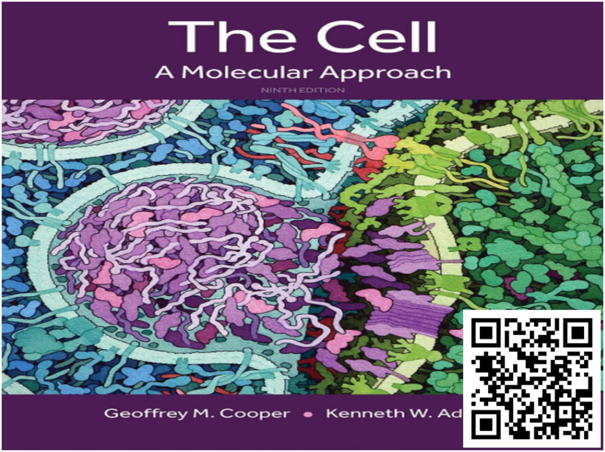
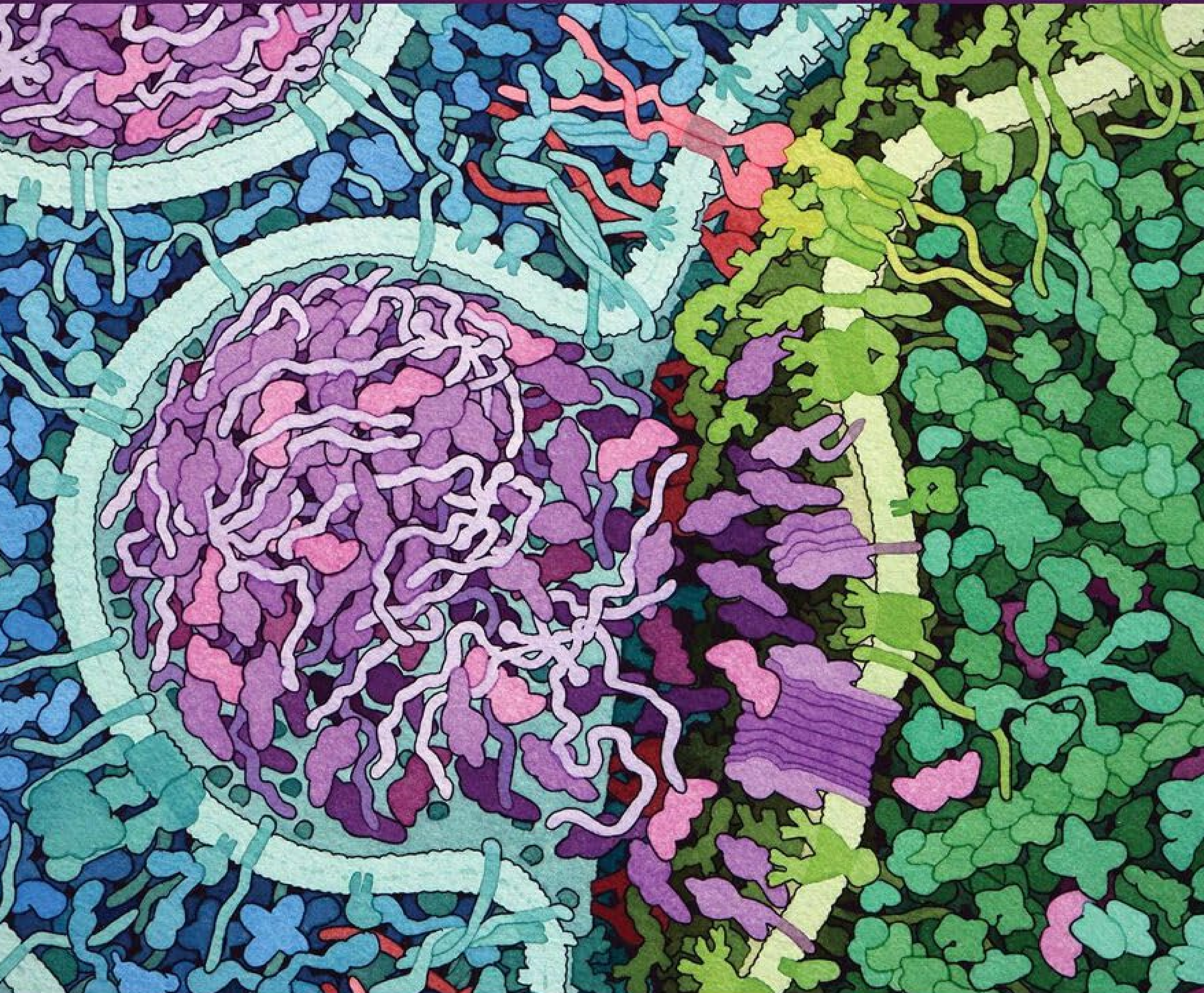

