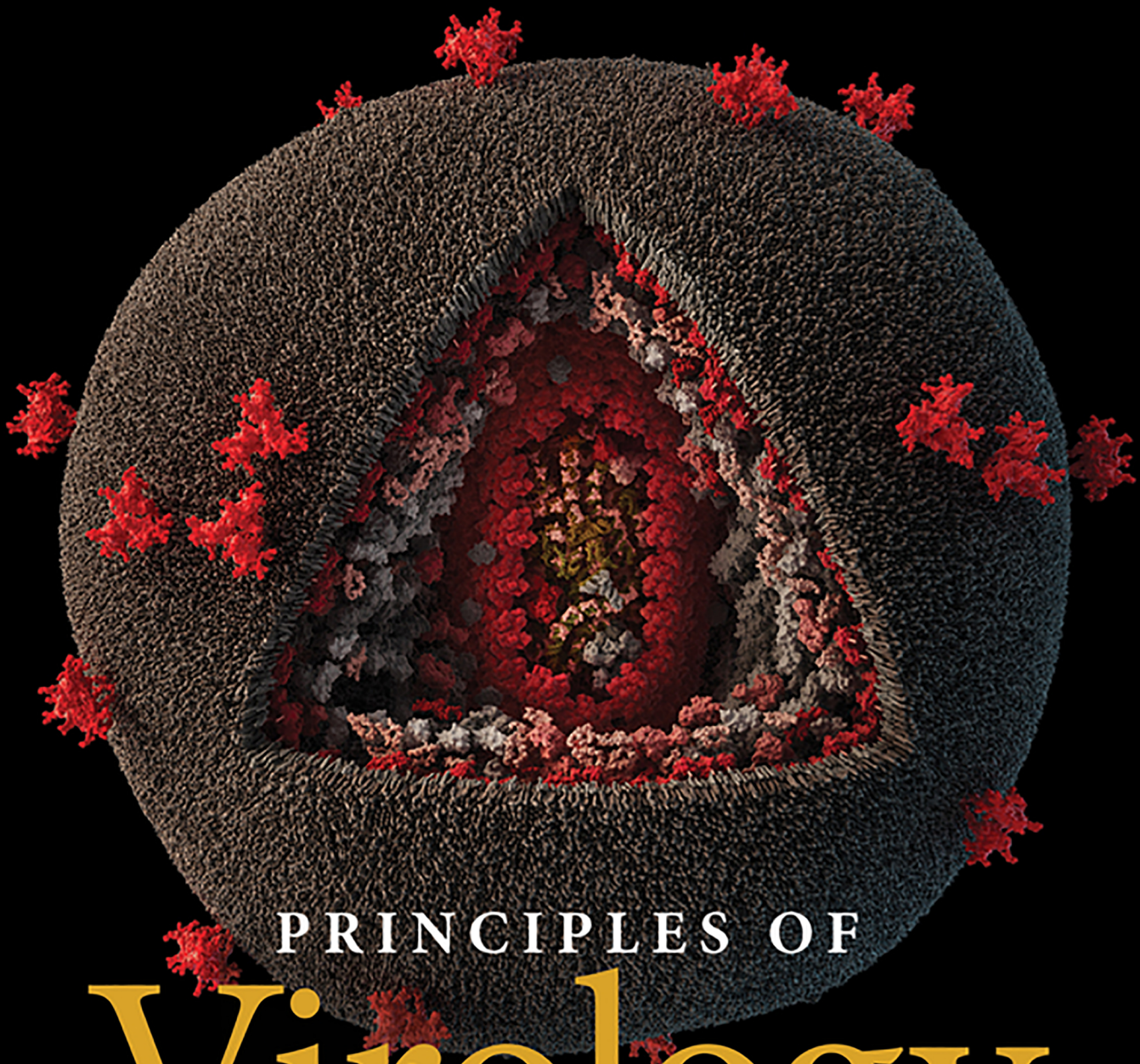
VOLUME I *Molecular Biology*



PRINCIPLES OF Virology

FIFTH EDITION

Jane Flint • Vincent R. Racaniello
Glenn F. Rall • Theodora Hatziioannou
Anna Marie Skalka

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Fifth Edition

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We dedicate this book to the students, current and future scientists, physicians, and all those with an interest in the field of virology, for whom it was written.
We kept them ever in mind.

