Preface

In the late 1990s, chemical genetics emerged to study the interaction or perturbation of cells with small molecules in order to mimic the effect of mutations investigated by functional genomics. While classical genetics shows particular advantages over chemical genetics regarding the high specificity that can be achieved with gene knockouts, chemical genetics could only meet this challenge if it could dissect the function of organisms and cells by having a specific small molecule partner for every gene product. While chemical genetics studies the changes of individual genes or one particular phenotype induced by small molecules, chemical genomics investigates the alteration of the whole genome *en masse* through the perturbation of the complex network of signaling pathways by small molecules; thus, chemical genomics is an extension of chemical genetics to a genome-wide scale. This basic concept found several innovative applications over the years from cell biology, to drug discovery, and more recently in diagnostics and clinical practice.

The pioneering first edition of this book, *Chemical Genomics*, was published by Marcel Dekker, Inc., more than 7 years ago. Since then, the area of chemical genomics has rapidly expanded and diversified; numerous novel methods and subdisciplines such as (chemical) glycomics and lipidomics have emerged as well, showing interdisciplinary features.

Chapter 1, while giving a short account of the general strategies and methodologies of chemical genomics, mainly focuses on the emerging technologies and recent applications in the areas of combination chemical genetics, toxicogenomics, drug chemical genomics/proteomics, and orthogonal chemical genetics, which utilizes small molecules and/or compound libraries.

The integration of cell-based assays with activity/affinity-based approaches allows us to identify the proteins targeted by the small molecules, the altered expression levels, and ultimately reveals the association with signaling pathways or disease states. Chemical genomics is closely related to the novel postgenomic discovery strategy, where target identification/validation is the key element. All these efforts help to understand

the cell functions as well as the pathomechanisms of diseases, which could open new opportunities for therapeutic interventions.

Chapter 2 discusses the development and application of novel analytical methods that are used in lipidomics (including steroidomics), which is one of the metabolomics approaches. Metabolomics, which is the systematic identification of the composition of low molecular weight materials within the cells/body upon small-molecule treatment or induced by disease, is closely related to chemical genomics since the direct binding interaction with proteins within the cells could also lead to changing the concentration of the small molecule metabolites. The primary objectives of lipidomics are to determine the quantitative lipid profile of a cell type, tissue, or biological fluid, and mass spectrometry is the dominant analytical technique together with its variants (shotgun lipidomics, gas or liquid chromatography, mass spectrometry, tandem mass spectrometry).

Since the cellular response (gene expression alterations or phenotypic changes) to small molecules can be significantly different in normal and in pathological states, differential *omics* technologies allow for the identification of gene or protein biomarkers.

In Chapter 3, biomarker discovery applications of microarray technologies using DNA, RNA, and protein and glycan arrays, with the advantage of requiring very small amounts of samples with excellent detection limits, are discussed. Microarray technology-based approaches have been applied in serum tumor marker profiling as well as in drug discovery and medicinal chemistry when the effects of small molecules in DNA–protein or protein–protein interaction are studied.

Chapter 4 describes further applications of biomolecular biomarkers often used in the diagnosis of diseases, at various stages in the small molecule drug R&D process and during the therapeutic use of marketed medicines. Throughout the process, the use of biomarkers is intended to secure the highest level of efficiency and safety possible for a given drug, that is, during the drug discovery phase to select the best chemical entity that hits the target or during the drug development phase, to define the target patient group which will respond to treatment. The major types of biomarkers are discussed in detail, for example, prognostic biomarkers, disease-specific biomarkers, response (surrogate) biomarkers, and toxicity biomarkers.

Since chemical genomics represents a holistic approach, in principle, the small molecules can interact with the whole proteome either through direct binding interaction or indirectly as a downstream effect through the signaling network. Furthermore, the cell response is the overall consequence of the interactions initiated by the small molecules, thus, chemical genomics is closely associated with systems biology and network theory.

The revolutionary development of chemical and functional omics approaches (genomics, proteomics, lipidomics, glycomics, etc.) has contributed to the emergence of database management, high-throughput

molecular technologies, and multivariant bioinformatic analysis technologies leading to an entire change in the paradigm of experimental biology and medicine. This new paradigm in biomedical sciences includes a network-oriented view and advanced statistical and informatics data management, which is based on network theories and mathematical modeling and opens the way toward personalized medicine. In Chapter 5, the principles of contemporary systems biology and genomics in experimental medicine are discussed.

Finally, the chemical genomics/proteomics methods are complemented by a much broader discipline called *chemogenomics*, which is in close relationship with system biology and investigates the matching of the chemical and biological space integrating experimental and *in silico* approaches. Chemogenomics is a recent global drug discovery paradigm integrating the knowledge of gene sequences, protein families, and protein–small molecule interaction based on experimental and 2D/3D molecular modeling.

Chapter 6 discusses the recent recognition that the significant attrition rate in clinical trials during the past decades has been due to the unexpected binding of drug candidates to additional targets, either off-targets or antitargets resulting in dubious pharmacological activities, side effects, and sometimes adverse drug reactions. In this chapter, various *in silico* chemogenomics approaches are discussed, which utilize annotated ligand-target as well as protein–ligand interaction databases, and could predict or reveal promiscuous binding and polypharmacology, the knowledge of which would help medicinal chemists in designing more potent clinical candidates with fewer side effects.

The book is supplemented with a glossary and a basic index.

In summary, the selected topics of *Chemical Genomics and Proteomics*, 2nd Edition, reflects the major directions of the field witnessed in the last couple of years together with the recently emerged interdisciplinary aspects of chemical genomics demonstrated by various applications. The target audience of this book has also been extended; not only to practitioners in drug discovery, medicinal chemistry, and molecular/cell biology, but also to physicians in clinical diagnostics as well as experts in the whole drug development pipeline, who could find valuable information in this second edition. This edition is equally useful for scientists working in laboratories and for students at the graduate and undergraduate levels, and it serves as a valuable textbook for university professors offering courses on medicinal chemistry, pharmacy, and medicine in the postgenomic era.

Ferenc Darvas
András Guttman
György Dormán