

# Varmus's Second Act

Years after steering the National Institutes of Health into a 5-year budget doubling, the Nobel Prize-winning virologist is now helping the cancer institute deal with the aftermath

WITH THE THREAT OF A GOVERNMENT shutdown days away, the mood here in the office of the scientist who leads the nation's efforts to beat cancer is tinged with gloom. National Cancer Institute (NCI) Director Harold Varmus reflects on the current state of biomedical research in the United States, which hasn't seen meaningful budget growth in a decade. "What bothers me most is this sense of hypercompetition," Varmus says. "There's an imbalance between the money available, the work that needs to be done, and the number of people who would need to be supported to make the world feel like a more comfortable place. ... The atmosphere is not as healthy as it ought to be."

No one is in a better position than Varmus to know what ails the U.S. biomedical research community and the agency that sustains it, NCI's parent, the National

Institutes of Health (NIH). His research career began here 45 years ago when the English graduate student-turned-physician joined an NIH lab as a research trainee. In November 1993, not long after he shared the 1989 Nobel Prize in physiology or medicine for using retroviruses to discover cancer genes, he returned to lead NIH.

When Varmus left in 1999, biomedical research was on a roll: Aided by a federal budget surplus, Congress had begun to double NIH's budget, which stood at \$13.7 billion in 1998, over 5 years. Although biomedical research lobbyists came up with the doubling plan, Varmus is credited with winning lawmakers' support with his effective political skills. Now, a decade after the doubling ended in 2003, Varmus is coping with its legacy: what many call the "undoubling."

By July 2010, when Varmus returned to NIH to direct NCI, the funding climate had decisively chilled. For a decade, NIH has received flat or declining budgets. And last year, thanks to the budget cuts known as the sequester, its \$30.6 billion budget dropped another 5.5%. "There was no soft landing," he says. Yet Varmus says his "mantra" is that NCI's \$4.8 billion a year—the largest single slice of NIH's spending—is still a lot of money, and NCI should focus on using it to fund the very best science. He has looked for bloated programs to trim and launched new efforts, such as one that explores the biggest mysteries in cancer and another to find drugs ≤ to target a family of mutated proteins that could be an Achilles' heel of many tumors (see sidebar, p. 418).

"You might think that in these times, you would go into a sort of bunker mentality and just hope for a better day. That's not what's happening. He's trying very hard to keep the ship sailing forward in an important new direction," says cancer biologist Tyler Jacks of the Massachusetts Institute of Technology in Cambridge, a former graduate student in Varmus's lab who now chairs NCI's main advisory board. "Harold's chief characteristic is that he's always focused on the science (in the broadest sense) and his judgments reflect that perspective," writes Thomas Kelly, chief of basic research at the Memorial Sloan-Kettering Cancer Center in New York City, in an e-mail. That hasn't stopped grumbling in the community, however, that Varmus isn't doing enough to rescue foundering research labs.

Although his brown hair has thinned more since his last tour at NIH, Varmus looks much the same: tall and slim, with a thick mustache and large, round wire-rimmed glasses. He still favors khaki pants and shirts without a tie. He often bikes his old route 12 miles to work from his apartment in Washington, D.C. But he now considers home to be Manhattan, where he lives with his wife in an apartment on the Upper West Side, not far from his two grown sons. The New York City area is also where he grew up, later went to medical school, and spent 10 years directing Sloan-Kettering between his two tours at NIH. He spends four long workdays in Bethesda—a "compressed week"—then often takes the train to New York City on Friday morning, or flies to his country home near Albany, to work remotely.

In a 1-hour interview in his office, where his staff members are scurrying around planning for the 1 October government shutdown that ended last week, Varmus is candid yet careful, and sometimes prickly. He notes that his middle name is misspelled in the Wikipedia entry someone wrote about him. (It is Eliot, not Elliot.) He alludes, as he often does in public meetings and speeches, to frustration with the government bureaucracy. He says he doesn't particularly want his age mentioned (he's 73) because he's now one of the oldest directors at NIH. But he notes that his "vitality," as he puts it, outstrips his age.

