Preface

Tremendous progress made in the past three decades of molecular biology studies of the cell signaling network has accumulated vast resources and knowledge that are ripe for harvesting for translational and therapeutic development. It is now clear that the traditional pharmaceutical Research & Development model may not be sustainable as evidenced by the recent flagging productivity in the pharmaceutical industry. New technological innovations in research of lead design, discovery, optimization, and validation, initiated by original ideas and concepts, may help mitigate the situation in the long run.

This volume of MiMM is aimed at offering some selected examples of novel methodologies involved in the dynamic and ever-changing field of rational drug design. The readers of this methodology reference book may adopt and modify the protocols and methods described in this volume in their efforts to translate unique bench-side ideas into discovering new leads of novel or established molecular targets in human diseases.

The areas covered in this volume include the following:

1. Virtual screening of chemical hits
2. Rational lead discovery by high-throughput screening
3. Combinatorial and fragment-based lead generation
4. Peptide-based drug discovery
5. Specificity and resistance
6. Effective delivery by RNA-based approach and nanotechnology
7. Animal models of lead validation

Structure-based virtual screening has emerged as an important tool in our quest to access novel drug-like compounds. There are a wide range of comparable and contrasting methodologies available in screening structural databases for hit identification. In Chap. 1 and several subsequent chapters, a strategy and several case studies utilizing the available virtual screening methods to identify hits and leads for small GTPases, phosphotases, or wnt pathway targets are presented. In addition to the traditional enzymatic targeting sites, such as the ATP-binding kinase domain or phosphotase domain, recent understanding of the structure–function relationship of many signaling proteins has allowed clever design of small molecule or peptidomimic inhibitors or activators against allosteric sites of the targets that significantly increase the specificity and efficacy. Examples of these also are discussed in the following chapters.

Complementary to the structure-based hit identification effort, mechanism-based screening approaches have proved fruitful leading to new leads of specific kinases and other enzymatic substrates. Examples in the successful application of yeast two-hybrid system, peptide aptamers, and peptide ligands are illustrated.

With the success of targeted therapy, development of drug resistance in disease cells has become an inevitable side effect. Recent progress in the drug discovery studies tackling the mechanism of drug resistance and applying rational designed second generation drugs to

overcome target expression/mutation changes for several kinases pioneers this future direction of rational drug design. This area of studies is represented by the identification, characterization, and rational design of new inhibitors in BCR-ABL targeted therapy.

Finally, a recent example of designing antisense microRNA and an example of delivering membrane-impermeable molecules into cells by nanotechnology, which can expand potential therapeutic options of rational designed drugs, are presented.

Overall, these complementary approaches to identify and validate hits specifically targeting a biologically implicated target, to overcome ensuing drug resistance and specificity issues, and to improve delivery efficiency to the target cells should be useful for the readers to appreciate the fast pace in rational drug design that may benefit future drug discovery effort.

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