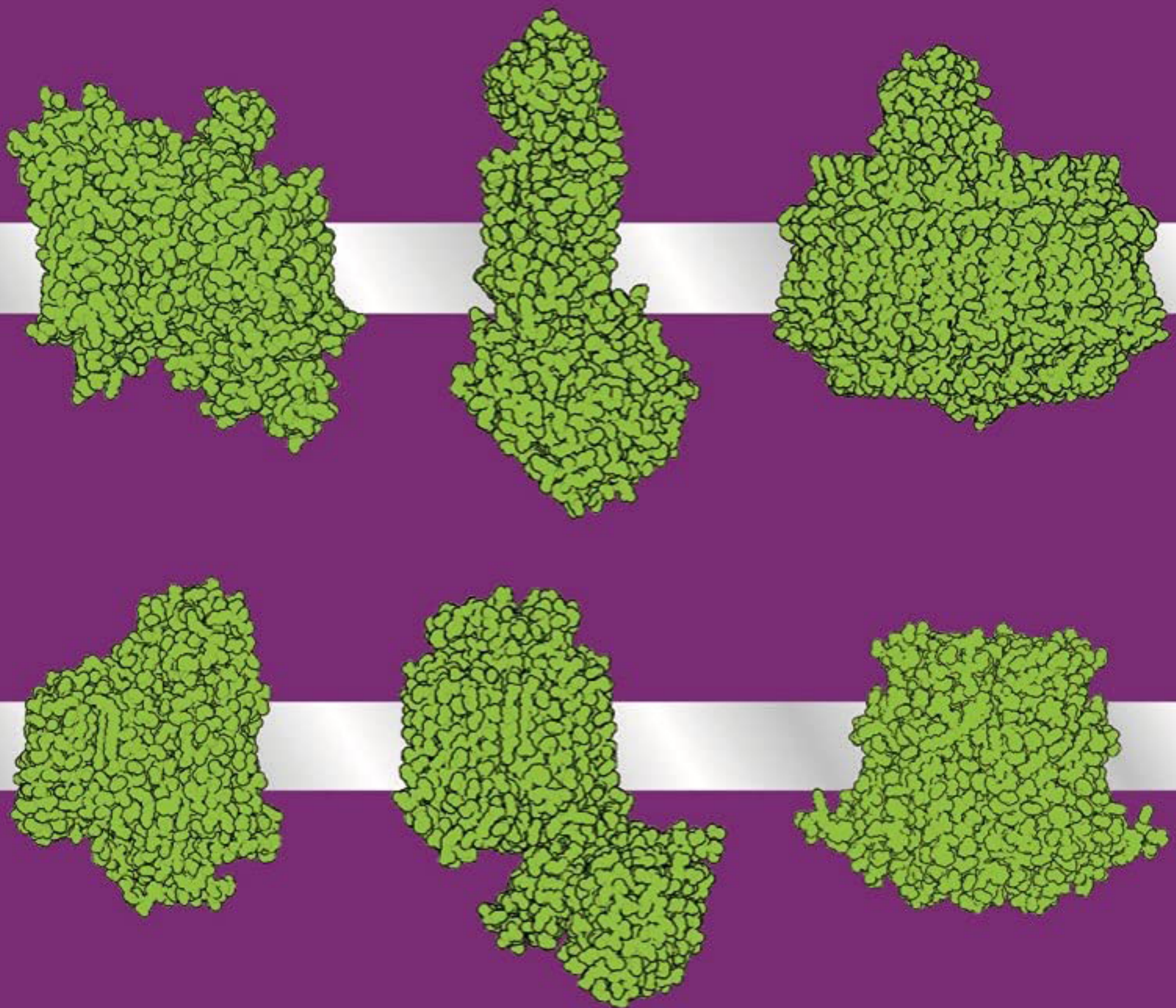


MOLECULAR BIOLOGY OF
THE CELL
SEVENTH EDITION



ALBERTS HEALD JOHNSON MORGAN RAFF ROBERTS WALTER

Molecular Biology of
THE CELL
Seventh Edition

Molecular Biology of THE CELL

Seventh Edition

Bruce Alberts

Rebecca Heald

Alexander Johnson

David Morgan

Martin Raff

Keith Roberts

Peter Walter

With problems by

John Wilson

Tim Hunt



W. W. NORTON & COMPANY

Independent Publishers Since 1923

W. W. Norton & Company has been independent since its founding in 1923, when William Warder Norton and Mary D. Herter Norton first published lectures delivered at the People's Institute, the adult education division of New York City's Cooper Union. The firm soon expanded its program beyond the Institute, publishing books by celebrated academics from America and abroad. By midcentury, the two major pillars of Norton's publishing program—trade books and college texts—were firmly established. In the 1950s, the Norton family transferred control of the company to its employees, and today—with a staff of five hundred and hundreds of trade, college, and professional titles published each year—W. W. Norton & Company stands as the largest and oldest publishing house owned wholly by its employees.

Copyright © 2022 by Bruce Alberts, Rebecca Heald, Alexander Johnson, David Morgan, Martin Raff, Keith Roberts, Peter Walter, the Estate of Julian Lewis, John Wilson, and Tim Hunt

All rights reserved
Printed in Canada

Editor: Betsy Twitchell
Editorial Advisor: Denise Schanck
Senior Associate Managing Editor, College: Carla L. Talmadge
Assistant Editor: Danny Vargo
Director of College Production: Jane Searle
Copyeditor: Christopher Curioli
Proofreaders: Julie Henderson, Susan McColl
Managing Editor, College: Marian Johnson
Media Editor: Todd Pearson
Smartwork Editor: Christopher Rapp
Media Project Editor: Jesse Newkirk
Associate Media Editor: Jasmine N. Ribeaux
Media Assistant Editor: Lindsey Heale
Ebook Production Manager: Kate Barnes
Managing Editor, College Digital Media: Kim Yi
Marketing Manager, Biology: Ruth Bolster
Director of College Permissions: Megan Schindel
Photo Editor: Thomas Persano
Permissions Associate: Patricia Wong
Design: Juan Paolo Francisco
Illustrator: Nigel Orme
Composition: Graphic World, Inc.
Manufacturing: Transcontinental—Beauceville

Permission to use copyrighted material is included alongside the appropriate content.

Library of Congress Cataloging-in-Publication Data

Names: Alberts, Bruce, author.
Title: Molecular biology of the cell / Bruce Alberts, Rebecca Heald, Alexander Johnson, David Morgan, Martin Raff, Keith Roberts, Peter Walter.
Description: Seventh edition. | New York : W. W. Norton & Company, [2022] | Includes bibliographical references and index.
Identifiers: LCCN 2021049376 | **ISBN 9780393884821 (hardcover)** | ISBN 9780393884630 (epub)
Subjects: MESH: Cells | Molecular Biology
Classification: LCC QH581.2 | NLM QU 300 | DDC 572.8—dc23/eng/20211015
LC record available at <https://lccn.loc.gov/2021049376>

W. W. Norton & Company, Inc., 500 Fifth Avenue, New York, NY 10110
wnorton.com

W. W. Norton & Company Ltd., 15 Carlisle Street, London W1D 3BS

1 2 3 4 5 6 7 8 9 0

Preface

Why a cell biology textbook? What is its value in a world of online resources so vast that any information you might want about cells is, in principle, freely available a few taps away?

The answer is that a textbook provides what open-ended Internet searches cannot—a curation of knowledge and an expert, accurate guide to the beauty and complexities of cells. Our book provides a narrative that leads the reader logically and progressively through the key concepts, components, and experiments in such a way that readers can build for themselves a memorable, conceptual framework for cell biology—a framework that will allow them to understand and critically evaluate the exciting rush of new discoveries. That is what we have tried to do in *Molecular Biology of the Cell* for each of its seven editions.

This edition was completed during the COVID-19 pandemic. Many of the questions that this global crisis generated are cell biological questions—including how the virus gets into our cells, how it replicates, how our immune system responds, how vaccines are developed, and how scientists produce the molecular details of virus structure. Required for the rapid development of safe and effective COVID-19 vaccines, answers to all of these questions can be found in this textbook. To make room for them, as well as for many other major recent advances in our knowledge, much previous content had to be removed.

Understanding the inner workings of cells requires more than words. Our book contains more than 1500 illustrations that create a parallel narrative, closely interwoven with the text. Each figure has been designed to highlight a key concept. The unique clarity, simplicity, and consistency of the figures across chapters, achieved by use of a common set of icon designs and colors (for example, DNA *red* and proteins *green*), enables students to scan them as chapter overviews. In this edition, important protein structures are depicted and their Protein Data Bank (PDB) codes provided; these codes link to tools on the RCSB PDB website (www.rcsb.org), where students can more fully explore the proteins that lie at the core of cell biology. In addition, more than 180 narrated movies have been produced for the book, each linked to the text to provide additional insights.

John Wilson and Tim Hunt have again contributed their distinctive and imaginative problems to help students gain a more active understanding of the text. The end-of-chapter problems emphasize experiments and quantitative approaches in order to encourage critical thinking. Their Digital Problems Book in Smartwork greatly expands on these self-assessment problems and includes data analysis and video review questions that are based on the movie links in the textbook.

Many millions of scientific papers are relevant to cell biology, and many important new ones are published daily. The challenge for textbook writers is to sort through this overwhelming wealth of information to produce a clear and accurate conceptual platform for understanding how cells work. We have aimed high, seeking primarily to support the education of cell biology students, including the next generation of bioscientists, but also to support active scientists pursuing new fundamental research and the search for practical advances to improve the human condition.

So, why read a textbook? We live in a world that presents humanity with many challenging problems related to cell biology, including declining biodiversity, climate change, food insecurity, environmental degradation, resource depletion, and animal and plant diseases. We hope that this new edition of our textbook will help the reader to better understand these problems and—for many—to contribute to solving them.

Note to the Reader

What's New in the Seventh Edition?

Every chapter in the Seventh Edition has been significantly updated with information on new discoveries in the field of cell biology. Examples of this new content include:

- Updated information on the continuing impact of human genome research, including what has been learned from sequencing hundreds of thousands of human genomes (Chapter 4), and updated coverage of tumor genomes (Chapter 20).
- New research on pathogens, diseases, and methods of combating them, including discussion of COVID-19 (Chapters 1, 5, and 23) and mRNA vaccines (Chapter 24).
- Updated research on cellular organization, including new information on biomolecular condensates (Chapters 3, 6, 7, 12, and 14) and on chromosome organization by DNA loop extrusion (Chapters 4, 7, and 17).
- Expanded coverage of new microscope technologies, including superresolution light microscopy and atomic resolution electron microscopy (Chapter 9), and new research breakthroughs from cryo-electron microscopy, such as stretch-activated Piezo channels (Chapter 11).
- New coverage of evolution, including a new discussion on the diversity of life (Chapter 1), plus updates on both human (Chapter 4) and HIV (Chapter 23) evolution.

In addition, a quarter of the book's illustrations are either completely new or significantly updated for accuracy, clarity, and visual appeal.

Finally, we are thrilled to offer online assessment, for the first time, with the Digital Problems Book in Smartwork—reimagining the classic companion text, *The Problems Book*, for twenty-first century instructors and students.

Structure of the Book

Although the chapters of this book can be read independently of one another, they are arranged in a logical sequence of five parts. The first three chapters of Part I cover elementary principles and basic biochemistry. They can serve either as an introduction for those who have not studied biochemistry or as a refresher course for those who have. Part II deals with the storage, expression, and transmission of genetic information. Part III presents the principles of the main experimental methods for investigating and analyzing cells; here, a section titled “Mathematical Analysis of Cell Function” in Chapter 8 provides an extra dimension in our understanding of cell regulation and function. Part IV describes the internal organization of the cell. Part V follows the behavior of cells in multicellular systems, starting with how cells become attached to each other and concluding with chapters on pathogens and infection and on the innate and adaptive immune systems.

End-of-Chapter Problems

A selection of problems, written by John Wilson and Tim Hunt, appears in the text at the end of each chapter. Solutions to these problems are available on the Norton Teaching Tools site.

References

A concise list of selected references is included at the end of each chapter. These are arranged in alphabetical order by author surname under the main chapter section headings. These references often include the original papers in which the most critical discoveries were first reported. The ebook also includes the DOI identifier for the references, making it easy for students to access the articles.

Glossary Terms

Throughout the book, boldface type has been used to highlight key terms at the point in a chapter where the main discussion occurs. Italic type is used to set off important terms with a lesser degree of emphasis. At the end of the book is an expanded glossary, covering all the major terms common to cell biology; it should be the first resort for a reader who encounters an unfamiliar technical word.

Website for Students

Resources for students are available at digital.wwnorton.com/mboc7. The complete glossary as well as a set of flashcards are available on this student website.

Nomenclature for Genes and Proteins

Each species has its own conventions for naming genes; the only common feature is that they are always set in italics. In some species (such as humans), gene names are spelled out all in capital letters; in other species (such as zebrafish), all in lowercase; in yet others (most mouse genes), with the first letter in uppercase and the rest in lowercase; or (as in *Drosophila*) with different combinations of uppercase and lowercase, according to whether the first mutant allele to be discovered produced a dominant or recessive phenotype. Conventions for naming protein products are equally varied.

This typographical chaos drives everyone crazy. Moreover, there are many occasions, especially in a book such as this, where we need to refer to a gene generically—without specifying the mouse version, the human version, the chick version, or the hippopotamus version—because the gene variants across species are all equivalent for the purposes of our discussion. What convention then should we use?

We have decided in this book to follow a uniform rule. We write all gene names with the first letter in uppercase and the rest in lowercase, and all in italics, thus: *Bazooka*, *Cdc2*, *Dishevelled*, *Egl1*. The corresponding protein, where it is named after the gene, will be written in the same way, but in roman rather than italic letters: Bazooka, Cdc2, Dishevelled, Egl1. When it is necessary to specify the organism, this can be done with a prefix to the gene name.

For completeness, we list a few further details of naming rules that we shall follow. In some instances, an added letter in the gene name is traditionally used to distinguish between genes that are related by function or evolution; for those genes, we put that letter in uppercase if it is usual to do so (*LacZ*, *RecA*, *HoxA4*). Proteins are more of a problem. Many of them have names in their own right, assigned to them before the gene was named. Such protein names take many forms, although most of them traditionally begin with a lowercase letter (actin, hemoglobin, catalase); others are acronyms (such as GFP, for green fluorescent protein, or BMP4, for bone morphogenetic protein 4). To force all such protein names into a uniform style would do too much violence to established usages, and we shall simply write them in the traditional way. For the corresponding gene names in all these cases, we shall nevertheless follow our standard rule: *Actin*, *Hemoglobin*, *Catalase*, *Bmp4*, *Gfp*.

For those who wish to know them, the table shows some of the official conventions for individual species—conventions that we shall mostly violate in this book, in the manner shown.

Organism	Species-specific convention		Unified convention used in this book	
	Gene	Protein	Gene	Protein
Mouse	<i>Hoxa4</i>	Hoxa4	<i>HoxA4</i>	HoxA4
	<i>Bmp4</i>	BMP4	<i>Bmp4</i>	BMP4
	<i>integrin α-1, Itgα1</i>	integrin α 1	<i>Integrin α1, Itgα1</i>	integrin α 1
Human	<i>HOXA4</i>	HOXA4	<i>HoxA4</i>	HoxA4
Zebrafish	<i>cyclops, cyc</i>	Cyclops, Cyc	<i>Cyclops, Cyc</i>	Cyclops, Cyc
<i>Caenorhabditis</i>	<i>unc-6</i>	UNC-6	<i>Unc6</i>	Unc6
<i>Drosophila</i>	<i>sevenless, sev</i> (named after recessive phenotype)	Sevenless, SEV	<i>Sevenless, Sev</i>	Sevenless, Sev
	<i>Deformed, Dfd</i> (named after dominant mutant phenotype)	Deformed, DFD	<i>Deformed, Dfd</i>	Deformed, Dfd
Yeast				
<i>Saccharomyces cerevisiae</i> (budding yeast)	<i>CDC28</i>	Cdc28, Cdc28p	<i>Cdc28</i>	Cdc28
<i>Schizosaccharomyces pombe</i> (fission yeast)	<i>Cdc2</i>	Cdc2, Cdc2p	<i>Cdc2</i>	Cdc2
<i>Arabidopsis</i>	<i>GAI</i>	GAI	<i>Gai</i>	GAI
<i>Escherichia coli</i>	<i>uvrA</i>	UvrA	<i>UvrA</i>	UvrA

Resources for Instructors

digital.wwnorton.com/mboc7

Designed to enrich the classroom experience, Instructor Resources are available at digital.wwnorton.com/mboc7. Adopting instructors can obtain access to the site from their sales representative, who can be identified by visiting www.wwnorton.com/educator and clicking the “Find My Rep” button.

The Digital Problems Book in Smartwork

For the first time, the popular print supplement *Molecular Biology of the Cell: The Problems Book* is now available in Smartwork. Easier for instructors to assign and more helpful to students because of each question’s pedagogical scaffolding, the Digital Problems Book in Smartwork features the questions authored by Tim Hunt and John Wilson adapted for digital delivery. An enormous library of almost 3500 questions that include critical thinking questions, data analysis questions, and animation and video questions, allows instructors to deliver the exact type of assessment that their students need. The Digital Problems Book in Smartwork comes at no additional cost with all new copies of *Molecular Biology of the Cell*.

Question Detail

ODD ENZYME KINETICS FOR O⁶-METHYLGUANINE REPAIR IN DNA [BLOOM'S 4] [ART]

1st attempt

See Hint

The alkylation repair system in bacteria removes the methyl group from O⁶-methylguanine, converting it to guanine and preventing mutation. The enzyme mechanism is somewhat peculiar. The kinetics of removal were studied by incubating 1.25, 2.50, or 5.00 ng of the pure enzyme with DNA containing ³H-O⁶-methylguanine. At various times, samples were taken, and the DNA was analyzed to determine how much of the mutagenic base remained (see the figure). When the experiment was repeated at 5°C instead of 37°C, the initial rates of removal were slower, but the same end points were achieved.

What, if anything, is peculiar about the kinetics of removal of the methyl group from the O⁶-methylguanine?

Time (minutes)	1.25 ng (% remaining)	2.50 ng (% remaining)	5.00 ng (% remaining)
0	100	100	100
1	85	60	10
2	80	55	5
4	75	50	5
6	75	50	5

Choose one:

- A. One would expect the extent of reaction to increase with increasing enzyme concentration, as seen here.
- B. It is strange that removal of the methyl groups stops at a plateau that depends on enzyme concentration.
- C. The extent of removal does not change with temperature, which is unusual for enzyme-catalyzed reactions.
- D. The rate of removal of methyl groups increases with increasing enzyme concentration, as expected.

SUBMIT ANSWER

Norton Teaching Tools

The Norton Teaching Tools site for *Molecular Biology of the Cell* provides creative and engaging resources to refresh a syllabus or to design a new one. Dynamic, experienced instructors have created primary literature suggestions, active learning activities, lecture PowerPoint files, descriptions of all of the animations and videos, and much more. All of the teaching tools are aligned with chapter topics and organized by activity type, making it easily sortable. The site also features tips for assigning Norton's digital learning tools and addressing the most common course challenges.

Animations and Videos

Under the authorial direction of Michele M. McDonough and Thomas A. Volpe, both of Northwestern University, the animations and video library has been thoroughly updated and expanded. The more than 180 animations and videos are integrated into the ebook and also available to students and instructors at digital www.norton.com/mboc7. Instructors can view descriptions of each on the Norton Teaching Tools site.

Norton Ebook

The purchase of any new print copy of the Seventh Edition of *Molecular Biology of the Cell* includes access to the Norton Ebook version of the text at no additional cost. The Norton Ebook can be purchased as an affordable stand-alone option that provides an active reading experience, enabling students to take notes, bookmark, search, highlight, and read offline. All of the videos and animations appear directly in the ebook, and instructors can add notes that students can see as they are reading the text.

Art of *Molecular Biology of the Cell*, Seventh Edition

The images from the book are available in two convenient formats: PowerPoint and JPEG, and in both labeled and unlabeled versions.

Figure-integrated Lecture Outlines

The section headings, concept headings, and figures from the text have been integrated into PowerPoint presentations and can be customized. For example, the content of these presentations can be combined with videos, questions from the book, or activities in the Norton Teaching Tools site, in order to create unique lectures that facilitate interactive learning.

Test Bank

Updated for the Seventh Edition, the test bank includes a variety of question formats: multiple choice, short answer, fill-in-the-blank, true-false, and matching. The test bank was created with the philosophy that a good exam should require students to reflect upon and integrate information as a part of a sound understanding. Questions are classified by section and difficulty, making it easy to construct tests and quizzes. The test bank question library includes about 70 questions per chapter, ensuring instructors can find the right questions for their exams. It will be delivered through Norton Testmaker, which brings the high-quality questions in the test bank online. Create assessments for your course without downloading files or installing specialized software, customize test bank questions, and easily export your tests to Microsoft Word or Common Cartridge files for your learning management system (LMS).

About the Authors

Bruce Alberts received his PhD from Harvard University and is the Chancellor's Leadership Chair in Biochemistry and Biophysics for Science and Education, University of California, San Francisco. He was the editor-in-chief of *Science* magazine from 2008 until 2013, and for twelve years he served as president of the U.S. National Academy of Sciences (1993–2005).

Rebecca Heald received her PhD from Harvard University and is professor of molecular and cell biology at the University of California, Berkeley. She also serves as the co-chair of that department.

Alexander Johnson received his PhD from Harvard University and is professor of microbiology and immunology at the University of California, San Francisco. He is also director of the Program in Biological Sciences (PIBS) at UCSE.

David Morgan received his PhD from the University of California, San Francisco, and is professor of the Department of Physiology there as well as vice dean for research in the School of Medicine.

Martin Raff received his MD from McGill University and is an emeritus professor of biology and an affiliated member of the Medical Research Council Laboratory for Molecular Cell Biology at University College London.

Keith Roberts received his PhD from the University of Cambridge and was deputy director of the John Innes Centre, Norwich. He is emeritus professor at the University of East Anglia.

Peter Walter received his PhD from the Rockefeller University in New York and is professor of the Department of Biochemistry and Biophysics at the University of California, San Francisco, and an investigator at the Howard Hughes Medical Institute.

John Wilson received his PhD from the California Institute of Technology. He is Distinguished Emeritus Professor of Biochemistry and Molecular Biology at Baylor College of Medicine in Houston.

Tim Hunt received his PhD from the University of Cambridge, where he taught biochemistry and cell biology for more than 20 years. He worked at Cancer Research UK from 1990 to 2010. He shared the 2001 Nobel Prize in Physiology or Medicine with Lee Hartwell and Paul Nurse. He moved to Okinawa in 2016.

Acknowledgments

We once again thank our spouses, partners, families, friends, and colleagues for their continuing patience and support, without which the writing of this new edition of our textbook would not have been possible. As always, we are also indebted to a large number of scientists whose generous help has been essential for making the text as clear, up-to-date, and accurate as possible.

