AIDS VACCINES

Testing Target Date Looms, but Will the Vaccines Be Ready?

For the past year, the National Institute of Allergy and Infectious Diseases (NIAID), the institute charged with pulling together the federal AIDS vaccine program, has been gearing up for efficacy trials of AIDS vaccines to start at the end of 1993 or, at worst, the beginning of the following year. But, with only a little more than a year to go—a blink of an eye to bureaucrats—NIAID officials are finding it necessary to dampen public expectations. "Nobody knows what the appropriate timetable is for clinical trials," says Sten Vermund, chief of the NIAID AIDS vaccine trials and epidemiology branch.

This backpedaling came through loud and clear at this year's annual AIDS vaccine meeting sponsored by the institute.* It is based on a sobering reality: Even if NIAID does succeed in putting the infrastructure in place for efficacy trials, no candidate vaccine is clearly going to be ready for testing. And that makes some researchers nervous, because they fear that once NIAID is geared up, federal AIDS officials will be forced to start testing, whether good candidate vaccines are ready or not. "It's hard to imagine that a vaccine will be ready [in 18 months]," says the Pasteur Institute's Marc Girard, who presented to the meeting some of the most promising experiments to date showing that chimps can be successfully immunized against challenge with HIV. And NIAID, caught between the pressure to be ready and the caution of scientists who want to know a lot more about AIDS before trials begin, was steering a carefully calibrated middle course: "It's not going to be a blind, 'We'll do it no matter what,' " NIAID director Anthony Fauci told *Science*. "It is a blind, 'We'll be prepared, no matter what.'"

But NIAID is discovering that there are still a lot of problems to be solved even in preparing for the trials. Take the question of who to enroll. To find out whether a vaccine works, you need to test it in a population that is likely to be exposed to HIV. In the United States, that means homosexual men (especially those considered unlikely to practice safe sex) or intravenous drug users who share needles. While cohorts of both groups have been studied in small trials of various strategies for slowing the spread of the disease, some seriously question whether researchers will be able to recruit from among these populations the thousands of volunteers needed for large-scale trials. AIDS activist groups, who are now taking part in the vaccine planning process, also worry that insurance companies will discriminate against trial participants. "If you think the insurance companies aren't going to be leery of someone in a high-risk seronegative trial, you're crazy," says Brenda Lein of the San Francisco-based Project Inform. Lein and others also argue that well-educated subjects will refuse to participate unless the trial vaccine has a high probability of being effective.

Even assuming those problems can be solved, there's a practical problem with trials in the United States: Too few people are being infected with HIV to make large efficacy trials practical. D. A. Henderson, deputy director of the White House Office of Science and Technology Policy, who directed the World Health Organization's (WHO) smallpox eradication program, says it will be necessary to turn to the developing countries where the incidence of infection is higher. But that presents new problems, some of them stemming from developing world sensitivities to the medical establishment. WHO has established four vaccine evaluation centers in Rwanda, Uganda, Brazil, and Thailand. Edward Katomgole-Mbidde, director of the Uganda Cancer Institute in Kampala, told last week's conference that U.S. researchers must "avoid the attitude of, 'I know it all, and I have the money.' " In addition, developing countries have asserted that if a vaccine is tested on their population and it works, then vaccine developers have a moral obligation to provide the vaccine to that country at a cost they can afford. Since first-generation vaccines are bound to be expensive, no one is sure how that can happen. But many believe it must happen. "[Vaccines] may be the only measure for much of the world," says Henderson.

These concerns have now become much more than just theoretical worries, because NIAID plans to award contracts within the next few months for an international HIV vaccine efficacy trials network that will store data and reagents, study the viral strains that predominate in geographical regions, recruit subjects, and train personnel to conduct the trials.

Once the infrastructure for a vaccine trial is put in place, researchers and policy makers will then have to confront a thorny scientific problem: which candidate vaccines to put to the test. About a dozen different vaccine candidates are now in Phase I safety trials around the world—eight of which, involving more than 400 human subjects, are in tests sponsored by NIAID (*see table*). The current crop of vaccines is primarily made from genetically engineered versions of the outer coat protein of HIV. While several candidate vaccines have stimulated production of antibodies against the virus, including some of the "neutralizing antibodies" thought to be involved in preventing infection, the significance of this immune reaction is not clear.

Indeed, some researchers have even questioned whether eliciting antibodies is the right way to go. Some have argued that the other arm of the immune system—cell-mediated immunity, which depends heavily on the key white blood cells called T-cells—is more important. None of the engineered coat protein vaccines has shown much effect on T-cells, however. Some experimental vaccines, which start with a pox virus vac-

NIAID SPONSORED SAFETY TRIALS

PRODUCT	HIV STRAIN	MANUFACTURER
Recombinant Subunit—cell expression system (adjuvant)		
gp-160—insect virus (alum)	LAI	MicroGeneSys
gp-160—mammalian (alum and DOC)	LAI	Immuno AG
env-2,3-yeast (gp120) (MF59/MTP-PE)	SF-2	Biocine/Chiron
gp-120—mammalian (alum)	LAI	Genentech
gp-120—mammalian (alum)	MN	Genentech**
gp-120—mammalian (MF59±MTP-PE)	SF-2	Biocine/Chiron
Combinations		
vaccinia-HIV env gp-160—insect	LAI LAI	Britol-Myers Squibb MicroGeneSys
vaccinia-HIV env plus different subunit vaccines	LAI	Britol-Myers Squibb** various manufacturers

**Trials just under way

*Fifth Annual Meeting of the National Cooperative Vaccine Development Groups for AIDS. Westfields International Conference Center, Chantilly, Virginia, 30 August to 3 September.

cine to stimulate the immune system (like the Bristol-Myers Squibb vac/env vaccine) and then follow up with a coat protein vaccine, do generate some T-cell responses, but is that enough? No one knows.

