

Standing firm: Elias Zerhouni, the director of the National Institutes of Health, has come under fire for encouraging applied research.



FACING THE OPPOSITION

Elias Zerhouni has one of the biggest jobs in biomedical research — running the massive US National Institutes of Health. But is he leading the agency up the right path? **Erika Check** examines his tenure.

On 6 April, Elias Zerhouni spent the morning on Capitol Hill, telling Congress to invest more money in the National Institutes of Health (NIH) — for the good of the country and its research enterprise. But even as he was making his case, scientists across the continent were e-mailing each other an angry editorial that blames Zerhouni for leading the NIH in the wrong direction.

Published in the *Journal of Clinical Investigation*, and penned by the journal's editor-in-chief Andrew Marks (A. R. Marks *J. Clin. Invest.* 116, 844; 2006), the piece hits Zerhouni in a sensitive spot. "The current state of the NIH," writes Marks, "prompts me to say to its director, Dr Elias Zerhouni: 'Obviously you are not a scientist.'"

Marks says he meant no personal disrespect for Zerhouni, who is a radiologist by training. "There's a real gap between the people that run the NIH and the people that depend on it for their survival to do research," says Marks, a physiologist at Columbia University in New York. He says he has received a steady stream

of e-mails from other researchers, praising him for writing the piece. "The tone of the editorial reflects a level of frustration that is not unique to the author," says one senior biomedical lobbyist in Washington DC, who asked not to be named.

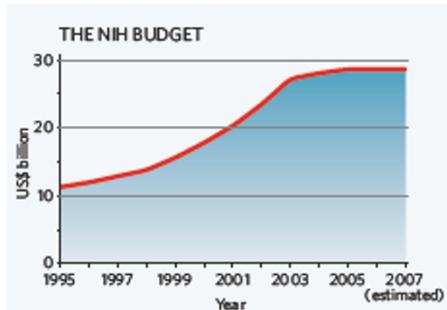
Zerhouni's many high-profile supporters say he is steering the NIH on the right course at a crucial time in the agency's history; after an unprecedented doubling of funds between 1998 and 2003, the NIH's budget has recently flattened and may even drop in the coming year (see graphic). But Zerhouni's vision of

streamlining the agency's management and sharpening its focus on clinical, interdisciplinary and technology-driven research has upset others, who say this is distracting the agency from what it has always done well: fund basic research.

Zerhouni cuts a sharp figure in Washington; he is charming and well-respected. But the former competitive swimmer is also unafraid to tussle with his critics. The changes he is making, he argues, are good for the NIH and for science. "You have to stand up for the integrity of the agency, no matter how popular or unpopular that is," he says.

Hard act to follow

The job of the NIH director is never easy, but Zerhouni inherited a particularly tough challenge in following Nobel laureate Harold Varmus, who headed the agency for six years. Previous directors were noted for either their administrative skills or their scientific achievements, but Varmus was a rare combination of world-class scientist and effective political operator. He left in 1999, and the Senate confirmed



FROM BENCH TO BEDSIDE

The promotion of translational research — basic-research discoveries that find their way directly into new treatments — may be the hardest pill to swallow for many of the scientists funded by the National Institutes of Health (NIH). But this issue is key for the agency's director Elias Zerhouni. "I'm very concerned that we have a disconnect

between basic science and translational science," he says. To try to spur change, Zerhouni allotted 40% of Roadmap dollars to projects that aim to change the way translational science is done, and created a programme called the Institutional Clinical and Translational Science Award. The agency intends to give out

60 of these institutional awards, worth a total of \$500 million, by 2012.

But Zerhouni's commitment to translational research goes beyond the Roadmap itself: it permeates his entire leadership of the agency. "He chose to articulate a slightly different vision for the NIH, connecting it more intimately to health and



medicine," says one biomedical research lobbyist. "How that plays out will be his legacy." **E.C.**

President George W. Bush's nomination of Zerhouni to replace him on 2 May 2002.

Some researchers were sceptical from the start. When he took the job, Zerhouni looked more like a successful chief executive than a traditional bench scientist. A radiologist, who did research on advanced imaging techniques and patented eight inventions, his many roles at the Johns Hopkins School of Medicine in Baltimore, Maryland, included being an administrator for six years. Helping run one of the country's premier translational science institutions had, he felt, prepared him for modernizing the NIH and its mission.

