

## Contents to Volume 1

**List of Contributors** *xiii*

**Foreword** *xxiii*

**Preface** *xxv*

### **Part I Fundamentals 1**

**1 Introduction to Tissue Engineering 3**

*Rami Mhanna and Anwarul Hasan*

**2 Biomaterials in Tissue Engineering 35**

*Samad Ahadian, Rahaf Rahal, Javier Ramón-Azcón, Raquel Obregón, and Anwarul Hasan*

**3 Harnessing the Potential of Stem Cells from Different**

**Sources for Tissue Engineering 85**

*Divya Murali, Kunal G. Kshirsagar, Anwarul Hasan, and Arghya Paul*

**4 Induced Pluripotent Stem Cells in Scaffold-Based Tissue**

**Engineering 111**

*Deepthi Rana, Minal Thacker, Maria Leena, and Murugan Ramalingam*

**5 Biosensors for Optimal Tissue Engineering: Recent**

**Developments and Shaping the Future 143**

*Jihane Abouzeid, Ghinwa Darwish, and Pierre Karam*

**6 Bioreactors in Tissue Engineering 169**

*Raquel Obregón, Javier Ramón-Azcón, and Samad Ahadian*

**Part II Applications 215**

7 **Tissue-Engineered Human Skin Equivalents and Their Applications in Wound Healing 217**  
*Lara Yildirimer, Divia Hobson, Zhi Yuan (William) Lin, Wenguo Cui, and Xin Zhao*

8 **Articular Cartilage Tissue Engineering 243**  
*Jiayin Fu, Pengfei He, and Dong-An Wang*

9 **Liver Tissue Engineering 297**  
*Jessica L. Sparks*

10 **Development of Tissue-Engineered Blood Vessels 325**  
*Haiyan Li*

**Contents to Volume 2****Foreword xv****Preface xvii**

11 **Engineering Trachea and Larynx 363**  
*Marta B. Evangelista, Sait Ciftci, Peter Milad, Emmanuel Martinod, Agnes Dupret-Bories, Christian Debry, and Nihal E. Vrana*

11.1 Introduction 363

11.2 Basic Anatomy and Histology of the Larynx and Trachea 364

11.2.1 The Larynx 364

11.2.2 The Trachea 365

11.3 Indications for Tracheal Resection 366

11.3.1 Laryngotracheal Stenosis 366

11.3.2 Benign Tumors of the Trachea 367

11.3.3 Primary Malignant Tumors of the Trachea 367

11.3.4 Secondary Malignant Tumors of the Trachea 368

11.3.5 Indications of Total Laryngectomy 368

11.3.5.1 Cancer of Larynx or Hypopharynx 368

11.3.5.2 Benign Tumors of the Larynx 368

11.3.5.3 Nonfunctioning Larynx 369

11.4 Available Remedies Following Total Laryngectomy 369

11.4.1 Laryngeal Transplantation 369

11.4.2 Grafts 369

11.4.2.1 Implantation of Nonviable Tissues 369

11.4.2.2 Tracheal Transplantation and Autografts (Viable Tissues) 370

11.4.3 Biomaterials 371

11.5 Regenerative Medicine Strategies and Tissue Engineering Tools for Tracheal and Larynx Replacement 372

11.5.1 Replacement of the Trachea 374

11.5.2	<i>Ex vivo</i> Tissue Engineering	375
11.5.3	<i>In vivo</i> Tissue Engineering	375
11.5.4	Inherent Needs of Trachea Tissue Engineering	376
11.5.4.1	Developing Strategies for Trachea Regeneration	376
11.5.5	Laryngeal Tissue Engineering	378
11.6	Conclusions and Future Directions	381
	Declaration/Conflict of Interest	382
	References	382
<b>12</b>	<b>Pulmonary Tissue Engineering</b>	<b>389</b>
	<i>Patrick A. Link and Rebecca L. Heise</i>	
12.1	Introduction	389
12.2	Clinical Need for Pulmonary Tissue Engineering	389
12.2.1	Restrictive Lung Disease	390
12.2.1.1	Interstitial Lung Disease	390
12.2.2	Obstructive Pulmonary Disorders	391
12.2.2.1	Asthma	391
12.2.2.2	COPD	391
12.2.3	Lung Cancer	392
12.2.4	Treatment Options – An Open Door for Tissue Engineering and Regenerative Medicine	393
12.3	Structure–Function Relationship in the Conducting Airways and the Lung	394
12.4	Tissue Engineering and Regenerative Medicine: Approaches for the Lung	397
12.4.1	Scaffold Approaches for Lung Tissue Engineering	397
12.4.1.1	Polymeric Scaffold Approaches	397
12.4.1.2	Decellularized Tissue Approach for Lung Tissue Engineering	400
12.4.1.3	Three-Dimensional Printing in Scaffold-Based Lung Tissue Engineering	403
12.4.2	Microfluidics and Assist Devices	403
12.4.3	Cell Source, Cell Therapies, and Regenerative Medicine Approaches for Lung Tissue Engineering and Regeneration	405
12.4.3.1	Cellular Source for Engineered Pulmonary Tissues	405
12.4.3.2	Cell Therapies for Lung Regeneration	406
12.5	Conclusions, Remaining Challenges, and Future Directions	408
	References	408
<b>13</b>	<b>Cardiac Tissue Engineering</b>	<b>413</b>
	<i>Eun Jung Lee and Pamela Hitscherich</i>	
13.1	Introduction	413
13.2	Cardiac Tissue Architecture	414
13.3	Cell Source Considerations	416
13.3.1	Mesenchymal Stem Cells	416
13.3.2	Embryonic Stem Cells	418
13.3.3	Induced Pluripotent Stem Cells	420