The Cell
A Molecular Approach
NINTH EDITION
Geoffrey M. Cooper • Kenneth W. Ad

# The Cell

## A Molecular Approach

NINTH EDITION



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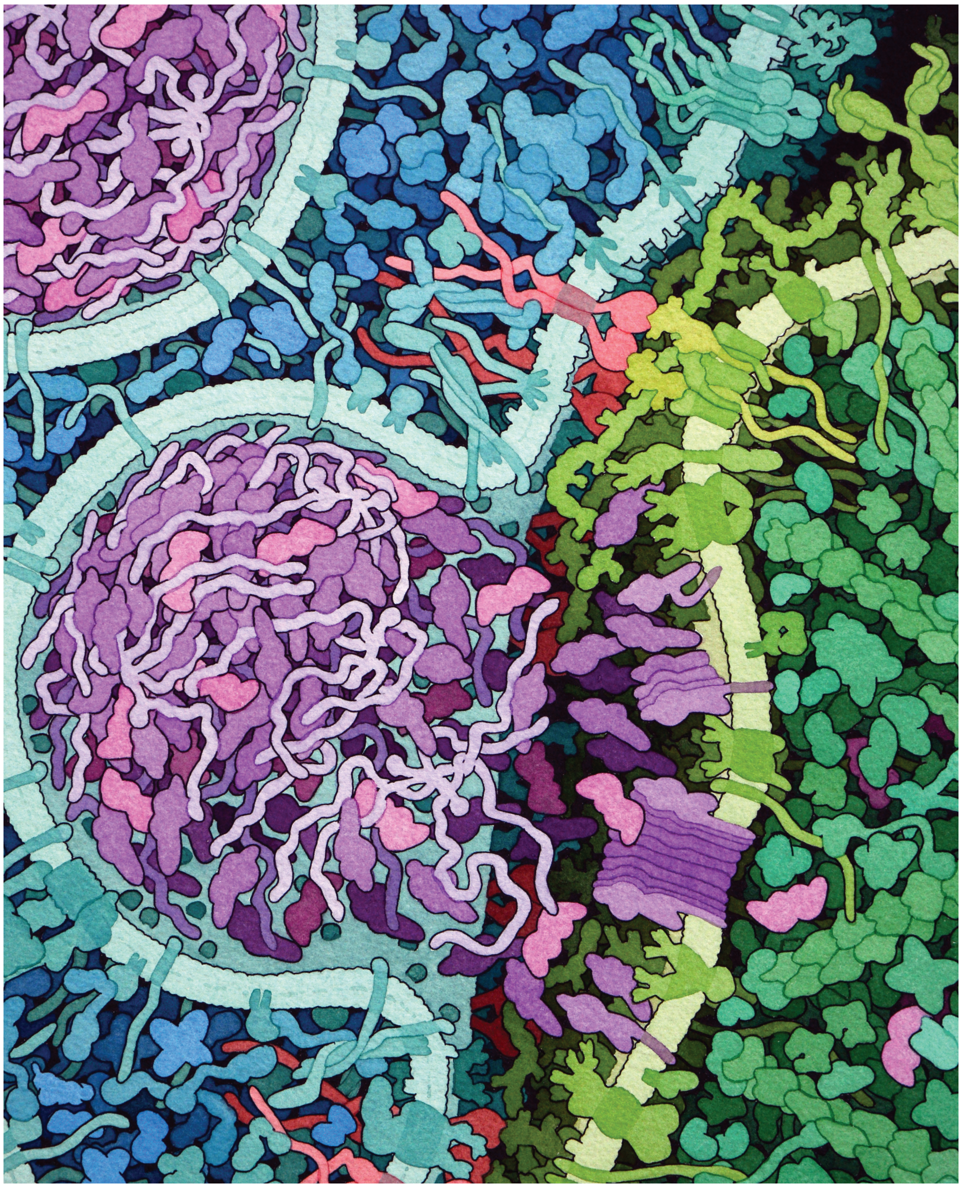

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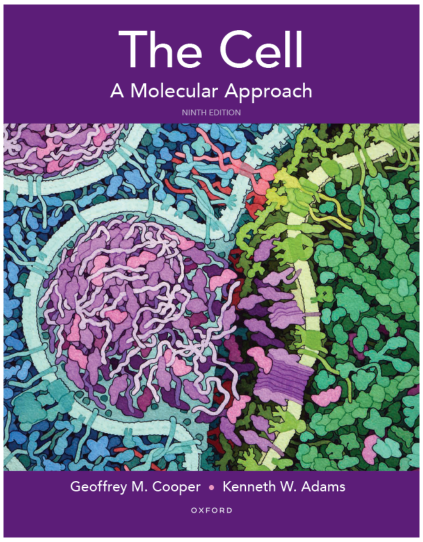


**The Cover**

The cover image shows the surface of a CART cell (left) recognizing the surface of an acute lymphoblastic leukemia (ALL) cell (right) and the release of toxic factors from the CART cell that penetrate and kill the leukemia. CART cells are engineered T cells that are remarkably effective for this particular form of cancer, leading to remission for most of the patients.

**The Artist**

David S. Goodsell, is a Professor of Computational Biology at the Scripps Research Institute and Research Professor at Rutgers University, where he is the Scientific Outreach Lead at the RCSB Protein Data Bank. His illustrated books, *The Machinery of Life* and *Our Molecular Nature*, explore biological molecules and their diverse roles within living cells, and his book *Bionanotechnology: Lessons from Nature*, presents the growing connections between biology and nanotechnology. More information may be found at: https://ccsb.scripps.edu/goodsell

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# About the Authors

**Geoffrey M. Cooper** is a Professor of Biology Emeritus at Boston University. Receiving a Ph.D. in Biochemistry from the University of Miami in 1973, he pursued postdoctoral work with Howard Temin at the University of Wisconsin, where he developed gene transfer assays to characterize the proviral DNAs of Rous sarcoma virus and related retroviruses. He then joined the faculty of Dana-Farber Cancer Institute and Harvard Medical School in 1975, where he pioneered the discovery of oncogenes in human cancers. He moved to Boston University as Chair of Biology in 1998 and subsequently served as Associate Dean of the Faculty for Natural Sciences, as well as teaching undergraduate cell biology and continuing his research on the roles of oncogenes in the signaling pathways that regulate cell proliferation and programmed cell death. He has authored over 100 research papers and two textbooks on cancer, as well as a series of medical thrillers based on his academic career.

