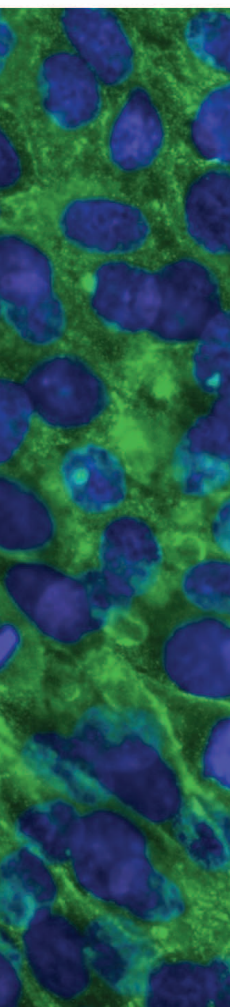


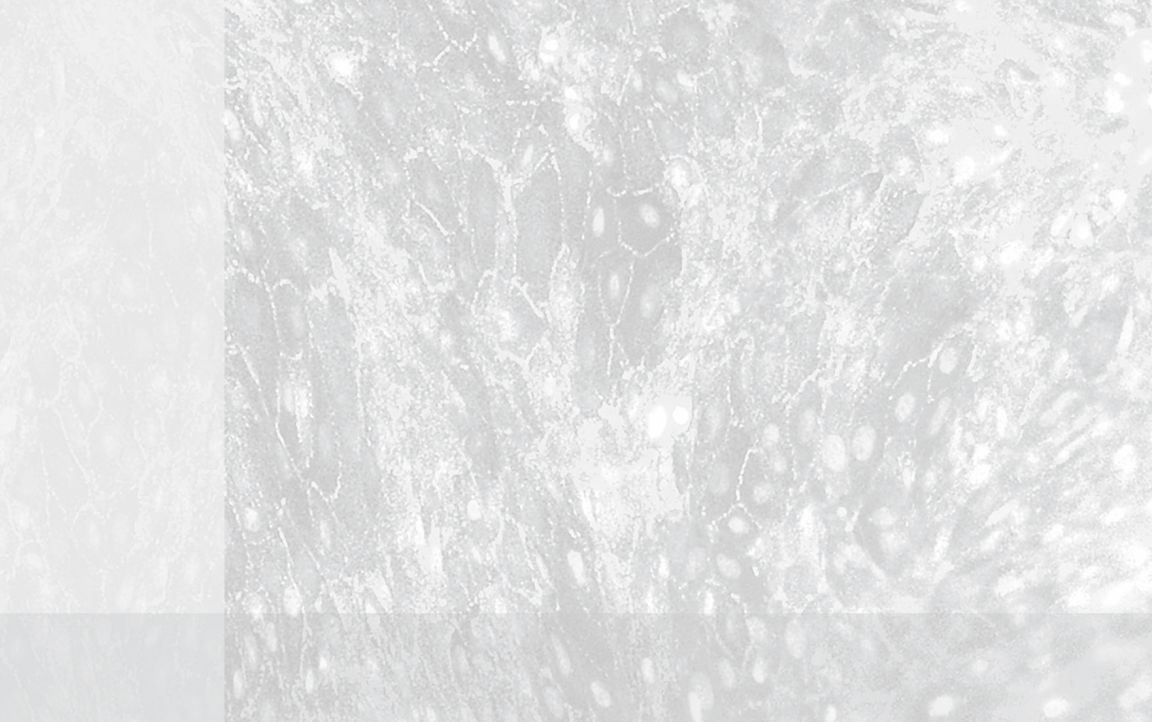
edited by **Gilson Khang**



Handbook of
**Intelligent Scaffolds for
Tissue Engineering and
Regenerative Medicine**

Second Edition





Handbook of
**Intelligent Scaffolds for
Tissue Engineering and
Regenerative Medicine**

Handbook of
**Intelligent Scaffolds for
Tissue Engineering and
Regenerative Medicine**

Second Edition

edited by
Gilson Khang

Published by

Pan Stanford Publishing Pte. Ltd.
Penthouse Level, Suntec Tower 3
8 Temasek Boulevard
Singapore 038988

Email: editorial@panstanford.com

Web: www.panstanford.com

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

Handbook of Intelligent Scaffolds for Tissue Engineering and Regenerative Medicine (2nd Edition)

Copyright © 2017 by Pan Stanford Publishing Pte. Ltd.

All rights reserved. This book, or parts thereof, may not be reproduced in any form or by any means, electronic or mechanical, including photocopying, recording or any information storage and retrieval system now known or to be invented, without written permission from the publisher.

For photocopying of material in this volume, please pay a copying fee through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, USA. In this case permission to photocopy is not required from the publisher.

ISBN 978-981-4745-12-3 (Hardcover)

ISBN 978-1-315-36469-8 (eBook)

Printed in the USA

*I would like to dedicate this handbook to my wife,
Isabella Seong Hee Koh, my children,
Jerome Taeuk and Daniel Taehoon, and my mother.*

Contents

<i>Preface to the 2nd Edition</i>	xxxvii
<i>Preface to the 1st Edition</i>	xxxix

PART I INTRODUCTION 1

1. Biomaterials and Manufacturing Methods for Scaffold in Regenerative Medicine: Update 2015 3

Gilson Khang

1.1	Introduction	4
1.2	Biomaterials for Regenerative Medicine and Tissue Engineering	11
1.2.1	Importance of Scaffold Matrices in Regenerative Medicine and Tissue Engineering	11
1.2.2	Bioceramic Scaffolds	11
1.2.2.1	Calcium phosphate	14
1.2.2.2	Tricalcium phosphate (TCP)	15
1.2.2.3	Hydroxyapatite	15
1.2.2.4	Bioglass	15
1.2.2.5	Demineralized bone particle	16
1.2.3	Synthetic Polymers	17
1.2.3.1	Poly(α -hydroxy ester)s	18
1.2.3.2	Polyanhydride	20
1.2.3.3	Poly(propylene fumarate)	20
1.2.3.4	PEO and its derivatives	21
1.2.3.5	Poly(vinyl alcohol)	22
1.2.3.6	Oxalate-based polyesters (polyoxalate)	22
1.2.3.7	Polyphosphazene	23
1.2.3.8	Biodegradable polyurethane	23
1.2.3.9	Other synthetic polymers	24
1.2.4	Natural Polymers	25
1.2.4.1	Fibrin	25
1.2.4.2	Collagen	26
1.2.4.3	Alginate	27

