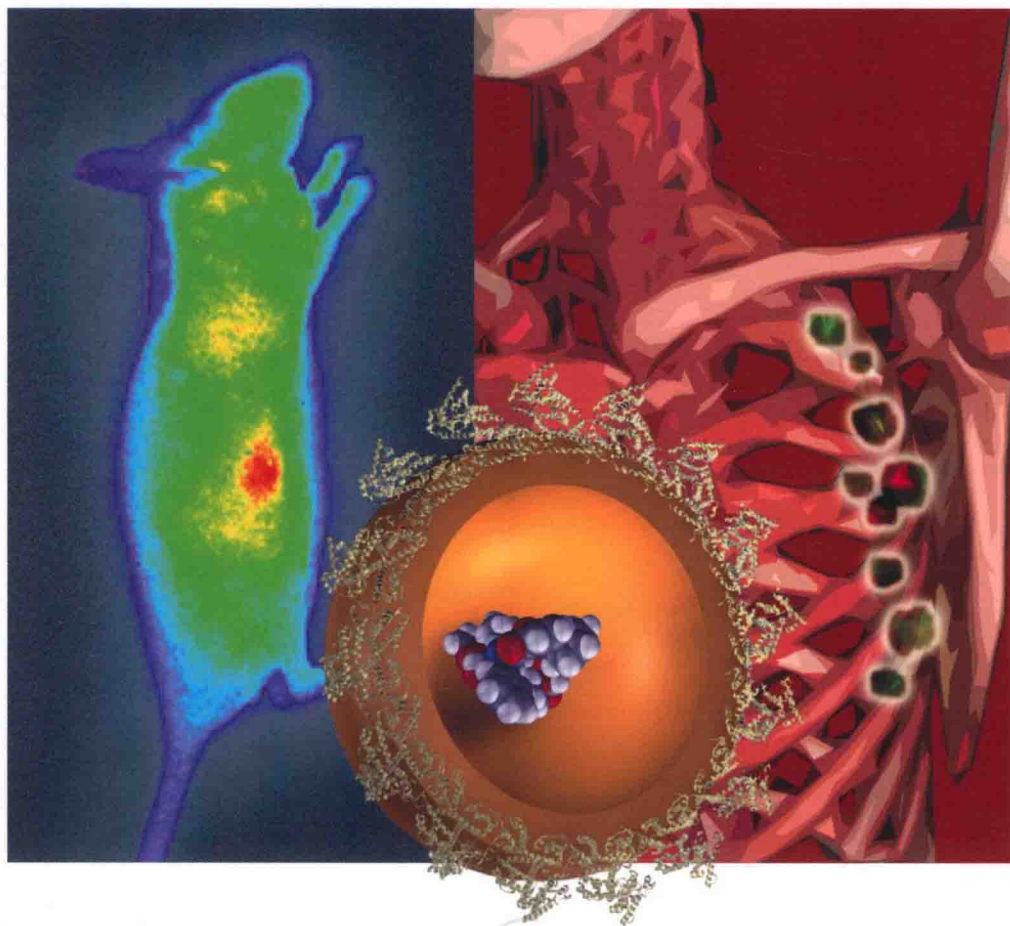


Edited by Felix Kratz, Peter Senter  
and Henning Steinhagen

 WILEY-VCH

# Drug Delivery in Oncology

From Basic Research to Cancer Therapy  
Volume 2



*Edited by Felix Kratz, Peter Senter, and Henning Steinhagen*

## **Drug Delivery in Oncology**

From Basic Research to Cancer Therapy

Volume 2



**WILEY-  
VCH**

WILEY-VCH Verlag GmbH & Co. KGaA

## The Editors

### **Dr. Felix Kratz**

Head of the Division of  
Macromolecular Prodrugs  
Tumor Biology Center  
Breisacherstrasse 117  
D-79106 Freiburg  
Germany

### **Dr. Peter Senter**

Vice President Chemistry  
Seattle Genetics, Inc.  
218, Drive S.E. Bothell  
Seattle, WA 98021  
USA

### **Dr. Henning Steinhagen**

Vice President  
Head of Global Drug Discovery  
Grünenthal GmbH  
Zieglerstr. 6  
52078 Aachen  
Germany

All books published by Wiley-VCH are carefully produced. Nevertheless, authors, editors, and publisher do not warrant the information contained in these books, including this book, to be free of errors. Readers are advised to keep in mind that statements, data, illustrations, procedural details or other items may inadvertently be inaccurate.

