Book Reviews

Functional Informatics in Drug Discovery. Edited by Sergey Ilyin. CRC Press, Taylor & Francis Group, Boca Raton, FL. 2008. xii + 146 pp. 16 × 24 cm. ISBN 978-1-57444-466-7. $99.95.

While there is no rigorous definition of functional informatics given in this book, it apparently involves the merger of experiment automation and informatics analysis, ideally with feedback to the experiment (p 1). Indeed, the book's eight chapters make the case that such systems are important for advancing many aspects of drug discovery and development.

Chapter 1 gives a good description of various analysis algorithms that are used to provide feedback to laboratory automation systems, with particular focus on optimizing chemical reactions and developing ELISA assays. Chapter 2 is an interesting review of recent research on how the human brain represents and retrieves higher-level information. Insights from this research, including synchronous oscillation of spiking signals, may lead to faster, more robust artificial neural network algorithms; however, there is little evidence in this chapter that these ideas have yet been reduced to practice. Chapter 3 is a good review of how early clinical drug development can be accelerated using pharmacodynamic biomarkers. The importance of validating the biomarker and its measurement is stressed, as well as the need to start biomarker development in the early discovery phase to ensure the method is validated before it is required for the clinical studies. A short Chapter 4 suggests how automated behavioral testing is increasing the objectivity of CNS animal experiments while enabling scale-up and points to the increasing use of molecular biomarkers to predict behavioral effects.

Chapter 5 is a nice review of the success of antibody therapeutics in clinical practice in oncology. For the eight oncology antibodies already approved by the FDA, mechanisms of action and clinical prospects are reviewed. It is suggested that current large-scale gene profiling efforts will identify "tumor-specific" antigens, enabling targeted therapies based on a tumor's genetic profile. There follows a consideration of strategies for enhancing antibody efficacy in the clinic, including enhancing immune response. Immunoconjugates, in which cytotoxic agents are linked to a tumor-targeting antibody, are well reviewed as is enhancement of drug delivery through ligand-targeted liposomes. Chapter 6 addresses the problem of relating target genetic sequence to biological function. It notes that 98% of the human genome does not code for proteins, and the major part of the human transcriptome is composed of RNAs that do not code for proteins; nevertheless, we still have much work to do characterizing the large number of protein-coding genes of unknown function. Forward genetics techniques are described for finding genes responsible for desired (or undesired) cellular functions, as well as reverse genetics techniques to validate the target gene's function. Techniques explored include using expression libraries for gain-of-function screens and using antisense RNA libraries, random fragment RNA libraries (from a starting cDNA population), random sequence libraries of ribozymes, random sequence libraries of peptides, and RNA interference expression libraries for loss-of-function screens. Validating gene function through gene-silencing techniques is then reviewed, specifically, use of ribozymes, DNAzymes, external guide sequences, and RNA interference.

Chapter 7 reviews the relatively new use of protein microarrays for molecular network analysis and signal-pathway profiling. It convincingly argues that "although DNA is the information archive of the cell, the execution of the disease process occurs through altered protein function." Genetic studies cannot illuminate complex protein–protein interactions, their localization, the protein's phosphorylation state, whether it is functionally active, etc. Furthermore, studies in cultured cells in vitro may not accurately represent the molecular events in the source tissue because of loss of context of the in situ tissue elements and effects of the culture medium. Fortunately, the combination of laser-capture microdissection of patient tissue samples to obtain homogeneous cell types, plus high-sensitive protein microarray analysis, can now provide molecular network maps for the individual tumor, indicating where the networks are deranged and ultimately enabling design of patient-optimized, multivalent therapies.

Finally, Chapter 8 indicates the promise of laser-microdissection-based transcriptomics using RNA amplification microarrays. The stability of tissue RNA to microdissection conditions is demonstrated through measurement of amplified complementary DNA, and microarray analysis of the RNA is shown to be feasible. Given the quantity of non-protein-coding RNA in the transcriptome and the importance of post-translational processing in cell function, this new technique promises to provide new insights into disease progression and therapeutic outcomes.

We are all aware that the ideal of a single major target for a disease, for which a "magic bullet" therapy can be designed, is seldom realized; disease (and life) is much more complex. But we can hope that the range of genomic, transcriptomic, proteomic, and functional informatics techniques described in this book, coupled with analyses of the resulting integrated data, can help us capture and understand this complexity and thereby develop more flexible and effective therapeutic interventions in the future.

This book will be of interest to medicinal chemists and other pharmaceutical scientists interested in expanding their knowledge of rapidly evolving functional informatics techniques. The chapter authors are practitioners in academia, research institutes, and pharmaceutical laboratories, and several chapters describe drug discovery approaches being used at Johnson & Johnson. The chapters are quite readable, relatively free of typographical errors, and well referenced to work published up to 2004. There is a good subject index.

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