Leslie W. Tari (ed.): Structure-based drug discovery. Volume 841 in methods in molecular biology

Humana Press, Springer Science + Business Media, 2012, 385 pp

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Received: 9 June 2012 / Accepted: 9 June 2012 / Published online: 28 June 2012
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This excellent book on Structure-Based Drug Discovery (SBDD) translates concise yet instructive description of principles into methodologies and technologies of SBDD all the way through the successful examples and state-of-the-arts approaches.

The introductory chapter “The Utility of Structural Biology in Drug Discovery” by Leslie W. Tari (Trius Therapeutics) demonstrates how the access to detailed three-dimensional data helped either recognition of dual bacterial DNA gyrase target-based broad-spectrum inhibitors or optimization providing a good drug (Tamiflu) as opposed to the good inhibitor (Relenza) of influenza virus neuraminidase. Also, the receptor protein tyrosine kinase inhibitor Gleevec or histone deacetylase HDAC8 inhibitor suberoyl anilide hydroxamic acid SAHA provide examples of protein structure-based development of drugs fighting highly malignant human cancer and cutaneous T-cell lymphoma.

Consecutive chapters illustrate the whole process leading to diffraction-quality protein crystals from protein engineering through purification to the crystallization that has remained the bottleneck of structure-based drug discovery. “Genetic Construct Design and Recombinant protein Expression for Structural Biology” by Suzanne C. Edavettal, Michael J. Hunter, and Ronald V. Swanson (Centocor R&D Inc.) presents access to troubleshooting practice decreasing heterogeneity of samples for protein crystallization through suitable and often iterative construct design, proper end-terminal boundary choices, codon

optimization to improve protein expression level, surface protein engineering or ligand addition to reduce regions of disorder and applying mutations of cysteine to serine or alanine, phosphomimetic mutations, co-expression with phosphatases avoiding aggregation, proteolysis, and premature translational termination. “Purification of Proteins for Crystallographic Applications” by Daniel C. Bensen (Trius Therapeutics) provides a useful practical guide of methodologies and techniques to attain purity and monodispersity of protein samples. Clues for selection of the appropriate purification scheme for a given protein are exemplified by a detailed protocol with useful notes enabling crystallization of the nucleotide binding domain of the human cancer target Hsp90. “Protein Crystallization for Structure-Based Drug Design” by Isaac D. Hoffman (Takeda San Diego) details the conceptual framework of current high-throughput and “by any means necessary” technologies allowing to obtain diffraction-quality protein crystals mostly in the presence of ligands. Beyond practical information, it is emphasized that the protein crystallization is unique, requiring careful consideration of the controllable variables.

The following overviews, including “X-Ray Sources and High-Throughput Data Collection Methods” by Gyorgy Snell (Takeda San Diego) and “The Use of Molecular Graphics in Structure-Based Drug Design” by Paul Emsley (Department of Biochemistry, University of Oxford) and Judit É. Debreczeni (AstraZeneca) offer excellent narratives. They discuss X-ray data generation on a large number of protein crystals and data depictions, endowing with the *good in silico practice*—all eminently timely topics.

The series of further well-selected thematic chapters follow. They include “Crystallographic Fragment Screening” by John Badger (Zenobia Therapeutics), “The Role of

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Enzimology in a Structure-Based Drug Discovery Program: Bacterial DNA Gyrase” by Mark L. Cunningham (Trius Therapeutics), “Leveraging Structural Information for the Discovery of New Drugs: Computational Methods” by Toan B. Nguyen, Sergio E. Wong, and Felice C. Lighstone (Lawrence Livermore National Laboratory), “Chemical Informatics: Using Molecular Shape Descriptors in Structure-Based Drug Design” by Andy Jennings (Takeda San Diego), “Accounting for Solvent in Structure-Based Drug Design” by Leslie W. Tari, “Structure-Based Drug Design on Membrane Protein Targets. Human Integral Membrane Protein 5-Lipoxygenase-Activating Protein by Andrew D. Ferguson (AstraZeneca), “Application of SBDD to the Discovery of New Antibacterial Drugs” by John Finn (Trius Therapeutics), “Leveraging SBDD in Protein Therapeutic Development: Antibody Engineering” by Gary L. Gilliland, Jinquan Luo, Omid Vafa, and Juan Carlos Almagro (Centocor R & D Inc.) and “A Medicinal

Chemistry Perspective on Structure-Based Drug Design and Development” by Shawn P. Maddaford (Neuraxon-Inc). They highlight hot issues as well as challenges of contemporary SBDD, and make its future appear promising and attractive.

By collecting effective state-of-the-arts methodologies, technologies, and protocols, the book provide a consistent guide pertaining to the complex, multi- and interdisciplinary SBDD operation. This book is recommended for researchers getting involved in SBDD projects as well as for scientists involved in the most diverse areas of protein chemistry, structural biology, medicinal chemistry, and chemical informatics.

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