

Contents

	List of Contributors	XI
	Preface	XV
	A Personal Foreword	XVII
1	Protein-Protein Interactions: An Overview	1
	<i>Christian Ottmann</i>	
1.1	Introduction	1
1.2	Role of PPIs in Human Physiology	2
1.3	Regulation of PPIs	3
1.4	Structural Features of PPI Interfaces	3
1.4.1	iNOS Homodimer	5
1.4.2	β -Catenin/Tcf4 Complex	5
1.4.3	LEDGF/HIV-IN Complex	6
1.4.4	HPV E1/E2 Complex	7
1.4.5	IFN- α /IFNAR Complex	8
1.4.6	TNF- α Trimer	9
1.5	Identification of PPI Inhibitors	10
1.6	Conclusions and Outlook	13
	References	14
2	Prediction of Intra- and Interspecies Protein-Protein Interactions Facilitating Systems Biology Studies	21
	<i>Sylvia Schleker, Seshan Ananthasubramanian, Judith Klein-Seetharaman, and Madhavi K. Ganapathiraju</i>	
2.1	Introduction: Relevance of Interactome Studies to Disease and Drug Discovery	21
2.2	Our Current Knowledge of Interactomes Identified from Experiments is Incomplete	23
2.3	Reliability of Interactions Identified Experimentally	24
2.4	Computational Methods for PPI Prediction	27
2.4.1	Conservation of Gene Neighborhood	27
2.4.2	Gene Fusion	28
2.4.3	Sequence-Based Coevolution	28

2.4.4	Phylogenetic Profiling	28
2.4.5	Gene Expression	29
2.4.6	Structural Similarity	29
2.4.7	Integration Approaches	29
2.5	Sources of Biological Data in Use to Predict PPIs	30
2.6	Survey of Current Interactomes	32
2.6.1	Human Intraspecies Interactomes	32
2.6.2	Bacteria Intraspecies Interactomes	37
2.6.2.1	High-Throughput Experimental Approaches to Identify Intraspecies Bacterial Interactions	37
2.6.2.2	Modeling Intraspecies Bacterial Interactions	39
2.6.3	Bacteria–Human Interspecies Interactomes	40
2.6.3.1	Experimental Approaches to Identify Bacteria–Human PPIs	40
2.6.3.2	Modeling Bacteria–Human PPIs	40
2.6.4	Non-PPI Intraspecies Bacterial and Bacteria–Human Interspecies Interactome Models	41
2.6.5	Virus–Human Interspecies Interactomes	42
	References	43
3	Modulators of Protein–Protein Interactions: Importance of Three-Dimensionality	55
	<i>David C. Fry and Sung-Sau So</i>	
3.1	Introduction	55
3.2	Study	56
3.3	Discussion	58
3.4	Summary	61
	References	61
4	A Leap into the Chemical Space of Protein–Protein Interaction Inhibitors	63
	<i>Bruno O. Villoutreix, C. Labbé, David Lagorce, Guillaume Laconde, and Olivier Sperandio</i>	
4.1	Introduction	63
4.2	Types of Interaction	64
4.3	Properties of the Interface	65
4.4	Orthosteric versus Allosteric Modulation	66
4.5	Leap into the iPPI Chemical Space	66
4.5.1	Seminal Works	66
4.5.2	Road to a Rationalization of the iPPI Chemical Space	67
4.6	Case Study	68
4.6.1	Visualizing the iPPI Chemical Space	70
4.6.2	iPPI versus ADME/Tox Properties	71
4.6.3	iPPI versus Aromaticity	75
4.6.4	iPPI versus Chemical Complexity	77