We also dedicate it to our families:
Jonn, Gethyn, and Amy Leedham
Doris, Aidan, Devin, and Nadia
Eileen, Kelsey, and Abigail
Paul, Stefan, and Eve
Rudy, Jeannie, and Chris

Oh, be wiser thou!
Instructed that true knowledge leads to love.

William Wordsworth
Lines left upon a Seat in a Yew-tree
1888

About the Instructor Companion Website

This book is accompanied by a companion website for instructors:

www.wiley.com/go/flint/pov5 

The website includes:

- PowerPoints of figures
- Author podcasts
- Study Questions and Answers

Contents

Preface

The enduring goal of scientific endeavor, as of all human enterprise, I imagine, is to achieve an intelligible view of the universe. One of the great discoveries of modern science is that its goal cannot be achieved piecemeal, certainly not by the accumulation of facts. To understand a phenomenon is to understand a category of phenomena or it is nothing. Understanding is reached through creative acts.

A. D. HERSHEY
Carnegie Institution Yearbook 65

All five editions of this textbook have been written according to the authors' philosophy that the best approach to teaching introductory virology is by emphasizing shared principles. Studying the common steps of the viral reproductive cycle, illustrated with a set of representative viruses, and considering mechanisms by which these viruses can cause disease provides an integrated overview of the biology of these infectious agents. Such knowledge cannot be acquired by learning a collection of facts about individual viruses. Consequently, the major goal of this book is to define and illustrate the basic principles of virus biology.

In this information-rich age, the quantity of data describing any given virus can be overwhelming, if not indigestible, for student and expert alike. The urge to write more and more about less and less is the curse of reductionist science and the bane of those who write textbooks meant to be used by students. In the fifth edition, we continue to distill information with the intent of extracting essential principles, while providing descriptions of how the information was acquired and tools to encourage our readers' exploration of the primary literature. Boxes are used to emphasize major principles and to provide supplementary material of relevance, from explanations of terminology to descriptions of trailblazing experiments. Our goal is to illuminate process and strategy as opposed to listing facts and figures. In an effort to make the book readable, we have been selective in our choice of viruses that are used as examples. The encyclopedic *Fields' Virology* [Knipe DM, Howley PM (ed). 2020. *Fields Virology*, 7th ed. Lippincott Williams & Wilkins, Philadelphia, PA] is recommended as a resource for detailed reviews of specific virus families.

What's New

This edition is marked by a welcome addition to the author team. Our new member, Theodora Hatziioannou, brings expertise in retrovirology, entry, and intrinsic immunity, as well as authority regarding ancient Greek mythology and philosophy that the attentive reader will see is generously sprinkled throughout the text.

We have added an important new chapter in Volume II, "Therapeutic Viruses." While the majority of the chapters define how viruses reproduce and cause mayhem to both cell and host, this new chapter turns the tables to discuss how viruses can be beneficial to eliminate tumor cells, deliver therapeutic genes to specific cells, and expand our arsenal of vaccines for prevention of virus-mediated diseases.

The authors continually strive to make this text accessible and relevant to our readers, many of whom are undergraduates, graduate students, and postdoctoral fellows. Consequently, for this edition, we enlisted the aid of more than twenty of these trainees to provide guidance and commentary on our chapters and ensure that concepts are clearly explained and that the text is compelling to read. This unique group of editors has been invaluable in the design of all of our fully reworked and up-to-date chapters and appendices, and we extend a particular thank-you to them for sharing their perspectives.

A new feature is the inclusion of a set of study questions and/or, in some cases, puzzles, as aids to ensure that the key principles are evident within each chapter. This section complements the Principles that begin each chapter, focusing on unifying core concepts.

Finally, although the SARS-CoV-2 pandemic began as we were preparing to go to press, we have included additions to relevant chapters on the epidemiology, emergence, and replication of this global scourge, as well as some hopeful information concerning vaccine development. What is apparent is that, now more than ever, an appreciation of how viruses impact their hosts is not just an academic pursuit, but rather literally a matter of life and death. We extend our gratitude to all those who serve in patient care settings.

Principles Taught in Two Distinct, but Integrated Volumes

Volume I covers the molecular biology of viral reproduction, and Volume II focuses on viral pathogenesis, control of virus infections, and virus evolution. The organization into two volumes follows a natural break in pedagogy and provides considerable flexibility and utility for students and teachers alike. The two volumes differ in content but are integrated in style and presentation. In addition to updating the chapters and appendices for both volumes, we have organized the material more efficiently, and as noted above, added a new chapter that we believe reflects an exciting direction for the field. Links to Internet resources such as websites, podcasts, blog posts, and movies are provided within each chapter; the digital edition provides one-click access to these materials.

