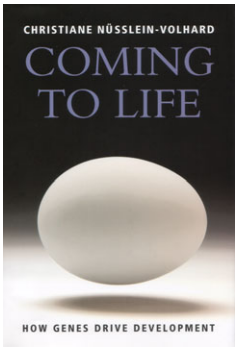
# Genetic screens to bioethics – developmental biology for the people




**Jonathan Slack**

Centre for Regenerative Medicine, Department of Biology and Biochemistry, University of Bath, Bath BA2 7AY, UK
e-mail: j.m.w.slack@bath.ac.uk
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## Coming to Life

**By Christiane Nüsslein-Volhard**

Yale University Press (2006) 224 pages
ISBN 0-300-12080-X
£18.99 (hardback)

Christiane (Janni) Nüsslein-Volhard is our representative in the wider world. Along with Eric Wieschaus and Ed Lewis, she was the recipient of the 1995 Nobel Prize for Physiology, which was awarded for her genetic screens on *Drosophila* that led to the discovery of most of the genes that control development, not just in *Drosophila*, but in all animals.

Her book *Coming to Life* was published in German in 2004, and is now issued as an English edition by Yale University Press. It is an account of modern developmental biology written for a general audience. In effect, it is a summary of the great endeavour that the readers of *Development* are engaged in, and with which some of us have been occupied for a very long time. She describes accounts of animal development written before the 1980s as: 'rather voluminous, full of highly complicated experiments'. Her work, and that of others in the 1980s and early 1990s, led to a revolution in our understanding of development that created the modern science of today, which has simple generally agreed principles that can be explained in undergraduate textbooks.

The first two chapters of this book contain an account of the basic concepts without which nothing in biology can be explained: evolution, cells, chromosomes and genes are all introduced at the level of an educated layman. The next three chapters deal with *Drosophila* development and cover the morphology of development, the different classes of developmental gene and how these genes work together to assemble an animal. Very modestly, Janni does not say that much of the material in these chapters was her own work. Then, there is a chapter about more general aspects of development, including cell division and growth, followed by one on the development of vertebrates, which is a sort of whistle-stop tour of the model organisms (*Xenopus*, zebrafish, chick and mouse). I think she might have said a little more about the inducing factors in vertebrates, as I believe that their discovery, along with that of the developmental genes of *Drosophila*, created a synergistic research programme that became the core of modern developmental biology.

Finally there are three chapters that extend the story in directions that Janni obviously feels will be of interest to her readers: human development, evolution from a molecular standpoint, and the ethical-legal debates about human embryo research and embryonic stem cells.

**In effect, it is a summary of the great endeavour that the readers of *Development* are engaged in, and with which some of us have been occupied for a very long time**

So, how much of a success is the book? It is clearly written and covers most of the main themes that I myself would include in an introductory account. I think it will be regarded as too technical for the general reader, but I would certainly recommend it to a high-school student or a new undergraduate who was interested in this area. It is also a success in that it brings to the front of my mind some topics for discussion, although here I suspect that the author will not agree with all of my reactions.

First, is developmental biology finished? If it is possible to write a book like this and have another professional developmental biologist to agree that the content and conclusions are appropriate for an introductory account, then it would seem that we have arrived at a 'classicism' – a mature subject that will, in future, not develop through basic concepts but just by increments of detail at the margins. Of course no subject is ever really finished, as there are always more details to elucidate. As long as science budgets are constantly expanding, every field can go on growing forever. But as budgets reach their natural limits, the relentless competition for funds may force a reduction in funding of fields that are perceived from outside as being 'mature'. I know that none of my colleagues agrees with this line of thought, but I mention it nonetheless, if only to encourage people to think of more arguments as to why developmental biology should continue to be funded.

Second, I am struck by the fact that the last three chapters do not really flow from the previous four, in which the principles of modern developmental biology are set out. All of us who engage in teaching know that students like to hear about human embryos, diseases and medical applications, and are less interested in lower organisms, techniques or theory. I don't really know what Janni's personal motivation was as she embarked on her historic genetic screens, but I doubt whether she did it in order to cure serious human diseases. What has actually happened is that collectively the community has solved the scientific problems of development, to a degree of detail that I would not have believed possible in the 1970s, but at the same time this knowledge has had remarkably little impact on practical affairs. I fear that this is why there is a significant disjunction in this book between chapters 2 and 6 (about developmental biology), and chapters 7 and 9 (about topics of interest to the public).