4.6.5	iPPI versus Molecular Shape	77
4.6.6	iPPI versus Potency	79
4.7	Conclusions	80
	References	81
5	Interactive Technologies for Leveraging the Known Chemistry of Anchor Residues to Disrupt Protein Interactions	85
	<i>Carlos J. Camacho, David R. Koes, and Alexander S. Dömling</i>	
5.1	Introduction	85
5.2	Druggable Sites in PPIs	86
5.3	Structure-Based Library Design – A Powerful Alternative to High-Throughput Screening	87
5.4	New MCR Chemistry to Design PPI Antagonists	89
5.5	Virtual Screening	90
5.6	New Interactive Modeling Techniques for Medicinal Chemists	93
5.7	New Ideas: Hit Rate Validation of Anchor-Centered Screening of p53/MDM2/4	95
5.8	Summary	96
	References	97
6	SH3 Domains as Drug Targets	101
	<i>James Luccarelli, Sam Thompson, and Andrew D. Hamilton</i>	
6.1	Introduction	101
6.2	Structure	101
6.3	Variability	102
6.4	SH3 Binding Motifs	104
6.4.1	Classical Binding Motifs	104
6.4.2	Tyrosine-Containing Motifs	107
6.4.3	RxxK Motif	108
6.4.4	Other Binding Motifs from Proteomic Screens	109
6.4.5	Tertiary Interactions	110
6.5	Selectivity	111
6.6	Drug Target Selection	114
6.7	Inhibition Strategies: Peptide and Peptoid Inhibitors	114
6.7.1	Peptide Ligands	114
6.7.2	Combinatorial Approaches	115
6.7.3	Peptide Dimers	116
6.7.4	Constrained Peptides	118
6.7.5	N-Substituted Peptoids	118
6.8	Small-Molecule Inhibitors	119
6.9	Conclusions	122
	References	122

7	p53/MDM2 Antagonists: Towards Nongenotoxic Anticancer Treatments 129
	<i>Kareem Khoury, Tad A. Holak, and Alexander Dömling</i>
7.1	Introduction 129
7.2	p53/MDM2 PPI is Characterized by Many Cocrystal Structures 130
7.3	Nutlins: First-In-Class MDM2 Antagonists 131
7.4	Johnson & Johnson: Benzodiazepines 133
7.5	Amgen: Chromenotriazolopyrimidines & Piperidones 137
7.6	University of Michigan: Spirooxindole 148
7.7	University of Pittsburgh: Ugi Based Compounds 153
7.8	University of Newcastle: Some Scaffolds With No Structural Biology Information 155
7.9	Outlook 161
	References 161
8	Inhibition of LFA-1/ICAM Interaction for the Treatment of Autoimmune Diseases 165
	<i>Kevin M. Guckian and Daniel M. Scott</i>
8.1	Introduction 165
8.2	Integrin Structure and Activation 166
8.3	Direct Inhibition of the LFA-1/ICAM Interaction 168
8.4	Allosteric Inhibitors of the LFA-1/ICAM interaction – IDAS Site 171
8.4.1	Abbott/ICOS/Biogen Series 171
8.4.2	Boehringer Ingelheim/Tanabe Seiyaku/Bristol-Myers Squibb Series 178
8.5	Summary 183
	References 183
9	The PIF Pocket of AGC Kinases: A Target Site for Allosteric Modulators and Protein–Protein Interaction Inhibitors 187
	<i>Matthias Engel</i>
9.1	Introduction 187
9.2	Discovery and Physiological Functions of the PIF Pocket 190
9.3	Properties of the PIF Pocket Relevant to Drug Development 192
9.3.1	The PIF Pocket Offers the Potential to Develop Highly Selective Ligands 192
9.3.2	Molecular Interactions of the Natural HM Peptide Ligands 193
9.3.3	Allosteric Mechanism of the PIF Pocket 196
9.3.4	Structural Plasticity of the PIF Pocket 198
9.4	Small-Molecule PIF Pocket Ligands 199
9.4.1	Allosteric Activators and PPI Inhibitors of PDK1 199
9.4.2	Identification of First Hit Compounds Using a Pharmacophore-Based Screening Approach 200

