Oral Session II - Herpesvirus Infections I

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A Potent Peptidomimetic Inhibitor of HSV Ribonucleotide Reductase with Antiviral Activity *in vivo*. R. Déziel, N. Moss, M Liuzzi, P. Beaulieu, A.-M. Bonneau, C. Bousquet, M. Llinas-Brunet, J. G. Chafouleas, J.-S. Duceppe, J.-M. Ferland, M. Garneau, J. Gauthier, E. Ghiro, S. Goulet, L. Grenier, J. Jaramillo, R. L. Krogsrud, L. Lagacé, R. McCollum, S. Nawoot, R. Plante, D. Wernic, and Y. Guindon. Bio-Méga/Boehringer Ingelheim Research Inc., 2100 Cunard Street, Laval, Québec, Canada, H7S 2G5.

Herpes simplex viruses (HSV-1 and HSV-2) are responsible for a variety of human maladies including genital and oral lesions, ocular diseases, and encephalitis. In order to develop novel antiherpes agents, we have been investigating the virally encoded ribonucleotide reductase (RR) as a target. This enzyme catalyzes the conversion of ribonucleoside diphosphates into their corresponding 2'-deoxy derivatives, the latter being key intermediates in DNA biosynthesis. The catalytically active HSV RR holoenzyme is formed by the association of two homodimeric subunits. Subunit association can be prevented by peptides that mimic the carboxy terminus of the enzyme's smaller subunit. These peptides bind to the enzyme's large subunit with concomitant loss of enzymatic activity. Here we report that **BILD 1263**, a very potent subunit association inhibitor of HSV RR, can inhibit HSV-1 and HSV-2 replication in cell culture (EC_{50}s of 3 μM and 4 μM respectively). **BILD 1263** also strongly potentiates the antiviral activity of acyclovir and suppresses replication of acyclovir-resistant strains in cell culture. The potential clinical utility of this RR subunit association inhibitor is highlighted by its activity *in vivo*. We find that **BILD 1263** as a 5% cream formulation is effective in blocking HSV-1 induced keratitis in a murine ocular model. A structure-activity study that lead to the discovery of **BILD 1263** will also be presented.