As in our previous editions, we have tested ideas for inclusion in the text in our own classes. We have also received constructive comments and suggestions from other virology instructors and their students. Feedback from our readers was particularly useful in finding typographical errors, clarifying confusing or complicated illustrations, and pointing out inconsistencies in content.

For purposes of readability, references are not included within the text; each chapter ends with an updated list of relevant books, review articles, and selected research papers for readers who wish to pursue specific topics. New to this edition are short descriptions of the key messages from each of the cited papers of special interest. Finally, each volume has a general glossary of essential terms.

These two volumes outline and illustrate the strategies by which all viruses reproduce, how infections spread within a host, and how they are maintained in populations. We have focused primarily on animal viruses, but have drawn insights from studies of viruses that reproduce in plants, bacteria, and archaea.

Volume I: The Science of Virology and the Molecular Biology of Viruses

This volume examines the molecular processes that take place in an infected host cell. Chapter 1 provides a general introduction and historical perspective, and includes descriptions of the unique properties of viruses. The unifying principles that are the foundations of virology,

including the concept of a common strategy for viral propagation, are then described. The principles of the infectious cycle, descriptions of the basic techniques for cultivating and assaying viruses, and the concept of the single-step growth cycle are presented in Chapter 2.

The fundamentals of viral genomes and genetics, and an overview of the surprisingly limited repertoire of viral strategies for genome replication and mRNA synthesis, are topics of Chapter 3. The architecture of extracellular virus particles in the context of providing both protection and delivery of the viral genome in a single vehicle is considered in Chapter 4. Chapters 5 to 13 address the broad spectrum of molecular processes that characterize the common steps of the reproductive cycle of viruses in a single cell, from decoding genetic information to genome replication and production of progeny virions. We describe how these common steps are accomplished in cells infected by diverse but representative viruses, while emphasizing common principles. Volume I concludes with a chapter that presents an integrated description of cellular responses to illustrate the marked, and generally irreversible, impact of virus infection on the host cell.

The appendix in Volume I provides concise illustrations of viral reproductive cycles for members of the main virus families discussed in the text. It is intended to be a reference resource when reading individual chapters and a convenient visual means by which specific topics may be related to the overall infectious cycles of the selected viruses.

Volume II: Pathogenesis, Control, and Evolution

This volume addresses the interplay between viruses and their host organisms. In Chapter 1, we introduce the discipline of epidemiology, and consider basic aspects that govern how the susceptibility of a population is controlled and measured. Physiological barriers to virus infections, and how viruses spread in a host, and to other hosts, are the topics of Chapter 2. The early host response to infection, comprising cell-autonomous (intrinsic) and innate immune responses, are the topics of Chapter 3, while the next chapter considers adaptive immune defenses, which are tailored to the pathogen, and immune memory. Chapter 5 focuses on the classical patterns of virus infection within cells and hosts, and the myriad ways that viruses cause illness. In Chapter 6, we discuss virus infections that transform cells in culture and promote oncogenesis (the formation of tumors) in animals. Next, we consider the principles underlying treatment and control of infection. Chapter 7 focuses on vaccines, and Chapter 8 discusses the approaches and challenges of antiviral drug discovery. In Chapter 9, the new chapter in this edition, we describe the rapidly expanding applications of viruses as therapeutic agents. The origin of viruses, the drivers of viral evolution, and host-virus conflicts are the subjects of Chapter 10. The principles of emerging virus infections, and humankind's experiences with epidemic and pandemic viral infections, are considered in Chapter 11. Chapter 12 is devoted entirely to the "AIDS virus," human immunodeficiency virus type 1, not only because it is the causative agent of the most serious current worldwide epidemic but also because of its unique and informative interactions with the human immune defenses. Volume II ends with a chapter on unusual infectious agents, viroids, satellites, and prions.

The Appendix of Volume II affords snapshots of the pathogenesis of common human viruses. This appendix has been completely re-envisioned in this edition, and now includes panels that define pathogenesis, vaccine and antiviral options, and the course of the infection through the human body. This consistent format should allow students to find information more easily, and compare properties of the selected viruses.

For some behind-the-scenes information about how the authors created the previous edition of *Principles of Virology*, see: http://bit.ly/Virology_MakingOf.

