DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Fiscal Year 2013 Budget Request

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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 overdive, 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 a

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

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-