Preface

“Structural Genomics” as an area of investigation arose from the recognition that genome sequence information could be combined with improved methods for macromolecular structure determination to allow high-throughput structure determination. One of the early justifications for developing the field was the potential to make use of the structural information in drug discovery efforts. All three of these areas, genome sequencing, macromolecular structure determination, and structure-aided drug discovery, have seen dramatic improvements in technology and methodology.

This volume focuses on high-throughput structure determination methods and how they can be applied to lay the groundwork for structure-aided drug discovery. The methods and protocols that are described can be applied in any laboratory interested in using detailed structural information to advance the initial stages of drug discovery. Due to the advances in technology and methodology that have occurred during the past 10–15 years, even the nonspecialist can apply structural biology to most biomedical problems. The methods and approaches that distinguish structural genomics from “classical” structural biology have been decreasing as more and more research groups adopt high-throughput methods and apply them to their specific biological research problems.

In some respects, structure-aided drug discovery is very specific to the one particular protein target being studied and the approaches of structural genomics would not seem to be appropriate. However, if one looks at the problem broadly, there often is more than one protein that could be targeted, and when multiple proteins are being investigated, the advantages of carrying out most of the steps in parallel can increase productivity.

The initial chapters deal with bioinformatics and data management because selecting target proteins and planning how the large amount of diverse data will be handled are the first steps. Following these are the chapters on high-throughput methods for cloning, expression and solubility testing, protein production, purification, crystallization screening, and screening for suitability for NMR structure determination. One of the continuing problems faced by structural genomics efforts is the limited success rate that, not surprisingly, accompanies increased throughput and the associated reduction in individual attention to each protein. Although there is no panacea, a number of chapters describe methods that can rescue, or salvage, target proteins that are failing as they proceed through the pipeline. Finally, the concluding chapters describe methods that use the proteins that have been produced in order to identify initial small molecule hits. These hits can then feed into drug discovery efforts. At this point in the process, the number of technically and biologically suitable targets will have been reduced and each protein, together with the hits that have been generated, will require individual attention.

The structural genomics approach provides an efficient initial step toward drug discovery and the methods described will be useful to anyone interested in moving in this direction.

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