Acknowledgments

These two volumes of *Principles* could not have been composed and revised without help and contributions from many individuals. We are most grateful for the continuing encouragement from our colleagues in virology and the students who use the text. Our sincere thanks also go to colleagues who have taken considerable time and effort to review the text in its evolving manifestations. Their expert knowledge and advice on issues ranging from teaching virology to organization of individual chapters and style were invaluable and are inextricably woven into the final form of the book.

We also are grateful to those who gave so generously of their time to serve as expert reviewers of individual chapters or specific topics in these two volumes: Siddharth Balachandran (Fox Chase Cancer Center), Paul Bieniasz (Rockefeller University), Christoph Seeger (Fox Chase Cancer Center), and Laura Steel (Drexel University College of Medicine). Their rapid responses to our requests for details and checks on accuracy, as well as their assistance in simplifying complex concepts, were invaluable.

As noted in "What's New," we benefited from the efforts of the students and postdoctoral fellows who provided critiques on our chapters and helped to guide our revisions: Pradeep Morris Ambrose, Ruchita Balasubramanian, Mariana Nogueira Batista, Pierre Michel Jean Beltran, Marni S. Crow, Qiang Ding, Florian Douam, Jenna M. Gaska, Laura J. Halsey, Eliana Jacobson, Orkide O. Koyuncu, Robert LeDesma, Rebecca Markham, Alexa McIntyre, Katelynn A. Milora, Laura A. M. Nerger, Morgan Pantuck, Chen Peng, Katrien Poelaert, Daniel Poston, Anagha Prasanna, Pavithran T. Ravindran, Inna Ricardo-Lax, Fabian Schmidt, Andreas Solomos, Nikhila Shree Tanneti, Sharon M. Washio, Riley M. Williams, and Kai Wu.

Since the inception of this work, our belief has been that the illustrations must complement and enrich the text. The illustrations are an integral part of the text, and credit for their execution goes to the knowledge, insight, and artistic talent of Patrick Lane of ScEYEnce Studios. A key to common figure elements is provided following the "About the Authors" section. As noted in the figure legends, many could not have been completed without the help and generosity of numerous colleagues who provided original images. Special thanks go to those who crafted figures or videos tailored specifically to our needs, or provided multiple pieces in this latest edition: Jônatas Abrahão (Universidade Federal de Minas Gerais), Mark Andrake (Fox Chase Cancer Center), Irina Arkhipova (Marine Biological Laboratory, Woods Hole), Brian Baker (University of Notre Dame), Ben Beaden (Australia Zoo, Queensland), Paul Bieniasz (Rockefeller University), Kartik Chandran (Albert Einstein College of Medicine), Elliot Lefkowitz (University of Alabama), Joseph Pogliano (University of California,

San Diego), B.V. Venkatar Prasad and Liya Hu (Baylor College of Medicine), Bonnie Quigley (University of the Sunshine Coast, Australia), Jason Roberts (Victorian Infectious Diseases Reference Laboratory, Doherty Institute, Melbourne, Australia), Michael Rout (Rockefeller University), and Nuria Verdaguer (Molecular Biology Institute of Barcelona, CSIC).

The collaborative work undertaken to prepare the fifth edition was facilitated greatly by several authors' retreats. ASM Press generously provided financial support for these as well as for our many other meetings over the three years that this edition has been in preparation. We thank all those who guided and assisted in its production: Christine Charlip (Director, ASM Press) for her enduring support of our efforts; Megan Angelini (Managing Developmental Editor, ASM Press) for steering us through the complexities inherent in a team effort, and for keeping us on track during production; Susan Schmidler for her elegant and creative designs for the layout and cover; and Lindsay Williams (Editorial Rights Coordinator, ASM Press) for obtaining permissions for images and figures.

There is little doubt that in undertaking such a massive effort typographical errors and/or confusing statements still remain; we hope that the readership of this edition will help to remedy any mistakes. Even so, the three authors who have been part of this endeavor since it was first published in 1995, and the two who joined along the way, feel that with each new edition we get closer to our idealized vision of what this book would be. We aspire to convey more than information: we hope to educate, excite, and encourage future generations of science consumers. As Antoine de Saint-Exupéry, author of *The Little Prince*, once said: "If you want to build a ship, don't drum up the workers to gather wood, divide the labor, and give orders. Instead, teach them to yearn for the vast and endless sea."

This often-consuming enterprise was made possible by the emotional, intellectual, and logistical support of our families, to whom the two volumes are dedicated.

