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) 2015 NCI budget of $4,930,715,000 includes an increase of $7,944,000, or 0.2 percent, compared to the FY 2014 level of $4,922,771,000.

Overview of NCI Research Priorities
This is an era of remarkable opportunity in cancer research. Armed with broad knowledge about how various cancers arise and with powerful new research tools, the NCI is well equipped to accelerate progress towards preventing, diagnosing, and treating cancer more effectively. This era of opportunity is due in significant part to the subcommittee’s consistent support for biomedical research at NCI and NIH.

The resources that you provide allow NCI to address an ambitious challenge: reducing the incidence, morbidity, and mortality for all of the many types of cancer, with tangible benefits for all Americans. The FY 2015 budget will allow the NCI to build on the tremendous progress in
many areas of cancer research, with the aim of improving outcomes for patients with all types of cancer.

I will summarize some recent accomplishments and highlight new opportunities in five areas of NCI-supported research – genomics, cancer immunology, targeted therapeutics, bioinformatics, and prevention – to illustrate the breadth and pace of NCI’s progress.

The **Cancer Genomics** research that NCI supports has dramatically altered our understanding of how cancer develops, identified the molecular signatures that can be used to diagnose and categorize cancer more precisely, and provided new targets for therapeutic intervention. For example, two major initiatives – TCGA (The Cancer Genome Atlas) and TARGET (Therapeutically Applicable Research to Generate Effective Treatments) – have addressed nearly twenty common adult cancers and several less common cancers that occur in adults and children, revealing both tissue-specific patterns of genetic changes and changes that are common to several types of cancers. During the past year, TCGA published comprehensive characterizations of acute myeloid leukemia, endometrial cancer, and clear cell renal carcinoma, among others. While every cancer is distinct genetically, many changes in the genome are shared among a wide array of cancer types, and each type of cancer has distinct patterns that often reflect exposure to carcinogenic agents, such as tobacco smoke and ultraviolet radiation. As these massive surveys come to conclusion, the NCI’s Center for Cancer Genomics is leading efforts to make full use of the TCGA results, including the best ways to incorporate genomic findings into the design of clinical trials.

Some of the surprising findings from the TCGA and TARGET projects – such as the involvement of genes that govern the chemistry of chromosomal proteins, that influence cell metabolism, and that guide the processing of RNAs and proteins – are influencing the study of cancer biology throughout the NCI’s programs. TCGA and TARGET will certainly enlarge our understanding of carcinogenesis and will likely open new frontiers for preventing, diagnosing, and treating cancers.

**Cancer immunology** is a rapidly advancing field that, in just the past few years, has dramatically altered our understanding of host defenses in response to cancers. It has also produced new and well-validated methods for treating cancer using antibodies that attach to proteins on cancer cell surfaces and using methods that modulate the complex behavior of the immune system to attack cancer cells.

For several years, monoclonal antibodies against cancer cell proteins have been used to treat blood cancers, such as certain lymphomas and leukemias, and subsets of several types of solid tumors, such as breast and colorectal cancer. More recently, immunotoxins have been created by genetic engineering to fuse antibodies with parts of bacterial toxins to selectively kill cancer cells. For example, such immunotoxins developed in the NCI intramural program have induced remissions in late stage cases of mesothelioma, ovarian cancer, triple-negative breast cancer, drug-resistant hairy cell leukemia, and childhood acute lymphoblastic leukemia.

There is also great optimism within the science community about modulating the immune system by introducing novel antigen receptors into cancer-killing T cells and especially by infusing antibodies that interfere with a system that impedes the immune response to cancer cells. These
“immune-modulating” antibodies have recently received FDA approval, and other antibodies that bond other immune cell regulators may soon follow. In 2011, FDA approved a monoclonal antibody, called ipilimumab, to treat advanced melanoma. Some patients with metastatic melanoma being treated with ipilimumab are still alive several years after completing treatment. In 2013, another promising antibody to treat melanoma – lambrolizumab – received "breakthrough" designation by the FDA, enabling its rapid use in clinical trials, with the possibility of an expedited FDA review. In recognition of these and other recent achievements in the field of immunology, and the promise of further developments, “cancer immunotherapy” was named this year’s Breakthrough of the Year by Science magazine.

**Targeted therapies**, based on the use of drugs that inhibit specific proteins implicated in the behavior of cancer cells, are now being developed and tested for their effects in patients with many types of cancer. Over the past decade, FDA has approved several drugs that rely on this therapeutic approach to treat cancers of blood cells, lung cancer, melanoma, and other cancers, and many more are in development. This activity has accelerated because of discoveries in genomics, cell signaling pathways, chemistry, and structural biology, and with the identification of new ways to inhibit proteins that are required for the integrity of cancer cells.

