

STRUCTURE-BASED DRUG DISCOVERY

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PREFACE

The last 25 years has seen structure-based drug discovery evolve from an interesting niche activity pursued by a relatively small number of companies to being a fully integrated series of techniques that are part of the core technologies within most large pharmaceutical companies. This increase in popularity has been driven to a large extent by significant technological advances that have allowed the three-dimensional structure of a target protein to be determined in a much shorter time frame. In the 1980's it could take several years to determine the crystal structure of a key drug target; obtaining structures of bound inhibitors could consume several more months. Today, protein crystal structures may be obtained in months rather than years and subsequent protein/inhibitor complexes often only take weeks (if not days) to solve. Another key factor in the uptake of structure-based discovery methods has been the availability of crystal structures for significantly more proteins at the start of a drug discovery program. This increase in the number of protein structures has also helped the development of improved computational chemistry methods for the prediction of the binding modes of compounds and binding energies.

Successful structure-based design thus requires the synthesis of several different techniques, both experimental and theoretical. This book is intended to provide an overview of some of the more recent developments, with a particular focus on structural genomics, biophysical techniques, fragment-based approaches and computational methods. The first two chapters outline the key advances in structural biology that have addressed some of the major bottlenecks, such as protein expression and crystallisation, in the process of solving protein crystal structures. They also include a review of the structural genomics initiatives intended to obtain novel protein structures that are being pursued around the world. The subsequent five chapters describe several aspects of fragment-based discovery as a major new approach to discovering new drug molecules. The essence of this approach involves the use of biophysical techniques, such as X-ray crystallography and NMR, to screen fragments that due to their limited size and complexity typically bind the drug target with significantly lower affinity than drug-sized molecules. The potential advantages of this approach over conventional drug discovery are discussed as well as the technological

advances required to undertake high-throughput X-ray crystallography and NMR experiments on the binding of molecular fragments to proteins. The final two chapters focus on the latest developments in computational techniques that are integral to applying structure-based methods to medicinal chemistry strategies. These include methodologies for improving the success of docking compounds to protein structures and the scoring of these binding modes in order to predict the free energy of binding.

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