

Contents

List of Contributors XI

Foreword XV

Preface XIX

A Personal Foreword XXI

Acronyms XXIII

- 1 Medicinal Chemistry Approaches to Creating Targeted Medicines** 1
Bruce D. Roth and Karen Lackey
- 1.1 Introduction 1
- 1.2 Role of Medicinal Chemistry in Drug Discovery 2
- 1.3 Evolution of Molecular Design for Subsets of Patients 4
- 1.4 Combinations for Effective Therapies 6
- 1.5 Biomarkers in Targeting Patients 9
- 1.6 Emerging Field of Epigenetics 9
- 1.7 Systems Chemical Biology 10
- 1.8 Theranostics and Designing Drug Delivery Systems 12
- 1.9 Rapid Progress in Further Personalizing Medicine Expected 15
- References 18
- 2 Discovery of Predictive Biomarkers for Anticancer Drugs** 21
Richard M. Neve, Lisa D. Belmont, Richard Bourgon, Marie Evangelista, Xiaodong Huang, Maik Schmidt, Robert L. Yauch, and Jeffrey Settleman
- 2.1 Introduction 21
- 2.2 “Oncogene Addiction” as a Paradigm for Clinical Implementation of Predictive Biomarkers 24
- 2.3 Cancer Cell Lines as a Model System for Discovery of Predictive Biomarkers 28
- 2.3.1 Historical Application of Cell Lines in Cancer Research 28
- 2.3.2 Biomarker Discovery Using Cell Line Models 29
- 2.3.3 Cell Lines as Models of Human Cancer 31
- 2.3.4 Challenges and Limitations of Cell Line Models 32
- 2.4 Modeling Drug Resistance to Discover Predictive Biomarkers 33

2.5	Discovery of Predictive Biomarkers in the Context of Treatment Combinations	38
2.6	Discovery of Predictive Biomarkers for Antiangiogenic Agents	42
2.6.1	Challenges	43
2.6.2	Pathway Activity as a Predictor of Drug Efficacy	44
2.6.3	Predicting Inherent Resistance	45
2.6.4	On-Treatment Effects as a Surrogate of Drug Efficacy	45
2.6.5	Summary	46
2.7	Gene Expression Signatures as Predictive Biomarkers	47
2.7.1	Signature Discovery: Unsupervised Clustering	47
2.7.2	Diagnostic Development: Supervised Classification	48
2.7.3	Summary	50
2.8	Current Challenges in Discovering Predictive Biomarkers	51
2.8.1	Access to Tumor Cells Is Limited during Treatment	51
2.8.2	Drivers and Passengers	53
2.8.3	Epigenetic Regulation Adds Another Layer of Complexity	54
2.8.4	Many Oncoproteins and Tumor Suppressors Undergo Regulatory Posttranslational Modifications	55
2.9	Future Perspective	56
	References	57
3	Crizotinib	71
	<i>Jean Cui, Robert S. Kania, and Martin P. Edwards</i>	
3.1	Introduction	71
3.2	Discovery of Crizotinib (PF-02341066) [40]	74
3.3	Kinase Selectivity of Crizotinib	77
3.4	Pharmacology of Crizotinib [45,46]	78
3.5	Human Clinical Efficacies of Crizotinib	80
3.6	Summary	83
	References	85
4	Discovery and Development of Vemurafenib: First-in-Class Inhibitor of Mutant BRAF for the Treatment of Cancer	91
	<i>Prabha Ibrahim, Jiazhong Zhang, Chao Zhang, James Tsai, Gaston Habets, and Gideon Bollag</i>	
4.1	Background	91
4.2	Discovery and Development of Vemurafenib (PLX4032)	92
4.3	Pharmacology	95
4.4	Clinical Efficacy and Safety	96
4.5	Companion Diagnostic (cobas 4800) Development	96
4.6	Synthesis	96
4.6.1	Discovery Route(s)	96
4.6.2	Process Route	97
4.7	Summary	98
	References	98

