Preface

Cell integrity and functions depend on a myriad of protein–protein interactions. Many of these interactions are involved in disease etiology and represent desirable targets for pharmacological intervention. However, the notion of modulating protein–protein binding with small molecules has historically raised serious concerns. The interface between two interacting proteins is typically large and devoid of sizable subpockets. It has been thought unlikely for a drug-like molecule to bind to such a landscape with high affinity and to effectively compete away one of the protein partners. However, this blanket characterization of protein–protein interfaces is overly simplistic. It has become clear that in certain cases reasonably sized pockets exist to support binding, or that in other cases the interface region is flexible and an incoming molecule can induce the formation of a suitable binding pocket. On the other side of the issue, the concept of what constitutes a drug-like molecule has been evolving, particularly in the context of protein–protein modulators. The traditional profile of an organic compound with a molecular weight in the 200–500 range has been expanded to include compounds of significantly higher molecular weight, and the possibility of using peptides and peptide-like molecules as drugs has become much more realistic.

In recent years, several success stories have appeared with regard to discovery of protein–protein interaction inhibitors. There is a growing understanding of the critical factors involved and of the fundamental issues relating to the many aspects of the process – choosing targets, finding leads, discerning and verifying binding strategies, and optimizing properties. In this volume, we have collected the knowledgeable insights of a number of leaders in this field – researchers who have achieved success in addressing the difficult problem of inhibiting protein–protein interactions. They describe their unique approaches and share experiences, results, thoughts, and opinions. The content of the chapters is rich, and in terms of scope ranges from generalized approaches to specific case studies. There are various focal points, including methodologies and the molecules themselves. Ultimately, there are numerous lessons to be taken away from this collection, and we hope that this snapshot of the current state of the art in developing protein–protein inhibitors
not only pays tribute to the past successes but also generates excitement about the future potential of this field.

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