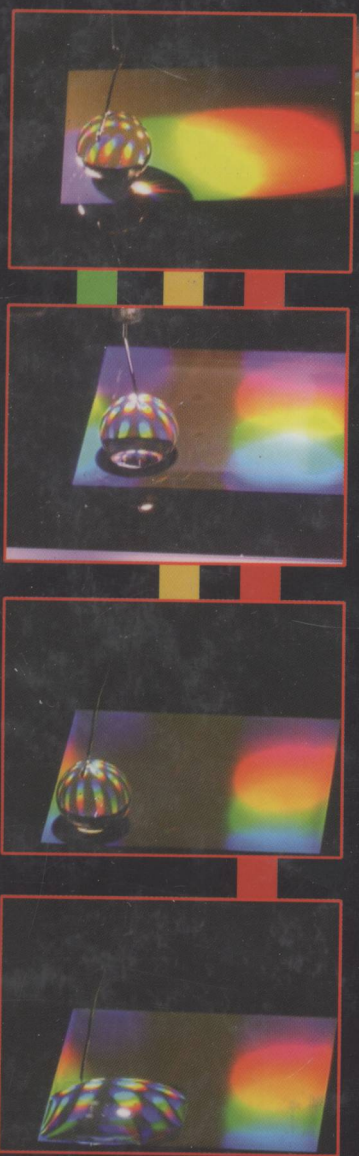
BIONANOTECHNOLOGY

GLOBAL PROSPECTS



Edited by

David E. Reisner

CRC Press
Taylor & Francis Group

BIONANOTECHNOLOGY

GLOBAL PROSPECTS

Edited by

David E. Reisner

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 in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-13: 978-0-8493-7528-6 (Hardcover)

Library of Congress Cataloging-in-Publication Data

Bionanotechnology: Global prospects / editor, David E. Reisner.
p. ; cm.
"A CRC title."
Includes bibliographical references and index.
ISBN 978-0-8493-7528-6 (hardback : alk. paper)
1. Nanotechnology. 2. Biotechnology. I. Reisner, David Evans
[DNLM: 1. Nanotechnology. 2. Biotechnology. QT 36.5 B6156 2008]

TP248.25.N35B565 2008
660.6--dc22 2008012855

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

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

BIONANOTECHNOLOGY

GLOBAL PROSPECTS

Preface

Nature has been engaged in its own unfathomable and uncanny nanotechnology project since the dawn of life, billions of years ago. It is only recently that humans have developed their own tools to observe Nature as she assembles and manipulates structures so complex and purposeful so as to defy the imagination. No one would argue that all molecular biology is based on nanotechnology. After all, these structural building blocks composed of ordered elements are well within the 100-nanometer scale that is generally agreed upon as the physical dimensional ceiling below which nanotechnology processes occur. It is no wonder that man is now attempting to mimic Nature by building analogous structures from the bottom up.

A few words about the book title: The temptation to consider "nanobiotechnology" as a subset of biotechnology fails to pay homage to the gargantuan impact of the burgeoning nanotechnology field—a field in the throes of revolutionary growth. The word *nanobiotechnology* feels redundant, a bromide. In distinction, the term *bionanotechnology* connotes a rapidly evolving sector of the nanotechnology field that deals strictly with biological processes and structures. Many refer to this synthesis as "convergence." As will be demonstrated in this monograph, the seeds of bionanotechnology development have been planted. Commercial products will likely be on the marketplace well before the next edition appears. Many nanotech soothsayers predict that as time goes on, this convergence of biotechnology and nanotechnology will become a dominant focus area for technological innovation worldwide and will impact all of our lives on a daily basis.

Naturally, this is also an engineering book. One need not stretch the imagination very far to appreciate that Nature has fundamentally engineered life as we know it, culminating in our own species. This fact has not gone unnoticed on the part of nanotechnologists, who have begun in earnest to mimic Nature's fundamental engineering processes through invoking precise controls over her building blocks. Self-assembly, a key construct of nanotechnology, forms the backbone of biological processes. For example, exploiting DNA as scaffolding for the engineering of DNA-templated molecular electronic devices is an inspiring example of our newfound ability to insinuate our own design skills at the nanoscale level in living systems. Using this approach, it is possible to create self-assembling electronic circuits or devices in solution. Directed evolution based on repeated mutagenesis experiments can be conducted at the nanoscale level. Along these lines, the use of the solar energy conversion properties of bacteriorhodopsin for making thin-film memories, photovoltaic convertors, holographic processors, artificial memories, logic gates, and protein-semiconductor hybrid devices is astounding.

