GENE THERAPY

A Speeding Ticket for NIH's Controversial Cancer Star

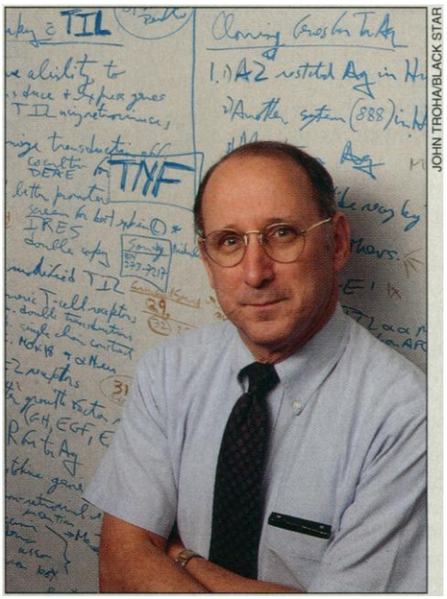
On the afternoon of Sunday, 21 February, several members of a National Institutes of Health (NIH) scientific advisory committee met in private with Steven Rosenberg, one of NIH's top cancer researchers. The group members were all scientists in cancer research or the new field of gene therapy, but the meeting was not social. The members of the National Cancer Institute's Division of Cancer Treatment (DCT) board of scientific counselors had concerns about one of Rosenberg's pioneering gene therapy experiments, and they called the meeting to raise a red flag about the experiment's future.

For more than 2 years, Rosenberg has been conducting a clinical trial of a technique to inject gene-modified immune cells into seriously ill cancer patients. The red flag is the panel members' concern that he hasn't generated enough data to suggest the experiment is working—or that it ever will work. And none of the additional data Rosenberg brought out changed their minds. "We reached the point where we couldn't convince each other," says board chairman Ronald Levy, a Stanford University oncologist.

When the panel met in public 2 days later, its members voted unanimously to delete $225,000 from an upcoming contract from an outside company to grow immune cells for Rosenberg's gene therapy work. The rest of the contract—$675,000 to grow cells for Rosenberg's other trials—was approved without much debate. But "in view of the serious reservations that remain" about the gene therapy experiments, board member Allen Oliff, the director of cancer research at Merck Sharp and Dohme Research Laboratories, announced, the board recommended that the entire gene therapy portion be deleted from the first year of the contract, which begins in October 1994. Although the board agreed to reexamine Rosenberg's data—and reconsider the cut—in a year's time, "if there is not substantial evidence of feasibility" by then, the board would delete the second- and third-year funding as well, Oliff announced.

Rosenberg insists that the vote will have no practical impact on his work. Indeed, he says, "I'm more enthusiastic than ever" about the trial. Most of his funding does not come under the DCT board's domain, and NIH officials say they have no plans to halt his trials. The DCT board has authority only over the outside contract, Rosenberg points out, and even if he cannot get the gene therapy portion of that contract restored, he has enough internal NIH funding to grow the immune cells himself. The amount deleted from the contract is "less than a fifth of my total funding," for the gene therapy experiments, he says. "It's just one contract." He also points out that he has approval from all the relevant review committees to proceed with the clinical trial.

But the vote does make it clear that Rosenberg, who is among the best known of the gene therapy pioneers, may have a difficult road ahead of him in his gene therapy experiments. His approach to cancer therapy has generated enormous interest in the scientific community and among cancer physicians. Yet he is also controversial, in part due to his history of aggressive trials and bold predictions of success—and to the publicity he has attracted, including an autobiography he published last year. And, by its unusual public criticism and efforts to halt the trial, the advisory committee is adding to the doubts about his methods. "I'm stunned," says French Anderson, a gene therapy pioneer who worked with Rosenberg on his early experiment. "Sure, there are enormous problems" with Rosenberg's gene therapy approach, he says, "but Steve is not a minor player. To cut the work off at this point would be premature."



JOHN TROHA/BLACK STAR

Data dispute. Steven Rosenberg's clinical results did not sway a skeptical advisory panel.

Many scientists interviewed by *Science* say that there have been concerns from the beginning that Rosenberg was moving too quickly into work with human subjects. When he first sought approval from NIH's Recombinant DNA Advisory Committee (RAC) in 1990 to conduct the trial, some members of the RAC were troubled by Rosenberg's lack of animal data. It only approved the protocol after Rosenberg testified that he and his NIH colleagues had been unable to modify the genes of mouse immune cells and therefore had no animal model for the procedure. Then the Food and Drug Administration (FDA), which must also approve gene therapy experiments, became concerned about possible toxic side effects from the procedure (a concern that remains and was discussed at the DCT board's meeting last week). The agency finally gave the go-ahead 6 months later, after Rosenberg agreed to use lower doses.

