

# Contents

<b>List of Contributors</b> .....	xvii
<b>Foreword</b> .....	xxi
<b>Preface</b> .....	xxiii
<b>I. Cell-based Therapeutics</b> .....	1
<b>1. Nano- and Micro-Technology to Spatially and Temporally Control Proteins for Neural Regeneration</b> .....	3
<i>Anjana Jain and Ravi V. Bellamkonda</i>	
1.1 Introduction.....	3
1.1.1 Response after Injury in CNS and PNS.....	4
1.1.2 Nano- and Micro-scale Strategies to Promote Axonal Outgrowth in the CNS and PNS.....	4
1.2 Spatially Controlling Proteins.....	6
1.2.1 Spatial Control: Permissive Bioactive Hydrogel Scaffolds for Enhanced Regeneration.....	7
1.2.2 Spatial Control: Chemical vs. Photochemical Crosslinkers for Immobilization of Bioactive Agents.....	8
1.2.3 Other Hydrogel Scaffolds.....	10
1.2.4 Spatial Control: Contact Guidance as a Strategy to Promote Regeneration.....	10
1.2.5 Spatial Control: Nerve Guide Conduits Provide an Environment for Axonal Regeneration.....	11
1.2.6 Spatial Control: Cell-scaffold Constructs as a Way of Combining Permissive Substrates with Stimuli for Regeneration.....	12
1.3 Temporally Controlling the Release of Proteins.....	13
1.3.1 Temporal Control: Osmotic Pumps Release Protein to Encourage Axonal Outgrowth.....	14
1.3.2 Temporal Control: Slow Release of Trophic Factors Using Microspheres.....	15
1.3.3 Temporal Control: Lipid Microtubules for Sustained Release of Stimulatory Trophic Factors.....	16
1.3.4 Temporal Control: Demand Driven Release of Trophic Factors.....	17

1.4 Conclusion .....	17
References.....	18
<b>2. 3-D Fabrication Technology for Tissue Engineering</b> .....	<b>23</b>
<i>Alice A. Chen, Valerie Liu Tsang, Dirk Albrecht, and Sangeeta N. Bhatia</i>	
2.1 Introduction .....	23
2.2 Fabrication of Acellular Constructs .....	24
2.2.1 Heat-Mediated 3D Fabrication .....	24
2.2.2 Light-Mediated Fabrication .....	27
2.2.3 Adhesive-Mediated Fabrication .....	28
2.2.4 Indirect Fabrication by Molding .....	29
2.3 Fabrication of Cellular Constructs .....	30
2.4 Fabrication of Hybrid Cell/Scaffold Constructs .....	31
2.4.1 Cell-laden Hydrogel Scaffolds by Molding .....	31
2.4.2 Cell-laden Hydrogel Scaffolds by Photopatterning .....	32
2.5 Future Directions .....	34
Acknowledgements.....	36
References.....	36
<b>3. Designed Self-assembling Peptide Nanobiomaterials</b> .....	<b>39</b>
<i>Shuguang Zhang and Xiaojun Zhao</i>	
3.1 Introduction .....	40
3.2 Peptide as Biological Material Construction Units .....	40
3.2.1 Lego Peptide .....	41
3.2.2 Surfactant/detergent Peptides .....	42
3.2.3 Molecular Ink Peptides .....	45
3.3 Peptide Nanofiber Scaffold for 3-D Cell Culture, Tissue Engineering and Regenerative Medicine .....	47
3.3.1 Ideal Synthetic Biological Scaffolds .....	47
3.3.2 Peptide Scaffolds .....	48
3.3.3 PuraMatrix <i>in vitro</i> Cell Culture Examples .....	49
3.3.4 Extensive Neurite Outgrowth and Active Synapse Formation on PuraMatrix .....	50
3.3.5 Compatible with Bioproduction and Clinical Application .....	51
3.3.6 Synthetic Origin and Clinical-Grade Quality .....	51
3.3.7 Tailor-Made PuraMatrix .....	51
3.4 Peptide Surfactants/Detergents Stabilize Membrane Proteins .....	52
3.5 Perspective and Remarks .....	52
Acknowledgements.....	53
References.....	53
<b>4. At the Interface: Advanced Microfluidic Assays for Study of Cell Function</b>	<b>55</b>
<i>Yoko Kamotani, Dongeun Huh, Nobuyuki Futai, and Shuichi Takayama</i>	
4.1 Introduction .....	55
4.2 Microfabrication .....	56
4.2.1 Soft Lithography .....	57

