Poster Session I — Retrovirus, Hepatitis Virus, Papillomavirus Infections

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ANTI-HIV ACTIVITY AND METABOLISM OF PHOSPHORAMIDATE DERIVATIVES OF D4T-MP WITH VARIATIONS IN THE AMINO ACID MOIETY.

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We have previously reported the anti-HIV activity and metabolism of So324, the prototype compound of a new series of phosphoramidate prodrugs of 2',3'-dideoxy-2',3'-didehydrothymidine 5'-monophosphate (d4T-MP), in which the phosphate group is linked to a phenyl group and the methylester of L-alanine (Balzarini et al., *Proc. Natl. Acad. Sci. USA* , 1996, **93**: 7295). In CEM cells, So324 is metabolized to the highly accumulating alaninyl d4T-MP metabolite, that acts as a depot form for d4T-MP, thus possibly accounting for the optimal antiviral activity of So324 in thymidine kinase deficient CEM cells. We now determined whether the formation of the amino acyl d4T-MP metabolite is a prerequisite for these nucleotide prodrugs to be antivirally active. When different d4T-MP prodrugs were incubated in crude CEM cell extracts, the order of conversion to the amino acyl d4T-MP metabolite was: L-alanine > L-aspartic acid > L-phenylalanine. No conversion to the amino acyl d4T-MP metabolite was seen with derivatives containing D-alanine, L-ß-alanine, L-leucine, L-valine or L-lactate. There was a clear correlation between the anti-HIV activity of these prodrugs and their conversion rate to the amino acyl d4T-MP metabolite. Our data suggest that the enzymes involved in the formation of the amino acyl d4T-MP metabolite have a rather stringent specificity for L-alanine as the amino acid moiety. In addition, these enzymes were found to be markedly species-dependent, their activities being highest in mouse serum, followed by guinea pig serum, but marginal (if any) in human serum. Mouse serum therefore appears to be the medium of choice to isolate and identify the enzymes that are involved in the metabolism of the phosphoramidate prodrugs.

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QSAR Studies of Nucleoside Analogs with Anti-HIV Activity

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The correlations between molecular structure and anti-HIV activity of nucleoside analogs have been investigated using molecular similarity analysis and structure-activity maps. Molecular descriptors such as molecular topology number (NAB), maximum common substructure (MaCS), minimum common superstructure (MiCS), and molecular similarity index (MSI) were used in the molecular similarity analysis. A super-integrated multi-formula approach using these descriptors (NAB, MaCS, MiCS and MSI) was used to perform quantitative molecular similarity analysis (QMSA) and quantitative structure activity relationship (QSAR) study of the structure and anti-HIV activity of nucleoside analogs. Structure-activity maps were also used to examine the structure and anti-HIV activity relationships of nucleoside analogs including dideoxynucleoside analogs and acyclic nucleoside analogs.