) is a Federally Funded Research and Development Center (FFRDC) supported by the NCI, providing a national resource with unique capabilities for the development of new technologies and the translation of

basic science discoveries into novel agents for the prevention, diagnosis and treatment of cancer and AIDS. NCI is poised to launch a large-scale project targeting *RAS*, an oncogene known for decades to drive the development of many types of cancers and about a quarter of all cancers in the U.S. However, despite that information, the cancer research community has failed to develop effective treatments. Now, with the knowledge of new chemical approaches to inhibit the *RAS* protein directly and a deeper understanding of how *RAS* signaling works, NCI is launching a large-scale project to develop therapeutic strategies against cancers driven by *RAS* through a national “hub and spoke” model with scientific leaders, core facilities and important technologies at the FNLCR hub, and research led by investigators at companies, academic institutions and the NCI intramural research program at the spokes.

We find ourselves at a time of tremendous opportunity in cancer research, building our knowledge of the genetic changes that cause cancer, and finding new ways to use this information to diagnose, treat and even prevent cancers. The President's budget for 2014 for the National Cancer Institute will support studies intended to foster the discoveries essential for this next frontier of cancer research.

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.