Oral Session II

Herpesvirus Infections – Part I

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Benzimidazole Ribonucleosides: A New Class of Antivirals with Potent and Selective Activity Against Human Cytomegalovirus. J.C. Drach, L.B. Townsend, M.R. Nassiri, S.R. Turk, L.A. Coleman, R.V. Devivar, G. Genzlinger, E.D. Kreske, T.E. Renau, A.C. Westerman, and C. Shipman, Jr. University of Michigan, Ann Arbor, MI, 48109; K.K. Biron and R. Dornsife, Burroughs Wellcome Co., Research Triangle Park, NC 27709; E.R. Kern, University of Alabama at Birmingham, Birmingham, AL 35294, U.S.A.

Benzimidazole nucleosides substituted with halogen in the 4, 5, or 6-positions were described as having activity against RNA viruses by Tamm and coworkers in 1954 . Townsend and Revenkar (1970) subsequently prepared 2-substituted analogs as potential anticancer agents. Our more recent interest in deazapurine nucleosides as potential anti-herpes agents led us to evaluate 2,5,6-trichloro-1-(ß-D-ribofuranosyl)benzimidazole (TCRB) and related analogs against human cytomegalovirus (HCMV). We found highly specific structure-activity relationships among these analogs (reported elsewhere in this conference) and herewith describe details of antiviral activity. TCRB and its 2-bromo analog (BDCRB) - but not its 2-unsubstituted analog (DRB; Tamm *et al., J. Exp. Med.* **99**:227, 1954) nor its heterocyclic base - reduced HCMV titers by at least five $\log_{10}$ units (100,000-fold) at non-cytotoxic concentrations (10 - 32 µM). Despite potent activity against HCMV, both compounds were only weakly active or inactive against other herpesviruses (HSV-1, HSV-2, VZV, murine CMV), HIV, and a panel of RNA viruses. Both compounds were as active against clinical isolates of HCMV both sensitive and resistant to ganciclovir as they were against laboratory strains of the virus. Initial mode of action studies revealed that neither compound inhibited HCMV or cellular DNA synthesis at concentrations which produced multiple $\log_{10}$ reductions in virus titer. Little to no cytotoxicity was observed in uninfected human cells (KB and WI-38) at concentrations up to 100 µM in cell growth, labeled precursor, plating efficiency, and DNA flow cytometry experiments. In comparison to ganciclovir, these concentrations were less toxic to the growth of granulocyte/macrophage and erythroid human bone marrow progenitor cells *in vitro*. We conclude that TCRB and BDCRB have potential as drugs for HCMV infections because they have potent activity against HCMV, act by a unique mechanism, and are non-cytotoxic in their antiviral dose range. This study was supported by contracts N01-AI42554, N01-AI72641 and grant U01-AI31718 from N.I.A.I.D.