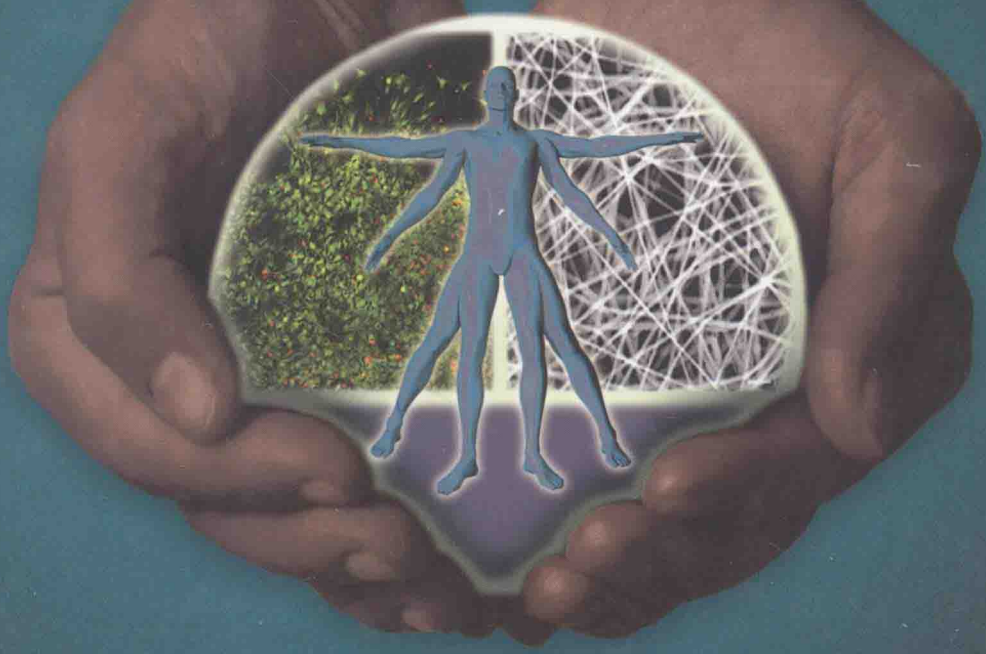
SECOND EDITION

Nanotechnology and Regenerative Engineering

The Scaffold

Foreword by C.N.R. Rao



Cato T. Laurencin, M.D., Ph.D.
Lakshmi S. Nair, M.Phil., Ph.D.

CRC Press
Taylor & Francis Group

Boimedical Engineering

"... essential reading for all those working in the area of biomaterials, tissue engineering, and bionanotechnology. ... The collection of 16 chapters written by experts in their fields from different parts of the world presents the state of the art, and the state of the art to come for a wide audience. In my opinion, the book will be a valuable resource to the fields of bionanotechnology and tissue regeneration."

—C.N.R. Rao, National Research Professor, Linus Pauling Research Professor & Honorary President Jawaharlal Nehru Center for Advanced Scientific Research, Bangalore, India

---

Nanotechnology and regenerative engineering have emerged to the forefront as the most versatile and innovative technologies to foster novel therapeutic techniques and strategies of the twenty-first century. The first edition of *Nanotechnology and Tissue Engineering: The Scaffold* was the first comprehensive source to explain the developments in nanostructured biomaterials for tissue engineering, the relevance of nanostructured materials in tissue regeneration, and the current applications of nanostructured scaffolds for engineering various tissues. This fully revised second edition, renamed **Nanotechnology and Regenerative Engineering: The Scaffold**, provides a thorough update to the existing material, bringing together these two unique areas to give a perspective of the emerging therapeutic strategies for a wide audience.

New coverage includes

- Updated discussion of the importance of scaffolds in tissue engineering
- Exploration of cellular interactions at the nanoscale
- Complete range of fabrication processes capable of developing nanostructured scaffolds for regenerative engineering
- Applications of nanostructured scaffolds for neural, skin, cardiovascular, and musculoskeletal regenerative engineering
- FDA approval process of nanostructure scaffolds
- Products based on nanostructured scaffolds

Due to the unique and tissue-mimic properties of the nanostructured scaffolds, the past five years have seen a tremendous growth in nanostructured materials for biological applications. The revised work presents the current state-of-the-art developments in nanostructured scaffolds for regenerative engineering.

