

# UPDATE

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**TITLE** ..... Phosphorothioate Analogs of Oligodeoxynucleotide  
 Inhibit Viral Replication of Human Immunodeficiency  
 Virus (HIV): Inhibition of de novo Infection in  
 Uninfected Cells and Regulation of Viral Expression  
 in Chronically Infected Cells

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and

**TITLE** ..... Physicochemical Properties of Phosphorothioate  
 Oligodeoxynucleotide Anti-HIV Agents

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**FOR RELEASE AT TIME**  
**OF PRESENTATION**

STOCKHOLM--Modified analogs of oligodeoxynucleotides (ODNs) inhibit the  
 AIDS virus from reproducing in infected T cells as well as from infecting  
 normal T cells, scientists from the U.S. National Cancer Institute (NCI)  
 reported today.

(more)

The analogs are novel because most other potential antiviral agents under study are aimed at inhibiting the AIDS virus from infecting normal cells, but they do not have an effect on already infected cells.

"The analogs are capable of inhibiting both viral infection in uninfected T cells and viral expression in chronically infected cells," said Makoto Matsukura, M.D., reporting on the study at the 4th International Conference on AIDS in Stockholm. The study was conducted by Dr. Matsukura, Dr. Samuel Broder, and colleagues at NCI, Bethesda, Md., in collaboration with Applied Biosystems Inc., Foster City, Calif.

Much further laboratory research will be needed to develop an appropriate treatment regimen for patients with AIDS or AIDS-related complex.

"The analogs, called phosphorothioate ODNs (S-ODNs), are short modified DNA sequences that are complementary, or 'antisense,' to a gene of the AIDS virus that is essential for the virus to replicate," Dr. Matsukura said.

"The analogs bind to the viral gene art/trs, stopping the gene's activity and, thus, the virus's ability to replicate."

In a 1987 study, Dr. Matsukura and colleagues unexpectedly found that S-ODNs that did not match the RNA of art/trs gene still inhibited the virus from infecting normal T cells.\* This finding, along with the findings reported today, suggests that the analogs have at least two ways of inhibiting the AIDS virus--an antisense way and some other way," Dr. Matsukura said. The precise mechanisms by which this happens are not fully understood.

Reporting on related research at the AIDS conference, NCI's Dr. Jack Cohen described the results of a detailed study on the physical and chemical

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\*Matsukura M, Shinozuka K, Zon G et al: Phosphorothioate analogs of oligodeoxynucleotides: Inhibitors of replication and cytopathic effects of human immunodeficiency virus. Proc Natl Acad Sci 84:7706-7710, 1987.

properties of S-ODNs. The analogs are very hardy. They do not appear to be easily degraded (destroyed) by enzymes like unmodified ODNs. At body temperature, they form stable bonds with the AIDS viral gene. Characteristics such as these may be important assets for an effective AIDS therapy,

—Dr. Matsukura said, but much work still needs to be done before such compounds can be used in patients.

The idea of using ODN as an antisense agent to inhibit viral replication was introduced in the late 1970s by Dr. Paul Zamecnik at the Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and colleagues. After the AIDS virus was discovered, NCI scientists began developing and studying modified DNA versions of ODN that were specific for the AIDS virus.

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