CLINICAL TRIALS

FIRST HURDLE IN AIDS VACCINE CLEARED

NEW YORK—The first Food and Drug Administration (FDA)-authorized experimental AIDS vaccine is now in Phase I clinical trials. This toxicity/immunogenicity study, conducted by the National Institute of Allergy and Infectious Diseases (NIAID), tests the recombinant subunit vaccine "VaxSyn HIV-1" developed by scientists at MicroGeneSys (West Haven, CT) in conjunction with NIAID. The vaccine consists of a recombinant HIV (human immunodeficiency virus) envelope protein precursor, gp160 (produced in insect cells), along with the adjuvant alum.

The Phase I trials, under the supervision of NIAID deputy clinical director Clifford Lane, are slated to involve 60 healthy male homosexual volunteers, and 21 controls. (Of the six control subjects with no history of risk behavior, three will receive the vaccine and three the control immunogen.) Elaine Baldwin from NIAID's office of communications says that the ongoing trials still don't have the full complement of volunteers. One problem is that once the volunteers learn the details of the protocol, many decide against participating. Also, some are apparently not confident that the documentation they will receive stating that they were *vaccinated* rather than infected with the AIDS virus will be sufficient to prevent future discrimination. Finally, there is a potential risk that a participant may not be able to mount an immune response to a different AIDS vaccine.

Anthony Fauci, NIAID's director, says, "At this stage it is too early to predict whether we will use this product [VaxSyn HIV-1] in widespread efficacy trials, but it is a very important first step and we are quite optimistic."

So are many of the research scientists at competing concerns. "It is encouraging that someone has gotten off the mark," exclaims Paul Luciw (Department of Medical Pathology, University of California, Davis). And Kathelyn S. Steimer, a member of Chiron's (Emeryville, CA) AIDS vaccine team, agrees that the first real hurdle in AIDS vaccine development was to actually get an antigen into people and see what happens. Because infected chimpanzees do not go on to develop AIDS, Fauci says, the data on vaccines' efficacy in chimps may not be transferrable to humans, anyway.

VaxSyn HIV-1 (cloned into a baculovirus expression vector) is able to stimulate the production of high levels of neutralizing antibodies in animal tests—mice, guinea pigs, rabbits, rhesus monkeys, and chimpanzees. The antibodies have been effective in protecting human lymphoid cell lines from infection by the virus.

In developing the vaccine, MicroGeneSys scientists Mark A. Cochran and Gale A. Smith decided to concentrate on HIV's envelope precursor protein gp160 rather than the outer envelope protein (gp120) because, they say, gp160 elicits a better immunological response. According to Luciw, some version of the envelope protein—whether under development now or still to come—will eventually be the vaccine: it is the most logical target.

Other players in the game, however, have concentrated on gp120 solely, or in combination with gp41 (the transmembrane portion). Repligen (Cambridge, MA), for instance, uses nonglycosylated COOH-terminal-half fragments of gp120. When these subunit fragments, made in an *Escherichia coli* expression system, are injected into animals, they are also able to stimulate the production of neutralizing antibodies (see Putney et al. *Science* **234:**1392, 1986). These results indicate that glycosylation is not necessary to induce neutralizing antibodies. Putney says that his group inoculated chimpanzees with the prototype vaccine about a year ago; to date, those chimps have not been challenged with virus. There is no point in doing that, according to Putney, until the results of parallel experiments conducted at the National Cancer Institute—in which chimpanzees inoculated with gp120 isolated from virally infected cells were not protected from challenge with virus—are analyzed. Putney's group wants to ensure an effective challenge.

And Chiron's AIDS vaccine group has produced various domains of the envelope gene product in *Saccharomyces cerevisiae* (see Barr et al. *Vaccine* **2:**90, 1987). Antibodies raised in rabbits to a recombinant polypeptide representing the majority of the gp120 coding region reacted with the gp120 of native HIV. Chiron's Steimer says that the nonglycosylated gp120 polypeptide can elicit neutralizing antibodies in experimental animals. These antibodies cross-neutralize HIV viruses that appear by sequence comparisons to be closely related (such as isolated from the United States); there is no cross neutralization with more distant isolates, such as those from Zaire.

Genentech (South San Francisco, CA) has taken the mammalian cell route to producing a gp120 subunit vaccine. Although the company is characteristically tight-lipped about experimental results, corporate communications officer Debra Bannister says the chimpanzee studies have been completed, and the company is hoping to start testing in humans; no time-line has been established.

Most research scientists agree that, if an envelope-type vaccine is to work at all against the majority of the strains an individual would likely encounter, it will probably be a cocktail of gp120 subunits from different isolates of the virus. As Luciw says, it now appears that there are at least four serotypes of the virus. If we can classify these viruses, he adds, then we may be able to determine how many envelope genes to include for an effective vaccine. But the bottom line, as echoed by Genentech's Laurence Lasky, is this: "We have zero idea of what protection means with this virus." **—Jennifer Van Brunt**

There are obviously many more companies and institutions involved in developing AIDS vaccines than mentioned here. These include: Viral Technology, Immune Response, Applied bioTechnology, Oncogen, and Cambridge BioScience.

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