4.3	Microscale Phenomena .....	58
4.3.1	Scaling Effects .....	59
4.3.2	Laminar Flow .....	59
4.3.3	Surface Tension .....	60
4.4	Examples of Advanced Microfluidic Cellular Bioassays .....	61
4.4.1	Patterning with Individual Microfluidic Channels .....	61
4.4.2	Multiple Laminar Streams .....	63
4.4.3	PARTCELL .....	66
4.4.4	Microscale Integrated Sperm Sorter (MISS) .....	68
4.4.5	Air-Sheath Flow Cytometry .....	69
4.4.6	Immunoassays .....	71
4.5	Conclusion .....	75
	References .....	75
<b>5.</b>	<b>Multi-phenotypic Cellular Arrays for Biosensing</b> .....	<b>79</b>
	<i>Laura J. Itle, Won-Gun Koh, and Michael V. Pishko</i>	
5.1	Introduction .....	79
5.2	Fabrication of Multi-Phenotypic Arrays .....	81
5.2.1	Surface Patterning .....	81
5.2.2	Photolithography .....	81
5.2.3	Soft Lithography .....	82
5.2.4	Poly(ethylene) Glycol Hydrogels .....	83
5.3	Detection methods for cell based sensors .....	84
5.3.1	Microelectronics .....	84
5.3.2	Fluorescent Markers For Gene Expression and Protein Up-regulation .....	84
5.3.3	Intracellular Fluorescent Probes for Small Molecules .....	86
5.4	Current Examples of Multi-Phenotypic Arrays .....	87
5.5	Future Work .....	88
	References .....	90
<b>6.</b>	<b>MEMS and Neurosurgery</b> .....	<b>95</b>
	<i>Shuvo Roy, Lisa A. Ferrara, Aaron J. Fleischman, and Edward C. Benzel</i>	
	Part I: Background .....	95
6.1	What is Neurosurgery? .....	95
6.2	History of Neurosurgery .....	95
6.3	Conventional Neurosurgical Treatments .....	99
6.3.1	Hydrocephalus .....	99
6.3.2	Brain Tumors .....	101
6.3.3	Parkinson Disease .....	103
6.3.4	Degenerative Disease of the Spine .....	104
6.4	Evolution of Neurosurgery .....	106
	Part II: Applications .....	107
6.5	MEMS for Neurosurgery .....	107
6.6	Obstacles to Neurosurgical Employment of MEMS .....	108
6.6.1	Biocompatibility Assessment .....	109

6.7 Opportunities .....	110
6.7.1 Intracranial Pressure Monitoring .....	110
6.7.2 Neural Prostheses .....	112
6.7.3 Drug Delivery Systems .....	113
6.7.4 Smart Surgical Instruments and Minimally Invasive Surgery .....	114
6.7.5 In Vivo Spine Biomechanics .....	116
6.7.6 Neural Regeneration .....	118
6.8 Prospects for MEMS in Neurosurgery .....	120
Acknowledgements .....	120
References .....	120
<b>II. Drug Delivery .....</b>	<b>125</b>
<b>7. Vascular Zip Codes and Nanoparticle Targeting .....</b>	<b>127</b>
<i>Erkki Ruoslahti</i>	
7.1 Introduction .....	127
7.2 In vivo Phage Display in Vascular Analysis .....	128
7.3 Tissue-Specific Zip Codes in Blood Vessels .....	128
7.4 Special Features of Vessels in Disease .....	129
7.5 Delivery of Diagnostic and Therapeutic Agents to Vascular Targets .....	131
7.6 Homing Peptides for Subcellular Targeting .....	131
7.7 Nanoparticle Targeting .....	132
7.8 Future Directions .....	133
Acknowledgements .....	134
References .....	134
<b>8. Engineering Biocompatible Quantum Dots for Ultrasensitive, Real-Time Biological Imaging and Detection .....</b>	<b>137</b>
<i>Wen Jiang, Anupam Singhal, Hans Fischer, Sawitri Mardiyani, and     Warren C. W. Chan</i>	
8.1 Introduction .....	137
8.2 Synthesis and Surface Chemistry .....	138
8.2.1 Synthesis of QDs that are Soluble in Organic Solvents .....	138
8.2.2 Modification of Surface Chemistry of QDs for Biological Applications .....	141
8.3 Optical Properties .....	142
8.4 Applications .....	146
8.4.1 In Vitro Immunoassays & Nanosensors .....	146
8.4.2 Cell Labeling and Tracking Experiments .....	149
8.4.3 In Vivo Live Animal Imaging .....	150
8.5 Future Work .....	152
Acknowledgements .....	152
References .....	152

