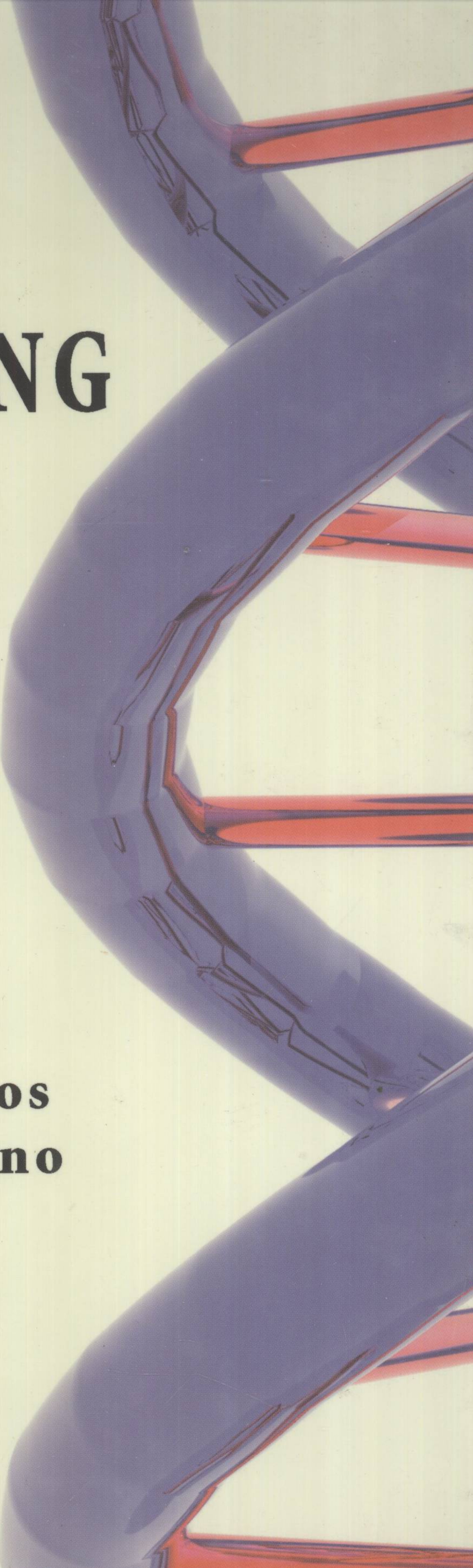
TISSUE ENGINEERING



Edited by
John P. Fisher
Antonios G. Mikos
Joseph D. Bronzino

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Tissue Engineering

Preface

Tissue engineering is increasingly viewed as the future of medicine. As evidenced in both the scientific and popular press, there exists considerable excitement surrounding the strategy of regenerative medicine. In an effort to put the numerous advances in the field into a broad context, this book is devoted to the dissemination of current thoughts on the development of engineered tissues. Three main topics are considered and form the basis for the three sections of the text: Fundamentals of Tissue Engineering, Enabling Technologies, and Tissue Engineering Applications. Fundamentals of Tissue Engineering examines the properties of stem cells, primary cells, growth factors, and extracellular matrix as well as their impact on the development of tissue-engineered devices. Enabling Technologies focuses upon those strategies typically incorporated into tissue-engineered devices or utilized in their development, including scaffolds, nanocomposites, bioreactors, drug delivery systems, and gene therapy techniques. Tissue Engineering Applications presents synthetic tissues and organs that are currently under development for regenerative medicine applications. The contributing authors are a diverse group with backgrounds in academia, clinical medicine, and industry. Furthermore, the text includes contributions from Europe, Asia, and North America, helping to broaden the views on the development and application of tissue-engineered devices.

The text is largely derived from the Advances in Tissue Engineering Short Course, a pioneering forum on regenerative medicine held at Rice University since 1993. The ATE Short Course has educated researchers, students, clinicians, and engineers on both the fundamentals of tissue engineering and recent advances in many of the most prominent tissue engineering laboratories around the world. For many of the contributors, the chapter included in this text presents findings that have been recently discussed at the Advances in Tissue Engineering Short Course.

The target audience for this text includes not only researchers, but also advanced students and industrial investigators. The text should be a useful reference for courses devoted to tissue engineering fundamentals and those laboratories developing tissue-engineered devices for regenerative medicine therapy.