13.3.4	Other Cell Sources	422
13.4	Engineering for Myocardial Tissue	422
13.4.1	Hydrogels	423
13.4.2	Prefabricated Scaffolds	423
13.4.3	Decellularized Scaffolds	426
13.4.4	Cell Sheets	426
13.4.5	Bioreactors	427
13.4.6	Engineered Cardiac Tissues (ECTs) as Advanced In Vitro Models	428
13.5	Conclusion and Future Directions	430
	References	430
<b>14</b>	<b>Approaches and Recent Advances in Heart Valve Tissue Engineering</b>	<b>445</b>
	<i>Anna Mallone, Benedikt Weber, and Simon P. Hoerstrup</i>	
14.1	Introduction	445
14.1.1	Heart Valve Biology	445
14.1.2	Heart Valve Disease and Valve Replacement	447
14.2	Principles of Tissue Engineering: Shaping the Valvular Construct	448
14.3	<i>In Vitro</i> Bioengineering of Heart Valves: Scaffold Materials	449
14.3.1	Polymeric Scaffolds from Synthetic Sources	450
14.3.1.1	Aliphatic Polyesters: PGA, PLA, and PCL	450
14.3.2	Polymeric Scaffolds from Biological Sources	451
14.3.2.1	Polysaccharide-Based Scaffolds	452
14.3.2.2	Protein-Based Scaffolds	453
14.3.3	Scaffolds Derived from Decellularized Tissues	453
14.4	Cells for Valvular Bioengineering	454
14.4.1	Cells Derived from Vasculature	455
14.4.2	Umbilical-Cord-Derived Cells	455
14.4.3	“Stem Cells”: A New Source for Valvular Bioengineering	455
14.4.3.1	Pluripotent and Induced Pluripotent Stem Cells	456
14.5	Challenges and Limitations	456
14.6	Conclusion and Future Directions	457
	References	457
<b>15</b>	<b>Musculoskeletal Tissue Engineering: Tendon, Ligament, and Skeletal Muscle Replacement and Repair</b>	<b>465</b>
	<i>Jorge A. Uquillas, Settimio Pacelli, Shuichiro Kobayashi, and Sebastián Uquillas</i>	
15.1	Introduction	465
15.2	Biology of Tendon, Ligament, and Skeletal Muscle	467
15.2.1	Structure and Biology of Tendon	467
15.2.2	Structure and Biology of Ligament	470
15.2.3	Structure and Biology of Skeletal Muscle	470