Deserving special credit are the following five outstanding scientists who accepted the task of re-drafting chapters in their areas of expertise: Chapters 12 and 13, Ramanujan Hegde (MRC Laboratory of Molecular Biology and Cambridge University, United Kingdom); Chapter 14, Jared Rutter (University of Utah); Chapter 21, David Bilder (University of California, Berkeley); Chapter 22, Yukiko Yamashita (Whitehead Institute, Massachusetts Institute of Technology); Chapter 23, Matthew Welch (University of California, Berkeley).

In what follows, we acknowledge and thank all of the scientists whose suggestions have helped us to prepare this edition. (A combined list of those who helped with our first, second, third, fourth, fifth, and sixth editions is also provided.)

General: Joseph Ahlander (Northeastern State University), Buzz Baum (Molecular Research Institute, United Kingdom), Michael Burns (Loyola University Chicago), Silvia C. Finnemann (Fordham University), Nora Goosen (Leiden University, The Netherlands), Harold Hoops (State University of New York, Buffalo), Joanna Norris (University of Rhode Island), Mark V. Reedy (Creighton University), Jeff Singer (Portland State University), Amy Springer (University of Massachusetts), Andreas Wodarz (University of Cologne, Germany). In addition, Tiago Barros produced new molecular models for the Seventh Edition.

Chapter 1: Sage Arbor (Marian University Indianapolis), Stephen E. Asmus (Centre College), Jill Banfield (University of California, Berkeley), Zoë Burke (University of Bath, United Kingdom), Elizabeth Good (University of Illinois, Urbana-Champaign), Julian Guttman (Simon Fraser University, Canada), Sudhir Kuman (Temple University), Sue Hum-Musser (Western Illinois University), Brad Mehrtens (University of Illinois, Urbana-Champaign), Inaki Ruiz-Trillo (University of Barcelona, Spain), David Stern (Janelia Research Campus), Andrew Wood (Southern Illinois University), Lidan You (University of Toronto, Canada).

Chapter 2: Sage Arbor (Marian University Indianapolis), Stephen E. Asmus (Centre College), Monica Brinchmann (Nord University, Norway), Michael Cardinal-Aucoin (Lakehead University, Orillia, Canada), Venugopalan Cheriyaath (Texas A&M University, Commerce), Mark Grimes (University of Montana), Sue Hum-Musser (Western Illinois University), Brad Mehrtens (University of Illinois, Urbana-Champaign), Richard Roy (McGill University, Canada), Seth Rubin (University of California, Santa Cruz), Laura Serbus (Florida International

University), Pei-Lan Tsou (Grand Valley State University), Andrew Wood (Southern Illinois University).

Chapter 3: Sage Arbor (Marian University Indianapolis), Jennifer Armstrong (Scripps College), David Baker (University of Washington, Seattle), Anne Bertolotti (MRC Laboratory of Molecular Biology, United Kingdom), Ashok Bidwai (West Virginia University), Douglas Briant (University of Victoria, Canada), Ken Dill (State University of New York, Stony Brook), David S. Eisenberg (University of California, Los Angeles), James Fraser (University of California, San Francisco), Elizabeth Good (University of Illinois, Urbana-Champaign), Ramanujan Hegde (MRC Laboratory of Molecular Biology, United Kingdom), Jerry E. Honts (Drake University), Sue Hum-Musser (Western Illinois University), Tony Hyman (Max Planck Institute of Molecular Cell Biology and Genetics, Germany), Albert Lee (Macquarie University, Australia), Susan Marqusee (University of California, Berkeley), Brad Mehrtens (University of Illinois, Urbana-Champaign), Jose Rodriguez (University of California, Los Angeles), Michael Rosen (University of Texas Southwestern), Seth Rubin (University of California, Santa Cruz), Jonathan Weissman (University of California, San Francisco), Andrew Wood (Southern Illinois University).

Chapter 4: Blake Bextine (University of Texas, Tyler), Wendy Bickmore (University of Edinburgh, United Kingdom), Zoë Burke (University of Bath, United Kingdom), Greg Cooper (HudsonAlpha Institute for Biotechnology, Huntsville), Caroline Dean (John Innes Centre, United Kingdom), Job Dekker (University of Massachusetts Medical School), Barbara Ehrling (University of Victoria, Canada), Lisa Farmer (University of Houston), Shiv Grewal (National Institutes of Health),

Paul Himes (University of Louisville), Sue Hum-Musser (Western Illinois University), Tom Misteli (National Institutes of Health), Rick Myers (HudsonAlpha Institute for Biotechnology, Huntsville), Geeta Nalakar (University of California, San Francisco), Craig Peterson (University of Massachusetts Medical School), Allison Piovesan (University of Bologna, Italy), Saumya Ramanathan (Fisk University), Irina Solovei (Ludwig Maximilians University, Germany), Chisato Ushida (Hirosaki University, Japan), Ken Zaret (University of Pennsylvania).

Chapter 5: Stephen E. Asmus (Centre College), Blake Bextine (University of Texas, Tyler), Stephen P. Bell (Massachusetts Institute of Technology), Michael Cardinal-Aucoin (Lakehead University, Orillia, Canada), Julie Cooper (National Institutes of Health), John Diffley (The Francis Crick Institute, United Kingdom), Barbara Ehrling (University of Victoria, Canada), Lisa Farmer (University of Houston), Elizabeth Good (University of Illinois, Urbana-Champaign), James Haber (Brandeis University), Paul Himes (University of Louisville), Sue Hum-Musser (Western Illinois University), Neil Hunter (University of California, Davis), Keiko Kono (Okinawa Institute of Science and Technology, Japan), Karim Labib (University of Dundee, United Kingdom), Joachim Li (University of California, San Francisco), Rob Martienssen (Cold Spring Harbor Laboratory), Luiza Nogaj (Mount St. Mary's University, Los Angeles), Bruce Stillman (Cold Spring Harbor Laboratory), Johannes Walter (Harvard Medical School), Stephen C. West (The Francis Crick Institute, United Kingdom), Richard D. Wood (MD Anderson Cancer Center).

Chapter 6: Katsura Asano (Kansas State University), Ahmed Badran (Broad Institute, Massachusetts Institute of Technology), Matthew Christians (Grand Valley State University), Patrick Cramer (Max Planck Institute for Biophysical Chemistry, Germany), Daniel J. Finley (Harvard Medical School), Stephen Floor (University of California, San Francisco), Elizabeth Good (University of Illinois, Urbana-Champaign), Michael R. Green (University of Massachusetts Medical School), Arthur L. Horwich (Yale School of Medicine), Hiten Madhani (University of California, San Francisco), Saumya Ramanathan (Fisk University), German Rosas-Acosta (University of Texas, El Paso), Mahito Sadaie (Tokyo University of Science, Japan), Eric Spana (Duke University), David Tollervy (University of Edinburgh, United Kingdom), Chisato Ushida (Hirosaki University, Japan), Alex Varshavsky (California Institute of Technology), Max Wilkinson (MRC Laboratory of Molecular Biology, United Kingdom).

Chapter 7: Katsura Asano (Kansas State University), David Auble (University of Virginia), David Bartel (Massachusetts Institute of Technology), Adrian Bird (University of Edinburgh, United Kingdom), Matthew Christians (Grand Valley State University), Kathleen Collins (University of California, Berkeley), Elizabeth Good (University of Illinois, Urbana-Champaign), Gordon Hagar (National Institutes of Health), Edith Heard (European Molecular Biology Laboratory, Heidelberg), Agnese Loda (European Molecular Biology Laboratory, Heidelberg), Sue Hum-Musser (Western Illinois University), Tracy Nissan (University of Sussex), Sofia Origanti (Saint Louis University), German Rosas-Acosta (University of Texas, El Paso), Schraga Schwartz (Weizmann Institute of Science),

Phillip A. Sharp (Massachusetts Institute of Technology), Kevin Struhl (Harvard Medical School), Igor Ulitsky (Weizmann Institute of Science), Ken Zaret (University of Pennsylvania, Perelman School of Medicine).

Chapter 8: Eric Chow (University of California, San Francisco), Barbara Ehrling (University of Victoria, Canada), Lisa Farmer (University of Houston), Daniel Frigo (University of Texas MD Anderson Cancer Center), Sue Hum-Musser (Western Illinois University), Véronique Moulin (Université Laval, Canada), John Steele (Humboldt State University), Venkat Ventkataraman (Rowan University).

Chapter 9: Eric Betzig (Howard Hughes Medical Institute), Stefano Guido (Università degli Studi di Napoli Federico II, Italy), Julian Guttman (Simon Fraser University, Canada), Richard Henderson (MRC Laboratory of Molecular Biology, United Kingdom), Sue Hum-Musser (Western Illinois University), Lee Ligon (Rensselaer Polytechnic Institute), Jennifer Lippincott-Schwartz (Janelia Research Campus), Eva Nogales (University of California, Berkeley), Helen Saibil (Birkbeck College, University of London, United Kingdom), Peter Shaw (John Innes Centre, United Kingdom), Phoebe Stavridis (University of Nicosia, Greece), John Steele (Humboldt State University), Paul Tillberg (Janelia Research Campus).

Chapter 10: Stephen E. Asmus (Centre College), Francis Barr (Oxford University, United Kingdom), Adam Frost (University of California, San Francisco), Mark Grimes (University of Montana), Ramanujan Hegde (MRC Laboratory of Molecular Biology and Cambridge University, United Kingdom), Gunnar von Heinje (Stockholm University, Sweden), Sue Hum-Musser (Western Illinois University), Michael Jonz (University of Ottawa, Canada), Keiko Kono (Okinawa Institute of Science and Technology, Japan), Werner Kühlbrandt (Max Planck Institute of Biophysics, Germany), Herman Lehman (Hamilton College), Satyajit Mayor (National Centre for Biological Sciences, India), Richard Posner (Northern Arizona University), Richard Roy (McGill University, Canada), Gregory Schmaltz (University of the Fraser Valley, Canada), Andrew Swan (University of Windsor, Canada), Tobias Walther (Harvard Medical School), Graham Warren (University College London, United Kingdom).

Chapter 11: Mauro Costa-Mattioli (Baylor College of Medicine), Robert Edwards (University of California, San Francisco), Zheng Fan (The University of Tennessee Health Science Center), Mark Grimes (University of Montana), Ramanujan Hegde (MRC Laboratory of Molecular Biology and Cambridge University, United Kingdom), Bertil Hille (University of Washington), Olivia S. Long (University of Pittsburgh, Greensburg), Werner Kühlbrandt (Max Planck Institute of Biophysics, Germany), Liqun Luo (Stanford University), Poul Nissen (Aarhus University, Denmark), Richard Posner (Northern Arizona University), Benoît Roux (University of Chicago), Gregory Schmaltz (University of the Fraser Valley, Canada), Susan Spencer (Saint Louis University), Robert Stroud (University of California, San Francisco), Christine Suetterlin (University of California, Irvine).

Chapter 12: Major contributor Ramanujan Hegde (MRC Laboratory of Molecular Biology and Cambridge University, United Kingdom), Cedric Asensio (University of Denver), Buzz Baum (MRC Laboratory of Molecular Biology, United

Kingdom) Mike Chao (California State University, San Bernardino), Edward B. Cluett (Ithaca College), Elizabeth Good (University of Illinois, Urbana-Champaign), Yun Hyun Huh (Gwangju Institute of Science and Technology, South Korea), Tim Levine (University College London, United Kingdom), Sue Hum-Musser (Western Illinois University), Wendy Innis-Whitehouse (University of Texas, Rio Grande Valley), Mack Ivey (University of Arkansas), Stephen Rogers (University of North Carolina), Michael Silverman (Simon Fraser University, Canada), Gina Voeltz (University of Colorado, Boulder), Graham Warren (University College London, United Kingdom), Weiliang Xia (Shanghai Jiao Tong University, China), Ge Yang (Carnegie Mellon University).

Chapter 13: Major contributor Ramanujan Hegde (MRC Laboratory of Molecular Biology and Cambridge University, United Kingdom). Swapna Bhat (University of North Georgia, Gainesville), Pete Cullen (University of Bristol, United Kingdom), Zheng Fan (The University of Tennessee Health Science Center), Adam Frost (University of California, San Francisco), Wendy Innis-Whitehouse (University of Texas, Rio Grande Valley), Reinhard Jahn (Max Planck Institute for Biophysical Chemistry, Germany), Elizabeth Miller (MRC Laboratory of Molecular Biology, United Kingdom), Sean Munro (MRC Laboratory of Molecular Biology, United Kingdom), Michael Silverman (Simon Fraser University, Canada), Susan Spencer (Saint Louis University), Christine Suetterlin (University of California, Irvine), Graham Warren (University College London, United Kingdom).

Chapter 14: Major contributor Jared Rutter (University of Utah). Cedric Asensio (University of Denver), Alice Barkan (University of Oregon), Tessa Burch-Smith (University of Tennessee, Knoxville), Navdeep Chandel (Northwestern University), Elizabeth Good (University of Illinois, Urbana-Champaign), Mark Grimes (University of Montana), Yun Hyun Huh (Gwangju Institute of Science and Technology, South Korea), Sue Hum-Musser (Western Illinois University), Mack Ivey (University of Arkansas), Werner Kühlbrandt (Max Planck Institute of Biophysics, Germany), Dario Leister (University of Munich, Germany), Song-Tao Liu (University of Toledo), Amit Singh (University of Dayton), Jonathan Snow (Barnard College), Amy Sprowles (Humboldt State University), Dennis Winge (University of Utah).

Chapter 15: Josefino Castillo (University of Santo Tomas, Philippines), Elizabeth Good (University of Illinois, Urbana-Champaign), Mark Grimes (University of Montana), Sue Hum-Musser (Western Illinois University), Natalia Jura (University of California, San Francisco), In Hye Lee (Ewha Womans University, South Korea), Song-Tao Liu (University of Toledo), Bruce Mayer (University of Connecticut), Alexandra Newton (University of California, San Diego), Roeland Nusse (Stanford University), Amit Singh (University of Dayton), Jonathan Snow (Barnard College), Amy Sprowles (Humboldt State University).

Chapter 16: Anna Akhmanova (Utrecht University, The Netherlands), Alexander Bershady (National University of Singapore, Singapore), David Bilder (University of California, Berkeley), Josefino Castillo (University of Santo Tomas, Philippines), Ann Cavanaugh (Creighton University), Andrew Carter (Medical Research Council, United Kingdom), Roger Craig (University of Massachusetts

Medical School), Lillian Fritz-Laylin (University of Massachusetts), Elizabeth Good (University of Illinois, Urbana-Champaign), Julian Guttman (Simon Fraser University, Canada), Sue Hum-Musser (Western Illinois University), Yulia Komarova (University of Illinois, Chicago), Arash Komeili (University of California, Berkeley), Chao Liu (Stanford University), Richard McIntosh (University of Colorado), Dyche Mullins (University of California, San Francisco), Maxence Nachury (University of California, San Francisco), Daniela Nicastro (University of Texas Southwestern), Sam Reck-Peterson (University of California, San Diego), Luke Rice (University of Texas Southwestern), Stephen Rogers (University of North Carolina), Trina Schroer (Johns Hopkins University), Michael Sixt (IST, Austria), Thomas Surrey (The Francis Crick Institute, United Kingdom), Tatyana Svitkina (University of Pennsylvania), Katherine Warpeha (University of Illinois, Chicago), Matthew Welch (University of California, Berkeley), Lidan You (University of Toronto, Canada).

Chapter 17: Michael W. Black (California Polytechnic State University), Ann Cavanaugh (Creighton University), Yu Chen (University of Massachusetts), Frederick Dick (University of Western Ontario, Canada), Bruce Edgar (University of Utah), Michael Glotzer (University of Chicago), Elizabeth Good (University of Illinois, Urbana-Champaign), Greg Hermann (Lewis and Clark College), Sue Hum-Musser (Western Illinois University), Peter Maying (Oregon Health and Science University), Mindy McCarville (Dalhousie University, Canada), Jennifer McDonough (Kent State University), Yuko Miyamoto (Elon University), Jonathon Pines (Institute of Cancer Research, United Kingdom), Stephen Rogers (University of North Carolina), Frank Uhlmann (The Francis Crick Institute, United Kingdom), Johannes Walter (Harvard Medical School), Katherine Warpeha (University of Illinois, Chicago), Christina Zito (University of New Haven).

Chapter 18: Stephen E. Asmus (Centre College), Yu Chen (University of Massachusetts), Elizabeth Good (University of Illinois, Urbana-Champaign), Douglas R. Green (St. Jude's Children's Research Hospital), Mindy McCarville (Dalhousie University, Canada), Sue Hum-Musser (Western Illinois University), Yuko Miyamoto (Elon University), Mark Running (University of Louisville), Christina Zito (University of New Haven).

Chapter 19: Stephen E. Asmus (Centre College), Zoë Burke (University of Bath, United Kingdom), John Couchman (University of Copenhagen, Denmark), Elizabeth Good (University of Illinois, Urbana-Champaign), Tony J.C. Harris (University of Toronto), Sue Hum-Musser (Western Illinois University), Yulia Komarova (University of Illinois, Chicago), Zhengchang Liu (University of New Orleans), Mark Running (University of Louisville), Kara Sawarynski (Oakland University), Masatoshi Takeichi (RIKEN Center for Developmental Biology, Japan), Zena Werb (formerly of University of California, San Francisco), Alpha Yap (University of Queensland, Australia), Christina Zito (University of New Haven).

Chapter 20: Alan Ashworth (University of California, San Francisco), Anton Berns (Netherlands Cancer Institute, The Netherlands), David Bilder (University of California, Berkeley), Fred Bunz (Johns Hopkins University), Venugopalan Cheriyaath (Texas A&M University,

Commerce), Michel DuPage (University of California, Berkeley), Paul Edwards (University of Cambridge, United Kingdom), Elizabeth Good (University of Illinois, Urbana-Champaign), Jeff Hadwiger (Oklahoma State University), Monika Haoui (University of California, Berkeley), Lin He (University of California, Berkeley), Dirk Hockemeyer (University of California, Berkeley), Sue Hum-Musser (Western Illinois University), Doug Kellogg (University of California, Santa Cruz), Maria Krasilnikova (Pennsylvania State University), Christopher Lassiter (Roanoke College), Kunxin Luo (University of California, Berkeley), Adam G. Matthews (Wellesley College), Mike Misamore (Texas Christian University), Alexander K. Murashov (East Carolina University), Kristina Pازهoski (Grove City College), David Pellman (Dana Farber Cancer Institute), Jody Rosenblatt (University of Utah), Peter Savage (University of Chicago), Kara Sawarynski (Oakland University), Timothy Shannon (Francis Marion University), Frederick Sproull (LaRoche University), Robert A. Weinberg (Massachusetts Institute of Technology), Harold Varmus (Weill Cornell Medicine), Kenneth Yip (University of Toronto, Canada), Christina Zito (University of New Haven).

Chapter 21: Major contributor David Bilder (University of California, Berkeley). Paul Cullen (State University of New York, Buffalo), Claude Desplan (New York University), Bruce Edgar (University of Utah), Stephen Jesch (Cornell University), Christopher Lassiter (Roanoke College), Laura Mathies (Virginia Commonwealth University), Mike Misamore (Texas Christian University), Alexander K. Murashov (East Carolina University), Nipam Patel (Marine Biological Laboratory), Ruth Phillips (Syracuse University), Olivier Pourquié (Harvard University), Joshua Sanes (Harvard University), Ramaswamy Sharma (University of Texas Health Science Center at San Antonio), Jan Skotheim (Stanford University), David Somers (The Ohio State University), Didier Stanier (Max Planck Institute for Heart and Lung Research, Germany), Shannon Stevenson (University of Minnesota, Duluth), Nancy Toffolo (University of Florida), Jean-Paul Vincent (The Francis Crick Institute, United Kingdom), John Wallingford (University of Texas, Austin), Neal Williams (University of California, Davis).

Chapter 22: Major contributor Yukiko Yamashita (Whitehead Institute, Massachusetts Institute of Technology). Stefano Biressi (University of Trento, Italy), Steven Clark (University of Michigan), Elizabeth Good (University of Illinois, Urbana-Champaign), Konrad Hocheldinger (Harvard University), Shagun Khera (University of Plymouth, United Kingdom), Carien Niessen (University of Cologne, Germany), Jenean O'Brien (The College of St. Scholastica), Peter Reddien (Massachusetts Institute of Technology), Edward Seto (George Washington University), Arianna Smith (Kenyon College), Elly Tanaka (Imperial College London, United Kingdom)

Chapter 23: Major contributor Matthew Welch (University of California, Berkeley). Steven Clark (University of Michigan), Ding Jeak Ling (National University of Singapore, Singapore), Stefan Fischer (Deggendorf Institute of Technology, Germany), Elizabeth Good (University of Illinois, Urbana-Champaign), Karen Guillemin (University of Oregon), Julian Guttman (Simon Fraser University, Canada), Jenean O'Brien (The College

of St. Scholastica), Daniel A. Portnoy (University of California, Berkeley), David Sibley (Washington University in Saint Louis), Michael Way (The Francis Crick Institute, United Kingdom)

Chapter 24: Steven Clark (University of Michigan), Elizabeth Good (University of Illinois, Urbana-Champaign), Jenean O'Brien (The College of St. Scholastica), Peter Parham (Stanford University), Shamith Samarajiwa (University of Cambridge, United Kingdom), Phoebe Stavride (University of Nicosia, Greece), Hariharan Subramanian (Michigan State University), Colin Watts (University of Dundee, United Kingdom), Donald Very (Duquesne University), Debby Walser-Kuntz (Carleton College).

