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**DECIPHERING HOW CD4 T CELLS DIE DURING HIV INFECTION**  
*Gladstone Investigators Solve Long-Standing HIV Mystery*

SAN FRANCISCO, CA—November 24, 2010—Scientists at Gladstone Institute of Virology and Immunology have solved a long-standing mystery about HIV infection—namely how HIV promotes the death of CD4 T cells. It is the loss of this critical subset of immune cells that leads to the development of AIDS. Most immune cells that die during HIV infection are seemingly not infected, a phenomenon formerly described as “bystander cell killing.” Now the Gladstone scientists report that these “bystander” cells are actually the victims of a failed or abortive form of viral infection. Their findings are published in today’s issue of the journal *Cell*.

Dr. Gilad Doitsh, who performed many of the studies and is the lead author of the paper stated, “Our study reveals that the virus actually enters the CD4 T cells that are destined to die and that the virus starts to make a DNA copy of its RNA, a process called reverse transcription. However, this process does not work well in the majority of these cells and the incomplete DNA intermediates that accumulate in the cytoplasm are sensed and trigger the cell to ‘commit suicide’ in an attempt to protect the body.”

The researchers identified the precise step in which the CD4 T cells die by using different anti-HIV drugs to arrest the virus at different points in its life cycle. Drugs that blocked viral entry or that blocked the start of reverse transcription stopped the killing. Conversely, drugs that acted later in the life cycle did not. Importantly,

the researchers used primary human lymphoid tissues, such as tonsil and spleen  
to uncover this death

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pathway. These and other lymphoid tissues contain over 98% of the body's CD4 T cells and represent the major site where the virus reproduces itself.

The team also found that the dying cells do not go silently into the night. As they die, these cells release proteins, called cytokines, that cause inflammation and that attract healthy cellular targets promoting repeated rounds of infection and cell death. Scientists have long been interested in why HIV infection and inflammation seem to go hand in hand. This study reveals a new mechanism linking the virus to inflammation.

“Our findings have revealed a completely unexpected mechanism for CD4 T-cell death during HIV infection” said Warner C. Greene, institute director and senior author of the paper. “These results highlight how a natural cellular defense normally used by the host to repel foreign invaders goes awry in HIV infection, resulting in a profound depletion of CD4 T cells. If untreated, this process ultimately causes AIDS.”

Of note, this finding comes only one week before the 15th Annual World AIDS day. Since the initial detection of AIDS 29 years ago, more than 60 million people have been infected worldwide and 25 million people have died of AIDS or AIDS-related diseases. Every year, over 2.5 million people are newly infected with most of these infections occurring in developing countries.

Other authors of the study include Gladstone scientists Marielle Cavois, Kara G. Lassen, Orlando Zepeda, Zhiyuan Yang, Mario L. Santiago, and Andrew M. Hebbeler.

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California HIV Research Program.

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**Warner Greene's primary affiliation is with the Gladstone Institute of Virology and Immunology**, where he is director and the Nick and Sue Hellman Distinguished Professor of Translational Medicine and where his laboratory is located and his research is conducted. He is also a professor of medicine, microbiology and immunology at UCSF.

#### **About the Gladstone Institutes**

Gladstone is an independent, nonprofit biomedical research organization dedicated to accelerating the pace of scientific discovery and biomedical innovation to prevent illness and cure patients suffering from cardiovascular disease, neurodegenerative disease, or viral infections. Gladstone is affiliated with the University of California, San Francisco. More information can be found at [www.gladstone.ucsf.edu](http://www.gladstone.ucsf.edu).

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