About the Authors

L to R: Jane Flint, Vincent Racaniello, Theodora Hatziioannou, Ann Skalka, Glenn Rall

Jane Flint is a Professor Emerita of Molecular Biology at Princeton University. Dr. Flint's research focused on investigation of the molecular mechanisms by which viral gene products modulate host cell pathways and antiviral defenses to allow efficient reproduction in normal human cells of adenoviruses, viruses that are widely used in such therapeutic applications as gene transfer and cancer treatment. Her service to the scientific community includes membership on various editorial boards, several NIH study sections, and the NIH Recombinant DNA Advisory Committee.

Vincent R. Racaniello is Higgins Professor of Microbiology & Immunology at Columbia University Vagelos College of Physicians & Surgeons. Dr. Racaniello has been studying viruses for over 40 years, including poliovirus, rhinovirus, enteroviruses, hepatitis C virus, and Zika virus. He teaches virology to undergraduate, graduate, medical, dental, and nursing students and uses social media to communicate the subject outside of the classroom. His Columbia University undergraduate virology lectures have been viewed by thousands at iTunes University, Coursera, and on YouTube. Vincent blogs about viruses at virology.ws and is host of the popular science program *This Week in Virology*, which, together with six other science podcasts, can be found at microbe.tv.

Glenn F. Rall is a Professor and the Chief Academic Officer at the Fox Chase Cancer Center in Philadelphia. He is an Adjunct Professor in the Microbiology and Immunology departments at the University of Pennsylvania and Thomas Jefferson, Drexel, and Temple Universities. Dr. Rall's laboratory studies viral infections of the brain and the immune responses to those infections, with the goal of defining how viruses contribute to disease in humans. His service to the scientific community includes former membership on the Autism Speaks Scientific Advisory Board, Editor of *PLoS Pathogens*, Career Development Chair and Program Chair of the American Society for Virology, and membership on multiple NIH grant review panels.

Theodora Hatziioannou is a Research Associate Professor at Rockefeller University in New York. Throughout her career, Dr. Hatziioannou has worked on multiple viruses, with a particular focus on retroviruses and the molecular mechanisms that govern virus tropism and on the improvement of animal models for human disease. She is actively involved in teaching programs at the Rockefeller University and the Albert Einstein College of Medicine, is an editor of *Journal of General Virology*, and serves as a reviewer for multiple scientific journals and NIH grant review panels.

Anna Marie Skalka is a Professor Emerita and former Senior Vice President for Basic Research at the Fox Chase Cancer Center in Philadelphia. Dr. Skalka's major research interests are the molecular aspects of retrovirus biology. Dr. Skalka is internationally recognized for her contributions to the understanding of the biochemical mechanisms by which such viruses (including the AIDS virus) replicate and insert their genetic material into the host genome. Both an administrator and researcher, Dr. Skalka has been deeply involved in state, national, and international advisory groups concerned with the broader, societal implications of scientific research. She has also served on the editorial boards of peer-reviewed scientific journals and has been a member of scientific advisory boards including the National Cancer Institute Board of Scientific Counselors, the General Motors Cancer Research Foundation Awards Assembly, the Board of Governors of the American Academy of Microbiology, and the National Advisory Committee for the Pew Biomedical Scholars.

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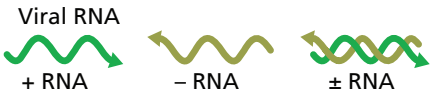
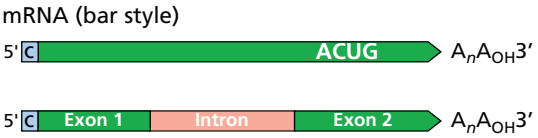
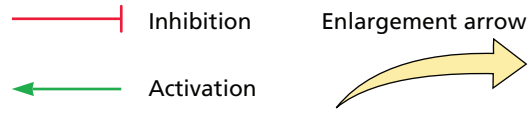
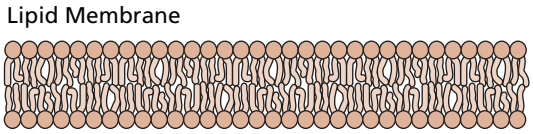
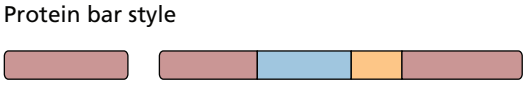
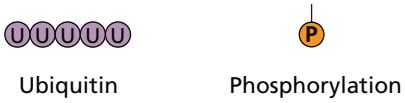


