COLD SPRING HARBOR PERSPECTIVES IN MEDICINE

Tissue Engineering and Regenerative Medicine

EDITED BY Joseph P. Vacanti

Tissue Engineering and Regenerative Medicine

Tissue engineering is an interdisciplinary field in which scaffolds, cells, and biologically active molecules are used to construct body tissues and organs. The field aims to find solutions for the repair of damaged tissues and enable the production of organs for transplantation.

Written and edited by experts in the field, this collection from *Cold Spring Harbor Perspectives in Medicine* surveys tools that are currently available to scientists and engineers in the field and how they have been used to fabricate physiologically appropriate tissues and organs. The contributors discuss the preparation of biologically active scaffolds that induce regenerative responses, three-dimensional bioprinting strategies to fabricate structures in preprogrammed patterns, and scaffold-free approaches using cells capable of self-assembly.

The authors also review recent advances in the fabrication of specific body structures, including the craniofacial complex, heart and blood vessels, intestine, and bone and cartilage. This book is therefore essential reading for all scientists, engineers, and physicians interested in the replacement, repair, or regeneration of human organs and tissues.

www.perspectivesinmedicine.org

ISBN 978-1-621821-28-1

COLD SPRING HARBOR
LABORATORY PRESS

Vacanti

Tissue Engineering and Regenerative Medicine

CSH PRESS

Tissue Engineering and Regenerative Medicine

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

EDITED BY

Joseph P. Vacanti

Harvard Medical School
Massachusetts General Hospital

COLD SPRING HARBOR LABORATORY PRESS
Cold Spring Harbor, New York • www.cshlpress.org

Tissue Engineering and Regenerative Medicine

A subject collection from *Cold Spring Harbor Perspectives in Medicine*
Articles online at www.perspectivesinmedicine.org

All rights reserved
© 2017 by Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York
Printed in the United States of America

Executive Editor	Richard Sever
Managing Editor	Maria Smit
Senior Project Manager	Barbara Acosta
Permissions Administrator	Carol Brown
Production Editor	Diane Schubach
Production Manager/Cover Designer	Denise Weiss
Publisher	John Inglis

Front cover artwork: Photo of a 3D printed skull using image data from a human cranial CT scan. (Photo credit: Joseph P. Vacanti.)

Library of Congress Cataloging-in-Publication Data

Names: Vacanti, Joseph, editor.
Title: Tissue engineering and regenerative medicine / edited by Joseph P. Vacanti, Massachusetts General Hospital and Harvard Medical School.
Description: Cold Spring Harbor, New York : Cold Spring Harbor Laboratory Press, [2017] | Series: Perspectives CSHI | Includes bibliographical references and index.
Identifiers: LCCN 2016057052 | ISBN 9781621821281 (hardback)
Subjects: LCSH: Tissue engineering. | Regenerative medicine. | BISAC: SCIENCE / Life Sciences / Biology / Developmental Biology. | SCIENCE / Life Sciences / Cytology. | MEDICAL / Diseases.
Classification: LCC R857.T55 T5687 2017 | DDC 612/.028--dc23
LC record available at https://lccn.loc.gov/2016057052

10 9 8 7 6 5 4 3 2 1

All World Wide Web addresses are accurate to the best of our knowledge at the time of printing.

Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Cold Spring Harbor Laboratory Press, provided that the appropriate fee is paid directly to the Copyright Clearance Center (CCC). Write or call CCC at 222 Rosewood Drive, Danvers, MA 01923 (978-750-8400) for information about fees and regulations. Prior to photocopying items for educational classroom use, contact CCC at the above address. Additional information on CCC can be obtained at CCC Online at www.copyright.com.

For a complete catalog of all Cold Spring Harbor Laboratory Press publications, visit our website at www.cshlpress.org.

