Preface

The last decade has been a difficult one for the pharmaceutical industry. The rate of new compound registrations has slowed from its peak in the 1990s, and efforts to shorten discovery times and streamline clinical paths have not resulted in increased efficiency overall. Moreover, biologics have become an increasingly large part of the field, and their higher success rate over the last several years has further disappointed prospects for small-molecule drug discovery going forward. Several explanations for this downturn have been put forward; one of the most commonly accepted is the idea that the 'low hanging fruit' has been picked, and the drug targets remaining are simply more challenging. With the synthetic, analytical, and structural technologies present today, the far greater understanding of relevant biology, and the vast and ever-growing historical knowledge of drug discovery at our fingertips, it is difficult to imagine that current practitioners in the field of small-molecule drug discovery are simply not as proficient as those of yesterday. While regulatory issues are more challenging than ever, it seems certain that the drug targets and biological mechanisms that the industry is focusing on are simply more difficult than those of 20 or 30 years ago. Thus the identification of high-quality drug targets – targets that are not only druggable, but of high biological relevance – is more crucial than ever.

Over roughly this same period of time, better understanding of biological systems – in particular of signaling pathways and various aspects of structural biology – has brought to the fore a new type of drug target for consideration. In addition to the enzymes, ion channels, and receptors that traditionally have comprised the domain of small-molecule drug targets, protein-protein interactions (PPIs) began to gain consideration. In the last two decades, the industry has taken on many PPIs, but few compounds have gained FDA approval, the vast majority of compounds that reached clinical trials have failed in the early stages, and the overall impression is one of higher-than-average failure in the discovery stage as well. Additionally, approved compounds have for the most part been intravenously delivered, and for narrow indications, and none have achieved 'blockbuster' status. All this has served to maintain and perhaps strengthen a common view of PPIs as being undruggable. PPIs are often seen as being part of the problem, rather than part of a possible way forward.

It is certainly true that thus far, the overall effort to modulate PPIs with small molecules has not constituted a successful venture. However, comparing the last two decades of PPI-targeted drug research to the success of earlier eras, or even to more conventionally targeted work over the same period, should not be of paramount concern. The important question is whether PPIs represent viable small-molecule drug targets now, and into the future. In order to answer this, it is necessary to look at what has been learned from two decades of work on PPIs in the pharmaceutical industry, and to consider how this experience can improve prospects for PPI-targeted drug discovery in coming years.

In this volume, we look at some of the most prominent and successful campaigns within the PPI field. In an introductory chapter, the field as a whole is appraised, with short summaries of several targeted PPIs. Classification of PPIs into structural types leads to some generalizations about the small-molecule inhibitors that emerge from projects targeting them; from a drug discovery standpoint, each type also has unique positive and negative aspects. Additionally, themes of the importance of structural and mechanistic understanding of targets are highlighted.

Chapter 2 surveys the field of inhibitors of the MDM2/p53 interaction, which essentially began with the high-profile disclosure of Nutlins, and quickly and steadily grew through programs at a number of pharmaceutical companies. The MDM2/p53 interaction constitutes a paradigm example of a relatively large, hydrophobic interaction surface for which lead compounds can easily be found. The success of several programs in deriving potent, orally bioavailable small molecules attests to the druggability of this target, and compounds have begun to enter clinical trials. Additionally, the use of many of these small molecules in elucidating additional biology around the MDM2/p53 axis is described. Chapter 3 covers IAP antagonists, also referred to as Smac mimetics, which are well-represented in the clinic for the treatment of cancer. The PPI targeted here involves recognition of a short peptide sequence, and is much different in character from the MDM2/p53 interaction. Drug discovery groups consequently had very different experiences in the course of finding and optimizing chemical matter. Additionally, this chapter, like Chap. 2, illustrates the complexity of signal transduction networks, and the complementary manner in which drug discovery programs are made more difficult by this complexity of relevant biological pathways, and can be of great aid in understanding them.

Chapters 4 and 5 look at PPIs in the field of antiinfective agents, with summaries of work targeted to inhibitors of various HIV-1-related processes, and to RSV fusion inhibitors. Many of these interactions are notable for being involved in structural recognition and reorganization processes instead of signaling pathways. Therapeutic compounds modulating these interactions can operate via a number of mechanisms, from simple blockade of a necessary conformational change or of the formation of a temporary complex, to

alteration of a pre-fusion oligomeric protein into a less-functional conformation. Defining these mechanisms of action adds to the difficulty of drug design. An additional complication, deriving from mutations leading to resistant varieties of targeted proteins, further hinders discovery efforts.

Many of the most challenging PPI interfaces involve widely separated contact points, which are particularly difficult to engage with a druglike small molecule. Therefore, general methods for reproducing this family of epitopes, and thereby substituting for or augmenting the usual drug discovery process, would be of great utility. Chapter 6 presents several approaches that have been taken in the area of α-helical peptide mimetics, primarily by academic laboratories. Designed molecules of this type have already proven valuable as biological probes and have attracted attention from major pharmaceutical companies, but questions remain as to their viability as drugs. The primary obstacles to these approaches concern stability and cell permeability of the mimetics, which continue to be addressed by researchers. However, it is expected that conventional small molecules directed to this type of PPI will tend to possess particularly difficult pharmacokinetic problems of their own. In the final chapter, a small-molecule effort directed at one of these PPIs is presented. Chapter 7 is a detailed case study of the Bcl-2 family inhibitors project at Abbott. Bcl-xL and Bcl-2 have much larger binding epitopes than conventional drug targets, larger even than many other PPIs, including MDM2/p53, and this program provides a rare example of a PPI with well-separated binding pockets that has yielded a fully optimized small-molecule clinical candidate. In this chapter, the particular challenges related to this type of PPI, such as lead identification and appropriate physicochemical characteristics of inhibitors are highlighted.

I thank the authors for their contributions to this volume, and hope that in total this book presents a suitably clear picture of where the field of PPI-directed small-molecule drug discovery has been, what lessons we can take from the past, and, armed with this experience, where the field might be headed.

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