Microsymposia

tetrahedron.


Keywords: quasicrystal, lattice dynamics, simulation

MS.85.1

Structural genomic of protein families and pathways in human disease
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Comprehensive molecular insights into a specific disease most often require whole pathways and processes to be considered. Structural biology together with complementing biochemical studies is the major means for achieving detailed insight into the molecular mechanisms of proteins in such pathways: how they interact, how they are regulated, and how enzymes recognize and transform substrates. This information provides a knowledge basis for current target drug design efforts and the structural information can directly assist in the rational drug design cycle. The Structural Genomics Consortium (SGC) is an Anglo-Canadian-Swedish consortium pursuing a systematic effort at generating structural insights into proteins of disease related pathways and structural families. At the SGC-Stockholm node, “the little brother” in the consortium, some 430 proteins are currently studied within areas such as; receptor signaling (Toll-, TGF-beta- and RTK-receptor based signalling), apoptosis signalling, phosphoinositol and other lipid signalling, ATPases (RNA-helicas and AAA-ATPases), poly-ADP ribose polymerase, as well as nucleotide and amino acid metabolism. Many of the proteins targeted are implied in diseases such as; cancer, inflammatory and infectious diseases. Approximately 70 novel human structures, plus follow-up structures, have been determined in the last three years at SGC-Stockholm. The specific structural genomic strategy applied on some of the pathways and families motioned above will be discussed, as well as examples of structural insights generated by this strategy.

Keywords: structural genomics, metagenomics, protein universe

MS.85.2

Structural genomics and the expanding protein universe
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Over the past 8 years, the JCSG has developed and integrated various methodologies and technologies into a very efficient high throughput production pipeline for all steps from target selection, cloning, expression, crystallization to structure determination. The pipeline, which was initially developed using a full proteome screen of T. maritima (TM), is in its 3rd year of operation as one of the 4 NIGMS, Protein Structure Initiative large-scale production centers. In order to explore the rapidly expanding sequence space from the growing genome sequencing projects, the PSI has focused on increasing coverage of the corresponding structural space at multiple levels: first, by selecting Pfam families without structural coverage; by identifying and validating new protein families; and by focusing on large families (MEGA) with inadequate structural coverage to assess evolution of structure and function. Our biomedical theme project revolves around the Central Machinery of Life, proteins that are conserved in all kingdoms of life. Other exciting new projects in our target portfolio are on metagenomes, in particular, Global Ocean Sampling and the human gut microbiome. To date, the JCSG has deposited over 555 novel structures (as of 2/19/08) in the PDB and recently completed the metabolic reconstruction of TM in collaboration with Dr. B. Palsson, UC San Diego, and Dr. A. Osterman, Burnham. The substantial contributions of the JCSG and the PSI to coverage of this expanding protein universe will be outlined. The JCSG, located at The Scripps Research Institute, Genomic Institute of the Novartis Research Foundation, U.C. San Diego, Burnham Institute, and the Stanford Synchrotron Radiation Laboratory/Stanford University, is supported through the NIGMS PSI (U54-GM074898).

Keywords: structural genomics, rational drug design, cancer, inflammation, protein production

MS.85.3

Using focused structural proteomics to elucidate the molecular basis of MAPK regulation in T cells
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Disruptions in the tight regulation of T cell activation and differentiation are correlated with numerous immunological cancers, including acute leukemias. One cause is the increased exposure of people to oxidative environmental toxins, a subset of which target and inhibit cysteine-based tyrosine phosphatases (CBTPs). Hematopoietic tyrosine phosphatase (HePTP) is a non-receptor CBTP that plays a critical role in the development of these immune disorders through its ability to regulate the activities of its only known target substrates, the MAP kinases Erk and p38. HePTP, and its only other known family members STEP and PTPRR, interacts with these targets via a unique 15 residue sequence in its N-terminus termed the kinase interaction motif (KIM). In order to investigate the regulation of MAPKs by KIM phosphatases at a molecular level, we have taken a focused structural proteomics approach. Specifically, we have produced a KIM phosphatase:MAPK specific ‘toolbox’, which includes KIM phosphatase substrate trapping mutants (STMs) whose activities are severely compromised, yet still able to bind target substrates, functional mutants that reflect distinct biological states of the complex and efficient methods for the robust, activation of the MAP kinases for studies of the active dephosphorylation complex, among others. Using these new biological tools, we are now investigating, using functional X-ray crystallography and NMR spectroscopy, the multiple, transient interactions of the KIM phosphatase:MAPK complexes that drive T cell differentiation at atomic detail. This work was supported through funding to RP from NIH-2P20RR016457-07 and ACS Research Scholar Grant RSG-08-