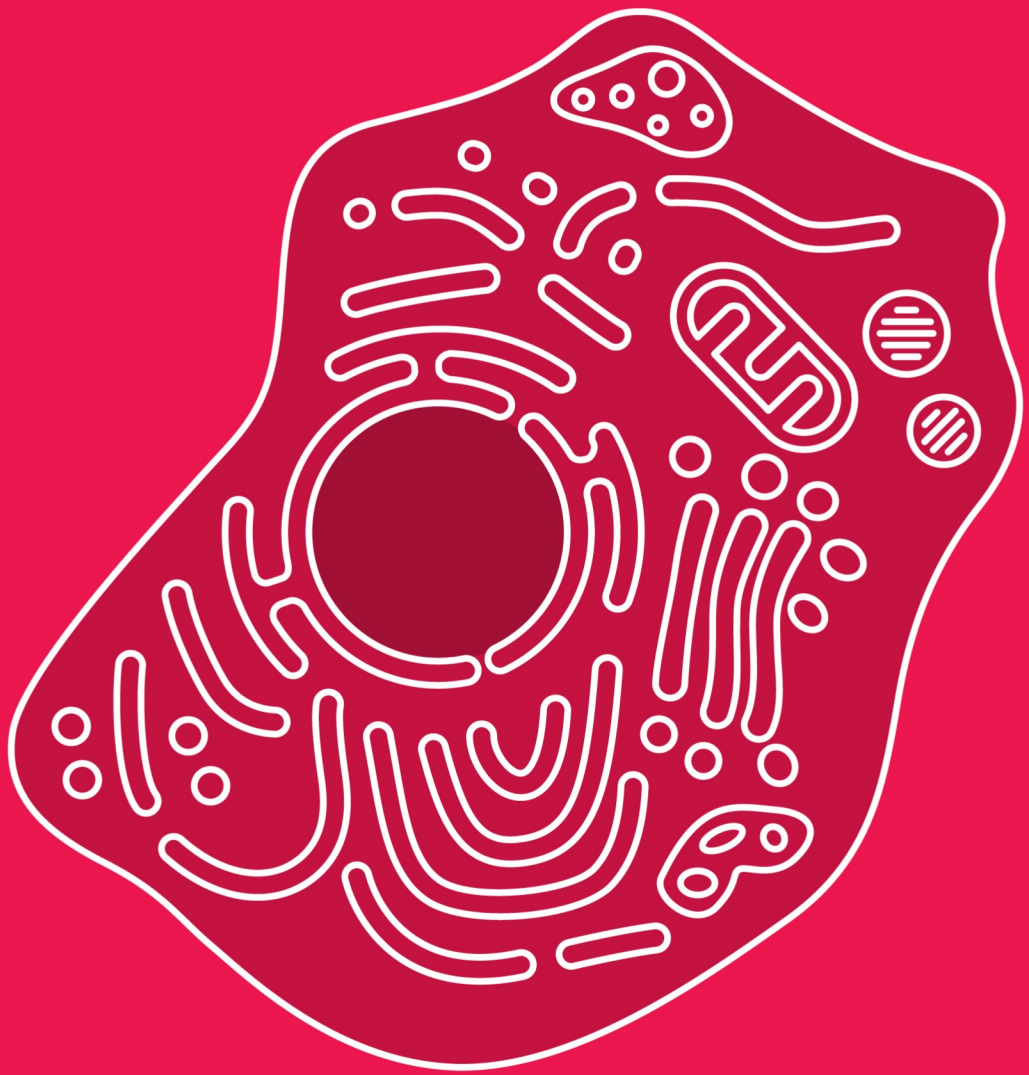
Molecular Biology of THE CELL

Fifth Edition



ALBERTS JOHNSON LEWIS RAFF ROBERTS WALTER

This page intentionally left blank.

Molecular Biology of THE CELL

Fifth Edition

This page intentionally left blank.

Molecular Biology of THE CELL

Fifth Edition

Bruce Alberts

Alexander Johnson

Julian Lewis

Martin Raff

Keith Roberts

Peter Walter

With problems by

John Wilson

Tim Hunt

Garland Science
Taylor & Francis Group

Garland Science
Vice President: Denise Schanck
Assistant Editor: Sigrid Masson
Production Editor and Layout: Emma Jeffcock
Senior Publisher: Jackie Harbor
Illustrator: Nigel Orme
Designer: Matthew McClements, Blink Studio, Ltd.
Editors: Marjorie Anderson and Sherry Granum
Copy Editor: Bruce Goatly
Indexer: Merrall-Ross International, Ltd.
Permissions Coordinator: Mary Dispenza

Cell Biology Interactive
Artistic and Scientific Direction: Peter Walter
Narrated by: Julie Theriot
Production Design and Development: Michael Morales

Bruce Alberts received his Ph.D. from Harvard University and is Professor of Biochemistry and Biophysics at the University of California, San Francisco. For 12 years, he served as President of the U.S. National Academy of Sciences (1993–2005). **Alexander Johnson** received his Ph.D. from Harvard University and is Professor of Microbiology and Immunology and Director of the Biochemistry, Cell Biology, Genetics, and Developmental Biology Graduate Program at the University of California, San Francisco. **Julian Lewis** received his D.Phil. from the University of Oxford and is a Principal Scientist at the London Research Institute of Cancer Research UK. **Martin Raff** received his M.D. from McGill University and is at the Medical Research Council Laboratory for Molecular Cell Biology and the Biology Department at University College London. **Keith Roberts** received his Ph.D. from the University of Cambridge and is Emeritus Fellow at the John Innes Centre, Norwich. **Peter Walter** received his Ph.D. from The Rockefeller University in New York and is Professor and Chairman of the Department of Biochemistry and Biophysics at the University of California, San Francisco, and an Investigator of the Howard Hughes Medical Institute.

Library of Congress Cataloging-in-Publication Data
Molecular biology of the cell / Bruce Alberts … [et al.].-- 5th ed.
p. cm
ISBN 978-0-8153-4105-5 (hardcover)---ISBN 978-0-8153-4106-2 (paperback)
1. Cytology. 2. Molecular biology. I. Alberts, Bruce.
QH581.2 .M64 2008
571.6--dc22
2007005475 CIP

Published by Garland Science, Taylor & Francis Group, LLC, an informa business, 270 Madison Avenue, New York NY 10016, USA, and 2 Park Square, Milton Park, Abingdon, OX14 4RN, UK.