15.3	Grafting Practices for Tendon, Ligament, and Skeletal Muscle Repair	473
15.3.1	Acellular Grafts	473
15.3.2	Autografts	474
15.3.3	Xenografts	474
15.3.4	Allografts	475
15.4	Factors in Musculoskeletal Tissue Engineering	477
15.4.1	Development of Natural Scaffolds in Tendon, Ligament, and Skeletal Muscle Tissue Engineering	477
15.4.2	Tissue-Engineered Collagenous Bioscaffolds for Tendon Repair	478
15.4.3	Development of Synthetic Bioscaffolds in Tendon, Ligament, and Skeletal Muscle Tissue Engineering	481
15.4.3.1	Synthetic Tendon, Ligament, and Skeletal Muscle Bioscaffolds	482
15.4.4	Mesenchymal Stem Cells in Tendon, Ligament, and Skeletal Muscle Tissue Engineering	485
15.4.5	Growth Factors in Tendon/Ligament and Skeletal Muscle Tissue Engineering	488
15.4.6	Bioreactors in Musculoskeletal Tissue Engineering	491
15.5	Recent Advancements in Musculoskeletal Tissue Engineering	494
15.5.1	Animal Models in Musculoskeletal Tissue Engineering	494
15.5.2	Current Musculoskeletal Tissue Engineering Repair Strategies in Clinical Trials	497
15.6	Conclusions and Future Directions	498
	References	499
16	<b>Bone Tissue Engineering: State of the Art, Challenges, and Prospects</b>	525
	<i>Jan O. Gordeladze, Håvard J. Haugen, Ståle P. Lyngstadaas, and Janne E. Reseland</i>	
16.1	Introduction	525
16.2	Factors Important in Tissue Engineering of Bone	526
16.2.1	Scaffolds and Biomaterials	526
16.2.2	Sourcing	528
16.3	Fabricated Tissues by 3D Printing of Suspensions of Cells on Micro-Carriers	529
16.3.1	Cellular Behavior: A Scrutiny of the Cell–Biomaterial Interface	529
16.3.2	Some Interesting Recent Discoveries	530
16.3.3	Behavior of Cells as an Approach to Understanding Interactions Between Cells and Biomaterials	530
16.3.4	Microarrays of Peptides as Useful Tools to Predict Signaling Mechanisms	531
16.3.5	Growth Factors	531

16.3.6	Bioreactors and Mechano-Chemical Stimulators of Bone Tissue Engineering	532
16.4	Recent Advances in Bone Tissue Engineering	533
16.4.1	What Are the Next Steps for 3D Bio-Printing?	534
16.4.1.1	A Typical Process for Bio-Printing of 3D Tissues	535
16.4.1.2	Materials Suitable for Bio-Printing for Generation of Artificial Tissues	536
16.4.1.3	3D-Shaped Biomaterials and Scaffold-Building Substances for Bone Tissue Engineering	537
16.4.2	Nanobiotechnology and Bone Regeneration	537
16.4.2.1	Nanostructured Scaffolds for Bone Repair	538
16.4.2.2	Nanoparticle Delivery Systems for Bone Repair	539
16.4.2.3	Connection between Mechanics and Bone Cell Activities	539
16.4.3	Novel Comprehension of the Role of Osteocytes in Bone Growth and Regrowth	541
16.4.3.1	Osteocytes as Mechano Sensors	541
16.4.3.2	Osteocyte–Osteoblast Communication	541
16.4.4	Advances in Vascularization of Tissue-Engineered Bones	542
16.4.4.1	The “Flap Prefabrication” Approach	542
16.4.4.2	Strategies Involving the “Pre-Existence of Vascular Networks”	543
16.4.4.3	Fat Tissue May Transform Into Vasculo- and Osteogenic Cells	543
16.4.4.4	Vasculogenic Progenitors	543
16.4.4.5	Osteogenic Progenitors	543
16.4.5	Advances in the Understanding and Control of Intracellular Signaling Pathways of Osteoblast Differentiation	544
16.4.5.1	LRP5 (Low-Density Lipoprotein Receptor-Related Protein 5) Signaling in BMSC Differentiation	545
16.4.5.2	Signaling Protein Kinases and Impact on hBMSC Adaptation/Differentiation	545
16.5	Conclusion and Future Prospects	546
	References	548
17	<b>Tissue Engineering of the Pancreas</b>	553
	<i>Masayuki Shimoda</i>	
17.1	Introduction	553
17.1.1	Biology of the Pancreas and Islets	554
17.2	Treatment Options for T1D	554
17.2.1	Exogenous Insulin Treatment	554
17.2.2	Whole Pancreas Transplantation	554
17.2.3	Pancreatic Islet Transplantation	555
17.2.4	Artificial Pancreas	555
17.3	Bioartificial Pancreas	556
17.3.1	Cell Sources	556
17.3.1.1	Pig Islets	556
17.3.1.2	Human Islets	557
17.3.1.3	Islet Isolation	557
17.3.1.4	Human Pluripotent Stem Cells	557