John P. Fisher
University of Maryland

Antonios G. Mikos
Rice University

Editors

John P. Fisher is an assistant professor in the Fischell Department of Bioengineering at the University of Maryland. Dr. Fisher completed his BS (1995) at The Johns Hopkins University in chemical engineering, MS (1998) at the University of Cincinnati, his PhD (2003) at Rice University in bioengineering, and postdoctoral fellowship (2003) at the University of California, Davis in cartilage biology and engineering. At Maryland, Dr. Fisher directs the Biomaterial Laboratory which is involved in the development of biomaterials for engineered tissues, especially bone and cartilage. The lab focuses on the development of novel materials that can support the growth of both adult progenitor and adult stem cells, and is particularly interested in how the supporting biomaterials affect communication among cell populations. Dr. Fisher has received a NSF CAREER Award (2005), an Arthritis Foundation Investigator Award (2006), and the University of Maryland Invention of the Year Award (2006). Dr. Fisher has served as editor of several works, and is currently the reviews editor of the journal *Tissue Engineering*.

Antonios G. Mikos is the J.W. Cox professor of bioengineering and professor of chemical and biomolecular engineering at Rice University. He received his Dipl.Eng. (1983) from the Aristotle University of Thessaloniki, Greece, and his PhD (1988) in chemical engineering from Purdue University under the direction of Professor Nicholas A. Peppas. He was a postdoctoral researcher at the Massachusetts Institute of Technology and the Harvard Medical School working with Professors Robert Langer and Joseph Vacanti before joining the Rice Faculty in 1992 as an assistant professor.

Mikos' research focuses on the synthesis, processing, and evaluation of new biomaterials for use as scaffolds for tissue engineering, as carriers for controlled drug delivery, and as non-viral vectors for gene therapy. His work has led to the development of novel orthopaedic, dental, cardiovascular, neurologic, and ophthalmologic biomaterials. He is the author of over 310 publications and 22 patents. He is the editor of nine books and the author of one textbook.

Mikos is a fellow of the International Union of Societies for Biomaterials Science and Engineering and a fellow of the American Institute for Medical and Biological Engineering. He has been recognized by various awards including the Distinguished Lecturer Award of the Biomedical Engineering Society, the Edith and Peter O'Donnell Award in Engineering of The Academy of Medicine, Engineering and Science of Texas, the Marshall R. Urist Award for Excellence in Tissue Regeneration Research of the Orthopaedic Research Society, and the Clemson Award for Contributions to the Literature of the Society for Biomaterials.

Mikos is a founding editor of the journal *Tissue Engineering* and a member of the editorial boards of the journals *Advanced Drug Delivery Reviews, Biomaterials, Cell Transplantation, Journal of Biomaterials Science Polymer Edition, Journal of Biomedical Materials Research (Part A and B)*, and *Journal of Controlled Release*. He is the organizer of the continuing education course Advances in Tissue Engineering offered annually at Rice University since 1993.

Joseph D. Bronzino received the B.S.E.E. degree from Worcester Polytechnic Institute, Worcester, MA, in 1959, the M.S.E.E. degree from the Naval Postgraduate School, Monterey, CA, in 1961, and the Ph.D. degree in electrical engineering from Worcester Polytechnic Institute in 1968. He is presently the Vernon

Roosa Professor of Applied Science, an endowed chair at Trinity College, Hartford, CT and President of the Biomedical Engineering Alliance and Consortium (BEACON), which is a nonprofit organization consisting of academic and medical institutions as well as corporations dedicated to the development and commercialization of new medical technologies (for details visit www.beaconalliance.org).

He is the author of over 200 articles and 11 books including the following: *Technology for Patient Care* (C.V. Mosby, 1977), *Computer Applications for Patient Care* (Addison-Wesley, 1982), *Biomedical Engineering: Basic Concepts and Instrumentation* (PWS Publishing Co., 1986), *Expert Systems: Basic Concepts* (Research Foundation of State University of New York, 1989), *Medical Technology and Society: An Interdisciplinary Perspective* (MIT Press and McGraw-Hill, 1990), *Management of Medical Technology* (Butterworth/Heinemann, 1992), *The Biomedical Engineering Handbook* (CRC Press, 1st ed., 1995; 2nd ed., 2000; Taylor & Francis, 3rd ed., 2005), *Introduction to Biomedical Engineering* (Academic Press, 1st ed., 1999; 2nd ed., 2005).

