

Contents

Preface XVII

List of Contributors XXI

Part I Examples of Natural and Nature-Inspired Materials 1

1	Biomaterials from Marine-Origin Biopolymers 3
	<i>Tiago H. Silva, Ana R.C. Duarte, Joana Moreira-Silva, João F. Mano, and Rui L. Reis</i>
1.1	Taking Inspiration from the Sea 3
1.2	Marine-Origin Biopolymers 6
1.2.1	Chitosan 6
1.2.2	Alginate 8
1.2.3	Carrageenan 9
1.2.4	Collagen 9
1.2.5	Hyaluronic Acid 10
1.2.6	Others 11
1.3	Marine-Based Tissue Engineering Approaches 12
1.3.1	Membranes 12
1.3.2	Hydrogels 13
1.3.3	Tridimensional Porous Structures 15
1.3.4	Particles 17
1.4	Conclusions 18
	References 18
2	Hydrogels from Protein Engineering 25
	<i>Midori Greenwood-Goodwin and Sarah C. Heilshorn</i>
2.1	Introduction 25
2.2	Principles of Protein Engineering 26
2.2.1	Protein Structure and Folding 26
2.2.2	Design of Protein-Engineered Hydrogels 28
2.2.3	Production of Protein-Engineered Hydrogels 30

2.3	Structural Diversity and Applications of Protein-Engineered Hydrogels	32
2.3.1	Self-Assembled Protein Hydrogels	32
2.3.2	Covalently Cross-Linked Protein Hydrogels	38
2.4	Development of Biomimetic Protein-Engineered Hydrogels for Tissue Engineering Applications	39
2.4.1	Mechanical Properties Mediate Cellular Response	40
2.4.2	Biodegradable Hydrogels for Cell Invasion	41
2.4.3	Diverse Biochemical Cues Regulate Complex Cell Behaviors	43
2.4.3.1	Cell–Extracellular Matrix Binding Domains	43
2.4.3.2	Nanoscale Patterning of Cell–Extracellular Matrix Binding Domains	44
2.4.3.3	Cell–Cell Binding Domains	45
2.4.3.4	Delivery of Soluble Cell Signaling Molecules	46
2.5	Conclusions and Future Perspective	48
	References	49
3	Collagen-Based Biomaterials for Regenerative Medicine	55
	<i>Christophe Helary and Abhay Pandit</i>	
3.1	Introduction	55
3.2	Collagens <i>In Vivo</i>	56
3.2.1	Collagen Structure	56
3.2.2	Collagen Fibrillogenesis	56
3.2.3	Three-Dimensional Networks of Collagen in Connective Tissues	57
3.2.4	Interactions of Cells with Collagen	57
3.3	Collagen <i>In Vitro</i>	59
3.4	Collagen Hydrogels	59
3.4.1	Collagen I Hydrogels	59
3.4.1.1	Classical Hydrogels	59
3.4.1.2	Concentrated Collagen Hydrogels	61
3.4.1.3	Dense Collagen Hydrogels Obtained by Plastic Compression	61
3.4.1.4	Dense Collagen Matrices	61
3.4.2	Cross-Linked Collagen I Hydrogels	62
3.4.2.1	Chemical Cross-Linking	62
3.4.2.2	Enzymatic Cross-Linking	62
3.4.3	Collagen II Hydrogels	63
3.4.4	Aligned Hydrogels and Extruded Fibers	64
3.4.4.1	Aligned Hydrogels	64
3.4.4.2	Extruded Collagen Fibers	65
3.5	Collagen Sponges	65
3.6	Multichannel Collagen Scaffolds	66
3.6.1	Multichannel Collagen Conduits	66
3.6.2	Multi-Channeled Collagen–Calcium Phosphate Scaffolds	66
3.7	What Tissues Do Collagen Biomaterials Mimic? (see Table 3.1)	66
3.7.1	Skin	66

