# CONTENTS

**Preface** xi

**Contributors** xvii

**Part A Methods for Synthetic Extracellular Matrices and Scaffolds** 1

**1 Polymers as Materials for Tissue Engineering Scaffolds** 3
*Ana Vallés Lluch, Dunia Mercedes García Cruz, Jorge Luis Escobar Ivirico, Cristina Martínez Ramos and Manuel Monleón Pradas*

1.1 The Requirements Imposed by Application on Material Structures Intended as Tissue Engineering Scaffolds, 3
1.2 Composition and Function, 5
1.2.1 General Considerations, 5
1.2.2 Some Families of Polymers for Tissue Engineering Scaffolds, 8
1.2.3 Composite Scaffold Matrices, 12
1.3 Structure and Function, 14
1.3.1 General Considerations, 14
1.3.2 Structuring Polymer Matrices, 15
1.4 Properties of Scaffolds Relevant for Tissue Engineering Applications, 24
1.4.1 Porous Architecture, 24
1.4.2 Solid State Properties: Glass Transition, Crystallinity, 25
1.4.3 Mechanical and Structural Properties, 26
1.4.4 Swelling Properties, 28
1.4.5 Degradation Properties, 29
1.4.6 Diffusion and Permeation, 30

1.4.7 Surface Tension and Contact Angle, 31
1.4.8 Biological Properties, 31
1.5 Compound, Multicomponent Constructs, 32
1.5.1 Scaffold-Cum-Gel Constructs, 32
1.5.2 Scaffolds and Membranes Containing Microparticles, 34
1.5.3 Other Multicomponent Scaffold Constructs, 34
1.6 Questions Arising from Manipulation and Final Use, 35
1.6.1 Sterilization, 35
1.6.2 Cell Seeding, Cell Culture, Analysis, 36
1.6.3 In the Surgeon's Hands, 37
References, 37

**2 Natural-Based and Stimuli-Responsive Polymers for Tissue Engineering and Regenerative Medicine** **49**
*Mariana B. Oliveira and João F. Mano*

2.1 Introduction, 49
2.2 Natural Polymers and Their Application in TE & RM, 52
2.2.1 Polysaccharides, 52
2.2.2 Protein-Based Polymers, 60
2.2.3 Polyesters, 65
2.3 Natural Polymers in Stimuli-Responsive Systems, 65
2.3.1 pH-Sensitive Natural Polymers, 67
2.3.2 Temperature Sensitive Natural Polymers, 67
2.3.3 Natural Polymers Modified to Show Thermoresponsive Behavior—Modifying Responsive Polymers and Agents, 71
2.3.4 Light-Sensitive Polymers—Potential Use of Azobenzene/α-Cyclodextrin Inclusion Complexes, 72
2.4 Conclusions, 73
References, 74

**3 Matrix Proteins Interactions with Synthetic Surfaces** **91**
*Patricia Rico, Marco Cantini, George Altankov and Manuel Salmerón-Sánchez*

3.1 Introduction, 91
3.2 Protein Adsorption, 92
3.2.1 Cell Adhesion Proteins, 93
3.2.2 Experimental Techniques to Follow Protein Adsorption, 94
3.2.3 Effect of Surface Properties on Protein Adsorption, 97
3.3 Cell Adhesion, 109
3.3.1 Experimental Techniques to Characterize Cell Adhesion, 112
3.3.2 Cell Adhesion at Cell–Material Interface, 115
3.4 Remodeling of the Adsorbed Proteins, 122

3.4.1 Protein Reorganization and Secretion at the Cell–Material Interface, 122
3.4.2 Proteolytic Remodeling at Cell–Materials Interface, 126
References, 128

**4 Focal Adhesion Kinase in Cell–Material Interactions** **147**
*Cristina González-García, Manuel Salmerón-Sánchez and Andrés J. García*

4.1 Introduction, 147
4.2 Role of FAK in Cell Proliferation, 149
4.3 Role of FAK in Migratory and Mechanosensing Responses, 150
4.4 Role of FAK in the Generation of Adhesives Forces, 152
4.5 Influence of Material Surface Properties on FAK Signaling, 156
4.5.1 Effect of Mechanical Properties on FAK Signaling, 156
4.5.2 Effect of Surface Topography on FAK Signaling, 160
4.5.3 Effect of Surface Chemistry on FAK Signaling, 163
4.5.4 Effect of Surface Functionalization in FAK Expression, 165
References, 168

**5 Complex Cell–Materials Microenvironments in Bioreactors** **177**
*Stergios C. Dermenoudis and Yannis F. Missirlis*

5.1 Introduction, 177
5.2 Cell–ECM Interactions, 178
5.2.1 ECM Chemistry, 179
5.2.2 ECM Topography, 181
5.2.3 ECM Mechanical Properties, 183
5.2.4 ECM 3D Structure, 184
5.2.5 ECM-Induced Mechanical Stimuli, 186
5.3 Cell–Nutrient Medium, 187
5.3.1 Composition and Volume-Related Phenomena, 188
5.3.2 Mechanical Stresses Induced by Nutrient Medium, 191
5.4 Other Aspects of Interaction, 194
5.4.1 Co-Culture Systems, 195
5.4.2 Material Interactions, 196
5.5 Conclusions, 197
References, 197

