Contents

Preface *xiii*

1	Exploring Protein-Protein Interactions: Concepts, Methods
	and Implications 1
	Mi Zhou and Renxiao Wang
1.1	General Concepts of Protein-Protein Interactions 1
1.1.1	Definition of Protein–Protein Interactions 1
1.1.2	Structural Properties of Protein-Protein Interactions 2
1.1.3	Diverse Types of Protein-Protein Interactions 3
1.1.3.1	Enzyme-Substrate Interactions 3
1.1.3.2	Receptor-Ligand Interactions 3
1.1.3.3	Antigen-Antibody Interactions 3
1.1.3.4	Chaperone-Client Interactions 4
1.1.3.5	Scaffold Interactions 4
1.2	Functional Significance of Protein-Protein Interactions 4
1.2.1	Cellular Signal Transduction 5
1.2.2	Regulation of Gene Expression 6
1.2.3	Immune Response 8
1.2.3.1	Immune Cell Migration 8
1.2.3.2	T-Cell Antigen Recognition and Activation 8
1.2.3.3	B-Cell Antigen Recognition and Activation 9
1.2.4	Protein Degradation Pathway 9
1.2.5	Disease Mechanisms 10
1.2.5.1	Cancer 10
1.2.5.2	Neurodegenerative Diseases 11
1.2.5.3	Infectious Disease 11
1.3	Methods for Analyzing Protein-Protein Interactions 12
1.3.1	Experimental Methods 12
1.3.1.1	Structure Determination 12
1.3.1.2	Affinity, Kinetics, and Thermodynamics Measurement 13
1.3.1.3	Large-Scale PPI Network Mapping 13
1.3.2	Computational Methods 14
1.3.2.1	Sequence-Based Methods 14
1.3.2.2	Structure-Based Methods 15



vi	Contents	
	1.3.2.3	Network-Based Methods 15
	1.4	Implications of the Basic Research on Protein-Protein Interactions 16
	1.4.1	Advancing Disease Understanding and Diagnosis 16
	1.4.2	Driving Target-Based Drug Discovery 17
	1.4.3	Fostering Innovations in Biotechnology 17
	1.5	Conclusions and Perspectives 19
		References 19
	2	Overview of Drug Discovery Targeting PPI Systems 29
		Hao Ma and Jian Zhang
	2.1	Introduction 29
	2.2	Fundamentals of Protein-Protein Interactions 30
	2.2.1	Basic Principles of Protein Structure and Function 30
	2.2.2	Types of Protein–Protein Interactions 32
	2.2.3	Significance of PPIs in Cellular Processes and Disease Pathways 32
	2.3	Challenges in Targeting PPI Systems 33
	2.3.1	Structural Complexities of PPI Interfaces 33
	2.3.2	Dynamics and Flexibility of Protein Complexes 34
	2.3.3	Druggability Issues Associated with PPI Targets 35
	2.4	Approaches in Drug Discovery Targeting PPI Systems 35
	2.4.1	High-Throughput Drug Design (HTS) Methods 35
	2.4.2	Structure-Based Drug Design (SBDD) Techniques 36
	2.4.3	Fragment-Based Drug Discovery (FBDD) Strategies 37
	2.4.4	Computational Methods for Predicting PPI Inhibitors 38
	2.5	Case Studies and Success Stories 40
	2.5.1	BCL Family 40
	2.5.1.1	Bcl-2 40
	2.5.1.2	Bcl-xL 42
	2.5.1.3	MCL-1 42
	2.5.2	p53-MDM2 43
	2.5.3	XIAP/c-IAP1 44
	2.5.4	CD40-CD40L 45
	2.5.5	Cyclin-Dependent Kinase (CDK) 46
	2.5.6	PD-1/PD-L1 47
	2.5.7	Hsp90-Cdc37 48
	2.5.8	Menin-MLL 48
	2.5.9	Kras-SOS1 49
	2.5.10	Keap1-Nrf2 PPI 49
	2.6	Conclusion 51
		References 53
	3	Fluorescence Resonance Energy Transfer Technology and its
		Applications 61
		Jing-Yu Lang
	3.1	Introduction 61
	3.2	Mechanism of FRET 61
	3.3	Applications of FRET 63