**Kenneth W. Adams** is an Associate Professor of Biology at Bridgewater State University. He earned a Ph.D. in Molecular Biology, Cell Biology, and Biochemistry from Boston University in 2006, where he investigated the role of Bcl-2 family members in the regulation of apoptosis downstream of PI 3-kinase signaling in the lab of co-author Geoffrey M. Cooper. His subsequent postdoctoral research was conducted with Bradley T. Hyman at Massachusetts General Hospital, where he investigated the mechanisms through which apolipoprotein E and its receptors affect susceptibility to Alzheimer's disease. He then joined the Undergraduate Neuroscience Program at Boston University as a postdoctoral faculty fellow and lecturer, during which his research focused on the transcriptional network that drives neuronal differentiation using PC12 cells as a model. In 2013, he joined the faculty of Bridgewater State University, where he initially continued his focus on the molecular mechanisms that mediate neuronal differentiation but has more recently returned to the Alzheimer's work he conducted during his postdoctoral research. In 2016, Kenneth was awarded the Presidential Award for Distinguished Teaching at Bridgewater State University, where he also serves as the Director of Undergraduate Research.

# Preface

Cell biology is a vast and rapidly progressing field in which discoveries are made at a staggering pace, continuously expanding our understanding of the molecular events that govern cell behavior in physiology as well as cell misbehavior in disease. Likewise, the tools and techniques through which such discoveries are made steadily advance, enabling experimental approaches with ever increasing sophistication. For college-level educators, this raises several pedagogical questions, including: *How can we best guide students toward an understanding of cell biology that aligns with the contemporary field? How do we avoid overwhelming students with never-ending details when many such details are necessary to understand* ***how*** *and* ***why*** *cells work instead of rotely memorizing* ***that*** *cells work? And how can we help students to integrate the product of science—knowledge—with the practice of science—experimentation and data interpretation?* Put another way, cell biology instructors face the challenge of cultivating both the foundational knowledge and analytical skills that students need for their entry into an increasingly complex field. From its First Edition to this Ninth, *The Cell: A Molecular Approach* has been designed to serve as a guide to meet that challenge.

## Organization

The book is divided into four parts. **Part I: Fundamentals and Foundations** summarizes how cells evolved and describers basic model systems and techniques—microscopy and cell fractionation—used throughout cell research. The physical and chemical principles underlying cell structure and function are described, including chemical bonds, the laws of thermodynamics, the ubiquitous role of ATP as an energy source, and the major classes of molecules that make up cells. The key experiments that identified DNA as the hereditary material are reviewed, followed by discussion of discoveries through which the basic factors and steps of gene expression were elucidated. Part I concludes with analysis of essential tools—recombinant DNA and antibodies—that launched research into the molecular mechanisms described throughout Parts II, III, and IV.

**Part II: The Flow of Genetic Information** focuses on the molecular biology of cells and begins by dissecting the types of DNA sequences that make up genomes of diverse organisms and the mechanisms through which genomes are replicated and repaired when damaged. The molecular mechanisms of transcription and RNA processing are then discussed, followed by mechanisms of translation, protein processing, and protein regulation. Additional research tools and techniques that have been particularly critical to characterizing those mechanisms are integrated within the corresponding sections, and the last chapter in Part II introduces methodologies used for large-scale analyses.

**Part III: Subcellular Structures and Functions** includes chapters on the nucleus, cytoplasmic organelles, the cytoskeleton, the plasma membrane, and the extracellular matrix. This part of the book starts with coverage of the nucleus, which puts the molecular biology of Part II within the context of the eukaryotic cell, and then works outward through cytoplasmic organelles and the cytoskeleton to the plasma membrane and the exterior of the cell. These chapters are relatively self-contained, however, and could be used in a different order should that be more appropriate for a particular course.

Finally, **Part IV: Cell Regulation** focuses on the exciting and fast-moving area of cell regulation, including coverage of topics such as cell signaling, the cell cycle, stem cells, and programmed cell death. This part of the book concludes with a chapter on cancer, which synthesizes the consequences of defects in basic cell regulatory mechanisms.

## New to this Edition

This Ninth Edition of *The Cell* is the result of a wholistic review of the previous edition. Not only has the content been updated to keep pace with key advances in the field but several additional changes have been incorporated, stemming from the following goals.

### Expedite Discussion of the Flow of Genetic Information

A major change in this edition relates to its overall organization. The mechanisms that mediate the flow of genetic information arguably represent the most fundamental basis for cellular life, which is reflected by *The Cell*'s dedication of five chapters to this content: Genes and Genomes; Replication, Maintenance, and Repair of Genomic DNA; RNA Synthesis and Processing; Transcriptional Regulation and Epigenetics; and Protein Synthesis, Processing, and Regulation. For this Ninth Edition, Parts I and II have been reorganized to place those five chapters earlier in the table of contents. To do so, the content covered in the Eighth Edition's Chapter 3, Bioenergetics and Metabolism, has been dispersed across several chapters. Given the centrality of the laws of thermodynamics in all cellular events (including the flow of genetic information) and the ubiquitous role of ATP as an energy source to drive those events, these concepts have been combined with discussion of molecules and membranes in Chapter 2, which is newly titled Physical Principles Underlying Cell Structure and Function. Discussion of glycolysis, oxidative phosphorylation, and photosynthesis have been moved to Chapter 12: Mitochondria, Chloroplasts, and Peroxisomes. Additionally, Chapter 5 in the Eighth Edition—Genomics, Proteomics, and Systems Biology—now follows discussion of Protein Synthesis, Processing, and Regulation. Not only does this revision move the chapters related to the flow of genetic information earlier in the book, it also allows students to develop a stronger foundational knowledge of the concepts therein before applying them in the context of methodologies for large-scale analysis discussed in Genomics, Proteomics, and Systems Biology.

