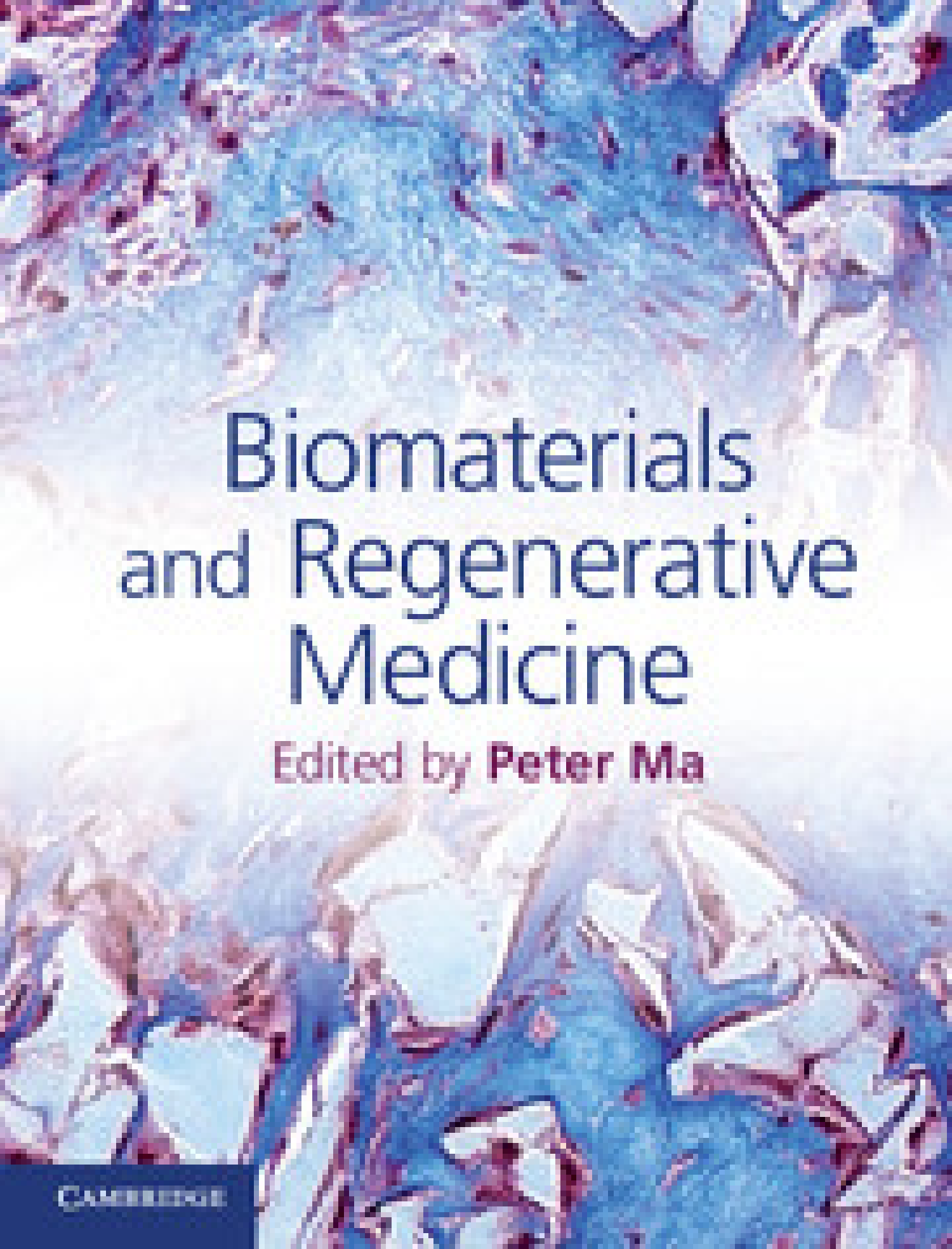
Biomaterials
and Regenerative
Medicine
Edited by Peter Ma
CAMBRIDGE

Biomaterials and Regenerative Medicine

Written by world-leading experts, this book focusses on the role of biomaterials in stem cell research and regenerative medicine. Emphasising basic principles and methodology, it covers stem cell interactions, fabrication technologies, design principles, physical characterization, and biological evaluation, across a broad variety of systems and biomaterials. Topics include:

- Stem cell biology, including embryonic stem cells, IPS, HSC and progenitor cells.
- Modern scaffold structures, including biopolymer, bioceramic, micro- and nanofiber, ECM and biohydrogel.
- Advanced fabrication technologies, including computer-aided tissue engineering and organ printing.
- Cutting-edge drug delivery systems and gene therapy techniques.
- Medical applications spanning hard and soft tissues, the cardiovascular system, and organ regeneration.

With a contribution by Nobel laureate Shinya Yamanaka, this is a must-have reference for anyone in the field of biomaterials, stem cell biology and engineering, tissue engineering and regenerative medicine.

Peter X. Ma is the Richard H. Kingery Endowed Collegiate Professor at the University of Michigan. A recent winner of the Clemson Award (2013) from the Society of Biomaterials, he is a Fellow of the American Institute for Medical and Biological Engineering (AIMBE), and a Fellow of the International Union of Societies for Biomaterials Science and Engineering (IUSBSE).