REVIEWERS OF PREVIOUS EDITIONS

Jerry Adams (The Walter and Eliza Hall Institute of Medical Research, Australia), Ralf Adams (London Research Institute, United Kingdom), Markus Affolter (University of Basel, Switzerland), David Agard (University of California, San Francisco), Julie Ahringer (The Gurdon Institute, United Kingdom), John Aitchison (Institute for System Biology, Seattle), Michael Akam (University of Cambridge, United Kingdom), Anna Akhmanova (Utrecht University, The Netherlands), David Allis (The Rockefeller University), Wolfhard Almers (Oregon Health and Science University), Fred Alt (CBR Institute for Biomedical Research, Boston), Victor Ambros (University of Massachusetts, Worcester), Linda Amos (MRC Laboratory of Molecular Biology, United Kingdom), Raul Andino (University of California, San Francisco), Oscar Aparicio (University of Southern California), Clay Armstrong (University of Pennsylvania), Martha Arnaud (University of California, San Francisco), Najla Arshad (Indian Institute of Science, India), Spyros Artavanis-Tsakonas (Harvard Medical School), Michael Ashburner (University of Cambridge, United Kingdom), Jonathan Ashmore (University College London, United Kingdom), Laura Attardi (Stanford University), Tayna Awabdy (University of California, San Francisco), Jeffrey Axelrod (Stanford University Medical Center), Peter Baker (deceased), David Baldwin (Stanford University), Michael Banda (University of California, San Francisco), Cornelia Bargmann (The Rockefeller University), Ben Barres (Stanford University), David Bartel (Massachusetts Institute of Technology), Konrad Basler (University of Zurich, Switzerland), Wolfgang Baumeister (Max Planck Institute of Biochemistry, Germany), Michael Bennett (Albert Einstein College of Medicine), Darwin Berg (University of California, San Diego), Anton Berns (Netherlands Cancer Institute, The Netherlands), Bradley E. Bernstein (Harvard Medical School), Merton Bernfield (Harvard Medical School), Michael Berridge (The Babraham Institute, United Kingdom), Wendy Bickmore (MRC Human Genetics Unit, United Kingdom), Walter Birchmeier (Max Delbrück Center for Molecular Medicine, Germany), Adrian Bird (Wellcome Trust Centre, United Kingdom), David Birk (UMDNJ—Robert Wood Johnson Medical School), Michael Bishop (University of California, San Francisco), Trevor Bivona (University of California, San Francisco), Elizabeth Blackburn (University of California, San Francisco), Tim Bliss (National Institute for Medical Research, United Kingdom), Hans Bode (University of California, Irvine), Piet Borst (Jan Swammerdam Institute, University of

Amsterdam, The Netherlands), Henry Bourne (University of California, San Francisco), Alan Boyde (University College London, United Kingdom), Donita Brady (Duke University), Martin Brand (University of Cambridge, United Kingdom), Carl Branden (deceased), Andre Brandli (Swiss Federal Institute of Technology, Zurich, Switzerland), Dennis Bray (University of Cambridge, United Kingdom), Mark Bretscher (MRC Laboratory of Molecular Biology, United Kingdom), Douglas J. Briant (University of Victoria, Canada), Jason Brickner (Northwestern University), James Briscoe (National Institute for Medical Research, United Kingdom), Neil Brockdorff (University of Oxford, United Kingdom), Marianne Bronner-Fraser (California Institute of Technology), Robert Brooks (King's College London, United Kingdom), Barry Brown (King's College London, United Kingdom), Donald Brown (Carnegie Institution for Science, Baltimore), Michael Brown (University of Oxford, United Kingdom), Michael Bulger (University of Rochester Medical Center), Fred Bunz (Johns Hopkins University), Steve Burden (New York University School of Medicine), Max Burger (University of Basel, Switzerland), Stephen Burley (SGX Pharmaceuticals), Briana Burton (Harvard University), Keith Burridge (University of North Carolina, Chapel Hill), John Cairns (Radcliffe Infirmary, United Kingdom), Patricia Calarco (University of California, San Francisco), Zacheus Cande (University of California, Berkeley), Lewis Cantley (Harvard Medical School), Charles Cantor (Columbia University), Roderick Capaldi (University of Oregon), Mario Capecchi (University of Utah), Michael Carey (University of California, Los Angeles), Adelaide Carpenter (University of California, San Diego), John Carroll (University College London, United Kingdom), Tom Cavalier-Smith (King's College London, United Kingdom), Pierre Chambon (University of Strasbourg, France), Moses Chao (New York University School of Medicine), Venice Chiueh (University of California, Berkeley), Hans Clevers (Hubrecht Institute, The Netherlands), Enrico Coen (John Innes Institute, United Kingdom), Philip Cohen (University of Dundee, United Kingdom), Robert Cohen (University of California, San Francisco), Stephen Cohen (EMBL Heidelberg, Germany), Roger Cooke (University of California, San Francisco), Steven Cook (Imperial College London, United Kingdom), John Cooper (Washington University School of Medicine, St. Louis), Julie P. Cooper (National Cancer Institute), John Couchman (University of Copenhagen, Denmark), Jose A. Costoya (Universidad de Santiago de Compostela, Spain), Michael Cox (University of Wisconsin, Madison), Nancy Craig (Johns Hopkins University), Emily D. Crawford (University of California, San Francisco), James Crow (University of Wisconsin, Madison), Stuart Cull-Candy (University College London, United Kingdom), Leslie Dale (University College London, United Kingdom), Caroline Damsky (University of California, San Francisco), Graeme Davis (University of California, San Francisco), Caroline Dean (John Innes Centre, United Kingdom), Johann De Bono (The Institute of Cancer Research, United Kingdom), Anthony DeFranco (University of California, San Francisco), Abby Dernburg (University of California, Berkeley), Johan de Rooij (The Hubrecht Institute, The Netherlands), Arshad Desai (University of California, San Diego), Michael Dexter (The Wellcome Trust, United Kingdom), John Dick (University of Toronto, Canada), Christopher Dobson (University of Cambridge, United Kingdom), Chris Doe (University of Oregon, Eugene), Russell Doolittle (University of California, San Diego), W. Ford Doolittle (Dalhousie University, Canada), Julian Downward (Cancer Research UK, United Kingdom), Uwe Drescher (King's College London, United Kingdom), Keith Dudley (King's College London, United Kingdom), Graham Dunn (MRC Cell Biophysics Unit, United Kingdom), Jim Dunwell (John Innes Institute, United Kingdom), Susan K. Dutcher (Washington University in St. Louis), Richard H. Ebright (Rutgers University), Bruce Edgar (Fred Hutchinson Cancer Research Center), Paul Edwards (University of Cambridge, United Kingdom), Robert Edwards (University of California, San Francisco), David Eisenberg (University of California, Los Angeles), Sarah Elgin (Washington University in St. Louis), Ruth Ellman (Institute of Cancer Research, United Kingdom), Michael Elowitz (California Institute of Technology), Hana El-Samad (University of California, San Francisco), Beverly Emerson (The Salk Institute), Charles Emerson (University of Virginia), Scott D. Emr (Cornell University), Sharyn Endow (Duke University), Amber English (University of Colorado at Boulder), Lynn Enquist (Princeton University), Tariq Enver (Institute of Cancer Research, United Kingdom), David Epel (Stanford University), Ralf Erdmann (Ruhr University of Bochum, Germany), Gerard Evan (University of California, Comprehensive Cancer Center), Ray Evert (University of Wisconsin, Madison), Matthias Falk (Lehigh University), Stanley Falkow (Stanford University), Douglas Fearon (University of Cambridge, United Kingdom), Gary Felsenfeld (National Institutes of Health), Stuart Ferguson (University of Oxford, United Kingdom), James Ferrell (Stanford University), Christine Field (Harvard Medical School), Daniel Finley (Harvard University), Gary Firestone (University of California, Berkeley), Gerald Fischbach (Columbia University), Gordon Fishell (New York University School of Medicine), Robert Fletcher (University of California, San Francisco), Harvey Florman (Tufts University), Judah Folkman (Harvard Medical School), Larry Fowke (University of Saskatchewan, Canada), Velia Fowler (The Scripps Research Institute), Thomas D. Fox (Cornell University), Jennifer Frazier (Exploratorium, San Francisco), Matthew Freeman (Laboratory of Molecular Biology, United Kingdom), Daniel Friend (University of California, San Francisco), Elaine Fuchs (University of Chicago), Joseph Gall (Carnegie Institution of Washington), Richard Gardner (University of Oxford, United Kingdom), Anthony Gardner-Medwin (University College London, United Kingdom), Peter Garland (Institute of Cancer Research, United Kingdom), David Garrod (University of Manchester, United Kingdom), Susan M. Gasser (University of Basel, Switzerland), Walter Gehring (Biozentrum, University of Basel, Switzerland), Benny Geiger (Weizmann Institute of Science, Rehovot, Israel), Vladimir Gelfand (Northwestern University), Larry Gerace (The Scripps Research Institute), Holger Gerhardt (London Research Institute, United Kingdom), John Gerhart (University of California, Berkeley), Günther Gerisch (Max Planck Institute of Biochemistry, Germany), Frank Gertler (Massachusetts Institute of Technology), Sankar Ghosh (Yale University School of Medicine), Alfred Gilman (The University of Texas Southwestern Medical Center), Andrew P. Gilmore (University of Manchester, United Kingdom), Reid Gilmore (University of

Massachusetts, Amherst), Bernie Gilula (deceased), Charles Gilvarg (Princeton University), Benjamin S. Glick (University of Chicago), Michael Glotzer (University of Chicago), Robert Goldman (Northwestern University), Larry Goldstein (University of California, San Diego), Bastien Gomperts (University College Hospital Medical School, United Kingdom), Daniel Goodenough (Harvard Medical School), Jim Goodrich (University of Colorado, Boulder), Jeffrey Gordon (Washington University in St. Louis), Peter Gould (Middlesex Hospital Medical School, United Kingdom), Alan Grafen (University of Oxford, United Kingdom), Walter Gratzer (King's College London, United Kingdom), Michael Gray (Dalhousie University, Canada), Douglas Green (St. Jude Children's Hospital), Howard Green (Harvard University), Michael R. Green (University of Massachusetts Medical School), Shiv Grewal (National Cancer Institute), Leslie Grivell (University of Amsterdam, The Netherlands), Carol Gross (University of California, San Francisco), Frank Grosveld (Erasmus Universiteit, The Netherlands), Michael Grunstein (University of California, Los Angeles), Barry Gumbiner (Memorial Sloan Kettering Cancer Center), Brian Gunning (Australian National University, Australia), Christine Guthrie (University of California, San Francisco), James Haber (Brandeis University), Ernst Hafen (University of Zurich, Switzerland), David Haig (Harvard University), Andrew Halestrap (University of Bristol, United Kingdom), Alan Hall (Memorial Sloan Kettering Cancer Center), Jeffrey Hall (Brandeis University), John Hall (University of Southampton, United Kingdom), Zach Hall (University of California, San Francisco), Douglas Hanahan (University of California, San Francisco), David Hanke (University of Cambridge, United Kingdom), Gregory Hannon (Cold Spring Harbor Laboratory), Nicholas Harberd (University of Oxford, United Kingdom), Graham Hardie (University of Dundee, United Kingdom), Richard Harland (University of California, Berkeley), Adrian Harris (Cancer Research UK, United Kingdom), John Harris (University of Otago, New Zealand), Tony Harris (University of Toronto, Canada), Stephen Harrison (Harvard University), F. Ulrich Hartl (Max Planck Institute of Biochemistry, Germany), Leland Hartwell (University of Washington), Adrian Harwood (MRC Laboratory for Molecular Cell Biology and Cell Biology Unit, United Kingdom), Scott Hawley (Stowers Institute for Medical Research), John Heath (University of Birmingham, United Kingdom), Ramanujan Hegde (National Institutes of Health), Gunnar von Heijne (Stockholm University, Sweden), Carl-Henrik Heldin (Uppsala University, Sweden), Ari Helenius (Swiss Federal Institute of Technology, Switzerland), Richard Henderson (MRC Laboratory of Molecular Biology, United Kingdom), Glenn Herrick (University of Utah), Ira Herskowitz (deceased), Martin W. Hetzer (The Salk Institute), Bertil Hille (University of Washington), Lindsay Hinck (University of California, Santa Cruz), Alan Hinnebusch (National Institutes of Health), Brigid Hogan (Duke University), Nancy Hollingsworth (State University of New York, Stony Brook), Frank Holstege (University Medical Center, The Netherlands), Leroy Hood (Institute for Systems Biology), Karen Hopkin, John Hopfield (Princeton University), Robert Horvitz (Massachusetts Institute of Technology), Art Horwich (Yale University School of Medicine), Alan Rick Horwitz (University of Virginia), David Housman

(Massachusetts Institute of Technology), Joe Howard (Max Planck Institute of Molecular Cell Biology and Genetics, Germany), Jonathan Howard (University of Washington), James Hudspeth (The Rockefeller University), Simon Hughes (King's College London, United Kingdom), Martin Humphries (University of Manchester, United Kingdom), Tim Hunt (Cancer Research UK, United Kingdom), Neil Hunter (University of California, Davis), Laurence Hurst (University of Bath, United Kingdom), Quyen Huynh (University of Toronto, Canada), Jeremy Hyams (University College London, United Kingdom), Tony Hyman (Max Planck Institute of Molecular Cell Biology and Genetics, Germany), Richard Hynes (Massachusetts Institute of Technology), Philip Ingham (University of Sheffield, United Kingdom), Kenneth Irvine (Rutgers University), Robin Irvine (University of Cambridge, United Kingdom), Norman Iscove (Ontario Cancer Institute, Canada), David Ish-Horowicz (Cancer Research UK, United Kingdom), Rudolf Jaenisch (Massachusetts Institute of Technology), Reinhard Jahn (Max Planck Institute for Biophysical Chemistry, Germany), Lily Jan (University of California, San Francisco), Charles Janeway, Jr. (deceased), Tom Jessell (Columbia University), Arthur Johnson (Texas A&M University), Louise Johnson (deceased), Andy Johnston (John Innes Institute, United Kingdom), Laura Johnston (Columbia University), E.G. Jordan (Queen Elizabeth College, United Kingdom), Ron Kaback (University of California, Los Angeles), Michael Karin (University of California, San Diego), Gary Karpen (University of California, Berkeley), Eric Karsenti (European Molecular Biology Laboratory, Germany), David Kashatus (University of Virginia), Stefan Kanzok (Loyola University Chicago), Ken Keegstra (Michigan State University), Doug Kellogg (University of California, Santa Cruz), Ray Keller (University of California, Berkeley), Douglas Kellogg (University of California, Santa Cruz), Regis Kelly (University of California, San Francisco), John Kendrick-Jones (MRC Laboratory of Molecular Biology, United Kingdom), Cynthia Kenyon (University of California, San Francisco), Roger Keynes (University of Cambridge, United Kingdom), Judith Kimble (University of Wisconsin, Madison), David Kimelman (University of Washington), David Kingsley (Stanford University), Robert Kingston (Massachusetts General Hospital), Marc Kirschner (Harvard University), Richard Klausner (National Institutes of Health), Nancy Kleckner (Harvard University), Mike Klymkowsky (University of Colorado, Boulder), Kelly Komachi (University of California, San Francisco), Rachel Kooistra (Loyola University Chicago), Eugene Koonin (National Institutes of Health), Juan Korenbrot (University of California, San Francisco), Roger Kornberg (Stanford University), Tom Kornberg (University of California, San Francisco), Stuart Kornfeld (Washington University in St. Louis), Daniel Koshland (University of California, Berkeley), Douglas Koshland (Carnegie Institution of Washington, Baltimore), Marilyn Kozak (University of Pittsburgh), Maria Krasilnikova (Pennsylvania State University), Mark Krasnow (Stanford University), Arnold Kriegstein (University of California, San Francisco), Werner Kühlbrandt (Max Planck Institute for Biophysics, Germany), John Kuriyan (University of California, Berkeley), Robert Kýmpta (MRC Laboratory for Molecular Cell Biology, United Kingdom), Karim Labib (University of Manchester, United Kingdom), Peter Lachmann (MRC Centre, United Kingdom), Ulrich

Laemli (University of Geneva, Switzerland), Trevor Lamb (University of Cambridge, United Kingdom), Hartmut Land (Cancer Research UK, United Kingdom), David Lane (University of Dundee, United Kingdom), Jane Langdale (University of Oxford, United Kingdom), Lewis Lanier (University of California, San Francisco), Nils-Göran Larsson (Max Planck Institute for Biology of Aging, Germany), Jay Lash (University of Pennsylvania), Peter Lawrence (MRC Laboratory of Molecular Biology, United Kingdom), Paul Lazarow (Mount Sinai School of Medicine), Jeannie Lee (Harvard Medical School), Robert J. Lefkowitz (Duke University), Michael Levine (University of California, Berkeley), Warren Levinson (University of California, San Francisco), Alex Levitzki (Hebrew University, Israel), Wes Lewis (University of Alabama), Ottoline Leyser (University of York, United Kingdom), Joachim Li (University of California, San Francisco), Jeffrey Lichtman (Harvard University), H. Lill (VU University Amsterdam, The Netherlands), Tomas Lindahl (Cancer Research UK, United Kingdom), Vishu Lingappa (University of California, San Francisco), Jennifer Lippincott-Schwartz (National Institutes of Health), Joseph Lipsick (Stanford University School of Medicine), Dan Littman (New York University School of Medicine), Clive Lloyd (John Innes Institute, United Kingdom), Richard Locksley (University of California, San Francisco), Richard Losick (Harvard University), Daniel Louvard (Institut Curie, France), Robin Lovell-Badge (National Institute for Medical Research, United Kingdom), Scott Lowe (Cold Spring Harbor Laboratory), Shirley Lowe (University of California, San Francisco), Reinhard Lührman (Max Planck Institute of Biophysical Chemistry, Germany), Michael Lynch (Indiana University), Laura Machesky (University of Birmingham, United Kingdom), Hitendra Madhani (University of California, San Francisco), James Maller (University of Colorado Medical School), Tom Maniatis (Harvard University), Richard Mann (Columbia University), Colin Manoil (Harvard Medical School), Elliott Margulies (National Institutes of Health), Philippa Marrack (National Jewish Medical and Research Center, Denver), Mark Marsh (Institute of Cancer Research, United Kingdom), Wallace Marshall (University of California, San Francisco), Gail Martin (University of California, San Francisco), Paul Martin (University College London, United Kingdom), Joan Massagué (Memorial Sloan Kettering Cancer Center), Christopher Mathews (Oregon State University), Satyajit Mayor (National Centre for Biological Sciences, India), Brian McCarthy (University of California, Irvine), Richard McCarthy (Cornell University), Melanie McGill (University of Toronto, Canada), William McGinnis (University of California, San Diego), Anne McLaren (Wellcome/Cancer Research Campaign Institute, United Kingdom), Frank McNally (University of California, Davis), James A. McNew (Rice University), J. Richard McIntosh (University of Colorado, Boulder), Andy McMahon (University of Southern California), Frederick Meins (Friedrich Miescher Institute, Switzerland), Stephanie Mel (University of California, San Diego), Ira Mellman (Genentech), Doug Melton (Harvard University), Barbara Meyer (University of California, Berkeley), Elliot Meyerowitz (California Institute of Technology), Chris Miller (Brandeis University), Robert Mishell (University of Birmingham, United Kingdom), Tom Misteli (National Cancer Institute), Avron Mitchison (University College London, United Kingdom), N.A. Mitchison (University College London, United Kingdom), Timothy Mitchison (Harvard Medical School), Quinn Mitrovich (University of California, San Francisco), Marek Mlodzik (Mount Sinai Hospital, New York), Alex Mogilner (University of California, Davis), Peter Mombaerts (The Rockefeller University), Mark Mooseker (Yale University), David Morgan (University of California, San Francisco), Michelle Moritz (University of California, San Francisco), Richard Morris (John Innes Centre, United Kingdom), Montrose Moses (Duke University), Keith Mostov (University of California, San Francisco), Anne Mudge (University College London, United Kingdom), Hans Müller-Eberhard (Scripps Clinic and Research Institute), Annette Müller-Taubenberger (Ludwig Maximilians University, Germany), Alan Munro (University of Cambridge, United Kingdom), J. Murdoch Mitchison (Harvard University), Richard Myers (Stanford University), Diana Myles (University of California, Davis), Andrew Murray (Harvard University), Maxence Nachury (Stanford School of Medicine), Shigekazu Nagata (Kyoto University, Japan), Eric Nam (University of Toronto, Canada), Geeta Narlikar (University of California, San Francisco), Kim Nasmyth (University of Oxford, United Kingdom), Mark E. Nelson (University of Illinois, Urbana-Champaign), Michael Neuberger (deceased), Walter Neupert (University of Munich, Germany), David Nicholls (University of Dundee, United Kingdom), Roger Nicoll (University of California, San Francisco), Poul Nissen (Aarhus University, Denmark), Suzanne Noble (University of California, San Francisco), Eva Nogales (University of California, Berkeley), Harry Noller (University of California, Santa Cruz), Peter Novick (University of California, San Diego), Susan Ferro-Novick (University of California, San Diego), Jodi Nunnari (University of California, Davis), Paul Nurse (The Francis Crick Institute, United Kingdom), Roel Nusse (Stanford University), Michael Nussenzweig (The Rockefeller University), Duncan O'Dell (deceased), Duncan Odum (Cancer Research UK, United Kingdom), Patrick O'Farrell (University of California, San Francisco), Bjorn Olsen (Harvard Medical School), Maynard Olson (University of Washington), Stuart Orkin (Harvard University), Terry Orr-Weaver (Massachusetts Institute of Technology), Erin O'Shea (Harvard University), Dieter Osterhelt (Max Planck Institute of Biochemistry, Germany), William Otto (Cancer Research UK, United Kingdom), John Owen (University of Birmingham, United Kingdom), Dale Oxender (University of Michigan), George Palade (deceased), Albert Pan (Georgia Regents University), Duoja Pan (Johns Hopkins Medical School), Barbara Panning (University of California, San Francisco), Roy Parker (University of Arizona, Tucson), William W. Parson (University of Washington), Terence Partridge (MRC Clinical Sciences Centre, United Kingdom), William E. Paul (National Institutes of Health), Tony Pawson (deceased), Hugh Pelham (Medical Research Council, United Kingdom), Robert Perry (Institute for Cancer Research, Philadelphia), Gordon Peters (Cancer Research UK, United Kingdom), Greg Petsko (Brandeis University), Nikolaus Pfanner (University of Freiburg, Germany), David Phillips (The Rockefeller University), Jeremy Pickett-Heaps (The University of Melbourne, Australia), Jonathan Pines (The Gurdon Institute, United Kingdom), Julie Pitcher (University College London, United Kingdom),

