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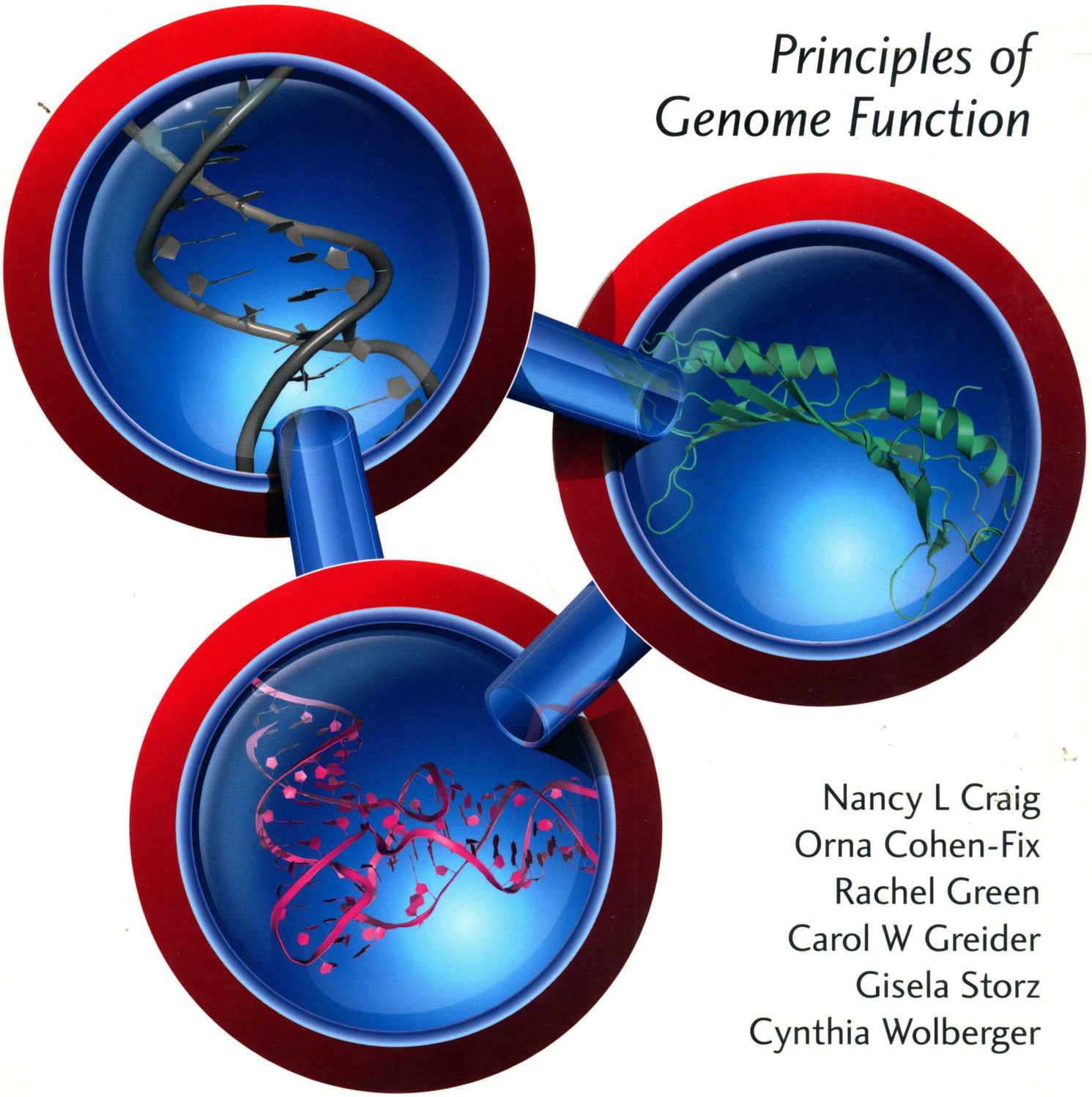
MOLECULAR BIOLOGY

