

## Contents to Volume 1

<b>Foreword</b>	V
<b>Preface</b>	XVII
<b>List of Contributors</b>	XIX
<b>Drug Delivery in Oncology – Challenge and Perspectives</b>	LIX

### Part I Principles of Tumor Targeting 1

<b>1</b>	<b>Limits of Conventional Cancer Chemotherapy</b>	<b>3</b>
	<i>Klaus Mross and Felix Kratz</i>	
1.1	Introduction: The Era of Cancer Chemotherapy	3
1.2	Dilemma and Challenge of Treating Malignant Diseases	14
1.3	Adverse Effects	16
1.3.1	Common Side-Effects	18
1.3.1.1	Depression of the Immune System	18
1.3.1.2	Fatigue	19
1.3.1.3	Tendency to Bleed Easily	19
1.3.1.4	Gastrointestinal Distress	19
1.3.1.5	Hair Loss	20
1.3.2	Damage to Specific Organs	20
1.3.2.1	Cardiotoxicity	20
1.3.2.2	Hepatotoxicity	21
1.3.2.3	Nephrotoxicity	22
1.3.2.4	Pulmonary Side-Effects	22
1.3.2.5	Vascular Adverse Effects	23
1.3.2.6	Tissue Damage (Extravasation)	23
1.3.2.7	Neurological Side-Effects	24
1.3.2.8	Secondary Neoplasms	25
1.3.2.9	Infertility	25
1.3.2.10	Other Side-Effects	25
1.4	Supportive Care	25
1.5	New Approaches Complementing Current Cancer Chemotherapy	26
1.6	Conclusions and Perspectives	28
	References	29

<b>2</b>	<b>Pathophysiological and Vascular Characteristics of Solid Tumors in Relation to Drug Delivery</b>	<b>33</b>
	<i>Peter Vaupel</i>	
2.1	Introduction	33
2.2	Basic Principles of Blood Vessel Formation in Solid Tumors	34
2.2.1	Angiogenesis	34
2.2.2	Vascular Co-option	36
2.2.3	Vasculogenesis	36
2.2.4	Intussusception	36
2.2.5	Vascular Mimicry	36
2.2.6	Microvessel Formation by Myeloid Cells	36
2.3	Tumor Lymphangiogenesis	37
2.4	Tumor Vascularity and Blood Flow	37
2.5	Arteriovenous Shunt Perfusion in Tumors	38
2.6	Volume and Characteristics of the Tumor Interstitial Space	40
2.7	Interstitial Fluid Pressure in Tumors	42
2.8	Role of the Disorganized, Compromised Microcirculation as an Obstacle in Drug Delivery	43
2.8.1	Blood-Borne Delivery	43
2.8.2	Extravasation of Anticancer Agents	45
2.9	Interstitial Barriers to Drug Delivery	46
2.10	Pathophysiological Tumor Microenvironment as an Obstacle in Tumor Therapy	47
2.10.1	Hypoxia as an Obstacle in Drug Therapy	48
2.10.1.1	Direct Effects	48
2.10.1.2	Indirect Effects Based on Changes in the Transcriptome, in Differential Regulation of Gene Expression, and in Alterations of the Proteome	49
2.10.1.3	Indirect Effects Based on Enhanced Mutagenesis, Genomic Instability, and Clonal Selection	51
2.10.1.4	Tumor Hypoxia: An Adverse Parameter in Chemotherapy	51
2.10.2	Tumor Acidosis and Drug Resistance	53
2.11	Conclusions	56
	Acknowledgments	56
	References	56
<b>3</b>	<b>Enhanced Permeability and Retention Effect in Relation to Tumor Targeting</b>	<b>65</b>
	<i>Hiroshi Maeda</i>	
3.1	Background and Status Quo	65
3.2	What is the EPR Effect: Mechanism, Uniqueness, and Factors Involved	66
3.3	Heterogeneity of the EPR Effect: A Problem in Drug Delivery	72
3.4	Overcoming the Heterogeneity of the EPR Effect for Drug Delivery and How to Enhance the EPR Effect	75
3.4.1	Angiotensin II-Induced High Blood Pressure	75