Kingdom), Jeffrey Pollard (Albert Einstein College of Medicine), Tom Pollard (Yale University), Bruce Ponder (University of Cambridge, United Kingdom), Prasanth Potluri (The Children's Hospital of Philadelphia Research Institute), Daniel Portnoy (University of California, Berkeley), Olivier Pourquie (Harvard Medical School), James Priess (University of Washington), Darwin Prockop (Tulane University), Andreas Prokop (University of Manchester, United Kingdom), Mark Ptashne (Memorial Sloan Kettering Cancer Center), Dale Purves (Duke University), Efraim Racker (Cornell University), Jordan Raff (University of Oxford, United Kingdom), Klaus Rajewsky (Max Delbrück Center for Molecular Medicine, Germany), George Ratcliffe (University of Oxford, United Kingdom), Elio Raviola (Harvard Medical School), Erez Raz (University of Münster, Germany), Martin Rechsteiner (University of Utah, Salt Lake City), Samara Reck-Peterson (Harvard Medical School), David Rees (National Institute for Medical Research, United Kingdom), Thomas A. Reh (University of Washington), Peter Rehling (University of Göttingen, Germany), Louis Reichardt (University of California, San Francisco), Renee Reijo (University of California, San Francisco), Caetano Reis e Sousa (Cancer Research UK, United Kingdom), Fred Richards (Yale University), Conly Rieder (Wadsworth Center, Albany), Phillips Robbins (Massachusetts Institute of Technology), Elizabeth Robertson (The Wellcome Trust Centre for Human Genetics, United Kingdom), Elaine Robson (University of Reading, United Kingdom), Robert Roeder (The Rockefeller University), Michael Rout (The Rockefeller University), Joel Rosenbaum (Yale University), Janet Rossant (Mount Sinai Hospital, Canada), Jesse Roth (National Institutes of Health), Jim Rothman (Memorial Sloan Kettering Cancer Center), Rodney Rothstein (Columbia University), Erkki Ruoslahti (La Jolla Cancer Research Foundation), Chris Rushlow (New York University), Gary Ruvkun (Massachusetts General Hospital), Vladislav Ryvkin (Stony Brook University), David Sabatini (New York University), Alan Sachs (University of California, Berkeley), Edward Salmon (University of North Carolina, Chapel Hill), Laasya Samhita (Indian Institute of Science, India), Aziz Sancar (University of North Carolina, Chapel Hill), Joshua Sanes (Harvard University), Peter Sarnow (Stanford University), Lisa Satterwhite (Duke University Medical School), Robert Sauer (Massachusetts Institute of Technology), Ken Sawin (The Wellcome Trust Centre for Cell Biology, United Kingdom), Howard Schachman (University of California, Berkeley), Gerald Schatten (Pittsburgh Development Center), Gottfried Schatz (Biozentrum, University of Basel, Switzerland), Randy Schekman (University of California, Berkeley), Richard Scheller (Stanford University), Stephen Scherer (University of Toronto, Canada), Giampietro Schiavo (Cancer Research UK, United Kingdom), Ueli Schibler (University of Geneva, Switzerland), Alex Schier (Harvard University), Joseph Schlessinger (New York University Medical Center), Danny J. Schnell (University of Massachusetts, Amherst), Sandra Schmid (University of Texas Southwestern), Michael Schramm (Hebrew University, Israel), Robert Schreiber (Washington University School of Medicine), Sebastian Schuck (University of Heidelberg, Germany), James Schwartz (Columbia University), Ronald Schwartz (National Institutes of Health), François Schweisguth (Institut Pasteur, France),

John Scott (University of Manchester, United Kingdom), John Sedat (University of California, San Francisco), Peter Selby (Cancer Research UK, United Kingdom), Zvi Sellinger (Hebrew University, Israel), Gregg Semenza (Johns Hopkins University), John Senderak (Jefferson Medical College), Philippe Sengel (University of Grenoble, France), Peter Shaw (John Innes Institute, United Kingdom), Michael Sheetz (Columbia University), Morgan Sheng (Massachusetts Institute of Technology), Charles Sherr (St. Jude Children's Hospital), David Shima (Cancer Research UK, United Kingdom), Marc Shuman (University of California, San Francisco), David Sibley (Washington University in St. Louis), Samuel Silverstein (Columbia University), Melvin I. Simon (California Institute of Technology), Kai Simons (Max Planck Institute of Molecular Cell Biology and Genetics, Germany), Philippa Simons (Imperial College, United Kingdom), Robert H. Singer (Albert Einstein School of Medicine), Jonathan Slack (Cancer Research UK, United Kingdom), Stephen Small (New York University), Alison Smith (John Innes Institute, United Kingdom), Austin Smith (University of Edinburgh, United Kingdom), Jim Smith (The Gurdon Institute, United Kingdom), John Maynard Smith (University of Sussex, United Kingdom), Mitchell Sogin (Woods Hole Oceanographic Institution), Frank Solomon (Massachusetts Institute of Technology), Michael Solursh (University of Iowa), Bruce Spiegelman (Harvard Medical School), Timothy Springer (Harvard Medical School), Mathias Sprinzl (University of Bayreuth, Germany), Scott Stachel (University of California, Berkeley), Andrew Staehelin (University of Colorado, Boulder), David Standing (University of California, San Francisco), Margaret Stanley (University of Cambridge, United Kingdom), Martha Stark (University of California, San Francisco), Wilfred Stein (Hebrew University, Israel), Malcolm Steinberg (Princeton University), Ralph Steinman (deceased), Len Stephens (The Babraham Institute, United Kingdom), Paul Sternberg (California Institute of Technology), Rolf Sternglanz (Stony Brook University), Chuck Stevens (The Salk Institute), Alastair Stewart (The Victor Chang Cardiac Research Institute, Australia), Murray Stewart (MRC Laboratory of Molecular Biology, United Kingdom), Bruce Stillman (Cold Spring Harbor Laboratory), Mike Stratton (Wellcome Trust Sanger Institute, United Kingdom), Charles Streuli (University of Manchester, United Kingdom), Monroe Strickberger (University of Missouri, St. Louis), Daniela Stock (The Victor Chang Cardiac Research Institute, Australia), Charles Streuli (University of Manchester, United Kingdom), Robert Stroud (University of California, San Francisco), Kevin Struhl (Harvard Medical School), Michael Stryker (University of California, San Francisco), Suresh Subramani (University of California, San Diego), William Sullivan (University of California, Santa Cruz), Azim Surani (The Gurdon Institute, United Kingdom), Jesper Svejstrup (Cancer Research UK, United Kingdom), Karel Svoboda (Howard Hughes Medical Institute), Daniel Szollosi (Institut National de la Recherche Agronomique, France), Jack Szostak (Harvard Medical School), Clifford Tabin (Harvard Medical School), Masatoshi Takeichi (RIKEN Center for Developmental Biology, Japan), Robert Tampé (Goethe University, Germany), Nicolas Tapon (London Research Institute, United Kingdom), Diethard Tautz (University of Cologne, Germany), Marc Tessier-Lavigne

(The Rockefeller University), Julie Theriot (Stanford University), Roger Thomas (University of Bristol, United Kingdom), Barry Thompson (Cancer Research UK, United Kingdom), Craig Thompson (Memorial Sloan Kettering Cancer Center), Kurt Thorn (University of California, San Francisco), Janet Thornton (European Bioinformatics Institute, United Kingdom), Vernon Thornton (King's College London, United Kingdom), Cheryl Tickle (University of Dundee, United Kingdom), Jim Till (Ontario Cancer Institute, Canada), Lewis Tilney (University of Pennsylvania), David Tollervey (University of Edinburgh, United Kingdom), Ian Tomlinson (Cancer Research United Kingdom), Nick Tonks (Cold Spring Harbor Laboratory), Alain Townsend (Institute of Molecular Medicine, John Radcliffe Hospital, United Kingdom), Paul Travers (Scottish Institute for Regeneration Medicine, United Kingdom), Robert Trelstad (UMDNJ—Robert Wood Johnson Medical School), Anthony Trewavas (Edinburgh University, United Kingdom), Nigel Unwin (MRC Laboratory of Molecular Biology, United Kingdom), Victor Vacquier (University of California, San Diego), Ronald D. Vale (University of California, San Francisco), Richard B. Vallee (Columbia University), Tom Vanaman (University of Kentucky), Harry van der Westen (Wageningen, The Netherlands), Harold Varmus (National Cancer Institute), Alexander J. Varshavsky (California Institute of Technology), Danielle Vidaurre (University of Toronto, Canada), Anna Constance Vind (University of Copenhagen, Denmark), Gia Voeltz (University of Colorado, Boulder), Donald Voet (University of Pennsylvania), Harald von Boehmer (Harvard Medical School), Amy Wagers (Harvard University), Madhu Wahi (University of California, San Francisco), Virginia Walbot (Stanford University), Frank Walsh (GlaxoSmithKline, United Kingdom), D. Eric Walters (Chicago Medical School), Tobias Walther (Harvard University), Trevor Wang (John Innes Institute, United Kingdom), Xiaodong Wang (The University of Texas Southwestern Medical School), Yu-Lie Wang (Worcester Foundation for Biomedical Research), Gary Ward (University of Vermont), Anne Warner (University College London, United Kingdom), Carmen Warren (University of California, Los Angeles), Graham Warren (Yale University School of Medicine), Paul Wassarman (Mount Sinai School of Medicine), Clare Waterman-Storer (The Scripps Research Institute), Fiona Watt (Cancer Research UK, United Kingdom), John Watts (John Innes Institute, United Kingdom), Michael Way (Cancer Research UK, United Kingdom), Klaus Weber (Max Planck Institute for Biophysical Chemistry, Germany), Martin Weigert (Institute for Cancer Research, Philadelphia), Robert Weinberg (Massachusetts Institute of Technology), Orion Weiner (University of California, San Francisco), Harold Weintraub (deceased), Karsten Weis (Swiss Federal Institute of Technology, Switzerland), Irving Weissman (Stanford University), Jonathan Weissman (University of California, San Francisco), Matthew Welch (University of California, Berkeley), Steve Wellard (Pennsylvania State University), Jim Wells (University of California, San Francisco), Susan R. Wente (Vanderbilt University School of Medicine), Norman Wessells (University of Oregon, Eugene), Stephen West (Cancer Research UK, United Kingdom), Judy White (University of Virginia), Evan Whitehead (University of California,

Berkeley), William Wickner (Dartmouth College), Carrie Wilczewski (Loyola University Chicago), Michael Wilcox (deceased), Lewis T. Williams (Chiron Corporation), Patrick Williamson (University of Massachusetts, Amherst), Keith Willison (Chester Beatty Laboratories, United Kingdom), John Wilson (Baylor College of Medicine), Anna Wing (Pennsylvania State University), Douglas J. Winton (Cancer Research UK, United Kingdom), Alan Wolffe (deceased), Richard Wolfenden (University of North Carolina, Chapel Hill), Sandra Wolin (Yale University School of Medicine), Lewis Wolpert (University College London, United Kingdom), Richard D. Wood (University of Pittsburgh Cancer Institute), Chris L. Woodcock (University of Massachusetts, Amherst), Ian Woods (Ithaca College), Abraham Worcel (University of Rochester), John Wright (University of Alabama), Nick Wright (Cancer Research UK, United Kingdom), John Wyke (Beatson Institute for Cancer Research, United Kingdom), Johanna Wysocka and lab members (Stanford School of Medicine), Michael P. Yaffe (California Institute for Regenerative Medicine), Kenneth M. Yamada (National Institutes of Health), Keith Yamamoto (University of California, San Francisco), Shinya Yamamaka (Kyoto University, Japan), Alpha Yap (The University of Queensland, Australia), Charles Yocum (University of Michigan, Ann Arbor), Peter Yurchenco (UMDNJ—Robert Wood Johnson Medical School), Rosalind Zalin (University College London, United Kingdom), Patricia Zambryski (University of California, Berkeley), Marino Zerial (Max Planck Institute of Molecular Cell Biology and Genetics, Germany).

OUR PUBLISHER

We thank the dozens of people whose dedication brought this project to fruition. Special thanks go to our editor, Betsy Twitchell, whose talents and personality kept everyone focused. As for previous editions, Denise Schanck directed operations, displaying unflinching patience, insight, tact, and energy throughout the entire journey. Once again, we are in debt to our talented artist, Nigel Orme, who—with author Keith Roberts—produced the captivating art and design that grace the covers, as well as the hundreds of distinctive, highly informative figures throughout the text. Carla Talmadge, our tireless project editor, juggled the many moving parts of this textbook and ushered it gracefully into the book you hold in your hands today. In addition, we are immensely grateful to our copyeditor, Christopher Curioli, who carefully read every page. We also thank Danny Vargo, our assistant editor who tracked the countless emails, chapter drafts, and Excel files that constantly zipped back and forth between editors, authors, and reviewers. And production manager Jane Searle adeptly managed the process of translating our raw material into the polished final product.

An absolutely tireless team at Norton created the print and digital supplementary resources for our book. Media editor Todd Pearson, associate editor Jasmine Ribeaux, and media assistant editor Lindsey Heale worked on every element of the package as a team. Chris Rapp's dedicated and focused efforts on the Smartwork course have produced an

invaluable resource for students and instructors. Megan Schindel, Patricia Wong, and Tommy Persano handled the permissions for this edition, and Kim Yi's media project editorial group, specifically Jesse Newkirk, skillfully shepherded the content through its many stages of development.

Marketing manager Ruth Bolster's expertise in direct marketing has helped ensure that this book makes it into

the hands of as many instructors and students as possible. We thank her and everyone involved in Norton's sales, marketing, and management teams for their unflagging support of our book, including Erik Fahlgren, Michael Wright, Ann Shin, and Julia Reidhead.

Brief Contents

PART I	INTRODUCTION TO THE CELL	
Chapter 1	Cells, Genomes, and the Diversity of Life	1
Chapter 2	Cell Chemistry and Bioenergetics	49
Chapter 3	Proteins	115
PART II	BASIC GENETIC MECHANISMS	
Chapter 4	DNA, Chromosomes, and Genomes	183
Chapter 5	DNA Replication, Repair, and Recombination	253
Chapter 6	How Cells Read the Genome: From DNA to Protein	321
Chapter 7	Control of Gene Expression	397
PART III	WAYS OF WORKING WITH CELLS	
Chapter 8	Analyzing Cells, Molecules, and Systems	475
Chapter 9	Visualizing Cells and Their Molecules	563
PART IV	INTERNAL ORGANIZATION OF THE CELL	
Chapter 10	Membrane Structure	603
Chapter 11	Small-Molecule Transport and Electrical Properties of Membranes	637
Chapter 12	Intracellular Organization and Protein Sorting	683
Chapter 13	Intracellular Membrane Traffic	749
Chapter 14	Energy Conversion and Metabolic Compartmentation: Mitochondria and Chloroplasts	811
Chapter 15	Cell Signaling	873
Chapter 16	The Cytoskeleton	949
Chapter 17	The Cell Cycle	1027
Chapter 18	Cell Death	1089
PART V	CELLS IN THEIR SOCIAL CONTEXT	
Chapter 19	Cell Junctions and the Extracellular Matrix	1105
Chapter 20	Cancer	1163
Chapter 21	Development of Multicellular Organisms	1217
Chapter 22	Stem Cells in Tissue Homeostasis and Regeneration	1279
Chapter 23	Pathogens and Infection	1313
Chapter 24	The Innate and Adaptive Immune Systems	1353

Special Features

TABLE 1–2	Some Model Organisms and Their Genomes	29
TABLE 2–1	Covalent and Noncovalent Chemical Bonds	51
TABLE 2–2	Relationship Between the Standard Free-Energy Change, ΔG° , and the Equilibrium Constant	69
PANEL 2–1	Chemical Bonds and Groups Commonly Encountered in Biological Molecules	94
PANEL 2–2	Water and Its Influence on the Behavior of Biological Molecules	96
PANEL 2–3	The Principal Types of Weak Noncovalent Bonds That Hold Macromolecules Together	98
PANEL 2–4	An Outline of Some of the Types of Sugars Commonly Found in Cells	100
PANEL 2–5	Fatty Acids and Other Lipids	102
PANEL 2–6	A Survey of the Nucleotides	104
PANEL 2–7	Free Energy and Biological Reactions	106
PANEL 2–8	Details of the 10 Steps of Glycolysis	108
PANEL 2–9	The Complete Citric Acid Cycle	110
PANEL 3–1	The 20 Amino Acids Found in Proteins	118
TABLE 3–3	Macromolecular Machines Compared to Biomolecular Condensates and Membrane-enclosed Compartments	175
TABLE 3–4	Some Molecules Covalently Attached to Proteins That Regulate Protein Function	175
TABLE 4–1	Some Vital Statistics for the Human Genome	194
TABLE 5–4	Three Major Classes of Transposable Elements	308
TABLE 6–1	Principal Types of RNAs Produced in Cells	327
PANEL 7–1	Common Structural Motifs in Transcription Regulators	404
PANEL 8–1	Review of Classical Genetics	520
PANEL 9–1	Protein Structure Determination Using CryoEM	594
TABLE 11–1	A Comparison of Inorganic Ion Concentrations Inside and Outside a Typical Mammalian Cell	638
PANEL 11–1	The Derivation of the Nernst Equation	656
TABLE 12–1	Relative Volumes Occupied by the Major Intracellular Compartments in a Liver Cell (Hepatocyte)	684
TABLE 14–1	Quantity of Organelles and Organelle DNA in Some Cells and Tissues	815
TABLE 14–2	Mitochondrial Functions	819
PANEL 14–1	Redox Potentials	825
TABLE 14–3	Product Yields from the Oxidation of Sugars and Fats	836
TABLE 15–3	Four Major Families of Heterotrimeric G Proteins	907
TABLE 15–4	Some Extracellular Signal Proteins That Act Via RTKs	911
TABLE 15–5	The Ras Superfamily of Monomeric GTPases	915
TABLE 15–6	Some Extracellular Signal Proteins That Act Through Cytokine Receptors and the JAK–STAT Signaling Pathway	925
PANEL 16–2	The Polymerization of Actin and Tubulin	960
TABLE 16–1	Chemical Inhibitors of Actin and Microtubules	964
PANEL 16–3	Actin Filaments	965
PANEL 16–4	Microtubules	994
TABLE 16–2	Major Types of Intermediate Filament Proteins in Vertebrate Cells	1007
TABLE 17–1	The Major Cyclins and Cdks of Vertebrates and Budding Yeast	1034
TABLE 17–2	Summary of the Major Cell-Cycle Regulatory Proteins	1041
PANEL 17–1	The Principal Stages of M Phase (Mitosis and Cytokinesis) in an Animal Cell	1048
TABLE 19–1	Anchoring Junctions	1107
TABLE 19–2	Some Types of Collagen and Their Properties	1134
TABLE 19–3	Some Types of Integrins	1149
TABLE 20–2	Viruses Associated with Human Cancers	1202
TABLE 22–1	Blood Cells	1286
TABLE 23–1	Viruses That Cause Human Disease	1323
TABLE 24–2	Properties of the Major Classes of Antibodies in Humans	1375
TABLE 24–3	Properties of Human Class I and Class II MHC Proteins	1388
TABLE 24–4	Some Vaccines Approved for Human Use	1398

Contents

Chapter 1 Cells, Genomes, and the Diversity of Life	1		
THE UNIVERSAL FEATURES OF LIFE ON EARTH	2		
All Cells Store Their Hereditary Information in the Form of Double-Strand DNA Molecules	2		
All Cells Replicate Their Hereditary Information by Templated Polymerization	3		
All Cells Transcribe Portions of Their DNA into RNA Molecules	5		
All Cells Use Proteins as Catalysts	6		
All Cells Translate RNA into Protein in the Same Way	6		
Each Protein Is Encoded by a Specific Gene	7		
Life Requires a Continual Input of Free Energy	7		
All Cells Function as Biochemical Factories	8		
All Cells Are Enclosed in a Plasma Membrane Across Which Nutrients and Waste Materials Must Pass	8		
Cells Operate at a Microscopic Scale Dominated by Random Thermal Motion	9		
A Living Cell Can Exist with 500 Genes	10		
Summary	10		
GENOME DIVERSIFICATION AND THE TREE OF LIFE	10		
The Tree of Life Has Three Major Domains: Eukaryotes, Bacteria, and Archaea	11		
Eukaryotes Make Up the Domain of Life That Is Most Familiar to Us	13		
On the Basis of Genome Analysis, Bacteria Are the Most Diverse Group of Organisms on the Planet	13		
Archaea: The Most Mysterious Domain of Life	15		
Organisms Occupy Most of Our Planet	15		
Cells Can Be Powered by a Wide Variety of Free-Energy Sources	15		
Some Cells Fix Nitrogen and Carbon Dioxide for Other Cells	17		
Genomes Diversify Over Evolutionary Time, Producing New Types of Organisms	18		
New Genes Are Generated from Preexisting Genes	19		
Gene Duplications Give Rise to Families of Related Genes Within a Single Genome	20		
The Function of a Gene Can Often Be Deduced from Its Nucleotide Sequence	20		
More Than 200 Gene Families Are Common to All Three Domains of Life	21		
Summary	21		
EUKARYOTES AND THE ORIGIN OF THE EUKARYOTIC CELL	22		
Eukaryotic Cells Contain a Variety of Organelles	23		
Mitochondria Evolved from a Symbiotic Bacterium Captured by an Ancient Archaeon	25		
Chloroplasts Evolved from a Symbiotic Photosynthetic Bacterium Engulfed by an Ancient Eukaryotic Cell	26		
Eukaryotes Have Hybrid Genomes	27		
Eukaryotic Genomes Are Big	28		
Eukaryotic Genomes Are Rich in Regulatory DNA	28		
Eukaryotic Genomes Define the Program of Multicellular Development	29		
Many Eukaryotes Live as Solitary Cells	30		
Summary	31		
MODEL ORGANISMS	31		
Mutations Reveal the Functions of Genes	32		
Molecular Biology Began with a Spotlight on One Bacterium and Its Viruses	33		
The Focus on <i>E. coli</i> as a Model Organism Has Accelerated Many Subsequent Discoveries	35		
A Yeast Serves as a Minimal Model Eukaryote	36		
The Expression Levels of All the Genes of an Organism Can Be Determined	37		
<i>Arabidopsis</i> Has Been Chosen as a Model Plant	38		
The World of Animal Cells Is Mainly Represented by a Worm, a Fly, a Fish, a Mouse, and a Human	38		
Studies in the Fruit Fly <i>Drosophila</i> Provide a Key to Vertebrate Development	39		
The Frog and the Zebrafish Provide Highly Accessible Vertebrate Models	40		
The Mouse Is the Predominant Mammalian Model Organism	41		
The COVID-19 Pandemic Has Focused Scientists on the SARS-CoV-2 Coronavirus	42		
Humans Are Unique in Reporting on Their Own Peculiarities To Understand Cells and Organisms Will Require Mathematics, Computers, and Quantitative Information	44		
Summary	45		
Problems	46		
References	47		
Chapter 2 Cell Chemistry and Bioenergetics	49		
THE CHEMICAL COMPONENTS OF A CELL	49		
Water Is Held Together by Hydrogen Bonds	50		
Four Types of Noncovalent Attractions Help Bring Molecules Together in Cells	51		
Some Polar Molecules Form Acids and Bases in Water	52		
A Cell Is Formed from Carbon Compounds	53		
Cells Contain Four Major Families of Small Organic Molecules	53		
The Chemistry of Cells Is Dominated by Macromolecules with Remarkable Properties	54		
Noncovalent Bonds Specify Both the Precise Shape of a Macromolecule and Its Binding to Other Molecules	55		
Summary	56		
CATALYSIS AND THE USE OF ENERGY BY CELLS	57		
Cell Metabolism Is Organized by Enzymes	57		
Biological Order Is Made Possible by the Release of Heat Energy from Cells	58		
Cells Obtain Energy by the Oxidation of Organic Molecules	61		
Oxidation and Reduction Involve Electron Transfers	62		
Enzymes Lower the Activation-Energy Barriers That Block Chemical Reactions	63		
Enzymes Can Drive Substrate Molecules Along Specific Reaction Pathways	64		
How Enzymes Find Their Substrates: The Enormous Rapidity of Molecular Motions	65		
The Free-Energy Change for a Reaction, ΔG , Determines Whether It Can Occur Spontaneously	66		
The Concentration of Reactants Influences the Free-Energy Change and a Reaction's Direction	67		
The Standard Free-Energy Change, ΔG° , Makes It Possible to Compare the Energetics of Different Reactions	67		
The Equilibrium Constant and ΔG° Are Readily Derived from Each Other	68		
The Free-Energy Changes of Coupled Reactions Are Additive	69		
Activated Carrier Molecules Are Essential for Biosynthesis	69		
The Formation of an Activated Carrier Is Coupled to an Energetically Favorable Reaction	70		
ATP Is the Most Widely Used Activated Carrier Molecule	71		
Energy Stored in ATP Is Often Harnessed to Join Two Molecules Together	72		

