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RESEARCH & TRIALS

◆ Merck to begin larger trial with adenovirus vector

At the AIDS Vaccine 04 Conference in Lausanne, Switzerland, Merck & Co. announced that it would begin a large-scale trial of its MRK-Ad5 vaccine candidate by the end of this year. The vaccine candidate is an adenovirus type 5 vector (see ***Primer***) that carries some HIV genes from a clade B virus. Vaccine researchers consider this candidate to be one of the most promising. In early clinical trials, the vaccine stimulated a strong cell-mediated immune response to HIV. This will be a Phase II "proof of concept" trial to determine whether one arm of the immune response, cell-mediated immunity, can either prevent HIV infection or lessen disease in vaccinated people who are later exposed to HIV through high-risk behavior.

A limitation of the vaccine candidate is that many people have already been naturally infected with the vector virus, adenovirus type 5. This virus causes a form of the common cold and many people have pre-existing immune responses to it, including antibodies. So people who have a strong antibody response and are given this vaccine candidate may have a decreased immune response to the HIV genes carried by the vector. To avoid this potential problem MRK-Ad5 will be tested in areas where people have low levels of antibodies to the adenovirus type 5 vector.

Researchers are already working to overcome the problem of pre-existing immunity. At Lausanne, Dan Barouch of Harvard Medical School reported on mouse studies using adenovirus types 11 and 35 that carry some simian immunodeficiency virus (SIV) genes. Scientists do not think that these two types of adenovirus will be affected as much by preexisting immunity because types 11 and 35 infect humans less commonly and don't cause such strong antibody responses. The mice showed strong immune responses to this vaccine candidate.

◆ Disappointing results from DNA/MVA AIDS vaccine candidates

At the Lausanne meeting, Walter Jaoko of the Kenya AIDS Vaccine Initiative (KAVI) reported disappointing early results from clinical trials testing two AIDS vaccine candidates: DNA.HIVA and MVA.HIVA. The trial was conducted in a partnership between IAVI, the University of Oxford, UK Medical Research Council, the University of Nairobi, KAVI and the Uganda Virus Research Institute. Both vaccines contain an HIV subtype A DNA carrying parts of the HIV genetic material. The DNA vaccine delivers the HIV DNA via a plasmid, a small circle of genetic material from bacteria. The MVA vaccine uses modified vaccinia Ankara as a vector (see ***Primer***). The data presented was from 205 volunteers taking part in trials in Kenya, Uganda, and the UK. The vaccine candidates raised immune responses in only about a quarter of the people vaccinated and these responses were not long-lasting.

"The data fell short of our expectations," said Emilio Emini of IAVI. Small clinical trials that have already been started to test DNA.HIVA and MVA.HIVA will continue for the next six to nine months in order to learn as much as possible about the candidates. "Unless the data significantly change, we're not going to be developing those candidates further," said Emini.

GLOBAL NEWS

◆ HIV and tuberculosis in Africa must be treated together

The World Health Organization and UNAIDS have issued a statement after a meeting of international health experts in Addis Ababa, Ethiopia, calling for wider access to tuberculosis (TB) treatment that includes testing for HIV and antiretroviral (ARV) therapy for HIV infection when needed. This could save the lives of 500,000 Africans living with HIV every year, the statement says.

People infected with HIV can be treated for TB just as successfully as people who are not infected with HIV. Currently, national programs in Africa to treat TB are treating less than half of HIV-infected people who also have TB. Also, few TB patients are offered HIV testing and even fewer receive ARV treatment. "If we jointly tackle TB and HIV, we can be much more effective in controlling both diseases," said Peter Piot, Executive Director of UNAIDS. Nelson Mandela has also recently called for improved coordination between HIV and TB programs. At the International AIDS Conference in Bangkok in July he said "we are calling on the world to recognize that we can't fight AIDS unless we do much more to fight TB as well."

