



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Attention Writers and Editors:

The National Institute of Allergy and Infectious Diseases (NIAID) is beginning Phase I clinical trials of an experimental AIDS vaccine. To explain the details of the study we have prepared the enclosed Questions and Answers.

We have available black and white 8 x 10 glossy photographs of the principal NIAID scientists involved in the study: Dr. Anthony S. Fauci, Director of NIAID; Dr. H. Clifford Lane, principal investigator of the study; and Dr. Malcolm A. Martin and Dr. Thomas Folks, who conducted some of the basic research involved in developing the vaccine and assessing immune responses to the product in experimental animals.

We also have available a new 15 minute "B roll" on 3/4" videotape showing laboratory procedures conducted by the above scientists and clinic scenes with a prospective study volunteer.

To request copies of these materials, please call Karen Leighty at (301) 496-5717.

For additional information about the study, and to request interviews with Dr. Fauci, please call me or Elaine Baldwin or Sandra Hecker at (301) 496-5717.

Sincerely,

Patricia Randall
Chief, Office of Communications
National Institute of Allergy and
Infectious Diseases

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOR RELEASE
Tuesday, August 18, 1987
12 noon, EDT

PUBLIC HEALTH SERVICE
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Dr. Robert E. Windom, assistant secretary for health, today announced that the National Institute of Allergy and Infectious Diseases is beginning tests in human volunteers of an experimental vaccine against acquired immunodeficiency syndrome (AIDS). This is the first clinical study of an AIDS vaccine to be approved by the Food and Drug Administration and to be conducted in the United States.

The vaccine is manufactured by MicroGeneSys, Inc., a biopharmaceutical firm in West Haven, Conn. It consists of the envelope protein derived from the genetic material of the human immunodeficiency virus, or HIV, the cause of AIDS.

HIV attacks and destroys key cells of the immune system, thus allowing usually controllable infections to invade the body and cause debilitating and life-threatening illnesses. More than 40,000 persons in the United States have been diagnosed with AIDS since 1981, and nearly 60 percent of them have died. Scientists estimate that over 1 million Americans are infected with the virus. There is no cure at present.

"Preventing the spread of infection with HIV in the United States and worldwide is of paramount importance," Dr. Windom said in announcing the vaccine study. "Although education is a powerful public health tool for limiting transmission of AIDS, in order to halt the global AIDS epidemic we must have an effective vaccine."

Dr. Anthony S. Fauci, NIAID director, said that the study will be carried out at the Clinical Center, National Institutes of Health, Bethesda, Md., by Dr. H. Clifford Lane, deputy clinical director of NIAID and a senior investigator in NIAID's laboratory of immunoregulation.

The NIAID researchers will study the vaccine in 75 healthy, HIV-antibody negative homosexual males whose current and recent sexual behavior can be described as "low risk." Dr. Fauci explained that volunteers must have had no possible exposure to HIV during the previous three months and they must agree to observe safe sexual practices while participating in the study.

FDA Commissioner Frank E. Young said he was pleased that the study was starting. "This is the first vaccine to reach the stage where we can
(more)

approve it for studies in humans, and we are optimistic about this approach." But he cautioned, "the public should realize that this is a first step--and many steps are still to be carried out before we have a vaccine, whether it is this one or another, that is safe and effective enough for general use."

Dr. Fauci emphasized that the study is designed to assess the vaccine's safety and ability to produce an immune response, and to determine proper dosage.

"The vaccine consists of purified protein from HIV and not the virus itself," Dr. Fauci stressed. "Therefore, no one can get AIDS from the vaccine, and we expect no adverse effects beyond those that sometimes occur from other immunizations, such as some redness and soreness at the site of the injection.

"At this stage, we are not attempting to determine whether the vaccine can actually protect people from HIV infection," Dr. Fauci said. "If we obtain good results from this study, we will expand our research. At this point, of course, it is too early to predict whether this vaccine will undergo wide-spread efficacy trials, but we are quite hopeful.

"This study is a natural outgrowth of the overall goal of NIAID's laboratory of immunoregulation, which is to understand the immunopathogenesis of AIDS," Dr. Fauci added. "NIAID scientists have been working closely with scientists at MicroGeneSys in developing the product and in assessing the results of animal studies using the vaccine."

Dr. Malcolm A. Martin, chief of the laboratory of molecular microbiology, NIAID, furnished the company with an HIV clone that he and his colleagues constructed from a North American HIV isolate, NY5, and a European isolate, LAV. The vaccine was developed using techniques similar to those employed in the manufacture of other "recombinant" vaccines.