Printed in the United States of America

15 14 13 12 11 10 9 8 7 6 5 4 3 2

Preface

In many respects, we understand the structure of the universe better than the workings of living cells. Scientists can calculate the age of the Sun and predict when it will cease to shine, but we cannot explain how it is that a human being may live for eighty years but a mouse for only two. We know the complete genome sequences of these and many other species, but we still cannot predict how a cell will behave if we mutate a previously unstudied gene. Stars may be 10^{43} times bigger, but cells are more complex, more intricately structured, and more astonishing products of the laws of physics and chemistry. Through heredity and natural selection, operating from the beginnings of life on Earth to the present day—that is, for about 20% of the age of the universe—living cells have been progressively refining and extending their molecular machinery, and recording the results of their experiments in the genetic instructions they pass on to their progeny.

With each edition of this book, we marvel at the new information that cell biologists have gathered in just a few years. But we are even more amazed and daunted at the sophistication of the mechanisms that we encounter. The deeper we probe into the cell, the more we realize how much remains to be understood. In the days of our innocence, working on the first edition, we hailed the identification of a single protein—a signal receptor, say—as a great step forward. Now we appreciate that each protein is generally part of a complex with many others, working together as a system, regulating one another's activities in subtle ways, and held in specific positions by binding to scaffold proteins that give the chemical factory a definite spatial structure. Genome sequencing has given us virtually complete molecular parts-lists for many different organisms; genetics and biochemistry have told us a great deal about what those parts are capable of individually and which ones interact with which others; but we have only the most primitive grasp of the dynamics of these biochemical systems, with all their interlocking control loops. Therefore, although there are great achievements to report, cell biologists face even greater challenges for the future.

In this edition, we have included new material on many topics, ranging from epigenetics, histone modifications, small RNAs, and comparative genomics, to genetic noise, cytoskeletal dynamics, cell-cycle control, apoptosis, stem cells, and novel cancer therapies. As in previous editions, we have tried above all to give readers a conceptual framework for the mass of information that we now have about cells. This means going beyond the recitation of facts. The goal is to learn how to put the facts to use—to reason, to predict, and to control the behavior of living systems.

To help readers on the way to an active understanding, we have for the first time incorporated end-of-chapter problems, written by John Wilson and Tim Hunt. These emphasize a quantitative approach and the art of reasoning from experiments. A companion volume, *Molecular Biology of the Cell, Fifth Edition: The Problems Book (*ISBN: 978-0-8153-4110-9), by the same authors, gives complete answers to these problems and also contains more than 1700 additional problems and solutions.

A further major adjunct to the main book is the attached Media DVD-ROM disc. This provides hundreds of movies and animations, including many that are new in this edition, showing cells and cellular processes in action and bringing the text to life; the disc now includes all the figures and tables from the main

book, pre-loaded into PowerPoint® presentations. Other ancillaries available for the book include a bank of test questions and lecture outlines, available to qualified instructors, and a set of 200 full-color overhead transparencies.

Different groups of readers will use different parts of the book. We anticipate that researchers, laboratories, and libraries will wish to have the full set of chapters in a single printed volume, as in the present Reference Edition. For those who prefer to have the core cell biology chapters in a somewhat more portable form, a Student Edition is also available, containing Chapters 1–20 as printed pages and Chapters 21–25 (on multicellular systems) in electronic (PDF) form on the accompanying disc.

Full details of the conventions adopted in the book are given in the Note to the Reader that follows this Preface. As explained there, we have taken a drastic approach in confronting the different rules for the writing of gene names in different species: throughout this book, we use the same style, regardless of species, and often in defiance of the usual species-specific conventions.

As always, we are indebted to many people. Full acknowledgments for scientific help are given separately, but we must here single out some exceptionally important contributions: Julie Theriot is almost entirely responsible for Chapters 16 (Cytoskeleton) and 24 (Pathogens, Infection, and Innate Immunity), and David Morgan likewise for Chapter 17 (Cell Cycle). Wallace Marshall and Laura Attardi provided substantial help with Chapters 8 and 20, respectively, as did Maynard Olson for the genomics section of Chapter 4, Xiaodong Wang for Chapter 18, and Nicholas Harberd for the plant section of Chapter 15.

We also owe a huge debt to the staff of Garland Publishing and others who helped convert writers' efforts into a polished final product. Denise Schanck directed the whole enterprise and shepherded the wayward authors along the road with wisdom, skill, and kindness. Nigel Orme put the artwork into its final form and supervised the visual aspects of the book, including the back cover, with his usual flair. Matthew Clements designed the book and its front cover. Emma Jeffcock laid out its pages with extraordinary speed and unflappable efficiency, dealing impeccably with innumerable corrections. Michael Morales managed the transformation of a mass of animations, video clips, and other materials into a user-friendly DVD-ROM. Eleanor Lawrence and Sherry Granum updated and enlarged the glossary. Jackie Harbor and Sigrid Masson kept us organized. Adam Sendroff kept us aware of our readers and their needs and reactions. Marjorie Anderson, Bruce Goatly, and Sherry Granum combed the text for obscurities, infelicities, and errors. We thank them all, not only for their professional skill and dedication and for efficiency far surpassing our own, but also for their unfailing helpfulness and friendship: they have made it a pleasure to work on the book.

Lastly, and with no less gratitude, we thank our spouses, families, friends and colleagues. Without their patient, enduring support, we could not have produced any of the editions of this book.

Contents

Special Features

Detailed Contents

Acknowledgments

In writing this book we have benefited greatly from the advice of many biologists and biochemists. We would like to thank the following for their suggestions in preparing this edition, as well as those who helped in preparing the first, second, third and fourth editions. (Those who helped on this edition are listed first, those who helped with the first, second, third and fourth editions follow.)