试读结束，需要全本PDF请购买 www.ertongbook.com

Tissue Engineering and Regenerative Medicine

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

OTHER SUBJECT COLLECTIONS FROM *COLD SPRING HARBOR PERSPECTIVES IN MEDICINE*

Chromatin Deregulation in Cancer
Malaria: Biology in the Era of Eradication
Antibiotics and Antibiotic Resistance
The p53 Protein: From Cell Regulation to Cancer
Aging: The Longevity Dividend
Epilepsy: The Biology of a Spectrum Disorder
Molecular Approaches to Reproductive and Newborn Medicine
The Hepatitis B and Delta Viruses
Intellectual Property in Molecular Medicine
Retinal Disorders: Genetic Approaches to Diagnosis and Treatment
The Biology of Heart Disease
Human Fungal Pathogens
Tuberculosis
The Skin and Its Diseases
MYC *and the Pathway to Cancer*
Bacterial Pathogenesis

SUBJECT COLLECTIONS FROM *COLD SPRING HARBOR PERSPECTIVES IN BIOLOGY*

Cell Polarity
Cilia
Microbial Evolution
Learning and Memory
DNA Recombination
Neurogenesis
Size Control in Biology: From Organelles to Organisms
Mitosis
Glia
Innate Immunity and Inflammation
The Genetics and Biology of Sexual Conflict
The Origin and Evolution of Eukaryotes
Endocytosis
Mitochondria
Signaling by Receptor Tyrosine Kinases

Preface

THE SCIENTIFIC FIELD OF TISSUE ENGINEERING and regenerative medicine is about 30 years old but it has its roots in science dating to the ancient Greeks. To understand its history, its goals, and its approaches, an acquaintance with the scientific tradition that contributed to its conceptualization is useful. A discussion of the human need it seeks to address is also important. Once contextualized, we can look at the development of the field over the last one-third of a century. This book's purpose is then to use several specific examples of progress in areas that not only are important but also serve as models for advancing the field into new areas.

The history of modern *Homo sapiens* has been recently summarized by Yuval Noah Harari in his 2015 book, *Sapiens: A Brief History of Humankind*. The relevant question is, "When did humans first start caring for others who were injured or infirmed?" The evidence indicates that as long as there have been humans other humans have tried to help individuals in need. Traditional twentieth century work demonstrates trephination of the human skull as early as the Mesolithic Period between 10,000 and 5000 BC. The purposes of this surgical procedure remain largely unknown as causes of mental and physical ailments were obscured by ignorance, belief in magic, and mysticism. But even more remarkable is more recent evidence summarized by Harari (2015):

> Archeologists have discovered the bones of Neanderthals who lived for many years with severe physical handicaps, evidence that they were cared for by their relatives.

Since we now know that *Homo sapiens* carries DNA from Neanderthals, our early caring dates to an era when they shared the planet with other human species. All of modern medicine and surgery has progressed through the ages based on this fundamental human trait. Progress and improvements in care, recovery, and cure are coincident with advances in our knowledge of nature and biologic systems, technologic development in multiple areas of human endeavor based on empiric trial and error, as well as scientific discovery.

When an individual suffers loss of living tissue from trauma, disease, or congenital malformation, loss of function as well as cosmetic deformity can result. In severe instances, death follows. The first historically documented attempts at reconstruction include reconstruction of the nose. Punishment for crimes in ancient India was amputation of the nose. Although there are claims to nose reconstruction in India as early as 1000 BC, sometime after 100 AD, a surgical technique employing a forehead skin flap is described in the *Sushruta Samhita*. This was translated into Arabic ~800 AD. In Europe, a forearm flap for nasal reconstruction was described in 1597 AD by Tagliacozzi of the University of Bologna, and it was in use through World War I (Rutkow 1993). These early forms of reconstruction involve the use of living tissue, taken from one position and moved to another location for a different purpose. The most radical application of this approach was the development of organ transplantation in the mid-twentieth century. Taking a living organ from one individual and transporting and successfully implanting it into another individual was a triumph of biology, surgery, and ingenuity.

