

NOVEMBER 21, 1997

Pushing the Envelope

Ben Doranz is pushing the envelope on AIDS research. He first helped discover one of the keys HIV uses to unlock and enter human cells, and now Doranz is part of a team that has built a new doorway into these infected cells.

In the November 21 issue of the journal *Science*, Doranz and other University of Pennsylvania researchers describe a novel method to gain access into immune cells already co-opted by HIV. The gene therapy technique could theoretically reach the hidden, latent reservoir of infected cells that escape drug therapy.

The immediate benefit "is that we will be able to track the cells that HIV targets and infects in such hidden areas as lymph nodes," said Doranz, an HHMI predoctoral fellow at the University of Pennsylvania. "It will help us further understand how HIV operates."

The Penn team led by James Hoxie and Michael Endres used a receptor discovered by Doranz and others in the lab of Robert Doms to turn the table on HIV. They gained entry into an infected cell by using the same molecular foothold that HIV uses.

Specifically, the HIV viral envelope protein gp160 binds to cell surface receptors on immune cells. The receptors that grip gp160 are CD4 and two new receptors discovered last year — CXCR4 and CCR5, the receptor that Doranz helped identify. In the earliest stages of infection, strains of HIV infect macrophages (immune system cells) through CCR5 and CD4. In the later phases of HIV infection, the virus attacks T cells through a portal provided by CXCR4 and CD4.

After HIV infects an immune cell, it displays its gp160 protein on the outside of the newly infected cell. The thousands of virus particles released by the infected cell pick up and carry along the gp160 protein to help them infect again, said Doranz.

The Penn researchers had a novel idea: Why not use the immune cell receptors CD4, CCR5 and CXCR4 to latch onto the gp160 dangling off the infected cells? This would provide a way to target HIV-infected cells for destruction.

They coated replication-defective retroviral vectors with a combination of either CD4 and CCR5, or CD4 and CXCR4 receptors and put the vectors into a batch of infected immune cells in the laboratory. A reporter gene in the vectors tracked their successful journey into cells infected by HIV.

Although in this case the vector's payload was a harmless reporter gene, the researchers are hopeful that they will be able to deliver therapeutics via this method to deliver a knockout blow to HIV.

For Doranz, the advance continues to shine a light on CCR5 and CXCR4 as a target for antiviral therapy: "This adds to a critical mass of tools with which we can address significant questions to push progress." He has been a lead author on three recent studies that detail how HIV gains entry to cells using CD4 and CCR5, and he has helped describe one of the first drug candidates to block CXCR4. CCR5, however, has captured his attention, especially since the recent finding that people who inherit a mutant form of CCR5 are resistant to infection by HIV.

"We know CCR5 is required for transmission but that it is also dispensable for normal human health," he said. "The next big step is to block CCR5, and we are hunting for ways to do that."