

# TISSUE ENGINEERING

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



CRC Press  
Taylor & Francis Group

Q813  
T616

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E2008000057



**CRC Press**

Taylor & Francis Group

Boca Raton London New York

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CRC Press is an imprint of the  
Taylor & Francis Group, an **informa** business

This material was previously published in *Tissue Engineering and Artificial Organs* © 2006 by Taylor & Francis Group, LLC.

CRC Press  
Taylor & Francis Group  
6000 Broken Sound Parkway NW, Suite 300  
Boca Raton, FL 33487-2742

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No claim to original U.S. Government works  
Printed in the United States of America on acid-free paper  
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8493-9026-5 (Hardcover)  
International Standard Book Number-13: 978-0-8493-9026-5 (Hardcover)

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#### Library of Congress Cataloging-in-Publication Data

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Tissue engineering / editors, John P. Fisher, Antonios G. Mikos, and Joseph D. Bronzino.

p. ; cm.

"A CRC title."

Includes bibliographical references and index.

ISBN-13: 978-0-8493-9026-5 (hardcover : alk. paper)

ISBN-10: 0-8493-9026-5 (hardcover : alk. paper)

1. Tissue engineering. I. Fisher, John P. II. Mikos, Antonios G. III. Bronzino, Joseph D., 1937-  
[DNLM: 1. Tissue Engineering. QT 37 T61545 2007]

R857.T55T548 2007

610.28--dc22

2007007401

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# Tissue Engineering

# Preface

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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.

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**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

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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.

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# I

# Fundamentals of Tissue Engineering

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# 1

## Fundamentals of Stem Cell Tissue Engineering

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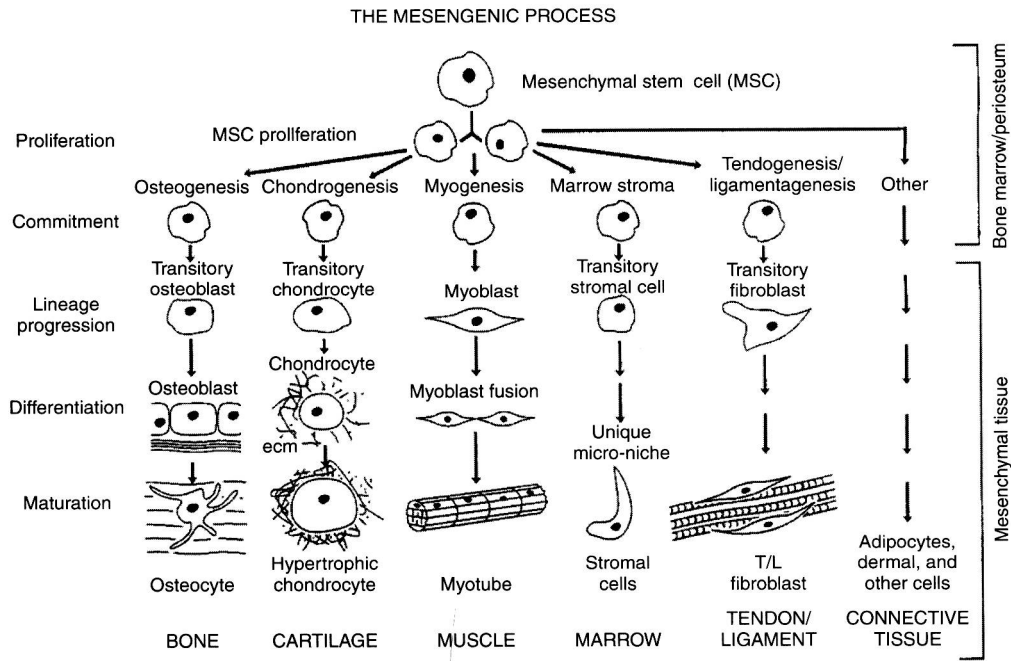
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### 1.1 Introduction

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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 Mesengenes, 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