

Contents

List of Contributors XV

1	Pharmacokinetics and Pharmacodynamics (PK/PD) of Bionanomaterials	1
	<i>Ergang Liu, Meng Zhang, and Yongzhuo Huang</i>	
1.1	Introduction	1
1.2	Commonly Utilized NMs in Pharmaceutical Research	2
1.2.1	Natural NMs	2
1.2.1.1	Lipid-Based NMs	2
1.2.1.2	Protein-Based NMs	3
1.2.1.3	Polysaccharide-Based NMs	3
1.2.2	Synthetic NMs	3
1.2.2.1	Diversity of Synthetic NMs in Forms	4
1.2.2.2	Drug Release Behaviors	4
1.2.3	Inorganic NMs	5
1.2.4	Other NMs	6
1.3	<i>In vivo</i> Biodistribution and the Evolving Targeting Principles for NMs	6
1.3.1	Organ Distribution versus Cell-Specific Targeting	6
1.3.2	Targeting Delivery Strategies	7
1.4	Processing NMs by the Biological Systems	9
1.4.1	Anatomic Basis of NMs' <i>in vivo</i> Biodistribution Behavior	10
1.4.2	Factors Affecting <i>in vivo</i> Biodistribution of NMs	11
1.4.2.1	Size	11
1.4.2.2	Zeta Potential	12
1.4.2.3	Shape and Deformability	12
1.4.2.4	Hydrophilicity and Hydrophobicity	13
1.4.3	Metabolism and Elimination of NMs	13
1.4.3.1	Common Metabolism	13
1.4.3.2	Degradable versus Nondegradable NMs	13
1.4.3.3	Free Drug versus Drug Encapsulated by NMs	13
1.5	Rational Design of Long-Circulating NMs	13
1.5.1	NMs with Optimal Physicochemical Characters	14

1.5.2	Surface Modification to Improve the Intrinsic Features of NMs	14
1.6	Mathematic Simulation of NM-Mediated Cancer Drug Delivery	15
1.6.1	Progress: From Experiment to Simulation	15
1.6.2	Compartment Models for PK Assessment of NMs	15
1.6.3	Physiologically Based Compartment Models	20
1.6.3.1	Protocols of Building a PBPK Model for NMs	21
1.6.3.2	Examples	21
1.6.4	Brief Summary	24
1.7	Experimental PK Data of the Applied NMs	25
1.7.1	PK Data of NMs Without Drugs	33
1.7.2	PK Differences Between Drugs Encapsulated by Different NMs	34
1.7.3	Reciprocal Blood and Tissue PK	40
1.7.4	PK Differences Between Different Components of the Drug-NM System	40
1.7.5	PK Variations Among Different Routes of Administration	40
1.8	Perspectives	50
1.8.1	Development of NMs	50
1.8.2	Pharmacokinetic Study and Model Development	50
	References	50
2	Targeted Dendrimers for Cancer Diagnosis and Therapy	61
	<i>Jingjing Hu, Ke Hu, and Yiyun Cheng</i>	
2.1	Introduction	61
2.2	Targeted Dendrimers for Cancer Therapy	63
2.2.1	Low Molecular Weight Ligand-Modified Dendrimers	63
2.2.1.1	Folic Acid-Modified Dendrimers	63
2.2.1.2	Carbohydrate-Modified Dendrimers	65
2.2.1.3	Biotin-Modified Dendrimers	66
2.2.1.4	Riboflavin-Modified Dendrimers	66
2.2.1.5	Estrogen-Modified Dendrimers	67
2.2.2	Macromolecular Ligand-Modified Dendrimers	68
2.2.2.1	Antibody-Modified Dendrimers	68
2.2.2.2	Transferrin (Tf)- and Lactoferrin (Lf)-Modified Dendrimers	69
2.2.2.3	EGF- and Fibroblast Growth Factor (FGF)-Modified Dendrimers	69
2.2.2.4	Peptide-Modified Dendrimers	70
2.2.2.5	Aptamer-Modified Dendrimers	71
2.2.2.6	Hyaluronic Acid (HA)-Modified Dendrimers	72
2.2.3	Dual-Targeting Ligand-Modified Dendrimers	72
2.3	Targeted Dendrimers for Cancer Diagnosis	73
2.3.1	Targeted Dendrimers in CT	73
2.3.2	Targeted Dendrimers in SPECT	74
2.3.3	Targeted Dendrimers in MRI	74
2.3.4	Targeted Dendrimers in NIR Fluorescence Imaging	75
2.3.5	Targeted Dendrimers in Multimodal Imaging	75

