

Contents

List of Contributors XI

About the Series Editors XVII

Preface XIX

Part I Microsystems for Single-Cell Analysis I

1	Types of Clinical Samples and Cellular Enrichment Strategies 3
	<i>Koh Meng Aw Yong, Zeta Tak For Yu, Krystal Huijiao Guan, and Jianping Fu</i>
1.1	Introduction 3
1.2	Types of Clinical Samples 4
1.2.1	Solid Clinical Samples 4
1.2.1.1	Cellular Subtypes Found in Solid Clinical Samples 5
1.2.2	Liquid Clinical Samples and Cellular Subtypes 8
1.2.2.1	Blood 8
1.2.2.2	Bone Marrow 9
1.2.2.3	Placental or Umbilical Cord Blood 10
1.2.2.4	Urine 10
1.2.2.5	Cerebrospinal Fluid (CSF) 10
1.2.2.6	Saliva 11
1.3	Sample Processing and Conventional Methods of Cell Enrichment 11
1.3.1	Processing Solid Clinical Samples 11
1.3.1.1	Processing Liquid Samples 12
1.3.2	Cell Enrichment 12
1.3.2.1	Laser Capture Microdissection (LCM) 12
1.3.2.2	Density Gradient Centrifugation 13
1.3.2.3	Fluorescence-Activated Cell Sorting (FACS) 13
1.3.2.4	Magnetic Activated Cell Sorting (MACS) 15
1.3.2.5	CellSearch TM 15
1.4	Microscale/Nanoscale Devices for Cellular Enrichment 16
1.4.1	Filtration Approaches 16
1.4.2	Hydrodynamic Mechanisms 17
1.4.3	Surface Treatments 19

1.4.4	Magnetophoresis	19
1.4.5	Electrophoresis	20
1.4.6	Acoustophoresis	21
1.4.7	Optical Tweezers/Traps	22
1.5	Conclusion	23
	References	23
2	Genome-Wide Analysis of Single Cells and the Role of Microfluidics	29
	<i>Sayantan Bose and Peter A. Sims</i>	
2.1	Motivation for Single-Cell Analysis of Genomes and Transcriptomes	29
2.2	Single-Cell Genomics	30
2.2.1	Major Technical Challenges	30
2.2.2	Approaches to Single-Cell Genomics	31
2.2.3	The Application and Impact of Microfluidics in Single-Cell Genomics	34
2.3	Single-Cell Transcriptomics	36
2.3.1	Major Technical Challenges	36
2.3.2	Approaches to Single-Cell Transcriptomics	39
2.3.3	Application and Impact of Microfluidics in Single-Cell Transcriptomics	42
2.4	The Future of Genome-Wide Single-Cell Analysis with Microfluidics	45
2.4.1	Recent Advances in the Scalability of Single-Cell Analysis using Microfluidics	45
2.4.2	How Microfluidics will Expand the Application-Space for Single-Cell Analysis	46
2.4.3	Outstanding Hurdles for Genome-Wide Analysis of Single Cells	47
2.4.4	Prospects for Clinical Applications of Microfluidic Single-Cell Analysis	48
	Keywords and Definitions	48
	References	49
3	Cellular Immunophenotyping: Industrial Technologies and Emerging Tools	57
	<i>Kara Brower and Rong Fan</i>	
3.1	Cellular Immune Status and Immunophenotyping	57
3.2	Surface Marker Phenotyping	60
3.2.1	Multicolor Flow Cytometry	60
3.2.2	Commercial Flow Cytometers	62
3.2.3	High-Content Imaging Cytometry	63
3.2.4	Current Limitations and Further Development of Flow Cytometry	64
3.3	Functional Phenotyping	65

