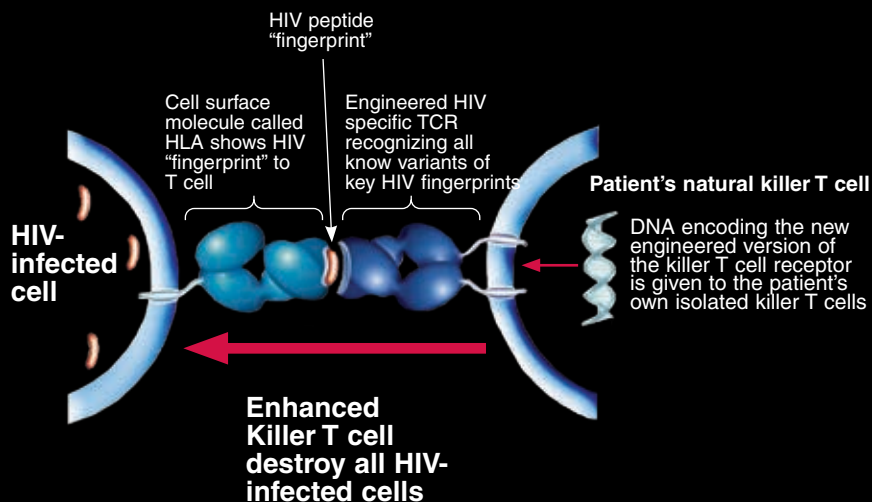


Engineered T Cells Gain a Weapon Against an Elusive Enemy:

HIV

By Karen Kreeger



Scientists have long noted the exceptional ability of HIV to evade the body's immune system. Compared to other viruses, HIV-1 has been a much more challenging foe.

Viruses that enter the body hijack the machinery of host cells to replicate and spread infection. When the body's cells are infected with a virus, they expose small parts of the virus on their surface. That exposure offers a molecular "fingerprint" (called an epitope) for killer T cells from the immune system to see. The immune system responds, sending the killer T cells to eliminate the virus and any cells involved in its production. But HIV has the ability to mutate quickly, swiftly disguising its fingerprints to allow it to hide from killer T-cells.

Until now. Researchers at the University of Pennsylvania School of Medicine and colleagues in the United Kingdom have engineered T cells that are able to recognize HIV-1 strains that have evaded the immune system. Their findings, published online in *Nature Medicine* (9 November 2008), have important implications for developing new treatments for HIV, especially for patients with chronic infection who fail to respond to antiretroviral regimens.

Natural T cells recognize their targets through weak molecular interactions me-

diated by the T cell receptor. Through a clever molecular process, the investigators were able to isolate a group of T-cell-receptor encoding genes that bind to HIV-1 about 450-fold more strongly. According to James Riley, Ph.D., research associate professor of pathology and laboratory medicine at Penn and senior co-author of the study, "Not only could T cells engineered to express the strongly binding T cell receptor see HIV strains that had escaped detection by natural T cells, but the engineered T cells responded in a much more vigorous fashion so that far fewer T cells were required to control infection."

Angel Varela-Rohena, Ph.D., the study's first author, points out another benefit: "With the present availability of potent systems to replicate and deliver high-affinity HIV-1 specific T-cell receptors, billions of these anti-HIV-1 warriors can be generated in two weeks." Varela-Rohena recently completed these studies as part of his doctoral dissertation at Penn.

"We knew there would never be a conventional vaccine for HIV," explains Professor Andrew K. Sewell from Cardiff University, United Kingdom, co-senior author of the study. "In the face of our engineered assassin cells, the virus will either die or be forced to change its disguises again, weakening itself along the way. We'd prefer the first option but I

suspect we'll see the latter."

Carl June, M.D., professor of pathology and laboratory medicine at Penn, describes the next steps: "We hope to begin clinical trials using the engineered T cells in patients with advanced HIV infection next year, a group for whom many drug regimens have stopped working." June, who is also director of translational research at the Abramson Family Cancer Research Institute at Penn, is co-author of the *Nature Medicine* study. "If the therapy in that group proves successful, we will treat patients with early-stage, well-controlled HIV infection. The goal of these studies is to establish whether the engineered killer T cells are safe and to identify a range of doses of the cells that can be safely administered."

The engineered receptor, says Bent Jakobsen, Ph.D., co-lead author of the study, "is able to detect HIV's key fingerprints and is able to clear HIV infection in the laboratory. If we can translate those results in the clinic, we could at last have a very powerful therapy on our hands." Jakobsen is chief scientific officer at Adaptimmune Ltd., a company based in the United Kingdom that owns the rights to the technology.

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