

# STATEMENT

National Cancer Institute

FOR RELEASE  
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## REMOVAL OF THE tat GENE RENDERS HTLV-III HARMLESS

Alterations of a key gene of HTLV-III, the virus that causes AIDS, render the virus harmless, according to two independent research teams, one at the National Cancer Institute and the other at Harvard's Dana-Farber Cancer Institute. The gene is the one called the transactivator (tat). The finding is expected to speed the development in new types of anti-AIDS drugs.

The National Cancer Institute research team is directed by Dr. Flossie Wong-Staal, and Harvard's Dana-Farber Cancer Institute research team is directed by Dr. William A. Haseltine.

HTLV-III, unlike most other retroviruses, has the ability to accelerate tremendously its own production. The acceleration is accomplished by tat. This gene acts not only to speed up its own production, but also to speed up the reproduction of other virus components. The important elements of this acceleration pathway have been identified earlier by the two research groups. One of the components is a tiny gene in the middle of the virus called tat, and the second is a small element in the control region of the virus called TAR for target or transacting responsive element.

The current work describes what happens to HTLV-III when the tat gene is removed. To remove the gene, both groups used the tools of gene splicing to snip out part of the genetic information that encodes the transactivator protein. The result, both groups found, is a virus incapable of growth.

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This result was surprising. Both groups had expected that the virus without the transactivator gene would grow, but grow slowly. This was expected as other similar retroviruses that do not have the transactivator gene grow well. However, the transactivator-defective viruses failed to grow at all. Growth of the transactivator-defective viruses could be restored by supplementing the defective virus with the transactivator gene or the product of the gene.

There are several potential clinical consequences of this observation. Since the transactivator gene is necessary for virus growth, drugs that prevent the transactivator gene from working should also prevent the virus from growing. Drugs that block either the transactivator itself or prevent interaction of the transactivator within the responder element should stop the spread of the virus. Such drugs might have a selective action against the virus, and therefore may not be toxic. The transactivator of HTLV-III is not present in normal cells, and therefore drugs that act against the transactivator should not affect normal cell growth.

These experiments could also provide an avenue for vaccine development. The virus lacking the transactivator gene, produced by cells which contain the transactivator gene, looks exactly like the real virus. However, the virus without the transactivator gene is dead. This dead virus contains all the viral proteins in all the correct conformations. However, the virus can't grow because it can't make its own transactivator gene. Such intact, but dead, virus might be useful for vaccine as it should appear to the immune system as if it were the virus itself.

The authors of the work from the National Cancer Institute group are: Amanda G. Fisher, Mark B. Feinberg, Steven F. Josephs, Mary E. Harper, Lisa M. Marselle, Gregory Reyes, Matthew A. Gonda, Anna Aldovini, Christine Debouk, Robert C. Gallo, and Flossie

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Wong-Staal. This research is published in the March 27 issue of Nature. The authors of the work from Harvard's Dana-Farber Cancer Institute are: Andrew Dayton, Craig Rosen, Joseph Sodroski, Wei Chun Goh, and William A. Haseltine. This research appears in the March 28 issue of Cell.

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