	1.2.4.4	Small intestine submucosa	28
	1.2.4.5	Silk	29
	1.2.4.6	Hyaluronan	29
	1.2.4.7	Chitosan	30
	1.2.4.8	Agarose	31
	1.2.4.9	Acellular dermis	31
	1.2.4.10	Polyhydroxyalkanoates	32
	1.2.4.11	Other natural polymers	32
	1.2.5	Bioactive Molecules Release System for Regenerative Medicine and Tissue Engineering	33
1.3		Scaffold Fabrication and Characterization	36
	1.3.1	Fabrication Methods of Scaffolds	36
	1.3.1.1	Electrospinning method	36
	1.3.1.2	PGA nonwoven sheet	37
	1.3.1.3	Porogen leaching methods	37
	1.3.1.4	Gas foaming method	38
	1.3.1.5	Phase separation method	38
	1.3.1.6	Rapid prototyping	39
	1.3.1.7	Injectable gel method	40
	1.3.2	Physicochemical Characterization of Scaffolds	40
	1.3.3	Sterilization Method for Scaffolds	41
1.4		Concluding Remarks and Future Directions	43
PART II CERAMIC AND METAL SCAFFOLDS			57
2. Biomaterialized Matrices as Intelligent Scaffolds for Bone Tissue Regeneration			59
<i>Heemin Kang, Yu-Ru V. Shih, Vikram Rao, and Shyni Varghese</i>			
2.1		Introduction	59
	2.1.1	Bone Tissue: A Mineralized Hierarchical Living Structure	60
	2.1.2	Mineralized Biomaterials for Bone Tissue Repair	62
2.2		CaP Biomaterials	63
2.3		CaP-Based Biomaterial-Assisted Osteogenic Differentiation of Stem Cells	65

2.4	CaP Matrices for Bone Tissue Engineering and Repair	67
2.5	CaP Mineral-Based Matrices as a Delivery Vehicle for Growth Factors and Genes	69
2.6	CaP-Assisted Stem Cell Osteogenesis and Bone Tissue Regeneration: Mechanistic Insights	70
2.7	Conclusion and Future Perspectives	72
3.	Bioceramic and Composite Scaffolds in Drug Delivery and Bone Tissue Engineering	85
	<i>Willi Paul and Chandra P. Sharma</i>	
3.1	Introduction	86
3.2	Bioceramics	87
3.3	Nanotechnology in Bioceramics	89
3.4	Nanoceramics in Drug Delivery	93
3.5	Bone Tissue Engineering	96
3.6	Research Perspective	98
3.7	Basic Questions in Bone Tissue Engineering	101
3.8	Conclusion	104
4.	Recent Development in Materials Innovation in Bone Tissue Regeneration	111
	<i>Swapan Kumar Sarakar and Byong-Taek Lee</i>	
4.1	Overview	111
4.2	Materials' Innovation	117
	4.2.1 Bioceramics	117
	4.2.2 Glass and Glass Ceramics	120
	4.2.3 Biopolymers and Hydrogels	123
4.3	Microstructure and Morphology Optimization of Bioceramic-Based Bone Substitutes	126
4.4	Current Challenges and Future Directions in Bone Substitute Research	127
4.5	Conclusions	128
5.	Carbonate Apatite Scaffolds for Regenerative Medicine	141
	<i>Kunio Ishikawa</i>	
5.1	Introduction	141
5.2	Fabrication of Carbonate Apatite by Compositional Transformation Based on Dissolution-Precipitation Reaction Using a Precursor	143

5.3	Cell and Tissue Response to Carbonate Apatite	146
5.4	Porous Carbonate Apatite	150
5.5	Conclusion	158
6.	Mg-Based Biodegradable Metals for Scaffolds	161
	<i>Yang Liu and Yufeng Zheng</i>	
6.1	Introduction	161
6.1.1	History of Mg-Based Metals for Scaffolds	161
6.1.2	Impact Factors on Scaffolds	163
6.1.2.1	Structure design	163
6.1.2.2	Surface design	163
6.2	Mg-Based Biodegradable Metals for Bone Scaffolds	164
6.2.1	Overview	164
6.2.2	Compact Mg-Based Biodegradable Metals as Bone Scaffolds	165
6.2.3	Porous Mg-Based Alloys as Bone Scaffolds	168
6.2.4	Mg-Based Composite as Bone Scaffolds	172
6.3	Mg-Based Biodegradable Metals for Blood Vessel Scaffolds/Stents	173
6.3.1	Overview	173
6.3.2	Bare Mg-Based Biodegradable Metal Stent	176
6.3.3	Drug-Eluting Mg-Based Biodegradable Metal Stent	182
6.4	Concluding Remarks	185
	PART III INTELLIGENT HYDROGELS	197
7.	Functional DNA Building Blocks and Their Hydrogel Scaffolds for Biomedical Application	199
	<i>Seung Won Shin, Kyung Soo Park, and Soong Ho Um</i>	
7.1	Overview	199
7.2	DNA Nanobuilding Blocks	202
7.3	DNA Hydrogels	204
7.3.1	Characteristics of DNA Hydrogels	204
7.4	Functionalized DNA Hydrogels	206
7.5	Protein-Producing DNA Hydrogels	208

7.5.1	Artificial Nucleus System Based on DNA Hydrogels	209
7.6	Conclusion	211
8.	Recent Progress of Intelligent Hydrogels for Tissue Engineering	217
	<i>S. V. Berwin Singh, Dong-Kwon Lim, and Gilson Khang</i>	
8.1	Introduction	217
8.2	History of Hydrogels	218
8.3	Properties of Hydrogel Scaffolds for Successful Tissue Engineering	219
8.4	Classification of Hydrogels	220
8.4.1	Innovative Smart Hydrogels in Tissue Engineering	221
8.4.1.1	Temperature-sensitive hydrogels in tissue engineering	224
8.4.1.2	pH-sensitive hydrogels in tissue engineering	225
8.4.1.3	pH-/temperature-sensitive hydrogels in tissue engineering	227
8.4.1.4	Biomolecule-sensitive hydrogels and photosensitive hydrogels in tissue engineering	228
8.4.1.5	Ion-sensitive hydrogels in tissue engineering	228
8.4.2	Three-Dimensional Bioprinting	229
8.4.2.1	Three-dimensional bioprinting modus operandi	230
8.4.2.2	Three-dimensional bioprinting in application	230
8.4.2.3	Skin cell gun	231
8.5	Conclusions	232
9.	Polyanionic Hydrogels as Biomaterials for Tissue Engineering	243
	<i>Hyuck Joon Kwon</i>	
9.1	Overview	243

9.2	Properties of Polyanionic Hydrogels	244
9.2.1	Electrical Properties	244
9.2.2	Electromechanical and Mechanoelectrical Properties	245
9.2.3	Polyanionic Gel as a Matrix for Protein Diffusion	246
9.2.4	Friction Reduction Effect of Polyanionic Gel	247
9.2.5	Tough Polyanionic Gel with an Interpenetrating Structure	248
9.3	Polyanionic Hydrogels for Replacement of Biotissues	249
9.3.1	Artificial Muscle	249
9.3.2	Artificial Cartilage	251
9.4	Polyanionic Hydrogels for Tissue Regeneration	252
9.4.1	Muscle Regeneration	252
9.4.2	Cartilage Regeneration	253
9.5	Conclusions	256
10.	Hyaluronic Acid–Based Hydrogel as a Scaffold for Tissue Engineering	263
	<i>Insup Noh and Sumi Bang</i>	
10.1	Introduction	264
10.2	Characteristics of Hyaluronic Acid in Tissue Engineering	264
10.3	HA Derivatives	266
10.3.1	Ester Derivatives	267
10.3.2	Carbodiimide ($R_1N=C=NR_2$)	268
10.3.3	Sulfydrylation (HA-SH)	268
10.3.4	Sulfation	268
10.3.5	Acryloyl Chloride	269
10.4	Fabrication of Hyaluronic Acid Hydrogels	269
10.4.1	Hydrogel Formation by Direct Crosslinking Methods	269
10.4.1.1	Diepoxy crosslinking method	269
10.4.1.2	Bifunctional amines as crosslinkers	270
10.4.1.3	Divinyl sulfone	271