SPOTLIGHT

◆ Bangkok report

Epidemic becomes more diverse

An important theme of July's International AIDS Conference in Bangkok was the genetic diversity of HIV infection. Populations in some parts of the world show a very high level of co-infection. Co-infection is when an individual is infected with more than one genetic form of HIV; this can mean infection with two or even three different genetic versions of HIV. This can occur when a person is originally infected with more than one genetic form of HIV. It also can occur when a person who is already infected with HIV becomes infected with a new viral strain, which is called "superinfection." These genetically different viruses can recombine within an infected person, meaning that the two viruses can swap parts of their genetic material to form a new virus (it is still HIV, but slightly altered). This leads to what are called "unique recombinant forms," or URFs, within a single person. These could be spread to other people, leading to "circulating recombinant forms" (CRFs). A recombinant form is an HIV that has genetic characteristics of two or more different subtypes.

HIV-1 is divided into three distinct genetic groups, M, N, and O. The M group is responsible for almost all of the HIV infections in the world. It originally came from the simian immunodeficiency virus (SIV) that is found in chimpanzees. Scientists think that HIV-1 jumped into humans from chimpanzees several different times, most likely through eating "bushmeat." This is when chimpanzees are slaughtered for food, and it is thought that the virus was passed from chimpanzees to humans either through a bite or a cut during butchering. Since these first events, over time additional genetic diversity has developed within each group. These regional subgroups are called clades or genetic subtypes.

In the past, it was thought to be sufficient to look at small parts of the HIV genetic material to be able to tell what subtype the virus was and where it was likely to have come from. But with increasing amounts of recombination seen, it is going to be necessary to do more extensive genetic studies. For example, Francine McCutchan and colleagues from the Henry M. Jackson Foundation found that in a group of high-risk, HIV-infected women in Tanzania, subtype C was the major single subtype found among women infected with one HIV subtype only. But 43% of the women carried recombinant forms of HIV. Furthermore, some of the women were infected with two or more different, unmixed subtypes at the same time. McCutchan and colleagues found that the subtypes and recombinant forms identified in the co-infected women differed at different points in time. Although the women remained co-infected, sometimes one form of the virus was found in study participants and other times other forms were found. "People who are co-infected are the source of many, many recombinant forms that presumably they can pass along," says McCutchan, "and they're continuously generated in those people over time."

But recombinant forms of HIV are not new. Marcia Kalish and colleagues at the US Centers for Disease Control and Prevention (CDC), the National Institute of Health (NIH) and Project SIDA in Kinshasa, analyzed blood samples collected in western Zaire in the mid-1980s, during the early years of the epidemic. They found that the samples also have recombinant forms of HIV in them. Samples collected in 1986 in Burkina Faso in west Africa had two recombinant forms of HIV and less genetic diversity. This suggests that in 1986, the Burkina Faso epidemic was more recent in origin than the one in western Zaire. Older epidemics will likely have more recombinants than newer ones because the viruses circulating in that population have had more opportunity to infect the same person and then recombine.

One of the major difficulties in obtaining a complete picture of the HIV epidemic is tracking the movement of the various viral types and subtypes throughout infected populations. Furthermore, a large amount of genetic research is required to get a full picture of where these viral subtypes are prevalent. This type of research requires much more intensive sampling and sequencing of the genetic material of the various HIV subtypes found. Researchers also need to know which subtypes are more likely to combine to create recombinants. All of this will help scientists understand the HIV epidemic so that they will be better able to develop vaccines to prevent it.

Recombinant forms may be a problem in developing an AIDS vaccine since many vaccine candidates in development are designed against only one subtype of HIV. If many recombinant forms are found in infected people, then protecting against one subtype may not be effective. Researchers are hoping that an immune response against one HIV subtype may also protect against another HIV subtype, so having a clearer picture of the subtypes and recombinants that are circulating in populations is important.

The presence of these recombinant subtypes makes it even more important that health care workers and governments stress HIV prevention and treatment, especially for those people who are most at risk of becoming infected.

Improving DNA vaccines

There were several interesting presentations that focused on vaccines at the International AIDS Conference in Bangkok.