Principles of Genome Function



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Rachel Green
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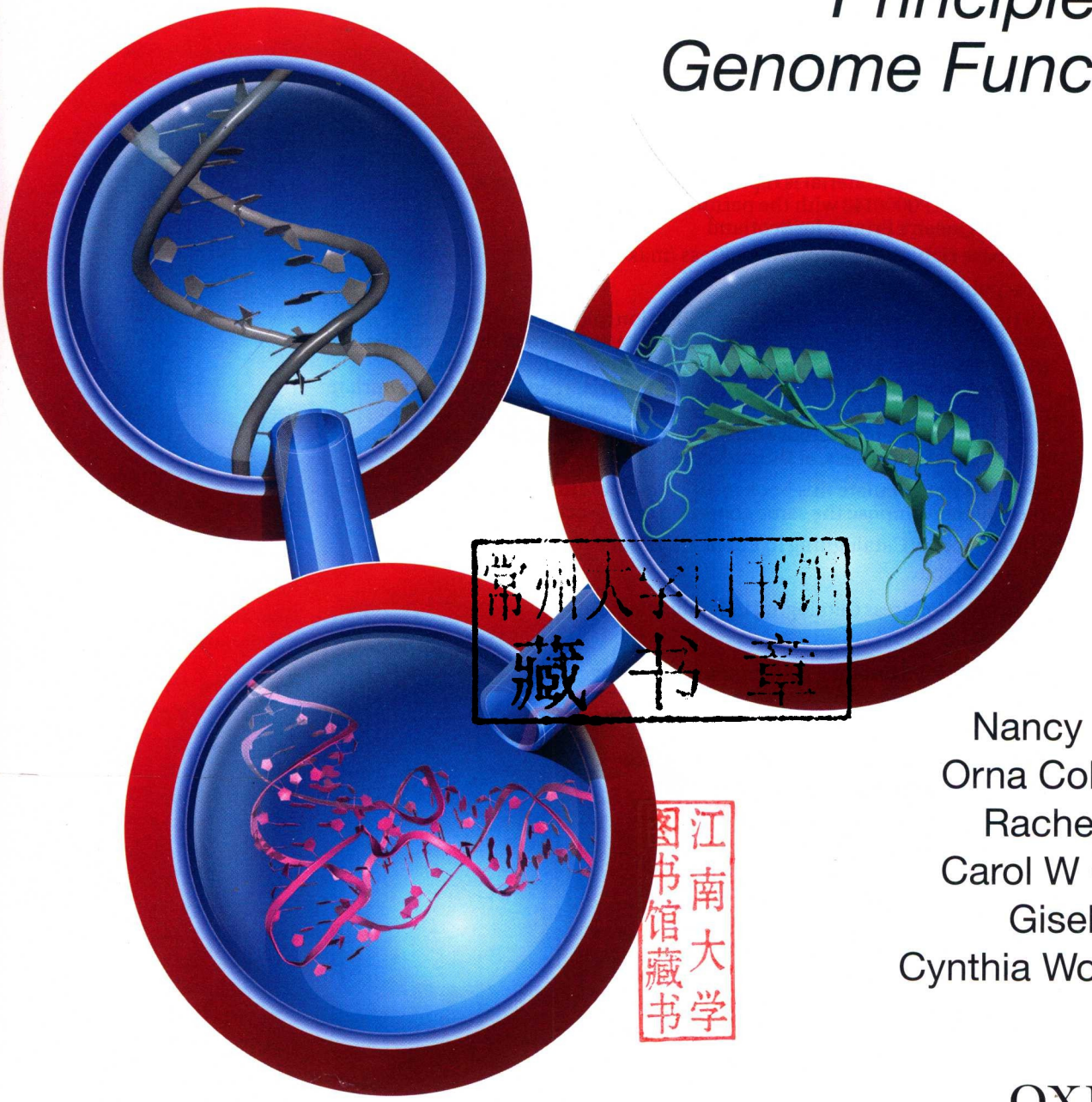

