## Contents

Forward xiii
Acknowledgements xv
List of contributors xvii

### SECTION I: Development of Anticancer Therapeutics 1

1 Exploring the Potential of Natural Products in Cancer Treatment 3  
*Fotini N. Lamari and Paul Cordopatis*

1.1 Introduction 3
1.2 Sources 4
1.3 Different Approaches to the Search for Bioactive Natural Products 6
1.4 Methodologies of Lead Compound or New Drug Identification 10
1.5 Chemoprevention – A New Area for Natural Product Research 13
1.6 Concluding Remarks 13

2 Combinatorial Approaches to Anticancer Drug Design 17  
*Sotiris Missailidis*

2.1 Introduction 17
2.2 Combinatorial Approaches for Small Molecule Drug Design 17
2.3 Display Technologies 21
2.4 Aptamer Selection 23
2.5 Conclusions 27

3 Rational Approaches to Anticancer Drug Design/*in silico* Drug Development 29  
*Stefano Alcaro, Anna Artese and Francesco Ortuso*

3.1 Introduction 29
3.2 Approaches to the Drug Discovery Process in Anticancer Research 31
<table>
<thead>
<tr>
<th>Section/Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>Ligand-based Examples</td>
<td>32</td>
</tr>
<tr>
<td>3.4</td>
<td>Structure-based Examples</td>
<td>36</td>
</tr>
<tr>
<td>3.5</td>
<td>Conclusions</td>
<td>44</td>
</tr>
<tr>
<td><strong>SECTION II: Anticancer Therapeutics</strong></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>Introduction to Anticancer Therapeutics</td>
<td>49</td>
</tr>
<tr>
<td><strong>Teni Boulikas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Problems in cancer</td>
<td>49</td>
</tr>
<tr>
<td>4.2</td>
<td>Cancer treatments</td>
<td>51</td>
</tr>
<tr>
<td>4.3</td>
<td>Classification of chemotherapy drugs</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>Platinum Drugs</td>
<td>55</td>
</tr>
<tr>
<td><strong>Teni Boulikas, Alexandros Pantos, Evagelos Bellis and Petros Christofis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Cisplatin</td>
<td>55</td>
</tr>
<tr>
<td>5.2</td>
<td>Lipoplatin</td>
<td>57</td>
</tr>
<tr>
<td>5.3</td>
<td>Carboplatin</td>
<td>61</td>
</tr>
<tr>
<td>5.4</td>
<td>Oxaliplatin</td>
<td>62</td>
</tr>
<tr>
<td>5.5</td>
<td>Lipoxal</td>
<td>62</td>
</tr>
<tr>
<td>5.6</td>
<td>New Platinum Compounds</td>
<td>64</td>
</tr>
<tr>
<td>5.7</td>
<td>Cisplatin Resistance and Chemotherapy</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>Antimicrotubule Agents</td>
<td>79</td>
</tr>
<tr>
<td><strong>Iain Brown, Jay N Sangrithi-Wallace and Andrew C Schofield</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.1</td>
<td>Taxanes</td>
<td>79</td>
</tr>
<tr>
<td>6.2</td>
<td>Vinca Alkaloids</td>
<td>82</td>
</tr>
<tr>
<td>6.3</td>
<td>Mechanisms of Resistance to Antimicrotubule Agents</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>Antimetabolites in Cancer Therapy</td>
<td>91</td>
</tr>
<tr>
<td><strong>Jessica Scaife and David Kerr</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.1</td>
<td>Introduction</td>
<td>91</td>
</tr>
<tr>
<td>7.2</td>
<td>Folate Antagonists</td>
<td>92</td>
</tr>
<tr>
<td>7.3</td>
<td>Pyrimidine Antagonists</td>
<td>96</td>
</tr>
<tr>
<td>7.4</td>
<td>Purine Antagonists</td>
<td>104</td>
</tr>
<tr>
<td>7.5</td>
<td>Summary</td>
<td>109</td>
</tr>
<tr>
<td>8</td>
<td>Antitumour Antibiotics</td>
<td>111</td>
</tr>
<tr>
<td><strong>Manuel M. Paz</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1</td>
<td>Introduction</td>
<td>111</td>
</tr>
</tbody>
</table>
## CONTENTS

8.2 Actinomycin 111
8.3 Mitomycin C 112
8.4 Bleomycin 115
8.5 Anthracyclines 118
8.6 Trabectedin (Ecteinascidin, ET-743) 121
8.7 Camptothecins 123
8.8 Podophyllotoxins 124

9 **Alkylating Agents** 133  
*Ana Paula Francisco, Maria de Jesus Perry, Rui Moreira and Eduarda Mendes*

9.1 Introduction 133
9.2 Nitrogen Mustards 133
9.3 Methylmelamines and Ethylenimines 140
9.4 Methylhydrazine Derivatives 141
9.5 Alkylsulfonates 143
9.6 Nitrosoureas 144
9.7 Triazenes 149

10 **Hormone Therapies** 159  
*George C. Zografos, Nikolaos V. Michalopoulos and Flora Zagouri*