3.4.2	Use of NO-Releasing Agents	78
3.4.3	Use of Other Vascular Modulators	79
3.5	PEG Dilemma: Stealth Effect and Anti-PEG IgM Antibody	79
3.6	Concluding Remarks	80
	Acknowledgments	81
	References	81
<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>	
4.1	Introduction	85
4.2	Discovery of FcRn	87
4.3	FcRn Structure	88
4.4	FcRn–Ligand Interactions	89
4.5	FcRn as a Multiplayer with Therapeutic Utilities	90
4.5.1	Directional Placental Transport	90
4.5.2	FcRn at Mucosal Surfaces	91
4.5.3	Systemic FcRn-Mediated Recycling	92
4.5.4	Role of FcRn in Antigen Presentation	93
4.5.5	FcRn at Immune-Privileged Sites	94
4.5.6	FcRn in the Kidneys	94
4.5.7	FcRn Expressed by the Liver	95
4.6	Engineering IgG for Altered FcRn Binding and Pharmacokinetics	95
4.6.1	IgG Fc Fusions	95
4.6.2	Engineered IgG Variants	96
4.6.3	Blocking FcRn Recycling	102
4.7	Targeting FcRn by SA	102
4.7.1	SA Fusions	102
4.7.2	Targeting SA	105
4.8	Considering Cross-Species Binding	111
4.9	Concluding Remarks	113
	Acknowledgment	113
	References	113
<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>	
5.1	Introduction	121
5.2	Overview of Cancer-Targeting Ligand–Drug Conjugates	122
5.3	Cancer-Targeting Ligands	125
5.3.1	Introduction	125
5.3.2	Phage-Display Library Approach	125
5.3.2.1	Phage-Display Library Screening and Decoding	127
5.3.2.2	Examples	127

5.3.3	OBOC Combinatorial Library Approach	131
5.3.3.1	OBOC Library Design	132
5.3.3.2	OBOC Library Construction	135
5.3.3.3	OBOC Library Screening	137
5.3.3.4	OBOC Library Decoding	138
5.3.3.5	Ligand Optimization	139
5.3.3.6	Examples	140
5.4	Linkers	143
5.4.1	Acid-Sensitive Linkers	143
5.4.2	Enzymatic Cleavage	143
5.4.3	Self-Immolative Spacers	145
5.4.4	Reductive Cleavage	146
5.4.5	On-Demand Cleavable Linker	146
5.5	Examples of Cancer-Targeting Ligand–Drug Conjugates	147
5.5.1	Folic Acid–Drug Conjugates	147
5.5.2	Peptide Ligand–Drug Conjugates	148
5.5.3	Peptide Hormone–Drug Conjugates	150
5.5.4	Antibody–Drug Conjugates	151
5.5.5	ADEPT	154
5.5.6	Polymer–Drug Conjugates	156
5.5.7	Targeting Liposomes and Nanoparticles	158
5.6	Conclusions and Perspectives	159
	Acknowledgments	160
	References	160
<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>	
6.1	Introduction	169
6.2	Principles and the Components of ADEPT	170
6.2.1	Target	170
6.2.2	Antibody	171
6.2.3	Enzyme	172
6.2.4	Prodrug and Drug	173
6.3	Third Essential	173
6.4	ADEPT Studies Elsewhere	175
6.5	Reagents for First Clinical Trials in London (1990–1995)	176
6.5.1	First ADEPT Clinical Trial	177
6.5.2	Subsequent ADEPT Clinical Studies in London	178
6.5.3	Two-Phase ADEPT Clinical Studies in London	179
6.6	Technology Advances	179
6.7	ADEPT Future	181
	References	181