Perhaps even older is another approach to replacement, which is the use of artificial materials to create artificial replacement structures, again, in an attempt to recreate form and function. Excellent examples of limb-replacement structures survive from the European Renaissance Period. A metal artificial hand with a mechanism for grasping from the 15th century is displayed at Museum of the History of Science (University of Oxford). Another metal upper limb prosthetic device from a

German feudal knight (1480–1562) is in the Science Museum of London. It has an articulated elbow, an articulated wrist, and movable articulated fingers, controlled from a cord operated from the shoulder. This approach to replacement has been improved and modernized to the present day, making use of remarkable materials, digital technologies, and modern science and engineering to improve and save lives.

Thus, with our ancient human trait of caring for others, two strategies evolved for replacing lost structure and function, namely, the use of living materials or the use of inanimate, nonliving materials. Tissue engineering and regenerative medicine have been conceptualized in the latter third of the 20th century to fill the void where the two old and enduring approaches fall short of their intended therapeutic goals. Tissue engineering seeks to fabricate living structures on demand to replace, repair, or regenerate organs and tissues that are damaged by trauma, disease, or congenital deformity. Organ transplantation is the best example because its very success has led to its most difficult barrier, the donor organ shortage. Multiple millions of people globally have a need for organs, but the supply is only in the thousands. In a sense, the idea is an inevitable outcome of history, but the road to success is dependent on biologic discovery and the application of engineering to biology, materials science, and design.

Although the science in these areas is complex and not directly the subject of this preface, we can look to a few historical observations in nature and mathematics, which have had a fundamental and profound effect on the development of this new approach to human therapy.

> The body of anything whatsoever that receives nourishment continually dies and is continually renewed. Unless therefore you supply nourishment equivalent to that which has departed the life fails in its vigors; and if you deprive it of this nourishment, the life is completely destroyed. (Leonardo da Vinci, Anat. Ms. B, fol. 28r)

This fundamental fact of all biological systems, both plant and animal, has never been more elegantly observed or stated since Leonardo da Vinci. It is a fundamental biophysical constraint for the design of all living systems for the field of tissue engineering. Its mathematical formulation was articulated by Folkman and Hochberg in 1973 when discussing the necessity of new blood vessel formation in the growth of tumors. To provide nourishment to the interior of a mass of living cells, new blood vessels need to form to deal with the problem that all nourishment to a sphere of living cells occurs at the surface of the cells (Folkman and Hochberg 1973). Mathematically, as the mass of cells grows, the surface increases only as the square of the radius, but the mass or volume of the cells needing nourishment increases as the cube of the radius. This mismatch of surface area to volume was solved by nature over the long experiment of evolution by breaking the surface into more and more subunits through branching algorithms that produce the vascular system in the case of mammals such as ourselves. This simple architectural solution continually matches surface area to volume to keep enlarging masses of cells alive, healthy, and functioning.

As an interesting historical footnote: the mathematics necessary to understand and solve this problem for our field were solved over 1700 years before da Vinci by the greatest scientist and mathematician of antiquity, the Greek Archimedes of Syracuse in Sicily (287 BC–212 BC). In the two books on the sphere and the cylinder found in the *Archimedes Palimpsest* (Netz 2011), he develops the mathematical treatment of spheres and cylinders, which leads to the relationship of surface area to volume. This finding was so important to Archimedes that legend has it that Archimedes requested that his grave marker be engraved with a sphere within a cylinder, as Cicero has claimed to have found. So important is this ratio in biology, that D'Arcy Wentworth Thompson begins the second chapter of his groundbreaking work *On Growth and Form* with a discussion of it and refers to Archimedes as its source. His brilliant book, first published in 1917, links biology with the fields of mathematics and physics (Thompson 1942).