Chapter 1: W. Ford Doolittle (Dalhousie University, Canada), Jennifer Frazier (Exploratorium®, San Francisco), Douglas Kellogg (University of California, Santa Cruz), Eugene Koonin (National Institutes of Health), Mitchell Sogin (Woods Hole Institute)

Chapter 2: Michael Cox (University of Wisconsin, Madison), Christopher Mathews (Oregon State University), Donald Voet (University of Pennsylvania), John Wilson (Baylor College of Medicine)

Chapter 3: David Eisenberg (University of California, Los Angeles), Louise Johnson (University of Oxford), Steve Harrison (Harvard University), Greg Petsko (Brandeis University), Robert Stroud (University of California, San Francisco), Janet Thornton (European Bioinformatics Institute, UK)

Chapter 4: David Allis (The Rockefeller University), Adrian Bird (Wellcome Trust Centre, UK), Gary Felsenfeld (National Institutes of Health), Susan Gasser (University of Geneva, Switzerland), Eric Green (National Institutes of Health), Douglas Koshland (Carnegie Institution of Washington, Baltimore), Ulrich Laemmli (University of Geneva, Switzerland), Michael Lynch (Indiana University), Hiten Madhani (University of California, San Francisco), Elliott Margulies (National Institutes of Health), Geeta Narlikar (University of California, San Francisco), Maynard Olson (University of Washington)

Chapter 5: Elizabeth Blackburn (University of California, San Francisco), James Haber (Brandeis University), Nancy Kleckner (Harvard University), Joachim Li (University of California, San Francisco), Thomas Lindahl (Cancer Research, UK), Rodney Rothstein (Columbia University), Aziz Sancar (University of North Carolina, Chapel Hill), Bruce Stillman (Cold Spring Harbor Laboratory), Steven West (Cancer Research, UK), Rick Wood (University of Pittsburgh)

Chapter 6: Raul Andino (University of California, San Francisco), David Bartel (Massachusetts Institute of Technology), Richard Ebright (Rutgers University), Daniel Finley (Harvard University), Joseph Gall (Carnegie Institution of Washington), Michael Green (University of Massachusetts Medical School), Carol Gross (University of California, San Francisco), Christine Guthrie (University of California, San Francisco), Art Horwich (Yale University School of Medicine), Roger Kornberg (Stanford University), Reinhard Lührman (Max Planck Institute of Biophysical Chemistry, Göttingen), Quinn Mitrovich (University of California, San Francisco), (Harry Noller (University of California, Santa Cruz), Roy Parker (University of Arizona), Robert Sauer (Massachusetts Institute of Technology), Joan Steitz (Yale University), Jack Szostak (Harvard Medical School, Howard Hughes Medical Institute), David Tollervey (University of Edinburgh, UK), Alexander Varshavsky (California Institute of Technology), Jonathan Weissman (University of California, San Francisco)

Chapter 7: Raul Andino (University of California, San Francisco), David Bartel (Massachusetts Institute of Technology), Michael Bulger (University of Rochester Medical Center), Michael Green (University of Massachusetts Medical School), Carol Gross (University of California, San Francisco), Frank Holstege (University Medical Center, The Netherlands), Roger Kornberg (Stanford University), Hiten Madhani (University of California, San Francisco), Barbara Panning (University of California, San Francisco), Mark Ptashne (Memorial Sloan-Kettering Center), Ueli Schibler (University of Geneva, Switzerland), Azim Surani (University of Cambridge)

Chapter 8: Wallace Marshall [major contribution] (University of California, San Francisco)

Chapter 9: Wolfgang Baumeister (Max Planck Institute of Biochemistry, Martinsried), Ken Sawin (The Wellcome Trust Centre for Cell Biology, UK), Peter Shaw (John Innes Centre, UK), Werner Kühlbrandt (Max Planck Institute of Biophysics, Frankfurt am Main), Ronald Vale (University of California, San Francisco), Jennifer Lippincott-Schwartz (National Institutes of Health)

Chapter 10: Ari Helenius (Swiss Federal Institute of Technology Zürich, Switzerland), Werner Kühlbrandt (Max Planck Institute of Biophysics, Frankfurt am Main), Dieter Osterhelt (Max Planck Institute of Biochemistry, Martinsried), Kai Simons (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden)

Chapter 11: Wolfhard Almers (Oregon Health and Science University), Robert Edwards (University of California, San Francisco), Bertil Hille (University of Washington), Lily Jan (University of California, San Francisco), Roger Nicoll (University of California, San Francisco), Robert Stroud (University of California, San Francisco), Patrick Williamson (University of Massachusetts, Amherst)

Chapter 12: Larry Gerace (The Scripps Research Institute), Ramanujan Hegde (National Institutes of Health), Nikolaus Pfanner (University of Freiburg, Germany), Daniel Schnell (University of Massachusetts, Amherst), Karsten Weis (University of California, Berkeley), Susan Wente (Vanderbilt University

Medical Center), Pat Williamson (University of Massachusetts, Amherst)

Chapter 13: Scott Emr (University of California, San Diego), Ben Glick (University of Chicago), Ari Helenius (Swiss Federal Institute of Technology Zürich, Switzerland), Ira Mellman (Yale University), Hugh Pelham (The Medical Research Council, Cambridge), Giampietro Schiavo (London Research Institute), Graham Warren (Yale University), Marino Zerial (Max Planck Institute of Molecular Cell Biology and Genetics, Frankfurt am Main)

Chapter 14: Michael Gray (Dalhousie University), Andrew Halestrap (University of Bristol, UK), Werner Kühlbrandt (Max Planck Institute of Biophysics, Frankfurt am Main), Craig Thompson (Abramson Family Cancer Research Institute, University of Pennsylvania), Michael Yaffe (University of California, San Diego)

Chapter 15: Nicholas Harberd [substantial contribution] (John Innes Centre, UK), Henry Bourne (University of California, San Francisco), Dennis Bray (University of Cambridge), James Briscoe (National Institute for Medical Research, UK), James Ferrell (Stanford University), Matthew Freeman (Laboratory of Molecular Biology, UK), Alfred Gilman (The University of Texas Southwestern Medical Center), Sankar Ghosh (Yale University School of Medicine), Alan Hall (Memorial Sloan-Kettering Cancer Center), Carl-Henrik Heldin (Ludwig Institute for Cancer Research, Sweden), Robin Irvine (University of Cambridge), Michael Karin (University of California, San Diego), Elliott Meyerowitz (California Institute of Technology), Roel Nusse (Stanford University), Tony Pawson (Mount Sinai Hospital, Toronto), Julie Pitcher (University College London), Len Stephens (The Babraham Institute, UK)

Chapter 16: Julie Theriot [major contribution] (Stanford University), Henry Bourne (University of California, San Francisco), Larry Goldstein (University of California, San Diego), Alan Hall (MRC Laboratory for Molecular Biology and Cell Biology, UK), Joe Howard (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden), Laura Machesky (The University of Birmingham, UK), Timothy Mitchison (Harvard Medical School), Ronald Vale (University of California, San Francisco)