NADH and NADPH Are Important Electron Carriers	73	Enzymes Speed Reactions by Selectively Stabilizing	
There Are Many Other Activated Carrier Molecules in Cells	75	Transition States	148
The Synthesis of Biological Polymers Is Driven by		Enzymes Can Use Simultaneous Acid and Base Catalysis	148
ATP Hydrolysis	76	Lysozyme Illustrates How an Enzyme Works	149
Summary	78	Tightly Bound Small Molecules Add Extra Functions to Proteins	152
HOW CELLS OBTAIN ENERGY FROM FOOD	80	The Cell Regulates the Catalytic Activities of Its Enzymes	155
Glycolysis Is a Central ATP-producing Pathway	80	Allosteric Enzymes Have Two or More Binding Sites That Interact	155
Glycolysis Illustrates How Enzymes Couple Oxidation		Two Ligands Whose Binding Sites Are Coupled Must Reciprocally	
to Energy Storage	83	Affect Each Other's Binding	157
Fermentations Produce ATP in the Absence of Oxygen	84	Symmetrical Protein Assemblies Produce Cooperative Allosteric	
Organisms Store Food Molecules in Special Reservoirs	85	Transitions	158
Between Meals, Most Animal Cells Derive Their Energy		Many Changes in Proteins Are Driven by Protein Phosphorylation	159
from Fatty Acids Obtained from Fat	86	A Eukaryotic Cell Contains a Large Collection of Protein Kinases	
Sugars and Fats Are Both Degraded to Acetyl CoA		and Protein Phosphatases	159
in Mitochondria	87	The Regulation of the Src Protein Kinase Reveals How a	
The Citric Acid Cycle Generates NADH by Oxidizing		Protein Can Function as a Microprocessor	161
Acetyl Groups to CO ₂	88	Regulatory GTP-binding Proteins Are Switched On and	
Electron Transport Drives the Synthesis of the Majority		Off by the Gain and Loss of a Phosphate Group	162
of the ATP in Most Cells	90	Proteins Can Be Regulated by the Covalent Addition	
Many Biosynthetic Pathways Begin with Glycolysis		of Other Proteins	162
or the Citric Acid Cycle	90	An Elaborate Ubiquitin-conjugating System Is Used	
Animals Must Obtain All the Nitrogen and Sulfur		to Mark Proteins	163
They Need from Food	91	Protein Complexes with Interchangeable Parts Make	
Metabolism Is Highly Organized and Regulated	92	Efficient Use of Genetic Information	164
Summary	93	A GTP-binding Protein Shows How Large Protein	
Problems	112	Movements Can Be Generated from Small Ones	166
References	114	Motor Proteins Produce Directional Movement in Cells	167
		Proteins Often Form Large Complexes That Function as Protein	
		Machines	167
Chapter 3 Proteins	115	The Disordered Regions in Proteins Are Critical for a	
		Set of Different Functions	168
THE ATOMIC STRUCTURE OF PROTEINS	115	Scaffolds Bring Sets of Interacting Macromolecules Together	
The Structure of a Protein Is Specified by Its Amino		and Concentrate Them in Selected Regions of a Cell	170
Acid Sequence	115	Macromolecules Can Self-assemble to Form Biomolecular	
Proteins Fold into a Conformation of Lowest Energy	121	Condensates	171
The α Helix and the β Sheet Are Common Folding Motifs	121	Classical Studies of Phase Separation Have Relevance	
Four Levels of Organization Are Considered to Contribute		for Biomolecular Condensates	173
to Protein Structure	123	A Comparison of Three Important Types of Large Biological	
Protein Domains Are the Modular Units from Which Larger		Assemblies	174
Proteins Are Built	124	Many Proteins Are Controlled by Covalent Modifications	
Proteins Also Contain Unstructured Regions	126	That Direct Them to Specific Sites Inside the Cell	175
All Protein Structures Are Dynamic, Interconverting Rapidly		A Complex Network of Protein Interactions Underlies	
Between an Ensemble of Closely Related Conformations		Cell Function	176
Because of Thermal Energy	126	Protein Structures Can Be Predicted and New Proteins	
Function Has Selected for a Tiny Fraction of the Many		Designed	178
Possible Polypeptide Chains	126	Summary	179
Proteins Can Be Classified into Many Families	127	Problems	179
Some Protein Domains Are Found in Many Different Proteins	129	References	181
The Human Genome Encodes a Complex Set of Proteins,			
Revealing That Much Remains Unknown	130		
Protein Molecules Often Contain More Than One		Chapter 4 DNA, Chromosomes, and Genomes	183
Polypeptide Chain	130		
Some Globular Proteins Form Long Helical Filaments	131	THE STRUCTURE AND FUNCTION OF DNA	185
Protein Molecules Can Have Elongated, Fibrous Shapes	132	A DNA Molecule Consists of Two Complementary Chains of	
Covalent Cross-Linkages Stabilize Extracellular Proteins	133	Nucleotides	185
Protein Molecules Often Serve as Subunits for the Assembly		The Structure of DNA Provides a Mechanism for Heredity	187
of Large Structures	134	In Eukaryotes, DNA Is Enclosed in a Cell Nucleus	189
Many Structures in Cells Are Capable of Self-Assembly	136	Summary	189
Assembly Factors Often Aid the Formation of Complex		CHROMOSOMAL DNA AND ITS PACKAGING	
Biological Structures	136	IN THE CHROMATIN FIBER	189
When Assembly Processes Go Wrong: The Case of		Eukaryotic DNA Is Packaged into a Set of Chromosomes	190
Amyloid Fibrils	137	Chromosomes Contain Long Strings of Genes	191
Amyloid Structures Can Also Perform Useful Functions in Cells	139	The Nucleotide Sequence of the Human Genome Shows	
Summary	140	How Our Genes Are Arranged	193
PROTEIN FUNCTION	140	Each DNA Molecule That Forms a Linear Chromosome	
All Proteins Bind to Other Molecules	140	Must Contain a Centromere, Two Telomeres,	
The Surface Conformation of a Protein Determines Its Chemistry	142	and Replication Origins	195
Sequence Comparisons Between Protein Family Members		DNA Molecules Are Highly Condensed in Chromosomes	197
Highlight Crucial Ligand-binding Sites	142	Nucleosomes Are a Basic Unit of Eukaryotic Chromosome	
Proteins Bind to Other Proteins Through Several Types		Structure	197
of Interfaces	143	The Structure of the Nucleosome Core Particle Reveals	
Antibody Binding Sites Are Especially Versatile	144	How DNA Is Packaged	198
The Equilibrium Constant Measures Binding Strength	145	Nucleosomes Have a Dynamic Structure and Are	
Enzymes Are Powerful and Highly Specific Catalysts	146	Frequently Subjected to Changes Catalyzed by	
Substrate Binding Is the First Step in Enzyme Catalysis	146	ATP-dependent Chromatin-remodeling Complexes	200

Attractions Between Nucleosomes Compact the Chromatin Fiber	202	We Can Trace Human History by Analyzing Genomes	244
Summary	203	The Sequencing of Hundreds of Thousands of Human Genomes Reveals Much Variation	245
THE EFFECT OF CHROMATIN STRUCTURE ON DNA FUNCTION	203	Most of the Variants Observed in the Human Population Are Common Alleles, with at Most a Weak Effect on Phenotype	246
Different Regions of the Human Genome Are Packaged Very Differently in Chromatin	204	Forensic Analyses Exploit Special DNA Sequences with Unusually High Mutation Rates	247
Heterochromatin Is Highly Condensed and Restricts Gene Expression	204	An Understanding of Human Variation Is Critical for Improving Medicine	248
The Heterochromatic State Can Spread Along a Chromosome and Be Inherited from One Cell Generation to the Next	205	Summary	248
The Core Histones Are Covalently Modified at Many Different Sites	206	Problems	249
Chromatin Acquires Additional Variety Through the Site-specific Insertion of a Small Set of Histone Variants	208	References	251
Covalent Modifications and Histone Variants Can Act in Concert to Control Chromosome Functions	208	Chapter 5 DNA Replication, Repair, and Recombination	253
A Complex of Reader and Writer Proteins Can Spread Specific Chromatin Modifications Along a Chromosome	210	THE MAINTENANCE OF DNA SEQUENCES	253
Barrier DNA-Protein Complexes Block the Spread of Reader-Writer Complexes and Thereby Separate Neighboring Chromatin Domains	212	Mutation Rates Are Extremely Low	253
Centromeres Have a Special, Inherited Chromatin Structure	213	Low Mutation Rates Are Necessary for Life as We Know It	254
Some Forms of Chromatin Can Be Directly Inherited	215	Summary	255
The Abnormal Perturbations of Heterochromatin That Arise During Tumor Progression Contribute to Many Cancers	215	DNA REPLICATION MECHANISMS	255
Summary	217	Base-pairing Underlies DNA Replication and DNA Repair	255
THE GLOBAL STRUCTURE OF CHROMOSOMES	217	The DNA Replication Fork Is Asymmetrical	256
Chromosomes Are Folded into Large Loops of Chromatin	217	The High Fidelity of DNA Replication Requires Several Proofreading Mechanisms	258
Polytene Chromosomes Are Uniquely Useful for Visualizing Chromatin Structures	218	DNA Replication in the 5'-to-3' Direction Allows Efficient Error Correction	260
Chromosome Loops Decondense When the Genes Within Them Are Expressed	220	A Special Nucleotide-polymerizing Enzyme Synthesizes Short RNA Primer Molecules	260
Mammalian Interphase Chromosomes Occupy Discrete Territories in the Nucleus, with Their Heterochromatin and Euchromatin Distributed Differently	220	Special Proteins Help to Open Up the DNA Double Helix in Front of the Replication Fork	261
A Biochemical Technique Called Hi-C Reveals Details of Chromosome Organization	221	A Sliding Ring Holds a Moving DNA Polymerase onto the DNA	262
Chromosomal DNA Is Organized into Loops by Large Protein Rings	223	The Proteins at a Replication Fork Cooperate to Form a Replication Machine	263
Euchromatin and Heterochromatin Separate Spatially in the Nucleus	225	DNA Replication Is Fundamentally Similar in Eukaryotes and Bacteria	265
Mitotic Chromosomes Are Highly Condensed	227	A Strand-directed Mismatch Repair System Removes Replication Errors That Remain in the Wake of the Replication Machine	267
Summary	228	The Accidental Incorporation of Ribonucleotides During DNA Replication Is Corrected	269
HOW GENOMES EVOLVE	229	DNA Topoisomerases Prevent DNA Tangling During Replication	269
Genome Comparisons Reveal Functional DNA Sequences by Their Conservation Throughout Evolution	230	Summary	272
Genome Alterations Are Caused by Failures of the Normal Mechanisms for Copying and Maintaining DNA, as Well as by Transposable DNA Elements	231	THE INITIATION AND COMPLETION OF DNA REPLICATION IN CHROMOSOMES	272
The Genome Sequences of Two Species Differ in Proportion to the Length of Time Since They Have Separately Evolved	232	DNA Synthesis Begins at Replication Origins	272
Phylogenetic Trees Constructed from a Comparison of DNA Sequences Trace the Relationships of All Organisms	233	Bacterial Chromosomes Typically Have a Single Origin of DNA Replication	273
A Comparison of Human and Mouse Chromosomes Shows How the Structures of Genomes Diverge	234	Eukaryotic Chromosomes Contain Multiple Origins of Replication	273
The Size of a Vertebrate Genome Reflects the Relative Rates of DNA Addition and DNA Loss in a Lineage	236	In Eukaryotes, DNA Replication Takes Place During Only One Part of the Cell Cycle	276
Multispecies Sequence Comparisons Identify Many Conserved DNA Sequences of Unknown Function	237	Eukaryotic Origins of Replication Are "Licensed" for Replication by the Assembly of an Origin Recognition Complex	276
Changes in Previously Conserved Sequences Can Help Decipher Critical Steps in Evolution	238	Features of the Human Genome That Specify Origins of Replication Remain to Be Fully Understood	277
Mutations in the DNA Sequences That Control Gene Expression Have Driven Many of the Evolutionary Changes in Vertebrates	239	Properties of the ORC Ensure That Each Region of the DNA Is Replicated Once and Only Once in Each S Phase	277
Gene Duplication Also Provides an Important Source of Genetic Novelty During Evolution	240	New Nucleosomes Are Assembled Behind the Replication Fork	279
Duplicated Genes Diverge	240	Termination of DNA Replication Occurs Through the Ordered Disassembly of the Replication Fork	280
The Evolution of the Globin Gene Family Shows How DNA Duplications Contribute to the Evolution of Organisms	241	Telomerase Replicates the Ends of Chromosomes	281
Genes Encoding New Proteins Can Be Created by the Recombination of Exons	242	Telomeres Are Packaged into Specialized Structures That Protect the Ends of Chromosomes	282
Neutral Mutations Often Spread to Become Fixed in a Population, with a Probability That Depends on Population Size	243	Telomere Length Is Regulated by Cells and Organisms	282
		Summary	284
		DNA REPAIR	284
		Without DNA Repair, Spontaneous DNA Damage Would Rapidly Change DNA Sequences	286
		The DNA Double Helix Is Readily Repaired	288
		DNA Damage Can Be Removed by More Than One Pathway	288

Coupling Nucleotide Excision Repair to Transcription Ensures That the Cell's Most Important DNA Is Efficiently Repaired	290	In Eukaryotes, Transcription Initiation Also Requires Activator, Mediator, and Chromatin-modifying Proteins	334
The Chemistry of the DNA Bases Facilitates Damage Detection	290	Transcription Elongation in Eukaryotes Requires Accessory Proteins	335
Special Translesion DNA Polymerases Are Used in Emergencies	292	Transcription Creates Superhelical Tension	335
Double-Strand Breaks Are Efficiently Repaired	292	Transcription Elongation in Eukaryotes Is Tightly Coupled to RNA Processing	337
DNA Damage Delays Progression of the Cell Cycle	295	RNA Capping Is the First Modification of Eukaryotic Pre-mRNAs	338
Summary	295	RNA Splicing Removes Intron Sequences from Newly Transcribed Pre-mRNAs	339
HOMOLOGOUS RECOMBINATION	296	Nucleotide Sequences Signal Where Splicing Occurs	341
Homologous Recombination Has Common Features in All Cells	296	RNA Splicing Is Performed by the Spliceosome	341
DNA Base-pairing Guides Homologous Recombination	296	The Spliceosome Uses ATP Hydrolysis to Produce a Complex Series of RNA–RNA Rearrangements	343
Homologous Recombination Can Flawlessly Repair Double-Strand Breaks in DNA	297	Other Properties of Pre-mRNA and Its Synthesis Help to Explain the Choice of Proper Splice Sites	345
Specialized Processing of Double-Strand Breaks Commits Repair to Homologous Recombination	298	RNA Splicing Has Remarkable Plasticity	346
Strand Exchange Is Directed by the RecA/Rad51 Protein	298	Spliceosome-catalyzed RNA Splicing Evolved from RNA Self-splicing Mechanisms	347
Homologous Recombination Can Rescue Broken and Stalled DNA Replication Forks	299	RNA-processing Enzymes Generate the 3' End of Eukaryotic mRNAs	348
DNA Repair by Homologous Recombination Entails Risks to the Cell	300	Mature Eukaryotic mRNAs Are Selectively Exported from the Nucleus	349
Homologous Recombination Is Crucial for Meiosis	301	Noncoding RNAs Are Also Synthesized and Processed in the Nucleus	351
Meiotic Recombination Begins with a Programmed Double-Strand Break	302	The Nucleolus Is a Ribosome-producing Factory	353
Holliday Junctions Are Recognized by Enzymes That Drive Branch Migration	302	The Nucleus Contains a Variety of Subnuclear Biomolecular Condensates	355
Homologous Recombination Produces Crossovers Between Maternal and Paternal Chromosomes During Meiosis	304	Summary	357
Homologous Recombination Often Results in Gene Conversion	305	FROM RNA TO PROTEIN	358
Summary	306	An mRNA Sequence Is Decoded in Sets of Three Nucleotides	358
TRANSPOSITION AND CONSERVATIVE SITE-SPECIFIC RECOMBINATION	306	tRNA Molecules Match Amino Acids to Codons in mRNA	359
Through Transposition, Mobile Genetic Elements Can Insert into Any DNA Sequence	307	tRNAs Are Covalently Modified Before They Exit from the Nucleus	361
DNA-only Transposons Can Move by a Cut-and-Paste Mechanism	307	Specific Enzymes Couple Each Amino Acid to Its Appropriate tRNA Molecule	361
Some DNA-only Transposons Move by Replicating Themselves	309	Editing by tRNA Synthetases Ensures Accuracy	363
Some Viruses Use a Transposition Mechanism to Move Themselves into Host-Cell Chromosomes	309	Amino Acids Are Added to the C-terminal End of a Growing Polypeptide Chain	364
Some RNA Viruses Replicate and Express Their Genomes Without Using DNA as an Intermediate	311	The RNA Message Is Decoded in Ribosomes	365
Retroviral-like Retrotransposons Resemble Retroviruses, but Cannot Move from Cell to Cell	313	Elongation Factors Drive Translation Forward and Improve Its Accuracy	368
A Large Fraction of the Human Genome Is Composed of Nonretroviral Retrotransposons	313	Induced Fit and Kinetic Proofreading Help Biological Processes Overcome the Inherent Limitations of Complementary Base-Pairing	369
Different Transposable Elements Predominate in Different Organisms	314	Accuracy in Translation Requires a Large Expenditure of Free Energy	370
Genome Sequences Reveal the Approximate Times at Which Transposable Elements Have Moved	314	The Ribosome Is a Ribozyme	371
Conservative Site-specific Recombination Can Reversibly Rearrange DNA	315	Nucleotide Sequences in mRNA Signal Where to Start Protein Synthesis	373
Conservative Site-specific Recombination Can Be Used to Turn Genes On or Off	316	Stop Codons Mark the End of Translation	374
Bacterial Conservative Site-specific Recombinases Have Become Powerful Tools for Cell and Developmental Biologists	317	Proteins Are Made on Polyribosomes	375
Summary	317	There Are Minor Variations in the Standard Genetic Code	375
Problems	318	Inhibitors of Prokaryotic Protein Synthesis Are Useful as Antibiotics	376
References	320	Quality-Control Mechanisms Act to Prevent Translation of Damaged mRNAs	378
		Stalled Ribosomes Can Be Rescued	379
		The Ribosome Coordinates the Folding, Enzymatic Modification, and Assembly of Newly Synthesized Proteins	380
Chapter 6 How Cells Read the Genome: From DNA to Protein	321	Molecular Chaperones Help Guide the Folding of Most Proteins	380
FROM DNA TO RNA	323	Proper Folding of Newly Synthesized Proteins Is Also Aided by Translation Speed and Subunit Assembly	383
RNA Molecules Are Single-Stranded	324	Proteins That Ultimately Fail to Fold Correctly Are Marked for Destruction by Polyubiquitin	384
Transcription Produces RNA Complementary to One Strand of DNA	325	The Proteasome Is a Compartmentalized Protease with Sequestered Active Sites	384
RNA Polymerases Carry Out DNA Transcription	325	Many Proteins Are Controlled by Regulated Destruction	386
Cells Produce Different Categories of RNA Molecules	327	There Are Many Steps from DNA to Protein	387
Signals Encoded in DNA Tell RNA Polymerase Where to Start and Stop	328	Summary	388
Bacterial Transcription Start and Stop Signals Are Heterogeneous in Nucleotide Sequence	329	THE RNA WORLD AND THE ORIGINS OF LIFE	389
Transcription Initiation in Eukaryotes Requires Many Proteins	331	Single-Strand RNA Molecules Can Fold into Highly Elaborate Structures	390
To Initiate Transcription, RNA Polymerase II Requires a Set of General Transcription Factors	332	Ribozymes Can Be Produced in the Laboratory	390