This large body of knowledge led to the observation of branching architecture in seaweed that informed the design of scaffolding systems for tissue engineering (Vacanti 1988). Between 1986 and 1998, it was the principal design approach for model systems in many structures, including liver, intestine, cartilage, bone, tendon, blood vessels, and heart valves (Vacanti 1988). The discovery of stem cells beyond those in the bone marrow led to the next major advance in tissue engineering and regenerative medicine.

This book examines many of the current tools available to scientists and engineers in the field and shows how their creative application can lead to therapeutically relevant living devices in many of the tissues and organs of the human body. The first chapter characterizes biologically active scaffolds that induce the regenerative response in healing. In contrast, the second chapter examines scaffold-free approaches using cells capable of self-assembly. The third chapter examines a powerful new technology for the creation of complex three-dimensional scaffolds and the very recent addition of 3D bioprinting strategies, which print cells along with matrix. The fourth chapter summarizes optimization of conditions needed to generate new bone and cartilage, while the fifth chapter focuses on the methods and possibilities of craniofacial tissue engineering. The sixth and seventh chapters focus on engineering of the heart and blood vessels, and the eighth chapter examines the role of stem cells and progenitor cells in the creation of new intestinal tissue. The final chapter covers tissue engineering and its place in art and design.

This amalgamation of many approaches, tools, and targets of tissue engineering and regenerative medicine speaks to its potential to be very broad and paradigm changing. This volume is not intended to be comprehensive nor detailed in its science. Rather it is intended to be a brief overview to entice the reader to be aware of what may be coming and perhaps even to participate in the discovery and invention required fulfill its promise of helping to alleviate human suffering. Archimedes, da Vinci, and Thompson likely had no idea that their creative thoughts might be applicable to better approaches to improve the human condition, but by systematic and rigorous study they wrote what they learned for future generations to read and apply to new ideas. Now we understand that our bodies are complex electro-chemical-mechanical-analog machines that are carbon based, optimized by 3.5 billion years of evolutionary trial and error, with self-awareness and an enormous capacity to care for other individuals and communities. We can understand these systems and we can repair and replace defective parts with new living parts indistinguishable from normal counterparts developed in utero. It is such an exciting and challenging time.

The book is the 25th in the series *Cold Spring Harbor Perspectives in Medicine*, the latest incarnation of a monograph series that started almost 50 years ago. In covering the emerging science and technology of tissue engineering and regenerative medicine, it is important to note that there are many examples of applications in clinical use with the promise of many more to come. The authors of the nine book chapters are all experts in the field and pioneers in the creation of the field. The breadth of the topics discussed foretell how widely applicable this field may become over the next decade and beyond. I thank all of the authors for their generosity of time and effort. I also thank the publishers for their invaluable efforts in bringing this book to fruition, especially our project manager Barbara Acosta. Finally, I thank my administrative assistant Jacquelyn Ferraro-Pipes for her tireless efforts in coordinating the project.

Joseph P. Vacanti, MD
Harvard Medical School
Massachusetts General Hospital

REFERENCES

Folkman J, Hochberg M. 1973. Self-regulation of growth in three dimensions. *J Exp Med* **138:** 745–753.
Harari YN. 2015. *Sapiens: A brief history of humankind.* Harper Collins, New York.

Netz R. 2011. *The works of Archimedes: Vol. 1: The two books on the sphere and the cylinder: Translation and commentary.* Cambridge University Press, Cambridge, UK.

Rutkow IM. 1993. *Surgery: An illustrated history.* Mosby, Maryland Heights, MO.

Thompson DW. 1942. *On growth and form*, 2nd ed. Cambridge University Press, Cambridge, UK.

Vacanti JP. 1988. Beyond transplantation. Third annual Samuel Jason Mixter lecture. *Arch Surg* **123:** 545–549.