K19089

CRC Press
Taylor & Francis Group
an **informa** business
www.crcpress.com

6000 Broken Sound Parkway, NW
Suite 300, Boca Raton, FL 33487
711 Third Avenue
New York, NY 10017
2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

Laurencin
Nair

Nanotechnology and Regenerative Engineering

SECOND
EDITION

CRC

SECOND EDITION

Nanotechnology and Regenerative Engineering

The Scaffold

Cato T. Laurencin, M.D., Ph.D.
University of Connecticut, USA

Lakshmi S. Nair, M.Phil, Ph.D.
University of Connecticut, USA

CRC Press
Taylor & Francis Group
Boca Raton London New York

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

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

Printed and bound in India by Replika Press Pvt. Ltd.

Printed on acid-free paper
Version Date: 20140815

International Standard Book Number-13: 978-1-4665-8537-9 (Hardback)

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

SECOND EDITION

Nanotechnology and Regenerative Engineering

The Scaffold

To my wonderful wife, Cynthia, and my fantastic children:

Ti, Michaela, and Victoria

Cato T. Laurencin

To my husband, Prem, and my son, Bharath

Lakshmi S. Nair

Foreword

I am immensely pleased to write the foreword for the second edition of *Nanotechnology and Regenerative Engineering: The Scaffold* edited by Professors Laurencin and Nair. This book will be essential reading for all those working in the area of biomaterials, tissue engineering and bionanotechnology. Indeed, I understand the first edition of the book was seen as extremely important across the world, thus it is wonderful to see this new book. Today, science and technology at the nanoscale is capable of providing unprecedented understanding, control and manipulation of matter at all levels. Nanotechnology has already had a significant impact on molecular medicine through the development of novel targeted therapies, diagnostic and imaging techniques, as well as by providing novel strategies to repair and regenerate tissues. Many of these technologies are currently used clinically. Nanofabrication techniques have opened the door to developing unique structures, which would be of great value in regenerative engineering, by giving us the ability to mimic biological structures with molecular-level precision, and thereby controlling or modulating cellular functions. The second edition of the book provides a fine summary of the present status of bionanotechnology aimed towards developing biomimetic scaffolds for tissue regeneration. The attraction of the book lies in the judicious combination of concise and comprehensive chapters covering the fundamentals of ideal scaffolds for engineering tissues, cellular behavior toward nanostructures, state-of-the art nanofabrication techniques for developing biomimetic nanostructures for regenerative engineering and regulatory processes involved in nanostructured tissue–engineered products. The collection of 16 chapters written by experts in their fields from different parts of the world presents the state of the art and the state of the art to come for a wide audience. In my opinion, the book will be a valuable resource to the fields of bionanotechnology and tissue regeneration.

C.N.R. Rao
National Research Professor
Linus Pauling Research Professor &
Honorary President
Jawaharlal Nehru Center for
Advanced Scientific Research
Bangalore, India

Distinguished Visiting Professor
Department of Materials
University of California, Santa Barbara
Santa Barbara, California

Preface

This second edition entitled *Nanotechnology and Regenerative Engineering: The Scaffold* consists of 16 chapters that provide a state-of-the-art, comprehensive account of research in the rapidly emerging area of regenerative engineering to regenerate complex tissues, organs, or organ systems. Regenerative engineering encompasses the elements of tissue engineering, advanced biomaterials, regenerative medicine, and morphogenesis to design strategies to regenerate complex tissues. The tremendous advances in bionanotechnology during the past decade have significantly impacted the area of tissue engineering, opening up new avenues to realize the dream of regenerative engineering. This book is a natural presentation of the marriage between nanotechnology and tissue engineering, technologies that have the potential to revolutionize tissue/organ engineering in the near future. Each chapter is written with a detailed background as the book covers a multidisciplinary area targeting audiences belonging to various professions ranging from engineers, clinicians, and scientists to graduate and senior undergraduate students. The chapters also provide an extensive bibliography for the reader who wants to explore the subject to a greater depth.

The chapters carry the reader through the fundamentals of tissue engineering, comprehensive analysis of the unique cellular responses toward nanostructured materials, emerging nanofabrication techniques, and state-of-the-art reviews on the exciting breakthroughs using nanostructures in engineering four major tissues of the human body—skin, neural, vascular, and musculoskeletal—followed by the FDA regulations pertaining to nanostructured materials. Each of the 16 chapters is subindexed and titled so that the book can easily be used as a reference source.