10.4.1.4	In situ HA hydrogels	272
10.4.1.5	HA-aldehyde hydrogels	278
10.4.1.6	Michael-type addition reaction method	281
10.4.1.7	Azaide	282
10.5	Hyaluronic Acid–Based Hybrid Hydrogels	283
10.5.1	HA–Collagen/Peptide Hydrogels	283
10.5.2	HA–Natural Polymer Hydrogels	285
10.5.3	HA–Synthetic Polymer Hydrogels	286
10.6	Conclusions and Outlook	287
11.	Biologically Triggered Injectable Hydrogels as Intelligent Scaffolds	293
	<i>Yoon Ki Joung, Kyung Min Park, and Ki Dong Park</i>	
11.1	Introduction	294
11.2	Injectable Hydrogels as a Regenerative Scaffold	295
11.3	Enzyme-Triggered Hydrogels	296
11.3.1	HRP-Catalyzed Systems	298
11.3.2	TGase-Catalyzed Systems	301
11.3.3	Other Enzyme-Catalyzed Systems	303
11.4	Conclusions and Outlook	304
12.	Cytocompatible and Reverse-Transformable Polymeric Hydrogel Matrices	309
	<i>Kazuhiko Ishihara, Haruka Oda, and Tomohiro Konno</i>	
12.1	Introduction	310
12.2	Polymer Hydrogel as an Artificial ECM	311
12.3	Physically Forming Crosslinkable Hydrogels	312
12.4	Stimuli-Responsive Hydrogels	314
12.5	Reversible and Spontaneously Forming Hydrogels	315
12.6	Rheological Properties of PMBV/PVA Hydrogel	318
12.7	Control of Cell Proliferation through PMBV/PVA Hydrogel	320
12.8	Differentiation Induction of Stem Cells Encapsulated in the PMBV/PVA Hydrogel	325
12.9	Conclusions and Future Perspective	327

13. “Smart” Hydrogels in Tissue Engineering and Regenerative Medicine Applications	333
<i>Ana H. Bacelar, Ibrahim F. Cengiz, Joana Silva-Correia, Rui A. Sousa, Joaquim M. Oliveira, and Rui L. Reis</i>	
13.1 Introduction	334
13.2 Stimuli-Responsive Hydrogels: Types, Properties, and Applications	338
13.2.1 Physical-Responsive Hydrogels	338
13.2.1.1 Temperature-responsive hydrogels	338
13.2.1.2 Photo-/light-responsive hydrogels	342
13.2.1.3 Electro- and magnetic-responsive hydrogels	343
13.2.2 Chemical-Responsive Hydrogels	346
13.2.2.1 pH-responsive hydrogels	346
13.2.2.2 Glucose-responsive hydrogels	348
13.2.3 Biological-/Biochemical-Responsive Hydrogels	350
13.3 Processing of Hydrogels	352
13.4 Final Remarks and Future Trends	356
14. Cell-Encapsulating Polymeric Microgels for Tissue Repair	369
<i>Baeckkyoung Sung and Min-Ho Kim</i>	
14.1 Introduction	370
14.2 Natural and Synthetic Polymers for Cell-Encapsulating Microgels	371
14.3 Fabrication Methods of Microgels for Cell Encapsulation	372
14.3.1 Emulsification	373
14.3.2 Microfluidics	373
14.3.3 Lithography	373
14.3.4 Bioprinting	374
14.4 Design Considerations of Microgels for Cell Encapsulation	374
14.4.1 Crosslinking Type	374
14.4.1.1 Physical crosslinking	375
14.4.1.2 Chemical crosslinking	376

14.4.2	Engineering Biophysical Cues	376
14.4.2.1	Molecular weight and concentrations of polymers	377
14.4.2.2	Crosslinking degree	377
14.4.3	Incorporation of Biochemical Cues	378
14.4.3.1	Cell-binding motif	378
14.4.3.2	Incorporation of bioactive ligands	379
14.4.3.3	Cell density	379
14.4.4	Engineering Biodegradation	380
14.4.5	Engineering Structures of Microgels	381
14.5	The Application of Cell-Encapsulating Microgels for Tissue Repair	382
14.6	Challenges for Clinical Translation	383
14.7	Summary and Future Perspectives	384
15.	Injection Materials for the Larynx	391
	<i>Dong Wook Kim and Seong Keun Kwon</i>	
15.1	Overview	391
15.2	Anatomy of the Vocal Fold	392
15.2.1	Neuromuscular Anatomy of the Vocal Fold	392
15.2.2	Microanatomy of the Vocal Fold	393
15.3	Pathologic Changes of the Vocal Fold in Glottal Insufficiency	395
15.4	General Principles of Injection Laryngoplasty for Vocal Fold Paralysis	396
15.5	General Characteristics of the Materials Currently Available for Vocal Fold Augmentation	397
15.5.1	Temporary Injection Materials	397
15.5.1.1	Collagen-based products	398
15.5.1.2	HA gels	398
15.5.2	Permanent Injection Materials	399
15.5.2.1	Autologous fat	399
15.5.2.2	Calcium hydroxylapatite	399
15.6	Ideal Materials for Injection Laryngoplasty	400
15.6.1	Animal Model of Unilateral Vocal Fold Paralysis for Evaluation of Newly Devised Injection Materials	401

15.6.2	Biosynthetic Degradable Polymers as Carriers for Injection Materials	402
15.6.3	Biosynthetic Scaffolds for Tissue Augmentation and Delivery of Bioactive Regenerative Agents	403
15.6.4	Injectable Forms of the ECM	406
15.7	Summary	408
16.	Bionanocrystals in Tissue Engineering Strategies: Tools for Reinforcement, Nanopatterning, and/or Nanostructuring of Polymeric Scaffolds and Hydrogels	413
	<i>Rui M. A. Domingues, Rui L. Reis, and Manuela E. Gomes</i>	
16.1	Introduction	414
16.2	Potential of PNCs in Tissue Engineering Strategies	416
16.3	Nanopatterned Surfaces	419
16.4	Nanostructured Films and Coatings	419
16.5	Porous Foam and Sponge Scaffolds	422
16.6	Fibrous Nanocomposites	423
16.7	Hydrogel Nanocomposites	426
16.8	Concluding Remarks	429
PART IV	ELECTROSPINNING SCAFFOLDS	439
17.	Porous Scaffolds Using Dual Electrospinning for in situ Cardiovascular Tissue Engineering	441
	<i>S. Thakkar, A. Driessen-Mol, F. Baijens, and C. Bouten</i>	
17.1	Introduction: Cardiovascular Tissue Engineering	442
17.2	Electrospinning	444
17.2.1	Single-Nozzle Electrospinning	444
17.2.2	Dual-Nozzle Electrospinning	447
17.2.3	Coaxial-Nozzle Electrospinning	449
17.3	Cell Infiltration into Electrospun Scaffolds	450
17.4	Scaffold (An)isotropy	451
17.5	Controlling Scaffold Porosity	452
17.5.1	Increasing Fiber Diameter	453
17.5.2	Tailoring Collectors	453