试读结束，需要全本PDF请购买 www.ertongbook.com

Tissue Engineering and Regenerative Medicine

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

Contents

Preface, vii

Biologic Scaffolds, 1
Alessandra Costa, Juan Diego Naranjo, Ricardo Londono, and Stephen F. Badylak

The Self-Assembling Process and Applications in Tissue Engineering, 25
Jennifer K. Lee, Jarrett M. Link, Jerry C.Y. Hu, and Kyriacos A. Athanasiou

Three-Dimensional Bioprinting Strategies for Tissue Engineering, 43
Yu Shrike Zhang, Rahmi Oklu, Mehmet Remzi Dokmeci, and Ali Khademhosseini

Honing Cell and Tissue Culture Conditions for Bone and Cartilage Tissue Engineering, 59
Johnny Lam, Esther J. Lee, Elisa C. Clark, and Antonios G. Mikos

Craniofacial Tissue Engineering, 79
Weibo Zhang and Pamela Crotty Yelick

The Heart and Great Vessels, 97
Ekene Onwuka, Nakesha King, Eric Heuer, and Christopher Breuer

Historical Perspective and Future Direction of Blood Vessel Developments, 117
Sashka Dimitrievska and Laura E. Niklason

Tissue Engineering Functional Gastrointestinal Regions: The Importance of Stem and Progenitor Cells, 131
Andrew Trecartin and Tracy Grikscheit

Tissue Engineering for Art, Design, and Other Cultural Artifacts, 147
Oron Catts and Ionat Zurr

Index, 159

Biologic Scaffolds

Alessandra Costa,[1] Juan Diego Naranjo,[1] Ricardo Londono,[1,2] and Stephen F. Badylak[1,3,4]

[1]McGowan Institute for Regenerative Medicine, Pittsburgh, Pennsylvania 15219

[2]School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania 15219

[3]Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania 15219

[4]Department of Bioengineering, University of Pittsburgh, Pittsburgh, Pennsylvania 15219

Correspondence: badylaks@upmc.edu

Biologic scaffold materials composed of allogeneic or xenogeneic extracellular matrix are commonly used for the repair and functional reconstruction of injured and missing tissues. These naturally occurring bioscaffolds are manufactured by the removal of the cellular content from source tissues while preserving the structural and functional molecular units of the remaining extracellular matrix (ECM). The mechanisms by which these bioscaffolds facilitate constructive remodeling and favorable clinical outcomes include release or creation of effector molecules that recruit endogenous stem/progenitor cells to the site of scaffold placement and modulation of the innate immune response, specifically the activation of an anti-inflammatory macrophage phenotype. The methods by which ECM biologic scaffolds are prepared, the current understanding of in vivo scaffold remodeling, and the associated clinical outcomes are discussed in this article.

Tissue engineering and regenerative medicine strategies for tissue and organ reconstruction/replacement vary widely but typically involve the in vitro and/or in vivo use of a scaffold material to support cell delivery and/or growth. Such scaffolds can be synthetic in nature, such as the polylactic glycolic acid (PLGA) used in the production of the Dermagraft skin substitute (Debels et al. 2015) or the polyglactin 910 used in the production of the Vicryl Mesh for ventral hernia repair (Levasseur et al. 1979). Alternatively, scaffolds can be composed of naturally occurring materials that are components of extracellular matrix (ECM) such as collagen (Glowacki and Mizuno 2008), laminin (Iorio et al. 2015), and chitosan, among others (Rodriguez-Vazquez et al. 2015), or the entire ECM itself.

Cell-laden autologous, allogeneic, and xenogeneic tissues have been used as viable grafts and transplants for heart valves (Angell et al. 1979; Jamieson et al. 1984), coronary arteries and peripheral vessels (Tice et al. 1976; Bortolotti et al. 1981), skin (Tavis et al. 1978; Peters 1980), the anterior cruciate ligament (Indelicato et al. 1992; Olson et al. 1992), and cornea (Tsai and Tseng 1994), among other clinical applications. The obvious limitations of these graft materials include the foreign antigens present on the allogeneic and xenogeneic cell component and the associated adverse immune response, the limited number of allogeneic do-

Copyright © 2017 Cold Spring Harbor Laboratory Press; all rights reserved
Cite this article as *Cold Spring Harb Perspect in Med* doi: 10.1101/cshperspect.a025676

nors, the devascularized state of free autografts, and the associated morbidity of the donor site with autologous grafts.