10.1 Introduction 159
10.2 Oestrogen Receptor Targeted Therapeutics 160
10.3 Progesterone-Targeted Therapy 174
10.4 Neuroendocrine Tumours 176

11 **Photodynamic Therapy of Cancer** 187  
*K. Eszter Borbas and Dorothée Lahaye*

11.1 Introduction 187
11.2 Photosensitizers 196
11.3 Outlook 212
11.4 Acknowledgement 212

12 **Target-directed Drug Discovery** 223  
*Tracey D. Bradshaw*

12.1 Introduction 223
12.2 Tyrosine Kinases – Role and Significance in Cancer 226
12.3 Targeted Therapy for the Treatment of Non-small Cell Lung Cancer (NSCLC) 226
12.4 Targeted Therapy for the Treatment of Chronic Myeloid Leukaemia 229
12.5 Targeted Therapy for the Treatment of Breast Cancer 230
12.6 Angiogenesis 231
CONTENTS

12.7 Targeting Cell Cycling 235
12.8 Targeting Apoptosis 237
12.9 Targeting mTOR 237
12.10 The Future of Molecularly Targeted Therapy 238

13 Tumour Hypoxia: Malignant Mediator 245
Jill L. O’Donnell, Aoife M. Shannon, David Bouchier-Hayes
13.1 Introduction 245
13.2 Hypoxia Inducible Factor-1 and Hypoxia 246
13.3 HIF-1α Post-translational Changes 247
13.4 How Genetics Can Modify HIF 248
13.5 How Tumours Overcome Hypoxia with HIF-1 249
13.6 HIF-1 Therapeutics 252
13.7 Conclusion 255

14 Resistance to Chemotherapy Drugs 263
Robert O’Connor and Laura Breen
14.1 Introduction 263
14.2 What are the Factors Limiting the Efficacy of Cancer Chemotherapy Treatment? 263
14.3 A Classification of the Important Chemotherapy Resistance Mechanisms 265
14.4 Illustrative Mechanisms of Pharmacokinetic Resistance 267
14.5 Illustrative Mechanisms of Pharmacodynamic Resistance 273
14.6 Conclusion 277

15 Cancer Immunotherapy 283
Maria Belimezi
15.1 The Molecular Basis of Cancer Immunotherapy and Gene Immunotherapy of Cancer 283
15.2 Recombinant Monoclonal Antibodies 284
15.3 Cell Immunotherapy 292
15.4 Cancer Vaccines 296

16 Gene Therapy 305
Maria Belimezi, Teni Boulikas and Michael L. Roberts
16.1 The Concept of Gene Therapy 305
16.2 Steps for Successful Gene Therapy 306
16.3 Retroviruses in Cancer Gene Therapy 307
16.4 Adenoviruses in Cancer Gene Therapy 308
16.5 Gene Therapy of Cancer 310
CONTENTS

16.6 Cancer Immunotherapy with Cytokine Genes 311
16.7 IL-12 in Cancer Immunotherapy 311
16.8 Viruses able to Kill Cancer Cells 314

17 Antisense Agents 317
Huma Khan and Sotiris Missailidis
17.1 Introduction 317
17.2 Traditional Antisense Oligonucleotides (ASOs) 318
17.3 Ribozymes and DNAzymes 320
17.4 RNA Interference and siRNAs 321
17.5 Shortcomings of Antisense Therapeutics 322
17.6 Antisense Agents in Clinical Trials 324
17.7 Concluding Remarks 329

18 Aptamers as Anticancer Agents 331
Vaidehi Makwana, Suzanne Simmons and Sotiris Missailidis
18.1 Introduction 331
18.2 Aptamers in Cancer 332
18.3 Final comments 341

SECTION III: Other Aspects in Anticancer Therapeutic Development 347

19 Treatment of Cancer in Conjunction with Other Agents 349
Gary Robert Smith
19.1 Introduction 349
19.2 Non-steroidal Anti-inflammatory Drugs 353
19.3 Angiotensin-converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockade 358
19.4 Partners in Crime – Dealing with Co-infections 362
19.5 Discussion 363

20 Clinical Trials in Oncology 365
Tim Friede, Janet Dunn and Nigel Stallard
20.1 Clinical Trials 365
20.2 Early-Phase (Phase I and Phase II) Clinical Trials in Oncology 368
20.3 Confirmatory (Phase III) Trials in Oncology 371
20.4 Further Issues in Clinical Trials in Oncology 374
CONTENTS

21 Representative Cancers, Treatment and Market 377
Teni Boulikas and Nassos Alevizopoulos
21.1 Lung Cancer 377
21.2 Breast Cancer 378
21.3 Prostate Cancer 378
21.4 Colorectal Cancer 379
21.5 Ovarian Cancer 380
21.6 Pancreatic Cancer 380
21.7 Gastric Cancer 381
21.8 Combination Chemotherapy 382
21.9 The Pharmaceutical World of Anticancer Drugs 383

22 Future Trends in Cancer Therapeutics 387
Sotiris Missailidis
22.1 Introduction 387
22.2 Personalized Medicines 388
22.3 Delivery Systems 390
22.4 Closing Remarks 391

Index 393