2.3.6	Targeted Dendrimers for <i>In Vitro</i> Cancer Diagnosis	77
2.4	Conclusions	77
	References	78
3	Polymeric Micelles for Drug Delivery	87
	<i>Wei Wu and Xiqun Jiang</i>	
3.1	Introduction	87
3.2	Amphiphilic Copolymers for Micelle Preparation	88
3.2.1	Amphiphilic Copolymers with PEG as Hydrophilic Blocks	89
3.2.2	Amphiphilic Copolymers with Poly(<i>N</i> -vinylpyrrolidone) (PVP) as Hydrophilic Blocks	90
3.2.3	Amphiphilic Copolymers with Polybetaine as Hydrophilic Blocks	91
3.3	Stability of Polymeric Micelles	91
3.4	Drug Incorporation of Polymeric Micelles	92
3.5	Functionalization of Polymeric Micelles	93
3.6	Conclusions	93
	References	94
4	Polymeric Micelle-Based Nanomedicine	99
	<i>Bin He</i>	
4.1	Introduction to Chemotherapy	99
4.2	Polymeric Micelle-Based Nanomedicine	100
4.2.1	Formulation of Polymeric Micelle-Based Nanomedicine	100
4.2.1.1	Size and Size Distribution	100
4.2.1.2	Surface Properties	101
4.2.1.3	Drug Loading	101
4.2.1.4	Drug Release Profiles	102
4.2.2	Interactions in Polymeric Micelle-Based Nanomedicine	102
4.2.2.1	Hydrophobic Interaction	102
4.2.2.2	Electrostatic Interaction	103
4.2.2.3	Hydrogen Bond	103
4.2.2.4	Host–Guest Interaction	103
4.2.2.5	π – π Stacking Interaction	103
4.2.2.6	Crystallization and Stereocomplex	104
4.2.3	Smart Drug Delivery	105
4.2.3.1	pH-Sensitive Micelles	105
4.2.4	Targeted Drug Delivery	108
4.3	Perspective	109
	References	110
5	Microfluidics Applications in Cancer Drug Delivery	117
	<i>Hao Zhang and Youqing Shen</i>	
5.1	Introduction	117
5.2	Basic Principles of Micellar Drug Carriers and Microfluidics	118

