Human AIDS vaccines: Mice offer shortcut

Using a novel strain of mice, scientists may learn within the next few weeks whether humans inoculated with the first U.S.-tested AIDS vaccines can indeed resist infection with the AIDS virus (HIV). If the mouse assay works, it may cut years off the time required to get evidence of AIDS-vaccine efficacy in humans, the researchers say.

Scientists currently are conducting U.S. clinical trials of two AIDS vaccines, using uninfected men at high risk of acquiring the disease. Some have responded by producing antibodies, but researchers don't know whether these antibodies can fight off an actual infection. And because AIDS develops so slowly in humans, investigators have anticipated a three-to five-year wait for efficacy data — even if some of the men acquire the infection soon after vaccination.

Donald E. Mosier, an immunologist at the Medical Biology Institute in La Jolla, Calif., says he now hopes to gain evidence of vaccine efficacy long before that by enlisting the help of hu-SCID mice — a strain he and his colleagues engineered to contain human immune systems (SN: 9/24/88, p.198). Previous work has shown that the mice can become infected with HIV, but unlike humans they develop symptoms within weeks after infection.

Mosier says he has taken blood from men inoculated with either of the U.S. experimental vaccines and transfused it into several hu-SCID mice. Six weeks ago, his team challenged these mice with doses of HIV. By watching for signs of disease over the next four weeks, the scientists should get a good indication of the vaccines' protective value, Mosier said in New Orleans this week at the annual meeting of the American Association for the Advancement of Science.

AIDS researchers express a growing belief that vaccine development may ultimately prove more important than drug treatment in stemming the global epidemic. The new emphasis builds upon promising vaccine studies in monkeys (SN: 12/9/89, p.372) and the recognition that most people with AIDS — both in the United States and abroad — are too poor to afford AIDS drugs. "Unless we come up with a vaccine, the future of this epidemic worldwide is extremely grim," says William Haseltine of the Dana-Farber Cancer Institute in Boston.

Mosier reports that his team's work with the hu-SCID mice has already identified experimental AIDS drugs that appear more potent than zidovudine (AZT), the only AIDS drug now licensed in the United States. The group has also provided some hu-SCID mice with blood and immune cells from HIV-infected human newborns to create an animal model for pediatric AIDS. And with researchers at the National Institutes of Health, Mosier

has created a gene-altered hu-SCID mouse that secretes constant supplies of an experimental AIDS drug called soluble CD4 (SN: 2/17/90, p.101) into its blood-stream. Some scientists anticipate a future in which altered human cells will produce constant supplies of CD4 in people infected with HIV.

Among other AIDS developments discussed at this week's meeting:

• Haseltine described ongoing work aimed at removing the genetic material from HIV to create an "eviscerated" version of the virus. He wants to fill the viral shell with an HIV-killing toxin, in hopes that the shell will serve as a Trojan horse capable of finding and killing white blood cells infected with real viruses.

 Norman L. Letvin of the Harvard Medical School in Boston dampened the enthusiasm some have expressed about the prospects of using soluble CD4 to deliver toxins to HIV-infected cells. He exposed cultured, HIV-infected human lymphocytes to soluble CD4 molecules bound to a powerful, bacterially produced toxin. The combo killed many infected cells, Letvin says, but it apparently left some HIV reservoirs intact. Once the researchers discontinued the treatment. HIV began to multiply again. Although CD4-bound toxins may someday prove useful in conjunction with other approaches, he concludes, "I'm not very optimistic" about its value alone. -R. Weiss

Plants under pressure: The touch that stunts

Plants feel — a fact recognized in the 1970s when scientists showed that many forms of touch affect plant growth. Now, researchers have isolated specific plant genes that "turn on" in response to pressure cues such as wind, rain and human touch.

Plants respond to changes in the environment, but unlike people, they can't run for shelter. Instead, they must adapt by changing their own development. For example, coastal trees buffeted by powerful winds and heavy rains assume a bent-over posture as they grow, which leaves them shorter and sturdier than more protected inland trees. In the laboratory, touching a plant's leaves can elicit the same growth changes as wind and rain.

In indoor experiments measuring the effects of environmental stimuli on the growth of *Arabidopsis*, a member of the mustard family, researchers at Stanford University found that pressure stimuli activated five genes. Moreover, plants touched twice daily by the researchers did not grow as tall as untouched plants, says Ronald Davis, who reports the work with Janet Braam in the Feb. 9 Cell.

Plants seem to sense touch and translate that information into increased gene expression, which ultimately alters their development, Davis says.

The researchers detected gene expression by measuring the amounts of messenger RNA (mRNA) in plant cells. Thirty minutes after spraying plants with water, they found that mRNA levels had increased 10 to 100 percent over those in unsprayed plants.

But the gene activation did not stem from any special property of water, the team found. The same genes switched on just as readily when the researchers touched leaves, cut them with a scissors or simulated blowing wind with a hair dryer. Plants receiving no direct stimulation showed no increase in mRNA, Davis says. Nor did genes turn on in plants exposed only to music, increased humid-

ity or a change of location.

To determine whether three weeks of human touch would affect growth patterns, the researchers measured the lengths of the stems and stalks of untouched plants and compared them with plants touched twice daily. They calibrated their measurements from photographs of the plants to avoid inadvertently turning on the touch-activated genes. They found that the stalks of untouched plants reached an average length of 41 centimeters, compared with 18 cm in touched plants.

Although scientists have yet to demonstrate a mechanism by which touch alters plant growth, the Stanford group suggests one, based on its discovery that three of the touch-activated genes code for calmodulin or related proteins. Scientists know that calmodulin, a receptor within cells, responds to environmental signals by binding calcium - a key cellular communicator. When a plant reponds to direct stimulation, calcium levels increase inside cells. And when enzymes act on calcium-saturated calmodulin receptors, a cascade of cellular events ensues. One such event might be the activation and regulation of the touch-activated genes, the Stanford researchers propose. In effect, calmodulin may turn on the very genes that encode it, Davis hypothesizes.

Calmodulin receptors also exist in human brains, where they are important in responding to sensory stimuli. Davis speculates that plants and people may detect environmental changes through similar sensory pathways. "It may be a very ancient conserved mechanism that evolved before animals and plants diverged during evolution," he suggests.

He also speculates that calmodulin plays a role in rearranging plant-cell structure. The rearrangement may be required for expanding cell diameter and inhibiting cell elongation, resulting in shorter plants, Davis says. — C. Decker

FEBRUARY 24, 1990 117