3.3.1	Molecular Interactions 63
3.3.2	Conformational Changes 64
3.3.3	Cellular Imaging 64
3.3.4	Drug Discovery 64
3.3.5	Clinical Diagnosis 65
3.3.6	Structural Biology 66
3.3.7	Materials Science 66
3.3.8	Environmental and Agricultural Sciences 66
3.4	Advantages and Limitations 67
3.5	Recent Advances 68
3.6	Conclusion 70
	Acknowledgements 71
	References 71
4	Dissect Protein Interactions Using Mass Spectrometry 75
	Bin Liao and Liang Zhang
4.1	Introduction 75
4.2	Affinity Purification Coupled with Mass Spectrometry (AP-MS) 76
4.3	Proximity Labeling 81
4.4	Cross-linking Mass Spectrometry (XL-MS) 84
4.5	Co-fractionation Coupled with Mass Spectrometry (CF-MS) 88
4.6	Thermal Proximity Co-aggregation (TPCA) 90
4.7	Limited Proteolysis-Mass Spectrometry (LiP-MS) 93
4.8	Conclusion and Outlook 95
	Acknowledgements 96
	References 96
5	Detection of Protein-Protein Interactions In Situ via Proximity
	Ligation Assay 105
	Xinyue Zhou and Peng Zou
5.1	Introduction 105
5.2	Implementations of Proximity Ligation Assay 106
5.3	Applications of PLA for Detecting Protein-Protein Interactions 108
5.4	Conclusions and Outlooks 109
	Acknowledgments 110
	References 110
5	Application of Surface Plasmon Resonance in the
	Characterization of Protein-Protein Interactions 115
	Yuanyuan Xie and Jianrong Xu
5.1	Introduction 115
5.1.1	Protein-Protein Interactions 115
5.1.2	Principle of Surface Plasmon Resonance 115
5.1.3	Advantage of SPR 116
5.2	Applications of SPR Assays in PPIs Characterization 117
5.2.1	SPR Application in Binary PPI Systems 117
5.2.1.1	SPR Assay in Verifying and Measuring PPIs 117

viii	Contents	
•	6.2.1.2	SPR-Guided Screening and Optimization in Drug Discovery 120
	6.2.1.3	SPR in the Validation of PPI Interface 123
	6.2.2	SPR Application in Ternary PPI Systems 126
	6.2.2.1	SPR-Based Epitope Competition Assays 126
	6.2.2.2	SPR-Based Drug Discovery of PPI Modulators 128
	6.2.2.3	SPR Applications in Targeted Protein Degradation 130
	6.3	Advantages and Limitations of SPR Application for PPIs 131
	6.4	Future Directions 132
		References 133
	7	Computational Methods for Protein-Protein
	•	Interactions 139
		Hao Li, Yurui Li, and Sheng-You Huang
	7.1	Introduction 139
	7.1	Protein-Protein Docking 140
	7.2.1	Sampling 142
	7.2.1.1	Traditional Search Algorithms 142
	7.2.1.2	Deep Learning-Based Search Algorithms 144
	7.2.1.2	Scoring 145
	7.2.2.1	Traditional Scoring Function 145
	7.2.2.2	Deep Learning-Based Scoring Function 146
	7.2.3	Template-based Docking 147
	7.3	End-to-end Structure Prediction 148
	7.4	CAPRI Experiments 151
	7.4.1	CASP13-CAPRI 152
	7.4.2	CASP14-CAPRI 152
	7.4.3	CASP15-CAPRI 153
	7.5	Challenges and Future Directions 154
		Acknowledgments 155
		Author Contributions 155
		References 155
	8	Foldamers as Inhibitors of Aberrant Protein – Protein
		Interactions 163
		Nicholas H. Stillman, Ryan A. Dohoney, Charles Z. Baysah, and Sunil Kumar
	8.1	Introduction 163
	8.2	The Evolution of Hamilton's Oligopyridylamides 164
	8.3	Limitations of a Tedious Synthetic Route 165
	8.4	OPs as Antagonists of Neurodegeneration 166
	8.5	OPs Inhibit HIV Infection 168
	8.6	OPs Targeting Type II Diabetes 169
	8.7	OPs Targeting and Reactivating Mutant Protein in Cancer 171
	8.8	Novel Synthesis of OPs and Alzheimer's Disease 173
	8.9	2D-FAST 174
	8.10	OQ Foldamers – Structure and Discovery 181
	8.11	Synthesis of OQ Foldamers 182