17.3.1.5	Other Cell Sources	558
17.4	Biomaterials/Encapsulation	558
17.4.1	Macroencapsulation	560
17.4.2	Microencapsulation	561
17.4.3	Cell Surface Coating	562
17.4.4	Prevention of Fibrosis	562
17.4.5	Protection from Immune Attack	563
17.4.6	Transplantation Site	563
17.5	Conclusion	564
	References	566
<b>18</b>	<b>Tissue Engineering of Renal Tissue (Kidney)</b>	<b>575</b>
	<i>Raquel Rodrigues-Díez, Valentina Benedetti, Giuseppe Remuzzi, and Christodoulos Xinaris</i>	
18.1	Introduction	575
18.2	Biology of the Kidney	576
18.2.1	Renal Anatomy	576
18.2.2	The Nephron	577
18.2.3	Renal Functions	577
18.3	Overview of Kidney Development and Vascularization	578
18.3.1	Early Kidney Development	578
18.3.2	Development and Maturation of the Glomerular Filtration Barrier	580
18.3.3	Kidney Vascularization	580
18.4	Developmental Engineering	581
18.4.1	Tissue-Based Strategies	581
18.4.2	Cell-Based Strategies	582
18.4.2.1	Generation of Kidney Tissues from Embryonic Kidney Cells	582
18.4.2.2	Generation of 3D Kidney Tissue from Pluripotent Stem Cells	585
18.5	Bio-Scaffold-Based Technologies	587
18.5.1	Decellularization to Generate Whole Kidney Scaffolds	587
18.5.2	Recellularization of Whole-Kidney Scaffolds	591
18.5.3	Recellularization of Acellular Renal Sections	592
18.5.4	Implantation and Vascularization of Kidney Scaffolds	593
18.5.5	Organ Printing	594
18.6	Conclusions and Future Directions	594
	Acknowledgments	595
	References	595
<b>19</b>	<b>Design and Engineering of Neural Tissues</b>	<b>603</b>
	<i>Muhammad N. Hasan and Umut A. Gurkan</i>	
19.1	Introduction	603
19.2	Natural Biomaterials for Nerve Tissue Repair	605
19.2.1	Acellular Tissue Grafts	606
19.2.1.1	Chemical Decellularization	607
19.2.1.2	Physical Decellularization	611
19.2.1.3	Enzymatic Decellularization	612

19.2.2	Collagen-Based Biomaterials	614
19.2.3	Hyaluronan-Based Biomaterials	616
19.2.4	Fibrin-Based Biomaterials	619
19.2.4.1	Agarose-Based Materials	621
19.3	Synthetic Biomaterials for Nerve Tissue Repair	623
19.3.1	Polymer-Based Materials	624
19.3.1.1	Poly(Lactic- <i>co</i> -Glycolic Acid)-Based Materials	624
19.3.1.2	Poly(Ethylene Glycol)-Based Materials	624
19.3.2	Peptide-Based Biomaterials	625
19.4	Development of Nanofibrous Scaffolds	625
19.4.1	Biodegradation of the Scaffold	627
19.4.2	Computational Modeling of Self-assembling Nanomaterials	628
19.4.3	Characterization	628
19.5	Summary and Future Direction	634
	References	634
20	<b>Neural-Tissue Engineering Interventions for Traumatic Brain Injury</b>	655
	<i>Tala El Tal, Rayan El Sibai, Stefania Mondello, and Firas Kobeissy</i>	
20.1	Introduction	655
20.2	Neurogenesis in CNS: Resident Neural Stem Cells	657
20.3	Cell-Based and Neuroprotection Therapeutic Strategies	658
20.4	Construct Technology: Biomaterials Approach	663
20.4.1	Scaffold-Based Treatment	664
20.4.1.1	Carbon Nanotubes Approach	667
20.4.2	Biologics and Drug-Based Treatment	667
20.5	Application to Living System: Translational Approaches	668
20.6	Future Outlook: Transition to the Clinic	669
	References	671
21	<b>Bionics in Tissue Engineering</b>	677
	<i>Thanh D. Nguyen and Brian P. Timko</i>	
21.1	Introduction	677
21.2	Electronics for Biointerfaces	678
21.2.1	Pioneering Devices	678
21.2.1.1	Cochlear Implants	678
21.2.1.2	Retinal Implants	679
21.2.1.3	Bionic Arms Employing Neuromuscular–Electrode Interface	679
21.2.2	Organic Electronics	681
21.2.2.1	Mechanism	681
21.2.2.2	Organic Device Applications in Bionic Tissues	681
21.2.3	Solid-State Nanomaterials	683
21.2.3.1	Nanocomposites in Tissue Engineering	683
21.2.3.2	Silicon Nanowire Nanoelectronics for Molecular-Scale Sensing	685
21.2.4	Flexible Solid-State Microelectronics	687
21.3	Novel Power Sources	688
21.3.1	Inductively Coupled Systems	689

21.3.2	Degradable Batteries	689
21.3.3	Piezoelectrics for Capturing Mechanical Energy	690
21.4	3D Printing	692
21.5	Conclusions and Future Directions	695
	References	695

<b>Index</b>	701
--------------	-----