### Fill Gaps in Molecular Explanations

In 13 years of teaching Cell Biology, I have been continuously inspired by students' thirst for molecular explanations on **how** and **why** cellular events take place. From questions on how transcription by RNA polymerase II is terminated to why kinases exhibit substrate specificity to how importins pass through the selective barrier of the nuclear pore complex, students are seldom satisfied unless molecular explanations that go beyond rote memorization are provided. Indeed, the recognition that molecular explanations for all cellular events must exist, whether understood by the field or not, and the curiosity to seek out those explanations are essential characteristics of a cell biologist. Thus, an overarching goal while revising this Ninth Edition was to fill in gaps where molecular explanations were less apparent or have changed since the Eighth Edition. Examples of where such details were added include descriptions of transcription termination by RNA polymerase II in Chapter 6, factors that mediate epigenetic inheritance of DNA methylation in Chapter 7, the roles of recognition motifs in kinase–substrate specificity in Chapter 8, and the characteristics of importins that enable their passage through the nuclear pore complex in Chapter 10.

To supplement updates to the text, several new figures are included—for example, Figure 6.9, which illustrates the key factors and events that cause transcription termination by RNA polymerase II, and Figure 8.32, which provides an example of elements that mediate kinase–substrate specificity. Existing figures were revised to incorporate molecular explanations for the events they depict—for example, Figure 7.26 was revised to include factors responsible for epigenetic inheritance of DNA methylation patterns and Figure 10.10 illustrates how importins interact with and penetrate the subunits that make up the selective barrier within the nuclear pore complex.

## Incorporate Recent Discoveries and Advances

A third goal in revising this edition was to incorporate key discoveries and concepts that have recently taken hold in the field. These include discussion of intrinsically disordered regions in protein structure in Chapter 2, their role in mediating liquid-liquid phase separation (LLPS) in Chapter 8, and the contributions of LLPS to formation of membraneless compartments (e.g., transcription hubs and the nucleolus in Chapter 10) and other molecular events (e.g., protein import into chloroplasts in Chapter 12). Updates on the ever-increasing list of noncoding RNAs (e.g., lncRNAs) expressed in eukaryotic organisms and their putative contributions to organismal complexity are added in the context of Chapter 4: Genes and Genomes and Chapter 9: Genomics, Proteomics, and Systems Biology and a more thorough analysis of the molecular machinery that mediates autophagy is provided in Chapter 11: Protein Processing and Sorting. Given the impact that CRISPR/Cas technology is having on research approaches, a new Key Experiment box in Chapter 3: Fundamentals of Molecular Biology describes the first demonstration by Jennifer Doudna and Emmanuelle Charpentier that bacterial CRISPR/Cas9 can be converted into an experimental tool for targeted genome modification. A new Molecular Medicine box is also added to Chapter 9, centered on the development of mRNA vaccines to combat the COVID-19 pandemic. The Molecular Medicine box on Alzheimer's Disease in Chapter 8: Protein Synthesis, Processing, and Regulation was also revised to include discussion of immunotherapy as an approach to treating the disease and the controversial approval of the first ever amyloid-$\beta$–directed immunotherapy (Aducanumab) by the US Food and Drug Administration in 2021.

## Develop the Data Analysis Problems

A fourth goal of this edition was to re-envision the Data Analysis Problems that conclude each chapter to provide tools that help students integrate the product of science—knowledge—with the practice of science—experimentation and data interpretation. There are 16 new Data Analysis Problems; others have been significantly revised. Each of these new or updated Data Analysis Problems now include a brief background section to provide students a context within which to consider the experiments. While the Data Analysis Problems for Chapters 1–5 include data from a single experiment, those for Chapters 6–19 include data from multiple experiments, mimicking how research studies most often entail series of experiments that build on each other.

The top priority in selecting data for the Data Analysis Problems was that they relate to and reinforce concepts discussed in the corresponding chapter. For example, the new Data Analysis Problem for Chapter 10: The Nucleus investigates the nature of the selective barrier within the nuclear pore complex and how importins pass through that barrier. Opportunities to link content from the chapter to disease also guided the selection of data. The Data Analysis Problem for Chapter 6: RNA Synthesis and Processing, for example, examines the potential contribution of TATA-binding protein to oncogenic transformation, the Data Analysis Problem for Chapter 13: The Cytoskeleton and Cell Movement examines the role of an actin-binding protein in metastasis, the Data Analysis Problem for Chapter 14: The Plasma Membrane evaluates whether receptor-mediated endocytosis may contribute to the spread of toxic tau proteins between neurons during Alzheimer's disease and other tauopathies, and the Data Analysis Problem for Chapter 18: Cell Renewal and Cell Death presents evidence that apoptosis induced through p53 and PUMA may contribute to neurodegeneration associated with amyotrophic lateral sclerosis and frontotemporal dementia.

Another priority in developing the Data Analysis Problems was to incorporate data from experimental techniques covered in the book and, in many cases, include multiple techniques to help students learn how different methods can complement each other to investigate an experimental question. For example, the new Data Analysis Problem for Chapter 7: Transcriptional Regulation and Epigenetics includes data from luciferase reporter assays, electrophoretic-mobility shift assays, and chromatin immunoprecipitation (all discussed in Chapter 7), whereas the Data Analysis Problem for Chapter 17: The Cell Cycle includes data from immunoblot, immunocytochemistry, and retroviral transduction (all discussed in Chapter 3: Fundamentals of Molecular Biology) as well as DNA content analysis by flow cytometry (discussed in Chapter 17). Whenever possible, data from recently published articles were selected, with many of the new Data Analysis Problems based on articles published since 2017.

To support students' understanding and analysis of the Data Analysis Problems, several figures from the Eighth Edition depicting research techniques have been revised to more thoroughly illustrate how they are conducted. Figures 3.18, 3.26, and 3.27 depict cDNA cloning, immunocytochemistry, and immunoblotting, respectively; Figure 7.5 depicts the use of reporter plasmids to identify *cis*-acting elements; and Figure 9.13 depicts yeast two-hybrid assays. Where appropriate, technique figures are cross-referenced to facilitate independent study of each Data Analysis Problem by students.

Another key resource added is interactive versions of each Data Analysis Problem (available online), which walk students through how each experiment was conducted to generate the data presented, using customized versions of the corresponding technique figures in the book. Overall, the goal is to provide a resource through which students can integrate and apply concepts from the book while simultaneously learning the intellectual process of scientific inquiry within the field of cell biology. Data Analysis Problems are available in Oxford Insight or via the enhanced e-book.