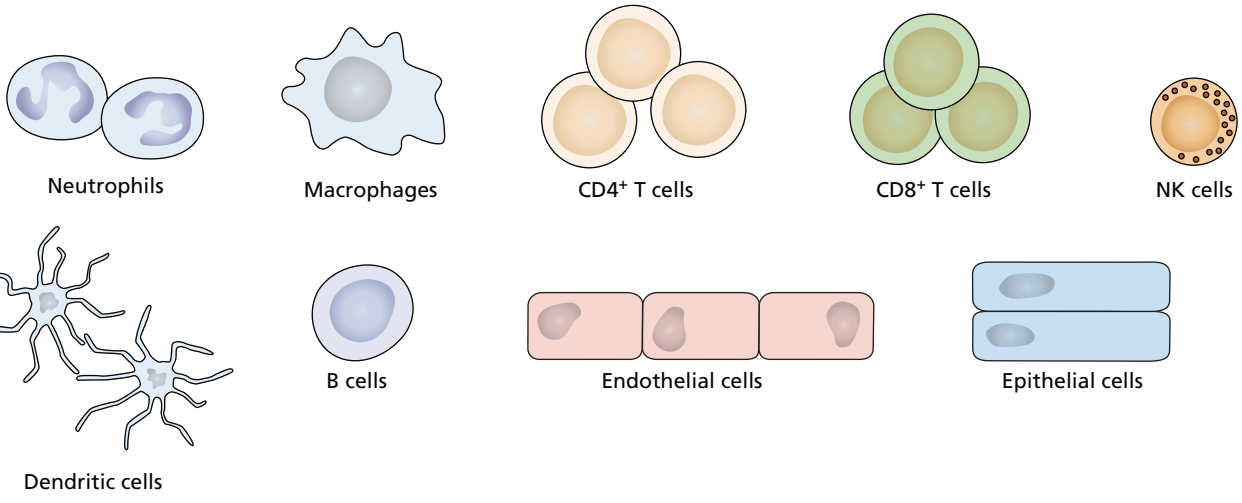






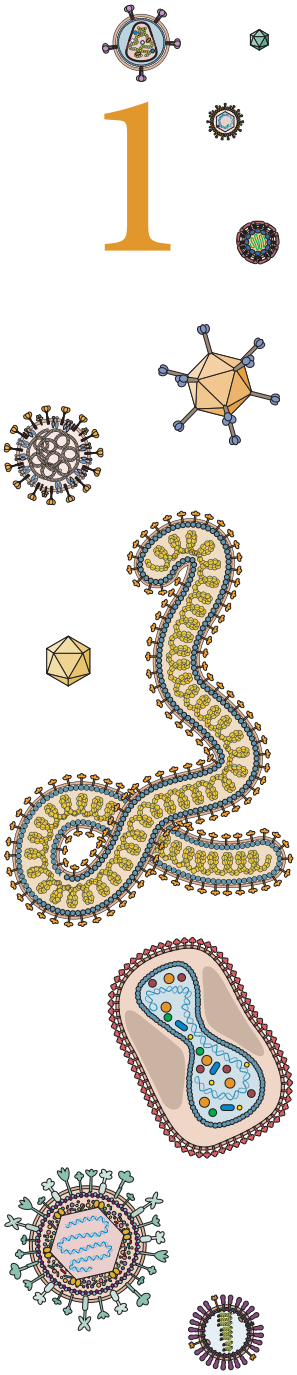






PART I

The Science of Virology



1 Foundations

LINKS FOR CHAPTER 1

- *Video: Interview with Dr. Donald Henderson*
  http://bit.ly/Virology_Henderson
- *This Week in Virology (TWIV): A weekly podcast about viruses featuring informal yet informative discussions and interviews with guests about the latest topics in the field*
  http://www.microbe.tv/twiv
- *Marine viruses and insect defense*
  http://bit.ly/Virology_Twiv301
- *Giants among viruses*
  http://bit.ly/Virology_Twiv261
- *Whiter reefs, fresh breath*
  http://www.microbe.tv/twiv/twiv-391/
- *Latest update of virus classification from the ICTV*
  https://talk.ictvonline.org/taxonomy/
- *The abundant and diverse viruses of the seas*
  http://bit.ly/Virology_3-20-09
- *How many viruses on Earth?*
  http://bit.ly/Virology_9-6-13