Mutant RAS proteins are perhaps the most prominent potential targets for new therapies that the academic and commercial research sectors have thus far failed to target with inhibitory drugs. The importance of the RAS gene family in cancer has been clear for over thirty years; one family member, K-RAS, is mutated in more than 90 percent of pancreatic adenocarcinomas, about 40 percent of colorectal cancers, and about 25 percent of lung adenocarcinomas. For this reason, the NCI recently launched the RAS Project, a large-scale collaboration between investigators at the NCI’s Frederick National Laboratory for Cancer Research and those in NCI’s intramural and extramural communities. The RAS Project is motivated in part by new developments in the study of RAS proteins, including new information about their structural properties, binding of mutant RAS proteins to mutant-specific inhibitors, interactions with other cellular proteins required for function, and new tests for genes required to allow RAS mutants to exert their effects.

Still, while pursuing a path that leads to “precision medicine,” the NCI must also maintain its capacity to test new ways to deploy the currently dominant means of therapy. For instance, a recent study of patients with metastatic prostate cancer showed markedly increased survival in men who received chemotherapy when starting anti-androgenic hormone therapy, a result that is likely to change clinical practice for a cancer that continues to kill about 30,000 American men annually.

Drug resistance commonly emerges in cancers being treated with either traditional chemotherapies or novel targeted therapies, allowing disease to progress. Over the past decade, NCI-supported studies have revealed several mechanisms by which resistance occurs, including additional mutations affecting the target molecules, mutations in related genes, and changes in gene expression. In some cases, especially chronic myeloid leukemias, drugs that overcome resistance have been identified, developed and FDA-approved. But in other situations, resistance to targeted drugs remains a major impediment to success, and the NCI is making major investments to study this problem.
Bioinformatics, the management of enormous sets of molecular and clinical data is a critical component of NCI’s toolkit to study cancer in all of its manifestations. In work that ranges from cancer genomics, to cell signaling, and to clinical trials, the proper collection, analysis, storage, retrieval, and distribution of “big data” are critical elements of the Institute’s charge. The NCI’s Center for Bioinformatics and Information Technology (CBIIT) is addressing these responsibilities, in conjunction with NCI divisions. Part of the current effort requires the costly development of “cloud computing” to work with the vast (petabyte) amounts of genomic data generated by TCGA, TARGET, and other projects, and to assemble and ultimately integrate clinical data with genomic data in manageable forms to promote further discovery and improve cancer care.

Prevention of cancer remains NCI’s most desired goal. While complete avoidance of cancer may be impossible, since cancers often arise through spontaneous mutations, the control of tobacco use, vaccination against cancer-causing viruses (human hepatitis B virus and human papillomaviruses), sunlight avoidance, and regulation of dietary and carcinogenic substances (such as asbestos) have already reduced the incidence and the mortality rates of many cancers. For instance, between 2001 and 2010, largely due to the earlier reductions in tobacco use, there was a 25 percent decrease in male death rates and an eight percent decrease in female death rates due to lung cancer, the major cause of death from cancer in the United States. Likewise, vaccination with current HPV vaccines can drastically reduce the incidence and mortality of several types of cancer, including cervical, anal, and oropharyngeal cancers that are caused by infection with certain strains of HPV.

Still, NCI recognizes that these successes are incomplete, and therefore invests heavily in efforts to address several pertinent behavioral and biological questions. For instance, despite dramatic declines in the use of tobacco, about 18 percent of Americans continue to smoke. New approaches are needed to convince young people not to use tobacco and to convince current smokers to quit. Use of HPV vaccines remains far from the desired levels among adolescent girls and boys in the United States, as the February 2014 report from the President’s Cancer Panel emphasized. Better methods to promote the use of these potentially lifesaving vaccines are needed, at the same time as the dosing schedules and the protective breadth of the vaccines are improved.

Conclusion
An important measure of the overall success of NCI’s work is the annual “Report to the Nation,” which describes trends in the incidence and death rates in the United States for many types of cancer. As has now been true for over a decade, the most reliable indicator – death rates from all cancers combined for men, women, and children – continues to decline by about one and a half percent per year. This reduction represents the savings of an enormous number of years of life and can be ascribed in large measure to the work of the NCI to prevent and treat cancers more effectively.

Still, although mortality rates have been decreasing for most cancers, progress has not occurred as rapidly as desired, and for some cancers the numbers have not improved – or have worsened. Thus, much work remains. But the overall success apparent from both the public health data and recent achievements in the laboratory and clinical sciences inspires the NCI’s conviction that
expanded efforts on all frontiers of cancer research will produce better health in the United States and around the globe.
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.