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MOLECULAR BIOLOGY

Organism	Gene name	Example	Mutant allele	Example	Protein name	Example
Bacteria	Three lowercase letters, followed by upper case letter, all italicized	*recA*	Same as gene name, followed by allele number (can have non-integer allele designations such as 'am' or 'ts' for amber- and temperature-sensitive mutants, respectively)	*recA11*	Same as gene name except first letter is upper case and gene name is not italicized	RecA
Saccharomyces cerevisiae	Letters (all uppercase if dominant, all lowercase if recessive) followed by an Arabic number, all italicized	*URA3*	Same as gene name followed by a hyphen and an Arabic number (can have additional information about how mutant was generated)	*ura3-52*	Uppercase first letter, followed by lowercase letters and number, not italicized	Ura3
Schizosaccharomyces pombe	Three lowercase letters followed by a number and superscript +, all italicized	*cdc2*$^{+}$	Same as gene name, followed by allele number (but no superscript +)	*cdc2-5*	Same as gene name except first letter is uppercase and gene name is not italicized	Cdc2
Caenorhabditis elegans	Three to four lowercase letters, followed by a hyphen and a number, all italicized	*dpy-5*	Same as gene name, followed by an allele name (one or two letters followed by a number) in parentheses	*dpy-5(e61)*	Same as gene name except all uppercase letters and gene name is not italicized	DPY-5
Drosophila melanogaster	Can be any word lowercase italicized (most genes also have a shorter unique symbol)	*dacapo* (*dap*)	Same as gene name followed by a superscript number(s) or letter(s) (for dominant mutants, the gene name is followed by a superscript D)	*dacapo*^{4}, *dacapo*^{D}	Same as gene name except first letter is uppercase and gene name is not italicized	Dacapo
Mus musculus	Usually three to five letters and Arabic numbers (maximum ten characters) begin with an uppercase letter (not a number), followed by lowercase letters and numbers, all italicized	*Grid2*	Same as the gene with the original mutant symbol added as a superscript to the gene symbol	*Grid2*^{ho}	Same as gene name except all uppercase letters and gene name is not italicized	GRID2
Homo sapiens	Maximum six characters: all uppercase letters or by a combination of uppercase letters and Arabic numbers, all italicized	*ATM*	Sequence variants are described by the specific sequence change in the DNA with sequence change, insertion, and deletions having specific nomenclature	c.1636C4G (p.Leu546-Val) (this example corresponds to a C to G change at position 1636 of the *ATM* coding sequence	Same as gene name except not italicized	ATM

Nomenclature table. Note that the names of some genes and proteins that have become accepted in the literature, such as the human Rb and p53 proteins, do not follow the conventions listed in this table.

To our teachers

ABOUT THE AUTHORS OF MOLECULAR BIOLOGY

Nancy L Craig received an A.B. in Biology and Chemistry from Bryn Mawr College in 1973 and a Ph.D. in Biochemistry in 1980 at Cornell University in Ithaca, New York, where she worked on DNA repair with Jeff Roberts. She then worked on phage lambda recombination as a postdoctoral fellow with Howard Nash at the National Institutes of Health. She joined the faculty of Department of Microbiology and Immunology at the University of California, San Francisco in 1984 and began her work on transposable elements. She joined the Department of Molecular Biology and Genetics at the Johns Hopkins University School of Medicine in 1991, where she is currently a Professor and a Howard Hughes Medical Institute Investigator, as well as the recipient of the Johns Hopkins University Alumni Association Excellent in Teaching Award. Nancy Craig is a Fellow of the American Academy of Microbiology, the American Academy of Arts and Sciences and the American Association for the Advancement of Science, and was elected to the National Academy of Sciences.

