



GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY

NEWS

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EMBARGOED FOR RELEASE

12 p.m. EDT October 16, 2001

To coincide with publication in the journal *Immunity*

HIV INFECTS SUBSET OF T CELLS LEADING TO DEPLETION, GLADSTONE RESEARCHERS FIND

The battalion of CD4+ T cells, which fight HIV and other pathogens, needs new recruits to replace the cells that fall. Researchers at the Gladstone Institute of Virology and Immunology and co-authors have found that these recruits, called naïve T cells, are susceptible to the bullets of HIV infection even before they step onto the battlefield.

The study, published in the October 17 issue of the journal *Immunity*, is among the first to show that HIV can indeed infect naïve T cells and brings some resolution to what was the subject of great debate among HIV researchers. The finding helps to explain how T-cell numbers diminish to levels that leave the body susceptible to opportunistic infections characteristic of AIDS.

“The collapse of the CD4+ T-cell system is the cardinal feature of AIDS, so understanding which subsets of T cells can be infected is important in providing a clear picture of how HIV reduces the number of T cells,” said senior co-author Mark A. Goldsmith, MD, PhD, associate investigator at Gladstone and UCSF associate professor of medicine.

CD4+ T cells are divided into two basic classes—naïve cells and memory cells. Once exposed to a pathogen, naïve cells become memory cells, which signal other immune system cells to mount an attack on the offending pathogen. Conventional wisdom was that HIV infected memory T cells nearly exclusively.

Such thinking resulted from studies that used T cells isolated from blood, Goldsmith said. But only 2 percent of all immune system cells are circulating in the blood at once, so these cells may not be sufficiently representative. Also, culturing these cells requires the use of artificial stimulants, changing the way they react to the environment.

Goldsmith and lead author Daniel A. Eckstein, a UCSF Biomedical Sciences Program graduate student at Gladstone, instead focused on the cells found in lymphoid organs, such as the spleen, lymph nodes, and tonsils, where most immune system cells are located. Because cells in these tissues can be cultured without artificial stimulants, their behavior closely mirrors that found in the body.

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Before this study, other researchers had claimed to have isolated HIV-infected naïve cells from infected individuals. Some HIV researchers, however, suspected that these cells were merely infected memory cells that had reverted back to a naïve character. The current study clears away those suspicions and shows that naïve cells themselves can indeed be infected.

In one experiment, the researchers infected naïve cells with HIV. In addition, they added BrdU, a substance that shows up in cells that have divided. Generally, naïve cells don't divide. Memory cells do. About 14 percent of the naïve cells were infected, while only 2 percent were labeled with BrdU. This shows that the vast majority of the cells that were infected had not divided. The infected cells were naïve cells and not dividing memory cells.

The discovery could change the way physicians think of the way HIV infection leads to AIDS. Infected naïve cells are a source of HIV, helping it to spread throughout the body. These infected naïve cells also die and then are no longer available to replenish the immune system.

Without these CD4+ T cells, the virus “eliminates the ability of the immune system to respond to the opportunistic infections characteristic of AIDS,” said Eckstein, who is also a medical student in UCSF School of Medicine’s Medical Scientist Training Program.

The specific HIV strain that the researchers employed is classified as an "X4" virus; such strains are found in 50 percent to 90 percent of patients during the later stages of infection. Eckstein said that the study underscores the importance of developing a drug to antagonize a specific protein involved in X4 HIV infection.

Gladstone researchers also involved in the study include Michael L. Penn, PhD, former graduate student in the UCSF Biomedical Sciences Program and medical student in the Medical Scientist Training Program in the UCSF School of Medicine; Jason F. Kreisberg, BS, graduate student in the UCSF Biomedical Sciences Program; research scientist Michael P. Sherman, MD, PhD, UCSF assistant clinical professor of medicine; and research associate Peggy S. Chin, BA.

Co-authors from the UCLA department of microbiology, immunology and molecular genetics include graduate student Dierdre D. Scripture-Adams, BS, and Jerome A. Zack, PhD, professor of hematology and oncology in the UCLA department of medicine. Also co-authors were Yael D. Korin, PhD, UCLA postdoctoral fellow in the department of medicine, and Mario Roederer, PhD, chief of the immunotechnology section of the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

The work was supported by grants from the National Institutes of Health, the UCSF Biomedical Sciences Graduate Program, the Medical Scientist Training Program at UCSF, the California Universitywide AIDS Research Program, the National Science Foundation, the UCSF-California AIDS Research Center, and the J. David Gladstone Institutes.

The Gladstone Institute of Virology and Immunology is one of three research institutes that comprise the J. David Gladstone Institutes, a private biomedical research institution affiliated with the University of California, San Francisco. The institutes are named for a

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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.

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