To make the vaccine, MicroGeneSys scientists inserted the modified gene for the entire HIV envelope precursor protein, gp160, into the genome of a baculovirus, a virus that infects such insects as moths and butterflies. The recombinant virus is grown in an insect cell tissue culture system, which produces the gp160.

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Background

THIS INFORMATION MAY NOT BE RELEASED BEFORE 6:00 A.M. WED., AUG.19, 1987

TOXICITY/IMMUNOGENICITY STUDY OF HIV-ENVELOPE PROTEIN (gp160) IN HUMANS

Q1. What is the product that is being used in this study?

A. A protein derived from genetic material from the human immunodeficiency virus (HIV), or AIDS virus, and produced using recombinant technology.

Q2. What company manufactures this product?

A. MicroGeneSys, Inc., of West Haven, Connecticut.

Q3. Who holds or will hold the patent on this vaccine?

A. The company, which will pay royalties to the Government for its technical contributions.

Q4. What role did NIAID scientists play in its development?

A. NIAID scientists had a major role in the research. Dr. Malcolm A. Martin, Chief of the Laboratory of Molecular Microbiology, NIAID, and his colleagues constructed an infectious molecular clone of HIV from a North American HIV isolate, NY5, and a European isolate, LAV. This clone was given to MicroGeneSys where the envelope gene was isolated and modified for placement into a biological system to produce the gene's product, a modified HIV envelope protein precursor, or modified gp160. The company inoculated animals with this protein, and Dr. Thomas Folks in NIAID's Laboratory of Immunoregulation (LIR) and his colleagues worked with MicroGeneSys scientists in assessing the animals' antibody responses. Most recently, NIAID scientists facilitated toxicity and immunogenicity studies in chimpanzees (required by the FDA prior to human trials of the vaccine).

Q5. Who is the principal investigator for this study, and was he involved in the basic research leading to the development of this vaccine?

A. Dr. H. Clifford Lane, senior investigator in NIAID's Laboratory of Immunoregulation (LIR), who has particular expertise in studies of immune responses to the AIDS virus. He has been working closely with scientists at MicroGeneSys and provided assessments of the animal studies.

Q6. Why isn't this vaccine being tested in NIAID's Vaccine Evaluation Units?

A. This study is a natural outgrowth of the overall goals of the LIR, which has concentrated on the immunopathogenesis of AIDS. In addition, there are numerous precedents for conducting Phase 1 studies of vaccines in the intramural program when NIAID scientists have been involved in the development

of the vaccine. Dr. Lane has maintained close working relationships with Dr. John La Montagne, Director of the AIDS Program, and with Dr. John Nutter, Chief of the Prevention Branch of the AIDS Program, in planning for Phase 2 and 3 testing of this vaccine if it shows promise in Phase 1 trials.

Q7. Why did you choose this product?

A. It produced high titers of neutralizing antibodies in animals, especially in guinea pigs.

Q8. How is the vaccine made?

A. The technique for making the vaccine is similar to that employed in making other "recombinant" vaccines. In this case, a modified gene for the HIV envelope precursor protein, gp160, is inserted into the genome of a baculovirus, which serves as a "vector" or carrier. The recombinant baculovirus is grown in an insect cell tissue culture system. The insect cells "express" or produce the modified gp160 protein. This protein is the vaccine. The baculovirus itself is NOT injected into the volunteer, nor is the complete HIV.

Q. 9. Are the volunteers at any risk of getting AIDS from the vaccine?

A. No; because only the portion of the HIV that codes for the envelope, gp160, is present in the insect cells used to produce the vaccine, no potentially infectious viral RNA or complete viral particles can be produced.

Q10. What does the baculovirus normally infect?

A. Baculovirus is a virus that infects insects of the Lepidoptera order, which includes moths and butterflies. Baculovirus is present naturally on many vegetables, such as lettuce, that are commonly eaten by humans. During the past 10 years, baculoviruses have been employed widely as "organic" insecticides against a wide variety of insect pests. Ingestion of baculovirus does not cause infection or disease in humans, and the virus does not reproduce in mammalian cells.

Q11. How pure is this vaccine?

A. The FDA requires that this product contain at least 70 percent gp160, and we now have a much purer product. The primary contaminant is baculovirus protein. There are no detectable insect cell proteins in the product.

Q12. How is the vaccine purified?

A. By chromatography, which separates gp160 protein from insect proteins.

Q13. What are the risks of putting insect virus proteins into humans?

A. We believe they are minimal. There is a theoretical risk that the vaccine could sensitize a person to insect protein and cause an allergic reaction upon subsequent exposure to the same protein. Many common vaccines are grown in materials containing proteins, such as eggs, to which sensitization can occur in some people.

Q14. Why don't you wait until the product can be further purified before you inoculate humans?

A. The urgency of the problem mandated human trials as soon as a product that elicited a strong immune response in animals. This product does that.