Orna Cohen-Fix received a B.A. from the Tel Aviv University in 1987 and a Ph.D. in Biochemistry with Zvi Livneh at the Weizmann Institute of Science in 1994. She did a post-doctoral fellowship with Doug Koshland at the Carnegie Institution of Washington in Baltimore, studying the regulation of chromosome segregation. In 1998, she moved to the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, where she is now a Senior Investigator. Her research focuses on cell cycle regulation and nuclear architecture, using budding yeast and *C. elegans* as model organisms. She is also the Co-Director of the NIH/Johns Hopkins University Graduate Partnership Program. She is a recipient of a Presidential Early Career Award for Scientists and Engineers, and an Association of Women in Science Mentoring Award for her work on promoting the retention of women in science.

Rachel Green received a B.S. in chemistry from the University of Michigan in 1986 and a Ph.D. in Biological Chemistry from Harvard University in 1992, where she worked with Jack Szostak studying catalytic RNA. She then did postdoctoral work in the laboratory of Harry Noller at the University of California, Santa Cruz, studying the role played by the ribosomal RNAs in the function of the ribosome. She is currently a Professor in the Department of Molecular Biology and Genetics at The Johns Hopkins University School of Medicine and an Investigator of the Howard Hughes Medical Institute. Her work continues to focus on the mechanism and regulation of translation in bacteria and eukaryotes. She is the recipient of a Johns Hopkins University School of Medicine Graduate Teaching Award.

Carol W Greider received a B.A. from the University of California at Santa Barbara in 1983. In 1987, she received her Ph.D. from the University of California at Berkeley, where she and her advisor, Elizabeth Blackburn, discovered telomerase, the enzyme that maintains telomere length. In 1988, she went to Cold Spring Harbor Laboratory as an independent Fellow and remained as a Staff Scientist until 1997, when she moved to The Johns Hopkins University School of Medicine. She is currently a Professor and Director of the Department of Molecular Biology and Genetics and her work focuses on telomerase and the role of telomeres in chromosome stability and cancer. She is a member of the National Academy of Sciences and is the recipient of numerous awards, including the Gairdner Foundation International Award, the Louisa Gross Horwitz Prize, and the Lasker Award for Basic Medical Research. In 2009, she was awarded the Nobel Prize in Physiology or Medicine together with Elizabeth Blackburn and Jack Szostak for the discovery of telomerase.

Gisela Storz graduated from the University of Colorado at Boulder in 1984 with a B.A. in Biochemistry and received a Ph.D. in Biochemistry in 1988 from the University of California at Berkeley, where she worked for Bruce Ames. After postdoctoral fellowships with Sankar Adhya at the National Cancer Institute and Fred Ausubel at Harvard Medical School, she moved to the National Institute of Child Health and Human Development in Bethesda, where she is now a Senior Investigator. Her research is focused on understanding gene regulation in response to environmental stress as well as elucidating the functions of small regulatory RNAs. She is a fellow of the American Academy of Microbiology and received the American Society for Microbiology Eli Lilly Award.

Cynthia Wolberger received her A.B. in Physics from Cornell University in 1979 and a Ph.D. in Biophysics from Harvard University in 1987, where she worked with Stephen Harrison and Mark Ptashne on the structure of the phage 434 cro repressor bound to DNA. She went on to study the structures of eukaryotic protein–DNA complexes as a postdoctoral fellow, first in the laboratory of Robert Stroud and the University of California, San Francisco and then in the laboratory of Carl Pabo at The Johns Hopkins University School of Medicine, where she is now Professor of Biophysics and Biophysical Chemistry and an Investigator of the Howard Hughes Medical Institute. Her research focuses on the structural and biochemical mechanisms underlying transcriptional regulation and ubiquitin-mediated signalling. She is a Fellow of the American Association for the Advancement of Science.

Molecular Biologists of Fells Point, Baltimore: (L–R) Rachel Green, Gisela (Gigi) Storz, Orna Cohen-Fix, Nancy Craig, Cynthia Wolberger and Carol Greider. The photo-digital illustration was created by Robert McClintock a Fells Point artist.