## Features

Several pedagogical features are incorporated into *The Cell* in order to help students master and integrate its contents. These features are reviewed below as a guide to students studying from this book.

### Chapter Organization

Each chapter is divided into three to five major sections, which are further divided into a similar number of subsections. An outline listing the major sections at the beginning of each chapter provides a brief overview of its contents. The major sections are numbered and self-contained to facilitate assignability.

## Learning Objectives

Each of the major sections begins with Learning Objectives, which help to organize and focus students' attention on the material.

## Summary and Questions

The major sections conclude with a review, including a section summary and questions (with answers in the back of the book). The questions span several levels of Bloom's taxonomy, ranging from knowledge and comprehension to analysis and synthesis.

## Marginal Notes

Major points are summarized as marginal notes throughout the text, providing a running outline of the material.

## Key Terms and Glossary

Key terms are identified as boldfaced words when they are introduced in each chapter and defined in the glossary at the end of the book.

## Illustrations and Micrographs

An illustration program of full-color art and micrographs has been carefully developed to complement and visually reinforce the text.

## Key Experiment and Molecular Medicine Essays

Each chapter contains either two Key Experiment essays or one Key Experiment and one Molecular Medicine essay. These features are designed to provide the student with a sense of both the experimental basis of cell and molecular biology and its applications to modern medicine. Additional questions are included in these essays, designed to focus attention on key aspects of the material. These essays are also a useful basis for student discussions, which can be accompanied with a review of the original paper upon which the experiments are based.

## Data Analysis Problem

Each chapter concludes with Data Analysis Problem that present data from original research papers, together with questions that engage students in the analysis of experimental methods and results (with answers in the back of the book). Like the Key Experiment and Molecular Medicine essays, the Data Analysis Problem provide excellent material for discussions and opportunities for student participation in active learning.

## FYIs

Each chapter contains sidebars that provide brief descriptive highlights of points of interest. The sidebars supplement the text and provide starting points for class discussion.

## References

Two key references for each major section are included at the end of each chapter. Comprehensive lists of references are provided as an online supplement.

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ACCESSIBLE COLOR CONTENT Every opportunity has been taken to ensure that the content herein is fully accessible to those who have difficulty perceiving color. Exceptions are cases where the colors provided are expressly required because of the purpose of the illustration.

## Acknowledgements

It has been an absolute honor and privilege to take on revising *The Cell* for this Ninth Edition. Geoffrey M. Cooper's vision and masterful writing are what made this book the success it has been through eight editions and his review and feedback on all edits and updates in this edition were essential. I could not ask for a better mentor, colleague, friend, and now co-author.

Thank you, first and foremost Alexandra Zilz Adams—without your boundless support, never-ending encouragement, and invaluable insight, this Ninth Edition would not have been possible. My heartfelt thanks are also extended to Ulla Hansen, Bradley T. Hyman, Amy Friedman, Merideth Krevosky, Karen Kane, Barbara Ott, Steve James, Joe Birzes, Dave Bergey, and Joseph Carapucci—the impact of your wisdom, care, and influence is interwoven throughout this edition of *The Cell*. Sincerest thanks to colleagues listed below for reviewing early drafts of this edition and providing insightful feedback.

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Kenneth W. Adams

# Digital Resources for
## *The Cell: A Molecular Approach*, NINTH EDITION

### Optimize Student Learning with Oxford Insight

*The Cell: A Molecular Approach*, Ninth Edition, is available in **Oxford Insight**. **Oxford Insight** delivers the trusted content of *The Cell* within a powerful, data-driven learning experience designed to increase student success. A guided and curated learning environment—delivered either via LMS/VLE integration or standalone—**Oxford Insight** provides access to the e-book, multimedia resources, assignable/gradable activities and exercises, and analytics on student achievement and progress. As students work through the course material, **Oxford Insight** automatically sets personalized learning paths for them, based on their specific performance.

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- Sync real-time assignments with LMS/VLE gradebooks
- Author new content and/or customize the publisher-provided content

For more information on how *The Cell: A Molecular Approach*, Ninth Edition, powered by **Oxford Insight**, can enrich the teaching and learning experience in your course, please visit oxfordinsight.oup.com or contact your Oxford University Press representative.

CONTENTS INCLUDE:

- *Interactive Data Analysis Problems*: New to this edition, these interactive activities bring the book's Data Analysis Problems to life, presenting data from original research papers and asking students to analyze experimental methods and results. The Interactive Data Analysis Problems include three components:
  - *Research Techniques*: Visual overviews of research techniques discussed throughout *The Cell* that are relevant to each problem, with a quiz to test understanding

  - *Experimental Questions*: Image walkthroughs of each Interactive Data Analysis Problem's experimental question and method, helping students envision the research process
  - *Assessment*: Quizzes and short answer questions that encourage students synthesize what they have learned and apply that knowledge to new research

ANIMATIONS AND VIDEOS

- *Videos*: Informative and engaging videos help students understand complex cellular and molecular structures and processes
- *Animations*: Narrated animations of key concepts and processes

Both videos and animations are accompanied by assignable quizzes

SELF-STUDY AND PERSONALIZED PRACTICE

- *Chapter Overviews*: Brief introductions to each chapter's content
- *Micrographs*: Interactive micrographs illustrating cellular structure accompanied by practice assessments for student self-study
- Additional *Data Analysis Problems*: Additional research papers accompanied by free response practice questions challenge students to work with data
- *Self-Assessment Quizzes*: End-of-section questions to reinforce understanding of chapter material
- *Flashcards*: Study aids to help students learn the key terminology introduced in each chapter
- *Suggested Reading and Web Links*: A comprehensive list of additional print and online reference material for every chapter

ASSESSMENT

- *Chapter Quizzes*: Multiple-choice quizzes test comprehension of the chapter's key material, assignable by the instructor

For more information on how *The Cell: A Molecular Approach*, Ninth Edition, powered by **Oxford Insight**, can enrich the teaching and learning experience in your course, please visit oxfordinsight.oup.com or contact your Oxford University Press representative.