Q15. Does the vaccine contain any adjuvants?

A. Yes, the gp160 protein is adsorbed to alum, an adjuvant commonly used in vaccines.

Q16. What kinds of side effects do you anticipate?

A. Pain, redness, swelling at the site of the injection, perhaps low grade fever, particularly when the booster injection is given. There is a rare possibility of a more severe systemic reaction. As a precaution, the first 3 people in each group to be inoculated will be observed in the clinic so that appropriate emergency intervention is immediately available in the unlikely case it is needed (i. e., they will have a running I.V. during the time of immunization).

Q17. What are the results of animal studies using this vaccine?

A. The gp160 preparation was tested in small animals (mice, guinea pigs, rabbits and Rhesus monkeys) and immune responses were highly encouraging. The Rhesus monkeys received up to 10 times the dose proposed for humans, a proportionately larger dose since humans are much larger than the monkeys, with no significant toxicity. At doses as high as 500 micrograms per animal, no serious adverse effect was noted.

Q18. Were chimpanzees studied?

A. At the request of the FDA, two chimpanzees were given doses of 40 and 80 micrograms, respectively, with the same doses given as boosters. The dosages are in the same range as those planned for humans.

Q19. How was the dosage determined for animals? Are animals usually given a proportionately higher dose of vaccine than are humans?

A. Yes, they are. The Rhesus monkeys received 10 times the human dose, (proportionately much more than 10 times when considering dose per weight). The FDA specified the dosage for chimps.

Q20. Did the chimpanzees develop neutralizing antibodies?

A. Yes, the vaccine elicited neutralizing antibodies as well as good levels of circulating antibodies that are specific for the HIV envelope. The vaccine also elicited a very good T cell response in the chimps.

Q21. What is the significance of the presence of neutralizing antibodies? Do they have a protective function?

A. Classically, neutralizing antibodies are an important component of the immune response to viral infection. That may or may not be true in AIDS. We are monitoring neutralizing antibody response as well as cell-mediated immunity.

Q22. What is the rationale for using gp160, the envelope precursor protein, rather than the gp120 outer envelope protein?

A. A variety of constructs were examined. This particular molecule, a modified gp160, appeared to be the most immunogenic, and elicits a better immunological response than does gp120.

Q23. Did you challenge the chimps with HIV to see if the vaccine protected against infection before you tried the vaccine in humans?

A. The AIDS virus appears to produce rather strikingly different responses in chimps and in humans. One important difference is that infected chimps do not develop AIDS. There is disagreement among researchers about whether protection against infection in chimps can be correlated with protection in humans. For these reasons, and because of the urgency of the situation, we decided to proceed.

Q24. What is keyhole limpet hemocyanin, and why is it used as the control immunogen? Why not use baculovirus without the HIV protein?

A. Keyhole limpet hemocyanin (KLH) is the oxygen-carrying protein of a shellfish (keyhole limpet). NIAID has extensive experience using KLH as an experimental antigen, having used it to evaluate immune responses of approximately 1000 persons.

Q25. Will the participants in this study be able to receive a vaccine in the future that has more potential for protection?

A. It is conceivable that the ability of a participant to mount an immune response to a different AIDS vaccine could be impaired. This risk is stated in the consent form.

Q26. Who will receive the vaccine?

A. Healthy, seronegative, male homosexual volunteers whose recent and current sexual behavior can be described as "low risk." Participants should have had no possible exposure to HIV during the previous 3 months. If a participant is in a sexual relationship, the partner must be known to be HIV antibody-negative. Participants must agree to observe safe sexual practices.

Q27. What are the reasons for choosing this population?

A. A number of previous studies have shown that as a group, male homosexuals have an immunological profile that differs significantly from the general population. We believe it is essential to determine what the immune responses to the vaccine will be in persons in this group, because they represent the population in the United States at greatest risk of being infected with HIV, and are ultimately the most likely group in the United States to receive a vaccine.

Q28. How many persons will receive the vaccine and in what doses?

A. The protocol specifies that 60 volunteers will receive the vaccine, 15 in each dose regimen (of 10, 20, 40, and 80 micrograms). Patient groups will be added sequentially, beginning with the lowest regimen, and Dr. Lane estimates that a new group will be added every 30 days. For each dose regimen, after 4 weeks, 5 persons will receive a booster identical to the primary dose, 5 will receive one-half dose as a booster, and 5 will receive no booster. In addition, the FDA has specified that 3 persons with no history of risk behaviors will be immunized at the highest dose regimen, to compare their immune responses to those of the study population. The control group, composed of 18 volunteers, including 3 with no history of risk behaviors, will receive KLH only. In other words, a total of 81 persons will participate in this phase of the study.