8.12	OQs as Modulators of Type II Diabetes-Related aPPIs 183
8.13	Mechanistic Insights into OQ Manipulation of aPPIs 186
8.14	Chemical Diversity and Structure Modulate Efficacy of OQs 188
8.15	Modulation of Alzheimer's Disease-Related Aβ 189
8.16	OQs for the Modulation of Synucleinopathies 191
8.17	Epilogue 194
	Acknowledgement 194
	References 195
9	Application of Sulfonyl-γ-AApeptides for PPI Drug
	Discovery 205
	Jarais Fontaine and Jianfeng Cai
9.1	Introduction 205
9.2	Application of Sulfonyl-γ-AApeptides 206
9.2.1	Modulation of PPIs Involved in Cancer 206
9.2.1.1	Inhibition of β-catenin/B-cell lymphoma 9 PPIs 206
9.2.1.2	p53-MDM2/MDMX PPIs Inhibitor 208
9.2.1.3	HIF-1α PPI's Inhibitor 209
9.2.2	Anti-Viral 210
9.2.2.1	HIV Fusion Inhibitor 210
9.2.2.2	Pan-Coronavirus Fusion inhibitor 212
9.2.3	Aβ-Oligomerization Modulation 213
9.2.4	Diabetes Therapeutics 216
9.3	Future Directions/Conclusion 216
	Acknowledgments 217
	References 217
10	Introduction of the Application of Stapled Peptides in
	Protein-Protein Interactions Drug Discovery and Their
	Successful Examples 219
	Maxwell J. Austin and Danny Hung-Chieh Chou
10.1	Introduction 219
10.1.1	Stapled Peptides as a Solution to PPI Challenges 219
10.1.2	Growing Importance of PPIs in Drug Discovery 220
10.1.3	Early Development and Success of Stapled Peptides 220
10.1.4	Overview of the Chapter 221
10.2	Stapled Peptides: Structure Features and Benefits 221
10.2.1	Importance of α-Helical Structures in PPIs 221
10.2.2	Designing Stapled Peptides: Mechanism of Stapling 221
10.2.3	Additional Stapling Strategies 222
10.2.3.1	Lactamization Between Lysine and Glutamate/Aspartate 222
10.2.3.2	Azide-Alkyne Cycloaddition 223
10.2.3.3	C—H Activation 224
	Cys-Cys Initiated Stapling Strategy 224
0.2.3.5	Tyrosine Stapling 224
0.2.4	Advantages of Stapled Peptides in Drug Discovery 225

