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Alkylglycerol Foscarnet Analogs Active Against Drug-Resistant HIV-1 Are Orally Bioavailable in Mice.

K.Y. Hostetler, K.N. Wright, M.F. Gardner and J.R. Beadle. Dept. of Medicine, VA Medical Center and Univ. of California, San Diego, La Jolla, CA 92093-0676

Batyl alcohol analogs of foscarnet (1-O-octadecyl-*sn*-glycerol; B-PFA) have substantially greater antiviral activity than foscarnet (PFA) against HIV-1 infected MT-2 and HT4-6C cells. Alkylglycerol foscarnets, including the 2-O-methyl and 2-O-ethyl analogs, MB-PFA and EB-PFA, are also highly active against a panel of drug resistant strains of HIV-1 including strains resistant to AZT, 3TC, NNRTIs, dideoxynucleosides and strains co-resistant to AZT & 3TC with EC_{50} values ranging from 0.13 to 1.34 μM. Preliminary data also indicates preservation of antiviral activity against multidrug resistant strains of HIV-1. The purpose of this study was to determine the oral pharmacokinetics of B-PFA, MB-PFA and EB-PFA in mice. We synthesized B-PFA, MB-PFA and EB-PFA where the carboxyl of foscarnet was labeled with ^{14}C. The radioactive compounds were administered by oral gavage at 20 mg/kg to fasted mice. We determined the plasma levels of radioactivity at 1, 3, 6, 9 and 24 hours and peak plasma levels and area under curve (AUC) were compared with an equimolar oral dose of [^{14}C]PFA. Peak plasma levels with B-PFA were 7 fold higher with B-PFA than with PFA and peak levels of MB-PFA and EB-PFA levels were intermediate. The plasma $AUC_{0\text{-}24hr}$ was calculated and found to be 28 fold greater with B-PFA and 6 to 8 fold greater with MB-PFA and EB-PFA versus PFA. At 24 hr, B-PFA levels were still above the EC_{50} values for drug-resistant HIV-1. In summary, alkylglycerol analogs of foscarnet may be useful for salvage therapy of drug-resistant HIV infection in man.

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Novel Peptides Inhibit HIV-1 Replication In SCID Mice: Relevance Of The SCID Mouse Model For Human Trials

PL Black[1], DM Lambert[2], RF Schinazi[3], and MA Ussery[4]. [1]QuadPharma, Inc., Decatur, GA 30033; [2]Trimeris, Inc., Research Triangle Park, NC; [3]VA Med. Ctr. & Emory Univ. School of Med., Atlanta, GA; and [4]Innogenetics, Inc., Alpharetta, GA.

The antiviral activity of novel fusion inhibitors T-20 and T-1249 was tested in the HuPBMC-SCID mouse model of HIV-1 infection. Mice were treated with antiviral agents for one week after infection. Recovery of infectious HIV-1 in blood cells, splenocytes, lymph nodes (LN), and peritoneal cells (PC) was assayed by quantitative coculture with human peripheral blood mononuclear cell (PBMC) blasts 1 wk after infection, and viral load was quantitated by the NASBA assay. T-20 and T-1249, synthetic peptides derived from gp41, reduced recovery of infectious virus and viral load by ≥4 logs to below detectable limits. A variety of other types of antiviral agents has also been tested in this model: a chemokine receptor antagonist (T-22), a zinc finger inhibitor, and several ribonucleotide reductase inhibitors (hydroxyurea, Didox, and Trimidox), nucleoside analog reverse transcriptase (RT) inhibitors (including AZT, ddI, FTC, D-DAPD, and D-D4FC), a non-nucleoside RT inhibitor (UC-781), and a protease inhibitor (KNI-272). Analysis of the data suggests that in this model:

- Viral load in plasma seems sufficient in general to assess antiviral activity.
- Antiviral activity correlated well with reported clinical results (*i.e.*, reductions in plasma viral load) for agents with a wide variety of mechanisms of action, provided that the pharmacology of the agent is similar in humans and mice.