<b>9. Diagnostic and Therapeutic Applications of Metal Nanoshells</b> .....	157
<i>Leon R. Hirsch, Rebekah A. Drezek, Naomi J. Halas, and Jennifer L. West</i>	
9.1 Metal Nanoshells .....	157
9.2 Biomedical Applications of Gold Nanoshells .....	161
9.2.1 Nanoshells for Immunoassays .....	161
9.2.2 Photothermally-modulated Drug Delivery Using Nanoshell-Hydrogel Composites .....	162
9.2.3 Photothermal Ablation .....	165
9.2.4 Nanoshells for Molecular Imaging .....	166
References .....	168
<b>10. Nanoporous Microsystems for Islet Cell Replacement</b> .....	171
<i>Tejal A. Desai, Teri West, Michael Cohen, Tony Boiarski, and Arfaan Rampersaud</i>	
10.1 Introduction .....	171
10.1.1 The Science of Miniaturization (MEMS and BioMEMS) .....	171
10.1.2 Cellular Delivery and Encapsulation .....	172
10.1.3 Microfabricated Nanoporous Biocapsule .....	174
10.2 Fabrication of Nanoporous Membranes .....	175
10.3 Biocapsule Assembly and Loading .....	178
10.4 Biocompatibility of Nanoporous Membranes and Biocapsular Environment .....	179
10.5 Microfabricated Biocapsule Membrane Diffusion Studies .....	181
10.5.1 IgG Diffusion .....	183
10.6 Matrix Materials Inside the Biocapsule .....	185
10.6.1 In-Vivo Studies .....	187
10.6.2 Histology .....	188
Conclusion .....	189
Acknowledgements .....	189
References .....	189
<b>11. Medical Nanotechnology and Pulmonary Pathology</b> .....	193
<i>Amy Pope-Harman and Mauro Ferrari</i>	
11.1 Introduction .....	193
11.1.1 Today's Medical Environment .....	194
11.1.2 Challenges for Pulmonary Disease-Directed Nanotechnology Devices .....	195
11.2 Current Applications of Medical Technology in the Lungs .....	196
11.2.1 Molecularly-derived Therapeutics .....	196
11.2.2 Liposomes .....	197
11.2.3 Devices with Nanometer-scale Features .....	198
11.3 Potential uses of Nanotechnology in Pulmonary Diseases .....	198
11.3.1 Diagnostics .....	198
11.3.2 Therapeutics .....	200
11.3.3 Evolving Nanotechnology in Pulmonary Diseases .....	203
11.4 Conclusion .....	207
References .....	208