**Library of Congress Card No.:** applied for

### **British Library Cataloguing-in-Publication Data**

A catalogue record for this book is available from the British Library.

### **Bibliographic information published by the Deutsche Nationalbibliothek**

The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

© 2012 Wiley-VCH Verlag & Co. KGaA,  
Boschstr. 12, 69469 Weinheim,  
Germany

All rights reserved (including those of translation into other languages). No part of this book may be reproduced in any form – by photoprinting, microfilm, or any other means – nor transmitted or translated into a machine language without written permission from the publishers. Registered names, trademarks, etc. used in this book, even when not specifically marked as such, are not to be considered unprotected by law.

**Composition** Laserwords Private Ltd.,  
Chennai

**Printing and Binding** betz-druck GmbH,  
Darmstadt

**Cover Design** Schulz Grafik-Design,  
Fußgönheim

Printed in the Federal Republic of Germany  
Printed on acid-free paper

**ISBN:** 978-3-527-32823-9

**eBook ISBN:** 978-3-527-63405-7

Edited by Felix Kratz, Peter Senter, and Henning Steinhagen

Edited by  
Felix Kratz, Peter Senter,  
and Henning Steinhagen

**Drug Delivery in Oncology**



AMERICAN  
CANCER SOCIETY

WILEY-Blackwell, John Wiley & Sons, Inc.

## **Related Titles**

Fialho, A., Chakrabarty, A. (eds.)

### **Emerging Cancer Therapy Microbial Approaches and Biotechnological Tools**

2010

ISBN: 978-0-470-44467-2

Jorgenson, L., Nielson, H. M. (eds.)

### **Delivery Technologies for Biopharmaceuticals Peptides, Proteins, Nucleic Acids and Vaccines**

2009

ISBN: 978-0-470-72338-8

Airley, R.

### **Cancer Chemotherapy Basic Science to the Clinic**

2009

ISBN: 978-0-470-09254-5

Missailidis, S.

### **Anticancer Therapeutics**

2009

ISBN: 978-0-470-72303-6

Dübel, S. (ed.)

### **Handbook of Therapeutic Antibodies**

2007

ISBN: 978-3-527-31453-9

Knäblein, J. (ed.)

### **Modern Biopharmaceuticals Design, Development and Optimization**

2005

ISBN: 978-3-527-31184-2

## Foreword

It is highly likely that the reason our therapies so often fail our patients with cancer is that either (i) those therapies actually never get to their intended targets or (ii) those therapies are “intercepted” by similar targets on normal cells. If we want to understand why many of our therapies fail our patients, and what we can do to possibly remedy those failures, this book *Drug Delivery in Oncology* can help all of us achieve that understanding – and with this book it will be a state-of-the-art understanding.

Drs. Kratz, Senter, and Steinhagen have assembled a respectable breadth of both seasoned and precocious investigators to put together this very special treatise (49 chapters in all). The chapters are well written with basic science, preclinical, and clinical perspectives.

The book begins with a history and the limitations of conventional chemotherapy. Expert discussions of the vascular physiology of tumors that affect drug delivery (and how to defeat those issues) then follow. There are excellent discussions of the neonatal Fc receptor, development of cancer targeted ligands, and antibody-directed enzyme prodrug therapy (ADEPT).

A very special part of this book is the emphasis on tumor imaging. Again, the authors are major experts in this field, which undoubtedly will continue to mature to enable us to document whether or not our therapeutics actually make it to their intended target(s) – and if not, why not.

There are impressive chapters on macromolecular drug delivery systems, including biospecific antibodies, antibody–drug conjugates, and antibody–radionuclide conjugates. Up-to-date discussions of polymer-based drug delivery systems including PEGylation, thermoresponsive polysaccharide-based and even low-density lipoprotein–drug complexes are also presented.

Those with an interest in learning about nano- and microparticulate drug delivery systems can study liposomes to immunoliposomes, to hydrogels, micelles, albumin–drug nanoparticles, and even carbon nanotubes, which are all covered in this book.

Other special delivery systems covered include peptides–drug conjugates, vitamin–drug conjugates, and growth factor–drug conjugates, conjugates of drugs with fatty acids, RNA and RNA interference delivery, and specific targeted organ drug delivery.