## For the Instructor

(Available at **oup.com/he/cooper9e**)

Instructors using *The Cell*, Ninth Edition, have access to a wide variety of resources to aid in course planning, lecture development, and student assessment. Contents include the following:

### Instructor's Manual:

- *Active Learning Guide* with in-class exercises, references to relevant media resources, clicker questions, and more, all structured around the in-text Learning Objectives and designed to help you create a dynamic learning environment in the classroom
- *Data Analysis Problems with answers* to challenge students by working with experimental data
- *Chapter overviews, reviews, and key terms*
- *Textbook Figures and Tables*: All available in PowerPoint slides

- *Animations and Videos*: A collection of *The Cell*'s animations and videos for use in lectures
- *Test Bank*: Revised and updated for the Ninth Edition, the Test Bank, which can be integrated directly into your learning management system, downloaded in Word Files, or downloaded as a Respondus package, includes more than 1,300 multiple-choice, fill-in-the-blank, true/false, and short-answer questions covering the full range of content in every chapter. All questions are referenced to Bloom's Taxonomy, making it easier to select the right balance of questions when building assessments.

## Enhanced E-book for the Student

(**ISBN 9780197583913**)

Ideal for self-study, *The Cell*, Ninth Edition, enhanced e-book delivers major components of the digital resources in a format independent from any courseware or learning management system platform, making its online resources more accessible for students.

The enhanced e-book is available via RedShelf, VitalSource, and other leading higher education e-book vendors and includes the following student resources:

- *Learning Objectives* outline the important takeaways of every major section.
- *Animations and Videos* help illustrate and bring to life concepts discussed in the text.
- *Interactive Data Analysis Problems* include image sequences of each problem's Research Techniques and Experimental Questions, bringing the experiments to life.
- Additional *Data Analysis Problems* are available for download and self-study.
- End-of-section *Review Questions* help students assess their own understanding.
- *Flashcards* help students master the hundreds of new terms introduced in the textbook.

# PART 1 Fundamentals and Foundations

# 1 Introduction to Cells and Cell Research



Understanding the molecular biology of cells is one of the most active and fundamental areas of research in the biological sciences. This is true not only from the standpoint of basic science, but also with respect to numerous applications of cell and molecular biology to medicine, biotechnology, and agriculture. Especially with the ability to rapidly obtain sequences of complete genomes, progress in cell and molecular biology is opening new horizons in the practice of medicine. Striking examples include genome editing; the identification of genes that contribute to susceptibility to a variety of common diseases, such as Alzheimer's disease, heart disease, rheumatoid arthritis, and diabetes; the development of new drugs specifically targeted to interfere with the growth of cancer cells; designer drugs for treatment of cystic fibrosis; and the potential use of stem cells to replace damaged tissues and treat patients suffering from conditions like diabetes, Parkinson's disease, and spinal cord injuries.

Because cell and molecular biology is such a rapidly growing field of research, it is important to understand its experimental basis as well as the current state of our knowledge. This chapter will therefore focus on how cells are studied, as well as review some of their basic properties. Appreciating the similarities and differences between cells is particularly important to understanding cell biology. The first section of this chapter discusses both the unity and the diversity of present-day cells in terms of their evolution from a common ancestor. On the one hand, all cells share common fundamental properties that have been conserved throughout evolution. For example, all cells employ DNA as their genetic material, are surrounded by plasma membranes, and use the same basic mechanisms for energy metabolism. On the other hand, present-day cells have evolved a variety of different lifestyles. Many organisms, such as bacteria, amoebas, and yeasts, consist of single cells that are capable of independent self-replication. More complex organisms are composed of collections of cells that function in a coordinated manner, with different cells specialized to perform particular tasks. The human body, for example, is composed of more than 200 different kinds of cells, each specialized for distinct functions such as memory, sight, movement, and digestion. The diversity exhibited by the many different kinds of cells is striking; for example, consider the differences between bacteria and the cells of the human brain.

The fundamental similarities between different types of cells provide a unifying theme to cell biology, allowing the basic principles learned from experiments with one kind of cell to be extrapolated and generalized to other cell types. Several kinds of cells and organisms are widely used to study different aspects of cell and molecular biology; the second section of this chapter discusses some of the properties of these cells that make them particularly valuable as experimental models. Finally, it is important to recognize that progress in cell biology depends heavily on the availability of experimental tools that allow scientists to make new observations or conduct novel kinds of experiments. This introductory chapter therefore concludes with a discussion of some of the experimental approaches used to study cells, as well as a review of some of the major historical developments that have led to our current understanding of cell structure and function.

## 1.1 The Origin and Evolution of Cells

LEARNING OBJECTIVES

**1.1.1** Explain how the first cell originated.
**1.1.2** Describe the major steps in evolution of metabolism.
**1.1.3** Illustrate the structures of eukaryotic and prokaryotic cells.
**1.1.4** Outline the evolution of eukaryotic cells and multicellular organisms.

Cells are divided into two main classes, prokaryotes and eukaryotes, initially defined by whether they contain a nucleus. Prokaryotic cells, such as bacteria, lack a membrane-bound nucleus and are generally smaller and simpler than eukaryotic cells, which include the highly specialized cells of multicellular organisms. In spite of these differences, the same basic molecular mechanisms govern the lives of both prokaryotes and eukaryotes, indicating that all present-day cells are descended from a single primordial ancestor. How did this first cell develop? And how did the complexity and diversity exhibited by present-day cells evolve?