Chapter 17: David Morgan [major contribution] (University of California, San Francisco), Arshad Desai (University of California, San Diego), Bruce Edgar (Fred Hutchinson Cancer Research Center, Seattle), Michael Glotzer (University of Chicago), Rebecca Heald (University of California, Berkeley), Eric Karsenti (European Molecular Biology Laboratory, Germany), Kim Nasmyth (University of Oxford), Jonathan Pines (Gurdon Institute, Cambridge), Charles Sherr (St. Jude Children's Hospital)

Chapter 18: Xiaodong Wang [substantial contribution] (The University of Texas Southwestern Medical School), Jerry Adams (The Walter and Eliza Hall Institute of Medical Research, Australia), Douglas Green (St. Jude Children's Hospital), Shigekazu Nagata (Kyoto University, Japan)

Chapter 19: Jeffrey Axelrod (Stanford University Medical Center), Walter Birchmeier (Max-Delbrück Center for Molecular Medicine, Germany), Keith Burridge (University of North Carolina, Chapel Hill), John Couchman (Imperial College, UK), Caroline Damsky (University of California, San Francisco), Matthias Falk (Lehigh University), David Garrod (University of Manchester, UK), Daniel Goodenough (Harvard Medical School), Martin Humphries (University of Manchester, UK), Richard Hynes (Massachusetts Institute of Technology), Ken Keegstra (Michigan State University), Morgan Sheng (Massachusetts Institute of Technology), Charles Streuli (University of Manchester, UK), Masatoshi Takeichi (RIKEN Kobe Institute, Japan), Kenneth Yamada (National Institutes of Health)

Chapter 20: Laura Attardi [substantial contribution] (Stanford University), Anton Berns (Netherlands Cancer Institute, The Netherlands), Michael Bishop (University of California, San Francisco), Fred Bunz (Johns Hopkins), Johann De-Bono (The Institute of Cancer Research, UK), John Dick (University of Toronto, Canada), Paul Edwards (University of Cambridge), Douglas Hanahan (University of California, San Francisco), Joseph Lipsick (Stanford University School of Medicine), Scott Lowe (Cold Spring Harbor Laboratory), Bruce Ponder (University of Cambridge), Craig Thompson (University of Pennsylvania), Ian Tomlinson (Cancer Research, UK), Robert Weinberg (Massachusetts Institute of Technology)

Chapter 21: Patricia Calarco (University of California, San Francisco), John Carroll (University College London), Abby Dernburg (University of Califonia, Berkeley), Scott Hawley (Stowers Institute for Medical Research, Kansas City), Neil Hunter (University of California, Davis), Nancy Kleckner (Harvard University), Anne McLaren (Wellcome/ Cancer Research Campaign Institute, Cambridge), Diana Myles (University of California, Davis), Terry Orr-Weaver (Massachusetts Institute of Technology), Renee Reijo (University of California, San Francisco), Gerald Schatten (Pittsburgh Development Center), Azim Surani (The Gurdon Institute, UK), Paul Wassarman (Mount Sinai School of Medicine)

Chapter 22: Julie Ahringer (The Gurdon Institute, UK), Konrad Basler (University of Zürich, Switzerland), Richard Harland (University of California, Berkeley), Brigid Hogan (Duke University), Kenneth Irvine (Rutgers University), Daniel St. Johnson (The Gurdon Institute, UK), Elliott Meyerowitz (California Institute of Technology), William McGinnis (University of California, San Diego), Elizabeth Robertson (The Wellcome Trust Centre for Human Genetics, UK), Francois Schweisguth (French National Centre for Scientific Research, France), Jim Smith (The Gurdon Institute, UK), Nicolas Tapon (London Research Institute)

Chapter 23: Ralf Adams (London Research Institute), Hans Clevers (Hubrecht Institute, The Netherlands), Jeffrey Gordon (Washington University, St. Louis), Holger Gerhardt (London Research Institute), Simon Hughes (Kings College, UK), Daniel Louvard (Institut Curie, France), Bjorn Olsen (Harvard Medical School), Stuart Orkin (Harvard Medical School), Thomas Reh (University of Washington, Seattle), Austin Smith (University of Edinburgh, UK), Charles Streuli (The University of Manchester, UK), Fiona Watt (Cancer Research Institute, UK)

Chapter 24: Julie Theriot [major contribution] (Stanford University), Michael Bishop (University of California, San Francisco), Harald von Boehmer (Harvard Medical School), Lynn Enquist (Princeton University), Stan Falkow (Stanford University), Douglas Fearon (University of Cambridge), Lewis Lanier (University of California, San Francisco), Richard Locksley (University of California, San Francisco), Daniel Portnoy (University of California, Berkeley), Caetano Reis e Sousa (Cancer Research, UK), Ralph Steinman (The Rockefeller University), Gary Ward (University of Vermont)

Chapter 25: Harald von Boehmer (Harvard Medical School), Douglas Fearon (University of Cambridge), Lewis Lanier (University of California, San Francisco), Philippa Marrack (National Jewish Medical and Research Center, Denver), Michael Neuberger (University of Cambridge), Michael Nussenzweig (Rockefeller University), William Paul (National Institutes of

Health), Klaus Rajewsky (Harvard Medical School), Caetano Reis e Sousa (Cancer Research, UK), Ralph Steinman (The Rockefeller University).

Glossary Eleanor Lawrence, Sherry Granum

Readers David Kashatus (Duke University), Emmanuel Kreidl (University of Vienna, Austria), Nick Rudzik (University of Toronto, Canada), Dea Shahinas (University of Toronto, Canada)