As investigators who want to more effectively treat and indeed cure cancer we have many worries. The first of these is that many of our therapeutics just do not make it into the targets in the tumors. This book gives the reader a comprehensive insight into multiple ways to address this problem. A second major worry is that we are losing our pharmacologists who can solve those drug delivery issues. The editors and the authors of this incredible treatise give us comfort that these pharmacologists are alive and well, and thinking as to how they can contribute to getting control of this awful disease.

*Daniel D. Von Hoff, MD, FACP  
Physician in Chief and Distinguished Professor,  
Translational Genomics Research Institute (TGen)  
Professor of Medicine, Mayo Clinic  
Chief Scientific Officer, Scottsdale Healthcare and US Oncology*

## Preface

Modern oncology research is highly multidisciplinary, involving scientists from a wide array of specialties focused on both basic and applied areas of research. While significant therapeutic advancements have been made, there remains a great need for further progress in treating almost all of the most prevalent forms of cancer. Unlike many other diseases, cancer is commonly characterized by barriers to penetration, heterogeneity, genetic instability, and drug resistance. Coupled with the fact that successful treatment requires elimination of malignant cells that are very closely related to normal cells within the body, cancer therapy remains one of the greatest challenges in modern medicine.

Early on, chemotherapeutic drugs were renowned for their systemic toxicities, since they poorly distinguished tumor cells from normal cells. It became apparent to scientists within the field that further advancements in cancer medicine would require new-generation drugs that ideally targeted critical pathways, unique markers, and distinguishing physiological traits that were selectively found within the malignant cells and solid tumor masses. Several new areas of research evolved from this realization, including macromolecular-based therapies that exploit impaired lymphatic drainage often associated with solid tumors, antiangiogenesis research to cut the blood supply off from growing tumors, antibody-based strategies that allow for selective targeting to tumor-associated antigens, and new drug classes that attack uniquely critical pathways that promote and sustain tumor growth. A large proportion of both recently approved and clinically advanced anticancer drugs fall within these categories.

Beyond the generation of such drug classes, it has also been recognized that approved cancer drugs could be made more effective and less toxic through delivery and transport technologies that maximize tumor exposure while sparing normal tissues from chemotherapeutic damage. By doing so, existing or highly potent cytotoxic drugs may display improved therapeutic indices. This has attracted considerable attention and has spawned the area of macromolecular-based delivery strategies.

There are few places where those actively engaged in drug delivery or who may wish to enter the field can find the major advancements consolidated in one place. This prompted us to organize the series of books entitled *Drug Delivery in Oncology* comprised of 49 chapters written by 121 internationally recognized



leaders in the field. The work within the book series overviews many of the major breakthroughs in cancer medicine made in the last 10–15 years and features many of the chemotherapeutics of the future. Included among them are recombinant antibodies, antibody fragments, and antibody fusion proteins as well as tumor-seeking ligands for selective drug delivery and tumor imaging, and passive targeting strategies using macromolecules and nano- and microparticulate systems.

One of the special distinguishing features of this series is that the chapters are written for novices and experts alike. Each chapter is written in a style that allows interested readers to not only to find out about the most recent advancements within the field being discussed, but to actually see the data in numerous illustrations, photos, graphs, and tables that accompany each chapter.

None of this would have been possible without the devoted efforts of the contributing authors, all of whom shared the common goal of creating a new series of books that would provide an important cornerstone in the modern chemotherapeutic treatment of cancer. We are all very thankful for their efforts.

We also wish to thank the publishing team at Wiley-VCH in Weinheim, Germany. In particular, we want to give our wholehearted thanks and kind acknowledgments to Frank Weinreich, Gudrun Walter, Bernadette Gmeiner, Claudia Nußbeck, Hans-Jochen Schmitt, and Ina Wiedemann, who were always helpful and supportive during the 2 years it took to put all this together. It is our hope that this series will provide readers with inspired ideas and new directions for research in drug delivery in oncology.

