



GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY

NEWS

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THE HIV NEF PROTEIN PLAYS BOTH OFFENSE AND DEFENSE IN THE BATTLE BETWEEN THE AIDS VIRUS AND THE BODY'S IMMUNE SYSTEM

In fighting the body's immune system, HIV owes part of its success to its ability to destroy those cells normally recruited to mount the body's counter-attack against the HIV-infected cells. Lying at the crux of such success is a viral protein called Nef, which protects its infected host while simultaneously destroying the neighboring uninfected cells of the immune system, according to scientists at the Gladstone Institute of Virology and Immunology.

"It's HIV going both ways, playing offense and defense," said Warner C. Greene, MD, PhD, director of the Gladstone Institute of Virology and Immunology and University of California, San Francisco professor in the departments of medicine and microbiology and immunology. "It is a rather remarkable example of the cunning strategy the AIDS virus employs to help ensure its survival and spread."

Researchers have long known that cells surrounding an HIV-infected cell are eliminated by way of a programmed self-destructive process known as apoptosis. And Nef, the researchers knew, somehow plays a key role in triggering this destruction. Now in a study published in the April 12, 2001 issue of *Nature*, Gladstone scientists have discovered that Nef also protects its infected host cell from the detrimental effects by using the same trigger. The new study shows that Nef does this by binding to and inhibiting a protein called ASK1, a key player in apoptosis.

"If we could effectively block the assembly of Nef and ASK1, it could lead to the premature death of the HIV-infected host cell," Greene said. "The HIV infection process would then be short-circuited and the virus might simply die out because it would not have sufficient time to fully reproduce itself."

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Achieving such a block will require discovering and developing a molecule that interrupts the assembly of Nef and ASK1, helping to “tip the balance in favor of the body effectively dealing with the virus,” he said.

Identifying such a molecule could lead to the development of a new class of drugs to fight HIV infection—an entirely new approach in the arsenal of anti-HIV arsenal, Greene said. Current drugs, such as reverse transcriptase and protease inhibitors, stop key viral protein enzymes from catalyzing reactions necessary to maintain the viral life cycle. But scientists are coming close to exhausting the number of viral protein enzymes as potential drug targets. Greene and his research team are among the first to focus on non-enzymatic viral proteins, such as Nef, which interact with host cell proteins that HIV needs for its own growth.

Strong support for developing drugs that specifically target Nef comes from the observation that people infected with HIV strains lacking the *nef* gene—a rarity—develop AIDS symptoms much more slowly than those infected with HIV strains containing the *nef* gene.

“If we can win the battle at the single cell level, then we will be in a better position to win the war in the millions of HIV infected patients,” Greene said.

Co-investigators in the study include Romas Geleziunas, PhD, formerly at Gladstone and now a principal research scientist in the Discovery Virology Department at the DuPont Pharmaceuticals Company; Weiduan Xu, MD, PhD, formerly at Gladstone and now associate scientist at Rigel in South San Francisco; Hidenori Ichijo, DDS, PhD, professor at the Tokyo Medical and Dental University in Japan; and Kohsuke Takeda, DDS, PhD, assistant professor also at the Tokyo Medical and Dental University.

Both the National Institutes of Health and the Center for AIDS Research, a collaboration of UC San Francisco and the Gladstone Institute for Virology and Immunology, funded this study.

The Gladstone Institute for Virology and Immunology is one of three premier research institutes that comprise the J. David Gladstone Institutes, a private biomedical research institution affiliated with UC San Francisco. The institution is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing personal interest in medical education and research.