# Session d'affichage
# Poster Session

## Recherche fondamentale (biomédicale)
## Basic Research (Biomedical)

### M.C.P.61

**ENHANCING THE RESEARCH AND DEVELOPMENT TIME FOR NEW AIDS DRUGS: THE PRE-IND PROGRAM AND PROACTIVE CLINICAL GUIDANCE AT FDA'S DIVISION OF ANTIVIRAL DRUGS.**

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The U.S. Food and Drug Administration (FDA) Division of Antiviral Drug Products (DAVDP) is responsible for the regulation of pharmaceuticals indicated for the treatment of AIDS and AIDS-related disorders in the U.S. The primary role of DAVDP scientists and physicians is to expeditiously review the nonclinical and clinical efficacy and toxicity data in Investigational New Drug Applications (INDs) and New Drug Applications (NDAs). However, to facilitate the rapid preclinical and clinical research and development of new AIDS drugs so that promising new therapies will be available without delay, DAVDP has created two programs for providing detailed guidance to drug developers during all phases of drug development, from the earliest preclinical studies, throughout clinical trials, to market approval. These programs focus on making the DAVDP reviewer's expertise in drug development available to pharmaceutical firms and individual investigators worldwide. The goal of the Pre-IND Program is to focus the drug developer's preclinical development program on those specific studies necessary to rapidly complete the preclinical work-up of promising new AIDS drugs, and move the drugs into well-designed clinical studies as quickly as possible. The purpose of the Proactive Clinical Guidance is to help the sponsor optimize the design of clinical trials to produce the most useful data possible upon which marketing approval can be based. The AIDS drug-review process in DAVDP will be described, and contact points for the Programs will be provided. Major problems seen in the development of AIDS drugs and viable solutions to facilitate drug development will be discussed.

### M.C.P.62

Low Dose Naltrexone in the Treatment of AIDS: Long Term Follow-up Results
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Objective. To evaluate the long term results of the treatment of AIDS with low dose (1.75 mg qhs) of naltrexone, an opiate antagonist.
Method. Thirty-eight patients with AIDS were treated in a 3 month placebo controlled trial of naltrexone, after which the placebo patients were switched to naltrexone and both groups followed on naltrexone since.
Results. During the placebo controlled period the treatment group showed significantly fewer O.I.s and a significant drop in their markedly elevated levels of sCD2FN. Twenty-five of the 38 patients while on naltrexone eventually showed a drop in sCD2FN levels from means of 160 U.u. to 11.75 U.u., over a 4 to 12 month period (called "responders"). The 13 patients whose interferon did not drop ("non-responders") all died within 9 months. Of the responder group 21/25 had survived at 12 months and 19/25 at 18 months. At 39 months 10 of the 25 responders are still alive, 4 years after AIDS diagnosis. Only one of these 10 has suffered an O.I. in the course of the trial. The other 9 are all working full-time and are essentially symptom free 4 years after AIDS diagnosis and 39 months after starting naltrexone. The mean T4 level in this group has not dropped during the trial. The responders also showed an increase in lymphocyte proliferative responses to PHA and have shown no decline in responses to CMV antigen. p24 antigen levels and anti p24 antibodies will be presented as well.
Conclusion. Low dose naltrexone may be a useful immunomodulating agent in AIDS related illness with 40% of responding patients with AIDS showing long term survival.

### M.C.P.63

ANTI-HIV-1 ACTIVITY, TOXICITY AND PHARMACOKINETICS OF TOTALLY NOVEL NUCLEOSIDE ANALOGS
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Objective: To test a number of nucleoside analogs in which the 3'-carbon of the pentose is replaced by an S or O atom.
Methods: Cpds. were assayed for anti-HIV-1 activity (RT, p24 Ag, cell viability) in T-cell lines (H-9, MT-4) and a monocyte/macrophage cell line (U-937).
Results: The lead cpd. NGPB-21 (base = cyt; 3' = S) had a therapeutic index (TI 100 (min. to MT) and, unlike AZT, had no cell toxicity at therapeutic concn. Also, NGPB-21 was very active in the HIV-1 infected U-937 cell line. Rats given NGPB-21 at 100 mg/kg p.o. daily for 14 days showed no inhibition of body growth, and had normal organ wts. (liver, spleen, testis, kidney) and hematologic profile. Rats given NGPB-21 at 200 mg/kg p.o. readily absorbed the drug and had peak blood levels at 1.5 hr. and t½ 1.0hr. Another cyt analog (NDII130A) in which 3'- = CH2 and the base linkage is in the unnatural α-configuration showed a favorable therapeutic index in vitro.
Conclusion: NGPB-21 and NDII130A are novel nucleosides showing high potential as anti-AIDS drugs.