5	Targeting Basal-Cell Carcinoma: Discovery and Development of Vismodegib (GDC-0449), a First-in-Class Inhibitor of the Hedgehog Pathway 101
	<i>James C. Marsters Jr. and Harvey Wong</i>
5.1	Introduction 101
5.2	Hedgehog and Basal-Cell Carcinoma 102
5.3	Cyclopamine as an SMO Antagonist 102
5.4	Small-Molecule Inhibitors of SMO 103
5.5	Preclinical Characterization of Vismodegib 107
5.5.1	Plasma Protein Binding and Blood Plasma Partitioning 107
5.5.2	<i>In Vitro</i> and Exploratory <i>In Vivo</i> Metabolism of Vismodegib 108
5.5.3	Drug–Drug Interaction Potential 109
5.5.4	Preclinical Pharmacokinetics 109
5.5.5	Predicted Human Pharmacokinetics 110
5.5.6	Summary 112
5.6	Vismodegib Clinical Experience in Phase I 112
	References 114
6	G-Quadruplexes as Therapeutic Targets in Cancer 117
	<i>Stephen Neidle</i>
6.1	Introduction 117
6.2	Quadruplex Fundamentals 117
6.3	Genomic Quadruplexes 119
6.4	Quadruplexes in Human Telomeres 120
6.5	Quadruplexes as Anticancer Targets – Evidence from <i>In Vivo</i> Studies 123
6.6	Native Quadruplex Structures 125
6.7	Quadruplex–Small-Molecule Structures 130
6.8	Developing Superior Quadruplex-Binding Ligands 130
6.9	Conclusions 134
	References 136
7	Identifying Actionable Targets in Cancer Patients 147
	<i>David Uehling, Janet Dancey, Andrew M.K. Brown, John McPherson, and Rima Al-awar</i>
7.1	Introduction and Background 147
7.2	Overview of Genomic Sequencing and Its Impact on the Identification of Actionable Mutations 149
7.3	Actionable Targets by Clinical Molecular Profiling: the OICR/PMH Experience 157
7.4	Some Experiences of Other Clinical Oncology Molecular Profiling Studies 163
7.5	Identifying Secondary and Novel Mutations through Molecular Profiling 165
7.6	Understanding and Targeting Resistance Mutations: a Challenge and an Opportunity for NGS 166

7.6.1	Identification and Treatment Strategies for Actionable Secondary Resistance Mutations	169
7.6.2	Toward the Identification of Actionable Primary Resistance Mutations	173
7.7	Concluding Remarks and Future Perspectives	175
	References	178
8	DNA Damage Repair Pathways and Synthetic Lethality	183
	<i>Simon Ward</i>	
8.1	Introduction	183
8.2	DNA Damage Response	184
8.3	Synthetic Lethality	185
8.4	Lead Case Study: PARP Inhibitors	188
8.4.1	Introduction	188
8.4.2	Discovery of PARP Inhibitors	189
8.4.3	Clinical Development of PARP Inhibitors	190
8.4.4	Future for PARP Inhibitors	192
8.5	Additional Case Studies	194
8.5.1	MLH1/MSH2	194
8.5.2	p53-ATM	197
8.5.3	Chk1-DNA Repair	197
8.5.4	DNA-PK – mTOR	197
8.5.5	DNA Ligases	198
8.5.6	WEE1	198
8.5.7	APE1	198
8.5.8	MGMT	199
8.5.9	RAD51	199
8.6	Screening for Synthetic Lethality	199
8.6.1	RAS	202
8.6.2	VHL	202
8.6.3	MRN	203
8.7	Contextual Synthetic Lethality Screening	203
8.8	Cancer Stem Cells	204
8.9	Conclusions and Future Directions	204
	References	205
9	Amyloid Chemical Probes and Theranostics: Steps Toward Personalized Medicine in Neurodegenerative Diseases	211
	<i>Maria Laura Bolognesi</i>	
9.1	Introduction	211
9.2	Amyloid Plaques as the Biomarker in AD	212
9.3	Detecting Amyloid Plaques in Patients: from Alois Alzheimer to Amyvid and Beyond	214
9.4	Same Causes, Same Imaging Agents?	218
9.5	Theranostics in AD	219

