Oral Session I — Retrovirus Infections I

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INTERACTION OF THE HIV FUSION INHIBITOR AR177 (ZINTEVIR) WITH THE HIV TYPE 1 SECOND RECEPTOR

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AR177 (Zintevir) is an oligonucleotide composed of only deoxyguanosine and thymidine of 17 nucleotides in length and containing a single phosphorothioate internucleoside linkage at its 5' and 3' ends. We have reported the anti-HIV activity of this G-quartet forming oligonucleotide with a 50% effective concentration ranging from 0.5 μg/ml to 16 μg/ml against multiple strains of HIV-1, including syncytium, and non-syncytium-inducing, T cell and macrophage tropic strains. Due to its anionic nature, the anti-HIV activity of AR177 can be attributed to the inhibition of an early stage (binding/fusion) of viral replication. Recently, the β-chemokines, RANTES MIP-1α and MIP-1β were found to be potent inhibitors of HIV replication. Their mode of action appears to be associated with the inhibition of the interaction of HIV with the β-chemokine receptor (HIV second receptor) required for fusion of the virus with the cell membrane. We have found that AR177 inhibits, in a dose-dependent manner, the binding of the chemokines RANTES, MIP-1α and MCP-3 to PHA-stimulated and non-stimulated peripheral blood mononuclear cells (PBMC) and to MT-4 and SUPT-1 cells. Studies in which the activity of the chemokines is monitored by intracellular Ca^{++} mobilization confirmed the inhibition of chemokine binding to active receptors. The bicyclam JM3100, a potent HIV fusion inhibitor, did not have any effect on chemokine binding or chemokine-dependent Ca^{++} mobilization. Moreover, when the cells were preincubated with AR177 for 1 hour and the compound was subsequently washed away, chemokine binding was also inhibited, suggesting that AR177 strongly binds to the HIV second receptor. Emergence of HIV resistance to AR177 appears to be mediated by changes in the viral envelope gp120 molecule, the putative target of action with the chemokine receptor. AR177 belongs to a new class of inhibitors that block binding and fusion of HIV with the host cells. While its potential applicability as a therapeutic agent will become clear from ongoing clinical trials, AR177 may also be useful as a tool to monitor the interaction of the HIV envelope glycoprotein gp120 with the HIV second receptor and, consequently, the HIV fusion process.

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SYNTHESIS, ANTI-HIV AND ANTI-HBV ACTIVITIES OF NOVEL OXASELENOLANE NUCLEOSIDES

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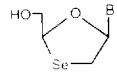
Synthesis of novel (±)-oxaselenolane nucleosides has been accomplished from ethyl bromoacetate in 8 steps. The key intermediate 1,3-oxaselenolan-5-one was prepared by the treatment of bis(selenoacetic acid) with benzoyloxyacetaldehyde. The anti-HBV and anti-HIV activities of the synthesized compounds were determined in



2.2.15 cells and human peripheral blood mononuclear (PBM) infected with HBV and HIV-1, respectively. 5-Fluorocytosine derivative was found to be the most potent among the synthesized compounds. The anti-HIV and anti-HBV activities were determined to be 0.068 μM and 1.2 μM, respectively without significant toxicities up to 100 μM in PBM, CEM and Vero cells. (This research was supported by grants AI 32351 and AI 33655).