DUKE TEAM SEEKS NOVEL VACCINE STRATEGY FOR HIV

DURHAM, N.C. – Researchers have noticed a curious phenomenon in sub-Saharan Africa: many female prostitutes who come in contact with men infected with HIV do not themselves become ill.

Further study of these women shows that the mucous lining their vaginas contains HIV-specific secretory immunoglobulin A (IgA) antibodies that may be able to stop the virus and keep it from entering the bloodstream. It is possible these women have become “naturally” immunized against future HIV infections.

A research team led by Duke University Medical Center is hoping to use this knowledge to create a vaccine that could stimulate similar responses in the uninfected. Additionally, they plan to employ a novel delivery system that can be easily used in underdeveloped nations.

Project leader Dr. Bart Haynes, chairman of the department of medicine at Duke, believes that the team will develop a vaccine that can be delivered nasally and would stimulate immune responses in the user at both the mucosal and systemic levels.

“I think we will be able to start testing our next generation of candidate vaccines in humans in a couple of years,” said Haynes -- a time-span that seems to be just around corner considering he has spent 15 years studying the virus. “Making a vaccine has turned out to be more difficult than we ever believed. The virus is more complex than we thought and is very cunning in its ability to subvert our immune systems. However, there will be a vaccine.”

To prove the merit of this approach, the National Institutes of Health is supporting the research in the amount of $5.5 million over the next five years.

According to a recent report by the U.S. surgeon general, of the estimated 33.4 million people worldwide who are infected with HIV, 22.5 million live in sub-Saharan Africa, 6.7 million in South and Southeast Asia, and 1.4 million in Latin America. By comparison, there are about 665,000 infected in the United States

More than 2.4 million have died worldwide in the past year.

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In the under-developed nations, the main route of virus transmission is sexual, the researchers said. That’s where the observations about the prostitutes come in. In the vaginal mucosal lining of these women, researchers have detected secretory IgA (S-IgA) that specifically binds to HIV. S-IgA is a type of antibody that is produced and secreted into mucosal secretions to protect the body against bacteria and viruses that attack the body mucosal tissues.

“These women were probably exposed to a low dose of the virus, then developed a local infection that was cleared up by the body’s defenses, inducing local S-IgA mucosal immunity,” explained Duke immunologist and co-investigator Herman Staats, Ph.D. “Over time, it seems, despite multiple exposures to the virus, these women don’t become infected.

“With HIV, traditional injected vaccines haven’t worked well,” Staats said. “A vaccine targeted to mucosal linings, however, may be able to stimulate an immune response that protects people by blocking the ability of HIV to infect at mucosal tissues, thereby preventing a full-blown infection.”

Researchers have known that if a mucosal surface at one part of the body is challenged -- for example, the lining of the nose -- any S-IgA immune response that is generated may also appear in other mucosal surfaces, such as the mouth, upper respiratory tract, GI tract or reproductive organs.

“One benefit of a nasally introduced vaccine is that it is non-invasive, so presumably it would be more feasible to use on a widespread basis throughout the world, especially in the more under-developed areas,” Staats said.

The task ahead -- and it is a daunting one, the researchers say -- is coming up with a potent method for stimulating the production of immune system cells that recognize HIV as an invader and destroy it.

In the Duke project, the researchers hope to develop a vaccine with a one-two punch. One would stimulate immunity in the form of S-IgA in the mucous to act as a first line of defense, while the second would come in the form of another type of immune response known as IgG antibodies. IgG antibodies, which are formed to defend the body against specific invaders, circulate throughout the bloodstream to neutralize any virus that gets through the first line of defense.

“This combination is important because either one alone is unlikely to be able to completely eliminate the virus,” said David Montefiori, Ph.D., Duke co-investigator who is focusing on neutralizing antibodies. “There are some areas, or compartments, in the body where the virus hides that the immune system can’t penetrate.

“With this in mind, the trick is to produce an immune response that constantly puts pressure on the virus and never lets it gain strength,” Montefiori said.

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In order for an antibody to kill, or neutralize a virus, it must first “latch” onto the invader. What makes HIV such a formidable foe for researchers is that since it is constantly mutating, finding a site on the surface that is the same for all variants of the virus is difficult.

The Duke researchers are focusing on a protein called gp120 that resides on the surface of the virus and is essential for viral infectivity.

When gp120 comes into contact with and latches onto its cellular receptor protein, CD4, the virus can enter the target cell and initiate a new round of infection. Neutralizing antibodies can block the ability of gp120 to attach to the target cells, thereby preventing the virus from gaining entry.

The Duke candidate vaccine is a mixture of synthetic peptides taken from the gp120 regions of four significantly different strains of HIV. This vaccine, developed by Haynes and colleagues, has been shown to be strong enough to stimulate neutralizing antibodies, and since it is based on synthetic peptides, there are no fears of the vaccine actually causing infection.

In general, the vaccines produced to date have not been sufficiently effective in generating strong and lasting immune responses.

To “boost” the ability of their vaccine to induce an immune response, the Duke researchers plan to add something -- called an adjuvant -- to increase the vaccine’s effectiveness and life-span. By interacting with the vaccine, the adjuvant serves to strengthen the antigenicity of the vaccine.

The researchers are evaluating a variety of proteins known as cytokines, as well as mutant cholera toxin, to act as adjuvants for their nasal vaccines.

“With peptide vaccines, an adjuvant is required to get potent, long-lived antibody and cellular responses to HIV,” Staats said.

Once candidate vaccines and adjuvants have been developed, they will first be tested in animals. Later this year, researchers hope to begin testing the vaccine in small mammals, and if all goes well, into non-human primates by next year before moving rapidly on to humans, Haynes said.

These experiments will be handled by project co-investigator Dr. Norman Letvin, an immunologist and virologist at Harvard Medical School’s Beth Israel Deaconess Medical Center in Boston.

“Our role in this project is to use our non-human primate models to explore novel vaccine strategies for preventing HIV infection,” Letvin said. “Any successes in these monkey studies should rapidly translate into success in humans. The power of the models we have developed is enormous.
“The virus (SIV) that we use to infect monkeys is a very close relative of HIV – it can infect monkeys and cause AIDS,” he said. “We can look at new vaccines in a monkey and can measure antibodies and T cell responses, but the challenge remains in seeing how effective the vaccine is in blunting infection.”

One major limitation of the SIV model is that the outer membrane of SIV is different from that of HIV, so if the goal is creating a vaccine based on a surface protein, the SIV model has limitations. So the researchers developed a SHIV animal model by combining human and monkey AIDS viruses to create a new virus that expresses a HIV envelope on the ‘backbone’ of SIV. Both the SIV and SHIV models will be used in the current project.

“HIV is making us look at vaccines in a totally new light,” Letvin said. “In making vaccines to prevent polio or measles, we didn’t have to understand the biology of the virus – we just made vaccines and they worked. We’ve had to go back to the basics for HIV and try to find out what is happening in HIV-infected humans that might result in the immunologic control of this virus.”

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