**Part II Tumor Imaging 187****7 Imaging Techniques in Drug Development and Clinical Practice 189***John C. Chang, Sanjiv S. Gambhir, and Jürgen K. Willmann*

- 7.1 Introduction 189
- 7.2 Cancer Biology 191
  - 7.2.1 Tumor Genetic Heterogeneity 191
  - 7.2.2 Altered Tumor Metabolism 191
  - 7.2.3 Tumor Angiogenesis 192
  - 7.2.4 Receptor Pathologies 194
- 7.3 Cancer Biomarkers 194
  - 7.3.1 Histological Biomarkers 194
  - 7.3.2 Hematological Biomarkers 196
  - 7.3.3 Imaging Biomarkers 196
- 7.4 Imaging Techniques 197
  - 7.4.1 SPECT 197
  - 7.4.2 PET/PET-CT 198
  - 7.4.3 MRI 198
  - 7.4.4 CT 199
  - 7.4.5 Ultrasound 199
  - 7.4.6 Fluorescence/Bioluminescence 200
- 7.5 Examples of Imaging Assessment of Tumor Response 200
  - 7.5.1 SPECT 200
  - 7.5.2 PET/PET-CT 201
    - 7.5.2.1 Microdosing 201
    - 7.5.2.2 Cancer Metabolism and Proliferation 202
    - 7.5.2.3 Hypoxia 204
    - 7.5.2.4 Biomarker Imaging 205
    - 7.5.2.5 Angiogenesis 207
    - 7.5.2.6 Apoptosis 207
  - 7.5.3 MRI 207
    - 7.5.3.1 Cellular Structure 209
    - 7.5.3.2 Metabolic Response 209
    - 7.5.3.3 Tumor Perfusion 210
  - 7.5.4 CT Imaging 211
  - 7.5.5 Ultrasound 212
  - 7.5.6 Fluorescence/Bioluminescence 213
- 7.6 Challenges of Imaging in Drug Development and Validation 214
- 7.7 Conclusions and Future Perspectives 215
- References 217

**8 Magnetic Nanoparticles in Magnetic Resonance Imaging and Drug Delivery 225***Patrick D. Sutherland, Efrén J. Flores, and Mukesh Harisinghani*

- 8.1 Introduction 225

8.2	Passive Targeting of Nanoparticles	227
8.2.1	Mechanism of Action	229
8.2.2	Lymphotropic Nanoparticle MRI	229
8.3	Active SPIO Nanoparticle Targeting	232
8.3.1	Creating the Targeted Imaging Agents	233
8.3.1.1	Transferrin–USPIO Nanoparticles	233
8.3.1.2	Folate Receptor	235
8.3.1.3	Integrins	235
8.4	Nanoparticles in Targeted Therapy	236
8.4.1	Nanoparticles in Gene Therapy	237
8.4.2	Nanoparticles in Molecularly Targeted Drug Delivery	238
8.4.3	Conversion of Therapeutic Agent to Imaging Agent	239
8.4.4	Toxic Payload	240
8.5	Conclusions	240
	References	242
<b>9</b>	<b>Preclinical and Clinical Tumor Imaging with SPECT/CT and PET/CT</b>	<b>247</b>
	<i>Andreas K. Buck, Florian Gärtner, Ambros Beer, Ken Herrmann, Sibylle Ziegler, and Markus Schwaiger</i>	
9.1	Introduction	247
9.2	Technical Aspects of Functional and Molecular Imaging with SPECT and PET	249
9.2.1	Principles of Clinical PET and Hybrid PET/CT Imaging	249
9.2.2	Biomarkers for PET and PET/CT Imaging	250
9.2.3	Principles of Clinical SPECT and Hybrid SPECT/CT Imaging	252
9.2.4	Biomarkers for SPECT and SPECT/CT Imaging	258
9.2.5	Principles of Preclinical Imaging with SPECT and PET	258
9.3	Preclinical and Clinical Developments	260
9.3.1	Imaging Neovascularization	260
9.3.1.1	VEGF/VEGFR Imaging	261
9.3.1.2	Radiolabeled Integrin Antagonists (RGD Peptides)	262
9.3.1.3	Monomeric Tracer Labeling Strategies	262
9.3.2	Imaging the Proliferative Activity of Tumors	264
9.3.3	Imaging the Hypoxic Cell Fraction of Tumors	267
9.3.4	Imaging Receptor Expression	269
9.4	Clinical Applications of SPECT/CT and PET	272
9.4.1	Differentiation of Benign from Malignant Tumors and Cancer Detection	272
9.4.2	Staging of Cancer: Prognostic Potential of Imaging Biomarkers	273
9.4.3	Assessment of Response to Therapy	274
9.4.4	Restaging of Cancer and Detection of Recurrence	274
9.4.5	PET for Radiation Treatment Planning	275
9.4.6	PET for Cancer Drug Development	275
9.4.7	SPECT/CT for Mapping of SLNs	276