Third, what about the much-vaunted model organisms? Janni states that 'knowledge gained from one organism can readily be transferred to another' (p. 91). Later, she suggests that cancer research will benefit from the study in model organisms of genes that, when mutated, contribute to the cause of cancer in humans. It is true that many human cancer genes do encode components of signal transduction pathways that are used in development. But I am worried. The long-range evolutionary homology of developmental mechanisms was one of the big discoveries of the past 20 years. These results are important, and are perhaps underemphasised in Chapter 9, which deals with evolutionary mechanisms. But the more work we do, the more we find

that the details are different. The august journal *Development* today contains plenty of keynote papers announcing, for example, that the Wnt pathway in zebrafish and *Drosophila* are slightly different. Given the nature of evolution by natural selection, it is hardly surprising that the broad brush picture is similar and the details are different. But it does inexorably follow that if your funding is coming from medical research bodies that want cures for human diseases, then the value of model organisms will decline once the early discoveries have been made. For example, just because APC (adenomatous polyposis coli) is involved in Wnt signal transduction in both human and *Drosophila*, does that really mean that study of the minutiae of functions of APC in *Drosophila* will really tell us useful things about human cancer? I doubt it. The more detailed the questions, the more important it will be to work on human cells and tissues.
Fourth, we authors are uncomfortably aware that books always contain errors or ambiguities. However hard you try, there are always a few that get through. We are actually grateful to reviewers for pointing them out, so that they can be removed from the next edition. So here goes. On p. 48, it should read nerve cord not chord. In Fig. 23, the explanation of maternal effect mutation is somewhat obscure to me, so might fool the general reader. On p. 85, somatic stem cells need not undergo asymmetrical cell division. On, p. 88, the text seems to suggest that jawless fish are not vertebrates. On p. 98, the text says that imprinting is unique to mammals but it does actually also occur in flowering plants. Imprinted genes also affect much more than just development of the trophectoderm. And finally, on p. 137, Gurdon did not carry out the first cloning experiments in amphibians. These were reported by Briggs and King in 1952. Gurdon did pursue the subject very thoroughly, to the limit of using nuclei from indubitably differentiated cells (adult keratinocytes), although he showed that these nuclei worked very much less well than embryonic nuclei.

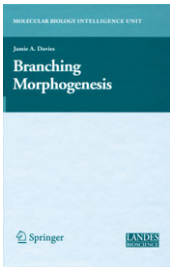
Finally, a word on stem cells. Many people, including myself, are thinking that stem cell research should represent the applied science that grows out of academic developmental biology. Stem cells feature in this book in Chapter 6 and again in Chapter 10. There is now a general consensus that the protocols for turning human embryonic stem cells into useful differentiated cells will need to recapitulate the normal sequence of inductive signals for each step of commitment from the inner cell mass to the final product. These steps have been worked out by developmental biologists and are currently being used in many laboratories to design a variety of relevant protocols.

In my view, Janni is unduly dismissive of adult stem cells (p. 143), suggesting that nothing is likely to come from them. In fact adult stem cells are already in clinical use and have saved many lives! These include haematopoietic stem cell grafts for haematological diseases or cancer therapy; in vitro expansion of keratinocyte holoclones to regenerate skin for severe burns; grafts of the limbus, which contains the stem cells for the cornea; and one might perhaps even include the grafting of pancreatic islets for treatment of diabetes, as this sometimes involves in vitro culture. However, we have to admit that none of these existing applications owe much to developmental biology. In future, I hope this will change and that the elegant science represented by this book does eventually deliver some practical benefits to wider society.

# Breaking the branching code

**Saverio Bellusci**

Children's Hospital Los Angeles, Saban Research Institute, 4650 West Sunset Boulevard, Los Angeles, CA 90027, USA
e-mail: sbellusci@chla.usc.edu
doi:10.1242/dev.02571




## Branching Morphogenesis

**Edited by Jamie A. Davies**

Springer (2005) 258 pages
ISBN 0-387-25615-6
$139 (hardback)

For centuries, curious observers have been intrigued by the formation of ramified structures. The complexity and diversity in branching patterns among trees, alga, lung and the mammary gland, to name a few biological examples, have left the impression that it will be difficult to understand the basic principles that orchestrate branching morphogenesis. However, discoveries made in the past decade in biological systems, as well as in physical ones, such as rivers, oil fields, viscous fingers (elongated duct-like structures that form when one fluid penetrates into a more viscous one) and metallurgy, indicate that apparently disparate branching systems seem to share deep similarities in the forces and processes that shape branching. Moreover, branching morphogenesis in vertebrate organs occurs for the most part during embryonic development, when progenitor cells are extremely abundant. Therefore, the study of branching, which involves characterizing the interactions between epithelial, mesenchymal and endothelial cells during development, is relevant to understanding the interplay that occurs between niche cells and stem cells in adult tissues. In addition, understanding how cell shape remodeling and cell matrix interaction are coordinated during the process of branching may also reveal the changes that occur in adult tissues during the repair process after injury or during regeneration. Finally, the field has also more recently benefited from the input of physicists interested in proposing theoretical models based on the different kinds of forces at work during branching. Therefore, putting together a book dedicated to the branching process of different organs is timely indeed.