Quantum dots are tiny light-emitting particles on the nanoscale. They have been developed as a new class of biological fluorophore. Once rendered hydrophilic with appropriate functional groups, quantum dots can act as biosensors that can detect biomolecular targets on a real-time or continuous basis. Different colors of quantum dots could be combined into a larger structure to yield an optical bar code. Gold nanoparticles can be functionalized to serve as biological tags.

Nanomedicine is a burgeoning area of development, encompassing drug delivery by nanoparticulates, including fullerenes, as well as new enabling opportunities in medical diagnostics, labeling, and imaging. Quantum dots will certainly play a large role in nanomedicine. Years from now, we will laugh at the archaic approach to treating disease we presently take for granted, carried over from the twentieth century, relying on a single drug formulation to treat a specific disease in all people without acknowledging each individual's unique genetic makeup. Nanocoatings also play an important near-term role in the lifetime of medical devices, especially orthopedic prosthetics. Nanocrystalline hydroxyapatite is far less soluble in human body fluid than conventional amorphous material, thereby anticipating great increases in its service life.

It is not the intention to provide a comprehensive treatise on bionanotechnology, rather I hope to provide representative reporting on a wide variety of activity in the field from all corners of the planet (now that the "world is flat" it has corners). I have attempted to assemble chapters that are relevant to looming product opportunities and instructional for those readers interested in developing the bionanotech products of the future. To that end, I felt it appropriate to conclude the discussion with a chapter that reviews the patent landscape for bionanotechnology, which is presently in a state of great flux. Now more than ever, intellectual property is relevant to both the academic and corporate sectors, and as such, patents are being ascribed greater value and importance. Bionanotechnology commercialization will be driven by the increases in government funding as well as the expiration of more traditional drug patents.

Accumulating author contributions from experts scattered across the globe acquired a life of its own in the evolution of this book. As a Technology Pioneer at the Annual Meeting of the World Economic Forum (WEF) in Davos, Switzerland, I was privy to a worldview that few technologists are able to enjoy. Klaus Schwab, WEF's driving force, has observed that everywhere in society and business, the power is moving from the center to the periphery. This monograph is a testimonial to that paradigm shift. Authors have contributed from 15 different countries in cities from as far as Florianópolis, Mumbai, Ramat-Gan, Pretoria, Havana, Tehran, Glasgow, Shenyang, and Kiev, just to name a few. Of course, this diaspora of academic excellence is largely enabled by the most pervasive technological innovation of our time, the Web.

Chris Anderson has postulated a compelling new economics of culture and commerce, dubbed the "Long Tail," so named because in statistics, the tail of a $1/x$ power law curve is very long relative to the head. Long Tail economics is about the economics of abundance (not scarcity), and we now see quantum shifts in customer buying habits at Amazon, Netflix, and eBay, as well as shifts in content distribution at Wikipedia, Google, and the emerging "Blogosphere." This phenomenon is also playing out in scientific research across the globe, where the Long Tail has now made possible world-class creative technology advances that not long ago were unimaginable. This monograph is proof in spades of this paradigm shift. I dedicate this book to all the authors who gave their valuable time to create the contributions that fill this volume. Many of those authors delivered expert chapters in the face of severe obstacles, some even endured personal hardship and loss over the course of their writing. They know who they are, and I thank them. I dedicate this book to the singer, not the song.

David E. Reisner
The Nano Group, Inc.
Farmington, Connecticut, USA

The Editor

David E. Reisner, Ph.D., is a well known entrepreneur in the burgeoning field of nanotechnology, having cofounded in 1996 two nanotech companies in Connecticut, Inframat® and US Nanocorp®. He has been the Chief Executive Officer of both companies since founding, which were recognized in Y2002–Y2005 for their fast revenue growth as Deloitte & Touche *Connecticut Technology Fast50 Award* recipients. In 2004, The Nano Group, Inc. was formed as a parent holding company for investment. Dr. Reisner and the cofounders were featured in *Forbes* magazine in 2004. He is also a Managing Director in Delta Capital Group.