- 9.4.8 SPECT/CT for Detection of Bone Metastases 277
- 9.4.9 SPECT/CT in Thyroid Cancer 278
- 9.4.10 SPECT/CT for Imaging of Adrenocortical Tumors 279
- 9.4.11 SPECT/CT in Neuroendocrine Tumors 281
- 9.5 Conclusions and Perspectives 281
- References 282

## Contents to Volume 2

### 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*
- 11 **Mapping Accessible Vascular Targets to Penetrate Organs and Solid Tumors** 325  
*Kerri A. Massey and Jan E. Schnitzer*
- 12 **Considerations of Linker Technologies** 355  
*Laurent Ducry*
- 13 **Antibody–Maytansinoid Conjugates: From the Bench to the Clinic** 375  
*Hans Erickson*
- 14 **Calicheamicin Antibody–Drug Conjugates and Beyond** 395  
*Puja Sapra, John DiJoseph, and Hans-Peter Gerber*
- 15 **Antibodies for the Delivery of Radionuclides** 411  
*Anna M. Wu*
- 16 **Bispecific Antibodies and Immune Therapy Targeting** 441  
*Sergej M. Kiprijanov*
- Polymer-Based Systems** 483
- 17 **Design of Polymer–Drug Conjugates** 485  
*Jindřich Kopeček and Pavla Kopečková*
- 18 **Dendritic Polymers in Oncology: Facts, Features, and Applications** 513  
*Mohiuddin Abdul Quadir, Marcelo Calderón, and Rainer Haag*

- 19 **Site-Specific Prodrug Activation and the Concept of Self-Immolation** 553  
*André Warnecke*
- 20 **Ligand-Assisted Vascular Targeting of Polymer Therapeutics** 591  
*Anat Eldar-Boock, Dina Polyak, and Ronit Satchi-Fainaro*
- 21 **Drug Conjugates with Poly(Ethylene Glycol)** 627  
*Hong Zhao, Lee M. Greenberger, and Ivan D. Horak*
- 22 **Thermo-Responsive Polymers** 667  
*Drazen Raucher and Shama Moktan*
- 23 **Polysaccharide-Based Drug Conjugates for Tumor Targeting** 701  
*Gurusamy Saravanakumar, Jae Hyung Park, Kwangmeyung Kim, and Ick Chan Kwon*
- 24 **Serum Proteins as Drug Carriers of Anticancer Agents** 747  
*Felix Kratz, Andreas Wunder, and Bakheet Elsadek*
- 25 **Future Trends, Challenges, and Opportunities with Polymer-Based Combination Therapy in Cancer** 805  
*Coralie Deladriere, Rut Lucas, and María J. Vicent*
- 26 **Clinical Experience with Drug–Polymer Conjugates** 839  
*Khalid Abu Ajaj and Felix Kratz*
- Part IV Nano- and Microparticulate Drug Delivery Systems** 885
- Lipid-Based Systems** 885
- 27 **Overview on Nanocarriers as Delivery Systems** 887  
*Haiya Shen, Elvin Blanco, Biana Godin, Rita E. Serda, Agathe K. Streiff, and Mauro Ferrari*
- 28 **Development of PEGylated Liposomes** 907  
*I. Craig Henderson*
- 29 **Immunoliposomes** 951  
*Vladimir P. Torchilin*
- 30 **Responsive Liposomes (for Solid Tumor Therapy)** 989  
*Stavroula Sofou*