PREFACE

A new approach to molecular biology for the twenty-first century

Molecular Biology: Principles of Genome Function offers a fresh, distinctive approach to the teaching of molecular biology. It is an approach that reflects the challenge of teaching a subject that is in many ways unrecognizable from the molecular biology of the twentieth century – a discipline in which our understanding has advanced immeasurably, but about which many intriguing questions remain to be answered. Among the students being taught today are the molecular biologists of tomorrow; these individuals will be in a position to ask fascinating questions about fields whose complexity and sophistication become more apparent with each year that passes.

We have written the book with several guiding themes in mind, all of which focus on providing a faithful depiction of molecular biology in the twenty-first century, and on communicating this reality to students in a way that will engage and motivate, rather than overwhelm and intimidate.

A focus on the underlying principles

Arguably one of the biggest challenges facing instructors and students of molecular biology today is the vast amount of information encapsulated by the field. It is impossible for an instructor to convey every last detail (and equally impossible for students to absorb everything that there is to know). Indeed, we believe that, in order to understand the main concepts of molecular biology and to appreciate their exquisite complexity, it is not necessary to delve into every fine detail. Therefore, our approach focuses on communicating the *principles* of the subject.

We believe it is better for students to truly understand the foundational principles rather than simply learn a series of facts. To this end, we do not try to be exhaustive in our coverage. In the digital age in which we live, it is easier than ever before for students to gather a vast amount of information on a particular topic of interest. This information is of little value, however, if the student lacks a conceptual framework within which to make sense of all the information to which they are exposed.

By focusing on key principles, we seek to equip students with a conceptual framework, which we believe will be invaluable to them during their later careers.

An emphasis on commonalities

Until relatively recently, much more was known about the molecular components and processes of bacterial systems than of their archaeal and eukaryotic counterparts. In recent years, however, our understanding of archaeal and eukaryotic systems has increased enormously. With this increased understanding has come the realization that bacterial, archaeal, and eukaryotic systems exhibit many commonalities – commonalities that point to the common ancestry of the three kingdoms of life.

Throughout this book, therefore, our emphasis is on the *common features* of bacterial, archaeal, and eukaryotic systems. Differences do exist, of course – an inevitable outcome of evolutionary processes generating biological diversity. However, we have strived where possible to present a single view of key topics based on conserved processes and components. We have then discussed key differences between bacterial processes and their archaeal and eukaryotic counterparts where they exist, and where they have helped to further our understanding.

We recognize that some may feel that the processes occurring in bacteria, and in eukaryotes and archaea, are best taught separately. However, our focus on principles – and on constructing an overarching conceptual framework – leads us strongly to believe that an emphasis on commonalities is a valuable educational approach.

Integration of key themes and concepts

One of the most startling realizations of recent years has been the widespread importance of certain molecular phenomena, such as chromatin modification, or RNA silencing, which have impacts on genome function in ways far more diverse than had previously been recognized. Rather than examining each of these phenomena in isolation, our approach reflects their diverse impacts by presenting them in the various contexts in which they function. Therefore, you will not see a separate chapter on such topics; instead, the impact of these basic processes on genome function is woven throughout the book.

Similarly, while many books deliberately separate the regulatory control of basic processes from the processes themselves, we have chosen to put them together. As more is learned about how regulation takes place, it becomes increasingly apparent that regulation is typically nothing more than the alteration of the core process, so that an alternative, but related, pathway is chosen. Regulation simply acts on the core mechanistic features of the process, and so it makes sense to present them side by side.

➔ Look at the *Map of key themes* in the Online Resource Center at www.oxfordtextbooks.co.uk/orc/craig/ for an illustration of how topics such as regulation are blended throughout the book.

We believe this overall approach reflects the reality of molecular biology, and helps students to appreciate molecular biology as a unified discipline, with many components and phenomena acting in concert, rather than as a series of isolated topics.

