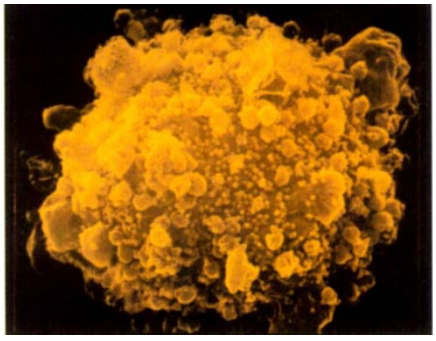
Latent HIV needs second knockout punch

Two recently published studies by AIDS research teams led by Anthony Fauci at the US National Institutes of Health (Bethesda, MD) and David Ho of the Aaron Diamond Research Center (New York, NY) show that powerful antivirals seem only to suppress HIV, and not to knock it out. To complete the job, other strategies will be needed.



T lymphocytes may harbor latent HIV, which can later be reactivated.

Ho's team studied a group of patients on highly active antiretroviral therapy—treatments that include protease and reverse transcriptase inhibitors. They found (*Science* **278**:1295–1300, 1997) that although the amount of HIV fell to levels that would usually be undetectable, small but constant amounts of the virus did remain latent in resting CD4 cells without decreasing over time. The virus they recovered did not show mutations associated with resistance to antiretroviral drugs. But, according to Ho, this reservoir of nonevolving latent virus means that clinicians cannot judge how long to keep patients on therapy.

Fauci went one step further: His study (*PNAS* **94**:13193–13197, 1997) found that the latent virus can be reactivated, and that a low level of viral replication may continue even during a regime of highly active therapy. "We thought that the virus when dormant couldn't reproduce—now we know it does replicate, in a smoldering, low-level manner." He says that his data suggest that virus replication was possibly contributing to the maintenance of the latently infected, resting, CD4 T-cells even though viral infection of plasma was eliminated by therapy. These cells probably have an extremely long half-life, he added, suggesting that "the time required for virus eradication, if indeed this is possible, will be considerably longer than previously predicted."

Researchers will need to follow the virus during therapy to see if it gradually declines, Fauci added. Flushing the latent cells out of their hiding places may be a beginning, and one strategy could be to develop treatments that target these cells. Another strategy, he said, would be to develop more potent antiretroviral drugs "if we are to speak of a real cure."

David Baltimore, president of the California Institute of Technology (Pasadena, CA) believes that focusing on new drug targets such as HIV intergrase may provide some answers. "But if these cells are extremely long lived, there may be almost no way to attack them," he said. "Inducing these cells to kill themselves or to leave their hiding places is another way of addressing the problem," he added. Putting a protective gene in stem cells may, in time, dilute the small reservoirs of viruses, Baltimore added.

Another promising approach in development is a gene therapy that delivers hairpin ribozymes to make existing healthy immune cells virus resistant. According to the University of California's (San Diego) Flossie Wong-Stahl, who is working with Immusol (San Diego, CA), this approach avoids problems of resistance, provides entry into nondividing cells (macrophages), treats uninfected cells, and can be combined with antiretroviral therapy (which treats infected cells). "The goal of this treatment is to build a counter reservoir of uninfected cells, a threshold that the virus cannot pass." A more ambitious future approach would be to try to regenerate the immune system from stem cells treated with HIV-resistant genes after ablating the system with radiation to kill those harboring viruses.

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Chiron (Emeryville, CA), Ribozyme Pharmaceuticals (Boulder, CO), and the City of Hope National Medical Center (Duarte, CA), are already conducting a phase I/IIa trial of ribozymes delivered to stem cells. The retroviral construct contains several ribozymes against different sites in HIV and is expected to be effective against mutated forms of the virus. Preclinical studies showed the construct protected stem cells of the immune system for their entire lifecycle. "Producing a population of leukocytes resistant to HIV should be complementary to other therapeutic modalities," said Rusty Williams, Chiron's chief executive officer.

Researchers from the University of Pennsylvania (State College, PA) have recently demonstrated one method by which the HIV-infected cells might be targeted. In the 21 November 1997 issue of *Science*, James Hoxie and his team demonstrated that a vector presenting CD4 and CCR5 receptors successfully located and entered cells infected by the macrophage viruses, and a vector bearing CD4 and CXCR4 did the same for T-cell virus-infected cells. Neither vector infected cells other than their target cells.

Cell Genesys (Foster City, CA) recently demonstrated early and efficient killing of HIV-infected macrophages and T-cells in vitro using genetically engineered T-cells; the chimeric T-cells, engineered with a universal receptor, were also able to kill mutated strains of HIV, killed as well as naturally occurring T-cells, and also inhibited viral replication. The company is now in Phase II trial with the therapy combined with antiretroviral drugs.

Immune Response (Carlsbad, CA) uses a version of the HIV surface glycoprotein gp120 protein as an immunotherapy. The product, Remune, stimulates chemokines such as RANTES—which has been shown to inhibit virus reproduction and decreases levels of TNF, which correlate to disease progression—and which has an impact on HIV-1-(cell-mediated) specific immunity. Immune Response's product is being positioned for use with antiviral therapies. According to president and CEO Dennis Carlo, "Remune stimulates the immune system to attack the cells that manufacture the virus—the reservoir of infectious virus in the blood."

It is not clear that any approach will address the problem of the resting virus. Antiviral specialist and coinventor of AZT, Dave Barry, chairman and CEO of Triangle Pharmaceuticals (Durham, NC), believes that addressing this may necessitate a combination approach. "Perhaps we need to view some infectious diseases more like chronic diseases—as manageable, not necessarily fatal, but perhaps not curable." Recently elected chairman of the 17-company consortium, the Inter-Company Collaboration (ICC) for AIDS drug development, Barry and his company are focusing on antiviral therapies. The ICC is addressing the problem of the resting virus, he said.

Vicki Brower