5.2.1	Use of Polymeric Micelles for Drug Delivery	118
5.2.2	Microfluidics as a New Solution	120
5.3	Microfluidic Fabrication of Polymer Micelles	121
5.3.1	Use of Diffusive Microfluidic Mixer to Fabricate Micelles	122
5.3.2	Use of Microarchitecture-Induced Mixing to Fabricate Micelles	126
5.3.3	Use of Droplet-Based Chaotic Mixing to Fabricate Micelles	127
5.4	On-Chip Characterization of Micelle Formation	128
5.4.1	Investigation of Self-Assembly Kinetics with High Temporal Resolution	128
5.4.2	Integrated Microfluidic Systems for High-Throughput Screening (HTS) of Copolymer Self-Assembly	131
5.4.3	Microfluidic Study of Micelle Kinetic Stability	132
5.5	Microfluidic Replications of Physiological Barriers During Delivery of Drug to Tumor	133
5.5.1	Microfluidic Models for Drug Testing	133
5.5.2	Transport Barriers of Nanomedicine to Tumors	134
5.5.3	Study of Microfluidic Micelle/Nanoparticle Vascular Transportation	135
5.5.4	Study of Microfluidic Micelle/Nanoparticle Transvascular Transportation	137
5.5.5	Use of Microfluidic Models to Investigate Tumor Interstitial Transportation	139
5.6	Conclusion and Implications for Future Research	141
	Acknowledgment	141
	References	142
6	Antibody–Drug Conjugates	149
	<i>Xinyu Liu and Weiping Gao</i>	
6.1	Introduction	149
6.2	History of ADCs	151
6.2.1	Concept of ADCs	151
6.2.2	First-Generation ADCs	151
6.2.3	Second-Generation ADCs	152
6.3	Components of ADCs	155
6.3.1	Drug	155
6.3.2	Antibody	158
6.3.3	Linker	161
6.3.3.1	pH-Responsive Linker	161
6.3.4	Redox-Responsive Linker	161
6.3.4.1	Enzyme-Responsive Linker	162
6.3.4.2	Noncleavable Linker	164
6.3.5	Design Strategy	165
6.4	Future Directions	167
6.4.1	Site-Specific Conjugation	167
6.4.2	Pharmacokinetics	169

6.4.3	New Paradigm Development	169
	References	170
7	Nano-Photosensitizer for Imaging-Guided Tumor Phototherapy	177
	<i>Zonghai Sheng, Mingbin Zheng, and Lintao Cai</i>	
7.1	Introduction for Tumor Phototherapy	177
7.1.1	PDT	177
7.1.2	PIT	178
7.1.3	PTT	178
7.2	Functionalized Nano-Photosensitizer for Tumor Targeting	178
7.2.1	PS Conjugated with Antibody	179
7.2.2	PS-Loaded Organic Nanoparticles	179
7.2.2.1	PS-Loaded Polymeric Nanomicelles	180
7.2.2.2	PS-Loaded Protein Nanoparticles	181
7.3	Nano-photosensitizer for Photodynamic Therapy	182
7.3.1	PS Conjugated Antibody for Photodynamic Therapy	183
7.3.2	PS-Loaded Nanoparticles for Photodynamic Therapy	183
7.4	Nano-Photosensitizer for Photothermal Therapy	184
7.4.1	Organic Photosensitizer for PTT	184
7.4.2	Carbon Photosensitizer for PTT	186
7.4.3	Gold Nanostructures for PTT	188
7.4.4	Other Inorganic Nanoparticles for PTT	190
7.5	Nano-Photosensitizer for Combination Therapy	191
7.5.1	Combined Photo/Chemotherapy	192
7.5.2	Combined PTT/PDT	195
7.6	Perspective and Application	197
	References	200
8	Quantum Dots for Cancer Diagnosis	207
	<i>Min Fang, Dai-Wen Pang, and Yan Li</i>	
8.1	Introduction	207
8.2	Detection of Solid Tumor Based on QDs	209
8.2.1	Breast Cancer (BC)	209
8.2.2	Prostate Cancer (PC)	212
8.2.3	Ovarian Cancer	212
8.2.4	Pancreatic Cancer	212
8.2.5	Liver Cancer	213
8.2.6	Lung Cancer	213
8.2.7	Other Tumors	215
8.3	SLN Mapping	215
8.4	Detection of Tumor-Associated Proteins in Blood	216
8.5	Detection of CTCs	217
8.6	Tumor Microenvironment for Invasion and Metastasis	217
8.7	Challenges of QDs into Clinical Practice Application	220

