Chemical Genomics

Small Molecule Probes to Study Cellular Function

S. Jaroch, H. Weinmann
Editors

With 87 Figures
Preface

In a time when the output of fewer NCEs affords even more significant investments into R&D, the paradigm of conducting drug discovery through a linear process entailing target identification/validation, lead discovery, lead optimization, and finally candidate selection is challenged by an ap-
proach called chemical genomics. Starting with small-molecule probes, synthesized by high-throughput chemistry, to conditionally modulate gene or protein function and to eventually identify therapeutically relevant targets, it places chemistry at the very beginning of the drug discovery process. Depending on a smart library design, the perturbing agent may ideally represent a lead structure, thus reducing development times by running lead identification and target identification/validation processes in parallel.

We initiated an Ernst Schering Research Foundation Workshop to bring together leading scientists from academia and pharmaceutical companies to learn more about progress in chemogenomics, chemical genomics, and chemical biology, and the proceedings of this symposium are detailed in this book.

Though the terms “chemical genomics” and “chemogenomics” are sometimes confused in the literature, the first three chapters point out that chemogenomics is an effort within pharmaceutical companies to integrate data on target protein sequences with molecular structures and selectivity data of small molecules. In contrast to the traditional focus on distinct targets, the chemogenomics approach considers target families and activity profiles. After a general overview by H. Kubinyi, W. Guba, T. Klabunde and R. Jäger present Roche’s and Sanofi-Aventis’s chemogenomics approach to identifying novel lead structures for drug discovery programs aiming at G-protein coupled receptor (GPCR) modulators.

Chemical genomics, entailing the synthesis of small-molecule probes and their use to study cellular function, depends on diversity-oriented synthesis (DOS) to set up large libraries as a toolbox in order to populate chemical space broadly. As D.R. Spring and colleagues demonstrate, these DOS libraries differ from the old combinatorial chemistry-derived libraries of the 1990s in that they exploit novel and richer chemistries leading to more elaborate architectures in terms of skeletal, stereochemical, and building block diversity. This is in contrast to the sole emphasis on building block diversity in “traditional” combinatorial or parallel high-throughput chemistry approaches.

A chemical genomics application is presented by J.D. Gough and C.M. Crews; they elegantly use the natural product fumagillin (TNP-470) as a chemical probe for studying endothelial biology. Further, they
describe the Proteolysis Targeting Chimerics (PROTAC) approach as a “chemical knockout” tool to study protein function.

R.V. Weatherman and colleagues discuss research in molecular endocrinology, particularly chemical approaches to selectively dissect complex biological processes related to the estrogen receptor.

Natural products already excel through constitutional diversity and are therefore ideal templates for chemical genomics efforts. M.A. Koch and H. Waldmann report on the clustering of natural product frameworks (SCNOP, structural classification of natural products) and their value as biologically validated starting points in structural space for library design.

Before small molecule-protein interactions are studied, a robust screening technology has to be put in place. Opportunities arising through improved capabilities are highlighted by L. Mayr discussing the highly minitiaturized high-throughput nanoscreen and the affinity-based assay technology behind speedscreen at Novartis.

The editors would like to acknowledge the generous support of the Ernst Schering Foundation, which allowed us to set up this exciting workshop. We trust that the reader will share the enthusiasm and excitement in the highly interdisciplinary field of chemical genomics and chemogenomics.

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