First, second, third, and fourth editions David Agard (University of California, San Francisco), Michael Akam (University of Cambridge), Fred Alt (CBR Institute for Biomedical Research, Boston), Linda Amos (MRC Laboratory of Molecular Biology, Cambridge), Raul Andino (University of California, San Francisco), Clay Armstrong (University of Pennsylvania), Martha Arnaud (University of California, San Francisco), Spyros Artavanis-Tsakonas (Harvard Medical School), Michael Ashburner (University of Cambridge), Jonathan Ashmore (University College London), Tayna Awabdy (University of California, San Francisco), Peter Baker (deceased), David Baldwin (Stanford University), Michael Banda (University of California, San Francisco), Cornelia Bargmann (University of California, San Francisco), Ben Barres (Stanford University), David Bartel (Massachusetts Institute of Technology), Michael Bennett (Albert Einstein College of Medicine), Darwin Berg (University of California, San Diego), Merton Bernfield (Harvard Medical School), Michael Berridge (The Babraham Institute, Cambridge), David Birk (UMNDJ—Robert Wood Johnson Medical School), Michael Bishop (University of California, San Francisco), Tim Bliss (National Institute for Medical Research, London), Hans Bode (University of California, Irvine), Piet Borst (Jan Swammerdam Institute, University of Amsterdam), Henry Bourne (University of California, San Francisco), Alan Boyde (University College London), Martin Brand (University of Cambridge), Carl Branden (deceased), Andre Brandli (Swiss Federal Institute of Technology, Zurich), Mark Bretscher (MRC Laboratory of Molecular Biology, Cambridge), Marianne Bronner-Fraser (California Institute of Technology), Robert Brooks (King's College London), Barry Brown (King's College London), Michael Brown (University of Oxford), Steve Burden (New York University of Medicine), Max Burger (University of Basel), Stephen Burley (SGX Pharmaceuticals), Keith Burridge (University of North Carolina, Chapel Hill), John Cairns (Radcliffe Infirmary, Oxford), 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), Tom Cavalier-Smith (King's College London), Pierre Chambon (University of Strasbourg), Enrico Coen (John Innes Institute, Norwich, UK), Philip Cohen (University of Dundee, Scotland), Robert Cohen (University of California, San Francisco), Stephen Cohen (EMBL Heidelberg, Germany), Roger Cooke (University of California, San Francisco), John Cooper (Washington University School of Medicine, St. Louis), Nancy Craig (Johns Hopkins University), James Crow (University of Wisconsin, Madison), Stuart Cull-Candy (University College London), Leslie Dale (University College London), Michael Dexter (The Wellcome Trust, UK), Anthony DeFranco (University of California, San Francisco), Christopher Dobson (University of Cambridge), Russell Doolittle (University of California, San Diego), Julian Downward (Cancer Research, UK), Keith Dudley (King's College London), Graham Dunn (MRC Cell Biophysics Unit, London), Jim Dunwell (John Innes Institute, Norwich, UK), Paul Edwards (University of Cambridge), Robert Edwards (University of California, San Francisco), David Eisenberg (University of California, Los Angeles), Sarah Elgin (Washington University, St. Louis), Ruth Ellman (Institute of Cancer Research, Sutton, UK), Beverly Emerson (The Salk Institute), Charles Emerson (University of Virginia), Scott Emr (University of California, San Diego), Sharyn Endow (Duke University), Tariq Enver (Institute of Cancer Research, London), David Epel (Stanford University), Gerard Evan (University of California, Comprehensive Cancer Center), Ray Evert (University of Wisconsin, Madison), Stanley Falkow (Stanford University), Gary Felsenfeld (National Institutes of Health), Stuart Ferguson (University of Oxford), Christine Field (Harvard Medical School), Gary Firestone (University of California, Berkeley), Gerald Fischbach (Columbia University), Robert Fletterick (University of California, San Francisco), Harvey Florman (Tufts University), Judah Folkman (Harvard Medical School), Larry Fowke (University of Saskatchewan, Canada), Daniel Friend (University of California, San Francisco), Elaine Fuchs (University of Chicago), Joseph Gall (Yale University), Richard Gardner (University of Oxford), Anthony Gardner-Medwin (University College London), Peter Garland (Institute of Cancer Research, London), Walter Gehring (Biozentrum, University of Basel), Benny Geiger (Weizmann Institute of Science, Rehovot, Israel), Larry Gerace (The Scripps Research Institute), John Gerhart (University of California, Berkeley), Günther Gerisch (Max Planck Institute of Biochemistry, Martinsried), Frank Gertler (Massachusetts Institute of Technology), Sankar Ghosh (Yale University School of Medicine), Reid Gilmore (University of Massachusetts, Amherst), Bernie Gilula (deceased), Charles Gilvarg (Princeton University), Michael Glotzer (University of Vienna, Austria), Larry Goldstein (University of California, San Diego), Bastien Gomperts (University College Hospital Medical School, London), Daniel Goodenough (Harvard Medical School), Jim Goodrich (University of Colorado, Boulder), Peter Gould (Middlesex Hospital Medical School, London), Alan Grafen (University of Oxford), Walter Gratzer (King's College London), Howard Green (Harvard University), Michael Green (University of Massachusetts, Amherst), 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, Canberra), Christine Guthrie (University of California, San Francisco), Ernst Hafen (Universitat Zurich), David Haig (Harvard University), Alan Hall (MRC Laboratory for Molecular Biology and Cell Biology, London), Jeffrey Hall (Brandeis University), John Hall (University of Southampton, UK), Zach Hall (University of California, San Francisco), David Hanke (University of Cambridge), Nicholas Harberd (John Innes Centre, Norwich, UK), Graham Hardie (University of Dundee, Scotland), Richard Harland (University of California, Berkeley), Adrian Harris (Cancer Research, UK), John Harris (University of Otago, New Zealand), Stephen Harrison (Harvard University), Leland Hartwell (University of Washington, Seattle), Adrian Harwood (MRC Laboratory for Molecular Cell Biology and Cell Biology Unit, London), John Heath (University of Birmingham, UK), Ari Helenius (Yale University), Richard Henderson (MRC Laboratory of Molecular Biology, Cambridge), Glenn Herrick (University of Utah), Ira Herskowitz (deceased), Bertil Hille (University of Washington, Seattle), Alan Hinnebusch (National Institutes of Health, Bethesda), Nancy Hollingsworth (State University of New York, Stony Brook), Leroy Hood (Institute for Systems Biology, Seattle), John Hopfield (Princeton University), Robert Horvitz (Massachusetts Institute of Technology), David Housman (Massachusetts Institute of Technology), Jonathan Howard (University of Washington, Seattle), James Hudspeth (The Rockefeller University), Simon Hughes (King's College London), Martin Humphries (University of Manchester, UK), Tim Hunt