RNA Can Both Store Information and Catalyze Chemical Reactions	391	Transcription Circuits Allow the Cell to Carry Out Logic Operations Summary	433 434
How Did Protein Synthesis Evolve?	392	MECHANISMS THAT REINFORCE CELL MEMORY IN PLANTS AND ANIMALS	435
All Present-Day Cells Use DNA as Their Hereditary Material	393	Patterns of DNA Methylation Can Be Inherited When Vertebrate Cells Divide	435
Summary	393	CG-Rich Islands Are Associated with Many Genes in Mammals	436
Problems	394	Genomic Imprinting Is Based on DNA Methylation	438
References	395	A Chromosome-wide Alteration in Chromatin Structure Can Be Inherited	440
Chapter 7 Control of Gene Expression	397	The Mammalian X-Inactivation in Females Is Triggered by the Synthesis of a Long Noncoding RNA	442
AN OVERVIEW OF GENE CONTROL	397	Stable Patterns of Gene Expression Can Be Transmitted to Daughter Cells	443
The Different Cell Types of a Multicellular Organism Contain the Same DNA	397	Summary	445
Different Cell Types Synthesize Different Sets of RNAs and Proteins	398	POST-TRANSCRIPTIONAL CONTROLS	445
The Spectrum of mRNAs Present in a Cell Can Be Used to Accurately Identify the Cell Type	400	Transcription Attenuation Causes the Premature Termination of Some RNA Molecules	445
External Signals Can Cause a Cell to Change the Expression of Its Genes	400	Riboswitches Probably Represent Ancient Forms of Gene Control	446
Gene Expression Can Be Regulated at Many of the Steps in the Pathway from DNA to RNA to Protein	401	Alternative RNA Splicing Can Produce Different Forms of a Protein from the Same Gene	446
Summary	402	The Definition of a Gene Has Been Modified Since the Discovery of Alternative RNA Splicing	448
CONTROL OF TRANSCRIPTION BY SEQUENCE-SPECIFIC DNA-BINDING PROTEINS	402	Back Splicing Can Produce Circular RNA Molecules	449
The Sequence of Nucleotides in the DNA Double Helix Can Be Read by Proteins	402	A Change in the Site of RNA Transcript Cleavage and Poly-A Addition Can Change the C-terminus of a Protein	449
Transcription Regulators Contain Structural Motifs That Can Read DNA Sequences	403	Nucleotides in mRNA Can Be Covalently Modified	450
Dimerization of Transcription Regulators Increases Their Affinity and Specificity for DNA	406	RNA Editing Can Change the Meaning of the RNA Message	451
Many Transcription Regulators Bind Cooperatively to DNA	407	The Human AIDS Virus Illustrates How RNA Transport from the Nucleus Can Be Regulated	452
Nucleosome Structure Promotes Cooperative Binding of Transcription Regulators	408	mRNAs Can Be Localized to Specific Regions of the Cytosol	453
DNA-Binding by Transcription Regulators Is Dynamic	409	Untranslated Regions of mRNAs Control Their Translation	456
Summary	410	The Phosphorylation of an Initiation Factor Regulates Protein Synthesis Globally	457
TRANSCRIPTION REGULATORS SWITCH GENES ON AND OFF	410	Initiation at AUG Codons Upstream of the Translation Start Can Regulate Eukaryotic Translation Initiation	458
The Tryptophan Repressor Switches Genes Off	410	Internal Ribosome Entry Sites Also Provide Opportunities for Translational Control	458
Repressors Turn Genes Off and Activators Turn Them On	411	Changes in mRNA Stability Can Control Gene Expression	459
Both an Activator and a Repressor Control the <i>Lac</i> Operon	412	Regulation of mRNA Stability Involves P-bodies and Stress Granules	461
DNA Looping Can Occur During Bacterial Gene Regulation	412	Summary	462
Complex Switches Control Gene Transcription in Eukaryotes	414	REGULATION OF GENE EXPRESSION BY NONCODING RNAs	462
A Eukaryotic Gene Control Region Includes Many <i>cis</i> -Regulatory Sequences	414	Small Noncoding RNA Transcripts Regulate Many Animal and Plant Genes Through RNA Interference	462
Eukaryotic Transcription Regulators Work in Groups	415	miRNAs Regulate mRNA Translation and Stability	463
Activator Proteins Promote the Assembly of RNA Polymerase at the Start Point of Transcription	416	RNA Interference Also Serves as a Cell Defense Mechanism	464
Eukaryotic Transcription Activators Direct the Modification of Local Chromatin Structure	417	RNA Interference Can Direct Heterochromatin Formation	465
Some Transcription Activators Work by Releasing Paused RNA Polymerase	418	piRNAs Protect the Germ Line from Transposable Elements	466
Transcription Activators Work Synergistically	419	RNA Interference Has Become a Powerful Experimental Tool	467
Condensate Formation Likely Increases the Efficiency of Transcription Initiation	420	Cells Have Additional Mechanisms to Hold Transposons and Integrated Viral Genomes in Check	467
Eukaryotic Transcription Repressors Can Inhibit Transcription in Several Ways	420	Bacteria Use Small Noncoding RNAs to Protect Themselves from Viruses	468
Insulator DNA Sequences Prevent Eukaryotic Transcription	420	Long Noncoding RNAs Have Diverse Functions in the Cell	469
Regulators from Influencing Distant Genes	422	Summary	471
Summary	422	Problems	472
MOLECULAR GENETIC MECHANISMS THAT CREATE AND MAINTAIN SPECIALIZED CELL TYPES	423	References	474
Complex Genetic Switches That Regulate <i>Drosophila</i> Development Are Built Up from Smaller Modules	423	Chapter 8 Analyzing Cells, Molecules, and Systems	475
The <i>Drosophila Eve</i> Gene Is Regulated by Combinatorial Controls	424	ISOLATING CELLS AND GROWING THEM IN CULTURE	476
Transcription Regulators Are Brought into Play by Extracellular Signals	426	Cells Can Be Isolated from Tissues and Grown in Culture	476
Combinatorial Gene Control Creates Many Different Cell Types	427	Eukaryotic Cell Lines Are a Widely Used Source of Homogeneous Cells	478
Specialized Cell Types Can Be Experimentally Reprogrammed to Become Pluripotent Stem Cells	428	Hybridoma Cell Lines Are Factories That Produce Monoclonal Antibodies	478
Combinations of Master Transcription Regulators Specify Cell Types by Controlling the Expression of Many Genes	429	Summary	480
Specialized Cells Must Rapidly Turn Some Genes On and Off	430	PURIFYING PROTEINS	480
Differentiated Cells Maintain Their Identity	431	Cells Can Be Separated into Their Component Fractions	480
		Cell Extracts Provide Accessible Systems to Study Cell Functions	482
		Proteins Can Be Separated by Chromatography	483

Immunoprecipitation Is a Rapid Affinity Purification Method	486	Expression of Individual Genes Can Be Measured Using	536
Genetically Engineered Tags Provide an Easy Way to Purify	486	Quantitative RT-PCR	
Proteins		Global Analysis of mRNAs by RNA-seq Provides a Snapshot	536
Purified Cell-free Systems Are Required for the Precise Dissection	486	of Gene Expression	
of Molecular Functions	487	Genome-wide Chromatin Immunoprecipitation Identifies	538
Summary	487	Sites on the Genome Occupied by Transcription Regulators	
ANALYZING PROTEINS		Ribosome Profiling Reveals Which mRNAs Are Being	538
Proteins Can Be Separated by SDS Polyacrylamide-Gel	487	Translated in the Cell	539
Electrophoresis		Recombinant DNA Methods Have Revolutionized Human Health	540
Two-dimensional Gel Electrophoresis Provides Greater Protein	489	Transgenic Plants Are Important for Agriculture	542
Separation		Summary	542
Specific Proteins Can Be Detected by Blotting with Antibodies	490	MATHEMATICAL ANALYSIS OF CELL FUNCTION	542
Hydrodynamic Measurements Reveal the Size and Shape	490	Regulatory Networks Depend on Molecular Interactions	543
of a Protein Complex	490	Differential Equations Help Us Predict Transient Behavior	545
Mass Spectrometry Provides a Highly Sensitive Method	491	Promoter Activity and Protein Degradation Affect the Rate	546
for Identifying Unknown Proteins		of Change of Protein Concentration	
Sets of Interacting Proteins Can Be Identified by	493	The Time Required to Reach Steady State Depends on	547
Biochemical Methods		Protein Lifetime	
Optical Methods Can Monitor Protein Interactions	493	Quantitative Methods Are Similar for Transcription Repressors	548
Protein Structure Can Be Determined Using X-ray Diffraction	494	and Activators	549
NMR Can Be Used to Determine Protein Structure in Solution	496	Negative Feedback Is a Powerful Strategy in Cell Regulation	549
Protein Sequence and Structure Provide Clues About	497	Delayed Negative Feedback Can Induce Oscillations	549
Protein Function	498	DNA Binding by a Repressor or an Activator Can Be	551
Summary	498	Cooperative	
ANALYZING AND MANIPULATING DNA		Positive Feedback Is Important for Switchlike Responses	551
Restriction Nucleases Cut Large DNA Molecules into	498	and Bistability	
Specific Fragments	499	Robustness Is an Important Characteristic of Biological	553
Gel Electrophoresis Separates DNA Molecules of Different Sizes	499	Networks	
Purified DNA Molecules Can Be Specifically Labeled	501	Two Transcription Regulators That Bind to the Same Gene	554
with Radioisotopes or Chemical Markers <i>in Vitro</i>	501	Promoter Can Exert Combinatorial Control	555
Genes Can Be Cloned Using Bacteria	503	An Incoherent Feed-forward Interaction Generates Pulses	556
An Entire Genome Can Be Represented in a DNA Library	503	A Coherent Feed-forward Interaction Detects Persistent Inputs	557
Hybridization Provides a Powerful but Simple Way to Detect	505	The Same Network Can Behave Differently in Different	557
Specific Nucleotide Sequences	506	Cells Because of Stochastic Effects	
Genes Can Be Cloned <i>in Vitro</i> Using PCR	507	Several Computational Approaches Can Be Used to Model	557
PCR Is Also Used for Diagnostic and Forensic Applications	510	the Reactions in Cells	
PCR and Synthetic DNA Are Ideal Sources of Specific	510	Statistical Methods Are Critical for the Analysis of Biological	558
Gene Sequences for Cloning	511	Data	558
DNA Cloning Allows Any Protein to Be Produced in Large	511	Summary	559
Amounts	512	Problems	561
DNA Can Be Sequenced Rapidly by Dideoxy Sequencing	512	References	
Next-Generation Sequencing Methods Have Revolutionized	514		
DNA and RNA Analysis	516	Chapter 9 Visualizing Cells and Their Molecules	563
To Be Useful, Genome Sequences Must Be Annotated	518		
Summary	518	LOOKING AT CELLS AND MOLECULES IN THE LIGHT	563
STUDYING GENE FUNCTION AND EXPRESSION		MICROSCOPE	
Classical Genetic Screens Identify Random Mutants with Specific	519	The Conventional Light Microscope Can Resolve Details	564
Abnormalities	522	0.2 μm Apart	
Mutations Can Cause Loss or Gain of Protein Function	523	Photon Noise Creates Additional Limits to Resolution	567
Complementation Tests Reveal Whether Two Mutations Are in the	523	When Light Levels Are Low	
Same Gene or Different Genes	523	Living Cells Are Seen Clearly in a Phase-Contrast or a	567
Gene Products Can Be Ordered in Pathways by Epistasis	523	Differential-Interference-Contrast Microscope	568
Analysis	524	Images Can Be Enhanced and Analyzed by Digital Techniques	569
Mutations Responsible for a Phenotype Can Be Identified	524	Intact Tissues Are Usually Fixed and Sectioned Before Microscopy	570
Through DNA Analysis	524	Specific Molecules Can Be Located in Cells by Fluorescence	570
Rapid and Cheap DNA Sequencing Has Revolutionized	524	Microscopy	572
Human Genetic Studies	525	Antibodies Can Be Used to Detect Specific Proteins	573
Linked Blocks of Polymorphisms Have Been Passed Down	525	Individual Proteins Can Be Fluorescently Tagged in Living Cells	575
from Our Ancestors	526	and Organisms	576
Sequence Variants Can Aid the Search for Mutations	527	Protein Dynamics Can Be Followed in Living Cells	577
Associated with Disease	527	Fluorescent Biosensors Can Monitor Cell Signaling	577
Genomics Is Accelerating the Discovery of Rare Mutations	527	Imaging of Complex Three-dimensional Objects Is Possible	577
That Predispose Us to Serious Disease	527	with the Optical Microscope	
The Cellular Functions of a Known Gene Can Be Studied	527	The Confocal Microscope Produces Optical Sections by	578
with Genome Engineering	528	Excluding Out-of-Focus Light	
Animals and Plants Can Be Genetically Altered	528	Superresolution Fluorescence Techniques Can Overcome	580
The Bacterial CRISPR System Has Been Adapted to Edit	530	Diffraction-limited Resolution	
Genomes in a Wide Variety of Species	531	Single-Molecule Localization Microscopy Also Delivers	583
Large Collections of Engineered Mutations Provide a Tool	531	Superresolution	
for Examining the Function of Every Gene in an Organism	533	Expanding the Specimen Can Offer Higher Resolution, but	585
RNA Interference Is a Simple and Rapid Way to Test Gene Function	534	with a Conventional Microscope	
Reporter Genes Reveal When and Where a Gene Is Expressed	534	Large Multicellular Structures Can Be Imaged Over Time	586
<i>In Situ</i> Hybridization Can Reveal the Location of mRNAs	535	Single Molecules Can Be Visualized by Total Internal Reflection	587
and Noncoding RNAs	535	Fluorescence Microscopy	
		Summary	588

LOOKING AT CELLS AND MOLECULES IN THE ELECTRON MICROSCOPE	588	A P-type ATPase Pumps Ca^{2+} into the Sarcoplasmic Reticulum in Muscle Cells	647
The Electron Microscope Resolves the Fine Structure of the Cell	588	The Plasma Membrane Na^+ - K^+ Pump Establishes Na^+ and K^+ Gradients Across the Plasma Membrane	648
Biological Specimens Require Special Preparation for Electron Microscopy	589	ABC Transporters Constitute the Largest Family of Membrane Transport Proteins	649
Heavy Metals Can Provide Additional Contrast	590	Summary	651
Images of Surfaces Can Be Obtained by Scanning Electron Microscopy	591	CHANNELS AND THE ELECTRICAL PROPERTIES OF MEMBRANES	651
Electron Microscope Tomography Allows the Molecular Architecture of Cells to Be Seen in Three Dimensions	593	Aquaporins Are Permeable to Water but Impermeable to Ions	652
Cryo-electron Microscopy Can Determine Molecular Structures at Atomic Resolution	595	Ion Channels Are Ion-selective and Fluctuate Between Open and Closed States	653
Light Microscopy and Electron Microscopy Are Mutually Beneficial	597	The Membrane Potential in Animal Cells Depends Mainly on K^+ Leak Channels and the K^+ Gradient Across the Plasma Membrane	655
Using Microscopy to Study Cells Always Involves Trade-Offs	598	The Resting Potential Decays Only Slowly When the Na^+ - K^+ Pump Is Stopped	655
Summary	599	The Three-dimensional Structure of a Bacterial K^+ Channel Shows How an Ion Channel Can Work	657
Problems	600	Mechanosensitive Channels Allow Cells to Sense Their Physical Environment	659
References	601	The Function of a Neuron Depends on Its Elongated Structure	661
Chapter 10 Membrane Structure	603	Voltage-gated Cation Channels Generate Action Potentials in Electrically Excitable Cells	662
THE LIPID BILAYER	604	Myelination Increases the Speed and Efficiency of Action Potential Propagation in Nerve Cells	666
Glycerophospholipids, Sphingolipids, and Sterols Are the Major Lipids in Cell Membranes	605	Patch-Clamp Recording Indicates That Individual Ion Channels Open in an All-or-Nothing Fashion	666
Phospholipids Spontaneously Form Bilayers	606	Voltage-gated Cation Channels Are Evolutionarily and Structurally Related	668
The Lipid Bilayer Is a Two-dimensional Fluid	608	Different Neuron Types Display Characteristic Stable Firing Properties	668
The Fluidity of a Lipid Bilayer Depends on Its Composition	609	Transmitter-gated Ion Channels Convert Chemical Signals into Electrical Ones at Chemical Synapses	669
Despite Their Fluidity, Lipid Bilayers Can Form Domains of Different Compositions	610	Chemical Synapses Can Be Excitatory or Inhibitory	670
Lipid Droplets Are Surrounded by a Phospholipid Monolayer	611	The Acetylcholine Receptors at the Neuromuscular Junction Are Excitatory Transmitter-gated Cation Channels	671
The Asymmetry of the Lipid Bilayer Is Functionally Important	612	Neurons Contain Many Types of Transmitter-gated Channels	672
Glycolipids Are Found on the Surface of All Eukaryotic Plasma Membranes	613	Many Psychoactive Drugs Act at Synapses	673
Summary	614	Neuromuscular Transmission Involves the Sequential Activation of Five Different Sets of Ion Channels	673
MEMBRANE PROTEINS	615	Single Neurons Are Complex Computation Devices	674
Membrane Proteins Can Be Associated with the Lipid Bilayer in Various Ways	615	Neuronal Computation Requires a Combination of at Least Three Kinds of K^+ Channels	675
Lipid Anchors Control the Membrane Localization of Some Signaling Proteins	616	Long-term Potentiation in the Mammalian Hippocampus Depends on Ca^{2+} Entry Through NMDA-Receptor Channels	677
In Most Transmembrane Proteins, the Polypeptide Chain Crosses the Lipid Bilayer in an α -Helical Conformation	617	The Use of Channelrhodopsins Has Revolutionized the Study of Neural Circuits	678
Transmembrane α Helices Often Interact with One Another	619	Summary	679
Some β Barrels Form Large Channels	619	Problems	680
Many Membrane Proteins Are Glycosylated	621	References	681
Membrane Proteins Can Be Solubilized and Purified in Detergents	622	Chapter 12 Intracellular Organization and Protein Sorting	683
Bacteriorhodopsin Is a Light-driven Proton (H^+) Pump That Traverses the Lipid Bilayer as Seven α Helices	625	THE COMPARTMENTALIZATION OF CELLS	683
Membrane Proteins Often Function as Large Complexes	627	All Eukaryotic Cells Have the Same Basic Set of Membrane-enclosed Organelles	683
Many Membrane Proteins Diffuse in the Plane of the Membrane	627	Evolutionary Origins Explain the Topological Relationships of Organelles	686
Cells Can Confine Proteins and Lipids to Specific Domains Within a Membrane	629	Macromolecules Can Be Segregated Without a Surrounding Membrane	688
The Cortical Cytoskeleton Gives Membranes Mechanical Strength and Restricts Membrane Protein Diffusion	630	Multivalent Interactions Mediate Formation of Biomolecular Condensates	690
Membrane-bending Proteins Deform Bilayers	632	Biomolecular Condensates Create Biochemical Factories	690
Summary	633	Biomolecular Condensates Form and Disassemble in Response to Need	693
Problems	634	Proteins Can Move Between Compartments in Different Ways	694
References	635	Sorting Signals and Sorting Receptors Direct Proteins to the Correct Cell Address	695
Chapter 11 Small-Molecule Transport and Electrical Properties of Membranes	637	Construction of Most Organelles Requires Information in the Organelle Itself	697
PRINCIPLES OF MEMBRANE TRANSPORT	637	Summary	697
Protein-free Lipid Bilayers Are Impermeable to Ions	638		
There Are Two Main Classes of Membrane Transport Proteins: Transporters and Channels	638		
Active Transport Is Mediated by Transporters Coupled to an Energy Source	639		
Summary	640		
TRANSPORTERS AND ACTIVE MEMBRANE TRANSPORT	640		
Active Transport Can Be Driven by Ion-Concentration Gradients	642		
Transporters in the Plasma Membrane Regulate Cytosolic pH	644		
An Asymmetric Distribution of Transporters in Epithelial Cells Underlies the Transcellular Transport of Solutes	645		
There Are Three Classes of ATP-driven Pumps	646		

THE ENDOPLASMIC RETICULUM	698	The Assembly of a Clathrin Coat Drives Vesicle Formation	752
The ER Is Structurally and Functionally Diverse	698	Adaptor Proteins Select Cargo into Clathrin-coated Vesicles	753
Signal Sequences Were First Discovered in Proteins Imported into the Rough ER	701	Phosphoinositides Mark Organelles and Membrane Domains	754
A Signal-Recognition Particle (SRP) Directs the ER Signal Sequence to a Specific Receptor at the ER	702	Membrane-bending Proteins Help Deform the Membrane During Vesicle Formation	755
The Polypeptide Chain Passes Through a Signal Sequence-gated Aqueous Channel in the Translocator	705	Cytoplasmic Proteins Regulate the Pinching off and Uncoating of Coated Vesicles	756
Translocation Across the ER Membrane Does Not Always Require Ongoing Polypeptide Chain Elongation	707	Monomeric GTPases Control Coat Assembly	756
Transmembrane Proteins Contain Hydrophobic Segments That Are Recognized Like Signal Sequences	709	Coat-recruitment GTPases Participate in Coat Disassembly	758
Hydrophobic Segments of Multipass Transmembrane Proteins Are Interpreted Contextually to Determine Their Orientation	710	The Shape and Size of Transport Vesicles Are Diverse	759
Some Proteins Are Integrated into the ER Membrane by a Post-translational Mechanism	711	Rab Proteins Guide Transport Vesicles to Their Target Membrane	760
Some Membrane Proteins Acquire a Covalently Attached Glycosylphosphatidylinositol (GPI) Anchor	712	Rab Proteins Create and Change the Identity of an Organelle	761
Translocated Polypeptide Chains Fold and Assemble in the Lumen of the Rough ER	712	SNAREs Mediate Membrane Fusion	762
Most Proteins Synthesized in the Rough ER Are Glycosylated by the Addition of a Common <i>N</i> -Linked Oligosaccharide	714	Interacting SNAREs Need to Be Pried Apart Before They Can Function Again	763
Oligosaccharides Are Used as Tags to Mark the State of Protein Folding	715	Viruses Encode Specialized Membrane Fusion Proteins Needed for Cell Entry	764
Improperly Folded Proteins Are Exported from the ER and Degraded in the Cytosol	716	Summary	764
Misfolded Proteins in the ER Activate an Unfolded Protein Response	717	TRANSPORT FROM THE ENDOPLASMIC RETICULUM THROUGH THE GOLGI APPARATUS	765
The ER Assembles Most Lipid Bilayers	720	Proteins Leave the ER in COPII-coated Transport Vesicles	765
Membrane Contact Sites Between the ER and Other Organelles Facilitate Selective Lipid Transfer	722	Only Proteins That Are Properly Folded and Assembled Can Leave the ER	766
Summary	723	Vesicular Tubular Clusters Mediate Transport from the ER to the Golgi Apparatus	766
PEROXISOMES	723	The Retrieval Pathway to the ER Uses Sorting Signals	768
Peroxisomes Use Molecular Oxygen and Hydrogen Peroxide to Perform Oxidation Reactions	724	Many Proteins Are Selectively Retained in the Compartments in Which They Function	768
Short Signal Sequences Direct the Import of Proteins into Peroxisomes	724	The Golgi Apparatus Consists of an Ordered Series of Compartments	769
Summary	726	Oligosaccharide Chains Are Processed in the Golgi Apparatus	771
THE TRANSPORT OF PROTEINS INTO MITOCHONDRIA AND CHLOROPLASTS	726	Proteoglycans Are Assembled in the Golgi Apparatus	772
Translocation into Mitochondria Depends on Signal Sequences and Protein Translocators	727	What Is the Purpose of Glycosylation?	773
Mitochondrial Proteins Are Imported Post-translationally as Unfolded Polypeptide Chains	728	Transport Through the Golgi Apparatus Occurs by Multiple Mechanisms	774
Protein Import Is Powered by ATP Hydrolysis, a Membrane Potential, and Redox Potential	730	Golgi Matrix Proteins Help Organize the Stack	775
Transport into the Inner Mitochondrial Membrane Occurs Via Several Routes	731	Summary	776
Bacteria and Mitochondria Use Similar Mechanisms to Insert β Barrels into Their Outer Membrane	733	TRANSPORT FROM THE TRANS GOLGI NETWORK TO THE CELL EXTERIOR AND ENDOSOMES	776
Two Signal Sequences Direct Proteins to the Thylakoid Membrane in Chloroplasts	733	Many Proteins and Lipids Are Carried Automatically from the <i>Trans</i> Golgi Network to the Cell Surface	777
Summary	735	A Mannose 6-Phosphate Receptor Sorts Lysosomal Hydrolases in the <i>Trans</i> Golgi Network	777
THE TRANSPORT OF MOLECULES BETWEEN THE NUCLEUS AND THE CYTOSOL	735	Defects in the GlcNAc Phosphotransferase Cause a Lysosomal Storage Disease in Humans	779
Nuclear Pore Complexes Perforate the Nuclear Envelope	736	Secretory Vesicles Bud from the <i>Trans</i> Golgi Network	780
Nuclear Localization Signals Direct Proteins to the Nucleus	738	Precursors of Secretory Proteins Are Proteolytically Processed During the Formation of Secretory Vesicles	781
Nuclear Import Receptors Bind to Both Nuclear Localization Signals and NPC Proteins	739	Secretory Vesicles Wait Near the Plasma Membrane Until Signaled to Release Their Contents	782
The Ran GTPase Imposes Directionality on Nuclear Import Through NPCs	740	For Rapid Exocytosis, Synaptic Vesicles Are Primed at the Presynaptic Plasma Membrane	782
Nuclear Export Works Like Nuclear Import, but in Reverse	741	Synaptic Vesicles Can Be Recycled Locally After Exocytosis	783
Transport Through NPCs Can Be Regulated by Controlling Access to the Transport Machinery	742	Secretory Vesicle Membrane Components Are Quickly Removed from the Plasma Membrane	784
The Nuclear Envelope Disassembles and Reassembles During Mitosis	743	Some Regulated Exocytosis Events Serve to Enlarge the Plasma Membrane	785
Summary	745	Polarized Cells Direct Proteins from the <i>Trans</i> Golgi Network to the Appropriate Domain of the Plasma Membrane	786
Problems	746	Summary	787
References	748	TRANSPORT INTO THE CELL FROM THE PLASMA MEMBRANE: ENDOCYTOSIS	788
Chapter 13 Intracellular Membrane Traffic	749	Pinocytic Vesicles Form from Coated Pits in the Plasma Membrane	789
MECHANISMS OF MEMBRANE TRANSPORT AND COMPARTMENT IDENTITY	751	Not All Membrane Invaginations and Pinocytic Vesicles Are Clathrin Coated	789
There Are Various Types of Coated Vesicles	751	Cells Use Receptor-mediated Endocytosis to Import Selected Extracellular Macromolecules	791
		Specific Proteins Are Retrieved from Early Endosomes and Returned to the Plasma Membrane	792
		Recycling Endosomes Regulate Plasma Membrane Composition	793
		Plasma Membrane Signaling Receptors Are Down-regulated by Degradation in Lysosomes	794

