2',3'-Dideoxy-2',3'-didehydrothymidine (D4T): A Potent and Selective Agent Against Human Immunodeficiency Virus (HIV). I. Ghazzouli*, M. Hitchcock*, V. Brankovan*, J. Desiderio*, J-P. Sommadossi§, M. August+, T-S. Lin+, W. Prusoff+, M. Mansuri* and J. Martin*. *Bristol-Myers Co., Wallingford, CT.; *Oncogen, Seattle, WA.; §University of Alabama, Birmingham, AL; +Yale University, New Haven, CT.

2',3'-Dideoxynucleoside derivatives have been shown to exhibit activity against HIV. The anti-HIV potency of D4T was evaluated, in vitro, using CEM cell cultures inoculated with 30 $TCID_{50}$ of HIV (LAV). Viral growth was measured as the amount of P_{24} antigen in the culture supernatant at day 8 post-infection. D4T inhibited HIV replication with an ID_{50} ranging from 1 to 0.25 μM and inhibited the incorporation of [^{3}H]TdR into DNA of CEM cells with an ID_{50} of 40 μM; cell growth at 72 hrs was inhibited with a $TCID_{50}$ of 40 μM. The in vitro effect of D4T on the growth of normal human hematopoietic progenitor cells showed it to be significantly less toxic than azidothymidine (AZT) and 2',3'-dideoxycytidine (DDC). The concentrations required for 50% inhibition of GM-CFU (granulocyte-monocyte colony-forming units) were 100 μM for D4T as compared to 1 μM for AZT and 10 μM for DDC. D4T is water soluble and stable in aqueous neutral and acidic solutions (pH 2-7). The anti-HIV potency, stability and the lack of bone marrow toxicity of D4T support the progression of this compound to clinical evaluation against AIDS.

Synergisitic Activity of 3'-Azido-3'-deoxythymidine (Zidovudine) and Phosphonoformate (Foscarnet) Against Human Immunodeficiency Virus Type 1 *In Vitro*. R. F. Schinazi*, B. F. H. Eriksson, B. H. Arnold, and D. L. Cannon. Veterans Administration Medical Center and Emory University School of Medicine, Department of Pediatrics, Atlanta, Ga.

3'-Azido-3'-deoxythymidine (AZT), has received considerable attention because it was the first agent shown in a double-blind placebo-controlled study to produce clinical benefits in certain patients with AIDS and advanced AIDS-related complex. Foscarnet (trisodium phosphonoformate, PFA), inhibits both HIV-1 and cytomegalovirus (CMV) *in vitro*. PFA is being investigated as a possible candidate for the treatment of HIV-1 and CMV infected patients. Since concomitant treatment of PFA is currently being considered in patients with CMV retinitis undergoing AZT therapy, it was important to determine the type of interaction produced by these drugs *in vitro*. The use of combinations of compounds with different modes of action is also an attractive and logical extension of any therapeutic approach to enhance efficacy. The effect of AZT and PFA in combination was examined on the replication of HIV in human peripheral blood mononuclear (PBM) cells. The median effect method and multiple drug effect analysis (for a mutually non-exclusive interaction) was used to calculate combined drug effects (AAC 30:491, 1986). The EC_{50} (μM) for the various drugs or combinations was: AZT = 0.0063, PFA = 22.0, AZT-PFA (1:1,000) = 3.5; and AZT-PFA (1:4,000) = 8.5. AZT-PFA produced a combination index below 1 over a wide range of effect values (F_a), suggesting synergism. At a ratio of 1:4,000 the combination of AZT and PFA produced no toxicity greater than the agents alone to uninfected proliferating PBM cells; the highest combined concentration tested was 128.032 μM. PFA was not toxic to PBM cells when tested up to 640 μM. These results demonstrate that, at concentrations easily attained *in vivo*, combinations of AZT and PFA interact synergistically in inhibiting HIV-1 replication in human PBM cells. Similar studies in CMV infected cells to determine if AZT interferes with the anti-CMV activity of PFA will be reported. *(Supported by USPHS grant 44094, and the Veterans Administration)*