Phillip Berman, Ph.D., '77: Vaccine adventures

By Amos Esty

Grew up: Los Angeles, Calif.

Education: University of California, Berkeley '71 (A.B. in biology); DMS '77 (Ph.D. in biochemistry)

Training: Postdoctoral fellowships at the Salk Institute and the University of California, San Francisco

Mentor at Dartmouth: Henry Harbury, Ph.D., then chair of the Department of Biochemistry

Title: Professor and Jack Baskin Chair, Department of Biomolecular Engineering, University of California, Santa Cruz

Hobbies: Hiking and surfing ("Santa Cruz has the best surf on the West Coast")

The vaccine failed, so Genentech discontinued its HIV vaccine program. But Berman kept working on it.

Time passed slowly for Phillip Berman during the fall of 1989. For years, he had been working on a vaccine against the human immunodeficiency virus (HIV). As 1989 eased into 1990, Berman, a scientist with the biotechnology firm Genentech, was waiting to learn whether a crucial test of a vaccine he'd developed would end in success.

Berman had joined Genentech in 1982, after earning a Ph.D. in biochemistry at DMS and completing two postdoctoral fellowships. One of his first assignments at the company was working on a vaccine against hepatitis B, a project that resulted in a successful vaccine.

By 1984, when Berman began working on HIV, AIDS had become an epidemic. Genentech's location in San Francisco, where AIDS was spreading quickly, made clear the need to develop a vaccine against the virus. He was part of a team that was among the first research groups anywhere to describe the structure of HIV, work that led to the discovery of a protein called gp120 on the virus's surface. That protein allows HIV to enter a type of cell critical to the human immune system—CD4 T cells. Once inside the cell, the virus hijacks the cell's machinery to produce endless copies of itself that infect other cells, eventually depleting the body's supply of CD4 T cells.

Berman used hamster ovary cells to produce gp120 ("gp" stands for glycoprotein, and 120 is the protein's molecular weight), a technique developed during his earlier work on hepatitis B. "Having previous experience with mammalian cell production," he says, "we were the first ones to apply it to HIV to show that you could make antibodies that would kill the virus *in vitro*," or in test tubes.

Armed with that technique, Berman worked to create a vaccine to stimulate the production of antibodies that would block the binding of gp120 to CD4 T cells. In theory, if someone later became exposed to HIV, that person's immune system should be primed to quickly create antibodies to block infection. In 1986, Berman and other researchers tested an early version of the vaccine in four chimpanzees—which, like humans, can be infected with HIV (though chimpanzees don't develop AIDS symptoms). But after vaccination, all four soon tested positive when exposed to HIV. The vaccine had failed.

As a result, Genentech discontinued its HIV vaccine program and assigned Berman to another project. But Berman still believed in the vaccine. He kept working on it when he could, trying to improve the vaccine and devise a better vaccination schedule. Genentech was famous for the antiauthoritarian attitude of its top-notch researchers, so Berman's backdoor approach was not surprising. "It was a new way of doing science," Berman says of Genentech. "There was a lot of freedom . . . to accomplish whatever you could."

Just after New Year's Day in 1989, he had a second chance to test the vaccine in chimpanzees. By that fall, two chimpanzees injected with the gp120 vaccine had completed the full vaccination regimen and had been exposed to HIV. Two other chimpanzees had been treated with a vaccine that targeted a different protein, and a fifth chimpanzee had been injected with a placebo. Within a matter of weeks, the latter three chimpanzees were all infected with the virus. But the two animals treated with the gp120 vaccine remained HIV-free.

Still, it was not until the spring of 1990 that Berman was confident about the effect. "It was phenomenal," Berman says. "We couldn't believe the results." Later that year, he published the findings in *Nature*, and Genentech resuscitated its HIV vaccine program.

The next step was clinical trials in humans. Phase I and II trials proved that the vaccine was safe and that it stimulated the production of antibodies. A phase III trial would find out if it worked as well in humans as in chimpanzees. But getting a phase III trial off the ground proved to be another long and arduous process.

In the early 1990s, Donald Francis, M.D., Ph.D., joined Genentech to help in the push for clinical trials. Francis was a long-time veteran of the Centers for Disease Control and Prevention. Early in the AIDS epidemic, he had been outspoken in his belief that more should be done to stem the spread of the virus. He criticized the Reagan administration and others who, he believed, failed to take the epidemic seriously enough. He joined Genentech because he felt a vaccine was the best solution to HIV, and he calls the development of the gp120 vaccine "brilliant work." Francis was also impressed with Berman's technical skills as a scientist. "He's kind of a classic techie geek," Francis says admiringly. Genentech scientists were known for working long hours and working fast. "Phil was just a classic example of