Dr. Reisner has more than 175 publications and is an inventor on 10 issued patents. He is the editor for the "Bionanotechnology" section of the 3rd Edition of *The BioMedical Engineering Handbook*. He has written articles on the business of nanotechnology in *Nanotechnology Law & Business* as well as the Chinese publication *Science & Culture Review.*

Dr. Reisner served a 3-year term as a Technology Pioneer for the World Economic Forum and was a panelist at the 2004 Annual Meeting in Davos. He is on the Board of the Connecticut Venture Group and is Chairman of the Board of the Connecticut Technology Council. He was a National Aeronautics and Space Administration (NASA) *NanoTech Briefs* Nano50 awardee in 2006. For his efforts in the field of medical implantable devices, Reisner won the 1st Annual BEACON Award for Medical Technology in 2004. He is a member of the Connecticut Academy of Science and Engineering.

Reisner is a 1978 University Honors graduate from Wesleyan University and received his Ph.D. at MIT in 1983 in the field of chemical physics. He was recognized for his historic preservation efforts in 1994 when he received the Volunteer Recognition Award from the Connecticut Historical Commission and the Connecticut Trust for Historic Preservation. Dr. Reisner is known nationally for his expertise in vintage Corvette restoration and documentation.

Contributors

Reinaldo Acevedo
Finlay Institute
Havana, Cuba

Fred Allen
Always Ready, Inc.
Little Falls, New Jersey, USA

André Avelino Pasa
Departamento de Física
Universidade Federal de Santa Catarina
Florianópolis, Brazil

Hossein Baharvand
Department of Stem Cells
Royan Institute
Tehran, Iran

Ramón Barberá
Finlay Institute
Havana, Cuba

Raj Bawa
Biology Department and Office of Tech Commercialization
Rensselaer Polytechnic Institute
Troy, New York, USA

Tânia Beatriz Creczynski-Pasa
Departamento de Ciências Farmacêuticas
Universidade Federal de Santa Catarina
Florianópolis, Brazil

Robert R. Birge
University of Connecticut
Storrs, Connecticut, USA

Gustavo Bracho
Finlay Institute
Havana, Cuba

Concepción Campa
Finlay Institute
Havana, Cuba

Shawn D. Carrigan
McGill University
Montreal, Quebec, Canada

Paul K. Chelule
Polymers and Bioceramics
Council for Scientific and Industrial Research (CSIR)
Pretoria, South Africa

Michael Connolly
Integrated Nano-Technologies
Henrietta, New York, USA

Michelle Critchley
Nanotechnology Victoria Ltd.
Victoria, Australia

Remy Cromer
Oxonica, Inc.
Mountain View, California, USA

Matthew J. Dalby
University of Glasgow
Glasgow, Scotland, United Kingdom

Glenn Davis
Oxonica, Inc.
Mountain View, California

Judith del Campo
Finlay Institute
Havana, Cuba

William E. Doering
Oxonica, Inc.
Mountain View, California, USA

Kimberly L. Douglas
McGill University
Montreal, Quebec, Canada

Rebekah A. Drezek
Rice University
Houston, Texas, USA

Dror Fixler
School of Engineering
Bar-Ilan University
Ramat-Gan, Israel

R. Griffith Freeman
Oxonica, Inc.
Mountain View, California, USA

Peter Gammel
SiGe Semiconductor
Andover, Massachusetts, USA

Javier García
Departamento de Optica
Universitat de Valencia
Burjassot, Spain

Magnus Gittins
Advance Nanotech, Inc.
New York, New York, USA

Domingo González
Finlay Institute
Havana, Cuba

David Guagliardo
Oxonica, Inc.
Mountain View, California, USA

Naomi J. Halas
Rice University
Houston, Texas, USA

Jie Han
NASA Ames Research Center
Moffett Federal Airfield, California, USA

Yulin Hao
Institute of Metal Research
Chinese Academy of Sciences
Shenyang, Liaoning, China

Michael N. Helmus
Medical Devices, Biomaterials, and Nanotechnology
Worcester, Massachusetts, USA

Jason R. Hillebrecht
University of Connecticut
Storrs, Connecticut, USA

Theodore R. Holford
Yale University School of Medicine
New Haven, Connecticut, USA

Bob Irving
Nanotechnology Victoria Ltd.
Victoria, Australia

Manoj Joshi
Nanoelectronics Centre, Department of Electrical Engineering
Indian Institute of Technology—Bombay
Mumbai, India

Nitin Kale
Nanoelectronics Centre, Department of Electrical Engineering
Indian Institute of Technology—Bombay
Mumbai, India

Lonji Kalombo
Polymers and Bioceramics
Council for Scientific and Industrial Research (CSIR)
Pretoria, South Africa

