Lobbying for an AIDS Trial

Biotech firm MicroGeneSys launched a lobbying blitz to get its "therapeutic vaccine" tested. Has their success skewed the effort to develop vaccines as a form of AIDS therapy?

One of the most intriguing ideas to come out of AIDS research in the past few years is the notion that a vaccine against HIV could not only protect healthy people against infection but might also serve as a form of therapy for those already infected. A number of labs, both academic and commercial, are furiously searching for a preparation that could turn this innovative idea into reality. But is any one experimental "therapeutic vaccine" ready for a large-scale, publicly funded trial?

Corporate headquarters. The Meriden, Connecticut, facilities of biotechnology firm MicroGeneSys.

Few topnotch AIDS researchers think the answer to that question is yes. But the U.S. Congress—with the help of a few high-powered lobbyists—thinks otherwise.

Two weeks ago the Senate slipped a last-minute provision into the Department of Defense appropriation bill, giving Army researchers $20 million to test a vaccine in HIV-infected people. But Congress didn't leave it up to researchers to decide which preparation the $20 million ought to be spent testing: Legislators specified a preparation called gp160, and though gp160 is made by several companies, everyone agrees that the appropriation refers to gp160 manufactured by MicroGeneSys, a Connecticut biotech firm (*Science*, 9 September, p. 211). That congressional appropriation—the first, experts say, to mandate human testing of a specific experimental product—has provoked fury in the AIDS research community. The director of the National Institutes of Health (NIH) and the commissioner of the Food and Drug Administration (FDA) have denounced the appropriation as an outrageous attempt to do an end-run around peer review.

If there is such outrage over this measure, how did it get passed in the first place? How did a small biotech firm obtain the political clout needed to steer a product-specific amendment through the U.S. Congress? That's a question that has the AIDS research community buzzing. To answer it, *Science* launched an investigation that ultimately included more than 100 interviews and hundreds of documents, some obtained through Freedom of Information Act requests.

At the center of the story is Franklin Volvovitz, an energetic scientist-turned-entrepreneur who is president of MicroGeneSys. With plenty of assistance from NIH researchers, Volvovitz made MicroGeneSys an early entrant in the race for a preventive AIDS vaccine. As the vaccine race heated up, MicroGeneSys also formed links with Army researchers, who became advocates for vaccine therapy in general—and gp160 in particular. With those researchers supporting their vaccine, the company hired heavy-hitting lobbyists and built a network of political contacts. The result was the recent product-specific amendment, which some researchers fear could skew the entire U.S. effort to develop a therapeutic AIDS vaccine. MicroGeneSys and its lobbyists, though, believe there was nothing nefarious about the process and that everyone will win here, since what they believe is the most promising therapeutic AIDS vaccine may now be put to the ultimate test sooner rather than later.

The genesis of MicroGeneSys

In the 1970s, Volvovitz, now 44, attended graduate school at New York University's School of Medicine and did research on interferons, dropping out just months before his Ph.D. thesis was due. His thesis adviser, Jan Vilcek, a leader in interferon work, was disappointed. But Vilcek had already noted that Volvovitz was different. "He was the only one I've ever seen reading *The Wall Street Journal* as a graduate student," says Vilcek.

Volvovitz launched a company specializing in interferons, but it quickly went under and in 1983 he founded MicroGeneSys. One of his first hires was Mark Cochran, a postdoc at the National Institute of Allergy and Infectious Diseases (NIAID). Cochran had worked with baculovirus, an insect virus that can be used to engineer genes into insect cells, turning them into factories for proteins that could be used for many purposes—including AIDS vaccines. From the beginning, Volvovitz had commercial dreams on a large scale. As far as backing for the fledgling company went, Cochran (who has since left MicroGeneSys) remembers Volvovitz saying "he had $250,000, but said there was more coming. He always talked in terms of millions."