17.5.3	Low-Temperature or Cryogenic Electrospinning	454
17.5.4	Multimodal Fiber Electrospinning	454
17.5.5	Selective Removal of a Polymer	455
17.5.6	Comparison of Techniques to Control Pore Size	457
17.6	Mechanical Properties and Degradation Rate	457
17.7	Conclusion	459
18.	Biofunctionalization of Electrospun Fibers for Tissue Engineering and Regenerative Medicine	479
	<i>Antonio G. B. Castro, Fang Yang, Jeroen J. P. van den Beucken, and John A Jansen</i>	
18.1	Introduction	479
18.2	Electrospinning Process	480
18.3	Functionalization of Electrospun Fibers	482
18.3.1	Co-electrospinning	482
18.3.1.1	Blending	482
18.3.1.2	Coaxial electrospinning	484
18.3.1.3	Emulsion-based fibers	485
18.3.2	Surface Modification	485
18.3.2.1	Adsorption	485
18.3.2.2	Covalent functionalization	486
18.4	Applications	490
18.4.1	Cell Adhesion	490
18.4.2	Growth Factors and Gene Delivery Systems	493
18.4.3	Drug Delivery Applications	494
18.4.3.1	Antibacterial strategies	494
18.4.3.2	Anticancer therapy	494
18.5	Conclusion	495
19.	Electrospun Fibrous Scaffolds	511
	<i>Sukhee Park, Ung Hyun Ko, and Jennifer H. Shin</i>	
19.1	Introduction	512
19.2	Electrospinning Process	513
19.2.1	Fundamentals of Electrospinning	513
19.2.2	General Materials	515
19.2.3	Functional Materials	519

19.2.4	Process Parameters	523
19.3	Advanced Fabrication Methods	530
19.3.1	Coaxial Electrospinning	530
19.3.2	Multiple Electrospinning	532
19.3.3	Control of Fiber Collection	534
19.3.4	Multiscale Assembly	536
19.4	Applications for Tissue Engineering	538
19.4.1	Skin	538
19.4.2	Blood Vessel	541
19.4.3	Bone and Cartilage	544
19.4.4	Muscle	547
19.4.5	Neural System	549
19.4.6	Stem Cell	551
PART V 3D PRINTING FOR SCAFFOLDS		565
20.	3D Printing of Tissue/Organ Scaffolds for Regenerative Medicine	567
	<i>Xiaohong Wang</i>	
20.1	Overview	567
20.2	The Modeling of Tissue/Organ Scaffolds	568
20.3	Material Selection	570
20.4	Technique Limitations	571
20.5	Conclusions and Prospects	573
21.	3D Printing Technology Applied to Tissue Scaffolds	581
	<i>Dong-Woo Cho, Jin Woo Lee, and Jong Young Kim</i>	
21.1	Introduction	582
21.2	3D Printing Methods Applied to Scaffolds	582
21.2.1	Stereolithography	582
	21.2.1.1 Photopolymer scaffold	584
	21.2.1.2 Biopolymer scaffold	589
21.2.2	Deposition Modeling	591
	21.2.2.1 Fused deposition modeling	591
	21.2.2.2 Organ printing system	596
21.2.3	Selective Laser Sintering	598
21.2.4	Inkjet-Based Printing	607
21.3	Summary	610

PART VI NANO-/BIOCONVERGENCE TECHNOLOGY FOR SCAFFOLDS	619
22. Nanomaterial-Assisted Tissue Engineering and Regenerative Medical Therapy	621
<i>Nirmalya Tripathy, Rafiq Ahmad, and Gilson Khang</i>	
22.1 Introduction	622
22.2 Nanomaterials for Tissue Engineering	625
22.2.1 Regeneration of Protective Tissues	627
22.2.2 Regeneration of Mechanosensitive Tissues	630
22.2.2.1 Bone regeneration	630
22.2.2.2 Cartilage regeneration	633
22.2.2.3 Ligament/tendon regeneration	634
22.2.3 Regeneration of Electroactive Tissues	636
22.2.3.1 Neuron regeneration	636
22.2.3.2 Skeletal muscle regeneration	639
22.2.3.3 Heart regeneration	640
22.2.4 Regeneration of Shear Stress–Sensitive Tissues	644
22.3 Potential Risk of Nanomaterials	647
22.4 Conclusion and Future Perspectives	648
23. Application of Nanodevices in Sensing and Regenerative Medicine	657
<i>Rafiq Ahmad, Nirmalya Tripathy, and Yoon-Bong Hahn</i>	
23.1 Introduction	658
23.2 Fabrication of Nanodevices	660
23.2.1 Bottom-Up Method	661
23.2.2 Top-Down Method	663
23.3 Applications of Nanodevices	663
23.3.1 Sensing Applications	663
23.3.2 Regenerative Medicine Applications	665
23.4 Conclusions	668
24. Micro-/Nanotech-Based Craniofacial Tissue Engineering	671
<i>Hemin Nie and Jeremy J. Mao</i>	
24.1 Overview	671

24.2	Micro-/Nanotech-Based Craniofacial Tissue Engineering	673
24.2.1	Selection of Materials	673
24.2.2	Micro-/Nanotech-Based Scaffolding	675
24.3	Conclusions	683
25.	Carbon Nanotubes: A Kind of Novel Biomaterials for Scaffolds of Tissue Engineering	689
	<i>Xiaoming Li, Rongrong Cui, Zheng Wang, Yubo Fan, and In-Seop Lee</i>	
25.1	Introduction	690
25.2	Carbon Nanotubes in Bone Tissue Engineering	691
25.2.1	F-US-Tube Nanocomposite Scaffolds	692
25.2.2	Composite Scaffolds Composed of PLGA and MWNTs	692
25.2.3	Composite Scaffolds Composed of Hydroxyapatite and CNTs	693
25.2.4	Composite Scaffolds Composed of Chitosan and CNTs	694
25.2.5	3D Scaffold Surface Coated with CNTs	694
25.2.6	Injectable Calcium Phosphate Cement Composites with MWCNTs	694
25.2.7	PCL-CNT Nanocomposites	695
25.2.8	Comparison to Other Nanomaterial in Bone Tissue Engineering	695
25.3	Nerve Tissue Engineering	696
25.3.1	PET-MWCNT Composites Scaffold	699
25.3.2	PLCL-MWCNT Composites Scaffold	699
25.3.3	SWNT-CS/PVA Scaffold	700
25.3.4	Silk-CNT Composite Scaffolds	701
25.3.5	PET-MWCNT Scaffold	702
25.4	The Others	704
PART VII	ACELLULAR NATURAL MATRICES FOR SCAFFOLDS	717
26.	Bacteriophage Scaffolds for Functional Assembly of Molecules and Nanomaterials	719
	<i>Mi Hwa Oh, Jeong Heon Yu, Moon Young Yang, and Yoon Sung Nam</i>	
26.1	Overview	719