# Lure of science

The son of a Long Island doctor and a social worker, Varmus was pulled between following his father's path and pursuing the humanities. He earned a master's degree in English literature, then went to medical school. which whetted his interest in research. He landed at NIH as a so-called "yellow beret," a participant in a program disc. Sicians to work for the Public Health Service a participant in a program that allowed phyinstead of going to Vietnam. There he joined the lab of endocrinologist Ira Pastan, studying bacterial genetics and witnessing the power of early molecular biology. He soon developed a fascination with understanding how some viruses can cause cancer, an interest also driven by the death of his mother from breast cancer.

At the University of California, San Francisco, he formed a 20-year collaboration with Michael Bishop that centered on a retrovirus that causes cancer in chickens. In work that won them the Nobel Prize, they found that such viruses don't cause cancer on their own, but instead carry mutated versions of genes picked up from

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**Political scientist.** Varmus's testimony in Congress during the 1990s helped win support for doubling NIH's budget over 5 years.

animals. Those genes control cells' normal growth and development but can go awry-revealing what are now known as proto-oncogenes.

When he accepted President Bill Clinton's offer to direct NIH, Varmus had virtually no administrative or political experience. He quickly learned the ropes of Washington, however, moderating demands from patient groups, fending off conservatives' efforts to ban stem cell research, and winning support from Congress to double NIH's budget. As NIH director, he also proposed a then-radical idea—that biomedical papers should be freely available online-

which led NIH to establish a free archive for full-text papers, PubMed Central, and seeded the open-access journals movement. Making papers and data free would speed the pace of scientific research, Varmus argued.

Years later, when he was preparing to step down after his 10-year stint as Sloan-Kettering president and was helping the Obama transition team look for an NCI director, he accepted a suggestion that he take the job himself, taking a sharp salary cut from \$2.6 million a year to a sum in the mid-\$300,000s. Despite flat budgets, there was "no better time" to head NCI, he later said, because genomics studies were revealing a detailed portrait of cancer cells that

> could transform treatment and diagnostics. Compared with heading the entire NIH, "this is much more fun. I don't want to go down to the department [of Health and Human Services] for meetings, I don't want to spend all my time on the Hill" testifying before Congress, he says. He's also said he came back because he has a "profound affection for the NIH."

> Varmus now works for NIH Director Francis Collins, who as genome institute director in the 1990s reported to Varmus. The two longtime friends have differed over at least one issue: Collins's swift decision in 2010 to create a new center at NIH aimed at speeding the translation of basic discoveries into treatments. Varmus and National Institute of Allergy and Infectious Diseases Director Anthony Fauci cautioned

that a new body devoted to translational research could overlap with other institutes' existing large translational programs. Years earlier, as NIH director, Varmus had warned that the proliferating number of institutes made NIH less effective; he wanted fewer. Varmus now says that Collins worked "collegially" with him and other directors "to make sure that the definition got right," adding that the National Center for Advancing Translational Sciences is "catalytic" and "works as partners" with other institutes.

Dealing with the pain of tight budgets has been unavoidable. Partly because rising salaries consume so much of NCI's intra-

# A Cancer To-Do List

Even as National Cancer Institute (NCI) Director Harold Varmus contends with tight budgets (see main story, p. 416) he has an unusually long list of priorities.

# **PROVOCATIVE QUESTIONS**

Why does obesity increase cancer risk? Why are some cancers easily cured with conventional chemotherapy? Those are among about two dozen little-explored or neglected cancer puzzles that Varmus wants researchers to explore in NCI's Provocative Questions initiative, which has awarded \$35 million in new grants since 2012 and is now taking proposals for a third round of funding.

#### **GLOBAL CANCER**

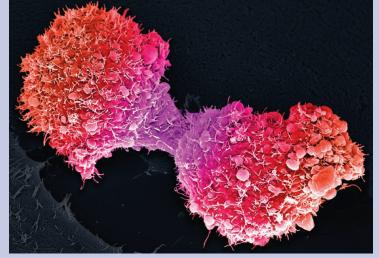
NCI's new Center for Global Health aims to help developing countries create cancer registries and national cancer plans. Another priority is to study the high rates of certain cancers in some countries—gallbladder cancer in Chile, for example.