MicroGeneSys's initial goal was to make insecticides, but soon, with the help of Cochran's NIAID contacts, the tiny Meriden, Connecticut, company began engineering proteins from human viruses, including HIV. "We helped them a lot," says Malcolm Martin, who heads NIAID's Laboratory of Molecular Microbiology. The first—and most important—boost from Martin came in 1985 when he provided the molecular clone (a purified isolate) of HIV that MicroGeneSys used to make its gp160 vaccine. Gp160 is the outer envelope protein of the AIDS virus. MicroGeneSys set out to use the baculovirus system to transplant copies of HIV's gp160 gene into insect cells, which then produced large quantities of the protein.

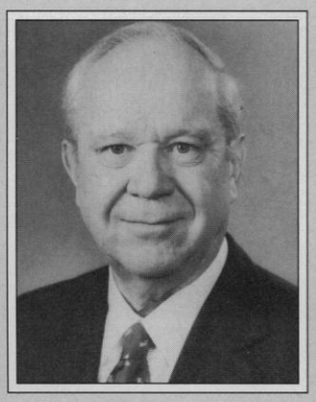
As big a boost as it was, the initial HIV clone was not the only help Martin and NIAID offered the young biotech firm. The institute helped gather the animal data FDA required before approving human tests of an AIDS vaccine; Martin presented some of the data to the agency. When FDA wanted safety data from studies in chimpanzees, "at our expense, we went and did chimpanzee studies in New Mexico," says Martin.

That kind of help put MicroGeneSys in an excellent position in the competition for an AIDS vaccine. On 18 August 1987, the company became the first to receive FDA approval to conduct safety tests of an experimental AIDS vaccine in healthy, uninfected people. The approval made MicroGeneSys a hot commodity in the research and business communities. As Volvovitz told the magazine *New England Business*: "Since we received approval to go into the trial, there has been more interest in the company, more inquiries. One thing that AIDS did was give

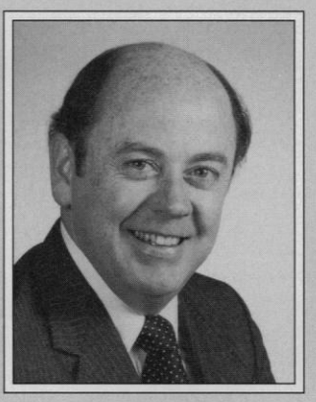
You Can't Tell the Players Without...

CHRIS FRENCH/THE RECORD JOURNAL

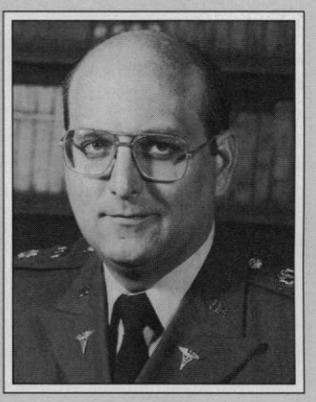
Corporate president.
Franklin Volvovitz.



Lobbyist extraordinaire.
Former Senator Russell Long.



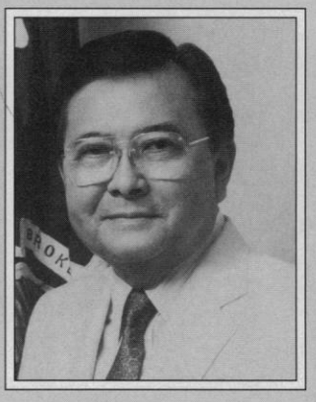
Executive access.
John O'Shaughnessy.



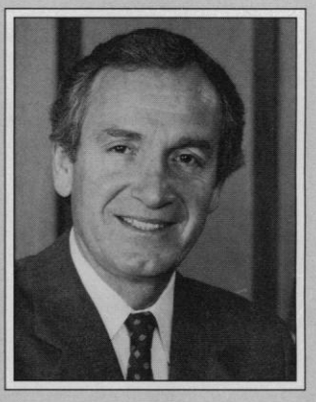
Vaccine therapy enthusiast.
Lt. Col. Robert Redfield.

Let me amend that.
Senator Sam Nunn.