26.2	Phage Display	721
26.3	Phage Platform for Biological Applications	726
	26.3.1 Discovery of Cancer Biomarkers	726
	26.3.2 Molecular Imaging for Diagnostics	730
	26.3.3 Applications to Drug and Gene Delivery	732
	26.3.4 Applications to Tissue Engineering	735
26.4	Genetic Modification of Phages to Create Inorganic Structures	737
	26.4.1 Synthesis of Functional Nanomaterials via Biomineralization	738
	26.4.2 Self-Assembly of Nanomaterials	741
26.5	Phage Display with Extended Genetic Codes	744
26.6	Conclusions	745
27.	Intelligent Scaffold–Mediated Enhancement of the Viability and Functionality of Transplanted Pancreatic Islets to Cure Diabetes Mellitus	757
	<i>Min Jun Kim, Haehyun Hwang, and Dong Yun Lee</i>	
27.1	Overview	757
27.2	Scaffolds Fabricated with ECM Molecules Decellularized from the Pancreas	758
	27.2.1 Methods of Whole-Organ Decellularization	759
	27.2.1.1 Perfusion of chemical agents	760
	27.2.1.2 Perfusion of enzymatic agents	763
	27.2.1.3 Physical methods	764
	27.2.2 Islet Matrix Components and Islet–ECM Interactions	764
	27.2.2.1 ECM composition of the pancreatic islets	765
	27.2.2.2 Islet–ECM interactions	766
	27.2.3 Application of ECM Molecules Decellularized from the Pancreas	767
27.3	Natural Polymer–Based Scaffolds	768
	27.3.1 Alginate Hydrogel as a Cell-Laden Scaffold	769
	27.3.2 Chitosan-Based Scaffold	771
	27.3.3 Collagen-Based Scaffold	772
27.4	Synthetic Polymer–Based Scaffold	775
	27.4.1 PEG Scaffold	775

27.4.2	PVA Scaffold	776
27.4.3	PLGA Scaffold	777
27.5	Natural and Synthetic Polymer Composite–Based Scaffold	778
27.6	Conclusion	779

28. Extracellular Matrix–Derived Biomaterials: Molecularly Defined Ingredients and Processing Techniques **793**

*H. R. Hoogenkamp, L. R. M Versteegden,
T. H. van Kuppevelt, and W. F. Daamen*

28.1	Introduction	793
28.2	Extracellular Matrix	794
28.2.1	Role of the ECM	794
28.2.2	ECM Constituents	795
28.3	Molecularly Defined Biomaterials	796
28.3.1	Mammalian ECM-Based Materials	797
28.3.1.1	Collagen	799
28.3.1.2	Gelatin	803
28.3.1.3	Elastin	804
28.3.1.4	Adhesive glycoproteins	805
28.3.1.5	Keratin	809
28.3.1.6	Proteoglycans and glycosaminoglycans	810
28.3.2	Nonmammalian-Based ECM Materials	815
28.3.2.1	Silk fibroin	815
28.3.2.2	Alginate	816
28.3.2.3	Chitosan	817
28.3.2.4	Other polysaccharides	818
28.4	Techniques and Major Tools for Scaffolding	819
28.4.1	Porous Materials	819
28.4.2	Hydrogels	822
28.4.3	Films and Coatings	823
28.4.4	Meshes: Spinnings, Knittings, and Windings	824
28.4.5	Computer-Controlled Fabrication	826
28.4.6	Decellularization	828
28.4.7	Crosslinking	830
28.4.8	Sterilization of Biomaterials	832

28.4.8.1	Chemical-based sterilization	833
28.4.8.2	Radiation-based sterilization	834
28.4.8.3	Biomaterial-specific sterilization	835
28.4.9	Regulatory Affairs	836
28.5	Summary and Future Perspectives	837
29.	Biological-Derived Biomaterials for Stem Cell Culture and Differentiation	875
	<i>Yen-Lin Wu and Jiashing Yu</i>	
29.1	Introduction	875
29.2	Stem Cell Engineering	877
29.3	Biological-Derived Materials	878
29.3.1	Collagen	878
29.3.1.1	Immunogenicity and biocompatibility	878
29.3.1.2	Biodegradability and collagenases	879
29.3.1.3	Cell interaction	879
29.3.2	Collagen-Based Biomaterials	880
29.3.2.1	Types of collagen biomaterials	880
29.3.2.2	Crosslinking methods and reinforcement with biopolymer combinations	880
29.3.2.3	Recent applications of collagen biomaterials	881
29.3.3	Chitosan	883
29.3.3.1	Structure–property relationship	883
29.3.3.2	Properties as biomaterials	884
29.3.3.3	Chitosan 3D scaffolds/ sponges	885
29.3.3.4	Chitosan 2D films/ nanofiber membranes	886
29.3.4	Decellularized Tissue Matrix	887
29.3.4.1	Whole-organ bioengineering	889
29.3.4.2	Heart	889
29.3.4.3	Lung	890

	29.3.4.4 Liver	891
	29.3.4.5 Kidney	891
29.4	Summary and Future Direction	893

30. Demineralized Dentin Matrix (DDM) Scaffolds for Alveolar Bone Engineering 903

Jong Ho Lee, Young Kyun Kim, Masaru Murata, and In Woong Um

30.1	History of the Demineralized Dentin Matrix	904
30.2	Characteristics of Scaffolds for Alveolar Bone Repair	904
30.3	Development of DDM Scaffolds	906
	30.3.1 Demineralized Bone Matrix	906
	30.3.2 Definition of DDM	907
	30.3.3 Structure of Dentin and DDM	907
	30.3.3.1 DDM powder and block	907
	30.3.3.2 Macroporosity and microporosity of DDM	907
	30.3.4 Components	910
	30.3.4.1 Organics	910
	30.3.4.2 Inorganics	912
	30.3.5 Growth Factors in Dentin	913
	30.3.6 Acid Treatments	914
	30.3.7 Biocompatibility of DDM	914
	30.3.8 Osteoinductivity of DDM	916
	30.3.9 Osteoconductivity of DDM	918
	30.3.10 Remodeling of DDM (Resorbability)	918
30.4	DDM Scaffolds with Recombinant Human BMP-2	920
	30.4.1 Recombinant Human BMP Molecules	921
	30.4.2 Bioassay at 3 Weeks after Implantation in Rats	921
	30.4.3 Acceleration of Bone Induction by BMP-2/DDM Scaffolds	921
	30.4.4 Comparison of AutoBT as an rhBMP-2 Carrier	923
30.5	Clinical Applications	924
	30.5.1 AutoBT Powder on Upper-Right Second Molar	924

30.5.2	AutoBT Block on Upper-Right First Premolar	925
30.5.3	Clinical Studies	926
30.6	Tooth Banks: Present and Future	929
31.	Biomimetic Scaffold Fabrication for Tissue Engineering	937
	<i>Junghwa Cha, Hyun-Gu Yim, Su-Hwan Kim, Pilnam Kim, and Nathaniel S. Hwang</i>	
31.1	Introduction	937
31.2	Biomimetic 2D Substrate Fabrication	939
31.2.1	Photolithography	939
31.2.2	Unconventional (Soft) Lithography Photolithography	940
31.2.3	Replica Molding	940
31.2.4	Microcontact Printing	942
31.2.5	Nanoimprinting Lithography	942
31.2.6	Capillary Force Lithography	943
31.3	Biomimetic 2D Substrate Modification	944
31.3.1	Protein Immobilization on 2D Substrates	944
31.3.2	ECM-Mimicking Peptide Modification on 2D Substrates	946
31.3.3	Carbohydrate Modification on 2D Substrates	946
31.4	Biomimetic Surface Modification Methods	947
31.4.1	Physical 2D Absorption	947
31.4.2	Covalent 2D Modification	947
31.5	3D Scaffold Fabrication	948
31.5.1	3D Bioprinting Scaffolds	948
31.5.2	Inkjet Bioprinter	948
31.5.3	Microextrusion Bioprinter	949
31.5.4	Laser-Assisted Bioprinter	950
31.5.5	Decellularized Tissue Scaffolds	951
31.5.5.1	Physical methods for decellularization scaffold fabrication	951
31.5.5.2	Chemical methods for decellularized scaffold fabrication	952