Frans W.H. Kampers
BioNT, Wageningen Bionanotechnology Centre
Wageningen, The Netherlands

Jeremy F. Koscielecki
University of Connecticut
Storrs, Connecticut, USA

Alexis Labrada
Finlay Institute
Havana, Cuba

R. Lal
Nanoelectronics Centre, Department of Electrical Engineering
Indian Institute of Technology—Bombay
Mumbai, India

Miriam Lastre
Finlay Institute
Havana, Cuba

Shujun Li
Institute of Metal Research
Chinese Academy of Sciences
Shenyang, Liaoning, China

V.A. Lifton
mPhase Technologies, Inc.
Little Falls, New Jersey, USA

Rogerio S. Lima
National Research Council of Canada
Industrial Materials Institute
Boucherville, Quebec, Canada

Basil R. Marple
National Research Council of Canada
Industrial Materials Institute
Boucherville, Quebec, Canada

Narges Zare Mehrjardi
Department of Stem Cells
Royan Institute
Tehran, Iran

Vicente Mico
AIDO, Technological Institute of Optics, Colour and Imaging
Parc Tecnològic
Valencia, Spain

Sarah Morgan
Nanotechnology Victoria Ltd.
Victoria, Australia

S. Mukherji
Nanoelectronics Centre and School of Biosciences and Bioengineering
Indian Institute of Technology—Bombay
Mumbai, India

Vijay M. Naik
Hindustan Unilever Research Centre
Bangalore, India

Michael J. Natan
Oxonica, Inc.
Mountain View, California, USA

Shuming Nie
Emory University
Georgia Institute of Technology
Atlanta, Georgia, USA

Joo L. Ong
University of Tennessee
Knoxville, Tennessee, USA

Richard O.C. Oreffo
University of Glasgow
Glasgow, Scotland, United Kingdom

Oliver Pérez
Finlay Institute
Havana, Cuba

Jeanette Pritchard
Nanotechnology Victoria Ltd.
Victoria, Australia

V. Ramgopal Rao
Nanoelectronics Centre and Department of Electrical Engineering
Indian Institute of Technology—Bombay
Mumbai, India

Alexandra A. Revina
A.N. Frumkin Institute of Physical Chemistry and Electrochemistry
Russian Academy of Sciences
Moscow, Russia

Gualberto Ruaño
Genomas, Inc.
Hartford, Connecticut, USA

Boitumelo Semete
Polymers and Bioceramics
Council for Scientific and Industrial Research (CSIR)
Pretoria, South Africa

Michael Y. Sha
Oxonica, Inc.
Mountain View, California, USA

Elena Shembel
Inter-Intel, Inc.
Coral Springs, Florida, USA

Alexandra Shmyryeva
National Technical University of Ukraine
Kiev Polytechnic Institute
Kiev, Ukraine

Gustavo Sierra
Finlay Institute
Havana, Cuba

S. Simon
mPhase Technologies, Inc.
Little Falls, New Jersey, USA

Andrew Michael Smith
Emory University
Georgia Institute of Technology
Atlanta, Georgia, USA

Hulda S. Swai
Polymers and Bioceramics
Council for Scientific and Industrial Research (CSIR)
Pretoria, South Africa

Maryam Tabrizian
McGill University
Montreal, Quebec, Canada

Weihong Tan
University of Florida
Gainesville, Florida, USA

Lin Wang
University of Florida
Gainesville, Florida, USA

Jennifer L. West
Rice University
Houston, Texas, USA

Andreas Windemuth
Yale University School of Medicine
New Haven, Connecticut, USA

Rui Yang
Institute of Metal Research
Chinese Academy of Sciences
Shenyang, Liaoning, China

Yunzhi Yang
University of Tennessee
Knoxville, Tennessee, USA

Zeev Zalevsky
School of Engineering
Bar-Ilan University
Ramat-Gan, Israel

Caridad Zayas
Finlay Institute
Havana, Cuba

Zongtao Zhang
Inframat Corporation
Farmington, Connecticut, USA

Contents

1 Nanotechnology in Stem Cell Biology and Technology*

Hossein Baharvand and Narges Zare Mehrjardi
Department of Stem Cells, Royan Institute, Tehran, Iran

