NATIONAL CANCER INSTITUTE

# Klausner's Unconventional 'Field Station' in Seattle

When a group of cell biologists decided last year that they wanted to try a new strategy in the war on cancer, they were fortunate that one of their own clan—Richard Klausner—had just been chosen to head the National Cancer Institute (NCI). Klausner, a well-known cell biologist, immediately grasped their proposed strategy, which involves transplanting human genes into yeast cells to develop a screen for anti-cancer drugs, and he responded enthusiastically. He was so enthusiastic, in fact, that he helped guide a proposal from the group through a set of reviews, hovered nearby as it worked its way through NCI, cast a vote in its favor as chair of NCI's executive committee, and presented it in November to NCI's top advisers. He also set up an unusual funding structure for it, in which intramural funds are being used to support the research at a "field station" in Seattle.

Cell biologists around the country agree with Sidney Salmon, director of the University of Arizona's cancer center, that "this is a fascinating project." But Salmon and others who are accustomed to a more deliberate style of government review have been taken aback by Klausner's wholehearted championship of the project and its unusual structure. Klausner, however, is unabashed about his unorthodox approach to getting a key project started fast. Agreeing that it is "experimental both in terms of the science and the mechanism we have used" to support it, Klausner has said that he regards it as a unique opportunity to build on research already being done in NCI labs in Bethesda and Frederick, Maryland. Klausner's effort to move the project from concept to reality in a few months epitomizes the activist-researcher approach he is bringing to NCI.

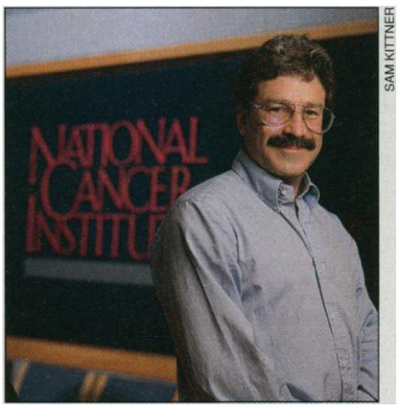
Known as the "Seattle Project," the venture represents an amalgam of basic and applied science. Its founders, cell biologist Leland Hartwell of the University of Washington, Seattle, and cancer researcher Steven Friend of the Fred Hutchinson Cancer Research Center in Seattle, view it as the beginning of a "drug discovery think tank," Friend says, which he hopes will involve academic and industrial researchers. Along with a 3-year, $3 million grant from NCI, the team has also obtained support from the Merck Pharmaceutical Co. for a linked but independent genetics research effort. A Merck spokesperson says the company's role is still being worked out, however, and one NCI official says NCI funding is contingent on keeping the two accounts separate.

THERESA NAUJACK

**Bold move.** Leland Hartwell *(left)* and Steven Friend try new strategy in the war on cancer.

While the project is new, Hartwell notes, the roots of the science go back several decades to research on cell division in yeast—fundamental studies that Hartwell pioneered and for which he was honored recently by the American Society for Cell Biology. Since the 1970s, Hartwell and many others in the field have built up a detailed description of the mechanisms yeast uses to control self-replication. This research revealed a set of developmental pathways that cells follow as they divide, along with checkpoints on each pathway that make progress conditional on success at earlier stages, such as accurate copying of DNA. These checkpoints—which Hartwell also calls the "police" of cellular integrity—prevent defective cells from replicating. But sometimes the police are corrupt. When the genes that enforce checkpoint control are damaged, they permit errors in DNA. This leads to "genetic instability" and uncontrolled growth, which Hartwell regards as the hallmarks of cancer.

A comparison of damaged checkpoints in brewer's yeast (*Saccharomyces cerevisiae*) and cancer-causing mutations in human cells has led to a remarkable discovery: The "police" genes in these different organisms are sometimes the same. Two stunning examples of such homology have come to light recently, one involving human genes that cause colon cancer and the other a set of genes involved in ataxia-telangiectasia and breast cancer (*Science*, 18 March 1994, p. 1559, and 23 June 1995, p. 1700). "It is a beautiful story," says yeast geneticist Philip Hieter of Johns Hopkins University. "The yeast-cancer connection is very strong."