3.7.2	Nerves	68
3.7.3	Tendons	68
3.7.4	Bone	69
3.7.5	Intervertebral Disk	69
3.7.6	Cartilage	70
3.8	Concluding Remarks	70
	Acknowledgments	71
	References	71
4	Silk-Based Biomaterials	75
	<i>Sílvia Gomes, Isabel B. Leonor, João F. Mano, Rui L. Reis, and David L. Kaplan</i>	
4.1	Introduction	75
4.2	Silk Proteins	76
4.2.1	<i>Bombyx mori</i> Silk	76
4.2.2	Spider Silk	77
4.2.3	Recombinant Silk	79
4.3	Mechanical Properties	82
4.4	Biomedical Applications of Silk	84
4.5	Final Remarks	87
	References	88
5	Elastin-like Macromolecules	93
	<i>Rui R. Costa, Laura Martín, João F. Mano, and José C. Rodríguez-Cabello</i>	
5.1	General Introduction	93
5.2	Materials Engineering – an Overview on Synthetic and Natural Biomaterials	94
5.3	Elastin as a Source of Inspiration for Nature-Inspired Polymers	94
5.3.1	Genetic Coding	94
5.3.2	Characteristics of Elastin	95
5.3.3	Elastin Disorders	97
5.3.4	Current Applications of Elastin as Biomaterials	97
5.3.4.1	Skin	97
5.3.4.2	Vascular Constructs	98
5.4	Nature-Inspired Biosynthetic Elastins	99
5.4.1	General Properties of Elastin-like Recombinamers	99
5.4.2	The Principle of Genetic Engineering – a Powerful Tool for Engineering Materials	100
5.4.3	From Genetic Construction to Molecules with Tailored Biofunctionality	102
5.4.4	Biocompatibility of ELRs	103
5.5	ELRs as Advanced Materials for Biomedical Applications	103
5.5.1	Tissue Engineering	104
5.5.2	Drug and Gene Delivery	106
5.5.3	Surface Engineering	108

5.6	Conclusions	110
	Acknowledgements	110
	References	111
6	Biomimetic Molecular Recognition Elements for Chemical Sensing	117
	<i>Justyn Jaworski</i>	
6.1	Introduction	117
6.1.1	Overview	117
6.1.2	Biological Chemoreception	118
6.1.3	Host–Guest Interactions	119
6.1.3.1	Lock and Key	119
6.1.3.2	Induced Fit	120
6.1.3.3	Preexisting Equilibrium Model	121
6.1.4	Biomimetic Surfaces for Molecular Recognition	121
6.2	Theory of Molecular Recognition	123
6.2.1	Foundation of Molecular Recognition	123
6.2.2	Noncovalent Interactions	123
6.2.3	Thermodynamics of the Molecular Recognition Event	125
6.2.4	Putting a Figure of Merit on Molecular Recognition	127
6.2.5	Multiple Interactions: Avidity and Cooperativity	128
6.3	Molecularly Imprinted Polymers	129
6.3.1	A Brief History of Molecular Imprinting	129
6.3.2	Strategies for the Formation of Molecularly Imprinted Polymers	129
6.3.3	Polymer Matrix Design	130
6.3.4	Cross-Linking and Polymerization Approaches	131
6.3.5	Template Extraction	132
6.3.6	Limitations and Areas for Improvement	133
6.4	Supramolecular Chemistry	134
6.4.1	Introduction	134
6.4.2	Macrocyclic Effect	134
6.4.3	Chelate Effect	135
6.4.4	Preorganization, Rational Design, and Modeling	135
6.4.5	Templating Effect	136
6.4.6	Effective Supramolecular Receptors for Biomimetic Sensing	137
6.4.6.1	Calixarenes	137
6.4.6.2	Metalloporphyrins	138
6.4.7	Recent Improvement	139
6.5	Biomolecular Materials	140
6.5.1	Introduction	140
6.5.2	Native Biomolecules	141
6.5.2.1	Polypeptides	141
6.5.2.2	Carbohydrates	142
6.5.2.3	Oligonucleotides	143
6.5.3	Engineered Biomolecules	144

6.5.3.1	<i>In vitro</i> Selection of RNA/DNA Aptamers	144
6.5.3.2	Evolutionary Screened Peptides	146
6.5.3.3	Computational and Rational Design of Biomimetic Receptors	150
6.6	Summary and Future of Biomimetic-Sensor-Coating Materials	151
	References	152