8.7.1	Biosafety	220
8.7.2	Stability and Reproducibility, Concordance, and Standard	221
8.8	Summary	221
	References	221
9	Luminescent Gold Nanoclusters for Biomedical Diagnosis	227
	<i>Hui Jiang and Xuemei Wang</i>	
9.1	Gold Nanostructures in Biomedical Diagnosis	227
9.2	Luminescent Au NCs for Biosensing	227
9.2.1	Detection of Reactive Oxygen Species (ROS) and Antioxidants	228
9.2.2	Detection of Heavy Metal Ions	228
9.2.3	Detection of Virus, Bacteria, and Cells	230
9.3	Au NCs for Cell Imaging	231
9.3.1	Thiols Stabilized Au NCs	231
9.3.2	Other Small-Molecule-Stabilized Au NCs	234
9.3.3	Protein-Stabilized Au NCs	236
9.3.4	Polymer-Coated Au NCs	240
9.4	Au NCs for <i>In Vivo</i> Imaging	241
9.5	Perspectives	245
	References	247
10	Nanographene in Biomedical Applications	251
	<i>Kai Yang and Zhuang Liu</i>	
10.1	Introduction	251
10.2	Nanographene for Drug Delivery	251
10.3	Nanographene for Gene Delivery	253
10.4	Graphene-Based Nanocomposite for Drug Delivery	255
10.5	Nanographene for Phototherapies of Cancer	259
10.5.1	Photothermal Therapy	259
10.5.2	Photodynamic Therapy	260
10.5.3	Combined Therapy Based on Nanographene	262
10.6	Graphene and its Nanocomposites for Biomedical Imaging and Imaging-Guided Therapy	263
10.6.1	Biomedical Imaging using Functionalized Nanographene	263
10.6.2	Graphene-Based Nanocomposites for Biomedical Imaging and Imaging-Guided Therapy	266
10.7	Toxicity of Nanographene	268
10.7.1	Cytotoxicity of Pristine Graphene and GO in Cell Culture	270
10.7.2	Cytotoxicity of Functionalized GO (Protein Coating, PEG Coating, etc.)	273
10.7.3	<i>In Vivo</i> Toxicity of GO and Functionalized GO After Intravenous Injection	273
10.7.4	Pulmonary Toxicity	276
10.8	Prospects and Challenges	276
	References	278

11	Molecular Imprinting Technique for Biomimetic Sensing and Diagnostics	283
	<i>Huiqi Zhang, Man Zhao, and Yaqiong Yang</i>	
11.1	Introduction	283
11.2	Molecularly Imprinted Polymers (MIPs)	283
11.3	MIPs for Biomimetic Sensing and Diagnostics	286
11.3.1	MIP-Based Electrochemical Sensors	287
11.3.2	MIP-Based Fluorescent Sensors	292
11.3.2.1	MIP-Based Fluorescent Sensors by Using Organic Fluorophores	293
11.3.2.2	MIP-Based Fluorescent Sensors by Using Quantum Dots (QDs)	297
11.3.3	MIP-Based SPR Sensors	300
11.3.4	MIP-Based QCM Sensors	305
11.4	Conclusions and Outlook	309
	Acknowledgments	311
	References	311
12	Magnetic Nanostructures for MRI-Based Cancer Detection	327
	<i>Yanglong Hou and Jing Yu</i>	
12.1	Introduction	327
12.2	Chemical Synthesis of Magnetic Nanostructures	328
12.2.1	Metal Nanoparticles	328
12.2.1.1	Iron Nanoparticles	328
12.2.1.2	Cobalt and Nickel Nanoparticles	332
12.2.2	Alloys	333
12.2.3	Metal Oxides	335
12.2.4	Metal Carbides	340
12.3	Magnetic Nanostructures for MRI-Based Cancer Detection	344
12.3.1	T ₂ -Weighted MRI Contrast Agents	344
12.3.2	T ₁ -Weighted MRI Contrast Agents	350
12.4	Conclusions and Perspective	354
	Acknowledgments	355
	References	355
13	Magnetic Iron Oxide Nanoparticles: Bioapplications and Potential Toxicity	361
	<i>Hongying Su, Yun Zeng, Chengchao Chu, and Gang Liu</i>	
13.1	Introduction	361
13.2	Bioapplications of Magnetic Iron Oxide Nanoparticles	362
13.2.1	MRI Contrast Agent	362
13.2.2	Drug Delivery	364
13.2.3	Gene Delivery	366
13.2.4	Cell Labeling and Tracking	367
13.2.5	Hyperthermia	368