**The techniques described in this book to study branching mophogenesis are relevant to biochemistry, molecular genetics, cell biology, anatomy, developmental biology, biophysics and computer modeling**

Jamie Davies, the editor of *Branching Morphogenesis*, has recruited a comprehensive team of experts to cover many important aspects of this field. The targeted audience for this book is both

developmental biologists and students. The book is divided into 13 chapters. Chapter 2 deals with branching morphogenesis in vertebrate neurons. Within the developing vertebrate nervous system, strict control of branching morphogenesis is essential to establish appropriate circuitry, as the geometry of neuronal arbors critically influences their functional properties. Chapter 3 focuses on the branching of single cells in *Arabidopsis*, whereas Chapter 4 covers branching in fungal hyphae and fungal tissues, in which the authors describe a sophisticated mathematical model that simulates fungal growth and branching. Chapter 5 discusses branching in colonial hydroids, which are the most-studied cnidarian group with respect to developmental biology. Chapter 6 describes how the tree-like vascular network is established, and Chapter 7 discusses the importance of extracellular matrix remodeling in mammary gland branching morphogenesis. Chapters 8 to 11 deal with branching in mammalian kidneys, salivary glands, prostate and uterine glands, whereas Chapter 12, which is written by a physicist, is dedicated to the physical mechanisms of branching morphogenesis.

### Why cover branching morphogenesis in different organs and organisms?

Some branching systems, such as the tracheal placode in *Drosophila*, or the lung or kidney in vertebrates, are more studied than others, and the information presented in this book will allow the reader to have an integrated view of the control of the branching process across a broader spectrum of organisms and tissues. Aficionados of branching morphogenesis can therefore apply techniques developed by others to their system of interest, to gain valuable information in the weak areas of their own system with relative ease. In particular, the various specialized techniques described in this book to study the process of branching mophogenesis are relevant to the fields of biochemistry, molecular genetics, cell biology, anatomy, developmental biology, biophysics and computer modeling.

### The morphogenetic code: still to be deciphered?

Chapter 12 presents Dr Fleury's view of branching morphogenesis. As an example, the fractal iterative model of the 'lung' based on simple building principles is discussed. It is proposed that these building principles are re-iterated many times to give rise to ramified structures. Identifying these building principles is crucial if we want to break the branching morphogenetic code, which involves a master routine that sequentially or simultaneously controls various branching subroutines. A key subroutine controlling bud formation, for example, involves the modulation of cellular properties such as differential cell adhesion, cell motility, cell-matrix interactions and cytoskeletal organization. How this basic subroutine coordinates with another subroutine that controls cell proliferation and differentiation is still unclear. This book gives an integrated view of the many parameters controlling branching morphogenesis.

### A view of how branching is regulated

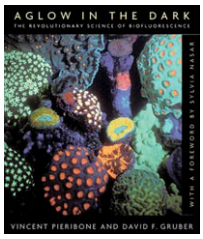
The importance of paracrine factors, such as members of the bone morphogenetic protein (Bmp), fibroblast growth factor (Fgf), Wnt and Hedgehog (Hh) families, which are produced locally in the immediate vicinity of the branching structure and which can positively or negatively regulate branching, has been established in vivo and in vitro in many systems. Interestingly, Chapter 7 (which deals with mammary gland branching morphogenesis) and Chapter 10 (which deals with the branching of the prostate) also underscore the role of sex hormones, which are produced at other locations in the body and which control organ development in association with local signals. Chapter 8, on kidney branching, discusses the importance of paracrine signals and associated feedback loops in controlling the branching process in this organ. In Chapter 5, the authors show that autocrine signaling is important in the development of branched structures, such as in the fungi described in Chapter 4, and in the hydroids described in Chapter 5. And finally, the importance of the extracellular matrix for the branching of the mammary gland comes under the spotlight in Chapter 7.

In conclusion, this book on branching morphogenesis contains an excellent combination of articles that will allow the reader to rapidly gain an overview of the current knowledge and ideas in the field, and that will inspire them to take their research on this topic to the next level of functional analysis.

# GFP: trip to the light fantastic

**Kat Hadjantonakis**

Developmental Biology Program, Sloan-Kettering Institute, New York, NY 10021, USA
e-mail: hadj@mskcc.org
doi:10.1242/dev.02681




## Aglow in the Dark

**By Vincent Pieribone and David Gruber**

Harvard University Press (2005) 863 pages
ISBN 0-674-01921-0
£15.95/$24.95 (hardback)

The emergence and exploitation of green fluorescent protein (GFP) has redefined our approach to, and our understanding of, development, homeostasis and disease progression. The utility of fluorescent proteins like GFP has revolutionized experimental approaches in biological research, advancing what is possible. Indeed, developmental biologists today are armed with a bastion of genetically encoded fluorescent proteins and are no longer confined to the study of fixed (i.e. dead) material. Together with recent advances in optical microscopy, fluorescent proteins have become an indispensable tool in a myriad of live imaging experiments. Such experiments now allow us to observe an event as it takes place in situ over time, thereby bringing us closer to understanding exactly how a process of interest actually takes place.

