05-Molecular Modelling and Design for Proteins and Drugs

PS-05.02.07 TOWARD THE DESIGN OF POTENT, DUAL INHIBITORS OF HIV-1 AND HIV-2 PROTEASES. By. B. Zhao, Department of Macromolecular Sciences, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA, 19406, USA.

The immunodeficiency virus (HIV) protease is a 99 amino acid residue protein that functions as a homodimer, and is required for the formation of infectious virons. Thus, it is a potential target of acquired immune deficiency syndrome (AIDS) therapy. Two therapeutically relevant strains of HIV have been identified. Type 1 is the most common strain of this virus in the United States and Europe, while type 2 is common in West Africa and is spreading rapidly else where. One goal of our research program is to design dual inhibitors active against both HIV-1 and 2. To that end we have determined the crystal structures of inhibitors bound to HIV-1 protease and simian immunodeficiency virus (SIV) protease, a highly homologous enzyme to HIV-2 protease. For example, SIV_{Mac} (that isolated from Macaca mulatta) protease differs by only 13 amino acid residues from HIV-2(ROD) but by 49 from HIV-1.

We have crystallized and determined the structures of HIV-1 and SIV proteases bound to various inhibitors. Crystals of HIV-1 protease-inhibitor complexes belong to the space group $P6_1$ with a = b = 63 A and c = 83 A, while SIV protease-inhibitor complexes belong to the space group I222 with a-46.3 A, b=101.7A, and c=118.9 A. These structures, determined to 2.3 A resolution by molecular replacement and refined using PROLSQ and XPLOR, will be compared and implication of their differences toward the design of dual inhibitors will be discussed.

PS-05.02.08 BINDING OF THE HYDROXYETHYL-UREA ISOSTERE TO HIV-1 PROTEASE. By W. C. Stallings, H. -S. Shieh*, R. A. Stegeman, G. A. DeCrescenzo, D. P. Getman, R. M. Heintz., K. L. Reed., J. J. Talley, M. E. Gustafson & K. D. Junger, Monsanto Corporate Research, 700 ChesterfieldParkway North, St. Louis, Missouri 63198 U.S.A.and M. Clare, K. A. Houseman R. A. Mueller & M. L. Vazquez, Searle Discovery Research, 4901 Searle Parkway, Skokie, Illinois 60077 U.S.A.

Human immunodeficiency virus-1 (HIV-1), the causative agent of AIDS, encodes in its RNA genome the sequence of a unique aspartyl protease which is critical to the life cycle of the virus. Inhibition of this enzyme could arrest the replication of the virus in an infected individual with AIDS. The structure of the complex of SC-52694 with HIV-1 protease has been determined at 2.3 Å resolution. The crystals were grown under conditions closely related to those described by Miller *et al.* (***Science* 246,** 1149-1152 (1989)), and protein coordinates from their structure provided the starting point for refinement. The chemical structure of SC-52694 is closely related to that of SC-52151 which has been shown to have antiviral activity and is currently being developed for clinical trials (Gatman *et al.* (***J. Med. Chem.* 36,** 288-291(1993)). Both peptidomimetics contain the **R**-(hydroxyethyl)-urea isostere. The mode of binding of SC-52694 was not anticipated and the results will be reported. The inhibitor extends from P3 to P2'. Solvent exposure of the P3 moiety will be demonstrated, but we show that it forms part of the S1 site. By contrast, the solvent accessible surface at S1' and S2' is concave and solvent is bound in this pocket.