Part II Surface Aspects 157

7	Biology Lessons for Engineering Surfaces for Controlling Cell–Material Adhesion	159
	<i>Ted T. Lee and Andrés J. García</i>	
7.1	Introduction	159
7.2	The Extracellular Matrix	159
7.3	Protein Structure	160
7.4	Basics of Protein Adsorption	161
7.5	Kinetics of Protein Adsorption	162
7.6	Cell Communication	164
7.6.1	Intracellular Communication	164
7.6.2	Intercellular Communication	165
7.7	Cell Adhesion Background	166
7.8	Integrins and Adhesive Force Generation Overview	167
7.9	Adhesive Interactions in Cell, and Host Responses to Biomaterials	170
7.10	Model Systems for Controlling Integrin-Mediated Cell Adhesion	170
7.11	Self-Assembling Monolayers (SAMs)	171
7.12	Real-World Materials for Medical Applications	172
7.12.1	Polymer Brush Systems	172
7.12.2	Hydrogels	173
7.13	Bio-Inspired, Adhesive Materials: New Routes to Promote Tissue Repair and Regeneration	174
7.14	Dynamic Biomaterials	176
7.14.1	Nonspecific “On” Switches	176
7.14.1.1	Electrochemical Desorption	176
7.14.1.2	Oxidative Release	177
7.14.2	Photobased Desorption	178
7.14.3	Integrin Specific “On” Switching	178
7.14.3.1	Photoactivation	178
7.14.4	Adhesion “Off” Switching	179
7.14.4.1	Electrochemical Off Switching	179
7.14.5	Reversible Adhesion Switches	181
7.14.5.1	Reversible Photoactive Switching	181
7.14.5.2	Reversible Temperature-Based Switching	182
7.14.6	Conclusions and Future Prospects	184
	References	185

8	Fibronectin Fibrillogenesis at the Cell–Material Interface	189
	<i>Marco Cantini, Patricia Rico, and Manuel Salmerón-Sánchez</i>	
8.1	Introduction	189
8.2	Cell-Driven Fibronectin Fibrillogenesis	189
8.2.1	Fibronectin Structure	190
8.2.2	Essential Domains for FN Assembly	192
8.2.3	FN Fibrillogenesis and Regulation of Matrix Assembly	194
8.3	Cell-Free Assembly of Fibronectin Fibrils	195
8.4	Material-Driven Fibronectin Fibrillogenesis	202
8.4.1	Physiological Organization of Fibronectin at the Material Interface	203
8.4.2	Biological Activity of the Material-Driven Fibronectin Fibrillogenesis	206
	References	210
9	Nanoscale Control of Cell Behavior on Biointerfaces	213
	<i>E. Ada Cavalcanti-Adam and Dimitris Missirlis</i>	
9.1	Nanoscale Cues in Cell Environment	213
9.2	Biomimetics of Cell Environment Using Interfaces	216
9.2.1	Surface Patterning Techniques at the Nanoscale	216
9.2.1.1	Surface Patterning by Nonconventional Nanolithography	216
9.2.1.2	Block Copolymer Micelle Lithography	217
9.2.2	Variation of Surface Physical Parameters at the Nanoscale	219
9.2.2.1	Surface Nanotopography	220
9.2.2.2	Interligand Spacing	221
9.2.2.3	Ligand Density	222
9.2.2.4	Substrate Mechanical Properties	223
9.2.2.5	Dimensionality	223
9.2.3	Surface Functionalization for Controlled Presentation of ECM Molecules to Cells	224
9.2.3.1	Proteins, Protein Fragments, and Peptides	224
9.2.3.2	Linking Systems	226
9.2.3.3	Modulation of Substrate Background	227
9.3	Cell Responses to Nanostructured Materials	227
9.3.1	Cell Adhesion and Migration	228
9.3.2	Cell–Cell Interactions	230
9.3.3	Cell Membrane Receptor Signaling	231
9.3.4	Applications of Nanostructures in Stem Cell Biology	232
9.4	The Road Ahead	233
	References	234
10	Surfaces with Extreme Wettability Ranges for Biomedical Applications	237
	<i>Wenlong Song, Natália M. Alves, and João F. Mano</i>	
10.1	Superhydrophobic Surfaces in Nature	237