Q29. How did you determine the number of participants for the Phase I trial of this vaccine?

A. We included enough individuals in each dose regimen group to compensate for anticipated variability in immune response in the study population.

Q30. How will volunteers be recruited to participate in this study? How can individuals volunteer to participate?

A. Dr. Lane has contacted physicians and agencies who will aid in recruiting volunteers. Individuals who wish to volunteer should contact Margaret Megill, R. N., at (301) 496-7196.

Q31. After vaccination are the vaccinees expected to test positive for HIV on standard ELISA and Western blot HIV tests?

A. Yes. However, with the Western blot we should be able to distinguish between persons who are actually infected with HIV and uninfected persons who have received the vaccine. Western blots for the vaccine group would show no antibody response to the HIV core proteins.

Q32. Would the p24 antigen test distinguish between HIV infection and immunization with this vaccine?

A. The p24 test, which detects a HIV core protein, is not a definitive indicator of infection. In many people there is a significant period of time between early infection and full-blown disease when p24 cannot be detected.

Q33. What documentation will vaccinees receive to show that they were vaccinated and not infected with HIV?

A. Each participant will receive a letter describing the study, affixed to a copy of the participant's Western blot. The Western blot of a vaccinee will show bands for HIV proteins gp160, gp120, and gp41. A notary seal will overlap the Western blot strip. If the participant were exposed to HIV itself later, a new test would look very different.

Q34. What steps will be taken to keep this documentation from becoming a black market item?

A. We believe the above procedure will be sufficient. If there are questions, participants may wish to refer questioners to Dr. Lane.

Q35. Has this issue of documentation come up previously in medicine or research, and if so, how was it handled?

A. As far as we know, this situation is unprecedented.

Q36. Is there a chance that the volunteers could lose their jobs or insurance coverage, or be denied entry to certain countries with border restrictions for HIV+ persons, as a result of having participated in the study?

A. Although we believe that our procedures will protect participants from such events, the consent form does point out that discrimination based on antibody positivity to HIV is a possible hazard.

Q37. Precisely how will potential vaccinees be informed of potential risks and other issues? Do you plan to counsel them? Will they be quizzed on their knowledge of the protocol and on potential risks?

A. We have established procedures to ensure that participants are fully informed every step of the way. At the first visit, at which time blood is drawn for testing, a study nurse will meet with the volunteer and explain the protocol. The volunteer is given a copy of the protocol. If the volunteer's antibody tests and viral cultures are HIV negative, he returns to give his medical history and have a physical examination, and a second ELISA and Western blot. The volunteer will see the clinic physician and the attending physician on this visit. A senior staff member (Dr. Lane, or Dr. Henry Masur, or Dr. Joseph Kovacs) will meet with the volunteer to go over the consent form in detail. Following a detailed physical and psychological assessment by the clinical staff, the volunteer is required to take a "post-education" quiz.

Q38. Are you cutting corners in the FDA process because of political pressure to begin vaccine trials?

A. We are not cutting corners, and in fact the FDA and our own Institutional Review Board (IRB) have been especially scrupulous in this regard. The pressure we feel is in response to the gravity of a worldwide public health emergency.

Q39. What are the steps in the FDA process for testing potential vaccines, and what is the purpose of each?

A. Vaccine trials are somewhat different from drug trials, in that not until Phase 3 do we look for efficacy or test the vaccine against a placebo. Phase 1 and 2 trials determine toxicity and immunogenicity and establish the optimum dosage.

Q40. How long is Phase 1 expected to last?

A. We should have sufficient toxicity data within 6 months. In order to establish the best dose we plan to add more patients at increasing doses until we see no additional immune response.

Q41. How will you decide when to proceed to studies in the Vaccine Evaluation Units?

A. When we have established safety, immunogenicity, and optimum dosage in this population, we can proceed to the Vaccine Evaluation Units. That could take up to one year.

Q42. How many people would be tested in Phase 2 and how long would that phase take?

A. Between 100 and 200 persons, for one year.

Q43. Can you estimate when Phase 3 trials will start? What population would you choose for such a large trial?

A. A Phase 3 study of an AIDS vaccine would require a large population who are at high risk of becoming infected.

Q44. What are you doing to ensure that the participants do not assume that they are protected from possible HIV infection and thus engage in unsafe sexual practices?

A. The study physicians and nurses will educate the participants on this and other issues.

Q45. Are other vaccines in the pipeline?

A. Questions about other vaccines should be directed to the FDA.

Q46. What are you doing to develop animal models that can be used for testing vaccines?

A. We have a number of projects, some being carried out through contracts, to develop animal models in mice, cats, monkeys and chimpanzees.

Prepared by

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