<b>12. Nanodesigned Pore-Containing Systems for Biosensing and Controlled Drug Release</b> .....	213
<i>Frédérique Cunin, Yang Yang Li, and Michael J. Sailor</i>	
12.1 System Design Considerations .....	214
12.2 Porous Material-Based Systems .....	214
12.3 Silicon-Based Porous Materials .....	215
12.4 “Obedient” Materials .....	216
12.5 Porous Silicon .....	216
12.6 Templated Nanomaterials .....	217
12.7 Photonic Crystals as Self-Reporting Biomaterials .....	217
12.8 Using Porous Si as a Template for Optical Nanostructures .....	217
12.9 Outlook for Nanotechnology in Pharmaceutical Research .....	219
Acknowledgements .....	219
References .....	220
<b>13. Transdermal Drug Delivery using Low-Frequency Sonophoresis</b> .....	223
<i>Samir Mitragotri</i>	
13.1 Introduction .....	223
13.1.1 Avoiding Drug Degradation in Gastrointestinal Tract .....	223
13.1.2 Better Patient Compliance .....	223
13.1.3 Sustained Release of the Drug can be Obtained .....	224
13.2 Ultrasound in Medical Applications .....	224
13.3 Sonophoresis: Ultrasound-Mediated Transdermal Transport .....	224
13.4 Low-Frequency Sonophoresis .....	225
13.5 Low-Frequency Sonophoresis: Choice of Parameters .....	226
13.6 Macromolecular Delivery .....	226
13.6.1 Peptides and Proteins .....	226
13.6.2 Low-molecular Weight Heparin .....	227
13.6.3 Oligonucleotides .....	228
13.6.4 Vaccines .....	228
13.7 Transdermal Glucose Extraction Using Sonophoresis .....	229
13.8 Mechanisms of Low-Frequency Sonophoresis .....	230
13.9 Conclusions .....	232
References .....	232
<b>14. Microdevices for Oral Drug Delivery</b> .....	237
<i>Sarah L. Tao and Tejal A. Desai</i>	
14.1 Introduction .....	237
14.1.1 Current Challenges in Drug Delivery .....	237
14.1.2 Oral Drug Delivery .....	238
14.1.3 Bioadhesion in the Gastrointestinal Tract .....	238
14.1.4 Microdevice Technology .....	240
14.2 Materials .....	241
14.2.1 Silicon Dioxide .....	242

14.2.2 Porous Silicon .....	242
14.2.3 Poly(methyl methacrylate) .....	242
14.3 Microfabrication .....	243
14.3.1 Silicon Dioxide [23] .....	243
14.3.2 Porous Silicon [25] .....	244
14.3.3 Pol(methyl methacrylate) [24] .....	246
14.4 Surface Chemistry .....	247
14.4.1 Aimine Functionalization .....	249
14.4.2 Avidin Immobilization .....	251
14.4.3 Lectin Conjugation .....	251
14.5 Surface Characterization .....	251
14.6 Microdevice Loading and Release Mechanisms .....	253
14.6.1 Welled Silicon Dioxide and PMMA Microdevices .....	254
14.6.2 Porous Silicon Microdevices .....	254
14.6.3 CACO-2 In Vitro Studies .....	255
14.6.4 Cell Culture Conditions .....	255
14.6.5 Assessing Confluency and Tight Junction Formation .....	256
14.6.6 Adhesion of Lectin-Modified Microdevices .....	256
14.6.7 Bioavailability Studies .....	257
Acknowledgements .....	258
References .....	259
<b>15. Nanoporous Implants for Controlled Drug Delivery .....</b>	<b>263</b>
<i>Tejal A. Desai, Sadhana Sharma, Robbie J. Walczak, Anthony Boiarski, Michael Cohen, John Shapiro, Teri West, Kristie Melnik, Carlo Cosentino, Piyush M. Sinha, and Mauro Ferrari</i>	
15.1 Introduction .....	263
15.1.1 Concept of Controlled Drug Delivery .....	263
15.1.2 Nanopore Technology .....	264
15.1.3 Comparison of Nanopore Technology with Existing Drug Delivery Technologies .....	267
15.2 Fabrication of Nanoporous Membranes .....	269
15.3 Implant Assembly and Loading .....	271
15.4 Nanoporous Implant Diffusion Studies .....	271
15.4.1 Interferon Release Data .....	272
15.4.2 Bovine Serum Albumin Release Data .....	273
15.4.3 Results Interpretation .....	275
15.4.4 Modeling and Data Fitting .....	276
15.5 Biocompatibility of Nanoporous Implants .....	277
15.5.1 In Vivo Biocompatibility Evaluation .....	278
15.5.2 Long-Term Lysozyme Diffusion Studies .....	279
15.5.3 In Vivo/In Vitro Correlation .....	281
15.5.4 Post-Implant Diffusion Data .....	282
15.6 Conclusions .....	283
References .....	283