With *Aglow in the Dark*, researcher Vincent Pieribone and scientific writer David Gruber have teamed up to produce a book that is both informative and entertaining. It chronicles the history of biofluorescence, and of genetically encoded fluorescent proteins in particular. Albeit an illuminating read (no pun intended!), this is not a textbook, nor a technology guide. Instead it describes an odyssey of discovery that starts with the scientific curiosity that ignited efforts that culminated in the purification of GFP, its subsequent cloning

and its later application as a readily visible molecular tag. It details some of the rationale and events that spawned the emergence of today's bumper crop of genetically encoded fluorescent proteins, representing a technicolour palette of increasing complexity. Just over a decade after the cloning of GFP, the use of fluorescent proteins is now commonplace. They represent routine, if not to say essential, tools for many fields of biology, including cell, developmental and neurobiology.

The story told in this book is in itself fascinating, and the authors make sure that the reader is introduced to the protagonists along with their major endeavours. However, as might be expected, and probably in order to make for better reading, many of the events concerned have been streamlined, with the frequent omission of key players, contributions and/or observations. The authors do not delve too deeply into their subject matter, but this may be intentionally to capture a wider audience. Furthermore, the discussion steers clear of the possible double-edged bioethical ramifications of genetically encoded fluorescent protein technology. The text is focused on providing a chronological overview of events, and (unfortunately) a rather superficial description of a few examples of the use of fluorescent proteins to provide the reader with only a glimpse of what might be possible.

In the first chapter, the authors set the stage by discussing bioluminescence, with the basic how and why of this primarily marine phenomenon. They detail how glowing proteins first evolved, and introduce us to the researchers who were inspired by the fluorescence of a variety of animals, including the eponymous jellyfish. They describe the quest to understand the chemical and physical properties of the bioluminescence reaction that led to the isolation of the responsible proteins. Indeed, it was this work that laid the foundations on which the GFP revolution was built, and resulted in the christening of a protein capable of producing green fluorescence when illuminated with ultraviolet light.

Occasionally the transitions between topics are somewhat obtuse, as with the discussion of the basic principles and history of optics, and the science of fluorescence that follows. This is also the case with the introduction of the nematode worm in later chapters.

As the authors continue to weave their story, the reader is taken through the endeavours of many individuals instrumental in taking genetically encoded fluorescent proteins out of their native context and into heterologous systems. The authors review some of the experiments that helped formulate our understanding of how GFP works, and they detail some of the reasons behind the development of an artillery of mutants, each having unique properties suitable for specific applications. The authors digress to mention a few applications, and also to discuss some of the more frivolous uses of fluorescent proteins, which are exemplified by the generation of transgenic 'glowing' domestic animals, marketed as pets and/or art.

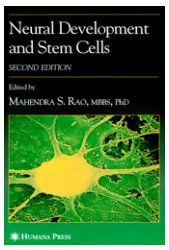
**Albeit an illuminating read…this is not a textbook, nor a technology guide. Instead it describes an odyssey of discovery…**

The authors go on to discuss the breakthrough that resulted in an increased assortment of fluorescent proteins being made available as a result of work that identified fluorescent proteins with structural similarity to GFP in non-bioluminescent corals. They also discuss the benefits and shortcomings of fluorescent proteins that exhibited longer wavelength (i.e. red and far-red) excitation and emission spectra. Indeed, we now know that the vivid fluorescent and non-fluorescent colouration of reef Anthozoa is primarily due to a mélange of GFP homologs. And it is the increasing catalogue of cloned GFP homologs that is responsible for the continual expansion of the available genetically encoded colour palette. Here, the authors pause to discuss the diversity of reef corals and highlight the pressing issue of ecological preservation.

The final chapters deal with current and future applications. Ideally, one would have liked to see case studies chosen to reveal the broader impact and potential of the available bounty of fluorescent proteins. Unfortunately, it is here that the authors fail to do the field justice, with vignettes drawn almost exclusively from the field of neurobiology. This section would certainly have benefited from a more expansive discussion of a broader set of applications that would illustrate the true promise of this technology.

That said, as popular science books go, the text is both concise and informative, and certainly worth a leisurely read. It is rather beautifully illustrated, with many of the images resulting from deep-sea excursions courtesy of the authors. Ultimately by telling this story, the authors feed our fascination with all that glows in the dark, and recount the work that laid the foundations of one of the most prolific contributions to modern-day biology.