Dr. Bronzino is a fellow of IEEE and the American Institute of Medical and Biological Engineering (AIMBE), an honorary member of the Italian Society of Experimental Biology, past chairman of the Biomedical Engineering Division of the American Society for Engineering Education (ASEE), a charter member and presently vice president of the Connecticut Academy of Science and Engineering (CASE), a charter member of the American College of Clinical Engineering (ACCE) and the Association for the Advancement of Medical Instrumentation (AAMI), past president of the IEEE-Engineering in Medicine and Biology Society (EMBS), past chairman of the IEEE Health Care Engineering Policy Committee (HCEPC), past chairman of the IEEE Technical Policy Council in Washington, DC, and presently editor-in-chief of Elsevier's BME Book Series and Taylor & Francis' *Biomedical Engineering Handbook*.

Dr. Bronzino is also the recipient of the Millennium Award from IEEE/EMBS in 2000 and the Goddard Award from Worcester Polytechnic Institute for Professional Achievement in June 2004.

Contributors

Alptekin Aksan
University of Minnesota
Center for Engineering in Medicine/Surgical Services
Massachusetts General Hospital
Harvard Medical School
Shriners Hospital for Children
Boston, Massachusetts

Kyle D. Allen
Department of Oral and Maxillofacial Surgery
Department of Bioengineering
University of Texas Dental Branch
Rice University
Houston, Texas

Jose F. Alvarez-Barreto
School of Chemical Engineering and Materials Science
Bioengineering Center
University of Oklahoma
Norman, Oklahoma

James M. Anderson
Department of Pathology
Macromolecular Science and Biomedical Engineering
Case Western Reserve University
Cleveland, Ohio

Anthony Atala
Department of Urology
Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

Kyriacos A. Athanasiou
Department of Oral and Maxillofacial Surgery
Department of Bioengineering
University of Texas Dental Branch
Rice University
Houston, Texas

C. Becker
Department of Pharmaceutical Technology
University of Regensburg
Regensburg, Germany

B.L. Beckstead
Department of Bioengineering
University of Washington
Seattle, Washington

François Berthiaume
Center for Engineering in Medicine/Surgical Services
Massachusetts General Hospital
Harvard Medical School
Shriners Hospital for Children
Boston, Massachusetts

Steven T. Boyce
Department of Surgery
University of Cincinnati
College of Medicine
Cincinnati, Ohio

Nenad Bursac
Department of Biomedical Engineering
Duke University
Durham, North Carolina

Baohong Cao
Department of Orthopaedic Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

Arnold I. Caplan
Skeletal Research Center
Case Western Reserve University
Cleveland, Ohio

Ayse B. Celil
Bone Tissue Engineering Center
Department of Biological Sciences
Carnegie Mellon University
Pittsburgh, Pennsylvania

Christina Chan
Center for Engineering in Medicine/Surgical Services
Massachusetts General Hospital
Harvard Medical School
Shriners Hospital for Children
Boston, Massachusetts
Michigan State University
Chemical Engineering and Materials Science
East Lansing, Michigan

Gang Cheng
Department of Chemical Engineering
Institute of Biosciences and Bioengineering
Rice University
Houston, Texas

K.S. Chian
School of Mechanical and Production Engineering
Nanyang Technological University
Singapore

Rena N. D'Souza
Department of Orthodontics
University of Texas Health Science Center at Houston-Dental Branch
Rice University
Houston, Texas

Brian Dunham
Department of Otolaryngology/Head and Neck Surgery
Department of Biomedical Engineering
Johns Hopkins School of Medicine
Baltimore, Maryland

Wafa M. Elbjeirami
Department of Biochemistry and Cell Biology
Rice University
Houston, Texas

Jennifer H. Elisseeff
Department of Biomedical Engineering
Johns Hopkins University
Baltimore, Maryland

Mary C. Farach-Carson
Department of Biological Sciences
University of Delaware
Newark, Delaware