A demonstration of how we know what we know

At heart, molecular biology is an experimental science. Our understanding of the field is increased through the accumulation of experimental evidence, which leads to the gradual emergence of key ideas and paradigms. Therefore, a central element to the understanding of molecular biology is an appreciation of the approaches taken to yield the information from which concepts and principles are deduced.

However, as instructors, we face a potential conflict: a mass of experimental evidence can often be overwhelming for students, and can make it more challenging for them to grasp the central ideas and paradigms that the experimental evidence has allowed us to elucidate. On the other hand, ignoring the experimental evidence deprives students from fully understanding the fundamental aspects of

molecular biology (and, indeed, of science in general). In response to this seeming conflict, our approach has been for the main body of the text to focus on the communication of key concepts, free from the layer of complexity that experimental evidence might introduce.

The 'experimental approach' panels

In recognizing the central importance of experimental evidence to furthering our understanding of molecular biology, we have complemented our coverage of key concepts in the main body of the text with separate panels entitled 'Experimental approach', which branch off from the text in a clearly signposted way. These panels describe pieces of research that have been undertaken and which have been particularly valuable in elucidating difference aspects of molecular biology.

Importantly, experimental research represents an ongoing journey of discovery, where the experimental approaches adopted develop as much as our understanding of the field. Uniquely, therefore, the experimental approach panels present, wherever possible, two approaches – one 'classic' and one 'contemporary'. Although all approaches have revealed valuable insights, regardless of whether they could be considered classic or contemporary, we believe that coupling the approaches in this way has additional educational value in terms of showing how both experimentation and the knowledge gained from such experimentation can evolve with time.

In addition to the experimental approach panels, further support for encouraging students to engage with experimental evidence is provided by an online Journal Club, as described more fully below.

The methods used in molecular biology

Many of the experimental approach panels (and the research work featured in the Journal Club papers) draw on certain laboratory techniques, which are used in different contexts throughout molecular biology research. The final chapter of this book, 'Tools and techniques in molecular biology', provides an overview of the basic techniques that are exploited during the course of much experimental work in molecular biology. Rather than describing general methods in detail within the experimental approach panels, we have directed the reader to appropriate coverage in Chapter 16, where they can learn more about the methodological tools that are at a molecular biologist's disposal, and how these tools work and what they can tell us.

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Baltimore, Maryland, July 2010

LEARNING FROM THIS BOOK

Beyond the overall approach adopted in writing this book, which we believe will make it a valuable teaching and learning resource, it includes a number of other features to help students get the most out of their molecular biology studies.

The experimental approach panels

As noted previously, molecular biology is an experimental science. To help you gain an understanding of how some of the key molecular processes and components described in this book were characterized, without overburdening the main text with lots of experimental detail, virtually every chapter features 'experimental approach' panels. These panels describe pieces of research that have been undertaken, and which have been particularly valuable in elucidating different aspects of molecular biology.

Further reading

Each chapter ends with a list of further reading materials, typically review articles, which we feel would make a good next step when looking to explore in more detail the topics covered in the book. Each further reading list is divided into chapter sections, to help you pinpoint articles that are of relevance to the particular topic you are interested in.

Glossary

Molecular biology, like many scientific disciplines, has its own particular vocabulary, and descriptions of molecular processes and procedures feature terms that may at first glance be unfamiliar. We have compiled an extensive glossary of all of the key terms featured in the book; we hope this will be of value as you master the language of the subject.

Cross-references

As we note previously, molecular biology comprises a range of interconnected topics, not a series of discrete, isolated ones. To help you make the connection between the topics presented in the book, and see how these topics come together to give a rounded picture of molecular biology, each chapter features numerous cross-references to other chapters in the book.