Contents	
10.2.4.1	Enhanced Proteolytic Stability 225
10.2.4.1	
	Ability to Target Previously "Undruggable" PPIs 226
10.2.4.4	Specificity and Affinity Considerations 227
10.2.4.4	Successful Applications of Stapled Peptides in Drug Discovery 227
10.3	Targeting the MDM2-p53 Interaction 227
10.3.1	Targeting BCL-2 Family Proteins 228
10.3.2	Targeting the β-Catenin/TCF Interaction 229
10.3.4	Infectious Diseases 230
10.3.4	Clinical Progress and Future Directions 231
10.3.3	Challenges and Limitations 232
10.4.1	Manufacturing and Cost Considerations 232
10.4.1	
	Delivery Issues: Overcoming Biological Barriers 232
10.4.3	Off-Target Effects and Safety Concerns 233 Resistance Mechanisms 233
10.4.4	Future Directions 234
10.5	
10.5.1	Expansion into New Disease Areas 234 Integration with Other Thermoutic Modelities 235
10.5.2	Integration with Other Therapeutic Modalities 235
10.5.3	Emerging Delivery Technologies 235
10.5.4	Summary 236
	Acknowledgments 237
	References 237
11	Cyclic Peptides for PPI Drug Discovery 243
11	Cyclic Peptides for PPI Drug Discovery 243 Hong-Gang Hu and Xiang Li
11 11.1	
	Hong-Gang Hu and Xiang Li
11.1	Hong-Gang Hu and Xiang Li Introduction 243
11.1 11.2	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244
11.1 11.2 11.2.1	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245
11.1 11.2 11.2.1 11.2.2	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251
11.1 11.2 11.2.1 11.2.2 11.2.3	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein Interactions in the BCL Protein 263
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein Interactions in the BCL Protein 263 Wenhua Zhu, Yangbo He, Gang Chen, and Di Zhu
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein Interactions in the BCL Protein 263 Wenhua Zhu, Yangbo He, Gang Chen, and Di Zhu Introduction 263
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein—Protein Interactions in the BCL Protein 263 Wenhua Zhu, Yangbo He, Gang Chen, and Di Zhu Introduction 263 Inhibitors of BCL-2 Family Antiapoptotic Proteins 264
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein Interactions in the BCL Protein 263 Wenhua Zhu, Yangbo He, Gang Chen, and Di Zhu Introduction 263 Inhibitors of BCL-2 Family Antiapoptotic Proteins 264 Members and Structure of BCL-2 Family Proteins 264
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein Interactions in the BCL Protein 263 Wenhua Zhu, Yangbo He, Gang Chen, and Di Zhu Introduction 263 Inhibitors of BCL-2 Family Antiapoptotic Proteins 264 Members and Structure of BCL-2 Family Proteins 264 Binding Sites and Key Interactions of BCL-2 Family Proteins 266
11.1 11.2 11.2.1 11.2.2 11.2.3 11.2.4 11.2.5 11.3 11.4 11.5	Hong-Gang Hu and Xiang Li Introduction 243 α-Helix Cyclic Peptides (Stapled Peptides) 244 Antitumor Stapled Peptides 245 Antiviral Stapled Peptides 251 Anti-osteoporosis Stapled Peptides 252 Anti-inflammation Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 Anti-diabetes Stapled Peptides 253 β-Hairpin Cyclic Peptides 253 Macrocyclic Peptides 255 Summary and Outlook 255 References 256 Small Molecule Inhibitors Targeting Protein-Protein Interactions in the BCL Protein 263 Wenhua Zhu, Yangbo He, Gang Chen, and Di Zhu Introduction 263 Inhibitors of BCL-2 Family Antiapoptotic Proteins 264 Members and Structure of BCL-2 Family Proteins 264