July 2011

Felix Kratz

Peter Senter

Henning Steinhagen

## Contents to Volume 1

	<b>Part I Principles of Tumor Targeting</b>	<b>1</b>
<b>1</b>	<b>Limits of Conventional Cancer Chemotherapy</b>	<b>3</b>
	<i>Klaus Mross and Felix Kratz</i>	
<b>2</b>	<b>Pathophysiological and Vascular Characteristics of Solid Tumors in Relation to Drug Delivery</b>	<b>33</b>
	<i>Peter Vaupel</i>	
<b>3</b>	<b>Enhanced Permeability and Retention Effect in Relation to Tumor Targeting</b>	<b>65</b>
	<i>Hiroshi Maeda</i>	
<b>4</b>	<b>Pharmacokinetics of Immunoglobulin G and Serum Albumin: Impact of the Neonatal Fc Receptor on Drug Design</b>	<b>85</b>
	<i>Jan Terje Andersen and Inger Sandlie</i>	
<b>5</b>	<b>Development of Cancer-Targeting Ligands and Ligand–Drug Conjugates</b>	<b>121</b>
	<i>Ruiwu Liu, Kai Xiao, Juntao Luo, and Kit S. Lam</i>	
<b>6</b>	<b>Antibody-Directed Enzyme Prodrug Therapy (ADEPT) – Basic Principles and its Practice So Far</b>	<b>169</b>
	<i>Kenneth D. Bagshawe</i>	
	<b>Part II Tumor Imaging</b>	<b>187</b>
<b>7</b>	<b>Imaging Techniques in Drug Development and Clinical Practice</b>	<b>189</b>
	<i>John C. Chang, Sanjiv S. Gambhir, and Jürgen K. Willmann</i>	

- 8      Magnetic Nanoparticles in Magnetic Resonance Imaging and Drug Delivery    225**  
*Patrick D. Sutphin, Efrén J. Flores, and Mukesh Harisinghani*
- 9      Preclinical and Clinical Tumor Imaging with SPECT/CT and PET/CT    247**  
*Andreas K. Buck, Florian Gärtner, Ambros Beer, Ken Herrmann, Sibylle Ziegler, and Markus Schwaiger*

## Contents to Volume 2

Foreword    V

Preface    XXIII

### Part III      Macromolecular Drug Delivery Systems    289

#### Antibody-Based Systems    289

- 10      Empowered Antibodies for Cancer Therapy    291**  
*Stephen C. Alley, Simone Jeger, Robert P. Lyon, Django Sussman, and Peter D. Senter*
- 10.1      Introduction and Rationale for Approach    291
- 10.2      Examples of Empowered Antibody Technologies    291
- 10.2.1      ADCC    291
- 10.2.2      Antibody–Drug Conjugates for Cancer Therapy    295
- 10.2.2.1      Target Antigen Selection    295
- 10.2.2.2      Conjugation Technologies    297
- 10.2.2.3      Drug and Linker Selection    301
- 10.3      Clinical Developments    307
- 10.3.1      Gemtuzumab Ozogamicin (Mylotarg) and Other Calicheamicin-Based ADCs    307
- 10.3.2      Brentuximab Vedotin and Other Auristatin-Based ADCs    309
- 10.3.3      Trastuzumab–DM1 and Other Maytansinoid-Based ADCs    310
- 10.4      Alternative Scaffolds    310
- 10.5      Conclusions and Perspectives    311
- References    311
- 11      Mapping Accessible Vascular Targets to Penetrate Organs and Solid Tumors    325**  
*Kerri A. Massey and Jan E. Schnitzer*
- 11.1      Introduction    325
- 11.2      Current Approaches to Therapy    325
- 11.3      Defining New Target Spaces    326
- 11.3.1      Vascular Endothelium as an Accessible Target Space    327
- 11.3.2      Pathways Across the Endothelium    328