John P. Fisher
University of Maryland
College Park, Maryland

William H. Fissell
Department of Internal Medicine
University of Michigan
Ann Arbor, Michigan

Paul Flint
Department of Otolaryngology/Head and Neck Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland

Andrés J. García
Woodruff School of Mechanical Engineering
Petit Institute for Bioengineering and Bioscience
Georgia Institute of Technology
Atlanta, Georgia

Andrea S. Gobin
Department of Bioengineering
Rice University
Houston, Texas

W.T. Godbey
Laboratory for Gene Therapy and Cellular Engineering
Department of Chemical and Biomolecular Engineering
Tulane University
New Orleans, Louisiana

Aaron S. Goldstein
Department of Chemical Engineering
Virginia Polytechnic Institute and State University
Blacksburg, Virginia

A. Göpferich
Department of Pharmaceutical Technology
University of Regensburg
Regensburg, Germany

K. Jane Grande-Allen
Department of Bioengineering
Rice University
Houston, Texas

Scott Guelcher
Bone Tissue Engineering Center
Department of Biological Sciences
Carnegie Mellon University
Pittsburgh, Pennsylvania

Kiki B. Hellman
The Hellman Group, LLC
Clarksburg, Maryland

Jeffrey O. Hollinger
Bone Tissue Engineering Center
Department of Biological Sciences
Carnegie Mellon University
Pittsburgh, Pennsylvania

Johnny Huard
Department of Orthopaedic Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

H. David Humes
Departments of Internal Medicine
University of Michigan and Ann Arbor Veteran's Affairs Medical Center
Ann Arbor, Michigan

Esmaiel Jabbari
Department of Orthopedic Surgery
Department of Physiology and Biomedical Engineering
Mayo Clinic College of Medicine
Rochester, Minnesota

John A. Jansen
Department of Biomaterials
University Medical Center St. Radboud
Nijmegen, The Netherlands

Kristi L. Kiick
Department of Materials Science and Engineering
University of Delaware
Newark, Delaware

Catherine Le Visage
Department of Biomedical Engineering
Johns Hopkins School of Medicine
Baltimore, Maryland

Kam Leong
Department of Biomedical Engineering
Johns Hopkins School of Medicine
Baltimore, Maryland

Yong Li
Department of Orthopaedic Surgery
University of Pittsburgh
Pittsburgh, Pennysylvania

Lichun Lu
Department of Orthopedic Surgery
Department of Physiology and Biomedical Engineering
Mayo Clinic College of Medicine
Rochester, Minnesota

Surya K. Mallapragada
Department of Chemical Engineering
Iowa State University
Ames, Iowa

Antonios G. Mikos
Department of Bioengineering
Rice University
Houston, Texas

Michael Miller
Department of Plastic Surgery
University of Texas
Houston, Texas

Amit S. Mistry
Department of Bioengineering
Rice University
Houston, Texas

David J. Mooney
Departments of Chemical Engineering, Biomedical Engineering
Biologic and Materials Sciences
University of Michigan
Ann Arbor, Michigan
Division of Engineering and Applied Sciences
Harvard University
Cambridge, Massachusetts

Michael J. Moore
Department of Orthopedic Surgery
Department of Physiology and Biomedical Engineering
Mayo Clinic College of Medicine
Rochester, Minnesota

J.M. Munson
Laboratory for Gene Therapy and Cellular Engineering
Department of Chemical and Biomolecular Engineering
Tulane University
New Orleans, Louisiana

Hairong Peng
Department of Orthopaedic Surgery
University of Pittsburgh
Pittsburgh, Pennsylvania

J. Daniell Rackley
Department of Urology
Wake Forest University Baptist Medical Center
Winston-Salem, North Carolina

B.D. Ratner
Department of Bioengineering
University of Washington
Seattle, Washington

Jennifer B. Recknor
Department of Chemical Engineering
Iowa State University
Ames, Iowa

A. Hari Reddi
Center for Tissue Regeneration and Repair
Department of Orthopaedic Surgery
University of California
Davis School of Medicine
Sacramento, California

A.C. Ritchie
School of Mechanical and Production Engineering
Nanyang Technological University
Singapore