For a number of years, vaccine researchers have discussed the potential of naked DNA vaccines. These vaccines would contain a piece of the HIV genetic material in the form of DNA. But there are several hurdles for naked DNA vaccines. First, the DNA vaccine must find its way into the vaccinated person's cells. To do that they have to get through the outer covering of the cell, the cell membrane. Although viruses are able to do this when they attach to receptors on the host cell's membrane, pieces of DNA cannot do this easily. So researchers are looking at new ways to deliver the naked DNA into the cell. Once this DNA is delivered to human cells this genetic material is converted to some of the HIV proteins. It is hoped that these HIV proteins will then cause an immune response that can act against the whole virus if a person is exposed later through high-risk behavior.

Researchers from Yiming Shao's group at China's National Center for AIDS/STD Control and Prevention had some success in delivering DNA into a cell by adding genetic material from a monkey virus called SV40 to portions of naked HIV DNA. They tested the naked DNA in mice and got some encouraging results; the vaccine stimulated an immune response against HIV. The scientists' next step is to test this potential vaccine in humans to see if it has the same effect as it does in mice.

A group of researchers led by George Pavlakis at the US National Cancer Institute is studying naked DNA that carries two HIV genes and an **adjuvant**. Researchers hope that this kind of vaccine could be used to prevent HIV transmission or to lower the amount of HIV in people who are already infected. Some preliminary studies show that these vaccines did not prevent SIV infection in monkeys that were later given SIV. However, the vaccines were successful in keeping the amount of circulating SIV low in these monkeys after they became infected. It is hoped that such a vaccine could possibly protect a person who is already infected with HIV from becoming sick with AIDS. The scientists are continuing their studies of this type of vaccine.

Two live-attenuated vaccinia AIDS vaccine candidates

Two vaccines based on vaccinia viruses were able to stimulate immune responses in Phase I studies in humans, but the responses were not as strong as had been hoped. (Phase I trials enroll small numbers of people who are at low risk for contracting HIV, mainly to test the safety of a vaccine candidate. For more information on trial design see *Primer*, August 2003).

Guiseppe Pantaleo and colleagues from the EuroVacc consortium reported on a Phase I trial of a NYVAC vector vaccine. This vaccine carries proteins from four different genes from a subtype C HIV. NYVAC is an altered vaccinia virus, related to the virus that is used in smallpox vaccine. It is highly weakened or "attenuated" and is not infectious in humans (see *Primer*, this issue). Nearly half the trial participants showed responses to one of the HIV proteins. Responses to two of the other HIV proteins were less common, and there were no responses to the fourth protein. EuroVacc is also looking at using other vectors, such as modified vaccinia Ankara (MVA), with the same proteins as used with NYVAC.

Researchers from the German company, Bavarian Nordic, gave early data on their Phase I trial of an MVA vector that carries one of the HIV proteins. The immune response directed against the MVA vector itself was good, with **T cells** responding specifically to the vector. But response to the HIV protein was not as impressive. Studies are continuing.

adjuvant: A substance that increases an immune response but is not specific. Adjuvants are used in many vaccines.

T cells: A type of immune cell (white blood cell) called a T lymphocyte. Immunogens activate T cells in what is called a cell-mediated immune response.

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IAVI is a global organization working to speed the development and distribution of preventive AIDS vaccines—the world's best hope for ending the AIDS epidemic. IAVI focuses on four areas: mobilizing support through advocacy and education, accelerating scientific progress, encouraging industrial participation in AIDS vaccine development and assuring global access.

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WHY USE VIRAL VECTORS FOR AIDS VACCINES?

Traditionally, most vaccines for diseases other than HIV/AIDS have used weakened versions of the pathogens (viruses and bacteria) that would normally cause the disease. Over 200 years ago, the first vaccine ever discovered was to protect against smallpox. A virus that causes a skin disease in cows was given to people to protect them from the related human virus that causes smallpox. The success of this vaccine led people, about 100 years later, to find ways to weaken the disease-causing pathogens. Often this is done by growing the virus for a long time in artificial conditions in tissue culture until the virus mutates—its genetic material changes—so that this "live–attenuated" (weakened) virus is safe and it protects against disease. The Sabin oral polio vaccine and vaccines against measles, mumps, rubella (German measles), chickenpox, and yellow fever, among others, are made in this way. Because they are still quite similar to the disease-causing (pathogenic) virus these vaccines cause a very strong immune response and often give lifelong protection against the disease. Other viruses, such as hepatitis A virus, are simply killed and used as vaccines.