(Cancer Research, UK), Laurence Hurst (University of Bath, UK), Jeremy Hyams (University College London), Tony Hyman (Max Planck Institute of Molecular Cell Biology & Genetics, Dresden), Richard Hynes (Massachusetts Institute of Technology), Philip Ingham (University of Sheffield, UK), Norman Iscove (Ontario Cancer Institute, Toronto), David Ish-Horowicz (Cancer Research, UK), Lily Jan (University of California, San Francisco), Charles Janeway (deceased), Tom Jessell (Columbia University), Arthur Johnson (Texas A & M University), Andy Johnston (John Innes Institute, Norwich, UK), E.G. Jordan (Queen Elizabeth College, London), Ron Kaback (University of California, Los Angeles), 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, Cambridge), Cynthia Kenyon (University of California, San Francisco), Roger Keynes (University of Cambridge), Judith Kimble (University of Wisconsin, Madison), 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), Eugene Koonin (National Institutes of Health), Juan Korenbrot (University of California, San Francisco), Tom Kornberg (University of California, San Francisco), Stuart Kornfeld (Washington University, St. Louis), Daniel Koshland (University of California, Berkeley), Marilyn Kozak (University of Pittsburgh), Mark Krasnow (Stanford University), Werner Kühlbrandt (Max Planck Institute for Biophysics, Frankfurt am Main), John Kuriyan (University of California, Berkeley), Robert Kypta (MRC Laboratory for Molecular Cell Biology, London), Peter Lachmann (MRC Center, Cambridge), Ulrich Laemmli (University of Geneva, Switzerland), Trevor Lamb (University of Cambridge), Hartmut Land (Cancer Research, UK), David Lane (University of Dundee, Scotland), Jane Langdale (University of Oxford), Jay Lash (University of Pennsylvania), Peter Lawrence (MRC Laboratory of Molecular Biology, Cambridge), Paul Lazarow (Mount Sinai School of Medicine), Robert J. Lefkowitz (Duke University), Michael Levine (University of California, Berkeley), Warren Levinson (University of California, San Francisco), Alex Levitzki (Hebrew University, Israel), Ottoline Leyser (University of York, UK), Joachim Li (University of California, San Francisco), Tomas Lindahl (Cancer Research, UK), Vishu Lingappa (University of California, San Francisco), Jennifer Lippincott-Schwartz (National Institutes of Health, Bethesda), Dan Littman (New York University School of Medicine), Clive Lloyd (John Innes Institute, Norwich, UK), Richard Losick (Harvard University), Robin Lovell-Badge (National Institute for Medical Research, London), Shirley Lowe (University of California, San Francisco), Laura Machesky (University of Birmingham, UK), James Maller (University of Colorado Medical School), Tom Maniatis (Harvard University), Colin Manoil (Harvard Medical School), Philippa Marrack (National Jewish Medical and Research Center, Denver), Mark Marsh (Institute of Cancer Research, London), Gail Martin (University of California, San Francisco), Paul Martin (University College London), Joan Massagué (Memorial Sloan-Kettering Cancer Center), Brian McCarthy (University of California, Irvine), Richard McCarty (Cornell University), William McGinnis (University of California, Davis), Anne McLaren (Wellcome/Cancer Research Campaign Institute, Cambridge), Frank McNally (University of California, Davis), Freiderick Meins (Freiderich Miescher Institut, Basel), Stephanie Mel (University of California, San Diego), Ira Mellman (Yale University), Barbara Meyer (University of California, Berkeley), Elliot Meyerowitz (California Institute of Technology), Chris Miller (Brandeis University), Robert Mishell (University of Birmingham, UK), Avrion Mitchison (University College London), N.A. Mitchison (University College London), Tim Mitchison (Harvard Medical School), Peter Mombaerts (The Rockefeller University), Mark Mooseker (Yale University), David Morgan (University of California, San Francisco), Michelle Moritz (University of California, San Francisco), Montrose Moses (Duke University), Keith Mostov (University of California, San Francisco), Anne Mudge (University College London), Hans Müller-Eberhard (Scripps Clinic and Research Institute), Alan Munro (University of Cambridge), J. Murdoch Mitchison (Harvard University), Richard Myers (Stanford University), Diana Myles (University of California, Davis), Andrew Murray (Harvard University), Mark E. Nelson (University of Illinois, Urbana-Champaign), Michael Neuberger (MRC Laboratory of Molecular Biology, Cambridge), Walter Neupert (University of Munich, Germany), David Nicholls (University of Dundee, Scotland), Suzanne Noble (University of California, San Francisco), Harry Noller (University of California, Santa Cruz), Jodi Nunnari (University of California, Davis), Paul Nurse (Cancer Research, UK), Duncan O'Dell (deceased), Patrick O'Farrell (University of California, San Francisco), Maynard Olson (University of Washington, Seattle), Stuart Orkin (Children's Hospital, Boston), Terri Orr-Weaver (Massachusetts Institute of Technology), Erin O'Shea (Harvard University), William Otto (Cancer Research, UK), John Owen (University of Birmingham, UK), Dale Oxender (University of Michigan), George Palade (deceased), Barbara Panning (University of California, San Francisco), Roy Parker (University of Arizona, Tucson), William W. Parson (University of Washington, Seattle), Terence Partridge (MRC Clinical Sciences Centre, London), William E. Paul (National Institutes of Health), Tony Pawson (Mount Sinai Hospital, Toronto), Hugh Pelham (MRC Laboratory of Molecular Biology, Cambridge), Robert Perry (Institute of Cancer Research, Philadelphia), Greg Petsko (Brandeis University), Gordon Peters (Cancer Research, UK), David Phillips (The Rockefeller University), Jeremy Pickett-Heaps (The University of Melbourne, Australia), Julie Pitcher (University College London), Jeffrey Pollard (Albert Einstein College of Medicine), Tom Pollard (Yale University), Bruce Ponder (University of Cambridge), Dan Portnoy (University of California, Berkeley), James Priess (University of Washington, Seattle), Darwin Prockop (Tulane University), Dale Purves (Duke University), Efraim Racker (Cornell University), Jordan Raff (Wellcome/CRC Institute, Cambridge), Klaus Rajewsky (University of Cologne, Germany), George Ratcliffe (University of Oxford), Elio Raviola (Harvard Medical School), Martin Rechsteiner (University of Utah, Salt Lake City), David Rees (National Institute for Medical Research, London), Louis Reichardt (University of California, San Francisco), Fred Richards (Yale University), Conly Rieder (Wadsworth Center, Albany), Phillips Robbins (Massachusetts Institute of Technology), Elaine Robson (University of Reading, UK), Robert Roeder (The Rockefeller University), Joel Rosenbaum (Yale University), Janet Rossant (Mount Sinai Hospital, Toronto), Jesse Roth (National Institutes of Health), Jim Rothman (Memorial Sloan-Kettering Cancer Center), Erkki Ruoslahti (La Jolla Cancer Research Foundation), Gary Ruvkun (Massachusetts General Hospital), David Sabatini (New York University), Alan Sachs (University of California, Berkeley), Alan Sachs (University of California, Berkeley), Edward Salmon (University of North Carolina, Chapel Hill), Joshua Sanes (Harvard University), Peter Sarnow (Stanford University), Lisa Satterwhite (Duke University Medical School), Howard Schachman (University of California, Berkeley), Gottfried Schatz (Biozentrum, University of Basel), Randy Schekman (University of California, Berkeley), Richard Scheller (Stanford University), Giampietro Schiavo (Cancer Research, UK), Joseph Schlessinger (New York University Medical Center), Michael Schramm (Hebrew University), Robert Schreiber (Scripps Clinic and Research Institute), James Schwartz (Columbia