When Zerhouni took the helm of the NIH, agency veteran Ruth Kirschstein had been serving as interim director, but of the 27 institutes and centres that comprise the NIH, 6 were without a permanent leader. And there was no clear plan for how the NIH would take advantage of its unprecedented rise in funds. "You couldn't help but think that you needed to create a vision for the NIH," Zerhouni says.

A year and a half after arriving at the agency, Zerhouni unveiled his signature 'Roadmap' initiative. This was designed to address a frequent criticism of the NIH: that it doesn't do a good job funding cross-disciplinary, risky and large-scale science.

More for the money

The Roadmap encourages translational research, or science that takes findings from the lab to the clinic (see 'From bench to bedside'). And it has created funding mechanisms

to promote innovation, such as the lucrative Pioneer Award for high-risk research. The Roadmap also funds team resources, such as chemical databases that can be searched for drug candidates.

At first, the Roadmap — projected to cost \$2.1 billion over five years — drew widespread praise as an attempt to reform some of the NIH's old ways of doing business. But soon after it was unveiled, Congress began passing budget increases that were far below what the NIH had been used to.

In his editorial, Marks taps into researchers' frustrations with the Roadmap. Some thought it should not have been started simultaneously with the flattening of the budget, and others felt it diverted funds away from the individual-focused, investigator grants called R01s on which basic-science researchers depend. "The NIH Roadmap is not a roadmap at all, but a yellow-brick road," writes Marks. "It looks like it will lead us back to Kansas, but the way is really fraught with danger, the end of the road is not really where we want to go, and it is all just a fantasy."

Marks told *Nature* that he feels a basic scientist would not have unveiled the Roadmap at a time when money was tight. "If the director of the NIH had a deep understanding of what it's like to be in the trenches supporting your labs with R01 grants, the timing would have been different," he suggests. "I thought that was perhaps insensitive."

Others think Marks himself was insensitive for penning the editorial. "The insulting nature of the whole piece was destructive to what we all need to do in the community," says Varmus, now president of the Memorial Sloan-Kettering Cancer Center in New York. An NIH advocate who did not want to be named, but who has worked on Capitol Hill on and off for years, put it more strongly: "He handed the people who want to hurt us a bat."

Poor connections

The editorial seems especially vitriolic because it echoes an unstated feeling in the community that Zerhouni is not 'one of the group'. Some say there is little he could do to overcome this bias. "Zerhouni doesn't have the lab-rat appearance, and there have been elements in the community that expect the NIH director to be exactly in their image," says Varmus.

Zerhouni served as a consultant to the White House when Ronald Reagan was president. That and his nomination by Bush — whose administration has

been accused of ignoring science at the expense of ideology — has not endeared him to many scientists. "I think that in a more open administration, Elias would have been a very good leader," says Jerry Keusch, associate dean for global health at Boston University in Massachusetts and former director of the Fogarty International Center at the NIH. For his part, Zerhouni says: "There is a little bit of a political overture in the comments I hear that suggests scientists are opposed to this administration. I'm pretty independent as a director, and that's unfair."

But others say Zerhouni could have strengthened his position by reaching out to researchers, both inside and outside the agency. For instance, embarrassing revelations about financial conflicts of interest in newspaper reports in December 2003 and in subsequent congressional hearings (see 'Congressional conflicts'), caught Zerhouni off-guard. "If he was the kind of leader who could have understood or connected better with the institute directors and bench scientists, it would have served him much better in that storm," says one researcher, who asked to remain anonymous. "He got no

"The NIH Roadmap is not a roadmap at all, but a yellow-brick road." — Andrew Marks

MONEY WORRIES

Scientists and advocates of the National Institutes of Health (NIH) are anxious about the funding outlook for biomedical research. After the agency's budget rose from \$13.6 billion in 1998 to \$27.3 billion in 2003, there began what some call the 'undoubling' of its budget.

The president's budget request to Congress this year included the first proposed cut in NIH



spending in 36 years. Some argue that young investigators could be especially hard-hit, and that

the investment in the doubling could rapidly be eroded. Biomedical advocates are scrambling to figure out how to reverse the trend, or at least keep the cuts from growing deeper.