10.2	Theory of Surface Wettability	239
10.2.1	Young's Model	239
10.2.2	Wenzel's Model	240
10.2.3	The Cassie–Baxter Model	240
10.2.4	Transition between the Cassie–Baxter and Wenzel Models	240
10.3	Fabrication of Extreme Water-Repellent Surfaces Inspired by Nature	241
10.3.1	Superhydrophobic Surfaces Inspired by the Lotus Leaf	241
10.3.2	Superhydrophobic Surfaces Inspired by the Legs of the Water Strider	243
10.3.3	Superhydrophobic Surfaces Inspired by the Anisotropic Superhydrophobic Surfaces in Nature	244
10.3.4	Other Superhydrophobic Surfaces	245
10.4	Applications of Surfaces with Extreme Wettability Ranges in the Biomedical Field	245
10.4.1	Cell Interactions with Surfaces with Extreme Wettability Ranges	246
10.4.2	Protein Interactions with Surfaces with Extreme Wettability Ranges	249
10.4.3	Blood Interactions with Surfaces with Extreme Wettability Ranges	251
10.4.4	High-Throughput Chips Based on Surfaces with Extreme Wettability Ranges	252
10.4.5	Substrates for Preparing Hydrogel and Polymeric Particles	254
10.5	Conclusions	254
	References	255
11	Bio-Inspired Reversible Adhesives for Dry and Wet Conditions	259
	<i>Aránzazu del Campo and Juan Pedro Fernández-Blázquez</i>	
11.1	Introduction	259
11.2	Gecko-Like Dry Adhesives	260
11.2.1	Fibrils with 3D Contact Shapes	262
11.2.2	Tilted Structures	263
11.2.3	Hierarchical Structures	265
11.2.4	Responsive Adhesion Patterns	265
11.3	Bioinspired Adhesives for Wet Conditions	268
11.4	The Future of Bio-Inspired Reversible Adhesives	270
	Acknowledgments	270
	References	270
12	Lessons from Sea Organisms to Produce New Biomedical Adhesives	273
	<i>Elise Hennebert, Pierre Becker, and Patrick Flammang</i>	
12.1	Introduction	273
12.2	Composition of Natural Adhesives	274
12.2.1	Mussels	274

12.2.2	Tube Worms	278
12.2.3	Barnacles	279
12.2.4	Brown Algae	280
12.3	Recombinant Adhesive Proteins	281
12.3.1	Production	281
12.3.2	Applications	283
12.4	Production of Bio-Inspired Synthetic Adhesive Polymers	284
12.4.1	Adhesives Based on Synthetic Peptides	285
12.4.2	Adhesives Based on Polysaccharides	285
12.4.3	Adhesives Based on Other Polymers	286
12.5	Perspectives	288
	Acknowledgments	288
	References	288

Part III Hard and Mineralized Systems 293

13	Interfacial Forces and Interfaces in Hard Biomaterial Mechanics	295
	<i>Devendra K. Dubey and Vikas Tomar</i>	
13.1	Introduction	295
13.2	Hard Biological Materials	298
13.2.1	Role of Interfaces in Hard Biomaterial Mechanics	299
13.2.2	Modeling of TC–HAP and Generic Polymer–Ceramic-Type Nanocomposites at Fundamental Length Scales	301
13.2.2.1	Analytical Modeling	302
13.2.2.2	Atomistic Modeling	304
13.3	Bioengineering and Biomimetics	306
13.4	Summary	308
	References	309
14	Nacre-Inspired Biomaterials	313
	<i>Gisela M. Luz and João F. Mano</i>	
14.1	Introduction	313
14.2	Structure of Nacre	316
14.3	Why Is Nacre So Strong?	318
14.4	Strategies to Produce Nacre-Inspired Biomaterials	320
14.4.1	Covalent Self-Assembly or Bottom-Up Approach	320
14.4.2	Electrophoretic Deposition	322
14.4.3	Layer-by-Layer and Spin-Coating Methodologies	323
14.4.4	Template Inhibition	325
14.4.5	Freeze-Casting	326
14.4.6	Other Methodologies	326
14.5	Conclusions	328
	Acknowledgements	329
	References	329