Second that amendment.
Senator John Warner.



Occupying the chair.
Senator Daniel Inouye.



Aggressive questioner.
Senator Tom Harkin.

Franklin Volvovitz, president of MicroGeneSys, hired Russell Long to lobby for his company's vaccine. John O'Shaughnessy's firm provided access to key officials in the executive branch. Army researcher Robert Redfield is enthusiastic about the potential of therapeutic vaccines; his opinions have lent such vaccines much credibility. Senators Nunn and Warner introduced an amendment that allocated funds to an appropriation that had been introduced by Senator Inouye's subcommittee. Senator Harkin's subcommittee questioned NIH officials about the MicroGeneSys vaccine.

us credibility." Some of that credibility came from the NIAID-sponsored clinical trials, which to date have included vaccination of more than 250 uninfected volunteers with the gp160 preparation, known commercially as VaxSyn.

But NIH wasn't the only government organization interested in the possibilities offered by gp160. Another was the Army. MicroGeneSys had ties to the Army dating to 1985, when the company won an Army contract to make hepatitis B vaccine; other Army contracts to make vaccines against Japanese encephalitis and dengue fever followed, bringing the company's total Army funding to more than $1 million. But AIDS remained a far more pressing problem—and an effective vaccine would be far more lucrative.

In 1989, Lieutenant Colonel Robert Redfield of the Walter Reed Army Institute of Research became interested in using VaxSyn not as a preventive vaccine but as a form of therapy. Redfield and a few other notable researchers reasoned that the same immune response they hoped would protect people against HIV infection could also help people who were already infected from becoming ill (see sidebar on page 538). In April 1989, human trials began, and by June 1991 Redfield and his colleagues published encouraging early results in the *New England Journal of Medicine*. Redfield concluded that, as a form of AIDS therapy, VaxSyn seemed safe and appeared to augment the immune responses of HIV-infected people. Sparked by those findings, a variety of clinical trials of VaxSyn as a therapeutic vaccine are now under way at other institutions, including NIH.

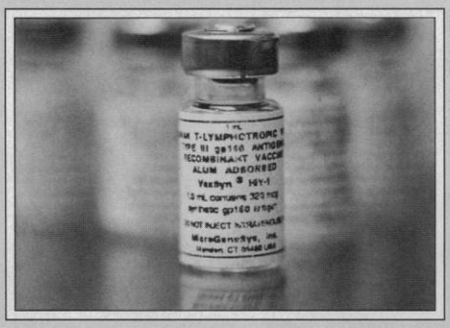
In spite of these early results, there is as yet no evidence that gp160 actually prevents people infected with HIV from becoming sicker. To find out whether it does, Redfield has initiated a 600-person, double-blind trial. But even without conclusive results, Redfield has become something of a cheerleader for vaccine therapy. Says Fred Valentine, a New York University researcher who has conducted a NIAID-sponsored trial of gp160, "Dr. Redfield's enthusiasm for this is greater than that of many other scientists who believe this is promising."

Redfield's boss, Col. Donald Burke, also had his eye on MicroGeneSys's gp160. Burke had discussed conducting trials of gp160—as a preventive vaccine—among soldiers in the Thai army. Soon Burke and Redfield's advocacy of VaxSyn was to become intertwined with a concerted effort by MicroGeneSys to bring gp160 to the attention of those in Congress who could provide funds.

These efforts began in earnest in April 1991, when the law firm of Russell Long reg-

How Should 'Therapeutic Vaccines' Be Tested?

Many top AIDS researchers are excited by the possibility of "therapeutic vaccines" for AIDS. They think stimulating the immune system may offer better early prospects for AIDS therapy than drugs attacking the virus directly. As a result of this excitement, about a dozen therapeutic vaccines are now under development. The National Institute of Allergy and Infectious Diseases (NIAID) is sponsoring trials in infected people of vaccines made by Genentech, Chiron, and Austria's Immuno AG in addition to gp160 made by MicroGeneSys. California's Immune Response Corp. has been testing a therapeutic vaccine in humans since 1987. And a vaccine developed by France's Daniel Zagury—the first researcher to test the concept of a therapeutic AIDS vaccine—is undergoing trials in France.