**Part B Nanostructures for Tissue Engineering** **207**

**6 Self-Curing Systems for Regenerative Medicine** **209**
*Julio San Román, Blanca Vázquez and María Rosa Aguilar*

6.1 Introduction, 209
6.2 Self-Curing Systems for Hard Tissue Regeneration, 210
6.2.1 Antimicrobial Self-Curing Formulations, 211
6.2.2 Self-Curing Formulations for Osteoporotic Bone, 214

6.2.3 Antineoplastic Drug-Loaded Self-Curing Formulations, 216
6.2.4 Nonsteroidal Anti-Inflammatory Drug-Loaded Formulations, 217
6.2.5 Self-Curing Formulations with Biodegradable Components, 218
6.3 Self-Curing Hydrogels for Soft Tissue Regeneration, 219
6.3.1 Chemically Cross-Linked Hydrogels, 220
6.3.2 Chemically and Physically Cross-Linked Hydrogels, 225
6.4 Expectative and Future Directions, 226
References, 226

**7 Self-Assembling Peptides as Synthetic Extracellular Matrices 235**
*M.T. Fernandez Muiños and C.E. Semino*

7.1 Introduction, 235
7.2 *In Vitro* Applications, 238
7.3 *In Vivo* Applications, 242
References, 245

**8 Polymer Therapeutics as Nano-Sized Medicines for Tissue Regeneration and Repair 249**
*Ana Armiñán, Pilar Sepúlveda and María J. Vicent*

8.1 Polymer Therapeutics as Nano-Sized Medicines, 249
8.1.1 The Concept and Biological Rationale behind Polymer Therapeutics, 249
8.1.2 Current Status and Future Trends, 252
8.2 Polymer Therapeutics for Tissue Regeneration and Repair, 254
8.2.1 Ischemia/Reperfusion Injuries, 255
8.2.2 Wound Healing/Repair, 260
8.2.3 Musculoskeletal Disorders, 263
8.2.4 Diseases of the Central Nervous System, 267
8.3 Conclusions and Future Perspectives, 272
References, 273

**9 How Regenerative Medicine Can Benefit from Nucleic Acids Delivery Nanocarriers? 285**
*Erea Borrajo, Anxo Vidal, Maria J. Alonso and Marcos Garcia-Fuentes*

9.1 Introduction, 285
9.1.1 Learning from Viruses: How to Overcome Cellular Barriers, 286
9.2 Nanotechnology in Gene Delivery, 292
9.2.1 Lipid Nanocarriers, 292
9.2.2 Polymeric Nanocarriers, 294
9.2.3 Inorganic Nanoparticles, 300
9.3 Nanotechnology in Regenerative Medicine, 302
9.3.1 Bone Regeneration, 303
9.3.2 Cartilage Regeneration, 305
9.3.3 Tendon Regeneration, 308

9.3.4 Myocardium Regeneration, 309
9.3.5 Neurological Tissue, 311
9.4 Conclusions, 313
References, 313

**10 Functionalized Mesoporous Materials with Gate-Like Scaffoldings for Controlled Delivery** **337**
*Elena Aznar, Estela Climent, Laura Mondragon, Félix Sancenón and Ramón Martínez-Máñez*

10.1 Introduction, 337
10.2 Mesoporous Silica Materials with Gate-Like Scaffoldings, 339
10.2.1 Controlled Delivery by pH Changes, 339
10.2.2 Controlled Delivery Using Redox Reactions, 345
10.2.3 Controlled Delivery Using Photochemical Reactions, 349
10.2.4 Controlled Delivery via Temperature Changes, 352
10.2.5 Controlled Delivery Using Small Molecules, 355
10.2.6 Controlled Delivery Using Biomolecules, 356
10.3 Concluding Remarks, 360
References, 361

**11 Where Are We Going? Future Trends and Challenges** **367**
*Sang Jin Lee and Anthony Atala*

11.1 Introduction, 367
11.2 Classification of Biomaterials in Tissue Engineering and Regenerative Medicine, 368
11.2.1 Naturally Derived Materials, 368
11.2.2 Biodegradable Synthetic Polymers, 370
11.2.3 Tissue Matrices, 372
11.3 Basic Principles of Biomaterials in Tissue Engineering, 373
11.4 Development of Smart Biomaterials, 374
11.5 Scaffold Fabrication Technologies, 376
11.5.1 Injectable Hydrogels, 376
11.5.2 Electrospinning, 377
11.5.3 Computer-Aided Scaffold Fabrication, 378
11.5.4 Functionalization of Tissue-Engineered Biomaterial Scaffolds, 379
11.6 Summary and Future Directions, 381
References, 384

**Index** **391**