31.5.5.3	Enzymatic methods for decellularized scaffold fabrication	953
31.5.6	Biomimetic Porous Scaffold Fabrication	953
31.5.7	Biomimetic Fibrous Scaffold Fabrication	955
31.5.8	Fabrication of Hydrogel Scaffolds	957
31.5.8.1	Chemical crosslinking of hydrogels	958
31.5.8.2	Photocrosslinking of hydrogels	958
31.5.8.3	Enzyme-catalyzed crosslinking of hydrogels	958
31.6	Biomimetic Modification of 3D Scaffolds	960
31.6.1	ECM-Based Hydrogels	960
31.7	Future Direction	961
31.8	Conclusion	961
PART VIII	SCAFFOLDS FOR TARGET ORGANS	969
32.	Scaffolds for Tracheal Regeneration	971
	<i>Seung Won Shin, Kyung Soo Park, and Soong Ho Um</i>	
32.1	Structure and Function of the Trachea	971
32.1.1	Basic Anatomy of the Trachea	972
32.1.2	Mucosal Lining of the Trachea	972
32.1.3	Biomechanical Properties of the Trachea	974
32.2	Tissue Engineering for Tracheal Stenosis	975
32.2.1	Conditions for Tracheal Regeneration	975
32.2.2	Need for Tissue Engineering and Prerequisites for Tracheal Replacement	976
32.3	Scaffolds for Tracheal Regeneration	976
32.3.1	The Biologic Scaffold	976
32.3.2	The Artificial Scaffold	977
32.4	Cells	980
32.4.1	Stem Cells	980
32.4.2	Differentiated Cells	981
32.5	Bioreactors	982
32.6	Summary	983

33. Bladder Tissue Engineering	987
<i>Weilun Sun and Egbert Oosterwijk</i>	
33.1 The Urinary Bladder: Function and Structure	988
33.2 Bladder Reconstruction and Augmentation	989
33.3 Materials for Bladder Tissue Engineering	990
33.4 Cell Seeding	993
33.5 Vascularization	995
33.6 Stem Cells in Bladder Tissue Engineering	996
33.7 Animal Studies and Clinical Trials	998
33.8 Future Perspectives: A Complete Bladder?	1000
34. Scaffold Applications for Vascular Tissue Engineering	1009
<i>Young Min Ju, Hyunhee Ahn, John Vossler, Sang Jin Lee, and James J. Yoo</i>	
34.1 Introduction	1009
34.2 Synthetic Biodegradable Polymer Scaffolds	1010
34.3 Collagen and Other Biopolymer Scaffolds	1012
34.4 Decellularized Tissue Scaffolds	1013
34.5 Cell-Based Vascular Tissue Engineering	1015
34.6 In situ “Cell Free” Vascular Tissue Engineering	1017
34.7 Conclusions	1018
35. Annulus Fibrosus Tissue Engineering: Achievements and Future Development	1029
<i>Bin Li, Jun Li, Pinghui Zhou, and Huilin Yang</i>	
35.1 Introduction	1030
35.2 Fundamentals of Annulus Fibrosus	1032
35.3 Cells for Annulus Fibrosus Tissue Engineering	1033
35.3.1 Annulus Fibrosus Cells	1033
35.3.2 Chondrocytes	1035
35.3.3 Mesenchymal Stem Cells	1035
35.4 Scaffolds for Annulus Fibrosus Tissue Engineering	1037
35.4.1 Microstructure of Scaffolds	1038
35.4.2 Mechanical Characteristics of Scaffolds	1047
35.5 Growth Stimuli for Annulus Fibrosus Tissue Engineering	1049
35.6 Concluding Remarks	1052

36. Corneal Endothelium Regeneration: Basic Concepts	1071
<i>Eun Young Kim and Gilson Khnag</i>	
36.1 Introduction	1071
36.2 Corneal Endothelium	1072
36.2.1 Corneal Endotheliopathies	1076
36.2.2 Transplantation	1076
36.3 Bioengineered Corneal Endothelium	1078
36.3.1 Scaffolds	1078
36.3.2 Cells	1080
36.4 Conclusion	1081
PART IX DRUG DELIVERY SYSTEM FOR SCAFFOLDS	1089
37. High-Throughput Screening of Extracellular Matrix-Based Biomaterials	1091
<i>Cintia D. S. Horinouchi, Willeke F. Daamen, Ruud A. Bank, and Toin H. van Kuppevelt</i>	
37.1 Basic Principles	1092
37.1.1 The Extracellular Matrix	1092
37.1.1.1 Diversity in ECM molecules	1093
37.1.1.2 Collagen	1093
37.1.2 ECM as a Biomaterial	1094
37.1.2.1 Safety and biocompatibility of biomaterials	1095
37.2 Relation to Materiomics	1096
37.2.1 High-Throughput Analysis Using Arrays of Biomaterials and Arrays for Gene Expression	1096
37.2.1.1 Arrays of biomaterials	1097
37.2.1.2 Comprehensive analysis of in vivo response to biomaterials using high-density gene expression arrays and gene ontology	1098
37.3 Future Perspectives	1101
37.4 Classical Experiment 1: Biomaterial Array	1104
37.5 Classical Experiment 2: Gene Expression Microarrays	1105

38. Effect of Scaffolds with Bone Growth Factors on New Bone Formation	1113
<i>Hae-Ryong Song, Swee-Hin Teoh, Hak-Jun Kim, Ji-Hoon Bae, Sung Eun Kim, Young-Pil Yun, Muhammad Qasim, Jerry Chan, Zhi-Yong Zhang, Chang-Wug Oh, and Jun-Ho Wang</i>	
38.1 Introduction	1114
38.2 Bone Lengthening in Preclinical Animal Studies	1115
38.2.1 Calcium Sulfate in Tibial Lengthening	1115
38.2.2 BMP-2-Coated Tricalcium Phosphate/Hydroxyapatite for Femoral Distraction Osteogenesis in a Rat Model	1120
38.2.3 Titanium with Heparin/BMP-2 Complex for Improving Osteoblast Activity	1123
38.2.4 rhBMP2 for Distraction Osteogenesis of Rat Tibias	1127
38.2.5 Cord Blood Stem Cells and rhBMP-2 in Tibial Lengthening	1131
38.3 Growth Factor-/Stem Cell-Mediated Scaffolds for Bone Tissue Engineering	1134
38.3.1 Use of Fibrin and Stem Cells for Bone Defect Healing in Rabbits	1134
38.3.2 Biphasic Calcium Phosphate Lyophilized with <i>Escherichia coli</i> -Derived rhBMP-2 for Bone Formation of Middle Ear Cavity in an Animal Model	1141
38.3.3 Discontinuous Release of BMP-2 from Honeycomb-Like Polycaprolactone Scaffolds for Healing in Large Bone Defects of Rabbit Ulnas	1142
38.3.4 Use of Bioreactors, Human Fetal Stem Cells, and 3D Scaffolds for Bone Tissue Engineering	1147