CONTENTS

1.1 INTRODUCTION

Nanotechnology is the science and engineering concerned with the design, synthesis, characterization, and application of materials and devices that have a functional organization in at least one dimension on the nanometer (nm) scale, ranging from a few to about 100 nm. Nanotechnology is beginning to help advance the equally pioneering field of stem-cell research, with devices that can precisely control stem cells (SCs) and provide nanoscaled-biodegradable scaffolds and magnetic tracking systems. SCs are undifferentiated cells generally characterized by their functional capacity to both self-renew and to generate a large number of differentiated progeny cells. The characteristics of SCs indicate that these cells, in addition to use in developmental biology studies, have the potential to provide an unlimited supply of different cell types for tissue replacement, drug screening, and functional genomics applications. Tissue engineering at the nanoscale level is a potentially useful approach to develop viable substitutes, which can restore, maintain, or improve the function of human tissue. Regenerating tissue can be achieved by using nanobiomaterials to convey signals to surrounding tissues to recruit cells that promote inherent regeneration or by using cells and a nanobiomaterial scaffold to act as a framework for developing tissue. In this regard, nanomaterials

* The authors would like to dedicate this chapter to the memory of Dr. Saeid Kazemi Ashtiani. He was a wonderful colleague, a great stem cell biologist, and an inspirational advocate of human stem cell research in Iran.

such as nanofibers are of particular interest. Three different approaches toward the formation of nanofibrous materials have emerged: self-assembly, electrospinning, and phase separation [1]. Each of these approaches is unique with respect to its characteristics, and each could lead to the development of a scaffolding system. For example, self-assembly can generate small-diameter nanofibers in the lowest end of the range of natural extracellular matrix (ECM) collagen, while electrospinning is more useful for generating large-diameter nanofibers on the upper end of the range of natural ECM collagen. Phase separation, on the other hand, has generated nanofibers in the same range as natural ECM collagen and allows for the design of macropore structures. Specifically designed amphiphilic peptides that contain a carbon alkyl tail and several other functional peptide regions have been synthesized and shown to form nanofibers through a self-assembly process by mixing cell suspensions in media with dilute aqueous solutions of the peptide amphiphil (PA) [2,3]. The challenges with the techniques mentioned above are that electrospinning is typically limited to forming sheets of fibers and thus limiting the ability to create a designed three-dimensional (3D) pore scaffold, and self-assembling materials usually form hydrogels, limiting the geometric complexity and mechanical properties of the 3D structure. Another class of nanomaterials includes carbon nanotubes (CNTs), which are a macromolecular form of carbon with high potential for biological applications due in part to their unique mechanical, physical, and chemical properties [4,5]. CNTs are strong, flexible, conduct electrical current [6], and can be functionalized with different molecules [7], properties that may be useful in basic and applied biological research (for review see [8]). Single-walled carbon nanotubes (SWNTs) have an average diameter of 1.5 nm, and their length varies from several hundred nanometers to several micrometers. Multiwalled carbon nanotube (MWNT) diameters typically range between 10 and 30 nm. The diameters of SWNTs are close to the size of the triple helix collagen fibers, which makes them ideal candidates for substrates for bone growth. As prepared CNTs are insoluble in most solvents, chemical modifications are aimed at increasing their solubility in water and organic solvents.

In this chapter, we aim to offer a basic understanding of this emerging field of SC nanoengineering based on the fusion of SCs, tissue engineering, and nanotechnology.

1.2 STEM CELLS AND TYPES

Although most cells of the body, such as heart cells or skin cells, are committed to conduct a specific function, a SC is an uncommitted cell that has the ability to self-renew and differentiate into a functional cell type [9–11]. Conventionally, SCs are classified as those derived either from embryo or adult tissues (Figure 1.1). Embryonic SCs, embryonic carcinoma cells, and embryonic germ cells are derived from the inner cell mass of blastocysts, teratocarcinoms, and primordial germ cells, respectively. These cells are pluripotent, because they have the ability to entirely colonize an organism and give rise to almost all cell types, except extracellular tissues (e.g., placenta). SCs found in adult organisms are referred to as adult SCs, and are present in most, if not all, adult organs [12]. They are considered multipotent, because they can originate mature cell types of one or more lineages but cannot reconstitute the organism as a whole. What determines SC potency is dependent to a large extent on the genetic makeup of the cell and whether it contains the appropriate genetic circuitry to differentiate to a specific cell type. However, the decision to differentiate or self-renew is often regulated by the SC microenvironment, also known as the SC niche. For example, changes in cytokine gradients, cell–cell, and cell–matrix contacts are important in switching "on" and "off" genes and gene pathways, thereby controlling the type of cell generated.