#### **ONCOGENE INITIATIVE**

Varmus is directing \$10 million at NCI's large contract lab in Frederick, Maryland, to finding drugs that target the cell signaling pathway controlled by RAS, a family of oncogenes. Mutations in RAS drive uncontrolled cell growth in one-third of all cancers, so drugs blocking this pathway could help many patients. The initiative is part of an effort to revamp Frederick to focus on large goal-oriented projects, following the model of the Department of Energy's major research labs.

#### THE CANCER GENOME ATLAS

The Cancer Genome Atlas (TCGA), a \$375 million sequencing project launched with the National Human Genome Research Institute 7 years ago, is winding



**Target.** Pancreatic cancer cells are usually driven to grow by mutations in RAS genes.

up its analysis of major mutations in 10,000 tumor samples covering about 20 cancer types. One of TCGA's original proponents, Varmus says NCI will soon launch a cloud computing pilot project to support further data mining.

## **UNCONVENTIONAL TRIAL**

NCI plans to genotype the tumors of about 1000 patients who are no longer helped by conventional treatments and match them with an experimental drug aimed at a mutation in the patient's tumor. NCI has assembled a medicine chest of about 30 drugs contributed by a dozen companies. This "unconventional" clinical trial is "one way to dramatically extend our efforts to explore new therapies with genetic tools," Varmus says.

#### **EXCEPTIONAL RESPONDERS**

Varmus has asked the research community to comb through their records for rare cases in which a patient's cancer shrank or disappeared in response to a drug that failed to help most patients. The goal is to learn whether specific genetic defects in the patient's tumor can explain such exceptional responses.

mural research budget, the program has closed about 130 of its 300 labs over the past 10 years and reopened only half with new recruits, a "dramatic" change, says intramural Center for Cancer Research Director Robert Wiltrout. Coupled with recent federal government-wide restrictions on travel and conferences-NIH cannot even pay for coffee at meetings-morale is very low on the Bethesda NCI campus, researchers say. Wiltrout credits Varmus with being "a strong advocate" for allowing staff to continue to travel to conferences.

Looking across NCI, Varmus has found a few places to trim sharply: communications and public relations, such as educational websites and newsletters, and a \$350 million effort to build data-sharing software that was widely recognized as a failure, for example. But in general, he has applied cuts fairly evenly across cancer centers and ongoing grants that have already been funded. His goal is to preserve money for new investigator-initiated grants, the mainstay of cancer research labs. He has also tried to dispel the notion held by some

researchers that NCI now favors translational research, not basic science. "I try to emphasize the fact that there is no one thing that's going to help you get a grant except by doing really interesting science."

To make the grant-review process fairer for proposals that are very similar in qual-

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ity, Varmus added new steps. Proposals that reviewers rank in roughly the top 9% are now funded without further review. But applications that score between 9% and about 25% get a second look from top NCI leaders, who consider program priorities, novelty, and how much funding a researcher already has. This means some grants far below the 9% cutoff receive funding.

### Unsustainable

Improving how NCI works won't solve a bigger problem: too many biomedical researchers chasing a dwindling pot of research money. "Our whole system of operating is basically one that is probably not sustainable. That is, the idea that we're going to continue to fund more and more people, train a lot of people, and expand to meet all the opportunities that are there scientifically just does not accord with the current economic situation," Varmus says.

The roots of the problem go back to the NIH doubling, he says. He has no regrets about his support of the doubling itself: "It o certainly wasn't a mistake," he says. "But we said at the time, and many people agreed, that this was only going to work well if the ... rapid increase was followed by what we called the soft landing"—budget increases that kept pace with rising costs of doing biomedical research.

Congress did not give NIH those increases, and meanwhile, research institutions built new buildings and labs and hired faculty in 🛱 the expectation that biomedical research

funding would keep growing. This "was understandable," Varmus says, but it has created cutthroat competition for grants, with only about one in six proposals now receiving funding, compared with one in three a decade ago. The result, Varmus says, is an "insidious and pervasive problem of people and labs competing for jobs, grants, etc."