38.3.5	Solid Freeform Fabrication-Based BMP-2-Releasing PCL/PLGA Scaffolds for in vitro and in vivo Bone Formation	1153
38.3.6	BMP-2-Immobilizing Heparinized-Chitosan Scaffolds for Enhanced Osteoblast Activity	1158
38.4	The Use of Scaffolds with or without Growth Factors and Cells for Clinical Trials	1162
38.4.1	CMC/BioC/BMP-2 Hybrid Hydrogels for Bone Formation in a Rat Tibial Defect Model	1164
39.	Drugs as Novel Biomaterials for Scaffolds	1175
	<i>Judee Grace E. Nemeño, Soojung Lee, Kyung Mi Lee, Jeewon Yoon, and Jeong Ik Lee</i>	
39.1	Overview	1175
39.2	Drug Repositioning	1177
39.2.1	Background	1177
39.2.2	Drugs as Biomaterials	1178
39.3	Background and Structure of Fragmin and Protamine	1184
39.3.1	Background of Fragmin and Protamine	1184
39.3.2	F/P Micro-/Nanoparticles as Biomaterials for Tissue Engineering and Regenerative Medicine	1187
39.4	Implications of Drug Repositioning in Tissue Engineering and Regenerative Medicine	1195
39.4.1	Use of Nanoparticles for Microencapsulation of Isolated Islets	1196
39.4.2	H/P as Cell Carriers: Cell Aggregation	1197
39.5	Conclusions	1199
PART X	FUTURE ENABLING TECHNOLOGY FOR SCAFFOLDS	1209
40.	Biocompatible Surface Coatings for Silicone-Based Implants	1211
	<i>Jiyeon Ham, Sunah Kang, Ji-Ung Park, and Yan Lee</i>	
40.1	Overview	1211

40.2	Surface Oxidation of Silicone Implants	1214
40.2.1	Plasma Treatment	1214
40.2.2	UV/Ozone Treatment	1215
40.2.3	Acid/Base Treatment	1215
40.3	Surface Coating with Bio-originated Materials	1215
40.3.1	Hyaluronic Acid	1216
40.3.2	Elastin Peptides	1216
40.3.3	Collagen	1218
40.3.4	Spider Silk Protein	1218
40.4	Surface Coating with Artificial Materials	1219
40.4.1	Fluorine-Based Molecules	1219
40.4.2	Poly(2-Hydroxyethyl Methacrylate)	1220
40.4.3	Polyacrylamide	1221
40.4.4	Poly(Acrylic Acid)	1223
40.4.5	Poly(Ethylene Glycol)	1223
40.4.6	Phospholipid-Mimicking Polymers	1227
40.5	Conclusions	1231
41.	Synthetic/PLGA Hybrid Scaffold for Tissue Regeneration: Update 2015	1243
	<i>Gilson Khang, Eun Young Kim, Jeong Eun Song, Chan Hum Park, Dong Sam Seo, and Jian-Qing Gao</i>	
41.1	Introduction	1244
41.2	Biomaterials for TERM	1247
41.2.1	Importance of Scaffold Matrices in TERM	1247
41.2.2	Natural Polymers	1248
41.2.3	Synthetic Polymers and Poly(α -Hydroxy Ester)s	1248
41.2.4	Bioceramic Scaffolds	1249
41.3	Hybrid and Composite Scaffold Biomaterials for TERM	1250
41.3.1	Poly(α -Hydroxy Acid) Family Hybrid Scaffolds	1250
41.3.2	Ceramic Hybrid Scaffolds	1256
41.3.3	Natural Polymer Hybrid Scaffolds	1262
41.3.4	Miscellaneous Scaffolds	1267
41.4	PLGA/Natural Hybrid Scaffolds in Our Laboratory	1269
41.5	Conclusions	1270

42. Biomedical Applications of Silk Fibroin	1285
<i>Chan Hum Park and Dong Kyu Kim</i>	
42.1 Overview	1285
42.2 Silk Fibroin Processing	1288
42.2.1 Preparation of Regenerated Silk Fibroin Solution	1288
42.2.2 Preparation of Silk Fibroin Membrane	1288
42.2.3 Preparation of Silk Fibroin Hydrogel and Sponge	1289
42.2.4 Preparation of Silk Fibroin Sponge	1290
42.2.5 Preparation of Electrospun Silk Fibroin	1291
42.3 Tissue Engineering Application of Silk Fibroin-Based Biomaterial	1293
42.3.1 Bone and Cartilage	1294
42.3.2 Skin	1294
42.3.3 Vasculature	1295
42.3.4 Ligament and Tendon	1297
42.3.5 Cornea	1297
42.3.6 Tympanic Membrane	1298
42.3.7 Esophagus	1298
42.4 Conclusion	1299
43. Tissue Fabrication and Regeneration by Cell Sheet Technology	1309
<i>Yuji Haraguchi, Tatsuya Shimizu, Masayuki Yamato, and Teruo Okano</i>	
43.1 Overview	1309
43.2 Temperature-Responsive Culture Surface and Cell Sheets	1310
43.2.1 Temperature-Responsive Culture Surface for Detaching Cell Sheets	1310
43.2.2 Further Improvement and Application of Temperature-Responsive Culture Surfaces	1313
43.2.3 Functional Tissue Fabrication Using Cell Sheet Engineering	1314

43.3	Fabrication and Regeneration of 3D Tissues Using Cell Sheet Technology	1316
43.3.1	Myocardial Tissue	1317
43.3.1.1	Autologous cell sheet therapy	1317
43.3.1.2	Beating cardiac tissue fabrication using cardiac cells	1318
43.3.1.3	Fabrication of vascularized thicker tissue using perfusable bioreactor systems	1319
43.3.2	Clinical Studies Using Cell Sheet Technology	1321
43.3.2.1	Cell sheet therapy for corneal limbal epithelial stem cell deficiency	1322
43.3.2.2	Prevention of esophageal strictures after endoscopic submucosal dissection by cell sheets	1322
43.3.2.3	Cell sheet therapy for periodontitis	1323
43.3.2.4	Cell sheet therapy for cartilage regeneration	1323
43.3.3	Other Tissue Regeneration Using Cell Sheet Technology	1325
43.3.3.1	Cell sheet therapy for treating diabetes mellitus	1325
43.3.3.2	Cell sheet therapy for treating hemophilia	1325
43.3.3.3	Hepatocyte tissue engineering using cell sheet technology	1326
43.3.3.4	Fabrication of hormone supplying renal cell sheet	1327
43.3.3.5	Reconstruction of functional endometrium-like tissue using cell sheet technology	1328

