



## **GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY NEWS**

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### **GLADSTONE INVESTIGATORS DISCOVER HOW RESTING T CELLS AVOID HIV INFECTION -- FINDING COULD LEAD TO NEW THERAPEUTIC STRATEGIES**

Scientists have discovered the mechanism that enables some CD4 T cells -- the main target of HIV -- to thwart the virus. The discovery, reported on April 13 in the online version of *Nature*, could open the door to an entirely new strategy for preventing the spread of HIV infection in the body's cells, according to the senior author of the study, Gladstone Institute of Virology and Immunology Director Warner C. Greene, MD, PhD.

The researchers, led by Ya-Lin Chiu, PhD, a postdoctoral fellow in the Greene lab, investigated why resting, nondividing CD4 T cells are impervious to HIV infection, while activated, dividing CD4 T cells are not. The team discovered that a potent antiviral factor called APOBEC3G (A3G) is the key.

The team, working in cell culture, found that A3G exists in two different-sized forms -- a small form that actively repels the virus, and a large form that is completely ineffective against it. Moreover, they detected only the small form in resting CD4 T cells, where HIV fails to grow, and only the large form in activated CD4 T cells, where the virus efficiently grows and wreaks havoc. They further showed that blocking production of the small, active form of A3G in resting CD4 T cells was sufficient to make these normally resistant resting cells highly susceptible to HIV infection.

"Until now, the prevailing belief has been that HIV failed to infect resting T-cells due to a simple lack of some essential factor or nutrient," says Greene, a professor of medicine, microbiology and immunology at the University of California, San Francisco. "This study now shifts the paradigm, showing that resting CD4 T cells actively repel HIV infection through the action of the small, enzymatically active form of A3G, which stops the virus in its tracks."

CD4 T cells are a class of lymphocytes, or white blood cells, that fight infection by orchestrating immune responses. They have the ability to recognize specific antigens - - foreign substances, such as toxins, bacteria or environmental factors -- through receptors on their surfaces. Roughly 95 percent of CD4 T cells in the blood stream exist in a resting, inactive state, awaiting the appearance of their specific antigen. When they detect its presence, they spring into action -- growing and dividing, releasing cytokines (proteins that the immune system uses to communicate between cells) and recruiting and activating additional T cells. The new study shows that this activation process dismantles the highly effective A3G antiviral shield, making these cells highly susceptible to HIV infection.

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Greene's group is now looking at ways to use this new knowledge therapeutically. One approach would involve converting the ineffective, large form of A3G into the protective, small form in activated CD4 T-cells. In this case, the goal would be to identify small molecules that promote the disassembly of the large A3G complex, which is shown by the Gladstone team to contain not only A3G but also a cellular RNA and possibly other host proteins.

A parallel strategy would involve finding ways to prevent the small form of A3G from converting to the large form in the first place, during the process of T cell activation. However, notes Greene, scientists would first need to determine whether preserving the antiviral shield provided by small A3G in activated and dividing CD4 T-cells does not produce any deleterious effects. These could include the early death of these cells or the creation of mutations in the chromosomes that might lead to cancer.

"The possibility of exploiting the natural and potent antiviral properties of A3G to control HIV infection is very exciting," says Greene. "We have learned a great deal from our studies of how the resting CD4 T cell resists HIV. Now, the challenge is for scientists at the Gladstone Institute of Virology and Immunology and elsewhere to translate these basic discoveries into novel treatments that could benefit HIV-infected patients around the world."

Four years ago, HIV biologists were galvanized by the discovery of A3G as a potent anti-HIV factor. Initially, scientists thought that A3G had to squeeze into new HIV viral particles in order to produce its antiviral effects. The new *Nature* study indicates that this is not the case in resting T-cells.

The Greene lab showed that in activated T cells, however, Vif, one of HIV's nine genes, counters the antiviral effect of A3G by binding to it and accelerating its destruction as well as decreasing its production. These effects of Vif were so complete that no A3G was left in infected activated CD4 T for incorporation into the new viral particles. Thus, this antiviral action of A3G that only occurs in activated T-cells can be overcome by Vif. These results have launched the search for a new class of antiviral drugs that block the action of Vif, which would leave A3G poised and able to unleash its antiviral effect from inside viral particles. In resting T cells, though, HIV is defenseless against A3G, because there is no Vif in the incoming viral particles and the virus has not advanced far enough into its life cycle to make new Vif.

The study was supported in part by grants from the National Institutes of Health, the University-wide AIDS Research Program and the American Foundation for AIDS Research.

Other co-authors of the *Nature* paper, "Cellular APOBEC3G restricts HIV-1 infection in resting CD4 T cells," at the Gladstone Institute of Virology and Immunology are Vanessa B. Soros, Jason F. Kreisberg, Kim Stopak, and Wes Yonemoto. Kreisberg and Stopak are students in the UCSF Biomedical Sciences Graduate Program.

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