PDB codes

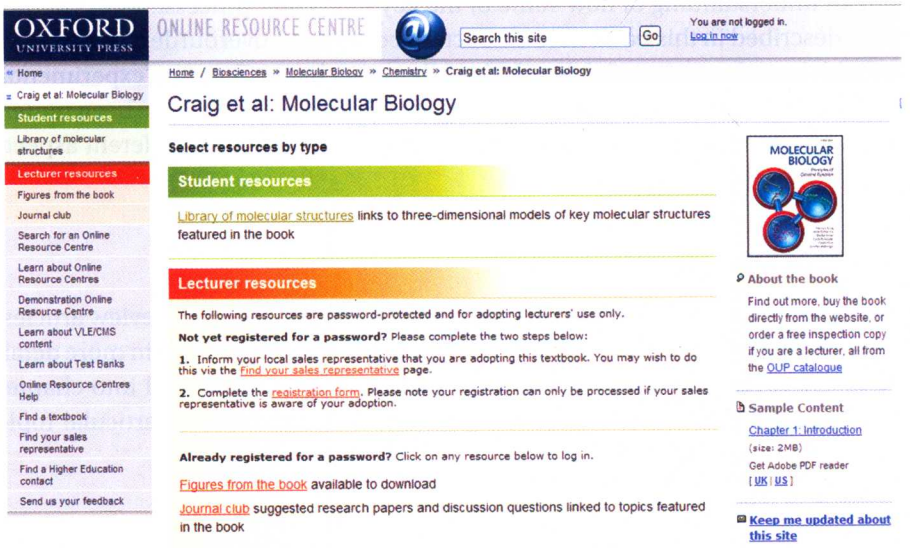
Many of the molecular structures that appear throughout this book have been generated from data deposited in the Protein Databank (PDB). Each entry in the PDB is assigned a unique code; this code can be used to retrieve the data related to the entry in question, which often includes crystallographic data, and onscreen renderings of molecular structures in three dimensions. The PDB codes relating

to many of the molecular structures in the book are given in the relevant figure legends. Visit the PDB website (http://www.rcsb.org/pdb/home/home.do) and enter the PDB codes related to molecules of interest to retrieve data related to those molecules for yourself.

Online Resource Center

Molecular Biology: Principles of Genome Function does not end with this printed book. Instead, additional resources for both instructors and their students are available in the book's Online Resource Center.

Go to http://www.oxfordtextbooks.co.uk/orc/craig/



For instructors

Electronic artwork

Figures from the book are available to download, for use in lectures.

Journal Club

Most chapters in the book are accompanied by an online Journal Club, which features suggested research papers and discussion questions linked to topics featured in the chapters. Understanding the details presented in primary literature articles can often be challenging; the purpose of the Journal Club is to guide students through some selected papers in a structured way, to build their confidence in reading and critically evaluating the work of others.

For students

New and noteworthy

This is a note of key highlights from the field of molecular biology since the book's publication, and is updated for the start of each semester.

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We were fortunate to have worked under the guidance of two gifted individuals. The project was begun with Miranda Robertson at New Science Press, who convinced us that we could write a new textbook and helped show us the way. We benefited from her tremendous vision, advice, and insistence on clarity, as well as from her many visits to work with us in Baltimore and Washington. It was Jonathan Crowe at Oxford University Press who ushered us across the finish line by providing superb editorial advice, while teaching us how to work ever more effectively. He made outstanding contributions to the writing and organization of this book, and we are grateful for his efforts in helping us bring this project to completion.

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Our work was supported by many others. Matthew McClements is responsible for the beautiful illustrations while Lore Leighton did the graphics rendering of macromolecules. At New Science Press, Karen Freeland, Joanna Miles, and Gina Lyons helped to keep us on track and organized despite ourselves, while Eleanor Lawrence and Matthew Day lent their excellent editing skills to the project. At Oxford University Press, Bethan Lee and Marionne Cronin provided organizational and editorial support, while Lotika Singha did an excellent job of copy editing. Our administrative assistants, particularly Patti Kodeck, helped to organize our meetings and carve out time for us to work on the book.

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Chapter 4

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Chapter 5

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Chapter 6

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Chapter 7

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Figure 7.27b from O'Connor, C. (2008). Meiosis, genetic recombination, and sexual reproduction. *Nature Education* 1 (1).