44

Combination of LY300082 with AZT and DDI Give Synergistic Effects on HIV Replication in Cells and on HIV Reverse Transcriptase. H. Zhang[1], L. Vrang[1], K. Backro[2], T. Unge[2], P. Engelhardt[1], M. Hogberg[1], J. Kangasmetsa[1], P. Lind[1], R. Noreen[1], C. Sahlberg[1], X.-X. Zhou[1], N. G. Johansson[1], J. M. Morin, Jr.[3], R. J. Ternansky[3], F. W. Bell[3], C. L. Jordan[3], M. D. Kinnick[3], J. A. Palkowitz[3], C. A. Parrish[3], P. Pranc[3], R. T. Vasileff[3], S. J. West[3], and B. Oberg[1,2].
[1]Medivir AB, Huddinge, Sweden; Department of Molecular Biology, BMC, Uppsala, Sweden; [3]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA.
LY300082, a member of a new class of non-nucleoside reverse transcriptase inhibitors related to LY73497, inhibits HIV-1 replication *in vitro* at nanomolar concentration. Combinations of LY300082 with AZT or DDI were tested on MT4 cells infected with HIV-1 IIIB or HIV-1 IIIB containing two mutations, Leu100 to Ile and Tyr188 to His in RT gene. LY300082 was also tested in combination with AZT-TP for inhibition of recombinant HIV-1 RT wt and HIV-RTs with Ile 100 or Cys181 mutations. Analysis by the median effect plot method (Chou and Talalay) gave combination indices below 1 for all tested viruses in cell culture, as well as for the wild type and mutated RTs indicating synergistic inhibitory effects for LY300082 in combination with AZT.

45

Comparative Efficacy of HIV Inhibitors on Cells Infected with Cell Free HIV or Cocultivated with HIV-Infected Cells . L. Vrang[1], C. Rydergard[1], C. Ahgren[1], P. Engelhardt[1], M. Hogberg[1], J. Kangasmetsa[1], P. Lind[1], R. Noreen[1], C. Sahlberg[1], X.-X. Zhou[1], N. G. Johansson[1], C. Lopez[2], J. M. Morin, Jr.[2], R. J. Ternansky[2], F. W. Bell[2], C. L. Jordan[2], M. D. Kinnick[2], J. A. Palkowitz[2], C. A. Parrish[2], P. Pranc[2], R. T. Vasileff[2], S. J. West[2], and B. Oberg[1].
[1]Medivir AB, Huddinge, Sweden; [2]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA.

Several anti-HIV compounds were tested in MT2 cells infected with cell-free virus at a multiplicity of 5-25 $TCID_{50}/10^4$ cells or cocultivated with infected MT2 cells in a ratio of 1000:1. Some cultures were maintained for three weeks and the compounds were removed at different time points. LY300082 and other compounds from this series of new non-nucleoside RT inhibitors were almost equally active in both systems, while compounds like AZT, DDC, DDI, 9-Cl-TIBO, and L697,661 lost efficacy in the cultures where the virus was introduced with infected cells. The inhibitory effect of LY300082 remained after three weeks of culture in a cocultivation assay even if the compounds was removed after two weeks.