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Molecular Biology of Organic Thiogold Compounds in the Chemotherapy of AIDS

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A study of the molecular mode of action of organic thiogold compounds on the polymerases (RT) of HIV-1 or AMV was done. An ultrasensitive primer extension system was used: 5'[^{32}P] primer, either P24 *gag* DNA or RNA matrices and purified RT of HIV-1 or AMV. Products were separated on PAGE-urea gels. The addition of an Au-S linkage to certain glucose analogues or aliphatic alcohols has been shown to be a potent inhibitor of HIV-1 RT. The most potent of these compounds was 1-aurothioglucose (GlcSAu). This compound inhibited the HIV-1 RT at 3.0 μM, was not sequence-dependent, and was unchanged by increasing concentrations of trinucleotide triphosphates. GlcSAu showed little inhibition of *Escherichia coli*- or alpha-polymerases (rat liver or human placenta). GlcSAu also blocked chain elongation, and, unlike AZTtriphosphate ($AZT\text{-}P_3$), did not require cellular kinases for activity. These studies suggest that chemotherapy against the RT of HIV-1 with compounds like GlcSAu to block access of the enzyme to the template, may be more efficacious in the chemoprophylaxis and/or treatment of AIDS.

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IN VITRO EVALUATION OF THE ANTIVIRAL EFFECTS OF ACEMANNAN ON THE REPLICATION AND PATHOGENESIS OF HIV-1 AND OTHER ENVELOPED VIRUSES: MODIFICATION OF THE PROCESSING OF GLYCOPROTEIN PRECURSORS

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Acemannan, a ß-(1,4)-linked acetylated mannan, is the nonproprietary name of the biologically active component of Carrisyn®. Protection of peripheral blood mononuclear cells and two well-defined T4 cell lines, MT-2 and CEM-SS, used as target cells for HIV-1 infections was shown to be MOI- and acemannan concentration-dependent. Along with an increase in target cell viability, a concentration-dependent reduction in HIV-1 replication and virus load was demonstrated by hybridization using a *POL* gene probe.

Passage of HIV-1, herpes simplex virus (HSV-1) and Newcastle disease virus (NDV) in the presence of 50-100 μg/ml of acemannan caused a reduction in, infectivity of viral progeny. A concentration-dependent reduction in viral-induced cell fusion was also observed. Processing of the F_o (fusion) glycoprotein of paramyxoviruses and the precursor to gp160 of HIV-1 have been shown to be critical to the pathogenic properties of these viruses. Glycosylation and processing of viral glycoproteins synthesized by NDV or HIV-1-infected cells cultured in the presence of acemannan were shown to be altered, i.e. precursors having increased molecular weights accumulated in acemannan treated cells. The observed changes were similar to those detected when cells were treated with deoxynojirimycin (DNM), a known inhibitor of α-glucosidase I. Thus, in part, acemannan appears to inhibit viral replication by altering glycosylation of viral glycoproteins and it acts synergistically with nucleoside analogues to inhibit the replication of HIV-1 and HSV-1. Acemannan was not cytotoxic at any concentration tested.