3.3.1	ELISpot Technologies	66
3.3.2	Multiplexed Immunoassays	67
3.3.3	Emerging Single-Cell Technologies	68
3.4	Conclusion	70
	Keywords and Definitions	71
	References	71
4	Microsystem Assays for Studying the Interactions between Single Cells	75
	<i>Vandana Kaul and Navin Varadarajan</i>	
4.1	Introduction	75
4.2	Advantages of Single-Cell Analysis over Conventional Assay Systems	80
4.3	Analysis of Cell–Cell Communication between Pairs of Single Cells	81
4.3.1	Integrated Microfluidic Coculture Systems and Microwell Arrays	81
4.3.1.1	Microengraving	81
4.3.1.2	T-Cell Proliferation	82
4.3.1.3	T-Cell Cytotoxicity	82
4.3.1.4	NK-Cell Cytotoxicity	84
4.3.1.5	High-Throughput Stem Cell Coculture Array	84
4.3.1.6	Microfluidics-Based Single-Cell RNA-seq for Intercellular Communication	85
4.3.1.7	Single-Cell Signaling Chip	85
4.3.2	DEP Arrays	87
4.3.2.1	Tumor Cell–Endothelial Cell Interaction	87
4.3.2.2	Immune-Cell Cytotoxicity	88
4.3.3	Microfluidic Hydrodynamic Trapping	89
4.3.3.1	Sequential Hydrodynamic Trapping Device	89
4.3.3.2	Intercellular Communication via Gap Junctions	89
4.3.3.3	Cell–Cell Fusion	90
4.3.4	Optical Methods	91
4.3.4.1	Laser-Guided Cell Micropatterning	91
4.3.4.2	Optical Tweezers	91
4.3.4.3	Optoelectronic Tweezers	93
4.3.5	Magnetic Methods	93
4.3.5.1	Magnetic Pattern Arrays	94
4.3.5.2	Magnetic Microflaps	94
4.3.6	Acoustic Methods	94
4.3.6.1	Ultrasonic Standing Waves (USWs) for 2D and 3D Cell–Cell Interaction	95
4.3.6.2	Standing Surface Acoustic Waves for Cell Patterning	96
4.3.6.3	Ultrasonic-Based Method for Cell–Cell Interactions in Microwell Arrays	96

4.4	Conclusions 97
	Acknowledgments 98
	References 98
5	Modeling Microvascular Disease 105
	<i>Hope K.A. Gole and Wilbur A. Lam</i>
5.1	Introduction 105
5.2	Microvascular Disease 106
5.3	Macromodeling 107
5.4	Micromodeling 109
5.4.1	Fabrication 110
5.4.2	Design and General Applications 112
5.4.3	Disease-Specific Applications 115
5.4.4	Advantages and Disadvantages 120
5.5	Summary 122
	References 122
Part II Tiny Technologies for Modulating Biological Systems 127	
6	Nanotechnologies for the Bioelectronic Interface 129
	<i>Benjamin W. Avants, Hongkun Park, and Jacob T. Robinson</i>
6.1	Introduction 129
6.2	Modeling the Bioelectronic Interface 130
6.3	Experimental Approaches for Extra-Cellular Coupling 132
6.4	State-of-the-Art Extra-Cellular Nanoscale Interfaces 133
6.5	Experimental Approaches for Intra-Cellular Coupling 134
6.6	State-of-the-Art Intra-Cellular Nanoscale Interfaces 135
6.7	Experimental Approaches for In-Cell Coupling 137
6.8	Outlook 138
	References 139
7	Intracellular Delivery of Biomolecules by Mechanical Deformation 143
	<i>Armon Sharei, Shirley Mao, Robert Langer, and Klavs F. Jensen</i>
7.1	Introduction 143
7.2	Delivery Concept 148
7.2.1	Design 149
7.2.2	Governing Parameters 150
7.3	Cytosolic Delivery by Diffusion 151
7.3.1	Modeling Diffusion 153
7.3.2	Imaging of Membrane Disruptions 157
7.4	Applicability across Cell Types and Delivery Materials 158
7.4.1	Flexibility in Addressing Different Delivery Material 162
7.4.2	Enabling New Research and Clinical Applications 164
7.4.2.1	Cell Reprogramming 164