- 31 Nanoscale Delivery Systems for Combination Chemotherapy 1013**  
*Barry D. Liboiron, Paul G. Tardi, Troy O. Harasym, and Lawrence, D. Mayer*
- Polymer-Based Systems 1051**
- 32 Micellar Structures as Drug Delivery Systems 1053**  
*Nobuhiro Nishiyama, Horacio Cabral, and Kazunori Kataoka*
- 33 Tailor-Made Hydrogels for Tumor Delivery 1071**  
*Sungwon Kim and Kinam Park*
- 34 pH-Triggered Micelles for Tumor Delivery 1099**  
*Haiqing Yin and You Han Bae*
- 35 Albumin–Drug Nanoparticles 1133**  
*Neil Desai*
- 36 Carbon Nanotubes 1163**  
*David A. Scheinberg, Carlos H. Villa, Freddy Escorcía, and Michael R. McDevitt*

## Contents to Volume 3

- Part V Ligand-Based Drug Delivery Systems 1187**
- 37 Cell-Penetrating Peptides in Cancer Targeting 1189**  
*Kaido Kurrikoff, Julia Suhorutšenko, and Ülo Langel*
- 38 Targeting to Peptide Receptors 1219**  
*Andrew V. Schally and Gabor Halmos*
- 39 Aptamer Conjugates: Emerging Delivery Platforms for Targeted Cancer Therapy 1263**  
*Zeyu Xiao, Jillian Frieder, Benjamin A. Teply, and Omid C. Farokhzad*
- 40 Design and Synthesis of Drug Conjugates of Vitamins and Growth Factors 1283**  
*Iontcho R. Vlahov, Paul J. Kleindl, and Fei You*
- 41 Drug Conjugates with Polyunsaturated Fatty Acids 1323**  
*Joshua Seitz and Iwao Ojima*

	<b>Part VI Special Topics</b>	1359
42	<b>RNA Drug Delivery Approaches</b>	1361
	<i>Yuan Zhang and Leaf Huang</i>	
43	<b>Local Gene Delivery for Therapy of Solid Tumors</b>	1391
	<i>Wolfgang Walther, Peter M. Schlag, and Ulrike Stein</i>	
44	<b>Viral Vectors for RNA Interference Applications in Cancer Research and Therapy</b>	1415
	<i>Henry Fechner and Jens Kurreck</i>	
45	<b>Design of Targeted Protein Toxins</b>	1443
	<i>Hendrik Fuchs and Christopher Bachran</i>	
46	<b>Drug Targeting to the Central Nervous System</b>	1489
	<i>Gert Fricker, Anne Mahringer, Melanie Ott, and Valeska Reichel</i>	
47	<b>Liver Tumor Targeting</b>	1519
	<i>Katrin Hochdörffer, Giuseppina Di Stefano, Hiroshi Maeda, and Felix Kratz</i>	
48	<b>Photodynamic Therapy: Photosensitizer Targeting and Delivery</b>	1569
	<i>Pawel Mroz, Sulbha K. Sharma, Timur Zhiyentayev, Ying-Ying Huang, and Michael R. Hamblin</i>	
49	<b>Tumor-Targeting Strategies with Anticancer Platinum Complexes</b>	1605
	<i>Markus Galanski and Bernhard K. Keppler</i>	
	<b>Index</b>	1631