University), Ronald Schwartz (National Institutes of Health), François Schweisguth (ENS, Paris), John Scott (University of Manchester, UK), John Sedat (University of California, San Francisco), Peter Selby (Cancer Research, UK), Zvi Sellinger (Hebrew University, Israel), Gregg Semenza (Johns Hopkins University), Philippe Sengel (University of Grenoble, France), Peter Shaw (John Innes Institute, Norwich, UK), Michael Sheetz (Columbia University), David Shima (Cancer Research, UK), Samuel Silverstein (Columbia University), Kai Simons (Max Planck Institute of Molecular Cell Biology and Genetics, Dresden), Melvin I. Simon (California Institute of Technology), Jonathan Slack (Cancer Research, UK), Alison Smith (John Innes Institute, Norfolk, UK), John Maynard Smith (University of Sussex, UK), 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 Standring (University of California, San Francisco), Margaret Stanley (University of Cambridge), Martha Stark (University of California, San Francisco), Wilfred Stein (Hebrew University, Israel), Malcolm Steinberg (Princeton University), Paul Sternberg (California Institute of Technology), Chuck Stevens (The Salk Institute), Murray Stewart (MRC Laboratory of Molecular Biology, Cambridge), Monroe Strickberger (University of Missouri, St. Louis), Robert Stroud (University of California, San Francisco), Michael Stryker (University of California, San Francisco), William Sullivan (University of California, Santa Cruz), Daniel Szollosi (Institut National de la Recherche Agronomique, France), Jack Szostak (Massachusetts General Hospital), Masatoshi Takeichi (Kyoto University), Clifford Tabin (Harvard Medical School), Diethard Tautz (University of Cologne, Germany), Julie Theriot (Stanford University), Roger Thomas (University of Bristol, UK), Vernon Thornton (King's College London), Cheryll Tickle (University of Dundee, Scotland), Jim Till (Ontario Cancer Institute, Toronto), Lewis Tilney (University of Pennsylvania), Nick Tonks (Cold Spring Harbor Laboratory), Alain Townsend (Institute of Molecular Medicine, John Radcliffe Hospital, Oxford), Paul Travers (Anthony Nolan Research Institute, London), Robert Trelstad (UMDNJ, Robert Wood Johnson Medical School), Anthony Trewavas (Edinburgh University, Scotland), Nigel Unwin (MRC Laboratory of Molecular Biology, Cambridge),Victor Vacquier (University of California, San Diego), Harry van der Westen (Wageningen, The Netherlands), Tom Vanaman (University of Kentucky), Harold Varmus (Sloan-Kettering Institute), Alexander Varshavsky (California Institute of Technology), Madhu Wahi (University of California, San Francisco), Virginia Walbot (Stanford University), Frank Walsh (Glaxo-Smithkline-Beecham, UK), Trevor Wang (John Innes Institute, Norwich, UK), Yu-Lie Wang (Worcester Foundation for Biomedical Research), Anne Warner (University College London), Graham Warren (Yale University School of Medicine), Paul Wassarman (Mount Sinai School of Medicine), Fiona Watt (Cancer Research, UK), Clare Waterman-Storer (The Scripps Research Institute), Fiona Watt (Cancer Research, UK), John Watts (John Innes Institute, Norwich, UK), Klaus Weber (Max Planck Institute for Biophysical Chemistry, Göttingen), Martin Weigert (Institute of Cancer Research, Philadelphia), Harold Weintraub (deceased), Karsten Weis (University of California, Berkeley), Irving Weissman (Stanford University), Jonathan Weissman (University of California, San Francisco), Norman Wessells (Stanford University), Judy White (University of Virginia), Steven West (Cancer Research, UK), William Wickner (Dartmouth College), Michael Wilcox (deceased), Lewis T. Williams (Chiron Corporation), Keith Willison (Chester Beatty Laboratories, London), John Wilson (Baylor University), Alan Wolffe (deceased), Richard Wolfenden (University of North Carolina, Chapel Hill), Sandra Wolin (Yale University School of Medicine), Lewis Wolpert (University College London), Rick Wood (Cancer Research, UK), Abraham Worcel (University of Rochester), Nick Wright (Cancer Research, UK), John Wyke (Beatson Institute for Cancer Research, Glasgow), Keith Yamamoto (University of California, San Francisco), Charles Yocum (University of Michigan, Ann Arbor), Peter Yurchenco (UMDNJ, Robert Wood Johnson Medical School), Rosalind Zalin (University College London), Patricia Zambryski (University of California, Berkeley).

A Note to the Reader

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 deals with the principles of the main experimental methods for investigating cells. It is not necessary to read these two chapters in order to understand the later chapters, but a reader will find it a useful reference.

Part IV discusses the internal organization of the cell.

Part V follows the behavior of cells in multicellular systems, starting with cell–cell junctions and extracellular matrix and concluding with two chapters on the immune system.

End-of-Chapter Problems

A selection of problems, written by John Wilson and Tim Hunt, now appears in the text at the end of chapters 1–20. The complete solutions to these problems can be found in *Molecular Biology of the Cell, Fifth Edition: The Problems Book*.

References

A concise list of selected references is included at the end of each chapter. These are arranged in alphabetical order under the main chapter section headings. These references frequently include the original papers in which important discoveries were first reported. Chapter 8 includes several tables giving the dates of crucial developments along with the names of the scientists involved. Elsewhere in the book the policy has been to avoid naming individual scientists.

