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ABSTRACTS

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010: Structural proteomics of mycobacterial recombination and repair

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Structural studies on proteins involved in recombination and repair, reviewed here, form a component of a larger programme, being pursued in this laboratory, on the structural biology of mycobacterial proteins. Crystallographic and related studies on RecA from *M. tuberculosis* and *M. smegmatis* have involved the wild type protein, mutants and their nucleotide complexes crystallized under different conditions. These studies provide a comprehensive picture of RecA-ATP interactions and lead to the proposal of a mechanism for the transmission of the information on nucleotide binding to the DNA binding region using a switch residue. Furthermore, the structures enable a thorough elucidation of the plasticity of the molecule resulting primarily from the movement of the C-terminal domain, which is related to the pitch of the RecA filament, several loops and the switch residue. They also provide snapshots of allosteric transitions involved in the activity cycle of RecA. Crystallographic and modeling studies of RuvA from *M. tuberculosis*, which plays an important role in resolving Holliday Junctions, provide a framework for understating the regional flexibility of the molecule and RuvA-Holliday Junction interactions. Single stranded DNA binding protein (SSB), an essential protein necessary for replication, recombination and repair, from *M. tuberculosis*, *M. smegmatis* and *M. lepre* have been studied using crystallography. The quaternary structure of the tetrameric molecule from mycobacteria is different from that of SSB from other sources. This difference has important implications in relation to DNA binding and the stability of the protein. The structure of uracil-DNA glycosylase, a repair enzyme involved in excision of uracil from DNA, from *M. tuberculosis* has been determined in its complex with a proteinaceous inhibitor. The structural and associated modeling studies reveal the unique features of the mycobacterial enzyme. In addition to providing valuable information pertaining to the function of the concerned proteins, the structures presented here bring out the critical differences of mycobacterial proteins form the homologues from other sources. These differences could be important in determining the special features of mycobacteria and in combating the pathogens among them.

011: G-protein coupled receptors and membrane cholesterol: from structure to pathogenesis

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The G-protein coupled receptors (GPCRs) are the largest class of molecules involved in signal transduction across membranes [1], and constitute $\sim$1–2% of the human genome [2]. GPCRs are involved in a multitude of physiological functions and therefore have emerged as major targets for the development of novel drug candidates in all clinical areas [3]. Interestingly, it is becoming increasingly clear that GPCRs need to be viewed in the context of the membrane lipid environment surrounding them. For example, membrane cholesterol has been reported to have a modulatory role in the organization and function of a number of GPCRs [4]. Importantly, recently reported crystal structures of GPCRs have shown structural evidence of cholesterol binding sites [5, 6]. Previous work from our laboratory has demonstrated that membrane cholesterol is required for the function of the serotonin1A receptor, a representative GPCR [4], and this dependence could be an important determinant in diseases such as the Smith–Lemli–Opitz syndrome [7]. In order to gain insight into interaction of cholesterol with the serotonin1A receptor, we recently analyzed putative cholesterol binding sites from protein databases in the serotonin1A receptor. Our analysis shows that cholesterol binding sites are inherent characteristic features of serotonin1A receptors and are conserved over evolution. Further, we propose a novel mechanism by which membrane cholesterol could affect structure and function of GPCRs. Progress in deciphering the nature of GPCR-cholesterol interaction in the membrane would lead to a better insight into our overall understanding of GPCR function, thereby enhancing our ability to design better therapeutic strategies to combat diseases related to malfunctioning of GPCRs.

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012: *Proteopedia*—a scientific 'Wiki' bridging the rift between 3D structure and function of biomacromolecules

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Biologists and biochemists are now able to access 3D images of biomacromolecules underlying biological functions and disease. Rather than relying on text to provide the understanding of biomacromolecule structures, a collaborative website called *Proteopedia* now provides a new resource by linking written information and 3D structural information. The wiki web resource, http://www.proteopedia.org/, displays protein structures and other biomacromolecules in interactive format. These interactive images are surrounded by descriptive text containing hyperlinks that change the appearance (such as view, representations, colors or labels) of the adjacent 3D structure to reflect the concept explained in the text. This makes the complex structural information readily accessible and comprehensible, even to people who are not structural biologists. Using *Proteopedia*, anyone can easily create descriptions of biomacromolecules linked to their 3D structure, e.g. see the page on 'HIV-1 protease' at: http://proteopedia.org/wiki/index.php/HIV-1_protease. Aside from content added by *Proteopedia's* existing users, pages on each of the more than 50,000 entries in the Protein Data Bank have been automatically created with 'seed' information, creating pages that are already useful and primed for expansion by users. Members of the scientific community are invited to request a user account to edit existing pages and to create new ones.

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013: Structural and functional insights in biosynthesis of complex virulent lipids

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Cell envelope of *Mycobacterium tuberculosis* (Mtb) is a treasure house of a variety of biologically active molecules of fascinating architectures. Many of these lipidic metabolites are known to play an important role in disease pathogenesis. In this talk, I would highlight the structural and functional role of polyketide synthase (PKS) proteins in the biosynthesis of complex mycobacterial lipids. The catalytic as well as mechanistic versatility of PKSs in generating metabolic diversity and the significance of recently discovered fatty acyl-AMP ligases in establishing "biochemical crosstalk" between fatty acid synthases (FASs) and PKSs would be discussed. Our studies apart from identifying novel pathways for developing anti-tuberculosis drugs have revealed unique mechanisms of enzymatic crosstalk in *M. tuberculosis* that reveal subtle ways in which pathogens evolve their gene products to generate metabolic diversity.