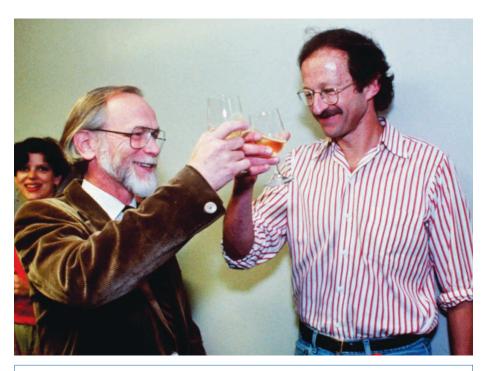
There are no easy solutions, he says, and one inevitable result-academic labs downsizing or closing altogether—is already under way. "We all know that, in a fashion nobody can be comfortable with, there's a certain amount of attrition going on," he says.

Meanwhile, a flood of young trainees are seeking scarce academic posts. Varmus says he sees "eye to eye" with Princeton University molecular biologist Shirley Tilghman, who led an NIH-commissioned report last year that urged the agency to shorten the number of training years and channel more young scientists into alternative careers. Like Tilghman, he also wants to encourage labs to rely more on permanent staff scientists rather than exploiting the labor of cheap trainees.

Varmus also wants to address what he calls the "flawed values system" that the competitive atmosphere has spawned. He laments that researchers feel they will win funding only if they publish in top journals such as Science, Nature, and Cell. At NCI, he is pilot-testing a way to change this part of the scientific culture: by revising the "biosketch," the summary of a researcher's record that accompanies a grant proposal. Varmus wants to replace a section that now lists major publications with a narrative describing the investigator's five major accomplishments.

This approach, already used by the Howard Hughes Medical Institute (HHMI), should not only discourage reviewers from assessing their colleagues based only on where they're published; it will also help researchers on large teams whose names are buried in a list of authors receive the credit they deserve, Varmus says. And he thinks that easing the rush to publish in highimpact journals might help address a muchdiscussed problem: that many NIH-funded studies have proved difficult to reproduce.

Encouraging openness among scientists could also help, Varmus says. He remains a staunch supporter of free access to research results, and he notes with satisfaction that PubMed, NIH's abstracts database, will soon add new tools so researchers can comment on published papers. This will "promote a



# Varmus Career Highlights

- 1962 M.A. in English literature from Harvard University
- 1966 M.D. from Columbia University
- 1968–1970 Research trainee in Pastan lab. NIH
- 1970 Postdoctoral fellowship in the lab of Michael Bishop at UCSF leads to collaboration
- 1976 Bishop/Varmus *Nature* paper reporting that cancer-causing gene in Rous sarcoma virus resembles noncancerous gene in normal bird cells
- 1989 Awarded Nobel Prize in physiology or medicine with Bishop (pictured)
- 1993–1999 Director of the National Institutes of Health
- 2000–2010 President of the Memorial Sloan-Kettering Cancer Center
- July 2010-present Director of the National Cancer Institute

on work that's been published," he says. He's pleased that the White House science office is now asking all research agencies to follow NIH's lead and require that grantees make their papers freely available within a year, although he thinks the directive "could have been stronger," with a shorter embargo period.

To relieve the constant pressure on investigators to write grant proposals to keep their labs afloat, Varmus is creating a new award at NCI for "outstanding investigators." It will give highly productive labs support for 7 years, with the possibility of renewal. Although NIH already has a longterm award for established investigators, the winners are chosen largely according to their peer-review scores for a specific project. The new award will go to researchers nominated by their institutions and will be based on their overall track record. Like HHMI awards, it will go to "people," not "projects." Varmus wants NCI to fund hundreds of these awards.

Varmus ticks off other items on his to-do list: controlling cancer in the developing world, for example, by expanding use of the vaccine against human papillomavirus, which causes cervical cancer; getting oncologists to incorporate tumor genetics into treatments; finding better ways to predict whether tumors detected early on will grow or remain small and harmless.

How many of these tasks he will accomplish will depend, he admits, on the next election. "I'm a presidential appointee. Some make it across that boundary, some don't," he says. But for now, he says, "I have no plans to leave."

-JOCELYN KAISER