Oral Session II — Herpesvirus Infections I

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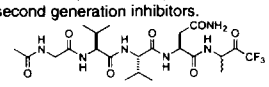
Peptidomimetic Inhibitors of HCMV Protease. W. Ogilvie, A. Abraham, M. Bailey, A. Bhavsar, P. Bonneau, J. Bordeleau, Y. Bousquet, C. Chabot, J.-S. Duceppe, G. Fazal, S. Goulet, C. Grand-Maître, I. Guse, T. Halmos, P. Lavallée, E. Malenfant, J. O'Meara, R. Plante, C. Plouffe, M. Poirier, M.-A. Poupart, F. Soucy, C. Yoakim, R. Déziel. *Bio-Méga/Boehringer Ingelheim Research, Inc., 2100 Cunard Street, Laval, Québec, Canada H7S 2G5*

The Human Cytomegalovirus (HCMV) is a highly prevalent member of the herpesvirus family which is responsible for opportunistic infections in immunocompromised individuals including organ transplant recipients, cancer patients and AIDS sufferers. Current treatments for HCMV infections include DNA polymerase inhibitors which show severe side effects when used alone or (in the case of AIDS) in combination with AZT. Therefore there exists a need for alternative anti-HCMV therapies. All members of the herpesvirus family express a protein late in the virus life cycle that appears to function as a self assembling scaffold during the maturation of the viral capsid. This assembly protein must be processed to remove a short segment of the C-terminus in order to permit the entry of viral DNA and produce an infectious virus particle. Recently it has been shown that this processing is mediated, at least in part, by a protease which is encoded by the virus. This suggests that specific inhibitors of this protease would have therapeutic value. The development of inhibitors of HCMV protease inhibitors based on the amino acid sequences of the peptide cleavage sites and showing sub micromolar potency *in vitro* is described. Optimization of the amino acid residues of these inhibitors has produced a 70 fold increase in inhibitor potency relative to the natural peptide sequence. This study also proposes possible roles for the various amino-acids of the resulting inhibitor sequence and provides a firm foundation for the design of second generation inhibitors.



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Structures of Herpes Virus Proteases: Exciting New Targets of Antiviral Drugs X Qiu, J Culp*, C Debouck#, B Hellmig*, S Hoog, C Janson*, K O'Donnell, W Smith & S Abdel-Meguid. Dept Macromol Sci, *Protein Biochem & #Mol Gen, SmithKline Beecham Pharm, King of Prussia, PA 19406, USA.

Human herpes viruses are divided into three subfamilies: the α-subfamily includes herpes simplex viruses (HSV-1 & HSV-2) and varicella-zoster virus (VZV), the β cytomegalovirus (CMV) and the γ Epstein-Barr virus (EBV). HSV-1 causes cold sores, HSV-2 causes genital herpes, VZV causes chickpox and shingles and CMV causes life-threatening infections in congenitally infected infants, immunocompromised individuals and immuno-suppressed cancer or transplant patients. Each virus encodes a serine protease that is essential for its replication and is a potential target for therapeutic intervention. Amino acid sequences of herpes virus proteases are not homologous to other know proteins, but are fairly conserved among themselves. Here we report the crystal structures of human herpes virus proteases at atomic resolutions. The structures revealed a new fold of serine protease that is presumably conserved among all herpes virus proteases. The active sites of herpes virus proteases consist of a novel Ser-His-His catalytic triad instead of the classical Ser-His-Asp triad, shining new light on understanding the mechanism of serine proteases in general. A dimer interface important to the protease activity was identified. The structures provide insights into the catalytic mechanism and substrate binding specificity of the enzymes and are templates for the structure-based design of anti-herpes drugs. The fact that herpes virus proteases are distinctly different from other known serine proteases greatly enhances the chances of obtaining inhibitors that selectively target herpes viruses without being toxic to human.