# A feast of neural stem cells




**Kate Storey**

Division of Cell & Developmental Biology, University of Dundee, Scotland, UK
email: k.g.storey@dundee.ac.uk
doi:10.1242/dev.02695

**Neural Development and Stem Cells, Second Edn**
**Edited by Mahendra S. Rao**

Humana Press (2005) 454 pages
ISBN 1-588-29-481-1
$145 (hardback or online copy)

It is now clear that neural stem cells, which are self-renewing multipotent cells able to give rise to neurons, astrocytes or oligodendrocytes, are found in a great variety of regions in the vertebrate developing and adult nervous system. Cells with these properties can also be derived from embryonic stem (ES) cells in vitro using protocols inspired by our understanding of neural stem cells in the intact nervous system. The ability to culture neural stem cells in vitro and to direct their differentiation into specific cell types has also opened up the possibility of generating neurons for therapeutic purposes; for example, transplantation of additional dopamine-producing neurons to alleviate loss of such cells in Parkinson's disease. With the advent of human ES cell lines,

interest in neural stem cells is growing apace. This book comprises a collection of chapters addressing the many different contexts in which neural stem cells are found, describing the developmental potential of these cells and their distinctive cellular and molecular characteristics, as well as the therapeutic applications of such cells. The book is intended as a handy guide for a course on stem cell biology for novice and expert alike. However, it is not a textbook, but rather a series of stand-alone essays organised into a loose progression from neural stem cells in the early embryo, in specific regions and in the adult nervous system.

This book is an updated version of the first edition, which was published in 2000, and now comprises fifteen chapters. An excellent opening essay from Sally Temple defines neural stem cells and describes their changing potency as development proceeds. This is followed by a series of partially overlapping chapters that address the properties of stem cells in the developing vertebrate central nervous system (by Larysa Pevny; John Kessler and colleagues; Douglas Falls and Marla Luskin), including in the retina (a new chapter for this edition from Iqbal Ahmad and colleagues). Peripheral nervous system/neural crest development and stem cells in cancer are then addressed by Marianne Bronner-Fraser and colleagues. Adult neurogenesis in the cortex and hippocampus, as well as in the olfactory epithelium (another new topic for this edition), is also well reviewed (Daniel Lim and Arturo Alvarez-Buylla; Steven Goldman; Theo Palmer and Fred Gage; James Schwob and Woochan Jang). Other focussed chapters consider the regulation of neural stem cell death (an additional new chapter, from Rizwan Akhtar and Kevin Roth), glial-restricted precursors (Mark Noble and Margot Mayer-Pröschel) and transdifferentiation in the nervous system (Ying Liu and Mahendra Rao). The final chapters address the derivation of neural stem cells from ES cells (Robin Wesselschmidt and John McDonald) and the use of neural stem cells for transplant therapy (Evan Snyder and colleagues).

Overall, these are scholarly, informative, well-written essays. There are, however, some omissions, including an account of vertebrate neural induction and of the multipotent, self-renewing, stem cell-like population in the tail bud, although this cell population gives rise to mesodermal as well as neural derivatives (Cambray and Wilson, 2002; Davis and Kirschner, 2000; Mathis and Nicolas, 2000). Our understanding of vertebrate neurogenesis is also greatly informed by analysis of this process in invertebrates and in *Drosophila* in particular. For example, recent experiments in the retina that assess loss of the mammalian homologue of Inscuteable have revealed yet again the conservation of gene function from fly to mammal and the crucial importance of mitotic spindle orientation for cell fate symmetry during neurogenesis (Zigman et al., 2005). Although this topic is included in Sally Temple's first chapter, it would also have been great to have a whole chapter on *Drosophila* neural stem cells from researchers working in the field.

**The book is not a textbook, but rather a series of stand-alone essays organised into a loose progression**

There is also just one chapter that covers the vast topic of neural differentiation of ES cells in vitro. This chapter outlines the basics, including culture methods and conditions for embryoid body formation and for the monolayer culture of ES cells. Protocols for the use of retinoic acid and sonic hedgehog to promote neural differentiation and the generation of specific neuronal cell types in embryoid bodies are also discussed. However, the chapter does not review experiments that directly implicate other signalling pathways (such as FGF, Wnt and Notch signals) in the regulation of ES cell neural differentiation. It would also have been interesting to discuss certain key issues, such as whether it is possible to generate a homogenous neural cell population in vitro and what differences are apparent between neural/neuronal/glial differentiation during embryonic development and in ES cells in vitro. The frequent references to the now discredited work of Hwang Woo Suk also jump out at you and are testimony to the great pressure that this area of research is under and the speed at which this field is moving.

