Oral Session IV

Targeting of Antiviral Agents

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The TIBO-site on HIV-1 reverse transcriptase represents a new target for anti-HIV chemotherapy

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Several tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione (i.e. TIBO derivatives) have proved to be potent, highly selective and specific inhibitors of HIV-1 replication *in vitro*. The 50% inhibitory concentration (IC_{50}) of these compounds for HIV-1 replication in various host-cell types are in the nanomolar range, whereas drug toxicity is observed only at 10,000- to 100,000-fold higher concentrations. Both virion-derived and recombinant reverse transcriptase (RT) of HIV-1, but not HIV-2 RT are sensitive toward TIBO compounds. No inhibition has been observed with other human and murine reverse transcriptases or any of the cellular DNA polymerases. Enzyme kinetic studies have indicated that TIBO compounds interact with HIV-1 RT in an uncompetitive fashion with regard to the template-primer complex. TIBO-mediated RT inhibition is dependent on the type of template-primer. The highest RT inhibition is observed when poly(C).oligo(dG) or the natural template is used. Moreover, TIBO's preferentially inhibit the RNA-dependent DNA polymerase function of HIV-1 RT. Several other molecules such as HEPT (an acyclic uridine derivative) and BI-RG-587 (a benzodiazepine derivative), have been described which show TIBO-type antiviral properties. The characteristics of RT inhibition by these compounds indicate that they are targeted at the TIBO-site of HIV-1 RT.