P. Quinten Ruhé
Department of Biomaterials
University Medical Center St. Radboud
Nijmegen, The Netherlands

Rachael H. Schmedlen
Department of Bioengineering
Rice University
Houston, Texas

Songtao Shi
National Institutes of Health
National Institute of Dental and Craniofacial Research
Craniofacial and Skeletal Diseases Branch
Bethesda, Maryland

Xinfeng Shi
Department of Bioengineering
Rice University
Houston, Texas

Yan-Ting Shiu
Department of Bioengineering
University of Utah
Salt Lake City, Utah

Vassilios I. Sikavitsas
School of Chemical Engineering and Materials Science
Bioengineering Center
University of Oklahoma
Norman, Oklahoma

Sunil Singhal
Department of General Surgery
Johns Hopkins School of Medicine
Baltimore, Maryland

David Smith
Teregenics, LLC
Pittsburgh, Pennsylvania

Paul H.M. Spauwen
Department of Plastic and Recontructive Surgery
University Medical Center St. Radboud
Nijmegen, The Netherlands

Dorothy M. Supp
Shriners Hospital for Children
Cincinnati Burns Hospital
Cincinnati, Ohio

Arno W. Tilles
Center for Engineering in Medicine/Surgical Services
Massachusetts General Hospital
Harvard Medical School
Shriners Hospitals for Children
Boston, Massachusetts

Mehmet Toner
Center for Engineering in Medicine/Surgical Services
Massachusetts General Hospital
Harvard Medical School
Shriners Hospital for Children
Boston, Massachusetts

Roger C. Wagner
Department of Biological Sciences
University of Delaware
Newark, Delaware

Jennifer L. West
Department of Bioengineering
Rice University
Houston, Texas

Joop G.C. Wolke
Department of Biomaterials
University Medical Center
St. Radboud
Nijmegen, The Netherlands

Mark E.K. Wong
Department of Oral and
Maxillofacial Surgery
Department of
Bioengineering
University of Texas Dental
Branch
Rice University
Houston, Texas

Fan Yang
Department of Biomedical
Engineering
Johns Hopkins University
Baltimore, Maryland

Martin L. Yarmush
Center for Engineering in
Medicine/Surgical Services
Massachusetts General
Hospital
Shriners Burns Hospital for
Children
Harvard Medical School
Boston, Massachusetts

Michael J. Yaszemski
Department of Orthopedic
Surgery
Department of Physiology and
Biomedical Engineering
Mayo Clinic College of Medicine
Rochester, Minnesota

Diana M. Yoon
Department of Chemical
Engineering
University of Maryland
College Park, Maryland

Yu Ching Yung
Department of Chemical
Engineering
University of Michigan
Ann Arbor, Michigan

Kyriacos Zygourakis
Department of Chemical
Engineering
Institute of Biosciences and
Bioengineering
Rice University
Houston, Texas

I

Fundamentals of Tissue Engineering

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1

Fundamentals of Stem Cell Tissue Engineering

Arnold I. Caplan
Case Western Reserve University

1.1 Introduction

In adults, stem cells are fundamental cell units within every tissue that function as a renewal source of highly specialized, terminally differentiated cells. The cell renewal serves to compensate for the normal cell turnover (cell death) or serves to provide reparative cells for the repair of minor defects. The stem cells can be thought of as the rejuvenation potential of the organism (high during the young or growth phase). Unfortunately, this renewal capacity decreases with age; even amphibians that are able to perfectly regenerate an entire limb lose this capacity with age [1]. Thus, one of the long-term goals of Tissue Engineering is to learn how to control and regulate this natural regeneration potential, so that tissue performance can be enhanced or massive defects can be repaired via an intrinsic regenerative pathway.

As a scientific discipline, Tissue Engineering is very young, and thus, is quite distant from its long-term goal. To approach this goal, a series of sequential technological advancements must be made. Our earliest achievements, material-assisted repair of various tissues, have been accomplished in a variety of preclinical models and, in the case of skin, with clinical success in humans [2–5]. In all these cases, scaffolds, cells and growth factors/cytokines, or a combination of these have been surgically implanted. Like the first crude cardiac pacemakers, their initial successful implantation served as a catalyst for their improvement and perfection, a process that is ongoing.