The experiment RAC and FDA approved involves extracting tumor-infiltrating lymphocyte (TIL) cells from cancer patients, growing them in the laboratory, and inserting into them the gene for tumor necrosis factor (TNF), a cytokine that interferes with the tumor's blood supply. Rosenberg's team then reinjects the TNF-producing TIL cells back into the patient in the expectation that because the cells were taken from tumors, they will home in on tumors in the body, infuse them with TNF, and kill them.

But the data Rosenberg presented to the DCT board indicate that at least two key elements of this process have so far failed to work as hoped, Levy said. The gene-modified TIL cells aren't secreting as much TNF in vitro as models predict is necessary to kill tumors. More seriously, it's not clear that enough TIL cells are localizing at the tumor sites.

Mouse models predict that, for tumor reduction, the TIL cells must secrete about 1000 picograms of TNF per ml (10^6 TIL cells) in 24 hours. But the average in vitro performance of the human TIL cells in Rosenberg's trials is just a quarter of that. Rosenberg, however, says that by using an improved viral vector to transfect the TIL cells, he can get TNF production up to more than 800 picograms, close to the predicted effective level. He says all his future trials will use the new vector.

The apparent problem in getting the TILs to localize could be more serious, however, for it could undercut not just the TNF studies but also several large trials based on injecting unmodified TIL cells into cancer patients in the hopes that they will attack and kill the tumors themselves. "The fundamental question is that of whether or not the TILs preferentially migrate to tumor sites," says RAC executive secretary Nelson Wivel. "If you don't get preferential migration, your whole hypothesis is on shaky ground." Even the data Rosenberg originally presented to the RAC "cast some doubt" on the propensity of TILs to localize, he adds. One RAC member noted at the time, for example, that high TIL recordings near tumor sites could just as eas-

ily reflect the increased blood supply at the site as any specific TIL homing.

Gene-modified TIL cells that don't localize not only have no therapeutic value but also may end up in the liver, where the TNF, which is toxic, could be a problem. So far, Rosenberg says, none of the nine patients he has enrolled in the study have shown any signs of toxicity. But with the relatively low levels of TNF the TIL cells were secreting, said Levy, that result is not surprising. And he questioned if it was "worth it" to continue toxicity testing "given these secretion and localization [levels]."

Hoping to answer some of these concerns, Rosenberg presented data to the board that showed that treating patients with cyclophosphamide, a chemotherapeutic drug, apparently doubled the likelihood of their TIL cells ending up at tumor sites. But the trial was unrandomized, a point the board noted in its criticism. "It was very clear that Rosenberg couldn't provide data to relieve [the DCT board's] anxieties," Wivel says. In response, Rosenberg announced that he intends to conduct a fully randomized trial on the influence of cyclophosphamide on TIL localization, which could finally resolve the point.

The board agreed to consider those data when they become available, but it was unwilling to lend its support to continuing the TNF/TIL trial based on the data it had seen so far. "When I go through your numbers, I come up very short of an effective gene therapy," Levy told Rosenberg at last week's public meeting. "I think it might be better to wait" for better preclinical data before continuing with the trial, he said.

NIH cancer researcher Michael Blaese, whose team collaborated with Rosenberg on many of the initial laboratory experiments, says that TNF/TIL initially looked like a good bet, but that difficulties in the approach soon arose. "The first experiments [with gene-modified TIL cells] were better than the later ones," he says. "In hindsight, the initial data were spotty. The initial promise they generated in the lab couldn't be maintained. It was really hard for us to get any cytokine genes expressed in TILs."

Nevertheless, Blaese defends Rosenberg's risk-taking: "Steve's controversial, but he's been remarkably effective at bringing new [technologies] to clinical trials. I hate to see him knocked for it. It's too bad that the [DCT] committee had to publicly slap him."

