High-tech gene therapy to target HIV

Molecular biologists have introduced another weapon to the growing arsenal of gene-therapy firepower against AIDS.

This new approach enables them to insert a gene for a ribozyme – a double-duty piece of RNA that both recognizes specific stretches of genetic material and acts as molecular scissors to cut those stretches in specific places – into cells of people infected with HIV, the virus leading to AIDS, says Flossie Wong-Staal of the University of California, San Diego. She and her colleagues plan to use a ribozyme to chop up HIV's genetic material.

Last week, experts advising the National Institutes of Health gave her group permission to test this approach in six patients. The NIH Recombinant DNA Advisory Committee (RAC) also approved a second anti-AIDS protocol, bringing to six the number of preliminary gene-therapy trials against AIDS it has reviewed (SN: 6/12/93, p.372). Both groups require Food and Drug Administration approval to proceed.

Wong-Staal's group will take a small number of the T-cells infiltrated by HIV from the blood of each study participant. Some cells will receive genetic material containing the gene for the ribozyme; other cells will get the same DNA, but without the gene for these molecular scissors, says Wong-Staal. The scientists will then grow millions of both groups of cells before putting them back into the person who donated them. They will then monitor how long the two groups of cells last in the body.

In laboratory tests, ribozymes greatly reduce viral replication in the genetically altered cells. Ribozymes do this by preventing the invading virus from incorporating its genome into the cell's DNA or, if incorporation has already occurred, by halting production of new viral genes. "There's very little viral expression," says Wong-Staal. The researchers hope that the T-cells with ribozymes will survive longer than other cells and eventually help reconstitute the body's defenses.

"It represents a novel and interesting use of a hairpin ribozyme sequence," comments RAC member Stephen E. Straus of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. "I think this is a creative protocol."

"I think the time is very appropriate for taking [ribozymes] to this next step," adds Nava Sarver, an AIDS researcher at NIAID. "[The study] could be instrumental in helping this group and others to proceed."

These sophisticated genetic manipulations will probably not slow AIDS in this study's participants, cautions Eric M. Poeschla, one of Wong-Staal's collaborators. "The number of cells used is too small," he says. This anti-AIDS strategy requires that a patient either receive cells periodically or receive a bone-marrow transplant of genetically altered cells that would become a perpetual source of cells with the ribozyme.

The second anti-AIDS approach approved by RAC last week revises an earlier study undertaken by Philip D. Greenberg and Stanley R. Riddell at the Fred Hutchinson Cancer Research Center in Seattle. By removing and sorting through immune-system cells called CD8 T-cells from AIDS patients, they plan to single out and then in the lab greatly boost the number of such cells that recognize HIV. When returned to the patient, these billion extra cells should help the body stem HIV infection by recognizing and destroying any cells containing the virus, Greenberg says.

The researchers add to these cells a "suicide" gene, so called because this gene makes cells containing it susceptible to a medication called ganciclovir. The gene allows researchers to track the genetically modified cells more easily in the body and to destroy those cells if necessary. Also, the techniques used to add this suicide gene may teach researchers how to insert other genes that might make the cells even more effective at routing out HIV.

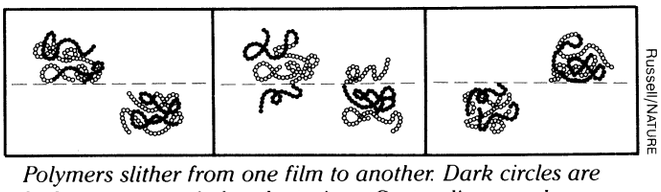
At first, the Seattle researchers tried to use AIDS patients who had undergone radiotherapy, chemotherapy, and a bone-marrow transplant to treat lymphoma. This cancer treatment devastates the immune system, making it possible for the researchers to observe more directly the effect of the added cells, Greenberg says.

That study was begun last February, but so far only one of about eight possible participants has undergone the gene-therapy treatment; the others did not live long enough, Greenberg says.

Now, the Seattle team will treat 15 people who have HIV infection but not lymphoma. Participants will receive cells every two weeks for two months. After the third treatment, three patients will take ganciclovir so researchers can assess whether this medication destroys the altered cells in humans. – *E. Pennisi*

Polymer chains: Like snakes, they wriggle

"Thy words are like a cloud of winged snakes," wrote Percy Bysshe Shelley. But what if polymers – those long, chain-like molecules – writhed in motion like a cloud of snakes?



Russell/NATURE

Polymers slither from one film to another. Dark circles are hydrogen; open circles, deuterium. Center diagram shows more deuterium above the weld.

Apparently, they do. A report in the Sept. 16 NATURE supports the theory that polymers move about in a snake-like manner, with one end of the molecular chain leading and the rest of the links wriggling along in tandem. The motion, called reptation, suggests a reptilian slithering, which approximates how a tangled polymer – like a basket of snakes – behaves as it diffuses from one surface to another.

Scientists have long suspected that polymer chains move in a serpentine way "through the entangled sea of surrounding molecules," says Thomas P. Russell, the report's lead author and a physicist at IBM's Almaden Research Center in San Jose, Calif. To show reptation, Russell and his colleagues prepared two foamy plastic surfaces – thin films of polystyrene – replacing half the hydrogen protons in each film with the isotope deuterium. However, in each film, the polymers had different patterns. In one film, the molecular chains had deuterium in the middle and hydrogen on both ends (HDH); polymers in the other film had hydrogen in the middle and deuterium on both ends (DHD).

Heating and pressing together the two surfaces welds them – "sort of like melting two foam coffee cups together," says Russell. Welding occurs when polymers reach from one film to the other.

As the polymer chains move from one film to the other, the balance of hydrogen and deuterium changes, causing a measurable imbalance – more deuterium on one side of the weld than the other. This imbalance, says Russell, shows that polymers had to wriggle from one side to the other by moving their front ends first, then their middles, then their back ends, rather than by diffusing randomly. In other words, the "chain ends led the chain centers," he says, "and reptation is the best explanation of this result."

Predicting how materials weld is critical, Russell says. "If a plastic cracks, people want to know how long will it take to heal, or reform, if you heat it." Knowing about reptation, "we can predict with confidence how polymers will diffuse" – as in microelectronics, where multilayer surfaces get laminated, says Russell. "Good adhesion is critical, and this model helps explain what kind of processing is most effective." Biologists too may benefit by seeing how "large biological molecules move about," he adds.

– *R. Lipkin*