of the membrane. Magnesium site is situated between heme a_3 and Cu_A. The O_2 binding site contains heme a_3 iron and copper (Cu_B) atoms with a distance of 4.5Å. There is no amino acid ligand bridging between the iron and the copper atoms in spite of a strong anti-ferromagnetic coupling between them. However, such a small bridging ligand between them as an oxygen atom is not excluded at present. The heme a and the heme a_3 are bridged by a polypeptide segment of His-Phe-His of which one histidine coordinates to the heme a iron and the other histidine to the heme a_3 iron.

The electron transfer path within the molecule has been established as follows: cytochrome c -> Cu_A -> heme a -> the O_2 binding site, which includes heme a_3 and Cu_B. Several hydrogen bonds providing electron transfer pathway were found between the Cu_A site and the hemes a. There exist several hydrogen bonds around the Cu_A, the heme a and the heme a_3. The structure implicates that Cu_A-His^{204}-CO of Arg^{438}-NH of Arg^{439}-a propionic group of the heme a is the primary electron transfer pathway between Cu_A and the heme a.

Hot Macromolecular Structures I

MS04.07a.01 THE STRUCTURE OF AN RNA PSEUDOKNOT THAT INHIBITS HIV-1 REVERSE TRANSCRIPTASE. Craig E. Kundrot, Cindy L. Barnes, and Susan E. Lietzke. Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0215.

An RNA pseudoknot inhibitor of HIV-1 reverse transcriptase was isolated by Tuerk, et al., using the *in vitro* selection technique SELEX. This 26 nucleotide RNA pseudoknot, PK26, specifically inhibits HIV reverse transcriptase with nanomolar affinity. PK26 and three bromo-uridine substituted derivatives were produced by chemical synthesis and crystallized from ammonium acetate. Two of the derivative crystals were suitable for data collection. Diffraction data were collected on cryocooled crystals stabilized with MPD. Native crystals diffracted to 2.9 Å and the derivatives to 3.0 Å. The crystals belong to space group $P4_{3/1}22$ and have unit cell dimensions a = b = 61.6 Å, c = 98.9 Å. The bromine atoms in the two derivatives were located by Patterson methods and difference Fourier maps and used to produce an initial electron density map to 4 Å resolution (figure of merit = 0.49). The initial map clearly shows that the PK26 molecules coaxially stack in a head-to-head and tail-to-tail orientation. The structure of PK26 will be described and analyzed in terms of extensive chemical modification and nucleotide substitution data available for free PK26 and PK26-HIV RT. Since PK26 also conforms to the pseudoknot motif that promotes ribosome frame shifting, the structure will also be analyzed in terms of potential frame shifting mechanisms.

MS04.07a.02 CRYSTAL STRUCTURE OF HUMAN CYCLIN H, A CELL CYCLE REGULATORY PROTEIN. Kyeong Kyu Kim*, Holly M. Chamberlin†, David O. Morgan†, Sung-Hou Kim*. *Department of Chemistry and Earnest Orlando Lawrence Berkeley National Laboratory, University of California, Berkeley, CA 94720, USA, †Department of Physiology, University of California, San Francisco, CA 94143-0444, USA

The structure of human cyclin H was determined to 3 Å resolution by multiple isomorphous replacement. Cyclins are positive regulatory subunits that activate the catalytic subunits of cyclin-dependent kinases (CDKs) and trigger cell cycle events. In contrast to other cycling, cyclin H is the positive regulatory protein that activates the catalytic subunit, CDK7, which, in turn, activates most or all other CDKs. The crystals of cyclin H were grown in the presence of lithium and ammonium sulfate as precipitants, and belong to the space group $I4_122$ with unit cell dimensions of a = b = 84.0 Å and c = 374.7 Å. Like cyclin A, cyclin H contains two α-helical domains that form a conserved cyclin fold. However, cyclin A and cyclin H show significant differences in the surface charge distribution and locations of the N- and C-terminal helices outside the cyclin fold. These differences may reflect the unique function of cyclin H.

MS04.07a.03 STRUCTURE OF Bcl-X_L, A DOMINANT INHIBITOR OF PROGRAMMED CELL DEATH. Steven W. Muchmore[1], Micheal Sattler[2], Heng Liang[2], Robert P Meadows[2], John E. Harlan[2], David Nettesheim[2], Brian Chang[3], Craig B. Thompson[3], Sui-Lam Wong[4], Shi-Chung Ng[4], Stephen W. Fesik[2], [1]Protein Crystallography, [2]NMR Research, [3]Aging and Degenerative Disease Research, Pharmaceutical Products Research Division, Abbott Laboratories , Abbott Park, IL 60064, USA, [4]Howard Hughes Medical Institute and Departments of Medicine, Molecula Genetics, and Cell Biology, University of Chicago, Chicago, IL 60637, USA.

The Bcl-2 family of proteins modulates programmed cell death (apoptosis) by an unknown mechanism. The structure of Bcl-X_L was solved by a combination of x-ray crystallographic and NMR spectroscopic techniques. The structure consists of a total of 7 alpha-helices, two of which form a central apolar pair. The remaining helices are amphipathic and flank the central pair. A loop of approximately 60 residues connecting the first two helices was found to be both flexible and dispersible for anti- apoptotic activity. Three functionally important homology domains (BH1, BH2, BH3) are located on the same face of the molecule and form a hydrophobic cleft which may represent the interaction site for proteins which promote apoptosis. Sequence alignments of other Bcl-2 family members suggests these proteins should exhibit the same overall fold. The Bcl-X_L structure is reminiscent of membrane translocation domains of bacterial toxins such as diphtheria toxin or colicin. This similarity suggests that the modulation of apoptosis by the Bcl-2, family of proteins may involve a membrane translocation event.

MS04.07a.04 CRYSTAL STRUCTURE OF THE IMMUNODOMINANT CHAPERONIN-10 OF MYCOBACTERIUM LEPRAE. Shekhar C. Mande[a,*], Vijay Mehra[b], Barry R. Bloom[b,c] and Wim G. J. Hol[d]. [a]Institute of Microbial Technology, Chandigarh 160 036, India; [b]Department of Microbiology and Immunology, and [c]Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, New York, USA; and [d]Biomolecular Structure Centre and the Howard Hughes Medical Institute, University of Washington, Seattle, WA 98195 USA.

Mycobacteria are amongst the most important human pathogens. In an effort to understand the immune response to mycobacterial infections, several antigens of these microbes have been identified. A 10kD antigen has been found to be the most immunogenic protein antigen of M.leprae. Interestingly it shares ~44% sequence identity with the well known chaperonin GroES of *E. coli* (1). We present the three dimensional structure of this protein, with possible hypothesis on the role of cpn-10 in the chaperonin mediated protein folding process.

The heptameric molecule has a dome like structure, with approximate dimensions of 80x80x35 angstroms (2). The overall architecture is strikingly similar to the pantheon in Rome. Residues important for its interaction with the larger chaperonin partner, cpn-60 (GroEL homologues) are sequestered on the lower surface of the dome. The interior of the dome is intensely hydrophilic. Residues lining the interior surface of the dome are conserved evolutionarily suggesting that GroES may take an active part in chaperonin mediated protein folding process.

(1) Mehra V et al., J. Exp. Med. (1992) v.175, 275-284.
(2) Mande S C et al., Science (1995) v.271, 203-207.