Early Endosomes Mature into Late Endosomes	795	CHLOROPLASTS AND PHOTOSYNTHESIS	843
ESCRT Protein Complexes Mediate the Formation of Intraluminal Vesicles in Multivesicular Bodies	796	Chloroplasts Resemble Mitochondria but Have a Separate Thylakoid Compartment	843
Summary	798	Chloroplasts Capture Energy from Sunlight and Use It to Fix Carbon	844
THE DEGRADATION AND RECYCLING OF MACROMOLECULES IN LYSOSOMES	798	Carbon Fixation Uses ATP and NADPH to Convert CO ₂ into Sugars	845
Lysosomes Are the Principal Sites of Intracellular Digestion	798	Carbon Fixation in Some Plants Is Compartmentalized to Facilitate Growth at Low CO ₂ Concentrations	846
Lysosomes Are Heterogeneous	799	The Sugars Generated by Carbon Fixation Can Be Stored as Starch or Consumed to Produce ATP	849
Plant and Fungal Vacuoles Are Remarkably Versatile Lysosomes	800	The Thylakoid Membranes of Chloroplasts Contain the Protein Complexes Required for Photosynthesis and ATP Generation	849
Multiple Pathways Deliver Materials to Lysosomes	801	Chlorophyll-Protein Complexes Can Transfer Either Excitation Energy or Electrons	850
Cells Can Acquire Nutrients from the Extracellular Fluid by Macropinocytosis	802	A Photosystem Contains Chlorophylls in Antennae and a Reaction Center	851
Specialized Phagocytic Cells Can Ingest Large Particles	802	The Thylakoid Membrane Contains Two Different Photosystems Working in Series	852
Cargo Recognition by Cell-surface Receptors Initiates Phagocytosis	803	Photosystem II Uses a Manganese Cluster to Withdraw Electrons from Water	853
Autophagy Degrades Unwanted Proteins and Organelles	804	The Cytochrome <i>b₆-f</i> Complex Connects Photosystem II to Photosystem I	854
The Rate of Nonselective Autophagy Is Regulated by Nutrient Availability	805	Photosystem I Carries Out the Second Charge-Separation Step in the Z Scheme	855
A Family of Cargo-specific Receptors Mediates Selective Autophagy	806	The Chloroplast ATP Synthase Uses the Proton Gradient Generated by the Photosynthetic Light Reactions to Produce ATP	855
Some Lysosomes and Multivesicular Bodies Undergo Exocytosis	807	The Proton-Motive Force for ATP Production in Mitochondria and Chloroplasts Is Essentially the Same	856
Summary	807	Chemiosmotic Mechanisms Evolved in Stages By Providing an Inexhaustible Source of Reducing Power, Photosynthetic Bacteria Overcame a Major Evolutionary Obstacle	857
Problems	808	The Photosynthetic Electron-Transport Chains of Cyanobacteria Produced Atmospheric Oxygen and Permitted New Life-Forms	857
References	810	Summary	860
Chapter 14 Energy Conversion and Metabolic Compartmentation: Mitochondria and Chloroplasts	811	THE GENETIC SYSTEMS OF MITOCHONDRIA AND CHLOROPLASTS	861
THE MITOCHONDRION	813	The Genetic Systems of Mitochondria and Chloroplasts Resemble Those of Prokaryotes	861
The Mitochondrion Has an Outer Membrane and an Inner Membrane	814	Over Time, Mitochondria and Chloroplasts Have Exported Most of Their Genes to the Nucleus by Gene Transfer	862
Fission, Fusion, Distribution, and Degradation of Mitochondria	815	Mitochondria Have a Relaxed Codon Usage and Can Have a Variant Genetic Code	864
The Inner Membrane Cristae Contain the Machinery for Electron Transport and ATP Synthesis	817	Chloroplasts and Bacteria Share Many Striking Similarities	865
The Citric Acid Cycle in the Matrix Produces NADH	817	Organellar Genes Are Maternally Inherited in Animals and Plants	866
Mitochondria Have Many Essential Roles in Cellular Metabolism	818	Mutations in Mitochondrial DNA Can Cause Severe Inherited Diseases	866
A Chemiosmotic Process Couples Oxidation Energy to ATP Production	821	Why Do Mitochondria and Chloroplasts Maintain a Costly Separate System for DNA Transcription and Translation?	867
The Energy Derived from Oxidation Is Stored as an Electrochemical Gradient	822	Summary	868
Summary	823	Problems	869
THE PROTON PUMPS OF THE ELECTRON-TRANSPORT CHAIN	823	References	871
The Redox Potential Is a Measure of Electron Affinities	823	Chapter 15 Cell Signaling	873
Electron Transfers Release Large Amounts of Energy	824	PRINCIPLES OF CELL SIGNALING	873
Transition Metal Ions and Quinones Accept and Release Electrons Readily	824	Extracellular Signals Can Act Over Short or Long Distances	874
NADH Transfers Its Electrons to Oxygen Through Three Large Enzyme Complexes Embedded in the Inner Membrane	827	Extracellular Signal Molecules Bind to Specific Receptors	875
The NADH Dehydrogenase Complex Contains Separate Modules for Electron Transport and Proton Pumping	828	Each Cell Is Programmed to Respond to Specific Combinations of Extracellular Signals	876
Cytochrome <i>c</i> Reductase Takes Up and Releases Protons on Opposite Sides of the Crista Membrane, Thereby Pumping Protons	829	There Are Three Major Classes of Cell-Surface Receptor Proteins	878
The Cytochrome <i>c</i> Oxidase Complex <i>Pumps</i> Protons and Reduces O ₂ Using a Catalytic Iron-Copper Center	831	Cell-Surface Receptors Relay Signals Via Intracellular Signaling Molecules	879
Succinate Dehydrogenase Acts in Both the Electron-Transport Chain and the Citric Acid Cycle	832	Intracellular Signals Must Be Specific and Robust in a Noisy Cytoplasm	881
The Respiratory Chain Forms a Supercomplex in the Crista Membrane	833	Intracellular Signaling Complexes Form at Activated Cell-Surface Receptors	882
Protons Can Move Rapidly Through Proteins Along Predefined Pathways	834	Modular Interaction Domains Mediate Interactions Between Intracellular Signaling Proteins	883
Summary	835	The Relationship Between Signal and Response Varies in Different Signaling Pathways	885
ATP PRODUCTION IN MITOCHONDRIA	835	The Speed of a Response Depends on the Turnover of Signaling Molecules	886
The Large Negative Value of ΔG for ATP Hydrolysis Makes ATP Useful to the Cell	835		
The ATP Synthase Is a Nanomachine That Produces ATP by Rotary Catalysis	837		
Proton-driven Turbines Are Ancient and Critical for Energy Conversion	839		
Mitochondrial Cristae Help to Make ATP Synthesis Efficient	840		
Special Transport Proteins Move Solutes Through the Inner Membrane	841		
Chemiosmotic Mechanisms First Arose in Bacteria	842		
Summary	842		

Cells Can Respond Abruptly to a Gradually Increasing Signal	887	Chapter 16 The Cytoskeleton	949
Positive Feedback Can Generate an All-or-None Response	888	FUNCTION AND DYNAMICS OF THE CYTOSKELETON	949
Negative Feedback Is a Common Feature of Intracellular Signaling Systems	890	Cytoskeletal Filaments Are Dynamic, but Can Nevertheless Form Stable Structures	951
Cells Can Adjust Their Sensitivity to a Signal	890	The Cytoskeleton Determines Cellular Organization and Polarity	952
Summary	892	Filaments Assemble from Protein Subunits That Impart Specific Physical and Dynamic Properties	953
SIGNALING THROUGH G-PROTEIN-COUPLED RECEPTORS	892	Accessory Proteins and Motors Act on Cytoskeletal Filaments	955
Heterotrimeric G Proteins Relay Signals from GPCRs	893	Molecular Motors Operate in a Cellular Environment Dominated by Brownian Motion	956
Some G Proteins Regulate the Production of Cyclic AMP	895	Summary	957
Cyclic-AMP-dependent Protein Kinase (PKA) Mediates Most of the Effects of Cyclic AMP	896	ACTIN	957
Some G Proteins Signal Via Phospholipids	898	Actin Subunits Assemble Head-to-Tail to Create Flexible, Polar Filaments	958
Ca ²⁺ Functions as a Ubiquitous Intracellular Mediator	899	Nucleation Is the Rate-limiting Step in the Formation of Actin Filaments	958
Feedback Generates Ca ²⁺ Waves and Oscillations	900	Actin Filaments Have Two Distinct Ends That Grow at Different Rates	962
Ca ²⁺ /Calmodulin-dependent Protein Kinases Mediate Many Responses to Ca ²⁺ Signals	902	ATP Hydrolysis Within Actin Filaments Leads to Treadmilling at Steady State	962
Some G Proteins Directly Regulate Ion Channels	904	The Functions of Actin Filaments Are Inhibited by Both Polymer-stabilizing and Polymer-destabilizing Chemicals	963
Smell and Vision Depend on GPCRs That Regulate Ion Channels	905	Actin-binding Proteins Influence Filament Dynamics and Organization	964
Nitric Oxide Gas Can Mediate Signaling Between Cells	908	Actin Nucleation Is Tightly Regulated and Generates Branched or Straight Filaments	964
Second Messengers and Enzymatic Cascades Amplify Signals	909	Actin Filament Elongation Is Regulated by Monomer-binding Proteins	967
GPCR Desensitization Depends on Receptor Phosphorylation	910	Actin Filament-binding Proteins Alter Filament Dynamics and Organization	968
Summary	910	Severing Proteins Regulate Actin Filament Depolymerization	970
SIGNALING THROUGH ENZYME-COUPLED RECEPTORS	911	Bacteria Can Hijack the Host Actin Cytoskeleton	971
Activated Receptor Tyrosine Kinases (RTKs) Phosphorylate Themselves	911	Actin at the Cell Cortex Determines Cell Shape	971
Phosphorylated Tyrosines on RTKs Serve as Docking Sites for Intracellular Signaling Proteins	913	Distinct Modes of Cell Migration Rely on the Actin Cytoskeleton	972
Proteins with SH2 Domains Bind to Phosphorylated Tyrosines	913	Cells Migrating in Three Dimensions Can Navigate Around Barriers	974
The Monomeric GTPase Ras Mediates Signaling by Most RTKs	915	Summary	975
Ras Activates a MAP Kinase Signaling Module	916	MYOSIN AND ACTIN	976
Scaffold Proteins Reduce Cross-Talk Between Different MAP Kinase Modules	918	Actin-based Motor Proteins Are Members of the Myosin Superfamily	976
Rho Family GTPases Functionally Couple Cell-Surface Receptors to the Cytoskeleton	919	Myosin Generates Force by Coupling ATP Hydrolysis to Conformational Changes	977
PI 3-Kinase Produces Lipid Docking Sites in the Plasma Membrane	920	Sliding of Myosin II Along Actin Filaments Causes Muscles to Contract	977
The PI-3-Kinase–Akt Signaling Pathway Stimulates Animal Cells to Survive and Grow	921	A Sudden Rise in Cytosolic Ca ²⁺ Concentration Initiates Muscle Contraction	981
RTKs and GPCRs Activate Overlapping Signaling Pathways	923	Heart Muscle Is a Precisely Engineered Machine	984
Some Enzyme-coupled Receptors Associate with Cytoplasmic Tyrosine Kinases	923	Actin and Myosin Perform a Variety of Functions in Non-Muscle Cells	984
Cytokine Receptors Activate the JAK–STAT Signaling Pathway	924	Summary	986
Extracellular Signal Proteins of the TGF β Superfamily Act Through Receptor Serine/Threonine Kinases and Smads	926	MICROTUBULES	987
Summary	927	Microtubules Are Hollow Tubes Made of Protofilaments	988
ALTERNATIVE SIGNALING ROUTES IN GENE REGULATION	928	Microtubules Undergo a Process Called Dynamic Instability	988
The Receptor Notch Is a Latent Transcription Regulator	928	Microtubule Functions Are Inhibited by Both Polymer-stabilizing and Polymer-destabilizing Drugs	991
Wnt Proteins Activate Frizzled and Thereby Inhibit β -Catenin Degradation	930	A Protein Complex Containing γ -Tubulin Nucleates Microtubules	991
Hedgehog Proteins Initiate a Complex Signaling Pathway in the Primary Cilium	932	The Centrosome Is a Prominent Microtubule Nucleation Site	991
Many Inflammatory and Stress Signals Act Through an NF κ B-dependent Signaling Pathway	934	Microtubule Organization Varies Widely Among Cell Types	993
Nuclear Receptors Are Ligand-modulated Transcription Regulators	935	Microtubule-binding Proteins Modulate Filament Dynamics and Organization	995
Circadian Clocks Use Negative Feedback Loops to Control Gene Expression	937	Microtubule Plus End-binding Proteins Modulate Microtubule Dynamics and Attachments	996
Three Purified Proteins Can Reconstitute a Cyanobacterial Circadian Clock in a Test Tube	938	Tubulin-sequestering and Microtubule-severing Proteins Modulate Microtubule Dynamics	998
Summary	939	Two Types of Motor Proteins Move Along Microtubules	999
SIGNALING IN PLANTS	940	Microtubules and Motors Move Organelles and Vesicles	1002
Multicellularity and Cell Communication Evolved Independently in Plants and Animals	940	Motile Cilia and Flagella Are Built from Microtubules and Dyneins	1004
Receptor Serine/Threonine Kinases Are the Largest Class of Cell-Surface Receptors in Plants	941	Primary Cilia Perform Important Signaling Functions in Animal Cells	1005
Ethylene Blocks the Degradation of Specific Transcription Regulatory Proteins in the Nucleus	941	Summary	1006
Regulated Positioning of Auxin Transporters Patterns Plant Growth	943	INTERMEDIATE FILAMENTS AND OTHER CYTOSKELETAL POLYMERS	1007
Phytochromes Detect Red Light, and Cryptochromes Detect Blue Light	944	Intermediate Filament Structure Depends on the Lateral Bundling and Twisting of Coiled-Coils	1007
Summary	945	Intermediate Filaments Impart Mechanical Stability to Animal Cells	1009
Problems	946	Linker Proteins Connect Cytoskeletal Filaments and Bridge the Nuclear Envelope	1011
References	948		

Septins Form Filaments That Contribute to Subcellular Organization	1012	Actin and Myosin II in the Contractile Ring Guide the Process of Cytokinesis	1065
Bacterial Cell Shape and Division Depend on Homologs of Eukaryotic Cytoskeletal Proteins	1013	Local Activation of RhoA Triggers Assembly and Contraction of the Contractile Ring	1065
Summary	1016	The Microtubules of the Mitotic Spindle Determine the Plane of Animal Cell Division	1066
CELL POLARITY AND COORDINATION OF THE CYTOSKELETON	1016	The Phragmoplast Guides Cytokinesis in Higher Plants	1068
Cell Polarity Is Governed by Small GTPases in Budding Yeast	1016	Membrane-enclosed Organelles Must Be Distributed to Daughter Cells During Cytokinesis	1069
PAR Proteins Generate Anterior–Posterior Polarity in Embryos	1018	Some Cells Reposition Their Spindle to Divide Asymmetrically	1069
Conserved Complexes Polarize Epithelial Cells and Control Their Growth	1019	Mitosis Can Occur Without Cytokinesis	1070
Cell Migration Requires Dynamic Cell Polarity	1020	Summary	1070
External Signals Can Dictate the Direction of Cell Migration	1022	MEIOSIS	1071
Communication Among Cytoskeletal Elements Supports Whole-Cell Polarity and Locomotion	1023	Meiosis Includes Two Rounds of Chromosome Segregation	1071
Summary	1023	Duplicated Homologs Pair During Meiotic Prophase	1073
Problems	1024	Homolog Pairing Culminates in the Formation of a Synaptonemal Complex	1073
References	1025	Homolog Segregation Depends on Several Unique Features of Meiosis I	1075
Chapter 17 The Cell Cycle	1027	Crossing-Over Is Highly Regulated	1076
OVERVIEW OF THE CELL CYCLE	1027	Meiosis Frequently Goes Wrong	1077
The Eukaryotic Cell Cycle Usually Consists of Four Phases	1028	Summary	1077
Cell-Cycle Control Is Similar in All Eukaryotes	1030	CONTROL OF CELL DIVISION AND CELL GROWTH	1077
Cell-Cycle Progression Can Be Studied in Various Ways	1030	Mitogens Stimulate Cell Division	1078
Summary	1031	Cells Can Enter a Specialized Nondividing State	1078
THE CELL-CYCLE CONTROL SYSTEM	1031	Mitogens Stimulate G ₁ -Cdk and G ₁ /S-Cdk Activities	1079
The Cell-Cycle Control System Triggers the Major Events of the Cell Cycle	1032	DNA Damage Blocks Cell Division	1080
The Cell-Cycle Control System Depends on Cyclically Activated Cyclin-dependent Protein Kinases	1033	Many Human Cells Have a Built-In Limitation on the Number of Times They Can Divide	1082
Protein Phosphatases Reverse the Effects of Cdks	1035	Cell Proliferation Is Accompanied by Cell Growth	1083
Hundreds of Cdk Substrates Are Phosphorylated in a Defined Order	1035	Proliferating Cells Usually Coordinate Their Growth and Division	1084
Positive Feedback Generates the Switchlike Behavior of Cell-Cycle Transitions	1036	Summary	1084
The Anaphase-promoting Complex/Cyclosome (APC/C) Triggers the Metaphase-to-Anaphase Transition	1038	Problems	1085
The G ₁ Phase Is a Stable State of Cdk Inactivity	1040	References	1087
The Cell-Cycle Control System Functions as a Linked Series of Biochemical Switches	1041	Chapter 18 Cell Death	1089
Summary	1042	Apoptosis Eliminates Unwanted Cells	1090
S PHASE	1042	Apoptosis Depends on an Intracellular Proteolytic Cascade Mediated by Caspases	1091
S-Cdk Initiates DNA Replication Once Per Cell Cycle	1043	Activation of Cell-Surface Death Receptors Initiates the Extrinsic Pathway of Apoptosis	1093
Chromosome Duplication Requires Duplication of Chromatin Structure	1045	The Intrinsic Pathway of Apoptosis Depends on Proteins Released from Mitochondria	1094
Cohesins Hold Sister Chromatids Together	1045	Bcl2 Proteins Are the Critical Controllers of the Intrinsic Pathway of Apoptosis	1095
Summary	1046	An Inhibitor of Apoptosis (an IAP) and Two Anti-IAP Proteins Help Control Caspase Activation in the Cytosol of Some Mammalian Cells	1098
MITOSIS	1046	Extracellular Survival Factors Inhibit Apoptosis in Various Ways	1098
M-Cdk and Other Protein Kinases Drive Entry into Mitosis	1047	Healthy Neighbors Phagocytose and Digest Apoptotic Cells	1100
Condensin Helps Configure Duplicated Chromosomes for Separation	1047	Either Excessive or Insufficient Apoptosis Can Contribute to Disease	1100
The Mitotic Spindle Is a Dynamic Microtubule-based Machine	1050	Summary	1102
Microtubules Are Nucleated in Multiple Regions of the Spindle	1051	Problems	1103
Microtubule Instability Increases Greatly in Mitosis	1052	References	1104
Microtubule-based Motor Proteins Govern Spindle Assembly and Function	1052	Chapter 19 Cell Junctions and the Extracellular Matrix	1105
Bipolar Spindle Assembly in Most Animal Cells Begins with Centrosome Duplication	1053	CELL–CELL JUNCTIONS	1108
Spindle Assembly in Animal Cells Requires Nuclear-Envelope Breakdown	1054	Cadherins Form a Diverse Family of Adhesion Molecules	1108
Mitotic Chromosomes Promote Bipolar Spindle Assembly	1055	Cadherins Mediate Homophilic Adhesion	1108
Kinetochores Attach Sister Chromatids to the Spindle	1056	Cadherin-dependent Cell–Cell Adhesion Guides the Organization of Developing Tissues	1110
Bi-orientation Is Achieved by Trial and Error	1057	Assembly of Strong Cell–Cell Adhesions Requires Changes in the Actin Cytoskeleton	1112
Multiple Forces Act on Chromosomes in the Spindle	1059	Catenins Link Classical Cadherins to the Actin Cytoskeleton	1113
The APC/C Triggers Sister-Chromatid Separation and the Completion of Mitosis	1060	Adherens Junctions Respond to Tension from Inside and Outside the Tissue	1113
Unattached Chromosomes Block Sister-Chromatid Separation: The Spindle Assembly Checkpoint	1062	Tissue Remodeling Depends on the Coordination of Actin-mediated Contraction with Cell–Cell Adhesion	1114
Chromosomes Segregate in Anaphase A and B	1062	Desmosomes Give Epithelia Mechanical Strength	1116
Segregated Chromosomes Are Packaged in Daughter Nuclei at Telophase	1063	Tight Junctions Form a Seal Between Cells and a Fence Between Plasma Membrane Domains	1116
Summary	1064		
CYTOKINESIS	1064		

