420 nM for ODE-HPMPA, 1400 nM for ODE-HPMPC, and >7800 nM for ODE-HPMPG. Time of addition studies revealed that the potency of each compound was constant for up to 8 h following adenovirus attachment. The results of this study support the further testing of these compounds as candidates for the clinical treatment of adenoviruses.

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## Indole Derivatives Are Potent Inhibitors of HIV Integrase

Periyasamy Selvam[1,*], Kasthuraiah Maddali[2], Yves Pommier[2]

[1] *Dept of Medicinal Chemistry, Amrita School of Pharmacy, Kochi-26, India;* [2] *Laboratory of Molecular Pharmacology, Centre for Cancer Research, NCI, NIH, Bethesda, USA*

HIV Integrase is a recently validated novel therapeutic target for designing potential antiviral agents for combating HIV/AIDS. Indole is versatile lead molecule for invention of newer class of anti-HIV therapeutic agents. The indole derivative Delarviridine (NNRTI) has been approved for the treatment of HIV/AIDS and another indole derivative 5CITEP was also investigated for inhibition of HIV integrase activity. Based on those prior findings, the present work is to design novel indole derivatives as HIV integrase inhibitors. Synthesized compounds were investigated for inhibition of crucial steps in HIV Integrase activity such as the 3′-Processing and Strand transfer reactions. Our results will show that lead molecules were not active against HIV integrase. But their three derivatives were found to be more active against both step, with some selectivity for the strand transfer step. Among the tested compounds compound B inhibits the 3′-processing at the concentration of 5.7 μ M and strand transfer at the concentration of 4.5 μM. Details of synthesis and HIV Integrase activity data will be presented.

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## Antiproliferative Effects of Octadecyloxyethyl-Phosphonomethoxyethylguanine (ODE-PMEG) on the Growth of Human Papilloma Virus Positive Cervical Carcinoma (ME-180) Cells In Vitro and Solid Tumors in Athymic Nude Mice

Julissa Trahan*, Kathy Aldern, Karl Hostetler

*University of California San Diego and the Veterans Medical Research Foundation, San Diego, USA*

Cidofovir (CDV) inhibits HPV DNA positive cervical cancer cell proliferation by reducing levels of HPV E6 protein which results in upregulation of p53. We previously showed that ODE-CDV was several logs more active than CDV in vitro versus Me-180 cervical cancer cells (HPV 69). To extend these findings, we have synthesized ODE-PMEG and compared its activity versus Me-180 cervical cancer cells with ODE-CDV. In primary human fibroblasts, ODE-CDV and ODE-PMEG have 50% inhibitory concentrations of 4.2 and 5.0 μM, respectively. However, against the human cervical cancer cell line, Me-180, ODE-CDV and ODE-PMEG had $IC_{50}$s of 0.39 and 0.002 μM, respectively. ODE-PMEG has a selectivity for cervical cancer cells of 2500 versus only 10 for ODE-CDV. Therefore, we decided to evaluate the in vivo effect of ODE-PMEG versus Me-180 solid tumors in athymic nude mice. We used 24 female mice injected subcutaneously with $5 \times 10^6$ Me-180 cervical cancer cells. The tumors were allowed to become established for 14 days. Tumor measurements were taken in two dimensions and multiplied to get a total tumor volume. Baseline tumor volume measurements were approximately 30–35 $mm^2$. Mice were then randomized into three groups of eight mice each. The mice were dosed by intratumor injection of 25 μg (1 mg/kg) of ODE-PMEG every other day for a total of 21 days. Control mice received 50 μl of 0.9% saline solution every other day. Tumor volume measurements and body weights were taken 3 times a week during the 21 day dosing period and continued to 39 days. Control mice injected with vehicle showed tumor size increases of 298%. Mice treated with 25 μg of ODE-PMEG every other day for 21 days (10 doses) resulted in a 38% decrease in tumor volume which remained stable after dosing was stopped. In conclusion, control Me-180 cervical cancers treated with vehicle increased by 298% while mice in the 1 mg/kg group showed a 38% decrease in tumor volume which was stable after dosing stopped. No significant changes in weight loss or other toxic effects were observed in the treated group.

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## Antiviral Activity of Geneticin Against Dengue Virus

Xianchao Zhang[1,*], Peter Mason[2], Edward Dubovi[3], Alex Birk[1]

[1] *Institute for Hepatitis and Virus Research, Doylestown, USA;* [2] *University of Texas Medical Branch, Galveston, USA;* [3] *Cornell University, Ithaca, USA*

The aminoglycoside, Geneticin (G418), was recently shown to have antiviral activity against bovine viral diarrhea virus (BVDV). Since BVDV, dengue virus (DENV) and yellow fever virus (YFV), all belong to the Flaviviridae family, it seemed possible that a common step in their life cycle might be affected by this aminoglycoside. Here it is shown that Geneticin prevented the BHK cells killing (CPE) resulting from DENV-2 infection, in a dose-dependent manner with an EC50 of 3 mcg/ml. Geneticin had no detectable effect upon YFV in BHK cells. Geneticin also inhibited DENV-2 viral yield with EC50 of 2 mcg/ml and EC90 of 20 mcg/ml. Selectivity index of anti-DENV activity of Geneticin in BHK cells was established to be about 70. Furthermore, 25 mcg/ml of Geneticin nearly completely blocked plague formation induced by DENV-2, but not YFV. In addition, Geneticin, inhibited DENV-2 viral RNA replication and viral translation. Gentamicin, Kanamycin, and the guanidinylated Geneticin showed no anti-DENV activity. Neomycin and Paromomycin demonstrated weak antiviral activity at high concentrations. Finally, aminoglycoside-3′-phosphotransferase activity of neomycin-resistant gene abolished antiviral activity of Geneticin. Our data indicate that, although the antiviral activity of Geneticin is broad, with activity against DENV-2, BVDV and other viruses, it is selective. That is, Geneticin has no activity against YFV. The work here also shows that the antiviral mechanism of Geneticin against DENV replication and translation is different from its ability to inhibit assembly and release of BVDV, suggesting that the drug can broadly target different viral functions. Furthermore, similar to its anti-BVDV activity, we conclude that the anti-DENV activity of Geneticin is likely to be due to its ring I and II. Overall, our data suggest that Geneticin represents a potentially novel class of virus-selective antivirals with broad-spectrum antiviral activity.

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