### M.C.P.64

**ISOLEUCINE ESTER OF ZIDOVUDINE (IAZT) AS A PRO-DRUG WITH ENHANCED EFFICACY AGAINST HIV-1.**

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Objective. To develop a pro-drug of zidovudine (AZT) with increased therapeutic index in an attempt to overcome the dose-related toxicity (anemia and neutropenia).
Methods. Among various approaches of developing pro-drugs, we have successfully inserted an amino acid, isoleucine, at the 5'-OH function of AZT by esterification. Peripheral blood lymphocytes (PBL) from seven donors were employed to determine cellular drug uptake, cytotoxicity and anti-HIV-1 activity. Murine bone marrow cells were used to determine toxicity by $^{3}$H-thymidine incorporation. Preliminary pharmacokinetic studies were conducted in rabbits.
Results. Cellular uptake studies in PBL demonstrated that $^{3}$H-IAZT achieved approximately 60% greater intracellular concentration than $^{3}$H-AZT within 2 hr. IAZT was significantly less toxic than AZT at various concentrations to murine bone marrow cells as measured by uptake of $^{3}$H-thymidine. The $ED_{50}$ concentration to inhibit the production of HIV-specific p24 antigen was 0.035 uM for IAZT whereas AZT required twice the amount of 0.07 uM level. Preliminary pharmacokinetic experiments in rabbits demonstrated a 2-compartment model in plasma with a $\beta$-elimination $T_{\frac{1}{2}}$ of 105 min for AZT and 187 min for IAZT.
Conclusion. These results demonstrated that IAZT has a higher therapeutic index than AZT as an anti-HIV-1 agent.
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### M.C.P.65

**THE CARBOCYCLIC ANALOGUE OF OXETANOCIN G INHIBITS THE REPLICATION OF CYTOMEGALOVIRUS AND HERPES SIMPLEX VIRUSES IN VITRO**

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Objective. To evaluate the in vitro antiviral activity of the newly synthesized (5)-9-[2',3'-bis(hydroxymethyl)-1-cyclobutyl]guanine (A-69992) against human cytomegalovirus (HCMV) and herpes simplex viruses type 1 and type 2 (HSV-1 and HSV-2).
Methods. The antiviral activity of A-69992 against HSV-1 and 2 was determined in Vero cells using a virus induced cytopathogenic effects (CPE)-inhibition assay. The minimum drug concentration which reduced the microscopically observed CPE by 50% ($ID_{50}$) was calculated by regression analysis, and drug toxicity was determined in uninfected control cells. Ara-A and acyclovir were tested concomitantly. Activity against HCMV was determined in a virus yield reduction assay in human diploid embryonic lung (MRC5) cells. After 6 days, drug cytotoxicity was quantitated by the ability of viable host cells to reduce the tetrazolium salt (MTT), and the relative yield of infectious virus from the drug treated and untreated cultures was determined by plaque assay in MRC5 cells. Ganciclovir was tested concomitantly.
Results. The following $ID_{50}$'s were determined for A-69992 and acyclovir (virus, $ID_{50}$ (ug/mL) for A-69992, $ID_{50}$ for acyclovir): HSV-1(E-377), 0.57,0.43; HSV-2(G), 1.00, 1.85; HSV-1(BW 10168 TK deficient), 4.06, 13.03; HSV-2(BW9767 TK deficient), 0.79, 12.65. A-69992 was partially cytotoxic to Vero cells at 100 ug/mL, while acyclovir showed no cytotoxicity at 225 ug/mL. At a nontoxic concentration of 32 ug/mL, A-69992 reduced the yield of infectious HCMV in MRC5 cells from $10^{4.25}$ PFU to below the detection limit ($<10^{0.5}$ PFU). At the lowest concentration tested, 1.0 ug/mL, the yield of infectious virus was reduced 14 fold. At the highest concentration tested, 320 ug/mL, the drug cytotoxicity was 24%. By comparison, ganciclovir appears to be about 10 times as potent as A-69992 in this system.
Conclusion. A-69992 exhibits selective in vitro antiviral activity against HSV-1, HSV-2, and HCMV at concentrations as low as 1 ug/mL, and it is more potent than acyclovir against TK deficient strains of HSV. These observations, and those of Hayashi et al ("Carbocyclic Oxetanocin Analogues that Inhibit Replication of Human Immunodeficiency Virus in T-Cells and Monocytes/Macrophages in Vitro"), may be of value in developing a new drug therapy for AIDS.

### M.C.P.66

**INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS INFECTIVITY BY CHLOROQUINE.**

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The effect of chloroquine, an anti-malarial drug known to affect cellular exocytic pathways, was studied in two retroviral systems: Human Immunodeficiency Virus (HIV-1) and avian reticuloendotheliosis virus (REV-A). With chloroquine treatment of virus infected cells (HIV-1/H9 and REV/cBMC), significant size reduction of the cell and virus associated surface glycoproteins, gp90 of REV-A and gp120 of HIV-1, was observed. In the case of HIV-1, extracellular virions derived from treated cells contained very little gp120. Infectivity and reverse transcriptase assays carried out with HIV-1 demonstrated that by chloroquine treatment virus yield was reduced and noninfectious virions were released. The data suggests that inhibition by chloroquine is most likely due to interference with terminal glycosylation in the trans-Golgi network. Studies are in progress to determine the effect of chloroquine on HIV-1 and its relatives produced by other cell types e.g. monocytes/macrophages and to evaluate whether chloroquine and its existing analogs or newly synthesized related weak bases could be useful either alone or in combination with other drugs to attack various stages of the virus life cycle.
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