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The impact of crystallization conditions protein constructs and space groups on structure based drug design

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The 3D structure of apo proteins and proteins with inhibitors provide the basis for structure-based drug design studies and is also utilized in docking procedures to search for more potent drug. Specific examples for drug design of Acetyl Cholinesterase (AChE) and Phosphotriesterase (PTE) using X-ray crystallography will be presented. Comparative analysis between the computational docking drug design approach and the AChE crystal structures revealed that the position of the ligands within the active-site gorge of the enzyme is influenced by the crystallization conditions. Spectroscopic evidence and thermal stability results supported such a difference in ligand positioning. These results have implications for structure-based drug design using docking procedures. We also analyzed nineteen crystal structures of the apo and several phosphonate (OP) analogs bound to few highly evolved PTE variants. In addition to providing insights into the binding modes of OPs into the active site of the different PTE variants, the data reveal the importance of tags used for protein expression, the 'choice of the appropriate' crystallization conditions, the protein constructs and the space groups and their implications for structure-based drug design.

Biography

Orly Dym completed her PhD in 1994 from the Weizmann Institute of Science, Israel under the supervision of Prof Joel Sussman and postdoctoral studies from the University of California Los Angeles, under the supervision of Prof David Eisenberg. Since 2003 she is the Crystallographer at the Structural Proteomics Unit (SPU), Weizmann Institute of Science, Israel. For the last 15 years she has been a member of the SPU where she lead the unit of protein crystallography which include protein crystallization, elucidating the three-dimensional (3D) structure of proteins. She had determined the 3D structure of 350 proteins and protein complexes, some related to human disease and others including engineered non-natural enzymes and non-natural protein complexes. Some has contributed to the development of drugs, while one has directly benefited enzyme replacement therapy for a human disease. In addition, she has carried out detailed structural analysis on many of these structures, which has greatly aided the understanding the correlation between 3D structure, function, selectivity and stability. She has published more than 50 papers in reputed journals, 10 of which as first author.

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