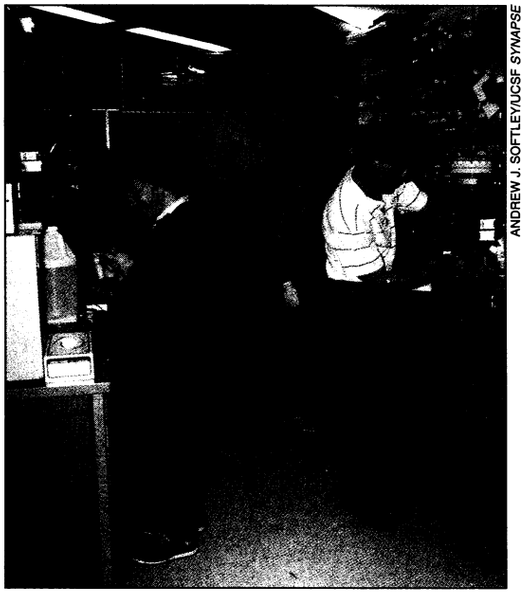
Yet Blaese is not surprised that Rosenberg is now being challenged for his aggressive approach. "Steve has his passionate supporters and his equally passionate detractors," he says. As Wivel sees it, Rosenberg is a victim of the publicity he has generated. "You have a choice which path you take," Wivel says. "If you chose high visibility, you've got to take your lumps."

–Christopher Anderson

RESEARCH INSTITUTIONS

Space Woes Begin to Take a Toll at UCSF

The University of California, San Francisco (UCSF), is legendary for its rapid rise to a place among the world's top biomedical research institutions. Considered average only 20 years ago, it now commonly ranks first or second among U.S. medical schools in annual grant support from the National Institutes of Health, and handily competes with the likes of the Massachusetts Institute of Technology, Stanford, and UC Berkeley for the best graduate students and junior faculty. But this thriving campus is also legendary for something else: its space problem. Hemmed in by an agreement not to expand at its main site at Parnassus Heights in San Francisco, and stymied by neighborhood activist groups in its efforts to grow elsewhere in the city, UCSF finds itself with a faculty crowded together like sardines in a can.



ANDREW J. SOFTLEY/UCSF SYMAPSE

Elbow to elbow. Researchers work together in cramped quarters in a typical laboratory at UCSF.

Now, faculty members and administrators are worried that their cramped quarters might be endangering the university's top-notch reputation. The reason: Three key faculty members have recently accepted offers from other institutions, at least partly because of space problems. Cell biologist Marc Kirschner is departing for Harvard and human geneticists Rick Myers and David Cox are moving to Stanford. Concerned UCSF faculty and administrators took their case to the UC regents on 18 February, asking for support in finding room to expand. Without space relief, they warned, UCSF's faculty and reputation are at risk of slipping away.

The current departures are no small loss to UCSF. Kirschner, a leader in cell biology, has been instrumental in recruiting outstanding young cell biologists to the faculty. He goes to Harvard Medical School next fall to chair a new cell biology department there. The widely respected Cox and Myers direct a Human Genome Project mapping center, which will move with them to Stanford this month.

Kirschner came to UCSF from Princeton in 1978 during a wave of hiring that included such appointments as biochemist Bruce Alberts (now president-elect of the National Academy of Sciences) from Princeton, yeast geneticist Ira Herskowitz from the University of Oregon, and then assistant professors Keith Yamamoto and Harold Varmus (who won a 1989 Nobel Prize with his UCSF colleague Michael Bishop). Sharing a philosophy of cooperation and minimal hierarchy, the evolving group created the spirit of collegiality, irrespective of both rank and department boundaries, for which UCSF is now known.

But while that community was forming, a decision was made that would constrain its future. Expansion of the Parnassus campus had sparked a lawsuit by neighbors over traffic and congestion, and that led to a promise from the UC regents to limit growth at Parnassus to 3.55 million gross square feet—a size it had almost reached when the promise was made in 1976.

Thus began a phase of decentralization, in which the university farmed out programs to other sites. The most notorious and ill-fated of those satellite sites was a 360,000-square-foot office building in the Laurel Heights district, a few miles from Parnassus Heights, which was purchased in 1985 as a new home for the school of pharmacy. When neighborhood residents learned that research labs were part of the plan, they filed lawsuits that kept the pharmacy school from moving in, tightening the vise even more on the research labs at Parnassus Heights (*Science*, 11 March 1988, p. 1229).

"We outgrew [the size limits on the Parnassus campus] 10 years ago, and we have just become more and more cramped," says neurobiologist Michael Stryker, who came to UCSF as an assistant professor in 1978. Adds another faculty member, who requested