Tight Junctions Contain Strands of Transmembrane Adhesion Proteins	1119	Cancer Cells Contain Somatic Mutations	1166
Scaffold Proteins Organize Junctional Protein Complexes	1120	A Single Mutation Is Not Enough to Change a Normal Cell into a Cancer Cell	1166
Gap Junctions Couple Cells Both Electrically and Metabolically	1121	Many Cancers Develop Gradually Through Successive Rounds of Random Inherited Change Followed by Natural Selection	1167
A Gap-Junction Connexon Is Made of Six Transmembrane Connexin Subunits	1122	Cancers Can Evolve Abruptly Due to Genetic Instability	1168
In Plants, Plasmodesmata Perform Many of the Same Functions as Gap Junctions	1123	Some Cancers May Harbor a Small Population of Stem Cells	1170
Selectins Mediate Transient Cell-Cell Adhesions in the Bloodstream	1125	A Common Set of Hallmarks Typically Characterizes Cancerous Growth	1171
Members of the Immunoglobulin Superfamily Mediate Ca ²⁺ -independent Cell-Cell Adhesion	1126	Cancer Cells Display an Altered Control of Growth and Homeostasis	1172
Summary	1127	Human Cancer Cells Escape a Built-in Limit to Cell Proliferation	1173
THE EXTRACELLULAR MATRIX OF ANIMALS	1127	Cancer Cells Have an Abnormal Ability to Bypass Death Signals	1174
The Extracellular Matrix Is Made and Oriented by the Cells Within It	1128	Cancer Cells Have Altered Sugar Metabolism	1175
Glycosaminoglycan (GAG) Chains Occupy Large Amounts of Space and Form Hydrated Gels	1129	The Tumor Microenvironment Influences Cancer Development	1175
Hyaluronan Acts as a Space Filler During Tissue Morphogenesis and Repair	1129	Cancer Cells Must Survive and Proliferate in a Foreign Environment	1176
Proteoglycans Are Composed of GAG Chains Covalently Linked to a Core Protein	1130	Summary	1178
Collagens Are the Major Proteins of the Extracellular Matrix	1132	CANCER-CRITICAL GENES: HOW THEY ARE FOUND AND WHAT THEY DO	1178
Collagen Chains Undergo a Series of Post-translational Modifications	1133	The Identification of Gain-of-Function and Loss-of-Function Cancer Mutations Has Traditionally Required Different Methods	1179
Secreted Fibril-associated Collagens Help Organize the Fibrils	1135	Retroviruses Led to the Identification of Oncogenes	1180
Elastin Gives Tissues Their Elasticity	1136	Genes Mutated in Cancer Can Be Made Overactive in Many Ways	1181
Cells Govern and Respond to the Mechanical Properties of the Matrix	1137	Studies of Rare Hereditary Cancer Syndromes First Identified Tumor Suppressor Genes	1182
Fibronectin and Other Multidomain Glycoproteins Help Organize the Matrix	1138	Both Genetic and Epigenetic Mechanisms Can Inactivate Tumor Suppressor Genes	1183
Fibronectin Binds to Integrins	1139	Systematic Sequencing of Cancer Cell Genomes Has Transformed Our Understanding of the Disease	1184
Tension Exerted by Cells Regulates the Assembly of Fibronectin Fibrils	1140	Many Cancers Have an Extraordinarily Disrupted Genome	1185
The Basal Lamina Is a Specialized Form of Extracellular Matrix	1141	Epigenetic and Chromatin Changes Contribute to Most Cancers	1185
Laminin and Type IV Collagen Are Major Components of the Basal Lamina	1141	Hundreds of Human Genes Contribute to Cancer	1186
Basal Laminae Have Diverse Functions	1143	Disruptions in a Handful of Key Pathways Are Common to Many Cancers	1187
Cells Have to Be Able to Degrade Matrix, as Well as Make It	1144	Mutations in the PI 3-kinase/Akt/mTOR Pathway Drive Cancer Cells to Grow	1188
Matrix Proteoglycans and Glycoproteins Regulate the Activities of Secreted Proteins	1145	Mutations in the p53 Pathway Enable Cancer Cells to Survive and Proliferate Despite Stress and DNA Damage	1189
Summary	1146	Studies Using Mice Help to Define the Functions of Cancer-critical Genes	1190
CELL-MATRIX JUNCTIONS	1147	Cancers Become More and More Heterogeneous as They Progress	1192
Integrins Are Transmembrane Heterodimers That Link the Extracellular Matrix to the Cytoskeleton	1147	Colorectal Cancers Evolve Slowly Via a Succession of Visible Changes	1192
Integrin Defects Are Responsible for Many Genetic Diseases	1148	A Few Key Genetic Lesions Are Common to a Large Fraction of Colorectal Cancers	1194
Integrins Can Switch Between an Active and an Inactive Conformation	1149	Some Colorectal Cancers Have Defects in DNA Mismatch Repair	1195
Integrins Cluster to Form Strong Adhesions	1151	The Steps of Tumor Progression Can Often Be Correlated with Specific Mutations	1196
Extracellular Matrix Attachments Act Through Integrins to Control Cell Proliferation and Survival	1151	The Changes in Tumor Cells That Lead to Metastasis Are Still Largely a Mystery	1197
Integrins Recruit Intracellular Signaling Proteins at Sites of Cell-Matrix Adhesion	1152	Summary	1197
Cell-Matrix Adhesions Respond to Mechanical Forces	1153	CANCER PREVENTION AND TREATMENT: PRESENT AND FUTURE	1198
Summary	1154	Epidemiology Reveals That Many Cases of Cancer Are Preventable	1198
THE PLANT CELL WALL	1154	Sensitive Assays Can Detect Those Cancer-causing Agents That Damage DNA	1199
The Composition of the Cell Wall Depends on the Cell Type	1155	Fifty Percent of Cancers Could Be Prevented by Changes in Lifestyle	1200
The Tensile Strength of the Cell Wall Allows Plant Cells to Develop Turgor Pressure	1155	Viruses and Other Infections Contribute to a Significant Proportion of Human Cancers	1201
The Primary Cell Wall Is Built from Cellulose Microfibrils Interwoven with a Network of Pectic Polysaccharides	1156	Cancers of the Uterine Cervix Can Be Prevented by Vaccination Against Human Papillomavirus	1202
Oriented Cell Wall Deposition Controls Plant Cell Growth	1157	Infectious Agents Can Cause Cancer in a Variety of Ways	1203
Microtubules Orient Cell Wall Deposition	1158	The Search for Cancer Cures Is Difficult but Not Hopeless	1204
Summary	1159	Traditional Therapies Exploit the Genetic Instability and Loss of Cell-Cycle Checkpoint Responses in Cancer Cells	1204
Problems	1160	New Drugs Can Kill Cancer Cells Selectively by Targeting Specific Mutations	1204
References	1162	PARP Inhibitors Kill Cancer Cells That Have Defects in <i>Brca1</i> or <i>Brca2</i> Genes	1205
Chapter 20 Cancer	1163		
CANCER AS A MICROEVOLUTIONARY PROCESS	1163		
Cancer Cells Bypass Normal Proliferation Controls and Colonize Other Tissues	1164		
Most Cancers Derive from a Single Abnormal Cell	1165		

Small Molecules Can Be Designed to Inhibit Specific Oncogenic Proteins	1207	A Gene Expression Oscillator Acts as a Clock to Control Vertebrate Segmentation	1249
Many Cancers May Be Treatable by Enhancing Immune Responses	1209	Cell-intrinsic Timing Mechanisms Can Lead to Different Cell Fates	1251
Immunosuppression Is a Major Hurdle for Cancer Immunotherapy	1210	Cells Rarely Count Cell Divisions to Time Their Development	1252
Cancers Evolve Resistance to Therapies	1212	MicroRNAs Can Regulate Developmental Transitions	1252
We Now Have the Tools to Devise Combination Therapies Tailored to the Individual	1212	Cell and Nuclear Size Relationships Schedule the Onset of Zygotic Gene Expression	1254
Summary	1213	Hormonal Signals Coordinate the Timing of Developmental Transitions	1255
Problems	1214	Environmental Cues Determine the Time of Flowering	1256
References	1216	Summary	1257
Chapter 21 Development of Multicellular Organisms	1217	MORPHOGENESIS	1257
OVERVIEW OF DEVELOPMENT	1218	Imbalance in Physical Forces Acting on Cells Drives Morphogenesis	1258
Conserved Mechanisms Establish the Core Tissues of Animals	1218	Tension and Adhesion Determine Cell Packing Within Epithelial Sheets	1258
The Developmental Potential of Cells Becomes Progressively Restricted	1219	Changing Patterns of Cell Adhesion Molecules Force Cells into New Arrangements	1259
Cell Memory Underlies Cell Decision-Making	1220	Repulsive Interactions Help Maintain Tissue Boundaries	1259
Several Model Organisms Have Been Crucial for Understanding Development	1220	Groups of Similar Cells Can Perform Dramatic Collective Rearrangements	1261
Regulatory DNA Seems Largely Responsible for the Differences Between Animal Species	1220	Planar Cell Polarity Orients Cell Behaviors Within an Embryo	1261
Small Numbers of Conserved Cell–Cell Signaling Pathways Coordinate Spatial Patterning	1221	An Epithelium Can Bend During Development to Form a Tube	1263
Through Combinatorial Control and Cell Memory, Simple Signals Can Generate Complex Patterns	1221	Interactions Between an Epithelium and Mesenchyme Generate Branching Tubular Structures	1264
Morphogens Are Diffusible Inductive Signals That Exert Graded Effects	1222	The Extracellular Matrix Also Influences Tissue Shape	1265
Lateral Inhibition Can Generate Patterns of Different Cell Types	1223	Cell Migration Is Guided by Environmental Signals	1266
Asymmetric Cell Division Can Also Generate Diversity	1224	The Distribution of Migrant Cells Depends on Survival Factors	1267
Initial Patterns Are Established in Small Fields of Cells and Refined by Sequential Induction as the Embryo Grows	1225	Cells Migrate in Groups to Achieve Large-Scale Morphogenetic Movements	1268
Developmental Biology Provides Insights into Disease and Tissue Maintenance	1225	Summary	1269
Summary	1226	GROWTH	1269
MECHANISMS OF PATTERN FORMATION	1226	The Proliferation, Death, and Size of Cells Determine Organ and Organism Size	1270
Different Animals Use Different Mechanisms to Establish Their Primary Axes of Polarization	1226	Changes in Cell Size Usually Result from Modified Cell Cycles	1271
Studies in <i>Drosophila</i> Have Revealed Many Genetic Control Mechanisms Underlying Development	1228	Animals and Organs Can Assess and Regulate Total Cell Mass	1272
Gene Products Deposited in the Egg Organize the Axes of the Early <i>Drosophila</i> Embryo	1228	Various Extracellular Signals Stimulate or Inhibit Growth	1273
Three Groups of Genes Control <i>Drosophila</i> Segmentation Along the A-P Axis	1230	The Hippo Pathway Relays Mechanical Signals Regulating Growth	1273
A Hierarchy of Gene Regulatory Interactions Subdivides the <i>Drosophila</i> Embryo	1231	Hormones Coordinate Growth Throughout the Body	1274
Egg-Polarity, Gap, and Pair-Rule Genes Create a Transient Pattern That Is Remembered by Segment-Polarity and <i>Hox</i> Genes	1233	The Duration of Growth Influences Organism Size	1275
<i>Hox</i> Genes Permanently Pattern the A-P Axis	1233	Summary	1275
<i>Hox</i> Proteins Give Each Segment Its Individuality	1234	Problems	1276
<i>Hox</i> Genes Are Expressed According to Their Order in the <i>Hox</i> Complex	1234	References	1278
Trithorax and Polycomb Group Proteins Regulate <i>Hox</i> Expression to Maintain a Permanent Record of Positional Information	1235	Chapter 22 Stem Cells in Tissue Homeostasis and Regeneration	1279
The D-V Signaling Genes Create a Gradient of the Transcription Regulator Dorsal	1236	STEM CELLS AND TISSUE HOMEOSTASIS	1279
A Hierarchy of Inductive Interactions Subdivides the Vertebrate Embryo	1238	Stem Cells Are Defined by Their Ability to Self-renew and Produce Differentiated Cells	1280
A Competition Between Secreted Signaling Proteins Patterns the Vertebrate Embryonic Axes	1239	The Epithelial Lining of the Small Intestine Is Continually Renewed Through Cell Proliferation in Crypts	1281
<i>Hox</i> Genes Control the Vertebrate A-P Axis	1240	Epidermal Stem Cells Maintain a Self-renewing, Waterproof, Epithelial Barrier on the Body Surface	1282
Some Transcription Regulators Can Activate a Program That Defines a Cell Type or Creates an Entire Organ	1241	Cell Lineage Tracing Reveals the Location of Stem Cells and Their Progeny	1284
Notch-mediated Lateral Inhibition Refines Cellular Spacing Patterns	1242	Quiescent Stem Cells Are Difficult to Identify by Lineage Tracing	1285
Cell-fate Determinants Can Be Asymmetrically Inherited	1244	Hematopoietic Stem Cells Can Be Identified by Transplantation	1286
Evolution of Regulatory DNA Explains Many Morphological Differences	1245	Some Tissues Do Not Require Stem Cells for Their Maintenance	1289
Summary	1247	In Response to Injury, Some Differentiated Cells Can Revert to Progenitor Cells and Some Progenitor Cells Can Revert to Stem Cells	1289
DEVELOPMENTAL TIMING	1248	Some Tissues Lack Stem Cells and Are Not Renewable	1290
Molecular Lifetimes Play a Critical Part in Developmental Timing	1248	Summary	1290
		CONTROL OF STEM-CELL FATE AND SELF-RENEWAL	1291
		The Stem-Cell Niche Maintains Stem-Cell Self-Renewal	1291
		The Size of the Niche Can Determine the Number of Stem Cells	1292
		Asymmetric Stem-Cell Division Can Maintain Stem-Cell Number	1293
		In Many Symmetric Stem-Cell Divisions, Daughter Cells Choose Their Fates Independently and Stochastically	1294
		A Decline in Stem-Cell Function Contributes to Tissue Aging	1294

Summary	1296	THE HUMAN MICROBIOTA	1347
REGENERATION AND REPAIR	1296	The Human Microbiota Is a Complex Ecological System	1347
Planarian Flatworms Contain Stem Cells That Can Regenerate a Whole New Body	1297	The Microbiota Influences Our Development and Health	1348
Some Vertebrates Can Regenerate Entire Limbs and Organs	1298	Summary	1349
Stem Cells Can Be Used Clinically to Replace Lost Hematopoietic or Skin Cells	1299	Problems	1350
Neural Stem Cells Can Be Manipulated in Culture and Used to Repopulate a Diseased Central Nervous System	1299	References	1351
Summary	1300		
CELL REPROGRAMMING AND PLURIPOTENT STEM CELLS	1300	Chapter 24 The Innate and Adaptive Immune Systems	1353
Nuclei Can Be Reprogrammed by Transplantation into Foreign Cytoplasm	1301	THE INNATE IMMUNE SYSTEM	1354
Reprogramming of a Transplanted Nucleus Involves Drastic Changes in Chromatin	1301	Epithelial Surfaces Serve as Barriers to Infection	1354
Embryonic Stem (ES) Cells Can Generate Any Part of the Body	1302	Pattern Recognition Receptors (PRRs) Recognize Conserved Features of Pathogens	1354
A Core Set of Transcription Regulators Defines and Maintains the ES-Cell State	1303	There Are Multiple Families of PRRs	1355
Fibroblasts Can Be Reprogrammed to Create Induced Pluripotent Stem (iPS) Cells	1303	Activated PRRs Trigger an Inflammatory Response at Sites of Infection	1356
Reprogramming Involves a Massive Upheaval of the Gene Control System	1304	Phagocytic Cells Seek, Engulf, and Destroy Pathogens	1358
An Experimental Manipulation of Factors That Modify Chromatin Can Increase Reprogramming Efficiencies	1305	Complement Activation Targets Pathogens for Phagocytosis or Lysis	1358
ES and iPS Cells Can Be Guided to Generate Specific Adult Cell Types and Even Organoids	1306	Virus-infected Cells Take Drastic Measures to Prevent Viral Replication	1360
Cells of One Specialized Type Can Be Forced to Transdifferentiate Directly into Another	1306	Natural Killer Cells Induce Virus-infected Cells to Kill Themselves	1361
ES and iPS Cells Are Also Useful for Drug Discovery and Analysis of Disease	1308	Dendritic Cells Provide the Link Between the Innate and Adaptive Immune Systems	1362
Summary	1309	Summary	1362
Problems	1310	OVERVIEW OF THE ADAPTIVE IMMUNE SYSTEM	1364
References	1312	B Cells Develop in the Bone Marrow, T Cells in the Thymus	1365
		Immunological Memory Depends on Both Clonal Expansion and Lymphocyte Differentiation	1366
		Most B and T Cells Continually Recirculate Through Peripheral Lymphoid Organs	1368
		Immunological Self-tolerance Ensures That B and T Cells Do Not Attack Normal Host Cells and Molecules	1370
		Summary	1372
Chapter 23 Pathogens and Infection	1313	B CELLS AND IMMUNOGLOBULINS	1372
INTRODUCTION TO PATHOGENS	1313	B Cells Make Immunoglobulins (Igs) as Both Cell-Surface Antigen Receptors and Secreted Antibodies	1373
Pathogens Can Be Viruses, Bacteria, or Eukaryotes	1314	Mammals Make Five Classes of Igs	1373
Pathogens Interact with Their Hosts in Different Ways	1314	Ig Light and Heavy Chains of Antibodies Consist of Constant and Variable Regions	1375
Bacteria Are Diverse and Occupy a Remarkable Variety of Ecological Niches	1315	Ig Genes Are Assembled from Separate Gene Segments During B Cell Development	1377
Bacterial Pathogens Carry Specialized Virulence Genes	1317	Antigen-driven Somatic Hypermutation Fine-Tunes Antibody Responses	1379
Bacterial Virulence Genes Encode Toxins and Secretion Systems That Deliver Effector Proteins to Host Cells	1319	B Cells Can Switch the Class of Ig They Make	1379
Fungal and Protozoan Parasites Have Complex Life Cycles Involving Multiple Forms	1321	Summary	1381
All Aspects of Viral Propagation Depend on Host-Cell Machinery	1322	T CELLS AND MHC PROTEINS	1382
Summary	1325	T Cell Receptors (TCRs) Are Ig-like Heterodimers	1382
CELL BIOLOGY OF PATHOGEN INFECTION	1325	Activated Dendritic Cells Activate Naïve T Cells	1383
Pathogens Breach Epithelial Barriers to Infect the Host	1326	T Cells Recognize Foreign Peptides Bound to MHC Proteins	1384
Pathogens That Colonize an Epithelium Must Overcome Its Protective Mechanisms	1326	MHC Proteins Are the Most Polymorphic Human Proteins Known	1388
Extracellular Pathogens Use Toxins and Contact-dependent Secretion Systems to Disturb Host Cells Without Entering Them	1328	CD4 and CD8 Co-receptors on T Cells Bind to Invariant Parts of MHC Proteins	1389
Intracellular Pathogens Have Mechanisms for Both Entering and Leaving Host Cells	1329	Developing Thymocytes Undergo Positive and Negative Selection	1389
Viruses Bind to Virus Receptors at the Host-Cell Surface	1329	Cytotoxic T Cells Induce Infected Target Cells to Undergo Apoptosis	1391
Viruses Enter Host Cells by Membrane Fusion, Pore Formation, or Membrane Disruption	1330	Effector Helper T Cells Help Activate Other Cells of the Innate and Adaptive Immune Systems	1392
Bacteria Enter Host Cells by Phagocytosis	1331	Naïve Helper T Cells Can Differentiate into Different Types of Effector T Cells	1393
Intracellular Eukaryotic Parasites Actively Invade Host Cells	1333	Both T and B Cells Require Multiple Extracellular Signals for Activation	1394
Some Intracellular Pathogens Escape from the Phagosome into the Cytosol	1334	Many Cell-Surface Proteins Belong to the Ig Superfamily	1396
Many Pathogens Alter Membrane Traffic in the Host Cell to Survive and Replicate	1335	Vaccination Against Pathogens Has Been Immunology's Greatest Contribution to Human Health	1396
Bacteria and Viruses Use the Host-Cell Cytoskeleton for Intracellular Movement	1338	Summary	1400
Many Microbes Manipulate Autophagy	1340	Problems	1402
Viruses Can Take Over the Metabolism of the Host Cell	1340	References	1404
Pathogens Can Evolve Rapidly by Antigenic Variation	1341		
Error-prone Replication Dominates Viral Evolution	1343	Glossary	G:1
Drug-resistant Pathogens Are a Growing Problem	1344	Index	I:1
Summary	1346		



INTRODUCTION TO THE CELL

Cells, Genomes, and the Diversity of Life

CHAPTER

1

The surface of our planet is populated by living things—*organisms*—curious, intricately organized chemical factories that take in matter from their surroundings and use these raw materials to generate copies of themselves. These organisms appear extraordinarily diverse. What could be more different than a tiger and a piece of seaweed or a butterfly and a tree? Yet our ancestors, knowing nothing of cells or DNA, saw that all these things had something in common. They called that something “life,” marveled at it, struggled to define it, and despaired of explaining what it was or how it worked in terms that relate to non-living matter.

The remarkable discoveries of the past 100 years or so have not diminished the marvel—quite the contrary. But they have removed the central mystery regarding the nature of life. We can now see that all living things are made of cells: small, membrane-enclosed units filled with a concentrated aqueous solution of chemicals and endowed with the extraordinary ability to create copies of themselves by growing and then dividing in two.

Because cells are the fundamental units of life, it is to *cell biology*—the study of the structure, function, and behavior of cells—that we must look for answers to the questions of what life is and how it works. With a deeper understanding of cells and their evolution, we can begin to tackle the grand historical problems of life on Earth: its mysterious origins, its stunning diversity, and its invasion of every conceivable habitat. Indeed, as emphasized long ago by the pioneering cell biologist E. B. Wilson, “the key to every biological problem must finally be sought in the cell; for every living organism is, or at some time has been, a cell.”

Despite their apparent diversity, living things are fundamentally similar inside. The whole of biology is thus a counterpoint between two themes: astonishing variety in individual particulars and astonishing constancy in fundamental mechanisms. In this chapter, we begin by outlining the universal features common to all life on our planet, along with some of the fundamental properties of their cells. We then discuss how an analysis of DNA *genomes* allows scientists to position the wide variety of organisms in an evolutionary “tree of life.” This

IN THIS CHAPTER

The Universal Features of Life on Earth

Genome Diversification and the Tree of Life

Eukaryotes and the Origin of the Eukaryotic Cell

Model Organisms