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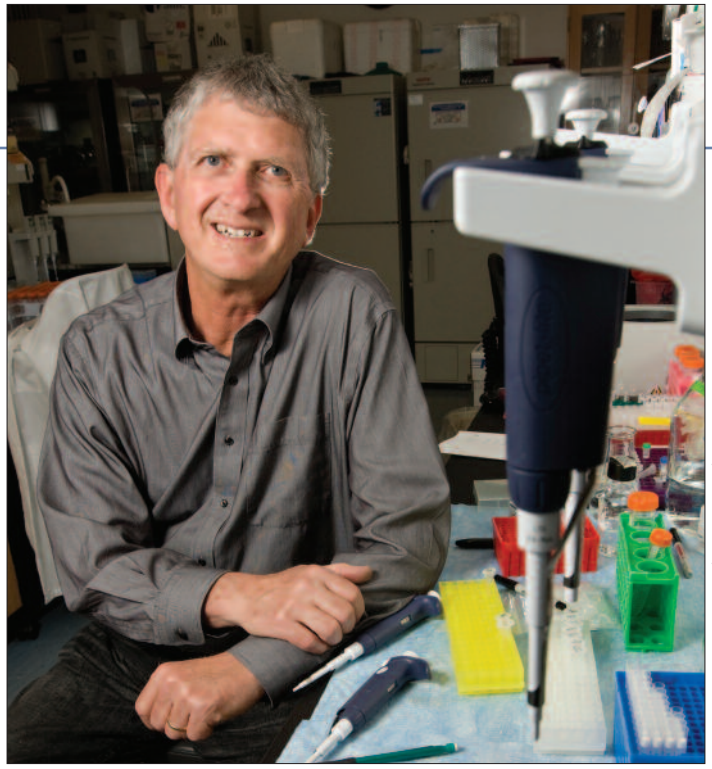
For a WEB EXTRA with more information about the HIV vaccine controversy, see dartmed.dartmouth.edu/f11/we05.



VICKI THOMPSON (SILICON VALLEY/SAN JOSE BUSINESS JOURNAL)

A vaccine developed by DMS alumnus Phillip Berman was one of two used in a 2009 trial that's the only successful human trial so far of vaccination against AIDS.

that," Francis says. "They'd live in the lab and grind away."

But not everyone was as convinced as Berman and Francis that a vaccine was the best way to combat AIDS. When Genentech requested funding from the National Institutes of Health (NIH) to support what would surely be a very expensive trial, some scientists and gay activists spoke out against the proposed trial because it would leave less money to develop treatments against AIDS. Other scientists, however, believed there was much to be learned from a trial, regardless of the results.

In a controversial decision, the NIH decided not to fund the study. And Genentech did not want to foot the bill on its own. But Berman and Francis weren't about to give up. "To keep on doing laboratory studies just wouldn't answer the question of whether this vaccine would work or not," Berman says. "We were the first ones to have a vaccine that had a chance to work." So they created a spin-off company, VaxGen, to do a phase III trial. To Berman, it was an easy choice, because even if the trial was unsuccessful it would produce more insight than anything else then under way. "It was absolutely the right thing to do," he says.

Francis, working with a veteran biotech entrepreneur, raised $27 million for VaxGen, and two trials were launched. One enrolled 5,000 participants, mostly gay men, in the U.S., Canada, and the Netherlands. The other enrolled drug users in Thailand. Both groups were considered at higher than normal risk of acquiring HIV.

After years of hard work, the results were ready in 2003; Berman announced them at a conference in Banff, Canada. The vaccine had induced the production of antibodies in participants—but it had not protected them from infection. "It was a huge disappointment," Berman says. "But I had been working in the pharmaceutical industry long enough to know that that's part of the business."

Berman says there are a number of possible reasons the vaccine didn't work. For one thing, it turned out that the trial subjects were at much higher risk than expected, and repeated exposure to HIV might have overcome any protection the vaccine provided. Another problem, Berman says, is that HIV is very adept at getting around any defenses, in part by rapid genetic mutation.

Still, he believes it was worthwhile to conduct the trial. "There's no question we pushed the field forward," he says. "We moved it from laboratory research to clinical trials. Now no one doubts that you can do clinical trials, and they're manageable, and you can get good data."

And the trial wasn't the end of the line for the gp120 vaccine. Berman has used results from the trial in his current effort to develop a vaccine that will stimulate the production of more effective antibodies. And in 2009, he, like everyone in the HIV field, was surprised to learn the results of another clinical trial—one that made use of VaxGen's vaccine.

A large trial in Thailand, supported by the Thai government and the U.S. military, used a combination of the gp120 vaccine and a second vaccine that had also failed in a clinical trial of its own. The latter vaccine was designed to stimulate the secondary immune system, whereas the gp120 vaccine prompts a response from the innate immune system. This trial enrolled over 16,000 participants, and the combination of vaccines proved about 30% effective.

"I didn't think it would work," Berman says. "I think most people in the field didn't think it would work. It was really a huge shock." But it was very significant, he says. "They've proved that vaccination can prevent HIV infection in people." No one yet knows why the combination vaccine worked when each vaccine failed individually. It's something Berman and others are now trying to figure out.

That's one reason why, in 2006, he moved from industry to academe, becoming chair of biomolecular engineering at the University of California, Santa Cruz. He feels the resources at UCSC will be a great help. "The big new tool in research is bioinformatics and computational biology," he says. He is using that tool to study genetic variation within HIV and how it evades the immune response. In 2009, he received a $3.5-million NIH grant to continue that work.

Berman is also excited to share with a new generation of students what he has learned over the years about drug development. He has a lot to tell them, from scientific hurdles to political and economic realities. He also serves as a model for the importance of moving research forward, even in the face of opposition.

"To me, the most basic principle of the scientific method is you formulate a hypothesis and test it," he says. "And if you're in a situation where you can never test a hypothesis, you're not doing science." ■