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primer grip because of its proximity to the phosphate that joins the nucleotides at the primer terminus, and a portion of the p66 palm and fingers that are closely associated with nucleotides of the template strand, therefore denoted as template grip. These structural elements, together with two  $\alpha$ -helices of the p66 thumb, act as a clamp to position the template-primer precisely relative to the polymerase active site. The 3'-hydroxyl of the primer terminus is close to the catalytically essential Asp110, Asp185, and Asp186 residues at the active site and is in a position for nucleophilic attack on the  $\alpha$ -phosphate of an incoming nucleoside triphosphate. Since the threedimensional structure of the active site of nucleic acid polymerases appears to be strongly conserved, the structure of the HIV-1 RT/DNA complex may aid our understanding of the mechanism of polymerization and facilitate the design of new and improved drugs against HIV-1 infections.

DS-05.02.03 STRUCTURAL STUDIES ON A NEW CRYSTAL FORM OF HIV REVERSE TRANSCRIPTASE By R. M. Esnouf, E. F. Garman, E. Y. Jones, D. I. Stuart, G. K. Darby, C. K. Ross, D. O'N. Somers and D. K. Stammers. Laboratory of Molecular Biophysics, Oxford University, UK and Wellcome Research Laboratories, Beckenham, Kent, UK

We have recently solved the structure of a new crystal form of HIV-1 reverse transcriptase (RT) at 3.4Å resolution. The crystals are orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>. The native crystals have cell dimensions a=147Å, b=112Å, c=79Å. However, under certain conditions a shrinkage in the a axis of 4Å is triggered. Native and heavy atom derivative data have been collected for both the large and small unit cells. The difference Pattersons for the large unit cell data were interpreted and led, with the aid of solvent flattening, to an electron density map at 6Å resolution of reasonable quality.

A polyalanine model was constructed (Esnouf, R. M., unpublished program) from the incomplete set of unrefined C<sup>α</sup> coordinates deposited by the Yale group (Kohlstaedt, L. A. et al., Science, 256, 1783 (1992)). The molecular replacement protocols of X-PLOR (Brünger, A. T., Acta Cryst., A46, 46 (1990)) were successful in locating this model in both the large and the small unit cells. Careful constrained refinement has revealed structural features not present in the phasing model.

The current status of the project will be reported with particular reference to the biological function of this molecule.

DS-05.02.04 INTERACTIONS OF THE CD4 AND CD8 T-CELL CO-RECEPTORS IN THE CELLULAR IMMUNE RESPONSE. Wayne A. Hendrickson, Peter D. Kwong, Daniel J. Leahy\*, Seong-Eon Ryu‡, Hao Wu and Hiroto Yamaguchi. Department of Biochemistry and Molecular Biophysics and Howard Hughes Medical Institute, Columbia University, New York, NY 10032, USA. (Present addresses: \*Department of Biophysics, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA; †Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, MA 02138, USA).

The cellular immune response is essential in the defense against pathogens, both by assisting in the generation of antibodies and also directly in the elimination of viral infected cells. These responses are mediated by T-cells that interact with peptide antigens presented on target cells as complexes with molecules of the major histocompatibility complex (MHC). Mature T-cells are principally distinguished by the exclusive occurrence of either CD4 or CD8 glycoproteins on their surfaces. These molecules serve as co-receptors in the interaction between T-cell antigen receptors and MHC-presented peptides. The extracellular portions of CD4 and CD8 interact respectively with Class II and Class I MHC molecules, and the cytoplasmic portions of both molecules associate non-covalently with the lymphocyte kinase p56lck.

We have determined crystal structures for extracellular fragments of both human CD4 and human CD8a. In both cases the amino-terminal domains are similar to the variable domains of immunoglobulins, but otherwise they are quite dissimilar. CD8 is a dimer, and the crystal structure reveals a mode of association like that in the Fv portions of antibodies. The whole extracellular portion of CD4 (sCD4) behaves as a monomer in solution, and a fragment comprising the first two domains (D1D2) for which the structure has been determined is also monomeric. On the other hand, the characteristics of crystals of whole sCD4 fragments suggest a specific mode of oligomerization that may be mediated by the D3D4 portion of CD4. The site on CD4 that interacts with HIV in A1DS infection has been mapped by mutation studies, and the structure of one of these mutant proteins have been determined. The structures of CD4 and CD8 fragments also provide a basis for interpreting mutational studies on the interactions between these T-cell co-receptors and their MHC targets. Work is in progress on the interactions of CD4 and CD8 with other components.

DS-05.02.05 THE CRYSTAL STRUCTURES OF HIV PROTEINASE INHIBITOR COMPLEXES. By K. Appelt, Agouron, USA

PS-05.02.06 STRUCTURAL STUDIES OF CD4: CRYSTAL STRUCTURE OF DOMAINS 3 AND 4 AND THEIR IMPLICATION FOR THE OVERALL RECEPTOR STRUCTURE by R.Leo Brady\*, Gudrun Lange, Eleanor J.Dodson, A.Neil Barclay# and G.Guy Dodson Department of Chemistry, University of York YO1 5DD & # MRC Cellular Immunology Unit, South Parks Road, Oxford

CD4 is a transmembrane glycoprotein present at the surface of T lymphocytes that interacts with Major Histocompatibility Complex Class II proteins at the surface of accessory cells, and is involved in the triggering of the lymphocytes by foreign antigens. CD4 is also the major receptor for the human immunodeficiency virus. The extracellular portion has been predicted to contain 4 immunoglobulin superfamily domains and the structure of the amino terminal 2 domains has previously been determined. We now report the expression of a form of CD4 containing only domains 3 and 4, its crystallisation and analysis of its structure by X-ray crystallography with 2.8A spacing data. Both of the carboxy terminal domains are immunoglobulin related as had been predicted. The implications of the structure will be discussed with respect to the structure of the complete extracellular portion of CD4, its function and evolution as a receptor built from a concatenation of Ig superfamily domains.