In most areas of medicine, these issues would be resolved with an animal model, but for AIDS, there isn't one that precisely mimics the human disease state. Recent work with pigtail macaques, and with hybrids of the simian AIDS virus, SIV, and HIV, suggests these might ultimately fill that void. But work with these systems is only just getting under way (*Science*, 19 June, p. 1630 & 14 July, p. 478). Other animal models have provided some answers, but not many. For example, several labs have now shown that a vaccinated chimp can be protected from infection when both virus and vaccine have been made from the same HIV strain. So far, however, no one has done the "heterologous" challenge, with vaccine made from one strain challenged with another.

Some researchers are arguing, however, that it's not necessary to answer all these questions before starting efficacy trials. Donald Burke of the Walter Reed Army Institute for Research says he would be prepared to move a vaccine into efficacy trials so long as it was safe, capable of inducing some kind of immune response, and able to demonstrate protection in at least some animal model. Burke is quite upbeat in part because some candidate vaccines—including one made by Genentech and based on the HIV coat protein known as gp120 from the LAI strain—already meets those minimal criteria. In fact, Burke is widely reported to be planning a trial of just such a vaccine among Thai soldiers.

Once large-scale trials do finally get under way, researchers will then have to grapple with a new set of issues: How do you decide when a vaccine has proved itself good enough to be released to the public? Some researchers argue that it isn't necessary to wait to develop an almost-perfect vaccine, because one that is far less than optimal would go a long way toward stemming the AIDS epidemic. NIAID's Vermund, for example, presented results of a simple model showing that even a 60% effective vaccine could save thousands of lives. And that, he argues, is realistic: "It's unlikely that the first efficacy trial will be a grand slam [success]."

The public message coming out of last week's meeting was, therefore, don't expect a magic bullet. Indeed, researchers were eager to get across the idea that it's going to be tough even to produce a less than ideal vaccine. "Efficacy testing is going to be a long and difficult exercise," says Jose Esparza of the WHO Global Program on AIDS. And, whatever their approaches, that was a message that all involved at last week's meeting could agree on.

–Joseph Palca

BIOTECHNOLOGY

Lithuanian Biochemist Builds Enzyme Empire

VILNIUS—If you like to browse through laboratory catalogs looking for the latest equipment and reagents, you might have come across a surprising entry in the most recent offering from New England Biolabs. There, on page 46, you'll find a whole set of new restriction enzymes—the enzymes that chop up DNA and are a vital part of every molecular biologist's toolbox. The surprise: The enzymes are all labeled "Made in Lithuania."

Lithuania? How could a small Baltic state, independent for less than a year, compete with hot shot Western biotech companies in supplying enzymes to the United States? Ask Rich Roberts, the former Cold Spring Harbor Laboratory molecular biologist who is now director of research for New England Biolabs and he will answer in a word: "Janulaitis." Vidas Janulaitis (pronounced Yanoo-LITEis), he will tell you, is professor of biochemistry at the University of Vilnius, head of the Institute of Applied Enzymology—and creator of one of the world's largest collections of restriction enzymes, with more than 100 on offer. He also appears to be the first successful biotechnology entrepreneur to emerge from the former Soviet Union—and New England Biolabs' competitors are well aware of his talents. "Formidable," is how Jeremy Walker of Amersham International describes Janulaitis' contribution to the number of new restriction enzymes marketed each year.

STEVEN DICKMAN

Beating the system. Against all the odds, Vidas Janulaitis made Fermentas a world leader.

The interesting question, of course, is how Janulaitis managed to rise above the chaos that has accompanied the dismantlement of the Soviet Union to become one of the world's top suppliers of new restriction enzymes—especially given that the venture capitalists who rushed off to make deals with Moscow labs in the early days of perestroika mostly came back disappointed. To find out, *Science* visited Janulaitis earlier this year at his institute on the outskirts of the 17th-century city of Vilnius.

As you approach the institute, it is hard to believe that you're about to meet a prime mover in the world of restriction enzymes. The road out of Vilnius passes clusters of old wooden farm huts with sagging roofs; hay wagons pulled by mules creak along the dirt roads; and in the surrounding potato fields, farmers trudge along behind horse and plow. Janulaitis, a stocky man who looks more like a Chicago Bears linebacker than a biochemist, sits down in his laboratory, lights the first of a chain of strong Russian cigarettes, and gives a rapid-fire discourse on the difficulties of dealing with the Soviet bureaucracy.

Contrary to what most Westerners think, he explains, the Soviet Union invested immense amounts in biotechnology—including in his own solid redbrick institute. In 1975, the Ministry of Microbiological Industry in Moscow built and staffed four huge institutes—two in or near Moscow, one in Novosibirsk, and the Vilnius institute. All were given huge budgets and massive numbers of researchers to make enzymes. The institute in Vilnius, which was one of the smallest, was allotted a total staff of 730.

The problem was that the research administrators had no idea how to create products. The Soviet government, says Janulaitis, poured "thousands and thousands of people and billions and billions of rubles" into biotechnology and wound up, at best, with "some pretty good basic research but virtually no worthwhile industry." Individual scientists were not to blame, he adds quickly. "Even if the scientists had been willing to come up with what was really needed, they would have had a nearly impossible time persuading industry to produce the new products—the communist system simply provided no incentives for such innovative production."

Janulaitis, who traces his own Lithuanian ancestry back to one of the original tribes that have lived on this territory since at least the 8th century, says he believed Moscow's orders to develop and produce bulk industrial enzymes would give Lithuania little advantage: The work was easy and could be done anywhere. Instead, as he rose through the ranks in the institute, becoming director in