	43.3.3.6 Thyroid cell sheet for rescuing hypothyroidism	1329
	43.3.3.7 Production of tumor- bearing animal models using cancerous cell sheets	1330
43.4	Automation and Mechanization for Fabrication of 3D Tissues	1331
	43.4.1 Semiautomatic Living-Cell Isolation System	1331
	43.4.2 Automated Cell Culture System	1332
	43.4.3 Automated Cell Sheet-Layering System for Fabricating 3D Tissues	1332
	43.4.4 Cell Sheet Transportation Technology	1333
	43.4.5 3D Tissue Transplantation Device	1334
43.5	Conclusions	1335
44.	Stem Cell Engineering Using Bioactive Molecules for Bone-Regenerative Medicine	1353
	<i>Jin Sook Suh and Yoon Jeong Park</i>	
44.1	Overview	1353
44.2	First-Generation Bioactive Molecules: Proteins	1356
	44.2.1 Recombinant Human Growth Factors	1357
	44.2.2 ECM	1359
44.3	Bioactive Molecules: Peptides	1360
	44.3.1 ECM-Derived Peptides	1360
	44.3.1.1 Collagen-derived peptides	1361
	44.3.1.2 Osteopontin-derived peptides	1362
	44.3.1.3 Bone sialoprotein-derived peptides	1364
	44.3.1.4 KRSR-containing peptides	1364
	44.3.1.5 RGD-containing peptides	1365
	44.3.2 Growth Factor-Derived Peptides	1365
	44.3.2.1 BMP-derived peptides	1366
	44.3.2.2 FGF-derived peptides	1367
44.4	Bioactive Molecules: Small Molecules	1368
	44.4.1 Sphingosine-1-Phosphate	1369
	44.4.2 Lysophosphatidic Acid	1370

44.4.3	Melatonin	1370
44.4.4	Purmorphamine	1371
44.4.5	Resveratrol	1372
44.4.6	Prostagladins	1373
44.4.7	Adenosine	1374
44.4.8	Statins	1375
44.5	Conclusions and Outlook	1376
	<i>Index</i>	1385

Preface to the 2nd Edition

I edited the 1st edition of *Handbook of Intelligent Scaffolds for Tissue Engineering and Regenerative Medicine* in 2012, which comprised 45 chapters. The very recent environment of academia and industry in these areas has quickly and extensively changed in comparison to 4 years ago. For example, 19 regenerative medicine and tissue engineering, including cell therapy, products were launched in the Korean market. Among them, 4 stem cell products, approved by the Korea FDA, were launched in the Korean market in 2012. They are the world's first-time-reported autologous bone marrow-derived stem cells (BMSCs), autologous adipose-derived stem cells (ASCs), and allogenic umbilical cord-derived stem cells (UBSCs) for the treatment of myocardial infarction, ALS, Crohn's disease, and chondyle defects, respectively.

From the global point of view, four stem therapy products have been introduced. Additionally, over 100–200 clinical trial phases I, II, and III with a wide arena of scientific fields are under development throughout the world. This may be a burgeoning step toward the advancement of regenerative medicine compared to that of conventional medication therapy.

This handbook focuses on all aspects of scaffolds, especially intelligent scaffolds, from basic science to industries to clinical applications. It is organized into 10 major areas. Part I, "Introduction," reveals some of fundamentals of biomaterials, scaffolds, and manufacturing methods. Part II covers ceramic and metal scaffolds. Part III, "Intelligent Hydrogels," deals with the various types of hydrogels for tissue regeneration. In Part IV, scaffolds from electrospinning nanofibers have been covered. In Parts V and VI, 3D printing and nano-/bioconvergence technology for scaffolds have been introduced, respectively. Part VII covers the recent development of an acellular natural matrix for smart scaffolds. Part VIII of this handbook deals with the recent clinical trial on specific target organs using intelligent scaffolds. Part IX introduces the drug delivery system, and Part X deals with future enabling technology for scaffolds.

The authors have tried to cover the entire area of smart scaffolds for regenerative medicine and tissue engineering through the 44 chapters. I am indebted to the authors for willing acceptance, devotion, and contribution to each topic.

I express my thanks to my students, Mr. Jae Hoon Shin and others, and the editor, Archana Ziradkar, for editing all chapters. Especially, Ms. Ziradkar was fighting against 44 huge chapters and 1400 pages every day. Finally, I really appreciate our publisher, Pan Stanford Publishing, especially Mr. Stanford Chong. Without his trust and guidance, this huge work could not have been accomplished.

Gilson Khang, PhD

Preface to the 1st Edition

It has been recognized that regenerative medicine and tissue engineering offer an alternative technique to whole-organ and tissue transplantation for diseased, failed, or malfunctioning organs. Millions of patients suffer from end-stage organ failure or tissue loss annually. The only way to solve this problem might be organ transplantation and biomaterials transplantation. However, in order to avoid the shortage of donor organs and other problems caused by poor biocompatibility of biomaterials, a new hybridized method combined with cells and biomaterials had been introduced as regenerative medicine and tissue engineering around 20 years ago. The specialty of regenerative medicine and tissue engineering continues to grow and change rapidly. This area saw major advances in the past few years. This field for academic research and commercialization is needed in multidisciplinary areas such as adult, embryonic, and induced pluripotent cells, genetic programming, nuclear transfer, cloning, genomics, proteomics, nanotechnology, biomaterials, etc. Thanks to the latest 20 years' endeavor, several tissue-engineered products (TEMPS) and regenerative medicinal products (RMP) are on the boundary of the translation of benchside discoveries to clinical therapies. For the reconstruction of a neotissue by regenerative medicine and tissue engineering, triad components such as (i) cells that are harvested and dissociated from the donor tissue, including nerve, liver, pancreas, cartilage, and bone, as well as embryonic stem cells, adult stem cells, induced pluripotent cells (iPS), or precursor cells; (ii) biomaterials as scaffold substrates whose cells are attached and cultured, resulting in the implantation at the desired site of the functioning tissue; and (iii) growth factors that are promoting and/or preventing cell adhesion, proliferation, migration, and differentiation by up-regulating or down-regulating the synthesis of protein, growth factors, and receptors are needed. This handbook has concentrated on all the things for scaffolds among triad components, especially intelligent scaffolds from basic science to industries to clinical applications. This textbook is organized into seven major areas.

Part I, "Introduction," reveals some of fundamentals of the biomaterials, scaffolds, and manufacturing methods. Part II covers ceramic and metal scaffolds. Part III, "Intelligent Hydrogels," deals with various types of hydrogels for tissue regenerations. In Part IV, topics of scaffolds from electrospinning nanofibers have been covered. In Part V, novel biomaterials for scaffolds have been introduced, especially to mimic Mother Nature. The sixth part covers the recent novel fabrication methods for smart scaffolds. The last part, Part VII, of this handbook deals with the recent clinical trial of specific target organs using intelligent scaffolds. The authors have tried to dedicate the 44 chapters to the whole area of the recent topic of smart scaffolds for regenerative medicine and tissue engineering. I am indebted to the authors for their willing acceptance, devotion, and contribution to each recent topic. I express my thanks to my students Mrs. Yong Ki Kim, Jung Bo Shim, and Young Un Kim for editing all manuscripts. Finally, I really appreciate our publisher, Mr. Stanford Chong. Without his trust and guidance, this huge work could not have been accomplished. Also, I would like to give special appreciation to Mr. Sarabjeet Garcha and Ms. Archana Ziradkar for their hard work.

Gilson Khang, PhD