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Edited by

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University of Michigan

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Preface

Regenerative medicine aims to regenerate tissues and organs for medical therapies by harnessing the regenerative potentials of various stem cells. Stem cells include embryonic stem cells, multipotent adult stem cells, tissue specific stem cells, and induced pluripotent stem cells. These stem cells are the driving force for regeneration. There is a growing recognition of the effect of the three-dimensional (3D) matrix microenvironment on the fate and function of stem cells. A key challenge facing regenerative medicine is to generate 3D microenvironments (matrix, signals, supporting cells etc.) that can recapitulate those in development or healing to maintain stemness, to accelerate proliferation, or to direct the stem cells to differentiate toward a specific therapeutic lineage. Biomaterials can serve as 3D matrices; they can play critical roles in creating the 3D microenvironments for stem cells to facilitate regeneration. As the interactions and the overlap of the fields of biomaterials, stem cells, and regenerative medicine are rapidly growing, there is an urgent need for understanding of, and technologies to utilize, the interactions between biomaterials and stem cells for regenerative medicine.

This book, *Biomaterials and Regenerative Medicine*, overviews the state-of-the-art knowledge on stem cells, interactions of biomaterials with stem cells, biomaterials design for regenerative medicine, and the animal models and clinical applications of biomaterials for regeneration. While providing a comprehensive overview of the field, the emphasis is on the design principles, fabrication technologies, physical characterization, and biological evaluation of the biomaterials for stem cell research and regenerative medicine.

The book aims to serve as a textbook for senior undergraduate students and graduate students in the fields of biomaterials, stem cell biology, regenerative medicine, tissue engineering, controlled release, biomedical engineering, biomedical sciences, life sciences, and surgery. This book is also intended to serve as a reference book for researchers, scientists, engineers, and medical doctors who are involved in biomaterials, stem cells, and regenerative medicine.

Considering the strong interdisciplinary and multidisciplinary nature of the topics covered in this book, I had to invite experts from various disciplines to participate in this project. I am extremely grateful to all the contributors, who are the authorities of their disciplines, including a Nobel laureate in Physiology or Medicine (Dr. Shinya Yamanaka), for their time and efforts in making this a high-quality book.

I would like to express my appreciation of two extremely capable assistants for me on this project, Mss. Deborah Keedy and Elizabeth Rodriguez, for tracking the progress of each chapter, and communicating with the authors, reviewers, and publisher on a daily basis. I also enjoyed the professional interactions with the editorial staff at Cambridge University Press during the entire process. Finally, I would like to express my gratitude to my family (Chaoying, Judy, Jane, and Leon) for their understanding and support for this very exciting and laborious project.

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PART I

1

Embryonic Stem Cells

Nicole Slawny and Gary D. Smith

1.1 Preimplantation embryo development sets the stage for pluripotency

Regenerative medicine has the potential to revolutionize health care by offering the promise of replacement cells, tissues, and organs to combat injury, disease, and aging. In an ideal setting, stem cell therapies would begin with a pluripotent cell that by definition is able to give rise to any cell formed in the embryo. Additionally this would most likely require that the stem cells could self-renew or were able to divide and give rise to either more pluripotent stem cells or progressively more differentiated cells under the control of extrinsic cues. Stem cells are biological cells found in multicellular organisms, that can mitotically divide and differentiate into specialized cell types and can self-renew to produce more stem cells. There are two broad types of stem cells: embryonic stem cells and adult stem cells. Embryonic stem cells originate from the inner cell mass of the preimplantation embryo and are considered pluripotent whereas *in situ* adult stem cells are considered multipotent. Embryonic stem cells (ESCs) possess characteristics that make them a potentially outstanding starting material for use in regenerative medicine. They are unique among cultured cells because they have an apparently limitless capacity to self-renew in vitro, as well as being pluripotent. Because of these extraordinary properties, ESCs have been an intense focus of research for more than 30 years.

In order to fully understand the basic properties of ESCs and how they are generated, it is important to consider the events of embryonic development that surround the timing of their formation. The events and molecular signaling required for embryonic development have been explored to a large extent using the laboratory mouse as a model system due to there being very limited material for experimentation and the inherent moral complexities of studies utilizing human embryos (Vassena *et al.*, 2011; Cockburn and Rossant, 2010). Therefore early mouse development will be used to illustrate the events critical to generating pluripotency in ESCs and other cells. While some developmental events are certainly conserved among all mammalian species, other aspects of rodent embryologic development beyond the scope of this chapter have made their ESCs unique and more amenable for use as a model system (Brons *et al.*, 2007; Tesar *et al.*, 2007; Nichols and Smith, 2009; Rossant, 2008). A more complete understanding of these species-specific differences may be important if hESCs are to be utilized to their fullest potential to improve human health.

Following fertilization of the egg by sperm the preimplantation embryo undergoes a series of cell divisions that generate smaller cells known as blastomeres (Figure 1.1).

Early cleavage divisions result in an eight-cell embryo when compaction or an increase in intracellular adhesion is initiated, an event believed to create the first molecular differences in polarity between blastomeres. Continued cell divisions give rise to a 32-cell morula where the first cell-fate choice occurs in the embryo. Cells on the outside differentiate into trophectoderm that gives rise to part of the placenta, while cells on the inside become the inner cell mass. The specification of trophectoderm versus inner cell mass occurs