News
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November 18, 1988

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Until Nov. 25

****Scientists kill cells carrying AIDS virus with assassin's poison

DALLAS--Scientists at The University of Texas Southwestern Medical Center here and Genentech Inc. of San Francisco report using a biochemical Trojan Horse to kill cells harboring the AIDS-causing virus in a test tube.

The scientists linked a potent plant toxin to a genetically engineered version of a molecule that is the target of HIV (human immunodeficiency virus) on human cells. This new substance apparently deceives the virus on the infected cell and instead of infecting another cell, it gets a dose of poison. The efficiency and selectivity of the new substance raises hopes that human clinical trials may be possible in the near future.

Reporting in the Nov. 25 issue of the magazine SCIENCE, the investigators say that if infected cells from HIV-positive individuals can be killed by the new substance, it might be possible to prevent or delay the onset of AIDS. They warn, however, that the effective application of the treatment strategy must take into account the way HIV sometimes lies dormant inside a cell, only to be activated later by unknown factors.

The scientists include Mark A. Till, Victor Ghetie, Jonathan W. Uhr and Ellen S. Vitetta of UT Southwestern; along with Timothy Gregory, Eric J. Patzer, John P. Porter and David J. Capon of Genentech.

The group reports that the hybrid substance--composed of a receptor or binding protein (CD4) that is normally on the surface of some white blood cells linked to the active "A-chain" portion of the plant poison--is a thousand times more toxic to HIV-infected cells than it is to uninfected cells. "Most individuals infected with HIV develop AIDS which is characterized by the progressive depletion of T cells expressing CD4, the cellular receptor for HIV," the authors say.

The new weapon takes advantage of the way the virus "hooks" onto its receptor (CD4) on the white blood cell. These CD4-expressing cells are important to the human immune defense system. It is a sugary protein coating on the HIV that binds to the CD4 protein. The coating, one of several, is called glycoprotein 120, and when it attaches, the virus enters the cell and splices its own genetic information into the cell's DNA. This enables new virus to grow inside and at some undetermined time later--perhaps even years--bud from the surface.

Since the HIV's receptor is the CD4 protein on normal cells, the scientists decided to use a genetically engineered version of CD4 constructed by the Genentech scientists and then link it to the active A-chain component of one of the most powerful plant poisons known--ricin. Derived from castor beans, ricin was used in the 1978 assassination of Bulgarian defector Georgi Markov.

Vitetta, who is director of UT Southwestern's Cancer Immunobiology Program, and Uhr, who is chairman of the Department of Microbiology, have used similar strategies to kill B-cell lymphomas. The method has been to hook ricin's A-chain to a monoclonal antibody that seeks out the cancerous cell and delivers the dose of poison to destroy it.

The pair and their co-workers are currently conducting Phase I clinical trials with human subjects in Dallas and in London. Earlier clinical trials with an objective of treating donated bone marrow to prevent graft-versus-host disease were carried out in Seattle in 1985 and 1986.

(More)

In September, Vijay Chaudhary and co-workers reported killing HIV infected cells using the same approach but with a different toxin bound to CD4. Vitetta and Uhr think the ricin A-chain may have some advantage because it already has been used in Phase I toxicity tests in more than 1,000 patients with cancer and graft vs host disease. However, they are hopeful that the other toxin may also have advantages and that perhaps at some point, a combined approach using both toxins may be tried.

Investigators including the Genentech authors are conducting trials in which only the engineered rCD4 receptor is used. Theoretically, this would have the effect of flooding the immune system and pre-empting HIV attachment to cells.

"The natural role of CD4 in the immune system is that it sits on certain cells like T-cells and monocytes and acts as a 'glue' molecule to allow these cells to contact other cells, i.e., those expressing Class II molecules. These Class II molecules are expressed on cells like B-cells and macrophages. In essence, CD4 helps bring cells together to talk to each other," Vitetta explained.

"This way, they activate each other and make antibodies and do various things that activate the immune system in fighting bacteria, viruses, parasites or other immunological insults," she added.

Vitetta said the next logical step in testing would be to use the rCD4-A-chain substance to kill different cell types infected with other strains of HIV in the test tube and to determine both toxicity and stability in mice.

"At that point we might be able to extrapolate quickly to establish human dosages and dose regimens." Still to be learned is whether an infected cell killed with the substance would release HIV that could then infect other cells.

Even if this were the case, the early intervention might prevent spread of the virus and slow down the onset of overt AIDS.

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Note: The University of Texas Southwestern Medical Center at Dallas comprises Southwestern Medical School, Southwestern Graduate School of Biomedical Sciences and Southwestern Allied Health Sciences School.