13.3	Potential Toxicity of Magnetic Iron Oxide Nanoparticles	369
13.3.1	Metabolism of Magnetic Iron Oxide Nanoparticles	369
13.3.2	Mechanism of Nanotoxicity	370
13.3.3	Parameters Affecting Toxicity of Nanoparticles	371
13.3.3.1	Effect of Dose	372
13.3.3.2	Effect of Particle Size	372
13.3.3.3	Effect of Surface Charge	373
13.3.3.4	Effect of Surface Coating	374
13.3.4	Protocols for Nanotoxicity Assessment	375
13.3.4.1	<i>In Vitro</i> Cytotoxicity Test	375
13.3.4.2	<i>In Vivo</i> Toxicity Test	376
13.4	Surface Engineering for Bioapplications	377
13.5	Conclusion	379
	Acknowledgments	379
	References	379
14	Nanostructured Hydrogels for Diabetic Management	387
	<i>Ying Guan and Yongjun Zhang</i>	
14.1	Introduction	387
14.2	Nanostructured Hydrogels for Insulin Releasing	388
14.2.1	Glucose-Sensitive Microgels	390
14.2.2	Glucose-Sensitive Layer-by-Layer Assembled Hydrogel Films	392
14.3	Nanostructured Hydrogels for Glucose Sensing	396
14.4	Nanostructured Hydrogels in Artificial Pancreas	403
14.4.1	Hydrogels for the Generation of β -Cell Spheroids	403
14.4.2	Hydrogels for Microencapsulation of Islets	404
14.4.3	LBL Hydrogel Films for Conformal Coating of Islets	407
14.5	Conclusions and Outlook	411
	References	412
15	Inorganic Nanomaterials for Bone Tissue Engineering	421
	<i>Yongxiang Luo, Chengtie Wu, and Jiang Chang</i>	
15.1	Introduction	421
15.2	Calcium Phosphate Nanomaterials for Bone Tissue Engineering	422
15.2.1	Nano-CaP Particles	422
15.2.1.1	Control Synthesis of Nano-CaP Particles	422
15.2.1.2	Interaction of CaP Nanoparticles with Bone Cells	423
15.2.2	Nano-CaP Particle/Polymer Composite	424
15.2.2.1	Preparation of Nano-CaP/Polymer Composites	424
15.2.2.2	Interaction of Nano-CaP/Polymer Composites with Bone Cells	426
15.2.2.3	<i>In Vivo</i> Study of Nano-CaP/Polymer Composites	426
15.3	CaP Blocks and Scaffolds with Surface Nanostructure	427
15.3.1	Preparation of CaP Blocks and Scaffolds with Surface Nanostructures	427

15.3.2	Interaction of Nanostructured Surface of CaP Blocks and Scaffolds with Bone Cells	428
15.3.3	<i>In Vivo</i> Study of Surface Nanostructured CaP Block and Scaffolds	429
15.4	Mesoporous Bioactive Glasses for Bone Tissue Engineering	430
15.5	Conclusions	431
	Acknowledgments	432
	References	432
16	Nanotechnology in Coronary Artery Stent Coating	437
	<i>Tao Liu and Junying Chen</i>	
16.1	Introduction	437
16.2	Biodegradable Polymer Coating	438
16.3	Nanocomposite Stent Coating	440
16.3.1	Carbon-Based Nanocomposites	440
16.3.2	Titanium Oxide Nanocomposites	442
16.3.3	POSS-Based Nanocomposite	443
16.4	Nanostructure in Stent Coating	443
16.4.1	Nanoporous and Nanotube	443
16.4.2	Nanoparticles	446
16.5	Bioactive Nanocoating	449
16.5.1	Extracellular Matrix Protein Coating	449
16.5.2	Cell Capture Nanocoating	451
16.5.3	Biological Induction Nanocoating	452
16.6	Summary and Future Outlook	453
	References	455
	Index	465