1.2.1 Embryonic Stem Cells

Embryonic stem cells (ESCs) from mice were first derived in 1981 from the inner cell mass (ICM) of developing mouse blastocysts [13,14]. Human ESCs were established by Thomson and

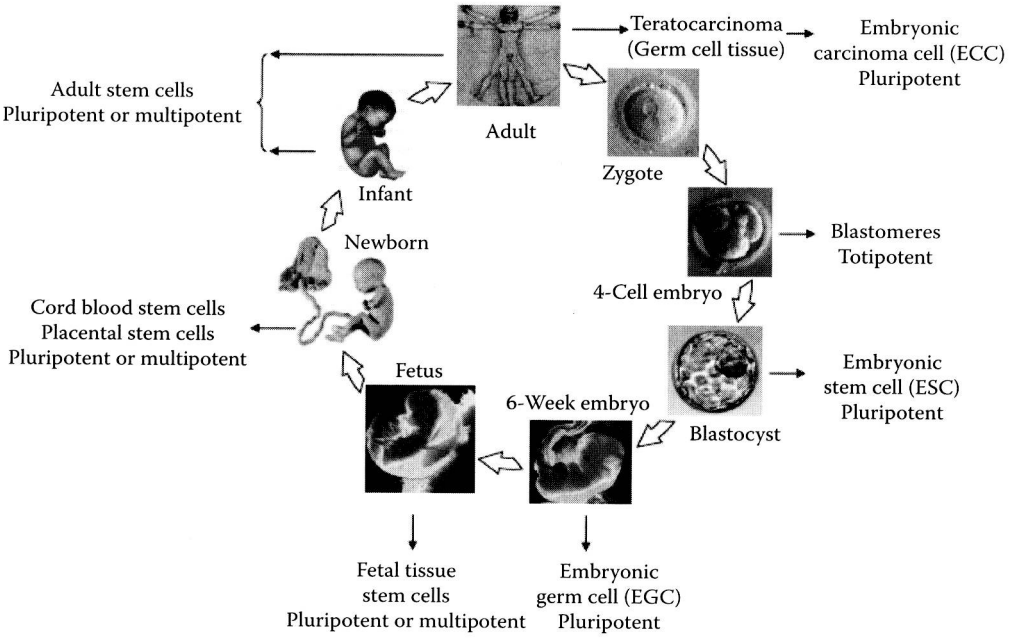


FIGURE 1.1 Origin of different stem cells. Stem cells at different developmental stages appear to have different capacities for self-renewal and differentiation.

colleagues in 1998 [15]. ESCs can be stably propagated indefinitely and maintain a normal karyotype without undergoing cell senescence *in vitro* when cultured in the presence of leukemia inhibitory factor (LIF) (in the case of the mouse) or over a layer of mitotically inactivated mouse embryonic fibroblasts (MEFs), in the monkey and human systems (Figure 1.2). Upon injection of mouse ESCs into blastocysts [16], their progeny is present in all tissues and organs, including the germ line of a chimeric individual (not shown in human ESC due to ethics) and can contribute in the formation of functional gametes [17]. The transmission of genetically manipulated ESCs *in vitro* can thus be passed into chimeric murine offspring and provide a useful approach for studying varying genetic aspects related to ESCs. Homologous recombination has become a useful transgenic approach for introducing selected mutations into the mouse germ line [16,18]. These mutant mice are useful animal models for studying gene function *in vivo* and for clarifying the roles of specific genes in all aspects of mammalian development, metabolic pathways, and immunologic functions.

Upon removal of ESCs from feeder layers and subsequent transfer to suspension cultures, ESCs begin to differentiate into 3D, multicellular aggregates, forming both differentiated and undifferentiated cells, termed embryoid bodies (EBs). Initiation of differentiation may also be induced following the addition of cells into two-dimensional (2D) cultures (i.e., on a differentiation inducing layer such as a matrix or feeder cells). EBs can spontaneously differentiate into different cells and the type of voluntary cells increased by addition of inducing substances or growth factors in their medium, including rhythmically contracting cardiomyocytes, pigmented and nonpigmented epithelial cells, neural cells with outgrowths of axons and dendrites, and mesenchymal cells (Figure 1.2) [19]. Recent studies have also demonstrated ESC differentiation into germ cells and more mature gametes, although significant unanswered questions remain about the functionality of these cells [20]. The derivation of germ cells from ESCs *in vitro* provides an invaluable assay both for the genetic dissection of germ cell development and for epigenetic reprogramming, and may one day facilitate nuclear transfer technology and infertility treatments.