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Long term suppression of human immunodeficiency virus type 1 activity *in vitro* by guanosine/thymidine oligonucleotides (GTOs).

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Oligonucleotide compounds composed of only guanosine and thymidine were able to significantly inhibit human immunodeficiency virus type-1 (HIV-1) induced syncytia formation and virus production (as measured by p24 core antigen expression) in an acute infection assay system. The oligonucleotides did not share any homology with, or possess any complementary (antisense) sequence motifs to the HIV-1 genome. The guanosine/thymidine containing oligonucleotides (GTOs) which demonstrated this anti-HIV activity contained natural phosphodiester (PD) linkages (backbones) between the nucleosides. One of the PD oligonucleotides tested was capable of inhibiting HIV-1 induced syncytium formation and p24 production with a median effective dose in culture (ED_{50}) in the submicromolar range. In addition, oligonucleotides tested were able to significantly suppress HIV-1 p24 production at least up to 7 days after removal of the drug from the infected cell culture medium. The growth inhibition properties (toxicity) of this genre of oligonucleotides was determined to be well above the ED_{50} values which yielded high selective indexes. All measured activities of these molecules were increased when the PD backbone was replace with a phosphorothioate (PT) backbone in a sequence dependent manner. The enhanced antiviral activity displayed by the sulfur group on the oligonucleotide backbone and the lack of any sequence specific interactions suggests that a percentage of antiviral activity of oligonucleotide based therapeutics is due to mechanisms other than those originally postulated for oligonucleotides. The good selective index of these compounds coupled with the prolonged suppression of HIV-1 in culture after their removal from the infected cell culture, make this a class of compounds which warrant investigation as therapeutic agents to be used against HIV-1.

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Development of an *In Vivo* Model of HIV Latency and Activation. P.M. Feorino,[1]* S.T. Butera,[2] J.R. Mead,[1] T.M. Folks,[2] R.F. Schinazi.[1] VA Medical Center/Emory University, Decatur, GA 30033;[1] and Centers for Disease Control and Prevention, Atlanta, GA 30333.[2]

To date, no easily accessible animal model of HIV latency and activation exists to pursue basic science issues and to evaluate therapies. To address the lack of an animal model for latency, 10^7 OM-10.1 cells, a promyelocytic HIV-containing cell line, were injected subcutaneously into SCID mice. These previously described (*Antiviral Chem Chemother*, 4:55-63, 1993) $CD4^+$ cells grow as a solid tumor within the mice. Cells within the tumor were found to be of human origin, i.e., HLA-A/B/C positive and $H\text{-}2K^d$ negative by flow cytometry. The mice were injected intraperitoneally at 30 and 36 hours prior to assay with varying doses of tumor necrosis factor-α (TNF). The tumor cells were monitored for activated HIV expression by direct anti-HIV immunofluorescence, surface $CD4^+$ down modulation, and peripheral p24 antigenemia. Evidence for the presence of HIV was found in the cells obtained from the tumor mass. An increase in HIV was observed in the TNF treated mice over control. Currently we are investigating different parameters to optimize virus activation in our *in vivo* system. The development of an animal model for HIV latency will permit a better appreciation for latency in HIV pathogenesis and rapid evaluation of novel therapies designed to block viral activation. *(Supported in part by the VA)*