A more discursive approach is taken by the editor Mahendra Rao, who should be applauded for tackling the controversial and fascinating topic of transdifferentiation. This chapter raises important issues that need to be addressed if this phenomenon is to be firmly established as taking place in neural tissue. These include the possibility that cells thought to have transdifferentiated may actually have changed their properties as a result of fusion with a different cell type, and that cells with apparently altered characteristics might have arisen as a result of the activity of contaminating stem cells, rather than owing to the redirection of the gene expression profile of a differentiated cell. There is also a tendency for over-interpretation in this field; for example, when a neural crest cell adopts a new fate, this could be interpreted as revealing the broad competence of these cells rather than evidence for a switch between differentiated cell states. As Rao points out, transdifferentiation has great potential as it could be used to generate new tissues from host cells, thereby removing the possibility of rejection by the immune system.

The chapters on adult neurogenesis are particularly well written, with clear nomenclature and a good balance between data and opinion. Daniel Lim and Arturo Alvarez-Buylla consider the similarities between glial cells and adult neural stem cells and conclude that in some cases these are one and the same cell. They also make the intriguing suggestion that the presence of a cilium on B cells (likely subventricular zone stem cells) is an indication of their cell cycle phase. Theo Palmer and Fred Gage provide a particularly thoughtful account of the realities of therapeutic approaches to neuron replacement in the adult brain, concluding that even when technical difficulties are overcome, we still know nothing of the cognitive repercussions of such manipulations. Transplantation therapy using ES cell-derived neural tissue is also discussed by Robin Wesselschmidt and John McDonald, who make the interesting observation that such cells differentiate faster than do adult neural stem cells, and that transplanted ES cells can also remodel the extracellular environment. They go on to suggest that ES cells might be used clinically to modulate the host environment to make it more conducive to regeneration. The use of ES cell-derived neural tissue for creating in vitro models of neurodegenerative diseases that are amenable to drug screening would also be a further topic for a future edition.

Overall, this is a useful collection of essays that is illustrated with plenty of diagrams and colour images, and it is really valuable to have all this information in one place. However, these kinds of collections do have some drawbacks. It is hard for an editor to tell invited authors what to write. This means that there is inevitably some overlap between chapters. Each chapter is also written as a stand-alone piece and

requires, particularly in the field of stem cell research, a clear set of definitions. Chapter introductions also serve to acknowledge the breath of the field before defining the specific area to be discussed. This can lead to further frustration for the reader. For example, in numerous introductions to the chapters in this book, we are told that there is some evidence for the existence of stem cells in the spinal cord, together with the suggestion that this evidence may not be compelling, but no one reviews the data. This tendency for repetition and the lack of overall coverage of the subject make the book less appropriate for the novice and as a course guide. I think it will most likely be read for specific chapters by graduate students and experienced researchers that are new to the field. On the other hand, this book really does document the great progress being made in this area of research, so much so that it seems time for a textbook on neural stem cells. Such a book would provide a simpler but more systematic overview of the subject; it might lose some of the very extensive references (including the duplications), but still retain space for inspiring speculation.

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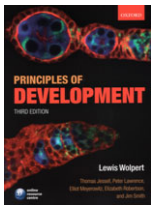
# Essential principles of developmental biology


**Christof Niehrs**

Department of Molecular Embryology, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany
e-mail: Niehrs@dkfz-heidelberg.de

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## Essential Developmental Biology, Second Edn

**By Jonathan M. W. Slack**

Blackwell Publishing (2005) 365 pages
ISBN 1405122161
£29.99 (paperback)

## Principles of Development, Third Edn

**By Lewis Wolpert, Thomas Jessell, Peter Lawrence, Elliot Meyerowitz, Elizabeth Robertson and Jim Smith**

Oxford University Press (2006) 551 pages
ISBN 0-19-927536-X
£34.99 (paperback)

The authors of today's developmental biology textbooks face the challenge of keeping up with a field in which the number of published papers is staggering and which is increasingly fragmenting into subdisciplines, such as developmental neurobiology, developmental cell and molecular biology, stem cell biology and Evo-Devo. The other challenge when writing an introductory textbook is to decide what to cover without going into too much detail.

Two textbooks from eminent British developmental biologists, which have successfully dealt with these challenges and which have been around for some years, have recently published new editions: Jonathan Slack's 2nd edition of *Essential Developmental Biology*, and Lewis Wolpert's 3rd edition of *Principles of Development*, which is co-authored by several other high calibre developmental biologists – Thomas Jessell, Peter Lawrence, Elliot Meyerowitz, Elizabeth Robertson and Jim Smith. It is interesting to compare how they differ in their approach, in particular since both target a similar readership, namely undergraduate and new graduate students, and have a similar goal in mind, to distill the *Essentials* (Slack) or *Principles* (Wolpert et al.) and present them in a compact and concise way. Both books are meant to be introductory and require no prior knowledge of the subject, and they compete with several similar textbooks on the market by Scott Gilbert (*Developmental Biology*), Alfonso Martinez Arias and Alison Stewart (*Molecular Principles of Animal Development*) and Fred Wilt and Sarah Hake (*Principles of Developmental Biology*).