9.6	Conclusions and Perspectives	220
	References	222
10	From Human Genetics to Drug Candidates: An Industrial Perspective on LRRK2 Inhibition as a Treatment for Parkinson's Disease	227
	<i>Haitao Zhu, Huifen Chen, William Cho, Anthony A. Estrada, and Zachary K. Sweeney</i>	
10.1	Introduction	227
10.2	Biochemical Studies of LRRK2 Function	229
10.3	Cellular Studies of LRRK2 Function	230
10.4	Animal Models of LRRK2 Function	233
10.5	Clinical Studies of LRRK2-Associated PD and Future Prospects	234
10.6	Small-Molecule Inhibitors of LRRK2	236
10.7	Structural Models of the LRRK2 Kinase Domain	237
10.8	Strategies Used to Identify LRRK2 Kinase Inhibitors (Overview)	238
10.9	Conclusions	246
	References	247
11	Therapeutic Potential of Kinases in Asthma	255
	<i>Dramane Lainé, Matthew Lucas, Francisco Lopez-Tapia, and Stephen Lynch</i>	
11.1	Introduction	255
11.2	Mitogen-Activated Protein Kinases	256
11.2.1	p38	257
11.2.2	JNK	259
11.2.3	ERK	260
11.3	Nonreceptor Protein Tyrosine Kinases	261
11.3.1	Syk	261
11.3.2	Lck	263
11.3.3	JAK	264
11.3.4	ITK	265
11.3.5	Btk	266
11.4	Receptor Tyrosine Kinases	266
11.4.1	EGFR	267
11.4.2	c-Kit	268
11.4.3	PDGFR	269
11.4.4	VEGFR	270
11.5	Phosphatidylinositol-3 Kinases	270
11.6	AGC Kinases	272
11.6.1	PKC	272
11.6.2	ROCK	273
11.7	I κ B Kinase	275
11.8	Other Kinases	276
11.8.1	SphK	276
11.8.2	GSK-3 β	277
11.9	Conclusions: Future Directions	278
	References	279

12	Developing Targeted PET Tracers in the Era of Personalized Medicine 289
	<i>Sandra M. Sanabria Bohorquez, Nicholas van Bruggen, and Jan Marik</i>
12.1	Imaging and Pharmacodynamics Biomarkers in Drug Development 289
12.2	General Considerations for Development of ^{11}C - and ^{18}F -labeled PET Tracers 292
12.3	Radiolabeling Compounds with ^{11}C 294
12.3.1	Preparation of ^{11}C and Basic Reactive Intermediates 294
12.3.2	^{11}C -Methylations, Formation of $^{11}\text{C}-\text{X}$ Bond ($\text{X} = \text{O}, \text{N}, \text{S}$) 295
12.3.3	^{11}C -Methylations, Formation of $^{11}\text{C}-\text{C}$ Bond 297
12.3.4	Reactions with $^{11}\text{CO}_2$ 299
12.3.5	Reactions with ^{11}CO 301
12.3.6	Reactions with H^{11}CN 303
12.4	Radiolabeling Compounds with ^{18}F 304
12.4.1	Formation of $\text{C}-^{18}\text{F}$ Bond, Nucleophilic Substitutions 304
12.4.2	Aliphatic Nucleophilic ^{18}F -Fluorination 306
12.4.3	Aromatic Nucleophilic ^{18}F -Fluorination 309
12.4.4	Electrophilic ^{18}F -Fluorination 313
12.4.5	Formation of ^{18}F -Al, Si, B Bond 314
12.5	PET Imaging in the Clinic, Research, and Drug Development 315
12.5.1	PET in Oncology 315
12.5.2	PET Neuroimaging 317
12.5.3	PET in Cardiology 319
12.6	PET Tracer Kinetic Modeling for Quantification of Tracer Uptake 320
12.7	Concluding Remarks 325
	References 325
13	Medicinal Chemistry in the Context of the Human Genome 343
	<i>Andreas Brunschweiler and Jonathan Hall</i>
13.1	Introduction 343
13.2	Drugs Targeting Kinases 344
13.3	Drugs Targeting Phosphatases 347
13.4	<i>In silico</i> -Based Lead Discovery in the GPCR Family 348
13.5	Targeting Epigenetic Regulation: Histone Demethylases 350
13.6	Targeting Epigenetic Regulation: Histone Deacetylases 351
13.7	A Family-Wide Approach to Poly(ADP-Ribose) Polymerases 352
13.8	Future Drug Target Superfamilies: Ubiquitination and Deubiquitination 353
13.9	Summary and Outlook 354
	References 355
	Index 365