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A Retrometabolic concept : The pronucleotide approach

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Mononucleotide delivery has been assessed for many years and recently it has been shown that nucleoside phosphotriesters substituted with enzyme-labile bioreversible phosphate protecting groups [such as POM, DTE or SATE] conduct to intracellular delivery of the first nucleotide metabolite.

In this respect, numerous biological consequences may arise in relation with the structure and the metabolic behavior of the parent nucleoside.

More precisely, focusing on the SATE protecting group, it will be shown on the basis of observed *in vitro* inhibition of various viruses that a such concept may be applied to :

- nucleotide analogues which do not efficiently cross the cell membrane (PMEA, HPMPC...),
- unactive nucleosides presenting a lack of phosphorylation due to the absence or mutation of the first kinase (ddU...),
- nucleosides which may be hampered at their first phosphorylation step (d4T, ddT...) or by catabolism (ddA...).

In this respect, it will be shown that the bis (SATE)-ddAMP derivative is a more potent HIV replication inhibitor than AZT in cell culture. In addition, the corresponding PMEA pronucleotide presents better anti-herpetic activities than the parent drug.

Data preluding to further *in vivo* experiments will be introduced, in order to modulate nucleoside bioavailability in relation with their route of administration and with their metabolism pattern.

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Suppression of Hematopoietic Support Function is Associate with Over-Expression of IL-4 and TGFβ1 in LP-BM5 MuLV Infected Stromal Cell Lines. Vincent S. Gallicchio, Kam-Fai Tse, Jennifer K. Morrow, Nedda K. Hughes. Hematology & Oncology Division, Departments of Internal Medicine, Clinical Sciences, Pathology and Toxicology, University of Kentucky Medical Center and Department of Veterans Affairs, Lexington, KY, USA.

Murine acquired immunodeficiency syndrome (MAIDS) induced by defective LP-BM5 murine leukemia virus is a disease which shares many similarities to human AIDS. The pathogenesis of MAIDS is currently not understood, but may involve the consequential effect of stroma infection in the bone marrow resulting in a defective hematopoietic microenvironment. To evaluate the effect of infection on the hematopoietic stroma, we generated permanent stromal cell lines for LP-BM5 infected and non-infected cell lines was confirmed by the expression of defective viral gag p12 sequence via RT-PCR and the production of viral particles. The ability of these cell lines to support in vitro hematopoiesis was studied. Results indicated that when co-cultured with either non-infected or infected nonadherent mononuclear cells, non-infected control cell lines efficiently supported the production of hematopoietic precursors, whereas viral-infected cell lines induced suppression of both non-infected and viral-infected progenitors. Expression of several cytokine genes in stromal cell lines was also determined by RT-PCR. All cell lines expressed equivalent levels of transcripts for stem cell factor, IL-3, IL-7 and TNFa. However, infection was associated with higher levels of IL-4 and TGFβ1 mRNA expression. These findings suggest that LP-BM5 infection of stromal cells leads to defective hematopoietic support function and altered cytokine expression. Further characterization of the defective cell lines should prove valuable for studies of the pathogenesis of murine AIDS.