### How did the first cell arise?

It appears that life first emerged at least 3.8 billion years ago, approximately 750 million years after Earth was formed. How life originated and how the first cell came into being are matters of speculation, since these events cannot be reproduced in the laboratory. Nonetheless, several types of experiments provide important evidence bearing on some steps of the process.

**Organic molecules formed spontaneously in primitive Earth's atmosphere.**

It was first suggested in the 1920s that simple organic molecules could form and spontaneously polymerize into macromolecules under the conditions thought to exist in primitive Earth's atmosphere. At the time life arose, the atmosphere of Earth is thought to have contained little or no free oxygen, instead consisting principally of $CO_2$ and $N_2$ in addition to smaller amounts of gases such as $H_2$, $H_2S$, and CO. Such an atmosphere provides reducing conditions in which organic molecules, given a source of energy such as sunlight or electrical discharge, can form spontaneously. The spontaneous formation of organic molecules was first demonstrated experimentally in the 1950s when Stanley Miller (then a graduate student) showed that the discharge of electric sparks into a mixture of $H_2$, $CH_4$, and $NH_3$, in the presence of water, leads to the formation of a variety of organic molecules, including several amino acids (**FIGURE 1.1**). Although Miller's experiments did not precisely reproduce the conditions of primitive Earth, they clearly demonstrated the plausibility of the spontaneous synthesis of organic molecules, providing the basic materials from which the first living organisms arose.

The next step in evolution was the formation of macromolecules. The monomeric building blocks of macromolecules have been demonstrated to polymerize spontaneously under plausible prebiotic conditions. Heating dry mixtures of amino acids, for example, results in their polymerization to form polypeptides. But the critical characteristic of the macromolecule from which life evolved must have been the ability to replicate itself. Only a macromolecule capable of directing the synthesis of new copies of itself would have been capable of reproduction and further evolution.

**RNA can catalyze its own replication.**

Of the two major classes of informational macromolecules in present-day cells (nucleic acids and proteins), only the nucleic acids are capable of directing

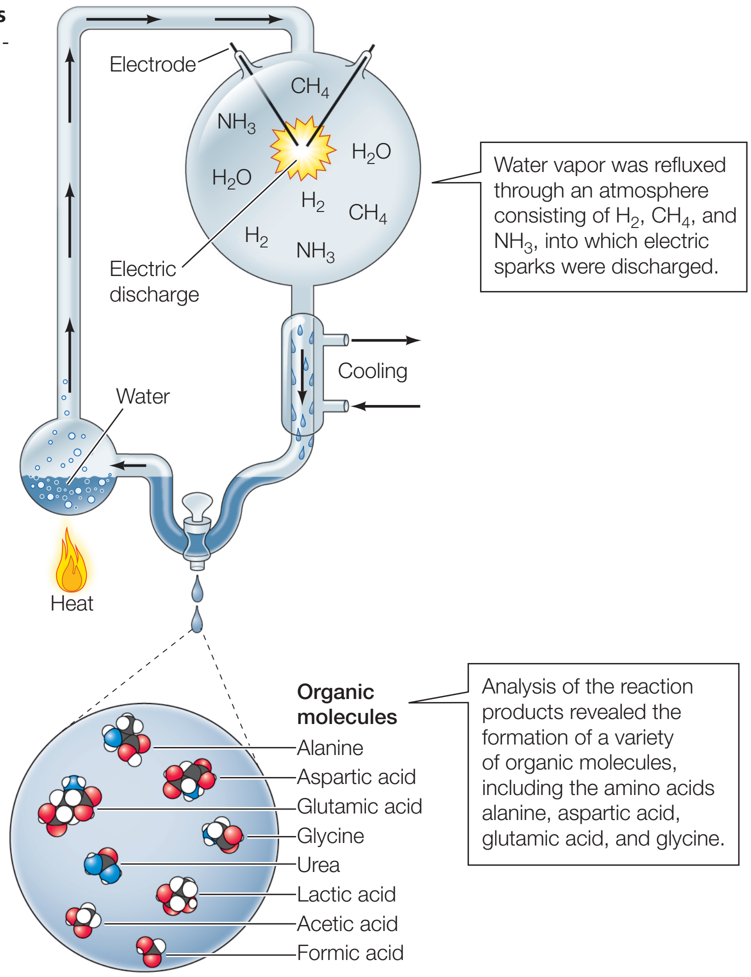


**FIGURE 1.1 Spontaneous formation of organic molecules** Experiments first conducted by Stanley Miller in the 1950s demonstrated that conditions similar to those of primitive Earth can give rise to several organic molecules that are critical to cellular life, including many amino acids.

their own self-replication. Nucleic acids can serve as templates for their own synthesis as a result of specific base pairing between complementary nucleotides (**FIGURE 1.2**). A critical step in understanding molecular evolution was thus reached in the early 1980s, when it was discovered in the laboratories of Sid Altman and Tom Cech that RNA is capable of catalyzing a number of chemical reactions, including the polymerization of nucleotides. Further studies have extended the known catalytic activities of RNA, including the description of RNA molecules that direct the synthesis of a new RNA strand from an RNA template. RNA is thus uniquely able to both serve as a template and to catalyze its own replication. Consequently, RNA is generally believed to have been the initial genetic system, and an early stage of chemical evolution is thought to have been based on self-replicating RNA molecules—a period of evolution known as the **RNA world**. Ordered interactions between RNA and amino acids then evolved into the present-day genetic code, and DNA eventually replaced RNA as the genetic material.