DARROW MONTGOMERY

VaxSynation. MicroGeneSys's gp160 is being tested both as a conventional, preventive AIDS vaccine and as a therapeutic product.

Given all these contenders, there's a strong push at the National Institutes of Health to carry out a trial comparing a variety of therapeutic AIDS vaccines in infected people; a protocol for such a trial is expected to be approved soon. Most AIDS scientists think a trial involving multiple vaccines going head-to-head is the best way to go now—distinctly better than a large-scale trial of only one product, such as the trial of MicroGeneSys's gp160 that Congress recently mandated.

That doesn't mean most researchers dismiss VaxSyn, as the MicroGeneSys product is known commercially. VaxSyn, made by manufacturing the AIDS virus envelope protein, gp160, in insect cells, has now been tested in more than 1000 people in the United States, Canada, and Sweden. A trial in pregnant, infected women is also planned to see whether the vaccine can halt transmission of the virus to newborns.

Trials have shown that VaxSyn can produce an augmented immune response in people infected with HIV. After infected people are vaccinated, researchers have observed improved function of cytotoxic T lymphocytes, and other components of the arm of the immune system that helps clear virus-infected cells from the body. Stanford University's Thomas Merigan, an investigator in those trials, says he and his colleagues have also found that the array of antibodies in patients is broadened after vaccination—though no one knows whether that is a functionally important change.

Like everything else in the AIDS vaccine field, these results evoke sharply divergent opinions. John Moore of the Aaron Diamond AIDS Research Center believes that because VaxSyn's protein is made in insect cells, its final form isn't comparable to the "native" gp160 made in mammalian cells (as most of its competitor's products are). Therefore, Moore thinks, VaxSyn is less capable of stimulating the human immune system than the other preparations. "In my opinion, this renders it inappropriate for large-scale therapeutic trials when high quality, native products are available from other manufacturers."

Steven Schnittman, chief of the medical branch at NIAID's Division of AIDS, is more circumspect. "In general, we're at a very early stage of understanding what these therapeutic vaccines do," says Schnittman. "There's more clinical data and more experience with safety with [VaxSyn]. But is it more promising? You can't say."

Ronald Kennedy of the Southwest Foundation for Biomedical Research thinks the MicroGeneSys vaccine probably should be tested further as a therapeutic vaccine, but he doesn't think much of its potential as a conventional preventive vaccine, a purpose for which gp160 is also being tried. "Based on the scientific data available from mice, rabbits, and primates, it's a very lousy antigen," asserts Kennedy, who has done some of these trials. "There's no data to indicate that this preparation should go further in any type of [preventive] human trials."

Far more hopeful is vaccine researcher Fred Valentine of New York University. Valentine makes clear he doesn't like lobbying as a way to choose vaccines for human trials but says he hopes MicroGeneSys's "corporate strategies" don't blind researchers to the quality of its preparation. If the company "had a vaccine that was a piece of junk, I'd say [MicroGeneSys president Franklin Volvovitz] was subverting the scientific process. But the vaccine's immunogenic."

–J.C.

istered as an official lobbyist for MicroGeneSys. Long, son of Huey Long and a Democrat who represented Louisiana in the Senate from 1948 to 1986, had connections with many senators who were in a position to help VaxSyn along. With clinical trials under Redfield and others looking promising, Long began putting his connections to work.

Science has confirmed meetings by Long and MicroGeneSys representatives with the staff of Senator Edward Kennedy (D–MA), and with Senators Christopher Dodd (D–CT), Joseph Lieberman (D–CT), Bennett Johnston (D–LA), Mark Hatfield (R–OR), and Orrin Hatch (R–UT). In addition, a letter that seemed to be advancing the case for efficacy trials of AIDS vaccines was sent by Senator Quentin Burdick (D–ND) to the acting head of the FDA branch that evaluates vaccines. Anthony Fauci, director of NIAID, received two similar letters about vaccine trials: one from Daniel Inouye (D–HI), another from Mark Hatfield. The letters "didn't specifically mention a product," says Fauci, "but it was so patently obvious what was going on."

