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New Antiretroviral Acyclic Nucleotide Analog: (R)-2'-Me-PMEG ((R)-N⁹(2-Phosphonylmethoxypropylguanine). H. Yang, C. Franco, R. Drain, V. Brankovan, M. Hitchcock, K-L. Yu, J. Bronson, J. Martin, and R. Datema, Bristol-Myers Squibb Company, Wallingford, CT.

(R)-2'-Me-PMEG ((R)-N⁹(2-phosphonylmethoxypropylguanine) is a more selective inhibitor of HIV and CMV replication than its congener PMEG (N⁹-(2-phosphonylmethoxyethyl guanine).

	IC_{50} (μM)				TC_{50} (μM)		CC_{50} (μM)
	HIV	HCMV	MCMV	MuLV	CEM	MRC_5	CEM
PMEG	0.2	.15	<.1	.005	15	100	0.2
R-2'-Me-PMEG	1	15	1	0.05	>500	>300	300

IC_{50}: conc. needed to inhibit virus replication by 50%; TC_{50}: toxicity to 50% of the uninfected cells; CC_{50}: 50% inhibition of growth of CEM cells. Because of the selective anti-HIV and anti-CMV effects, (R)-2'-Me-PMEG was tested in vivo against an MuLV (RVB-3) and MCMV infection, measuring effects on splenomegaly and survival, respectively. The doses tested were 30, 10 and 3 mg/kg/day and were given 1x per day, ip. At 30 mg/kg/day, the compound demonstrated 92% inhibition of splenomegaly, but treatment had to be discontinued after 16 days because of toxicity. A dose-dependent effect was observed and the PD_{50} in the MuLV-model was ~3 mg/kg/day. When the total dose corresponding to 3 mg/kg/day was administered every other day for 3 wk rather than daily, the compound was equally efficacious but not toxic. Inhibition of splenomegaly was associated with a decrease in viral titers in the spleen. The compound was not active against MCMV in vivo. These results show that modification of PMEG can lead to compounds with improved antiretroviral selectivity in vitro and in vivo.

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Treatment of Chronic Carriers of Woodchuck Hepatitis Virus Infection with Thymosin Alpha-1. **Brent Korba[1], Bud Tennant[2], Paul Cote[1] and John Gerin[1]. 1-Division of Molecular Virology and Immunology, Georgetown Univ., Rockville, MD and 2-College of Veterinary Medicine, Cornell University, Ithaca, NY.**

Thymosin alpha-1 [TA1] is a member of a class of naturally occurring, small thymic peptides which have a variety of immunoregulatory functions. Since TA1 is highly conserved among all mammalian species studied, human TA1 is useful for studies in a variety of animal model systems. The Eastern woodchuck and its naturally-associated hepadnavirus, WHV (woodchuck hepatitis virus), constitute a relevant model for the study of HBV (hepatitis B virus) infection and virus-associated disease in man, including hepatocellular carcinoma. In a controlled study, 6 chronic WHV carrier woodchucks were treated with twice weekly subcutaneous injections of 10μg/Kg TA1 for 6 months. No changes in the levels of viremia or WHV DNA replication intermediates [RI] in the liver tissues of the untreated group of 6 woodchucks was observed during the study period. At the end of the treatment period, serum WHV DNA levels were depressed 100 to over 10,000-fold in all 6 treated animals (relative to pretreatment levels); viremia was undetectable in 4 of the treated animals. Analysis of liver biopsies demonstrated a 3 to 300-fold decline in the levels of RI (relative to pretreatment levels) in the treated animals, which correlated with the relative levels of viremia observed in the individual animals. As of 3 months following the end of the treatment period, viremia remained undetectable in 4 of 6 treated animals and the levels of RI in liver tissues were still depressed more than 100-fold in these 4 woodchucks; WHV replication in the remaining 2 treated animals returned to pretreatment levels. No clinical signs of toxicity were observed and the levels of markers of WHV replication were significantly different between the treated and untreated groups of woodchucks ($p < 0.05$). TA1 appears to be a safe and effective anti-hepadnaviral agent.