SAM KITTNER

**Agent of change.** NCI chief Klausner brings a cell biologist's perspective.

Hartwell says there is now "a long list" of human cancer genes that match genes in yeast. This similarity in control mechanisms suggests that it may be possible to insert defective human genes into yeast DNA and use the yeast cells to model human cancer. Unlike cultured human cancer cells, which are typically loaded with four or five genetic flaws, the yeast cells should carry a single defect each. But studies suggest that, like ordinary cancer cells, these model tumor cells "should be more vulnerable than normal cells" to attack by toxic agents, Hartwell explains. "The idea," he says, "is that if you can match the genetic defect in a tumor cell with the agents that it is vulnerable to, then you can preferentially kill tumor cells." Their plan calls for using a robot and computers to help screen 40,000 compounds in 30 mutant yeast types.

The researchers originally intended to start a biotech company to exploit this idea, Hartwell says, but "we discovered that what we wanted to do was more basic" than private investors would support. Enter Klausner. The Seattle researchers talked to Klausner about their ideas several months before Klausner became NCI director in August 1995. Klausner recalls being "excited" because their proposal had many promising features. As he told an NCI advisory group, it was based on "a fundamental reconceptualization of cancer as a disease—not of proliferation, but ... of genomic instability." In addition, Klausner says, he saw it as a way to "build bridges" among academic researchers, pharmaceutical companies, and cancer clinicians. And it offered a "testable hypothesis."

After discussing the idea with Hartwell and Friend at a scientific meeting early in 1995, Klausner encouraged them to submit a proposal to NCI. He suggested that it be considered an extension of NCI's intramural drug screening effort. That meant that unlike ordinary extramural funding, support for the work would not be held up until after NCI had issued a request for proposals and reviewed competitive bids. Klausner added that he saw the field-station arrangement as temporary: If it succeeds, he said, "the project has to move onto campus."

After the Seattle project won high marks

from a set of "very tough" outside reviewers, Klausner says, it went to the NCI executive committee—which Klausner chairs—in October. There it received another favorable vote, and in November it went before the National Cancer Advisory Board (NCAB).

When Klausner presented the Seattle Project to the NCAB on 29 November, no one objected to its substance, but several questioned what Klausner called the "innovative use of intramural mechanisms" by which it was funded. Salmon said: "I do not see why this has to be done in the intramural program." And Philip Schein, chair and chief executive of U.S. Bioscience in West Conshohoken, Pennsylvania, questioned the decision to move it to Bethesda if it succeeds. "Rick," Schein said, "not everything exciting needs to expand the intramural program. Leave some of it out there" in the community. The lack of open competition led one adviser, requesting anonymity, to grumble to *Science* about NCI's "new old-boy network."

Asked to respond to concerns about the use of intramural funds to create a West Coast field station, Klausner told *Science*: "This is not something we're going to be doing" often. In this case, Klausner said, "we did it because of the unique intramural setup of the Developmental Therapeutics Program" at NCI, which can provide confidential feedback to companies that submit a compound for testing as a potential anti-cancer drug. This program uses cultured mammalian cells to test the effects of potential anti-cancer compounds—over 40,000 candidates have been submitted by a variety of researchers. It's much easier to handle intellectual property issues in an intramural program, Klausner claimed. Edward Sausville, who directs the Developmental Therapeutics Program, said it made sense to link this project to it because "it is a logical extension" of NCI's intramural research and should not be regarded as "a rabbit pulled out of a hat."

Whatever their qualms about using intramural funds to support extramural scientists, cancer experts agree about the merits of the project. John Mendelsohn, chair of medicine at the Memorial Sloan Kettering Cancer Center in New York, who is running a clinical trial of substances that block cell growth receptors, says the Seattle project has "a very cogent rationale" and appears to be "very creative ... innovative and important."

Whether the yeasts will actually serve as good models of human cancer cells and their susceptibility to toxic attack is unknown. The answers to those questions, as Friend says, "we can only get by doing the work, not by guessing." But preliminary results are promising, Friend said: After an initial screening run last year the Seattle group has already identified one promising candidate that deserves more investigation.