12.2.4.1 Selective Bcl-2/Bcl-xL Inhibitors 268

12.2.4.2	Selective Mcl-1 Inhibitor 280
12.2.4.3	Compounds 54-59 292
12.3	Inhibitors of β-catenin/BCL9 300
12.3.1	Physiological Functions of BCL9 300
12.3.2	β-catenin/BCL9 PPI 300
12.3.3	Targeting β-catenin/BCL9 Small Molecule Inhibitors 301
12.3.3.1	Natural Products and Their Derivatives 301
12.3.3.2	Phenyl-piperidine Derivatives 303
12.3.3.3	3-(4-fluorophenyl)- <i>N</i> -phenylbenzamide Derivatives 305
12.3.3.4	Other β-catenin/BCL9 Small Molecule Inhibitors 307
12.4	Targeting BCL-6 Small Molecule Inhibitors 307
12.4.1	Biological Functions of BCL6 307
12.4.2	Structural Characteristics of the BCL6 BTB/POZ Domain 308
12.4.3	BCL6-targeted Diseases 309
12.4.4	
12.4.4.1	79-6, FX1 and AP-4-287 310
12.4.4.2	BI3812 and TMX-2164 310
12.4.4.3	BCL6-i and Compound 107 316
12.4.4.4	Compounds 109, 111, WK500B, and GSK137 316
12.4.4.5	•
12.5	BCL-3 Inhibitors 318
12.5.1	Structural Characteristics of BCL-3 318
12.5.2	Biological Functions of BCL-3 318
12.5.3	BCL-3/P50 Inhibitors 320
12.6	BCL-10 Inhibitors 320
12.6.1	Biological Functions of BCL-10 320
12.6.2	Structural Characteristics of BCL-10 321
12.6.3	BCL-10 and Cancer 322
12.7	Summary 322
	References 323
13	Molecular Glues as Activators for PPI 343
	Xiangbing Qi
13.1	Introduction 343
13.1.1	Significance of PPI in Biology and Disease 343
13.1.2	Opportunities and Challenges for PPI Drug Discovery 344
13.1.3	Four Classes of PPI Modulators 344
13.2	Molecular Glues as Orthosteric PPI Stabilizers/Activators 347
13.2.1	Design Principles of MG 347
13.2.2	Classification of MGs 347
13.2.2.1	
13.2.2.2	
13.2.2.3	MG Inhibitors 357
13.3	Methods for MG Discovery 358
13.3.1	Modifications of E3 Ligands: Discovery of New CRBN Ligands 360
13.3.2	Phenotype-Based Screening 361

xii	Contents	
	13.3.2.1	Scalable Chemical Profiling 361
	13.3.2.2	Proteomics-Based Screening 362
	13.3.3	Target-Based Screening 363
	13.3.3.1	HTS for PPI Stabilizers 363
	13.3.3.2	Rational Design: Discovery of KRAS-CYPA Molecular Glue 363
	13.4	Conclusions and Outlook 364
		Contributors 364
		References 364
	14	Targeting APC-Asef Protein-Protein Interaction for Drug
		Discovery in Colorectal Cancer Therapy 373
		Jie Zhong and Xiuyan Yang
	14.1	Introduction 373
	14.2	Structural Insights into APC-Asef Interaction 375
	14.3	Current APC-Asef Inhibitors 376
	14.3.1	•
	14.3.1.1	•
	14.3.1.2	
	14.3.1.3	
	14214	Anti-CRC Migration Activity 377
	14.3.1.4	Intramolecular Hydrogen Bond Strategy Leading to the Best-in-Class Inhibitor MAI-400 379
	14.3.1.5	
	14.5.1.5	and Potent Inhibitor, MAI-516 380
	14.3.1.6	
	1 1.5.1.0	APC-Asef Interaction 381
	14.3.2	Small Molecule Inhibitors of APC–Asef PPI 381
	14.4	A More Sensitive FP Method for Identifying Highly Active
		APC-Asef Inhibitors 382
	14.5	Conclusions and Outlook 383
		References 385
	15	Computational Methods Applied to Drug Discovery of
		Protein-Protein Interaction Systems 389
		Zhiyong Gu and Xi Cheng
	15.1	Introduction 389
	15.2	Computational Methods for PPI Prediction 390
	15.2.1	PPI Network Mapping 390
	15.2.2	Protein Complex Prediction 394
	15.2.3	
	15.2.3.1	
	15.2.3.2	
	15.2.3.3	
	15.3	Conclusions and Outlook 401
		References 402

Index 409