The lobbying campaign reached one of its high points at the 1991 meeting of the Senate appropriations subcommittee that oversees the NIH budget. Among the members of the committee were three senators who had written letters: Inouye, Burdick, and Hatfield. But at the meeting, it was the committee's chairman, Tom Harkin (D–IA), who took the lead. Harkin told Fauci he had recently been contacted about "the AIDS vaccine which has been developed by MicroGeneSys." The senator, apparently focusing on preventive vaccines, began peppering Fauci with questions about VaxSyn and why it wasn't being tested in efficacy trials.

That kind of effort at persuasion worried Fauci. At NIAID's advisory council meeting on 20 May 1991, he described the "extraordinary pressure from the Congress and others about going into efficacy trials now with a given vaccine preparation" and asked for "suggestions of how we can circumvent that pressure." The scientific problem, he said, was figuring out which preventive vaccine, among those available, to choose for an efficacy trial—and he didn't think Congress should make the choice. But, based on previous evidence of "earmarking," or the mandating of research projects at specific institutions, Fauci warned that Congress might choose which vaccine to test: "Don't think that is beyond the realm of reality. We've seen things written into appropriation bills before."

But for all the high-powered activity gen-

erated by Long in 1991, MicroGeneSys still hadn't received a large, product-specific dose of funding from Congress. So they stepped up their efforts. Long's work, which had initially concentrated on Fauci, began aiming higher: over Fauci's head to his boss, NIH Director Bernadine Healy. Healy remembers a meeting earlier this year, which she describes as "peculiar," with Long, who visited her to discuss VaxSyn. Not long afterwards, a senator whose name Healy says she can't recall invited her and Fauci to give a confidential briefing on AIDS vaccine research. When she heard Long was also invited, she says she was "outraged." The lobbyist's presence, she adds, was "totally inappropriate." She skipped the meeting.

Elements of a winning strategy

But Russell Long wasn't the only one talking up VaxSyn in Washington. In the fall of this year, Redfield, with Surgeon General Antonia Novello and assistant secretary of health James Mason, had a series of meetings with representatives of key agencies, including FDA, the Centers for Disease Control, and NIH, to advance the idea of a clinical trial of an AIDS vaccine in pregnant women infected with HIV, both to treat the women's infection and possibly to prevent transmission to their fetuses. While no one thought the trial they were advocating was a bad idea, some in the AIDS research establishment were puzzled, because similar trials were already planned at NIAID. And because people associate Redfield so strongly with VaxSyn, some thought that was what these meetings were about.

With the Army association—which has led many to think mistakenly that VaxSyn is, in fact, "the Army's vaccine"—and Long's clout in Congress, MicroGeneSys had assembled almost all the elements needed for a winning strategy. Only one was lacking: access to the executive branch. The company didn't have to look far for that, since John O'Shaughnessy, onetime consultant for MicroGeneSys and a member of its Advisory Council, was president of Strategic Management Associates—a Washington company specializing in providing contact with executive branch agencies. O'Shaughnessy himself had served from 1983 to 1986 as assistant secretary for management and budget in the Department of Health and Human Services (HHS), the parent organization of NIH. And his experience was complemented by that of his colleague, Donald Clarey, who had served as special assistant to President Reagan.

As the 1992 budget process gathered momentum, O'Shaughnessy and Clarey worked the executive branch on MicroGeneSys's behalf. They let Long "handle Congress," Clarey says, while they "backed him up" by going to "the budget people" who work for the assistant secretary of defense for health affairs. Their contacts, combined with Long's, did the trick: On 16 September, late in the legislative session, the subcommittee on defense appropriations, chaired by Inouye, tacked $20 million on to the military budget to fund a large-scale clinical investigation of one product: gp160. Two days later, on a separate allocations bill, Senators Nunn and Warner introduced an amendment to fund the appropriation.