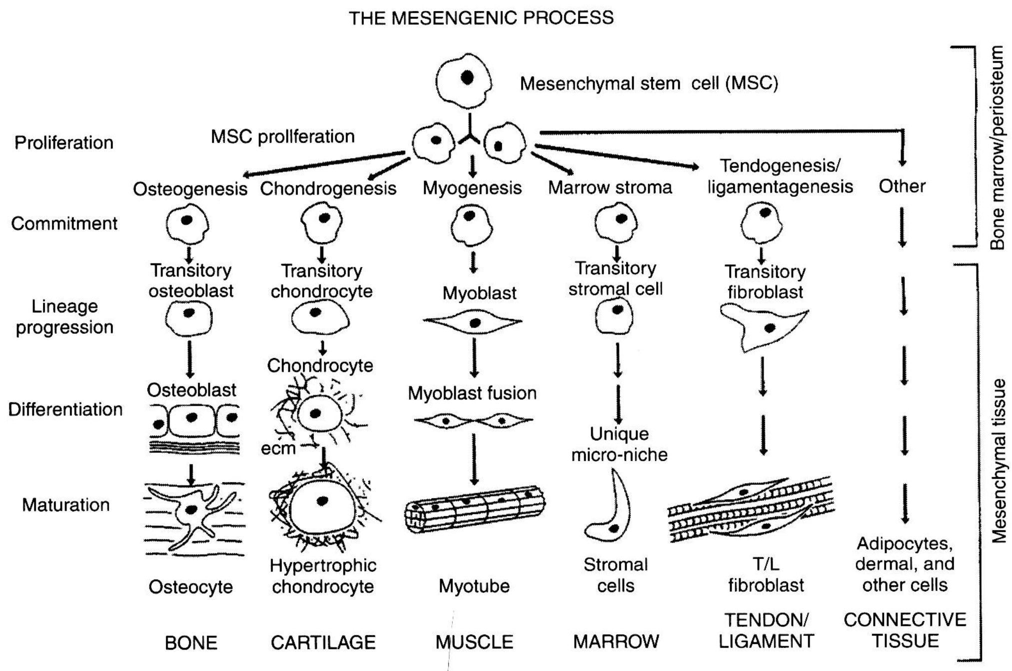

FIGURE 1.1 The mesengenic process involves the replication of MSCs and their entrances along multistep lineage pathways to produce differentiated cells that fabricate specific tissues such as bone, cartilage, and so on. We know most about the lineages on the left and least about those on the right of the diagram.

It follows that if we are to learn how to manage the various intrinsic organ stem cells to reconstruct or repair specific tissues, we must first obtain a deep understanding of these unique stem cells; we must understand what makes these cells divide, differentiate, grow old, and expire. We must learn how to position these stem cells in defects, how to coordinate the integration of blood vessels and nerves, and how to integrate the host tissue with the *neo*-tissue. Lastly, as Tissue Engineers, we must recognize that each individual has a genetically controlled variation, even between close family members, that will affect the fine-tuning of every repair logic.

It would be impossible to review the fundamental characteristics of every stem cell/organ system in the body in this chapter. Thus, I will focus on only one stem cell system, the mesenchymal stem cells (MSCs), that has already proven to be a versatile source of reparative cells for Tissue Engineering applications.

1.2 Mesenchymal Stem Cells

I suggested long ago that bone marrow contained a stem cell capable of differentiating into a number of mesenchymal tissues; I call this cell a mesenchymal stem cell (MSC) and the lineage sequences Mesengenesis, as pictured in Figure 1.1 [6–11]. This suggestion was based on my familiarity with embryonic mesenchymal progenitors [12–14] and partially on the early studies of Freidenstein [15] and, in particular, of Owen. Indeed, it was Owen [16] who drew me into the adult MSC realm by her scholarly treatise. In the late 1980s, Stephen Haynesworth and I [10,17,18] embarked in the task of isolating these rare MSCs from human bone marrow; the key to our success was a selected batch of fetal bovine serum that worked quite well with embryonic chick limb bud mesenchymal progenitor cells [19]. Subsequently, my collaborators have shown that marrow-derived MSCs are capable of differentiating into cartilage [20,21], bone [22,23], muscle [24,25], bone marrow stroma (hematopoietic support tissue) [26–28], fat [29], tendon [30,31], and other connective tissues. Other laboratories have provided evidence that MSCs can