Oral Session IV — Hepadnavirus Infections

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Identification of BMS-200,475 as a Novel and Potent Inhibitor of Hepatitis B Virus Replication. R.J. Colonno, S.F. Innaimo, M. Seifer, E. Genovesi, J. Clark, G. Yamanaka, R. Hamatake, B.Terry, D. Standring, G. Bisacchi, J. Sundeen, and R. Zahler. Bristol-Myers Squibb Pharm. Res. Inst., Wallingford, CT, USA

BMS-200,475, a cyclopentyl guanosine analog with an exo carbon-carbon double bond, was identified as a potent inhibitor (EC_{50} = 3.75 nM, CC_{50} = 30 μM) of hepatitis B virus (HBV) replication using HepG2.2.15 cells. Structually related compounds with adenine, iodouracil or thymine base substitutions were significantly less potent. BMS-200,475 is highly selective, showing no significant inhibitory activity against a panel of unrelated RNA and DNA viruses (EC_{50} >10 μM). BMS-200,475 was efficiently phosphorylated to its active triphosphate form by cellular enzymes. BMS-200,475-TP has a half-life of 15 hr in HepG2 cells. *In vitro* biochemical assays demonstrated that BMS-200,475-TP is a potent inhibitor of HBV polymerase, inhibiting both the priming and elongation steps of HBV DNA replication. Oral administration of as little as 0.02 mg/kg/day BMS-200,474 proved highly efficacious in woodchuck animal studies. Comparative *in vitro* and *in vivo* studies demonstrated the clear superiority of BMS-200,475 to 3TC. These results indicate that BMS-200,475 is a potent and selective inhibitor of HBV and an excellent candidate for further development.

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Synergistic Inhibition of *In Vitro* Hepadnaviral Replication by PMEA and Penciclovir or Lamivudine. T. Shaw, D. Colledge and S.A. Locarnini. Victorian Infectious Diseases Reference Laboratory, Fairfield, Victoria, 3078, AUSTRALIA.

Combination chemotherapy has a number of well-recognised advantages over monotherapy and is likely to be used increasingly in future to treat persistent viral infections, where there is an increased risk of development of viral resistance and cumulative toxicity. The broad-spectrum antiviral acyclic nucleotide analog PMEA [9-(2-Phosphonyl methoxy-ethyl)adenine)] has been recently identified as a potent inhibitor of hepadnaviral replication with antiviral activity comparable to that of the "new" anti-HBV nucleoside analogs lamivudine ([-]-β-L-2',3'-dideoxy-3'-thiacytidine; 3TC) and penciclovir (9-[2-hydroxy-1-(hydroxymethyl) ethoxymethyl]guanine; PCV). How PMEA interacts with 3TC and PCV is therefore of practical importance. In primary duck hepatocyte (PDH) cultures derived from ducklings congenitally infected with the duck hepatitis B virus (DHBV), 0.15 and 2.2 μM PMEA inhibited viral DNA replication by 50% and 90% respectively. These concentrations were reduced aproximately 5- fold in the presence of 0.05 μM 3TC and approximately 20-fold in the presence 0.05 μM PCV. 0.05 μM 3TC or PCV alone inhbited DHBV DNA replication by 33% and 37% respectively. Three-dimensional dose-response surface analysis of PMEA in combination with 3TC or PCV confirmed that the combinations acted synergistically over a wide range of clinicaly relavent drug concentrations.Cytotoxicity was not observed at drug concentrations up to 100-fold greater than required to reduce viral replication by 90%. These results suggest that combinations of PMEA with either 3TC or PCV may act synergistically against HBV in vivo.