HIV Provides Tools for Gene Therapy

The potential of gene therapy as a treatment for AIDS received a boost on two continents this week. In the United States, experts advising the National Institutes of Health (NIH) gave the nod to two preliminary trials involving the transfer of genes into AIDS patients. Meanwhile, in Berlin, at the Ninth International Conference on AIDS, other scientists described progress in their efforts to treat AIDS and other diseases by harnessing HIV's ability to infect nondividing cells.

Two of 13 gene therapy protocols approved by the NIH Recombinant DNA Advisory Committee target HIV infection. One uses genes to boost the immune response, while the second "is really an antiviral strategy," says Gary J. Nabel of the University of Michigan Medical Center in Ann Arbor.

The first protocol will assess the safety of transferring DNA that will cause the recipients' cells to make HIV proteins—in particular, a viral envelope protein. These proteins should help activate the body's immune response and slow the progression of disease, says Steven J. Mento of Viagene, Inc., in San Diego. For the study, Jeffrey E. Galpin of the University of Southern California in Los Angeles and Dennis A. Casciato at the University of California, Los Angeles, will inject a disabled mouse virus once a month for three months into five people infected with HIV who are not sick. The mouse virus contains the genes for the HIV proteins. Five more people will get injections that lack this virus and the genes.

The researchers will then monitor the number of killer T cells, a kind of immune system cell, in each volunteer but will not know which patients received the genes until the study is finished. If the transferred genes increase the number of T cells without causing severe side effects or other safety problems, five additional participants will receive a higher dose of the genes.

The second gene therapy trial will involve a dozen AIDS patients now receiving the anti-HIV agent AZT (zidovudine). Nabel and his colleagues will separate and grow T cells from each patient's blood. The researchers will genetically alter some cells to produce a mutated form of an HIV protein called rev. This aberrant protein inhibits viral replication and should prolong the life of altered cells, Nabel explains. Other cells will receive an inactivated form of the same gene, so they will make no rev protein. The scientists will then return the cells to each participant and compare the survival of the two groups of cells to assess rev's protective effects.

Neither Nabel nor other scientists developing anti-AIDS gene therapy expect this approach to cure the disease. "But it could be a valuable tool," says Nabel. "It gives us an independent way of attacking the disease."

Most gene therapists transfer genes using disabled mouse retroviruses. However, these viruses work only in actively dividing cells, explains Mario Stevenson, a virologist at the University of Nebraska Medical Center in Omaha. At that time, the cell's nuclear membrane breaks down, so the virus' genetic material can join the cell's own DNA.

But HIV sneaks through the intact nuclear membrane of cells that are not dividing, using the cells' energy to do so, reports Michael Bukrinsky of the Picower Institute for Medical Research in Manhassett, N.Y. While working with Stevenson in Nebraska, Bukrinsky and his colleagues found that one HIV protein contains a five-amino-acid sequence that enables it to bind to a chaperone protein inside the cells it infects. At the Berlin meeting, Bukrinsky described how that chaperone then actively transports the guts of the virus into a nucleus.

Knowing that amino acid sequence helps pave the way for creating new gene transporters, says Michael Emerman, a virologist at the Fred Hutchinson Cancer Research Center in Seattle. He and his colleagues are now trying to splice the gene that specifies this sequence into the genetic material of mouse viruses used in gene therapy. "We can then use existing [transfer] technology and have it work in nondividing cells," says Stevenson.

They have yet to figure out how much HIV genetic material they need to insert and how to add it without disrupting the mouse virus' genome. But once they do, they hope the new hybrid virus will surpass existing gene transfer mechanisms. "Ours would be able to target more cells," says Emerman.

"The use of gene therapy to deal with AIDS will accelerate the state of the art to the point where gene therapy will be much more easily applied to other diseases," Stevenson predicts. —*E. Pennisi*

Some lasting memories emerge at age 2

Sigmund Freud asserted in 1916 that people generally forget the first few years of life. In experiments conducted since then, adults have placed their earliest memories at around 3 ½ years of age.

But recall for particular kinds of events may extend back to 2 years of age, according to a report in the June JOURNAL OF EXPERIMENTAL PSYCHOLOGY: GENERAL.

"Going to the hospital or the birth of a new sibling are memorable events even when they occur at age 2," conclude JoNell Adair Usher and Ulric Neisser, both psychologists at Emory University in Atlanta. "Other events, even those as important as a move or a death in the family, are not recalled in adulthood unless they occur somewhat later."

These early memories prove relatively accurate, contend Usher and Neisser. Ironically, repeated exposure to family stories and photographs concerning such an experience may worsen memory of the actual event, the psychologists add.

The researchers studied 222 college students, each of whom experienced one of four events at age 1, 2, 3, 4, or 5. The events were the birth of a sibling, being hospitalized, the death of a family member, and a family move.

Participants answered questions — such as when and where a student found out that his or her mother was having a baby — and cited related information sources, such as family stories. The mothers of 53 students reviewed their children's answers and rated them as largely accurate.

About 60 percent of the volunteers who were 2 years old at the time of a sibling birth or a hospitalization answered three or more questions about those events, as did more than three-quarters of those who were at least 3 years old. But only a few of those who were 1 year old at the time of a sibling birth or a hospitalization answered at least three of the questions.

In contrast, only around 10 percent of the students who were 2 years old at the time of a family member's death or a family move answered more than three questions about these occurrences. This proportion reached 80 percent for those who were 5 years old, but fell to zero for those who were 1 year old.

Volunteers who had been 3 years old or younger recalled less if they had access to family stories or photographs, perhaps because this information replaced their few memories of the actual event, the researchers suggest.

Brain mechanisms that handle personal memories may not reach maturity until after age 4, Usher and Neisser note. But by age 2, events that prove especially meaningful to a child may make a mark on memory, they argue. —*B. Bower*