We have chosen to present the materials under five sections: Section I clearly emphasizes the importance of scaffolds in tissue regeneration. This section includes four chapters. Chapter 1 presents a broad overview of the area of tissue engineering and sets the stage for the rest of the book. Chapter 2 vividly presents the structure and functions of the extracellular matrix, the structure that tissue engineers are attempting to recreate using novel technologies. Chapter 3 discusses the functions and requirements of synthetic scaffolds for engineering tissues and Chapter 4 reviews the various microfabrication techniques currently being investigated for developing scaffolds to support tissue regeneration. Section II is meant to emphasize the effect of nanostructures on cellular responses and tissue regeneration. Chapter 5 presents an in-depth discussion of the current literature on cellular responses toward nanostructured materials. Chapter 6 provides an overview of the various nanoscale biological surface modifications of biomaterials to improve cellular responses. Section III presents an overview of some of the most promising nanofabrication techniques to develop scaffolds to support tissue regeneration. Chapters 7 through 9 give a comprehensive account of the process of electrospinning and its versatility as a fabrication technique to form scaffolds. Chapter 10 discusses the various lithographic techniques toward developing nanostructured scaffolds. Chapter 11 presents self-assembly as a unique fabrication method for developing biologically active scaffolds for accelerated tissue regeneration. Section IV provides an overview of some of the applications of nanostructured scaffolds in biology and medicine. Chapter 12 discusses the applications of nanostructured materials in skin tissue engineering. Chapter 13 discusses the applications in neural tissue engineering, Chapter 14 in cardiovascular tissue engineering, and Chapter 15 in

musculoskeletal tissue engineering. Section V provides a summary of the current FDA regulations pertaining to nanostructured materials for biological applications.

It is our hope that all the chapters, written by eminent experts in the field, will provide a platform to better understand the impact of nanotechnology in the field of regenerative engineering.

We are particularly grateful to Dr. Raymond Sackler for his recognition and encouragement of our work and his endowment of our center.

Cato T. Laurencin, MD, PhD
Lakshmi S. Nair, PhD

Editors

Cato T. Laurencin, MD, PhD, is a university professor at the University of Connecticut (the seventh in the institution's history). He is the Van Dusen Distinguished Endowed Professor of Orthopaedic Surgery, professor of chemical and biomolecular engineering, and professor of materials engineering and biomedical engineering at the school. Dr. Laurencin is the founder and director of both the Institute for Regenerative Engineering and the Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences at the University of Connecticut.

Dr. Laurencin earned his undergraduate degree in chemical engineering from Princeton University and his medical degree magna cum laude from Harvard Medical School. In addition, he earned his PhD in biochemical engineering/biotechnology from the Massachusetts Institute of Technology where he was named a Hugh Hampton Young Fellow.

Dr. Laurencin's research focuses on regenerative engineering, biomaterials, nanotechnology, drug delivery, and stem cell science. His work on engineering tissues was honored by *Scientific American* magazine as one of the 50 greatest achievements in science in 2007. Dr. Laurencin was named the 2009 winner of the Pierre Galletti Award, medical and biological engineering's highest honor, and was named one of the 100 Engineers of the Modern Era by the American Institute of Chemical Engineers at its Centennial celebration. In 2012, his work was highlighted by *National Geographic* magazine in its "100 Discoveries That Have Changed Our World" edition.

Dr. Laurencin is dedicated to mentoring, and he has received the Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring in ceremonies at the White House, and the American Association for the Advancement of Science's Mentor Award.

Dr. Laurencin is active nationally in science leadership. Formerly chair of the College of Fellows for the American Institute for Medical and Biological Engineering, he has served on the National Science Advisory Board for the FDA and the National Science Foundation's Engineering Advisory Committee. He has served as chair of the Engineering Section for the National Academy of Sciences, Institute of Medicine, and the Peer Committee for Bioengineering for the National Academy of Engineering. At the National Institutes of Health (NIH), he is a member of the Advisory Committee to the Director of the National Institutes of Health and a member of the NIH National Advisory Council for Biomedical Imaging and Bioengineering.

Dr. Laurencin is an elected member of the National Academy of Engineering and the Institute of Medicine of the National Academy of Sciences.