11.3.3	Caveolae as a Transvascular Pumping Target Space	329
11.3.4	Applying the Concept of New Target Spaces to Solid Tumors	330
11.4	Difficulties in Studying Endothelial Cells	332
11.4.1	Endothelial Cells in Culture	332
11.4.2	Historic Approaches to Vascular Mapping	333
11.5	Methods to Identify Tissue-Specific Targets	334
11.5.1	Antibody-Based Approaches	334
11.5.2	Phage-Based Approaches	335
11.5.3	Large-Scale Approaches	335
11.6	MS-Based Approaches to Map the Vascular Endothelial Cell Proteome	336
11.6.1	Defining Analytical Completeness	337
11.6.2	Quantification and Normalization of MS Data	338
11.7	Means to Validation	339
11.8	<i>In vivo</i> Tissue Targeting: The Lungs as Proof of Principle	341
11.9	Targeting Lung Tumors	343
11.10	Future Directions	346
	References	346
<b>12</b>	<b>Considerations of Linker Technologies</b>	<b>355</b>
	<i>Laurent Ducry</i>	
12.1	Introduction	355
12.2	Linkage Site and Cross-Linking Chemistry	355
12.3	Linkers for Cytotoxic ADCs	357
12.3.1	Chemically Labile Linkers	357
12.3.2	Enzyme-Labile Linkers	361
12.3.3	Noncleavable Linkers	367
12.4	Linkers for Radioactive Immunoconjugates	369
12.5	Conclusions	370
	References	371
<b>13</b>	<b>Antibody–Maytansinoid Conjugates: From the Bench to the Clinic</b>	<b>375</b>
	<i>Hans Erickson</i>	
13.1	Introduction	375
13.2	Conjugation Strategies	376
13.3	Selecting the Optimal Linker	381
13.4	Clinical Candidates	384
13.5	Activation of AMCs by Targeted Cancer Cells	385
13.5.1	Isolation of Maytansinoid Metabolites	385
13.5.2	Target Cell Metabolites of AMCs with SMCC-DM1, SPP-DM1, and SPDB-DM4 Linker-Maytansinoid Combinations	386
13.5.3	Lysosomal Activation is Necessary for both Cleavable and Uncleavable Conjugates	387

13.5.4	Efficiency of Antigen-Mediated Processing	387
13.5.5	Efflux of Metabolites from Targeted Cancer Cells and Bystander Effects	388
13.5.6	Target Cell Activation of Cleavable and Uncleavable AMCs	389
13.6	<i>In Vivo</i> Tumor Delivery Studies	390
13.7	Conclusions	392
	References	392
<b>14</b>	<b>Calicheamicin Antibody–Drug Conjugates and Beyond</b>	<b>395</b>
	<i>Puja Sapra, John DiJoseph, and Hans-Peter Gerber</i>	
14.1	Introduction	395
14.2	Discovery of Calicheamicin and Mechanism of Action	397
14.3	Calicheamicin ADCs	399
14.3.1	Gemtuzumab Ozogamicin (Mylotarg)	399
14.3.2	Clinical Development of Gemtuzumab Ozogamicin (Mylotarg)	400
14.3.3	CMC-544	402
14.3.3.1	CD22 Expression and Function	402
14.3.4	Preclinical Activity of CMC-544, an Anti-CD22–Calicheamicin Conjugate, in Models of NHL	402
14.3.5	Effect of CMC-544 in a Model of ALL	403
14.4	Clinical Development of Calicheamicin Conjugates: CMC-544	404
14.5	Conclusions and Future Directions	405
	References	407
<b>15</b>	<b>Antibodies for the Delivery of Radionuclides</b>	<b>411</b>
	<i>Anna M. Wu</i>	
15.1	Introduction	411
15.2	Rationale for Using Antibodies for Radionuclide Delivery	413
15.2.1	Radionuclides for Imaging	415
15.2.1.1	$\gamma$ Emitters	417
15.2.1.2	Positron Emitters	417
15.2.2	Radionuclides for Therapy	418
15.2.2.1	$\beta$ Emitters	421
15.2.2.2	$\alpha$ Emitters	422
15.2.2.3	Auger Electron Emitters	423
15.2.3	Antibodies as Delivery Agents	423
15.2.3.1	Intact Antibodies	424
15.2.3.2	Engineered Antibody Fragments	424
15.2.3.3	Pretargeting	429
15.3	Clinical Development	431
15.3.1	Radioimmunoimaging	431
15.3.2	Radioimmunotherapy	434

