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Keywords: quasicrystal, lattice dynamics, simulation

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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 signaling, phosphoinositol and other lipid signaling, ATPases (RNA-helicases 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: protein structure, structural genomics, rational drug design, cancer, inflammation, protein production

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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, metagenomics, protein universe

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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 'toolkit', 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-5P20RR016457-07 and ACS Research Scholar Grant RSG-08-

067-01-LIB.

Keywords: protein tyrosine phosphatase families, MAP kinase families, focused structural proteomics

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Focused structural proteomics of protein synthesis systems

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Protein synthesis is performed by a large number of proteins and RNAs. We have been doing structural proteomics focused on protein synthesis in bacteria, archaea, and eukarya. The crystal structures of tRNAs, aminoacyl-tRNA synthetases, translation factors, and the ribosomal subunits will be discussed to describe the process of protein synthesis.

Keywords: protein synthesis, tRNA, ribosome

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Complex perovskites: Chemical order, crystallographic distortions and physical properties

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This contribution surveys our studies of complex perovskites with a particular emphasis on atomic ordering over various length scales and its impact on the structural distortions and physical properties of these materials. I will show some examples of perovskites where cation ordering is critical for properties and applications. In the A_2MnMO_6 systems the coupling between orbital ordering (cooperative Jahn-Teller distortions) and octahedral tilting is demonstrated and exploited to control the magnetic properties of double perovskites. Next I will discuss $ALnMM'O_6$ (A = Li^+, Na^+, K^+, Ln = rare-earth cation) perovskites where strong coupling between A-site ordering, B-site ordering and second order Jahn-Teller distortions of the B-site cations are all closely linked. Some of these materials show a fascinating periodic phase separation. They also exhibit coupling between magnetic ordering of transition metal and lanthanide ions that is promising for multiferroic behavior. Finally time permitting I will discuss our studies of oxynitride perovskites, AMO_2N (A = Ba, Sr, Ca; M = Ta, Nb), where novel dielectric behavior (high, nearly temperature independent permittivity) is closely linked to the details of the anion order.

Keywords: perovskites, magnetic oxides, oxynitrides

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Local and long-range structure in LLTO perovskites with Li^+ superionic mobility

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LLTO ($Li_xLa_{2/3-x/3}TiO_3$) is an excellent Li^+ ion conductor at room temperature (10^{-3} S cm^{-1} for x=0.3), of interest as solid electrolyte in electrochemical devices. Structural studies by neutron powder diffraction showed perovskite superstructures with $2^{1/2}a_p \times 2^{1/2}a_p \times 2a_p$ tetragonal (x>0.24) and $2a_p \times 2a_p \times 2a_p$ orthorhombic (x<0.24) unit-cells, and *P4/nbm* and *Cmmm* symmetries. A partial La-Li ordering according to (001) layers is coupled to anti-phase octahedral tilts $a^0a^0c^-$ and $a^0b^-c^0$ for the tetragonal and orthorhombic cases. Li is heavily disordered within the A-type cage, accounting for the high ionic mobility. The local Li environment was studied by ab initio periodic quantum-mechanical simulations of selected ordered structural models. The phases $Li_{1/8}La_{5/8}TiO_3$ ($2a_p \times 2a_p \times 2a_p$, Z=8) and $Li_{5/16}La_{9/16}TiO_3$ ($2a_p \times 2a_p \times 4a_p$, Z=16) were considered, with *Pm* or *P1* symmetry, to represent the Li-poor and Li-rich compositions. Several different La-Li-vacancy ordering patterns within the (001) layers of A cages were devised. The structures were optimized by energy minimization, so as to localize the preferred lithium sites for each ordering scheme. It was found that the Rietveld-refined most populated Li site, close to the O_4 windows separating adjacent A cavities in the layer, corresponds to La-poor local configurations, and is actively involved in the ion migration process. The second populated site is related to La-rich local environments, and is a trapping location less favourable to ionic transport. By combining NPD results (long-range Li disorder) and ab initio simulations (local Li order), one- and two-dimensional atomistic pathways are proposed for Li^+ ion diffusion within the perovskite framework, including the prediction of activation energy barriers for ionic hopping.

Keywords: solid electrolytes, *ab-initio* calculations, neutron powder diffraction

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Size and strain effects in nanostructured relaxor and morphotropic compounds

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The field of morphotropic systems with giant dielectric and piezoelectric properties is very active, and many interesting results have been obtained, in particular in lead based-systems. However up to now, only very few papers have addressed the question of grain size reduction and its effect on the physical and structural properties of these materials. We will report results obtained in nanocrystalline powders and ceramics with controlled grain size from 15nm up to micrometric sizes, as well in thin films with several thicknesses from 40nm and different substrates, in $PbMg_{1/3}Nb_{2/3}O_3$-$PbTiO_3$, $PbSc_{1/2}Nb_{1/2}O_3$-$PbTiO_3$, and $BiScO_3$-$PbTiO_3$ systems. The consequences on the dielectric properties and on the rotation of polarisation will be discussed and compared with the situation in bulk materials. In particular it will be shown that changing the grain sizes provides an easy way to tailor the direction of the polarization