oligomerisation state of a given molecule both in solution and in the crystal.

This strategy combines the information coming out from experimental data such as the existence of a non crystallographic symmetry in the crystal, reinforced by electronic microscopy data of the oligomeric structure in solution.

Computational methods are then used to extract the orientations and relative positions of each molecule in the oligomer in order to build an oligomeric model to search for a molecular replacement solution.

The closest monomer model in the PDB has 26% identity and, although accurate enough to detect the crystal structure, more contrasted results are obtained by using normal mode analysis to generate a series of models, including NMR-like ensembles.

Keywords: molecular replacement, normal modes, non-crystallographic symmetry

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Disorder and Twinning: New Equations and Applications to the Structure Determination of Proteins from the Carboxysome Shell

Todd Yeates, Cheryl Kerfeld, Michael Sawaya, Shiho Tanaka, Morgan Beeby, Martin Phillips, *Department of Chemistry and Biochemistry, University of California, Los Angeles.* E-mail: yeates@mbi.ucla.edu

Although crystal structure determination for proteins is sometimes routine, this is often not the case. Structure determination may be complicated by a number of factors, including certain kinds of crystal growth disorders, of which merohedral twinning is one particularly interesting type. Twinning can prevent successful structure determination if it goes undetected, but it is often treatable if it is correctly identified. The effects of twinning are sometimes masked by other phenomena, such as pseudo-centering, scattering anisotropy, and non-crystallographic symmetry. Recently developed intensity statistics equations for dealing with these complications will be discussed, along with the emerging structure of proteins from the carboxysome shell, determined from crystals suffering from merohedral twinning. The carboxysome is a polyhedral protein shell, which resembles a viral capsid and is found in many bacteria. Bacteria employ the carboxysome shell as a primitive organelle by enclosing RuBisCO and other enzymes in its interior, in order to carry out cellular CO_2 fixation in a sequestered environment. This work is supported by the NIH and the BER Office of the DOE.

Keywords: disorder,twinning, structure determination

MS65 PROTEIN INTERACTIONS WITH OTHER BIOLOGICAL MACROMOLECULES

Chairpersons: Zihe Rao, Brian W. Matthews

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Protein-protein Complexes in Cell Adhesion

E. Yvonne Jones, A. Radu Aricescu, Wai-Ching Hon, Christian Siebold, Weixian Lu, *Cancer Research UK Receptor Structure Research Group, Division of Structural Biology, Wellcome Trust Centre for Human Genetics, University of Oxford.* E-mail: yvonne@strubi.ox.ac.uk

Recent structural results will be presented for the extracellular region of receptor protein tyrosine phosphatase μ (RPTPμ). RPTPμ mediates stable, homophilic cell adhesion. Strategies to produce well-ordered crystals of the full, multidomain, extracellular region will be described and the resulting insights into homophilic adhesion discussed.

Keywords: glycoprotein, receptor, protein-protein complex

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Activating the Molecule of Mass Destruction

Christopher P Hill, *Department of Biochemistry, University of Utah School of Medicine, U.S.A.* E-mail: chris@biochem.utah.edu

Proteasomes are 700 kDa complexes of 28 protein subunits that are assembled in a barrel-like architecture. They are abundant in the cytosol and nucleus of eukaryotic cells, where they degrade numerous protein substrates in order to perform housekeeping and regulatory functions. The proteolytic active sites are sequestered inside the hollow proteasome structure, thereby protecting inappropriate substrates from degradation. Proteasomes are activated in vivo by activators that bind to the end rings of alpha subunits. The best known of these is the 19S activator, which mediates degradation of polyubiquitylated substrates. Two other activators, 11S and Blm10/PA200, stimulate hydrolysis of small peptide substrates. Structural and biochemical data will be presented on the interaction of an 11S activator with proteasome, and the mechanism of opening the entrance port into the proteasome interior will be discussed. Preliminary studies on the Blm10 activator will also be presented.

Keywords: proteins structure, proteasome, macromolecular structures

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Structure and Mechanism of RecBCD

Dale B. Wigley, *Cancer Research UK Clare Hall Laboratories, South Mimms, Potters Bar, Herts EN6 3LD, U.K.* E-mail: Dale.Wigley@cancer.org.uk

Double strand breaks in bacterial cells can result from a variety of things including collapsed replication forks or other DNA damage. One mechanism for repair of breaks involves the multifunctional enzyme complex, RecBCD. RecBCD comprises two distinct DNA helicase subunits, a number of differentially regulated nuclease activities, and the ability to recognise a recombinational hotspot called Chi. In order to understand more about the molecular basis of these activities we have determined the crystal structure of RecBCD complexed with DNA. The structure reveals the basis for the two different helicase activities and explains the regulation of nuclease digestion. The structure also suggests how the enzyme might be able to scan DNA for Chi sequences as the DNA passes through the protein complex.

Keywords: helicase, recombination, structure

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Molecular Basis for the Allosteric Inhibition of JNKs by the Peptide Fragment from the Scaffolding Protein JIP1

Yong-Seok Heo, S.-K. Kim, C. I. Seo, Y. K. Kim, B.-J. Sung, H. S. Lee, J. I. Lee, S.-Y. Park, J. H. Kim, K. Y. Hwang, Y.-L. Hyun, Y. H. Jeon, S. Ro, Y. Kwon, J. M. Cho, T. G. Lee, *Department of Drug Discovery, CrystalGenomics,Inc. Seoul, Korea.* E-mail: ysheo@crystalgenomics.com

The c-jun N-terminal kinase (JNK) signaling pathway is regulated by JNK-interacting protein-1 (JIP1), which is a scaffolding protein assembling the components of the JNK cascade. Overexpression of JIP1 deactivates the JNK pathway selectively by cytoplasmic retention of JNK and thereby inhibits gene expression mediated by JNK, which occurs in the nucleus. Here, we report the crystal structures of human JNK1, 2, and 3 complexed with pepJIP1, the peptide fragment of JIP1, revealing its selectivity for JNKs over other MAPKs and the allosteric inhibition mechanism. The specific hydrogen bonds between JNKs and pepJIP1 can provide the selective regulation. Binding of the peptide also induces a hinge motion between the N- and C-terminal domains of JNKs and distorts the ATP-binding cleft, reducing the affinity of the kinase for ATP. Considering the value of JNKs as therapeutic targets for several diseases, the information from these structures can contribute to the optimization of JNK inhibitors of high affinity and specificity, which can be derived from pepJIP1. In addition, we also determined the ternary complex structures of pepJIP1-bound JNK1, 2, and 3 complexed with SP600125, an ATP-competitive inhibitor of JNKs, providing the basis for the JNK specificity of the compound.

Keywords: JNK, scaffolding protein, JIP1