Chemical Biology: From Small Molecules to Systems Biology and Drug Design. Volumes 1−3. Edited by Stuart L. Schreiber, Tarun M. Kapoor, and Günther Wess. Wiley/VCH Verlag GmbH, Weinheim, Germany. 2007. lxiii + 1205 pp. 18 × 24.5 cm. ISBN 978-3-527-31150-7. $625.00.

Chemical Biology, according to the view of Editor Stuart Schreiber (*Nat. Chem. Biol.* **2005**, *1*, 64−66) seeks to identify and characterize the naturally occurring and synthetic small molecules that bind to and modulate the actions of "nature's DNA, RNA, and protein macromolecules residing within their cellular contexts". In the words of the publisher's statement on the back cover of the books, "Chemical biology has become the new buzz-word in organic chemistry and in the life sciences, describing a new era in the interplay between the two disciplines and still on the rise." Yet, as is made clear in the very first essay, chemical biology and medicinal chemistry share closely related procedures and goals, as well as an extensive network of philosophical, historical, theoretical, and experimental roots. Although it may be an overstatement to suggest, as Gough and Crews do in their discourse, that chemical biology is established on a "unique foundation", many of the contributions to this treatise, briefly considered here, are of special importance to medicinal chemists and the drug discovery community.

The three volumes comprise 39 themes edited and written by major investigators in chemical biology from 74 academic and 23 industrial institutions located in Europe (51), the U.S. (45), and Japan (1). Most articles include sections on the outlook, introduction, history and development, general considerations,

applications, future development, conclusions, and up-to-date references. An extensive index is provided in the final volume.

A number of papers are concerned with the action of naturally occurring and synthetic small-molecule "perturbogens" to produce cellular phenotypes that provide help to unravel the biochemical basis of physiological processes such as the mechanism of heat and cold sensation produced by capsaicin and menthol, respectively. Likewise, such small molecules can be used as "conditional alleles" or "inducible alleles" to "knock in" or "knock down" cell-signaling events at specific time points. A comprehensive treatment of the application of such forward chemical genetics is provided by Haggarty and Schreiber, who point out that "the logic of forward chemical genetics is a reversal of the logic of most of the current efforts in drug discovery" with a consequent "paucity of information about the phenotypic effects of large collections of small molecules". An excellent contribution by Simon and Shokat considers the effect of point mutations in controlling ligand selectivity and especially the application of such studies to the development of gatekeeper residues in the binding pocket of kinases. Through the creation of a uniquely sensitive kinase allele, it is possible to target a kinase inhibitor selectively to any one of the more than 500 kinases coded by the human genome. Claxon's outstanding discussion of chemically induced dimerization of proteins points to the creation of inducible animal models of diseases such as prostate cancer and liver disease, with obvious applications to drug development. Likewise, chemically induced dimerization of proteins has potential direct therapeutic applications.

Volume 3 comprises a group of presentations directed to specific interests of the drug discovery community. F. Douglas reviews managerial challenges encountered at Aventis in implementing chemical biology platforms. Groom and coauthors provide an extremely interesting and challenging updated categorization of the druggable genome. They determined that approximately 3500 genes encode proteins druggable via druglike small molecules, whereas only 170 are targets for approved small molecule drugs. Other papers are directed to the subjects of target families, NMR studies of kinase–ligand interactions, nuclear receptors and their interactions with ligands, GPCR targets and their interactions with ligands, protein–protein interactions, and the prediction of ADMET properties. Final discussions include the systems biology of cellular signal transduction and gene profiling by means of genome-wide expression analysis.

In general, this compendium is very well-written and produced, although some figures are too small to be useful (e.g., Figures 6.4, 6.20, 9.2-7, and 17.2-6). Figure 3.1-8, intended for color, is confusingly printed in black. This valuable and thought-provoking series is highly recommended for acquisition by individuals and libraries in the drug discovery community.

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