New approaches needed for HIV

HIV mutates very rapidly, changing its genetic structure even within one infected individual. So it is not practical to make a live-attenuated AIDS vaccine that could grow since it might mutate to become pathogenic and then cause disease in the vaccinated person. A killed AIDS vaccine has been considered, but the practical problem of proving that the HIV is completely inactivated (dead) and the failure of killed vaccines to protect monkeys against simian immunodeficiency virus (SIV, the monkey equivalent of HIV) have led scientists to look for better and safer ways of making an AIDS vaccine.

PRIMER
UNDERSTANDING
viral VECTORS

Viral vectors as delivery systems

Most of the more promising AIDS vaccine candidates currently being developed and tested use viral vectors. A vector is another virus that is not harmful and acts as the delivery system to carry HIV antigens to the immune system. Scientists design a vector to carry only a small part of the HIV genetic material so that there is no way it can cause HIV infection. Once inside the body's cells, this genetic material is converted to protein. The small piece of HIV protein is called an "immunogen" because it causes an immune response.

Researchers are trying to develop a vaccine so that when the immune system sees the HIV immunogen it responds just as it does to any foreign substance. It is hoped that T and B cells, which are part of the immune system, will respond strongly to the immunogen and some of these cells will then survive for many years (see *Primers*, February and March 2004). The aim is to get the immune system to recognize the HIV proteins and prepare long-lived memory cells that will "remember" the HIV proteins and act against the whole virus if a person later becomes exposed naturally through high-risk behavior.

Different viral vectors

Scientists have been developing a number of different viruses as vectors for vaccines. The different vectors all have their own advantages and disadvantages.

Several viral vectors belong to the poxvirus family, relatives of vaccinia (the smallpox vaccine). Some members of this family are safe because they cannot replicate (grow) in humans. Among the poxviruses are modified vaccinia Ankara (MVA), which is weakened vaccinia virus. Scientists have studied MVA as a vector for many years and candidate MVA vector vaccines are in clinical trials. These trials are still ongoing but unfortunately the MVA vaccines have not produced very strong immune responses so far. Other poxvirus vectors in testing include canarypox (made from a vaccine for birds) and fowlpox.

Another viral vector that is being tested in human clinical trials is adenovirus type 5 (Ad5), which is related to the virus that causes some forms of the common cold. The Ad5 vector is modified so that it cannot grow. The current Ad5 vaccine candidate induces strong cell-mediated immunity (see *Primer*, March 2004). A "proof of concept" Phase II trial is about to begin that will test whether cell-mediated immunity can either prevent infection or lessen disease if vaccinated people are later exposed to HIV through high-risk behavior.

Other viral vector AIDS vaccines in clinical trials include adeno-associated viruses and alphaviruses. Adeno-associated virus is not an adenovirus but is often found in adenovirus infections. The alphaviruses being developed as vaccine vectors include weakened forms of three viruses named VEE, Sindbis and SFV. The VEE vector is currently being tested in clinical trials.

Combinations

Sometimes a viral vector vaccine may be used in a two-step "prime boost" strategy. Usually a small portion of HIV genetic material (in the form of a DNA vaccine) is given first to "prime" the immune system, followed by a viral vector vaccine "boost." The hope is that the "prime" inoculation will focus the immune response better against the HIV immunogen rather than the proteins that make up the viral vector. Some scientists have used the same immunogen carried by two different viral vectors, one to prime and the other to boost at a later time.

The use of viral vectors is a promising method for developing an effective AIDS vaccine that is safe and effective, but more clinical trials will be needed before the ideal vector or combination is identified and the full potential of this approach is shown.