"We're losing buying power every year," says Harold Varmus, president of the Memorial Sloan-Kettering Cancer Institute in New York and a former director of the NIH. **E.C.**



Low morale: after a doubling of its budget, the National Institutes of Health is now facing tougher times.

backup, and he did contribute to that.”

Zerhouni attributes much of the discontent to the flattened budget, and notes that competition for NIH grants has accelerated dramatically in recent years. From 1999 to 2003, the agency attracted 5,300 new grant applicants. Then, the agency gained an additional 5,000 new applicants just in 2004 and 2005 combined. Zerhouni calls it “a perfect storm that is hitting the NIH”.

Some say it was clear that the agency couldn't keep getting double-digit increases for ever, and that the NIH leadership should have devised a better plan earlier on for dealing with the end of the budget hike. And even though Zerhouni arrived towards the end of the budget doubling, his critics say he hasn't done enough to soften the blow. “I think he's dealt with it through prayer,” says Arthur Caplan, a bioethicist at the University of Pennsylvania in Philadelphia. “It hasn't been addressed head-on.”

Ring the changes

But an analysis by Howard Garrison, director of public affairs for the Federation of American Societies for Experimental Biology, suggests that the total proportion of funding for R01 grants, seen as the mainstay of traditional investigator-initiated research, is about the same as it was before the doubling began. “What has happened is that the awards have gotten bigger and the competition has gotten fiercer, expectations have risen, and the number of new grants has not gone up,” Garrison says. Zerhouni says this means that the Roadmap is not killing off investigator-initiated research, as critics have charged.

Many scientists defend Zerhouni's decision to launch the Roadmap when he did. They argue that it was an astute political move at a time when the NIH needed a new vision to

move forward from budgetary and conflict-of-interest woes. Some researchers think the Roadmap helped win congressional support by showing that the agency had a bold vision that would guide new spending.

CONGRESSIONAL CONFLICTS

In January 2004, Congress began investigating conflicts of interest for the National Institutes of Health (NIH) investigators who consulted for private companies.

The NIH director Elias Zerhouni initially tried to take a moderate approach. But Congressional outrage grew in 2004; in one particularly embarrassing moment, Zerhouni was confronted with cancelled cheques showing that NIH scientists had accepted consulting payments that they hadn't revealed to their bosses. In February 2005, Zerhouni announced stringent restrictions — later tempered — for NIH employees on consulting and investing in biomedical arenas.

Many employees felt stung by the investigations, and are dismayed at the increasing paperwork and restrictions imposed on the agency. Some blame Zerhouni. “It's hard to figure out what are his decisions and what are the administration's decisions,” says one NIH employee, adding, “Internally, morale is a problem.” **E.C.**



“I share with Elias the feeling that the Roadmap stimulates Congress to reinvest, to get over their feeling that they've doubled the budget and nothing more is needed,” says Gerald Fischbach, who headed the NIH's National Institute of Neurological Disorders and Stroke from 1998 to 2001, and who is now vice-president for health and biomedical sciences at Columbia University.

Zerhouni argues that the research community has long called for the NIH to become a more flexible, forward-thinking enterprise that is in touch with the emerging need for technology-driven, interdisciplinary work. A 2003 report from the Institute of Medicine, ‘Enhancing the vitality of the NIH’, explicitly called for such an approach. “I've not yet heard a scientific criticism of the Roadmap,” says Zerhouni. “I've only heard: ‘It's taking away money from my programme or my institute.’”

With no term limit, Zerhouni could potentially stay in his post for as long as it takes to fully implement the Roadmap. As stormy as his first four years have been, it's not likely to get much easier, say observers such as former Congressman Jim Greenwood, who investigated conflicts of interest at the NIH. Greenwood, now president of the Biotechnology Industry Organization, based in Washington DC, gives Zerhouni high marks for starting the NIH down a new path. But he says it will take time for the agency and its constituents to come along.

“This is about turning around an aircraft carrier,” he says. “You can't measure the radius of the turn at first. But you don't make the turn unless you take the wheel and start spinning it — and that's what he's done.”

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