



GLADSTONE INSTITUTE OF VIROLOGY AND IMMUNOLOGY

NEWS

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THE FUTURE OF HIV THERAPEUTICS IS BRIGHTENING, ACCORDING TO GLADSTONE INSTITUTES DIRECTOR

***Nature Immunology* Commentary Highlights Promising Advances in the Field**

Recent discoveries about the way that HIV infects cells are propelling the development of a broad spectrum of promising new antiviral drugs, according to an invited commentary on the topic in the current issue of *Nature Immunology* (August 27, 2004).

The assessment is made by Gladstone Institute of Virology and Immunology (GIVI) Director Warner Greene, MD, PhD, who also serves as professor of medicine, microbiology and immunology at the University of California, San Francisco.

In the piece, Greene points out that basic research on HIV, a relatively simple pathogen with only nine genes encoding 15 proteins, are leading to compelling new therapies that deny the initial entry of HIV into its cellular host. In addition, fast-moving research of naturally occurring factors with potent antiviral properties is opening the way for future development of an entirely new class of anti-HIV drugs.

New agents that block the first step in HIV's life cycle, the entry of the HIV virion (a single virus particle) into host CD4 T-cells, are quickly moving down the drug development pipeline. Chief among these therapeutics are drugs known as chemokine receptor antagonists that interfere with HIV's ability to bind to CCR5, one of two key surface receptors needed for the virus to penetrate into the cell. Although these HIV co-receptors were identified only seven years ago, basic studies performed by both GIVI investigators and scientists around the world have helped accelerate clinical development of CCR5 antagonists as a new class of anti-HIV drugs. Several major pharmaceutical companies are now racing to the finishing line.

These advances address but one of the three steps required for successful entry of the HIV virus. The other two steps, involving the attachment of HIV virions to surface CD4 receptors and the final fusion of virions to target cells, are also being targeted with new antiviral drugs. Combinations of inhibitors acting at each of these three steps in the viral entry sequence could soon form a new "triple cocktail" therapy for HIV-infected patients.

Prospects in the longer term are also bright, with the recent discovery of natural antiviral factors that are very active against specific forms of HIV. "The single most exciting new area of HIV basic research with strong therapeutic implications involves a host-encoded antiviral factor, APOBEC3G," explains Greene. "We all produce this factor. It's quite potent, and it can halt the growth of HIV dead in its tracks, provided the virus lacks its Vif, or viral infectivity factor, gene."

(more)

HIV attacks APOBEC3G through its Vif protein. GIVI scientists were the first to show that Vif not only targets intracellular APOBEC3G for accelerated destruction but also impairs new production of this antiviral factor. Vif's combined effects effectively overcome the antiviral action of APOBEC3G.

The fact that Vif must bind to APOBEC3G and recruit enzymes triggering APOBEC3G degradation provides an exciting window of opportunity for future drug development. The goal is to block the assembly or ensuing action of Vif on APOBEC3G, thereby preserving intracellular expression of APOBEC3G. GIVI scientists are now launching a search for small molecules that display these properties. If these molecules can be identified and successfully developed into drugs, they would unleash potent antiviral effects of APOBEC3G, even in the presence of Vif.

"HIV biologists agree that the Vif-APOBEC3G axis forms the single most promising drug target since the discovery of chemokine receptors," explains Greene.

While the future of HIV therapeutics is brightening, it is essential that these drugs be made available in such areas of the world as Africa and Asia, where the virus continues to spread unchecked, concludes Greene. "Such an effort is required if we are to blunt the expanding global HIV epidemic in a truly meaningful way," he explains. "This will require commitment and investment by the world community not only for the key drugs but also for the infrastructure and training required to ensure their effective use."

The Gladstone Institute of Virology and Immunology is one of three research institutes of The J. David Gladstone Institutes, an independent, nonprofit biomedical research institution affiliated with UCSF. For further information, visit www.gladstone.ucsf.edu.

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