9.4.3	Current State of Research on PIF Pocket-Directed PDK1 Modulators	203
9.4.4	Allosteric Inhibitors	207
9.5	Potential Supportive Effects Enhancing the Cellular Activity of PIF Pocket-Binding Modulators	209
9.5.1	Allosteric Activators of PDK1	209
9.5.2	PIF Pocket-Directed Inhibitors of AGC Kinases	210
9.6	Conclusions	212
9.6.1	Is the PIF Pocket a Druggable Site?	212
9.6.2	General Medicinal Chemistry Aspects and Outlook	213
	References	215
10	Retosiban and Epelsiban: Potent and Selective Orally Available Oxytocin Antagonists	225
	<i>Alan D. Borthwick and John Liddle</i>	
10.1	Introduction	225
10.2	Aryl-2,5-DKP Template Discovery and Initial Structure-Activity Relationship Studies	227
10.3	Synthesis of the RRR and RRS 6-Indanyl-3-isobutyl-7-aryl-2,5-DKP Secondary Amides	231
10.4	Comparison of Crystal Structures of Oxytocin and 2,5-DKPs	231
10.5	Pharmacokinetics and Property-Based Design	232
10.6	<i>In Vivo</i> Potency of 2',4'-Difluorophenyl Dimethylamide 22	235
10.7	Synthesis of Tertiary Amides	236
10.7.1	Synthesis of Five- and Six-Membered Heterocyclic 2,5-DKPs	237
10.8	Summary of Lead Oxytocin Antagonist 2',4'-Difluorophenyl Dimethylamide 22	238
10.9	Further Modifications, Five- and Six-Membered Heterocyclic Derivatives	238
10.10	Five-Membered Heterocyclic Derivatives and Retosiban	239
10.10.1	Oxytocin Antagonist Activity and Selectivity versus Human Vasopressin Receptors	242
10.10.2	<i>In Vivo</i> Potency and Synthesis	243
10.11	Summary of Lead Oxytocin Antagonist Retosiban 56	244
10.12	Six-Membered Heterocyclic Derivatives and Epelsiban	244
10.12.1	Monosubstituted Pyridyl isoButyl Derivatives	246
10.12.2	Modification of isoButyl in 6'-MePyridyl Derivatives	246
10.12.3	Dimethylpyridyl (S)-sec-Butyl Amides	246
10.12.4	Further Evaluation of 2',6'-Dimethyl-3'-pyridine Morpholine Amide 77	250
10.13	Summary of Lead Oxytocin Antagonist Epelsiban 77	252
10.14	Comparison of Lead Compounds	252
10.15	Conclusions	254
	References	254

11	Peptidic Inhibitors of Protein-Protein Interactions for Cell Adhesion Receptors: RGD Peptides and Beyond	257
	<i>Carlos Mas-Moruno and Horst Kessler</i>	
11.1	Introduction	257
11.2	From the Discovery of the RGD Motif in FN to the First Selective Cyclic RGD Peptide	258
11.2.1	RGD Sequence, Integrins, and Receptor Selectivity	258
11.2.2	Concept of Spatial Screening in Cyclic RGD Peptides	261
11.2.3	Conformational Aspects and Selectivity of c(RGDfV)	263
11.2.4	Pharmacophoric Requirements of c(RGDfV) to Bind $\alpha_v\beta_3$	265
11.3	N-Methylation of c(RGDfV): Cilengitide and Beyond	267
11.3.1	Concept of N-Methylation	267
11.3.2	N-Methyl Scan of c(RGDV): Synthesis, Biological Activity, and Structural Considerations of Cilengitide	268
11.3.3	Beyond Cilengitide: di-N-Methylated Analogs of c(RGDfV) and $\alpha_v\beta_3$ Selectivity	271
11.4	isoDGR Sequence as a New Integrin-Binding Motif	274
11.4.1	Formation of isoAsp Residues in Peptides and Proteins	274
11.4.2	NGR Deamidation to isoDGR Yields a New Integrin-Binding Motif	275
11.4.3	Design of Cyclic Peptides Containing the isoDGR Motif as New Integrin Antagonists	276
11.4.4	Receptor Selectivity of Cyclic isoDGR Peptides	279
11.5	Conclusions	281
	References	282
12	REPLACE Strategy for Generating Non-ATP-Competitive Inhibitors of Cell Cycle Protein Kinases	291
	<i>Campbell McInnes</i>	
12.1	Introduction	291
12.2	Inhibition of CDKs Through the Cyclin Groove	291
12.3	Inhibitors of PLKs	298
12.3.1	PB Domain	298
12.4	Conclusions	301
	References	302
	Index	305