Media Codes

Media codes are integrated throughout the text to indicate when relevant videos and animations are available on the DVD-ROM. The four-letter codes are enclosed in brackets and highlighted in color, like this <ATCG>. The interface for the *Cell Biology Interactive* media player on the DVD-ROM contains a window where you enter the 4-letter code. When the code is typed into the interface, the corresponding media item will load into the media player.

Glossary Terms

Throughout the book, **boldface type** has been used to highlight key terms at the point in a chapter where the main discussion of them occurs. *Italic* is used to set off important terms with a lesser degree of emphasis. At the end of the book is the expanded **glossary**, covering technical terms that are part of the common currency of cell biology; it is intended as a first resort for a reader who encounters an unfamiliar term used without explanation.

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 lower case; in yet others (most mouse genes), with the first letter in upper case and rest in lower case; or (as in *Drosophila*) with different combinations of

upper and lower case, according to whether the first mutant allele to be discovered gave a dominant or recessive phenotype. Conventions for naming protein products are equally varied.

This typographical chaos drives everyone crazy. It is not just tiresome and absurd; it is also unsustainable. We cannot independently define a fresh convention for each of the next few million species whose genes we may wish to study. 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 they are all equivalent for the purposes of the discussion. What convention then should we use?

We have decided in this book to cast aside the conventions for individual species and follow a uniform rule: we write all gene names, like the names of people and places, with the first letter in upper case and the rest in lower case, but all in italics, thus: *Apc*, *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: Apc, 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 upper case if it is usual to do so (*LacZ, RecA, HoxA4*). We use no hyphen to separate added letters or numbers from the rest of the name. 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 lower-case letter (actin, hemoglobin, catalase), like the names of ordinary substances (cheese, nylon), unless they 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 (actin, GFP, etc.). For the corresponding gene names in all these cases, we shall nevertheless follow our standard rule: *Actin*, *Hemoglobin*, *Catalase*, *Bmp4*, *Gfp*. Occasionally in our book we need to highlight a protein name by setting it in italics for emphasis; the intention will generally be clear from the context.

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

	SPECIES-SPECIFIC CONVENTION		UNIFIED CONVENTION USED IN THIS BOOK	
ORGANISM	GENE	PROTEIN	GENE	PROTEIN
Mouse	*Hoxa4*	Hoxa4	*HoxA4*	HoxA4
	Bmp4	BMP4	*Bmp4*	BMP4
	integrin α-1, Itgα1	integrin α1	*Integrin α1, Itgα1*	integrin α1
Human	*HOXA4*	HOXA4	*HoxA4*	HoxA4
Zebrafish	*cyclops, cyc*	Cyclops, Cyc	*Cyclops, Cyc*	Cyclops, Cyc
Caenorhabditis	*unc-6*	UNC-6	*Unc6*	Unc6
Drosophila	*sevenless, sev* (named after recessive mutant phenotype)	Sevenless, SEV	*Sevenless, Sev*	Sevenless, Sev
	Deformed, Dfd (named after dominant mutant phenotype)	Deformed, DFD	*Deformed, Dfd*	Deformed, Dfd
Yeast				
Saccharomyces cerevisiae (budding yeast)	*CDC28*	Cdc28, Cdc28p	*Cdc28*	Cdc28
Schizosaccharomyces pombe (fission yeast)	*Cdc2*	Cdc2, Cdc2p	*Cdc2*	Cdc2
Arabidopsis	*GAI*	GAI	*Gai*	GAI
E. coli	*uvrA*	UvrA	*UvrA*	UvrA

Ancillaries

Molecular Biology of the Cell, Fifth Edition: The Problems Book
by John Wilson and Tim Hunt (ISBN: 978-0-8153-4110-9)
The Problems Book is designed to help students appreciate the ways in which experiments and simple calculations can lead to an understanding of how cells work. It provides problems to accompany Chapters 1–20 of *Molecular Biology of the Cell*. Each chapter of problems is divided into sections that correspond to those of the main textbook and review key terms, test for understanding basic concepts, and pose research-based problems. *Molecular Biology of the Cell, Fifth Edition: The Problems Book* should be useful for homework assignments and as a basis for class discussion. It could even provide ideas for exam questions. Solutions for all of the problems are provided on the CD-ROM which accompanies the book. Solutions for the end-of-chapter problems in the main textbook are also found in *The Problems Book*.

***MBoC5* Media DVD-ROM**
The DVD included with every copy of the book contains the figures, tables, and micrographs from the book, pre-loaded into PowerPoint® presentations, one for each chapter. A separate folder contains individual versions of each figure, table, and micrograph in JPEG format. The panels are available in PDF format. There are also over 125 videos, animations, molecular structure tutorials, and high-resolution micrographs on the DVD. The authors have chosen to include material that not only reinforces basic concepts but also expands the content and scope of the book. The multimedia can be accessed either as individual files or through the *Cell Biology Interactive* media player. As discussed above, the media player has been programmed to work with the Media Codes integrated throughout the book. A complete table of contents and overview of all electronic resources is contained in the *MBoC5 Media Viewing Guide,* a PDF file located on the root level of the DVD-ROM and in the Appendix of the media player. The DVD-ROM also contains Chapters 21–25 which cover multicellular systems. The chapters are in PDF format and can be easily printed or searched using Adobe® Acrobat® Reader or other PDF software.

Teaching Supplements
Upon request, teaching supplements for *Molecular Biology of the Cell* are available to qualified instructors.

MBoC5 Transparency Set
Provides 200 full-color overhead acetate transparencies of the most important figures from the book.

MBoC5 Test Questions
A selection of test questions will be available. Written by Kirsten Benjamin (Amyris Biotechnologies, Emeryville, California) and Linda Huang (University of Massachusetts, Boston), these thought questions will test students' understanding of the chapter material.

MBoC5 Lecture Outlines
Lecture outlines created from the concept heads for the text are provided.

Garland Science Classwire™
All of the teaching supplements on the DVD-ROM (these include figures in PowerPoint and JPEG format; Chapters 21–25 in PDF format; 125 videos, animations, and movies) and the test questions and lecture outlines are available to qualified instructors online at the Garland Science Classwire™ Web site. Garland Science Classwire™ offers access to other instructional resources from all of the Garland Science textbooks, and provides free online course management tools. For additional information, please visit http://www.classwire.com/garlandscience or e-mail science@garland.com. (*Classwire* is a trademark of Chalkfree, Inc.)

I

INTRODUCTION TO THE CELL

Part I
Chapters