As discussed further in Chapter 3, all present-day cells use DNA as the genetic material and employ the same basic mechanisms for DNA replication and expression of the genetic information. **Genes** are the functional units of inheritance, corresponding to segments of DNA that encode proteins or RNA molecules. The nucleotide sequence of a gene is copied into RNA by a process called **transcription**. For

**All present-day cells use the same genetic mechanisms.**

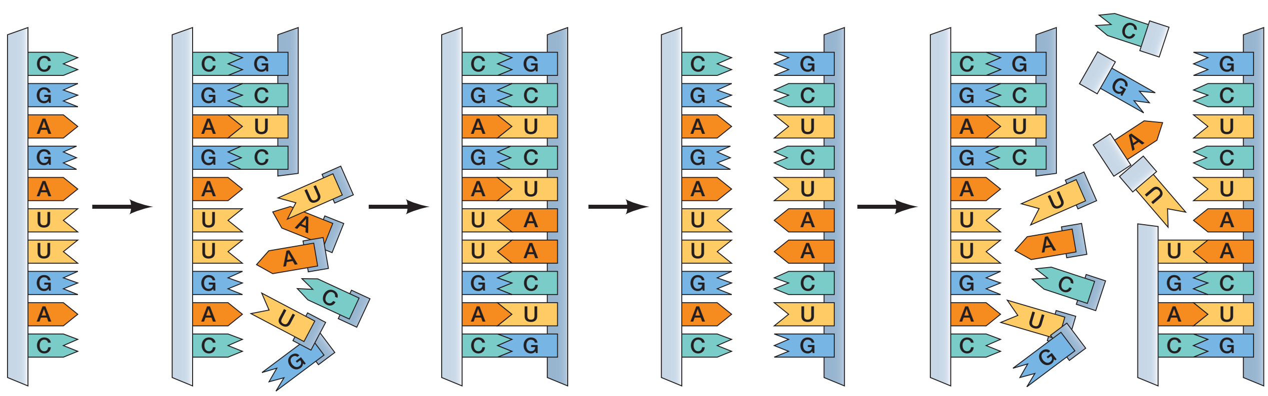


**FIGURE 1.2 Self-replication of RNA** Complementary pairing between nucleotides (adenine [A] with uracil [U] and guanine [G] with cytosine [C]) allows one strand of RNA to serve as a template for the synthesis of a new strand with the complementary sequence.

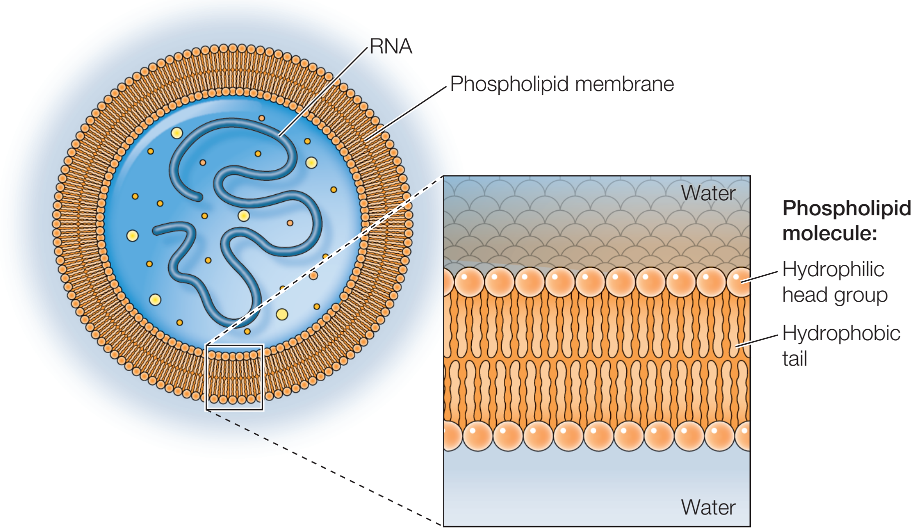


**FIGURE 1.3 Enclosure of self-replicating RNA in a phospholipid membrane** The first cell is thought to have arisen by the enclosure of self-replicating RNA and associated molecules in a membrane composed of phospholipids. Each phospholipid molecule has two long hydrophobic tails attached to a hydrophilic head group. The hydrophobic tails are buried in the lipid bilayer; the hydrophilic heads are exposed to water on both sides of the membrane.

RNAs that encode proteins, their nucleotide sequence is then used to specify the order of amino acids in a protein by a process called **translation**.

The first cell is presumed to have arisen by the enclosure of self-replicating RNA in a membrane composed of **phospholipids** (**FIGURE 1.3**). As discussed in detail in the next chapter, phospholipids are the basic components of all present-day biological membranes, including the plasma membranes of both prokaryotic and eukaryotic cells. The key characteristic of the phospholipids that form membranes is that they are **amphipathic** molecules, meaning that one portion of the molecule is soluble in water and another portion is not. Phospholipids have long, water-insoluble (**hydrophobic**) hydrocarbon chains joined to water-soluble (**hydrophilic**) head groups that contain phosphate. When placed in water, phospholipids spontaneously aggregate into a bilayer with their phosphate-containing head groups on the outside in contact with water and their hydrocarbon tails in the interior in contact with each other. Such a phospholipid bilayer forms a stable barrier between two aqueous compartments—for example, separating the interior of the cell from its external environment.

The enclosure of self-replicating RNA and associated molecules in a phospholipid membrane would thus have maintained them as a unit, capable of self-reproduction and further evolution. RNA-directed protein synthesis may already have evolved by this time, in which case the first cell would have consisted of self-replicating RNA and its encoded proteins.

## The evolution of metabolism

Because cells originated in a sea of organic molecules, they were able to obtain food and energy directly from their environment. But such a situation is self-limiting, so cells needed to evolve their own mechanisms for generating energy and synthesizing the molecules necessary for their replication. The generation and controlled utilization of metabolic energy is central to all cell activities, and the principal pathways of energy metabolism (discussed in detail in Chapter 12) are highly conserved in present-day cells. All cells use **adenosine 5′-triphosphate** (**ATP**) as their source of metabolic energy to drive the synthesis of cell constituents and carry out other energy-requiring activities, such as movement (e.g., muscle contraction). The mechanisms used by cells to generate ATP are thought to have

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