AIDS activists, lobbyists for competing companies, and other members of Congress protested. In spite of the outcry, the amendment was approved by a joint House-Senate conference on the bill and approved by the full Congress on 6 October. The only chance that the trial will not take place comes from a provision declaring that if the director of NIH, the commissioner of FDA, and the secretary of the Army all agree in writing that the trial should not be held, it will be canceled, with the $20 million appropriation being added to the Army's $50 million AIDS research budget—swelling it by a staggering 40%.

"This kind of a rip-off going on in the defense budget is just outrageous."

–Barry Bloom

As a result of that provision, it isn't yet certain that the huge VaxSyn trial will take place. But it is clear that all those involved in the legislation have strong—and strongly opposed—views of the outcome.

Volvovitz, predictably, couldn't be more pleased over the process or the outcome. Lobbying, he says, is a way of "providing information" to "educate as wide an audience as possible in terms of the clinical results that have been achieved with gp160." The day the defense appropriations bill passed Congress, he issued a press release saying he was "delighted." "In advocating that the funds be used for a Phase III efficacy test for MicroGeneSys's gp160 vaccine, VaxSyn, Congress is recognizing the need to move forward promptly on treatments for AIDS." (Long's law firm said in a statement that they do not comment on matters pertaining to their clients.)

AIDS researchers, on the other hand, are fuming. Says virologist Martin Hirsch of Harvard Medical School: "It's lobbying and pork barreling of the worst sort." Adds David Ho of the Aaron Diamond AIDS Research Center: "This sounds to me politically pretty screwy, morally pretty corrupt, and scientifically slippery." Echoes immunologist Barry Bloom of the Albert Einstein College of Medicine: "This kind of a rip-off going on in the defense budget is just outrageous. The one credibility we should have in science is the process."

To lobbyist Donald Clarey, those cries of anger are the complaints of scientific losers. When told that the legislation rankled NIH and many researchers, Clarey says that's because "they didn't get the $20 million, if you want to know the truth." Clarey's view seems to imply that there are two equally competent groups of scientists competing for the funding and that one is angry simply because it lost out. And, indeed, in introducing his amendment, Nunn said that according to "Army medical experts" the large-scale trial should happen "as soon as possible."

But it has become very difficult to find any scientific experts who will defend the appropriation. Many researchers contacted by *Science* presume Robert Redfield or his colleagues at Walter Reed must have been in support of it. That's a supposition Redfield denies categorically. "Neither I nor any of the Army scientists associated with the HIV research program had anything to do with [the amendment]," says Redfield. "I'm not a proponent of product-specific legislation," says Redfield, who adds that the questions of which AIDS vaccine preparations should be tested and the timing of human trials should be left to researchers.

In addition, both the Army and the Department of Defense have officially told *Science* that they believe a VaxSyn trial now would be premature. Redfield agrees, saying he wants to proceed in a "stepwise" fashion, seeing whether data from the 600-person trial warrant a larger one. So, for the moment, the question of whether any medical experts favor the VaxSyn trial now remains a mystery. But it may not remain mysterious much longer. Bernadine Healy, one of the first to condemn the appropriation, has announced she is convening a blue-ribbon panel to discuss the appropriation and the politicization of AIDS research generally. The panel is tentatively scheduled to hold its first meeting on 29 October.

Healy says she believes the questions here—particularly that of the need for scientists rather than politicians to decide which drugs are tested—are fundamental and go far beyond anger over losing $20 million in AIDS research funding. "To choose drugs because of lobbying...would lead to an erosion of the entire system of clinical research," says Healy. FDA commissioner David Kessler, who has been named to Healy's panel, says he and Healy "speak with one voice" on this issue. And that is a voice that is likely to be heard, loud and clear, when the saga of MicroGeneSys and its lobbying efforts is examined in detail at the first meeting of Bernadine Healy's blue-ribbon panel.

–Jon Cohen