<b>III. Molecular Surface Engineering for the Biological Interface</b> .....	287
<b>16. Micro and Nanoscale Smart Polymer Technologies in Biomedicine</b> .....	289
<i>Samarth Kulkarni, Noah Malmstadt, Allan S. Hoffman, and Patrick S. Stayton</i>	
16.1 Smart Polymers .....	290
16.1.1 Mechanism of Aggregation .....	290
16.2 Smart Meso-Scale Particle Systems .....	291
16.2.1 Introduction .....	291
16.2.2 Preparation of PNIPAAm-Streptavidin Particle System .....	293
16.2.3 Mechanism of Aggregation .....	293
16.2.4 Properties of PNIPAAm-Streptavidin Particle System .....	293
16.2.5 Protein Switching in Solution using Aggregation Switch .....	294
16.2.6 Potential uses of Smart Polymer Particles in Diagnostics and Therapy .....	296
16.3 Smart Bead Based Microfluidic Chromatography .....	296
16.3.1 Introduction .....	296
16.3.2 Preparation of Smart Beads .....	297
16.3.3 Microfluidic Devices for Bioanalysis .....	298
16.3.4 Microfluidic Affinity Chromatography Using Smart Beads .....	298
16.3.5 Microfluidic Immunoassay Using Smart Beads .....	301
16.3.6 Smart Polymer Based Microtechnology—Future Outlook .....	301
Acknowledgements .....	301
References .....	302
<b>17. Supported Lipid Bilayers as Mimics for Cell Surfaces</b> .....	305
<i>Jay T. Groves</i>	
17.1 Introduction .....	305
17.2 Physical Characteristics .....	306
17.3 Fabrication Methodologies .....	310
17.4 Applications .....	313
17.4.1 Membrane Arrays .....	313
17.4.2 Membrane-Coated Beads .....	314
17.4.3 Electrical Manipulation .....	316
17.4.4 Live Cell Interactions .....	317
17.5 Conclusion .....	319
References .....	320
<b>18. Engineering Cell Adhesion</b> .....	325
<i>Kiran Bhadriraju, Wendy Liu, Darren Gray, and Christopher S. Chen</i>	
18.1 Introduction .....	325
18.2 Regulating Cell Function via the Adhesive Microenvironment .....	327
18.3 Controlling Cell Interactions with the Surrounding Environment .....	330
18.3.1 Creating Defined Surface Chemistries .....	330
18.3.2 The Development of Surface Patterning .....	332
18.3.3 Examples of Patterning-Based Studies on Cell-To-Cell Interactions .....	333
18.3.4 Examples of Patterning-Based Studies on Cell-Matrix Interactions .....	336
18.4 Future Work .....	337
18.4.1 Developing New Materials .....	337
18.4.2 Better Cell Positioning Technologies .....	338

18.4.3	Patterning in 3D Environments .....	338
18.4.4	Patterning Substrate Mechanics .....	339
18.5	Conclusions .....	339
	References .....	340
<b>19.</b>	<b>Cell Biology on a Chip</b> .....	<b>345</b>
	<i>Albert Folch and Anna Tourovskaia</i>	
19.1	Introduction .....	345
19.2	The Lab-on-a-chip Revolution .....	346
19.3	Increasing Experimentation Throughput .....	347
19.3.1	From Serial Pipetting to Highly Parallel Micromixers .....	347
19.3.2	From Incubators to “Chip-Cubators” .....	349
19.3.3	From High Cell Numbers in Large Volumes (and Large Areas) to Low Cell Numbers in Small Volumes (and Small Areas) .....	349
19.3.4	From Milliliters to Microliters or Nanoliters .....	350
19.3.5	From Manual/Robotic Pipetting to Microfluidic Pumps and Valves .....	351
19.3.6	Single-Cell Probing and Manipulation .....	354
19.4	Increasing the Complexity of the Cellular Microenvironment .....	354
19.4.1	From Random Cultures to Microengineered Substrates .....	355
19.4.2	From “Classical” to “Novel” Substrates .....	356
19.4.3	From Cells in Large Static Volumes to Cells in Small Flowing Volumes .....	359
19.4.4	From a Homogeneous Bath to Microfluidic Delivery of Biochemical Factors .....	359
19.5	Conclusion .....	360
	References .....	360
	<b>About the Editors</b> .....	<b>365</b>
	<b>Index</b> .....	<b>367</b>