15.4	Conclusions and Perspectives	434
	Acknowledgments	435
	References	435
<b>16</b>	<b>Bispecific Antibodies and Immune Therapy Targeting</b>	<b>441</b>
	<i>Sergej M. Kiprijanov</i>	
16.1	Introduction	441
16.2	Treatment Options in Cancer in the Pre-Antibody Era	442
16.3	Antibodies as Therapeutic Agents	443
16.4	Next Generation of Therapeutic Antibodies	449
16.5	Rationale for Immunotherapy with BsAbs	450
16.5.1	Retargeting BsAbs	450
16.5.2	BsAbs of Dual Action	452
16.5.3	BsAbs of Enhanced Selectivity	453
16.6	BsAb Formats	454
16.6.1	Hetero-Oligomeric Antibodies	455
16.6.2	Bispecific Single-Chain Antibodies	457
16.6.3	Recombinant IgG-Like BsAbs	460
16.6.4	Other Novel BsAb Constructs	463
16.7	BsAbs in the Clinic	463
16.7.1	Clinical Data for First-Generation BsAbs	464
16.7.2	Recombinant Bispecific Molecules Entering Clinical Trials	464
16.7.2.1	Bispecific T-Cell Engager Molecules	464
16.7.2.2	Other scFv–scFv Tandem Molecules	468
16.7.2.3	TandAbs	469
16.7.2.4	BsAbs of Dual Action	471
16.8	Conclusions and Future Prospects	472
	References	473
	<b>Polymer-Based Systems</b>	<b>483</b>
<b>17</b>	<b>Design of Polymer–Drug Conjugates</b>	<b>485</b>
	<i>Jindřich Kopeček and Pavla Kopečková</i>	
17.1	Introduction	485
17.2	Polymer Carriers	486
17.2.1	Impact of the Molecular Weight of the Polymer Carrier on its Fate and Efficiency	488
17.2.2	Structural Factors Influencing the Cellular Uptake and Subcellular Fate of Macromolecules	490
17.2.3	Other Design Factors	493
17.3	Binding Drugs to Polymer Carriers	496
17.4	Attachment of Targeting Moieties	498
17.4.1	Subcellular Targeting	500
17.4.1.1	Mitochondrial Targeting	501

17.4.1.2	Hormone-Mediated Nuclear Delivery	501
17.5	Novel Designs of Polymer Therapeutics	503
17.5.1	Design of Backbone Degradable, Long-Circulating Polymer Carriers	503
17.5.2	Drug-Free Macromolecular Therapeutics	504
17.6	Conclusions and Perspectives	506
	Acknowledgments	506
	References	507
<b>18</b>	<b>Dendritic Polymers in Oncology: Facts, Features, and Applications</b>	<b>513</b>
	<i>Mohiuddin Abdul Quadir, Marcelo Calderón, and Rainer Haag</i>	
18.1	Introduction	513
18.2	Chemistry and Architecture	515
18.3	Dendritic Architectures and Oncology: Background and Application	517
18.3.1	Complexation of Anticancer Agents by Dendritic Architectures	520
18.3.2	Anticancer Agents can be Chemically Conjugated with Dendrimer Functional Groups	523
18.3.3	Tumor Microenvironment and Attachment of Targeting Moiety to the Dendrimer	528
18.4	Intracellular Trafficking, Cytotoxicity, and Pharmacokinetics of a Dendritic Architecture are Tunable	535
18.5	Other Medical Applications of Dendritic Polymers	537
18.5.1	Photodynamic Therapy	537
18.5.2	Boron Neutron Capture Therapy	538
18.5.3	Diagnostic Application of Dendrimers	539
18.5.4	Gene Delivery with Dendrimers	542
18.6	Novel Therapeutic Approaches with Dendrimers	545
18.7	Conclusions	547
	Acknowledgments	547
	References	547
<b>19</b>	<b>Site-Specific Prodrug Activation and the Concept of Self-Immolation</b>	<b>553</b>
	<i>André Warnecke</i>	
19.1	Introduction	553
19.2	Rationale and Chemical Aspects of the Concept of Self-Immolation	554
19.2.1	Cyclization Strategies	556
19.2.2	Elimination Strategies	558
19.2.3	Self-Immolative versus Classic Strategies –A Comparison	562
19.3	Elimination-Based Trigger Groups for Tumor-Specific Activation	564
19.3.1	Enzymatic and Related Biocatalytic Activation	564
19.3.2	Reductive Activation	566
19.3.3	Oxidative Activation	569

