97

_n_-Docosanol prevents vaginal transmission of SIVmac251 in rhesus macaques. C.J. Miller[1], M.J. Gersten[2], R.C. Davis[2] and D.H. Katz[2],. California Regional Primate Research Center and Department of Veterinary Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California, Davis, CA 95616[1] and LIDAK Pharmaceuticals, 11077 North Torrey Pines Road, La Jolla, CA 92307[2].

Vaginal microbicides provide the best opportunity to develop a practical method for preventing sexual transmission of HIV. Spermicides containing nonoxynol-9 may inactivate HIV but the tissue irritation produced by these products may abrogate their ability to prevent HIV transmission. *n*-Docosanol is a saturated alcohol which inhibits the replication of enveloped viruses *in vitro* and is non-irritating to rabbit vaginal mucosa. The potential of this compound as a topical microbicide to prevent HIV transmission was tested in the SIV/rhesus macaque system. Six mature female rhesus macaques were treated by placing 12% *n*-docosanol cream into the vagina before vaginal challenge with SIVmac251. Prior to SIV challenge each animal was treated twice with the *n*-docosanol cream (1 hour and 5 minutes prior to SIV challenge) and care was taken to insure that the cream completely covered the cervicovaginal mucosa. The animals were then challenged with 1 ml of SIVmac251 (10^2 $TCID_{50}$) mixed with 0.25 ml human seminal plasma, inoculum which has been shown previously to infect 7 of 7 female rhesus macaques. One hour after SIV challenge, a third application of 1 ml *n*-docosanol was placed in the vagina of the animals. Two naive control animals were challenged vaginally with the same virus inoculum. The animals were monitored for SIV infection by virus isolation and PCR from peripheral blood mononuclear cell (PBMC) samples collected at 7, 14, 28 days PI and every 2 weeks thereafter. The animals were monitored for seroconversion using whole virus ELISA and Western blot assays. PBMC samples were scored as SIV positive when both virus isolation and PCR assays revealed presence of SIV. Both naive control animals and one *n*-docosanol-treated animal became persistently viremic and seroconverted to SIV antigens. Significantly, the remaining five *n*-docosanol-treated animals resisted infection and remain seronegative more than 4 months after inoculation. These preliminary results demonstrate that *n*-docosanol cream is capable of preventing the vaginal transmission of SIV and suggest that a preparation containing this compound may be useful in preventing sexual transmission of HIV.

98

Pharmacokinetics in Mice of Bis(POM)-PMEA, the Bis(pivaloyloxymethyl) Ester Prodrug of 9-(2-Phosphonylmethoxyethyl)adenine.

L. Naesens[1], J. Neyts[1], J. Balzarini[1], N. Bischofberger[2] and E. De Clercq[1].

[1]Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium and [2]Gilead Sciences, Inc., 353 Lakeside Drive, Foster City, California 94404.

Bis(POM)-PMEA is a lipophilic ester prodrug of the potent broad-spectrum antiviral agent PMEA. In retrovirus-infected mice, oral treatment with bis(POM)-PMEA proved equally effective as subcutaneous PMEA administration at equimolar doses, suggesting a favorable oral bioavailability for bis(POM)-PMEA. We now compared the pharmacokinetics of bis(POM)-PMEA and PMEA in mice. The animals were given an oral gavage of bis(POM)-PMEA or PMEA, or an intravenous bolus injection of PMEA (all doses at 50 mg of PMEA equivalent per kg). Plasma concentrations of free PMEA were measured by HPLC analysis with fluorescence detection. The oral bioavailability (as calculated from the AUC values of the plasma elimination curves) was 57% and 16% for bis(POM)-PMEA and PMEA, respectively. Following intravenous injection, PMEA was rapidly cleared from plasma (elimination half-life: 8.7 min; total body clearance: 1.8 l/kg/hr). By contrast, oral administration of bis(POM)-PMEA resulted in the prolonged presence of free PMEA in plasma, its plasma concentration being 0.8 µg/ml at 8 hours after oral administration of the prodrug. Bis(POM)-PMEA as such was not detected in plasma, and only minute amounts of mono(POM)-PMEA were found shortly after oral administration of bis(POM)-PMEA. It therefore appears that oral bis(POM)-PMEA is readily absorbed and cleaved to PMEA, that then accumulates in the liver from where it is slowly released in the circulation. In contrast, oral administration of the diphenyl ester prodrug of PMEA resulted in high plasma levels of diphenyl-PMEA, yet low concentrations of free PMEA. Our plasma data were confirmed by the results on urinary excretion of PMEA after oral administration of bis(POM)-PMEA, diphenyl-PMEA or PMEA (urinary recovery of PMEA: 42%, 4% and 5%, respectively). Overall, these pharmacokinetic data are in agreement with the *in vivo* data on the antiviral efficacy of oral bis(POM)-PMEA, diphenyl-PMEA and PMEA.