It is unfair to compare too closely each book's coverage of the field, as Slack's *Essentials* is almost 200 pages shorter than the 550 page book by Wolpert et al., which is a bit surprising given that both cost around £30 in paperback. Slack's textbook appears even more overpriced given that it reproduces almost no photographs, unlike that of Wolpert and colleagues. This is a shortcoming of *Essential Developmental Biology* because photos give a more realistic idea to a student (who may never see embryos in a practical course) of what a particular phenomenon or tissue being described looks like. What Slack decided to sacrifice entirely given these page constraints is the development of plants and of the lower eukaryotes, other than *Drosophila* and *C. elegans*. Furthermore, most topics are dealt with in a shorter fashion by Slack than by Wolpert, or topics are not accompanied by illustrations. For example, where Wolpert and colleagues present the dorsoventral patterning of *Drosophila* over two pages, Slack covers this topic in one paragraph. The Nieuwkoop center gets four lines in *Essential Developmental Biology* and one and a half pages in *Principles of Development*. That said, the conciseness of Slack's book can help to focus a reader's attention and avoids sometimes confusing detail.

*Principles of Development* is up to date and in terms of its scope provides a comprehensive overview of the field, covering the development of plants, as well as of less 'famous' invertebrates, such as sea urchins, ascidians, slime molds and Hydra. Wolpert does a particularly great job on 'morphogenesis', a topic close to his heart. His approach is factual, and experimental evidence is provided for most key findings. By contrast, Slack systematically aims to derive conclusions from experimental evidence. This is very laudable, but I wonder if his main audience would appreciate this mature approach. I am afraid that much of this good intention might be lost given the reality of most university courses, from which a certain factual canon needs to be acquired, regardless of all the experimental history that led to it.

Although boxes appear in both textbooks, a particular feature of Slack's book is a box called 'Classic Experiments' and another

called 'New Directions in Research'. Again, I wonder how useful these are for the average student, who is looking for a concise introduction to developmental biology, particularly when space is already a constraint. Furthermore, methods such as morpholinos and domain swaps may become easily outdated, just like earlier molecular methods not mentioned anymore. Molecular methods come and go, the fate map stays forever.

While writing this review, I faced a similar problem to the authors of these books when deciding whether to cover the different vertebrate model organisms one after the other or side-by-side, according to the distinctive features of embryonic development. As Slack writes in his preface, his book differs in this respect from other similar books on the market, as it keeps the organisms separate to avoid confusing the student, who might think that 'knockouts can be made in *Xenopus*' and the like. This approach does have a lot going for it, especially for beginners, and makes his chapters and writing very clear. Conversely, in *Principles of Development*, the patterning of the vertebrate body plan is covered side by side in two chapters dedicated to 'Axes and germ layers' and 'The somites and early nervous system'. By doing so, Wolpert and colleagues try to minimize the other common cause of confusion to students, when they are confronted with different nomenclatures in vertebrate models and need to memorize a plethora of seemingly differing phenomenology, while they are told in the first lecture that a key aspect of animal development is its evolutionary conservation. Alas, how could these authors succeed, where the field itself fails! Wolpert's 'Summary Table' on 'Vertebrate Axis Determination' reads as if lower vertebrates and Amniotes evolved on different planets. As another example, the parallels of limb/wing development in vertebrates and insects are hardly discussed. This may have to do with the fact that *Principles of Development* has become a multi-author book. In addition, various parts of the book have apparently been more or less amended by various experts in the field. For example, the writing of Claudio Stern in the chick neural induction section is unmistakable. All of this makes for very precise and up-to-date factual presentations, but it makes integration much more difficult. This is why *Principles of Development* reads a bit like a mosaic, whereas *Essential Developmental Biology* is made from one casting.

Most of us who teach developmental biology present in our early lectures the basic concepts of determination and specification relative to cell fate, and of course both authors go to great length to introduce these concepts. However, these terms hardly appear later on in these books, and, if I reflect on my own lectures, then the same holds true, as I don't use them when I discuss the various model organisms. The reason for this is that specification and determination are concepts from a pre-molecular era. We now refer to marker genes becoming induced at certain stages, without mentioning specification or determination in the classical sense. Similarly outdated may be the distinction between regulative versus mosaic development, terms intimately connected to induction. We know now that inductive processes occur in *C. elegans* just as much as they do in vertebrates, and that regulative versus mosaic development reflect experimental design more than fundamental biological differences. New editions of these textbooks may want to take into account this conceptual progress, particularly as both books are very molecular in their approach. Another complex term that is covered in both books is the zootype, which remains conspicuously lifeless in Wolpert et al.'s book, whereas Slack, who originated the concept, illustrates it convincingly.