7.4.2.2	Quantum Dot delivery	166
7.4.2.3	Immune Cell Delivery	166
7.5	Summary	167
7.6	Appendix	169
7.6.1	Device Design Guidelines for New Cell Types	169
7.6.2	Design Parameters	169
7.6.3	Device Nomenclature	170
7.6.4	Defining Delivery Efficiency	171
7.6.5	Device Recovery	171
7.6.6	Reagent Use	171
	Acknowledgments	173
	Conflict of Interest	173
	Keywords and Definitions	174
	References	174
8	Microfluidics for Studying Pharmacodynamics of Antibiotics	177
	<i>Ritika Mohan, Amit V. Desai, Chotitath Sanpitakseree, and Paul J.A. Kenis</i>	
8.1	Background on Antibiotic Resistance	177
8.2	Methods for Antibiotic Susceptibility Testing (AST)	178
8.2.1	Conventional Methods	178
8.2.2	Integrated Microfluidic-Based Approaches	179
8.2.3	Translation of Microfluidic-Based Approaches	182
8.3	Applying Pharmacokinetics/Pharmacodynamics to AST	184
8.3.1	Significance of PK/PD	184
8.3.2	Advantages of Microfluidic-Based Approaches for PK/PD Analysis	185
8.4	Application of Microfluidic-Based Approach for PK/PD Modeling	185
8.4.1	PD Modeling	186
8.4.1.1	Monomicrobial Cultures: MIC Determination of <i>E. coli</i> against Amikacin	188
8.4.1.2	Polymicrobial AST: MIC Determination of <i>E. coli</i> and <i>P. aeruginosa</i> against Amikacin	189
8.4.2	PK Modeling	192
8.5	Summary and Future Outlook	194
	Acknowledgments	196
	References	196
9	Microsystems Models of Pathophysiology	203
	<i>Marie-Elena Brett and David K. Wood</i>	
9.1	Vascular and Hematologic Pathologies	205
9.1.1	Thrombosis	205
9.1.2	Sickle Cell Disease	208
9.1.3	Malaria	212
9.1.4	Atherosclerosis	213

9.1.5	Model Limitations and Future Opportunities	214
9.2	Organ-Specific Pathologies	217
9.2.1	Lung	218
9.2.2	Brain	220
9.2.3	Kidney	222
9.2.4	Liver	224
9.2.5	Challenges and Opportunities	226
9.2.5.1	Considerations and Challenges	227
9.2.5.2	Opportunities	230
9.3	Cancer	230
9.3.1	Microscale Tumor Models	231
9.3.2	Metastasis	232
9.3.3	Drug Delivery and Pharmacokinetics	236
9.4	Summary	237
	References	238
10	Microfluidic Systems for Whole-Animal Screening with <i>C. elegans</i>	245
	<i>Navid Ghorashian, Sertan Kural Gökçe, and Adela Ben-Yakar</i>	
10.1	Importance	245
10.2	Introduction	245
10.3	A Versatile Animal Model: <i>Caenorhabditis elegans</i> (<i>C. elegans</i>)	246
10.3.1	<i>C. elegans</i> Culturing Techniques	247
10.3.2	<i>C. elegans</i> as a Model of Neurological Disease	247
10.3.3	<i>C. elegans</i> as a Drug-Screening Model	249
10.3.4	Current State of the Art in Automated <i>C. elegans</i> Screening	249
10.4	Microfluidics	251
10.4.1	Microfluidic Device Fabrication	251
10.4.2	Fluid Dynamics Modeling in Microfluidics	252
10.4.3	Microfluidics Interfacing with Multiwell Plates	255
10.4.4	Microfluidic Flow Control and Valve Multiplexing	255
10.5	Microfluidics for <i>C. elegans</i> Biology	257
10.5.1	Microfluidic Worm Immobilization and High-Resolution Optical Interrogation Platforms	257
10.5.1.1	Single Trap Microfluidic Platforms for Worm Processing One at a Time	258
10.5.1.2	Multitrap Microfluidic Platforms to Enable Parallel Worm Processing	262
10.5.2	Microfluidic Population Delivery for Serial Processing	264
10.6	Conclusions and Future Directions	266
	Author Contributions	266
	References	266
	Index	273