15	Surfaces Inducing Biomineralization	333
	<i>Natália M. Alves, Isabel B. Leonor, Helena S. Azevedo, Rui. L. Reis, and João. F. Mano</i>	
15.1	Mineralized Structures in Nature: the Example of Bone	333
15.2	Learning from Nature to the Research Laboratory	336
15.2.1	Bioactive Ceramics and Their Bone-Bonding Mechanism	337
15.2.2	Is a Functional Group Enough to Render Biomaterials Self-Mineralizable?	338
15.2.2.1	How the Surface Charge of Functional Group Can Be Correlated to Apatite Formation?	338
15.2.2.2	Designing a Properly Functionalized Surface	339
15.3	Smart Mineralizing Surfaces	343
15.4	<i>In Situ</i> Self-Assembly on Implant Surfaces to Direct Mineralization	345
15.5	Conclusions	348
	Acknowledgments	348
	References	348
16	Bioactive Nanocomposites Containing Silicate Phases for Bone Replacement and Regeneration	353
	<i>Melek Erol, Jasmin Hum, and Aldo R. Boccaccini</i>	
16.1	Introduction	353
16.2	Nanostructure and Nanofeatures of the Bone	354
16.2.1	The Structure of Bone as a Nanocomposite	354
16.2.2	Cell Behavior at the Nanoscale	356
16.3	Nanocomposites-Containing Silicate Nanophases	356
16.3.1	Nanoscale Bioactive Glasses	356
16.3.1.1	Synthetic Polymer/Nanoparticulate Bioactive Glass Composites	357
16.3.1.2	Natural Polymer/Bioactive Glass Nanocomposites	360
16.3.2	Nanoscaled Silica	363
16.3.2.1	Composites Containing Silica Nanoparticles	364
16.3.3	Nanoclays	365
16.3.3.1	Composites Containing Clay Nanoparticles	366
16.4	Final Considerations	372
	References	375
	Part IV Systems for the Delivery of Bioactive Agents	381
17	Biomimetic Nanostructured Apatitic Matrices for Drug Delivery	383
	<i>Norberto Roveri and Michele Iafisco</i>	
17.1	Introduction	383
17.2	Biomimetic Apatite Nanocrystals	384
17.2.1	Properties	384
17.2.2	Synthesis	386

17.3	Biomedical Applications of Biomimetic Nanostructured Apatites	390
17.4	Biomimetic Nanostructured Apatite as Drug Delivery System	394
17.4.1	Adsorption and Release of Drugs	397
17.5	Adsorption and Release of Proteins	402
17.5.1	Adsorption and Release of Bisphosphonates	406
17.6	Conclusions and Perspectives	409
	Acknowledgments	411
	References	411
18	Nanostructures and Nanostructured Networks for Smart Drug Delivery	417
	<i>Carmen Alvarez-Lorenzo, Ana M. Puga, and Angel Concheiro</i>	
18.1	Introduction	417
18.2	Stimuli-Sensitive Materials	419
18.2.1	pH	419
18.2.2	Glutathione	420
18.2.3	Molecule-Responsive and Imprinted Systems	420
18.2.4	Temperature	422
18.2.5	Light	423
18.2.6	Electrical Field	425
18.2.7	Magnetic Field	426
18.2.8	Ultrasounds	427
18.2.9	Autonomous Responsiveness	428
18.3	Stimuli-Responsive Nanostructures and Nanostructured Networks	428
18.3.1	Self-Assembled Polymers: Micelles and Polymersomes	429
18.3.2	Treelike Polymers: Dendrimers	433
18.3.3	Layer-by-Layer Assembly of Preformed Polymers	436
18.3.4	Polymeric Particles from Preformed Polymers	438
18.3.5	Polymeric Particles from Monomers	439
18.3.6	Chemically Cross-Linked Hydrogels	444
18.3.7	Grafting onto Medical Devices	447
18.4	Concluding Remarks	449
	Acknowledgments	449
	References	450
19	Progress in Dendrimer-Based Nanocarriers	459
	<i>Joaquim M. Oliveira, João F. Mano, and Rui L. Reis</i>	
19.1	Fundamentals	459
19.2	Applications of Dendrimer-Based Polymers	460
19.2.1	Biomimetic/Bioinspired Materials	460
19.2.2	Drug Delivery Systems	461
19.2.3	Gene Delivery Systems	463
19.2.4	Biosensors	465