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Antiretroviral therapy during primary immunodeficiency virus infection can induce persistent suppression of virus load and protection from heterologous challenge in rhesus macaques

B. Rosenwirth[1], P. ten Haaft[1], W.M.J.M. Bogers[1], I.G. Nieuwenhuis[1], H. Niphuis[1], E.-M. Kuhn[1], N. Bischofberger[2], J.L. Heeney[1], and K. Überla[3] [1]Biomedical Primate Research Center (BPRC), Rijswijk, The Netherlands; [2]Gilead Sciences Inc., Foster City, California, U.S.A.; [3]Institute of Virology, University of Leipzig, Leipzig, Germany.

A limited period of chemotherapy initiated at a time point when virus is already detectable in plasma may provide a long-term clinical benefit. To evaluate this strategy we infected rhesus macaques with the pathogenic simian/human immunodeficiency virus RT-SHIV and treated them with the antiretroviral drug PMPA for eight weeks starting 7 or 14 days post infection. PMPA treatment suppressed viral replication efficiently in all monkeys. After stop of chemotherapy virus replication rebounded and viral RNA in plasma reached in four of the six monkeys levels comparable to the controls. In two animals, however, virus loads increased only moderately after withdrawal of the drug and became low and even undetectable shortly thereafter. These low levels of viremia remained stable for 16 months. To evaluate, whether the host responses, which were capable to keep RT-SHIV replication under control, were also sufficient to effectuate protection against infection with a heterologous highly pathogenic virus, we challenged those two animals which had established low RT-SHIV viremia with SIV_{8980}. Both monkeys proved protected against the heterologous virus. Only in one of the two animals low levels of SIV_{8980} replication were detected. Thus, by chemotherapy during the acute phase of pathogenic virus replication we could not only achieve persistent suppression of virus load in two out of six monkeys, but also protection from subsequent heterologous challenge. By this "chemotherapeutic attenuation" the replication kinetics of attenuated viruses could be mimicked and, in addition, a vaccination effect similar to that induced by live attenuated SIV vaccines was achieved.

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Effects in macaques of SHIV infection and HAART on the expression of P-gp and cellular kinases

S. JORAJURIA[1], P. CLAYETTE[1,2], N. DEREUDDRE-BOSQUET[1,2], J. LARGHERO[1], H. THIEBOT[1], O. NEILDEZ[1], B. BOSON[1], P. SELLIER[1], B. VASLIN[1], R. LE GRAND[1] and D. DORMONT[1]

[1] CEA, Service de Neurovirologie, DSV/DRM, CRSSA, Fontenay-aux-Roses, France;
[2] SPI-BIO, Massy, France.

Highly active antiretroviral therapy (HAART) improves both biological and clinical features of HIV-infected patients. Nevertheless, HIV infection is not eradicated: 30-50 percent of these patients develop mechanisms of therapeutic escape. The role of cell factors, particularly the one of P-glycoprotein (P-gp) and of cellular kinases which phosphorylate the nucleoside reverse transcriptase inhibitor (NRTI), was suspected.

In this study, we evaluated the effects of retroviral infection and HAART on the mRNA expression of P-gp and cellular kinases (thymidine kinase (TK), thymidylate kinase (TMPK), nucleoside diphosphate kinase (NDPK), and deoxycytidine kinase (dCK)) in SHIV89.6P-infected macaques treated with AZT, 3TC and indinavi r 4 or 72 h post-infection. Doses were equivalent to those administered in HIV-infected patients.

In these experimental conditions, cynomolgus macaques were not protected of SHIV infection, only a decrease in plasma SHIV RNA was evidenced. Concerning cell kinases, a significant over-expression of TK and TMPK was observed, concomitant of SHIV RNA plasma peak. Alternatively, the expression of P-gp was decreased in parallel with T CD4+ cell number drop. These effects of SHIV infection were abolished by HAART.

Altogether, these results confirm that the nucleoside metabolism could be disorganised in HIV patients, and it could be important to consider these effects to ameliorate the antiretroviral efficiency of HAART. Acute infection of cynomolgus macaques by SHIV89.6P may be an excellent animal model to evaluate *in vivo* antiretroviral effects of new HAART as well as these disorders.