19.3.4	pH-Dependent Activation	569
19.3.5	Other Methods of Activation	571
19.4	Branched Elimination Linkers—Chemical Adaptors or Building Blocks for More Complex Self-Immolative Architectures	573
19.5	Clinical Impact	582
19.6	Conclusion and Perspectives	584
	References	585
<b>20</b>	<b>Ligand-Assisted Vascular Targeting of Polymer Therapeutics</b>	<b>591</b>
	<i>Anat Eldar-Boock, Dina Polyak, and Ronit Satchi-Fainaro</i>	
20.1	Overview of Tumor Angiogenesis	591
20.2	Potential Angiogenic Markers	596
20.2.1	Integrins	596
20.2.2	Selectins	596
20.2.3	APN (CD13)	598
20.2.4	Hyaluronic Acid Binding Receptor (CD44)	598
20.3	Drug Delivery Strategy: Targeted Polymer Therapeutics	599
20.4	Novel Targeted Polymeric Drug Delivery Systems Directed to Tumor Endothelial Cells	601
20.4.1	RGD-Based Polymer–Drug Conjugates	601
20.4.2	Selectin-Targeted Polymer–Drug Conjugates	612
20.4.3	APN-Targeted Polymer Therapeutics	613
20.4.4	HA-Based Polymer Therapeutics	615
20.5	Opportunity for Dual Targeting of Angiogenesis-Related Markers	616
20.6	Tumor Angiogenesis-Targeted Polymeric Drug Delivery Systems: Summary and Lessons Learnt	617
	References	619
<b>21</b>	<b>Drug Conjugates with Poly(Ethylene Glycol)</b>	<b>627</b>
	<i>Hong Zhao, Lee M. Greenberger, and Ivan D. Horak</i>	
21.1	Introduction	627
21.2	Rationale for PEGylation and PEG-Drug Conjugates	627
21.3	Permanent PEGylation	630
21.3.1	First-Generation PEG Linker: SS-PEG	630
21.3.2	Second-Generation PEG Linkers	631
21.3.2.1	SC-PEG	631
21.3.2.2	PEG-Aldehyde	632
21.3.2.3	U-PEG	633
21.3.2.4	Other Permanent Linkers	637
21.4	Releasable PEGylation	638
21.4.1	Releasable PEG Linkers Based on Ester Linkage	638
21.4.1.1	PEG–Paclitaxel	638
21.4.1.2	PEG–Camptothecin Analogs	641



21.4.2	Releasable PEG Linkers Based on Amide or Other Amino-Derived Linkages	646
21.4.2.1	Releasable PEG Linkers Based on Aromatic Systems	646
21.4.2.2	Releasable PEG Linkers Based on an Aliphatic System	649
21.4.2.3	Aromatic Amides	651
21.4.2.4	Acid-Activated PEG–Drug Conjugates	651
21.4.2.5	Other Releasable Linkers	653
21.5	Summary of Clinical Status	653
21.6	Conclusions and Perspectives	655
	Acknowledgments	656
	References	657
<b>22</b>	<b>Thermo-Responsive Polymers</b>	667
	<i>Drazen Raucher and Shama Moktan</i>	
22.1	Introduction	667
22.2	Hyperthermia in Cancer Treatment	668
22.3	Synergistic Advantages of Combining Thermo-Responsive Polymers and Hyperthermia	670
22.4	Selected Thermo-Responsive Polymer Classes	671
22.4.1	Synthetic Polymers	671
22.4.2	N-Isopropylacrylamide-Based Polymers	671
22.4.3	PEO-Based Polymers	674
22.4.4	Poly(Organophosphazene)-Based Polymers	677
22.4.5	Miscellaneous	678
22.5	Elastin-Like Biopolymers	678
22.5.1	ELP Synthesis	678
22.5.2	Cell-Penetrating Peptides for Intracellular Delivery of ELPs	680
22.5.3	Efficiency and Mechanism of CPP-ELP Cellular Uptake	681
22.5.4	ELPs for Delivery of Peptides	682
22.5.5	Delivery of c-Myc Inhibitory Peptides by ELPs	684
22.5.6	ELP-Based Delivery of a Cell Cycle Inhibitory p21 Mimetic Peptide	685
22.5.7	ELP Delivery of Conventional Drugs	690
22.5.8	<i>In Vivo</i> Studies with Thermo-Responsive ELP Carriers	692
22.5.9	Optimizing <i>In Vivo</i> Delivery of ELP Carriers with CPPs	693
22.6	Conclusions and Perspectives	695
	Acknowledgements	696
	References	697
<b>23</b>	<b>Polysaccharide-Based Drug Conjugates for Tumor Targeting</b>	701
	<i>Gurusamy Saravanakumar, Jae Hyung Park, Kwangmeyung Kim, and Ick Chan Kwon</i>	
23.1	Introduction	701
23.2	Chemistry of Polysaccharide–Drug Conjugation	707
23.3	Polysaccharide-Drug Conjugates	711