Lakshmi S. Nair, MPhil, PhD, is an assistant professor at the Department of Orthopaedic Surgery, Institute for Regenerative Engineering, and Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences at the University of Connecticut Health Center. She is also a faculty in the departments of Biomedical Engineering and Materials Engineering at the University of Connecticut. Dr. Nair earned her PhD in polymer chemistry from Sree Chitra Tirunal Institute for Medical Sciences and Technology, India. Her research interests include injectable hydrogels and nanostructured materials for tissue engineering and drug delivery. She has more than 100 publications in the area of biomaterials and tissue engineering.

Contributors

C. Mauli Agrawal
Department of Biomedical Engineering
The University of Texas at San Antonio
San Antonio, Texas

Keshia Ashe
Department of Chemical Engineering
University of Connecticut
Storrs, Connecticut

S. Balakrishna Pai
WHC Department of Biomedical Engineering
Georgia Institute of Technology
Emory University
Atlanta, Georgia

Ravi Bellamkonda
WHC Department of Biomedical Engineering
Georgia Institute of Technology
Emory University
Atlanta, Georgia

Christopher J. Bettinger
Biomedical Engineering and Material Science
Carnegie Mellon University
Pittsburgh, Pennsylvania

Mina J. Bissell
Life Sciences Division
Lawrence Berkeley National Laboratory
Berkeley, California

Jeffrey T. Borenstein
Charles Stark Draper Laboratory
Biomedical Engineering Center
Cambridge, Massachusetts

Edward A. Botchwey
Department of Biomedical Engineering
Georgia Institute of Technology
Atlanta, Georgia

Casey K. Chan
Department of Orthopaedic Surgery
Yong Loo Lin School of Medicine
National University of Singapore
Singapore, Singapore

Michael Cho
Department of Bioengineering
University of Illinois at Chicago
Chicago, Illinois

Batur Ercan
Department of Chemical Engineering
Northeastern University
Boston, Massachusetts

Shalini V. Gohil
Department of Orthopaedic Surgery
University of Connecticut Health Center
Farmington, Connecticut

Akihiro Horii
Center for Biomedical Engineering
Massachusetts Institute of Technology
Cambridge, Massachusetts

Eric N. James
Department of Orthopaedic Surgery
University of Connecticut Health Center
Farmington, Connecticut

Tejas Shyam Karande
Department of Biomedical Engineering
The University of Texas at Austin
Austin, Texas
and
Department of Orthopaedics
The University of Texas Health Science Center at San Antonio
San Antonio, Texas

Jeffrey M. Karp
Department of Medicine
Center for Biomedical Engineering
Brigham and Women's Hospital
Harvard Medical School
and
Harvard-MIT Division of Health Science and Technology
Massachusetts Institute of Technology
Cambridge, Massachusetts

J. Jordan M. Kaufmann
Cardiovate, Inc.
San Antonio, Texas

Yusuf M. Khan
Department of Orthopaedic Surgery
and
Department of Materials Science & Engineering
and
Department of Biomedical Engineering
and
Institute for Regenerative Engineering
Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences
University of Connecticut
Farmington, Connecticut

Sangamesh G. Kumbar
Department of Orthopaedic Surgery
and
Department of Materials Science & Engineering
and
Department of Biomedical Engineering
and
Institute for Regenerative Engineering
Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences
University of Connecticut
Farmington, Connecticut

Robert Langer
Department of Chemical Engineering
and
Department of Bioengineering
and
Department of Mechanical Engineering
and
Harvard-MIT Division of Health Science and Technology
Massachusetts Institute of Technology
Cambridge, Massachusetts

Cheryl M. Lau
Department of Biomedical Engineering
Georgia Institute of Technology
Atlanta, Georgia

Cato T. Laurencin
Department of Orthopaedic Surgery
and
Department of Materials Science & Engineering
and
Department of Biomedical Engineering
and
Institute for Regenerative Engineering
Raymond and Beverly Sackler Center for Biomedical, Biological, Physical and Engineering Sciences
University of Connecticut
Farmington, Connecticut

Duron A. Lee
Department of Biomedical Engineering
Drexel University
Philadelphia, Pennsylvania

Susan Liao
School of Materials Science and Engineering
Nanyang Technological University
Singapore, Singapore