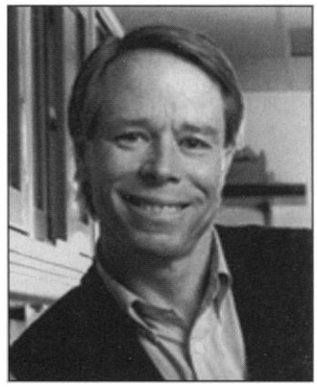
AIDS RESEARCH

Impending AIDS Vaccine Trial Opens Old Wounds

In the early 1980s, virologist Donald Francis, then with the Centers for Disease Control and Prevention in Atlanta, was one of the first to sound the alarm about the AIDS epidemic. Later this year, Francis may score another first: As president of VaxGen, a biotechnology company in South San Francisco, California, Francis hopes this year to launch the first ever full-scale trials of an AIDS vaccine. After years of slow progress in the AIDS vaccine field, that might sound like good news. But VaxGen's plans to begin so-called phase III trials in the United States and Thailand have provoked strong reactions from AIDS researchers, who remain badly split over what kinds of vaccines are likely to work (*Science*, 23 May 1997, p. 1197). And a report in the February issue of the *Journal of Virology*, which casts doubts on whether vaccines like VaxGen's protect against HIV, has fueled the debate.



GENENTECH

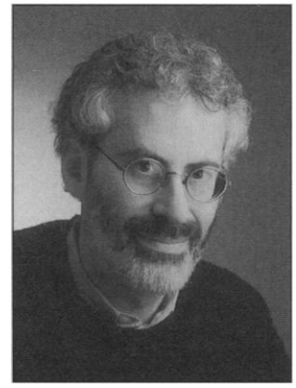
Pushing ahead. AIDS pioneer Francis plans full-scale trials.

VaxGen does not yet have formal approval from U.S. or Thai authorities to proceed with phase III trials, but Francis told *Science* that he expects to get the green light soon. The U.S. Food and Drug Administration (FDA) has approved phase I and II trials—which test for safety and early signs of efficacy—of a modified version of a vaccine that has already gone through toxicity testing, and Thai authorities are expected to give their nod in the coming weeks. Moreover, Francis says, the FDA's vaccine advisory committee has given its blessing to VaxGen's plans to move to phase III once these trials reconfirm the safety of the vaccine, which is made from a genetically engineered version of a protein called gp120 that makes up much of the outer coat of HIV.

The FDA declined to comment on pending clinical trials for confidentiality reasons. But Mary Lou Clements-Mann, a vaccine expert at Johns Hopkins University School of Medicine in Baltimore and a member of the FDA advisory committee, confirmed Francis's account. "The committee felt comfortable with their overall strategy," she says. But this feeling of comfort is not shared by all AIDS researchers. "It is evident that gp120-based vaccines have not yielded antibodies that neutralize most natural strains of HIV," says Nobel laureate David Baltimore, head of a special committee that advises the U.S. government on AIDS vaccines. "This raises serious doubts about the utility of these vaccines." Indeed, disappointing early results from trials of gp120 vaccines led the U.S. National Institute of Allergy and Infectious Diseases (NIAID), which coordinates federally funded AIDS vaccine trials, to decide in June 1994 not to devote its own funds to phase III tests (*Science*, 24 June 1994, p. 1839).

Thus VaxGen, which spun off from the biotechnology giant Genentech in 1995 and in which Genentech still holds a 25% stake, is raising some $20 million in private funds to pay for the trials, which—if they are approved—will involve some 5000 volunteers in the United States and 2500 in Thailand. Francis argues that none of the previous trials with gp120 vaccines have been designed to test their actual efficacy in preventing HIV infection. VaxGen's vaccine, Francis adds, has a proven ability to protect chimpanzees against HIV and to produce strong immune responses in humans. "What is the argument against [phase III trials]?" Francis asks. "If you don't follow the process completely, you may make premature conclusions and stop the progress of vaccine development."

But a study in the current issue of the *Journal of Virology*, led by virologist Steven Wolinsky at Northwestern University Medical School in Chicago, has heightened the concerns of many researchers that the gp120 formulation is unlikely to work. The Wolinsky team—which includes David Ho and John Moore at the Aaron Diamond AIDS Research Center in New York City, Bruce Walker at the Massachusetts General Hospital in Charlestown, and others—focused on 18 volunteers who received gp120 vaccines during an earlier trial and later became infected with HIV. A small number of such "breakthrough" infections should be expected, even with an effective vaccine, but Wolinsky's team could find no significant differences between those who became infected and those who did not. For example, the infected subjects had the same concentrations of anti-HIV antibodies in their blood as uninfected vaccine recipients had, and the amount of virus in their blood was no lower than in unvaccinated HIV-positive patients.



JIM BALLARD

Disappointed. Wolinsky's team found no benefits from vaccine.

Ronald Desrosiers, a vaccine researcher at the New England Regional Primate Research Center in Southborough, Massachusetts, says that "if a vaccine did have at least partial protective efficacy, one would expect noticeable viral load reductions," even in people who became infected. "The bottom line," Wolinsky says, "is that we had neither beneficial nor adverse effects in any of the individuals we studied." While he cautions that the study does not prove that the vaccine is ineffective, Wolinsky concludes that "the results are very disappointing." Anthony Fauci, director of NIAID, agrees. The study "fortifies the decision I made 3 years ago" not to fund gp120 vaccine trials.

But Francis and some other AIDS researchers hotly dispute the Wolinsky conclusions. They cite a study of seven breakthrough patients published last year in the *Journal of Infectious Diseases* by a team led by immunologist Phillip Berman, VaxGen's vice president of research. The Berman team found that all seven subjects were infected by viruses whose gp120 proteins were structurally different from that used in the vaccines. Berman and Francis argue that these results suggest gp120 vaccines could be effective if they include proteins from more than one HIV strain. Hence, the vaccines VaxGen plans to subject to phase III testing contain two types of gp120s: one from a laboratory strain already used in previous tests, and a second that corresponds to currently circulating natural viruses either in the United States or Thailand, depending on where the vaccine is being tested.

Susan Zolla-Pazner, an immunologist at the New York University School of Medicine, says that because the Wolinsky and Berman papers were asking different experimental questions, "I don't think anyone can say who is right and who is wrong." And, she and others argue, the issue will never be resolved until some sort of AIDS vaccine is put to the acid test of a phase III trial. Indeed, the frustration over not knowing what will work and what will not, which is shared by all AIDS vaccine researchers, may eventually tip the scales in favor of VaxGen's trials. Says Clements-Mann: "If we don't move forward to phase III, we will never have a vaccine."

–Michael Balter