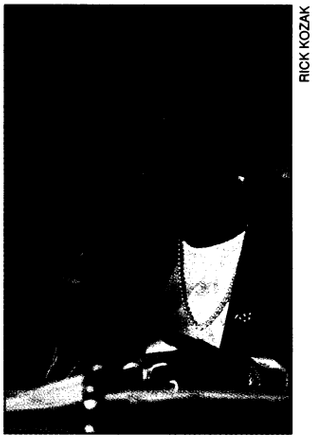
**–Eliot Marshall**

*SCIENCE* INTERVIEW

# Donna Shalala: 'Leaving Footprints' at HHS

When Donna Shalala, secretary of Health and Human Services (HHS), visited *Science* 3 years ago in June 1993, she had been on the job only a few months, but she made a bold suggestion: "Forget what people are saying. Watch what we actually do and judge us by where we end up." At that time, the Administration was just starting to write its health insurance reform proposal, Bernadine Healy was still director of the National Institutes of Health (NIH), and Shalala was excited about the prospect for increased funding of preventive health care. Much has changed since then.

The Clintons' insurance package went down to an ignominious defeat in Congress in 1994, and with it, the preventive health plan. Healy was replaced by Harold Varmus, who has instituted critical administrative reforms at NIH. Congress has switched from Democratic to Republican leadership, and the entire government has gone through a series of wrenching battles over federal social spending and tax policy. Yet during this period, NIH's budget has grown at a rate higher than general inflation.



RICK KOZAK

Against this background, *Science*'s editors and reporters earlier this month took Shalala up on her offer to review the Administration's record on biomedical research. In her feisty style, Shalala defended the Administration's policies and rattled off answers to questions about a wide variety of subjects—ranging from support for AIDS research, the congressional ban on human embryo research, and HHS's role in determining basic science budgets.

Shalala readily agreed that Republican congressional leaders like Representative John Porter (R–IL) and Senator Mark Hatfield (R–OR) deserve credit for their support of biomedical research—especially for securing a 5.7% increase in NIH's budget, a full 1.5% more than the Administration requested. But she argued that the Administration's appointments to NIH and other health agencies also helped by raising these agencies' visibility and status. She claimed that a reorganization of HHS carried out last year that eliminated the office of the assistant secretary for health has improved efficiency and elevated the status of NIH. Specifically, Shalala said that former assistant secretary for health Philip Lee has been freed up "from the minutiae of budgeting and personnel to really be the public health leader." Doing away with an entire layer of bureaucracy and allowing the health agencies direct access to the HHS secretary, Shalala added, "frees topnotch senior" people to work on "big-time issues."

Organizational changes such as these, Shalala argued, had enabled HHS to "be a bigger player in science policy" at the White House. She noted that HHS controls two seats on the President's National Science and Technology Council—one held by HHS itself and the other by NIH. However, she rejected the suggestion that as head of the department with the biggest science budget, she should be an advocate for research funding in general. "I am not the president's science adviser," she said. "I am not required to balance off the interests between various agencies. My job is to be an advocate for the scientific enterprise which is within the department of HHS." However, she added that "I try to be helpful to science and technology, because I think it's clearly a national function, and that we ought to [be] steady in funding it, so that we can train the next generation of scientists."

On the always volatile topic of AIDS, Shalala said that the Administration had strongly opposed any reduction in budget authority of NIH's Office of AIDS Research (OAR). Legislation proposed by Representative Porter, chair of the subcommittee that writes NIH's budget, and passed by the House sought to weaken OAR's clout, but Shalala said that she, Varmus, and President Clinton "continue to believe that a single OAR appropriation is essential for better management and scientific oversight of the vast HIV/AIDS research effort at NIH," and she vowed to fight to include full budget authority for OAR in future appropriations bills.

Shalala said that one of her goals is to shield basic research in her department from undue political meddling and excessive bureaucratic burdens. Speaking of NIH staffers, she said "I've got to protect them" while ensuring that they get reviewed critically. For the long haul, she said, her goal is to see that administrative reforms are made permanent.