19.2.5	Theranostics	466
19.3	Final Remarks	467
	References	467

Part V Lessons from Nature in Regenerative Medicine 471

20	Tissue Analogs by the Assembly of Engineered Hydrogel Blocks	473
	<i>Shilpa Sant, Daniela F. Coutinho, Nasser Sadr, Rui L. Reis, and Ali Khademhosseini</i>	

20.1	Introduction	473
20.2	Tissue/Organ Heterogeneity <i>In Vivo</i>	474
20.3	Hydrogel Engineering for Obtaining Biologically Inspired Structures	477
20.3.1	Structural Cues	477
20.3.2	Mechanical Cues	478
20.3.3	Biochemical Cues	480
20.3.4	Cell–Cell Contact	482
20.3.5	Combination of Multiple Cues	483
20.4	Assembly of Engineered Hydrogel Blocks	485
20.5	Conclusions	488
	Acknowledgments	489
	References	489

21	Injectable <i>In-Situ</i>-Forming Scaffolds for Tissue Engineering	495
	<i>Da Yeon Kim, Jae Ho Kim, Byoung Hyun Min, and Moon Suk Kim</i>	

21.1	Introduction	495
21.2	Injectable <i>In-Situ</i> -Forming Scaffolds Formed by Electrostatic Interactions	496
21.3	Injectable <i>In-Situ</i> -Forming Scaffolds Formed by Hydrophobic Interactions	497
21.4	Immune Response of Injectable <i>In-Situ</i> -Forming Scaffolds	500
21.5	Injectable <i>In-Situ</i> -Forming Scaffolds for Preclinical Regenerative Medicine	500
21.6	Conclusions and Outlook	501
	References	502

22	Biomimetic Hydrogels for Regenerative Medicine	503
	<i>Iris Mironi-Harpaz, Olga Kossover, Eran Ivanir, and Dror Seliktar</i>	

22.1	Introduction	503
22.2	Natural and Synthetic Hydrogels	503
22.3	Hydrogel Properties	505
22.4	Engineering Strategies for Hydrogel Development	506
22.5	Applications in Biomedicine	508
	References	511

23	Bio-inspired 3D Environments for Cartilage Engineering	515
	<i>José Luis Gómez Ribelles</i>	
23.1	Articular Cartilage Histology	515
23.2	Spontaneous and Forced Regeneration in Articular Cartilage	517
23.3	What Can Tissue Engineering Do for Articular Cartilage Regeneration?	517
23.4	Cell Sources for Cartilage Engineering	519
23.4.1	Bone Marrow Mesenchymal Cells Reaching the Cartilage Defect from Subchondral Bone	519
23.4.2	Autologous Mesenchymal Stem Cells from Different Sources	520
23.4.3	Mature Autologous Chondrocytes	521
23.5	The Role and Requirements of the Scaffolding Material	524
23.5.1	Gels Encapsulating Cells as Vehicles for Cell Transplant	524
23.5.2	Macroporous Scaffolds: Pore Architecture	524
23.5.3	Cell Adhesion Properties of the Scaffold Surfaces	525
23.5.4	Mechanical Properties	525
23.5.5	Can Scaffold Architecture Direct Tissue Organization?	526
23.5.6	Scaffold Biodegradation Rate	527
23.6	Growth Factor Delivery <i>In Vivo</i>	528
23.7	Conclusions	528
	Acknowledgment	529
	References	529
24	Soft Constructs for Skin Tissue Engineering	537
	<i>Simone S. Silva, João F. Mano, and Rui L. Reis</i>	
24.1	Introduction	537
24.2	Structure of Skin	537
24.2.1	Wound Healing	538
24.3	Current Biomaterials in Wound Healing	539
24.3.1	Alginate	539
24.3.2	Cellulose	540
24.3.3	Chitin/Chitosan	541
24.3.4	Hyaluronic Acid	543
24.3.5	Collagen and Other Proteins	544
24.3.6	Synthetic Polymers	545
24.4	Wound Dressings and Their Properties	545
24.5	Biomimetic Approaches in Skin Tissue Engineering	546
24.5.1	Commercially Available Skin Products	549
24.6	Final Remarks	549
	Acknowledgments	552
	List of Abbreviations	552
	References	553
	Index	559