Although the concept of cell removal from various tissues with retention of the ECM had been described as early as 1975 (Meezan et al. 1975), the production of such materials explicitly for the purpose of recellularization, remodeling, and functional tissue reconstruction was not introduced until the early 1990s. Decellularized forms of human dermis (AlloDerm, LifeCell) and porcine small intestinal submucosa (Restore, DePuy, and Surgisis, Cook Biotech) were provided as surgical mesh materials for general surgery, wound care, and orthopedic soft tissue applications. The fundamental difference between these bioscaffolds composed of intact ECM and the above-mentioned scaffolds composed of individual matrix molecules is the retention of both the complex mixture of structural and functional ECM molecules and the native three-dimensional ultrastructure. Recognition of the natural ligand landscape and three-dimensional matrix ultrastructure of the ECM by responding host cells initiates scaffold degradation and the subsequent exposure, release, and/or formation of effector molecules such as embedded growth factor (GF), matrix-bound vesicles (MBVs) (Huleihel et al. 2016), cytokines, and chemokines. These signaling molecules can have profound biologic activity, including the recruitment of endogenous stem/progenitor cells (Beattie et al. 2009; Reing et al. 2009; Crapo et al. 2014) and the modulation of the innate immune response (Brown and Badylak 2014), the sum of which facilitates a constructive and functional remodeling outcome.

In many respects, it is useful to think of an ECM-based bioscaffold as a surgically placed microenvironmental niche rather than simply as a guiding template or a mechanical support device. ECM bioscaffolds have been shown to favorably influence the mitogenesis, chemotaxis (Bornstein and Sage 2002; Vorotnikova et al. 2010), and differentiation fate (Cheng et al. 2009; Ross et al. 2009; Stern et al. 2009; Allen et al. 2010; Barkan et al. 2010; Cortiella et al. 2010; Sellaro et al. 2010) of cells participating in the scaffold-remodeling process, events that are not typically associated with bioscaffolds composed of individual components of the ECM (such as purified collagen).

Presently, there are well more than 80 commercially available products composed of intact ECM. These bioscaffolds are derived from a wide variety of source tissues and organs, and are typically regulated as devices by the FDA and allowed for use in a wide variety of clinical applications. A partial list of these products can be found in Table 1.

The decision of whether to use a synthetic versus biologic material for a given clinical application depends on factors such as required mechanical strength, history of comorbidities and previous surgeries, the risk of bacterial contamination, and cost. The present article will discuss the methods of production, the current understanding of in vivo tissue remodeling of the biologic scaffolds, and an overview of some of the successes and failures in the clinical application of these biomaterials.

PRODUCTION OF ECM BIOSCAFFOLDS

Extracellular Matrix Composition and Structure

Before describing the manufacture of ECM bioscaffolds, it will be helpful to briefly review the composition and structure of ECM as it exists in situ. Indeed, the ultimate goal of ECM bioscaffold production would be the perfect preservation of both composition and structure, an impossible task. Mammalian tissues are composed of cells, a complex mixture of ions and soluble signaling molecules (i.e., growth factors, cytokines, and chemokines), and structural proteins, all of which are arranged in a tissue-specific three-dimensional ultrastructure ideally suited to maintain homeostasis, participate in mechanotransduction events, and respond to injury. ECM composition and structure vary between tissues; however, many functional and structural molecules are common:

1. Collagen represents ~85% of the dry weight of ECM. More than 20 different types of

试读结束，需要全本PDF请购买 www.ertongbook.com