***Essential Developmental Biology* provides a highly readable, well-structured and nicely illustrated book. To the novice, but also to the more initiated, I would recommend *Principles of Development***

When covering such a broad field, certain omissions, typos, errors and the like are always likely to occur. Although Slack had to sacrifice covering certain topics because of his space constraints, certain terms should nevertheless have been explained or discussed. For example, 'neural induction' is missing in the index, and the Evo-Devo chapter fails to introduce 'neoteny'. Given Slack's explicit aim to write also for medical students, the absence of any reference to human embryos is a shortcoming. Teaching experience shows that referring to human congenital malformations is always very stimulating for students. *Principles of Development* extensively discusses vertebrate organogenesis, but the authors do not seem to be very fond of endodermal derivatives. The index of *Principles* furthermore lacks the important terms 'hypomorph' and 'cell polarity'. Moreover the statement in this book that the mouse node is unable to induce forebrain is outdated (see Kinder et al., 2001). Finally, hyphens in certain species' gene and protein symbols should be avoided, as recommended by various nomenclature committees, and no attention has been paid to this issue in either book.

A great feature of *Principles of Development* is the website that accompanies it, where one can download the illustrations featured in the book. This online resource used to be freely accessible but is now unfortunately password protected. To register for access to this website, you must now be a lecturer at a teaching institution and have adopted this textbook for one of your courses. The website is very extensive, with well-organized web links to every chapter for those who want to learn more, and which feature multiple choice and concept questions to use to check a student's understanding. Although the web companion to *Essential Developmental Biology* is less extensive, it features many nice animations that will be useful for teaching. The site also features 'Student review questions and instructor resources', which can be accessed at an extra cost of £10.

Given their different approaches and scopes, to whom would I recommend these books? To the student who takes an introductory course in developmental biology and who wants to focus on the basics, Slack's *Essential Developmental Biology* provides a highly readable, well-structured and nicely illustrated book. Slack's ability to present an integrated view of the field and his ability to simplify complex issues is an impressive aspect of this book. To the novice, but also to the more initiated, I would recommend *Principles of Development*, as its generous, multi-color illustrations make it a great learning companion. It is a very comprehensive book, which is loaded with information, including some of the latest findings on various hot topics. It does justice to its aim of outlining the key concepts and principles of development.

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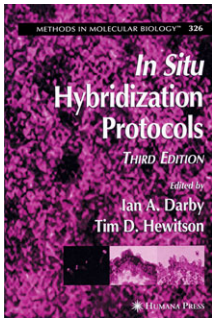
# One ISH, two ISH, red ISH, blue ISH: choosing the right in situ hybridisation protocol




**Jeffrey H. Christiansen**

MRC Human Genetics Unit, Edinburgh EH4 2XU, UK
e-mail: jeff.christiansen@hgu.mrc.ac.uk
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## In Situ Hybridization Protocols, Third Edn

**Edited by Ian A. Darby and Tim D. Hewitson**

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ISBN 1-588-29-402-1
$99.50 (hardback)

It is nearly a quarter of a century since the groundbreaking experiments of Ernst Hafen (Hafen et al., 1983) and Mike Levine (Levine et al., 1983), who first applied the technique of in situ hybridisation (ISH) to embryo specimens. These experiments provided the first insights into the spatial distribution patterns of specific transcripts in different regions of the embryo. Since then, the technique of mRNA ISH has become central to the study of developmental biology and is routinely used to assess the spatiotemporal expression pattern of newly identified genes, which is a necessary first step towards understanding the roles of such genes during embryogenesis. More recently, other techniques, such as microarray-based expression profiling, have been increasingly used to assess gene expression patterns on a genomic scale from dissected or micro-dissected embryonic material. However, as these methods do not yield spatial information about a gene's expression pattern, ISH is now often used to validate such data. When used in this context, ISH helps to refine our understanding of the spatiotemporal expression patterns of molecules that have been identified by high-throughput methods.

Despite being a commonly employed technique, ISH still retains its reputation of being notoriously difficult to perform. For the novice especially, it can be a daunting prospect to trouble-shoot if, at the end of several days of diligently following a protocol, applying and removing one reagent after another, either no staining pattern is obvious or background staining obscures all. Was it the preparation of the specimen that was the problem? Was there RNase contamination of a reagent? Perhaps the choice of probe was unsuitable? Maybe the hybridisation temperature was too high or too low? Because of the relatively complex nature of the technique, the list of problems to troubleshoot can appear to be endless. As such, no one embarking on experiments that require the use of ISH should be without at least one manual that contains various methods for this technique. In addition to the technical difficulties that can be encountered with ISH, it is also a method that is continuing to develop with recent advances in new probe chemistries, non-radioactive detection methods, signal amplification and the development of derivative techniques. Thus, even those experienced in the art of ISH need to keep up-to-date with these exciting advances in order to apply them to areas of their own research. In these regards, the third edition of *In Situ Hybridization Protocols* is a book that goes someway to satisfying both the novice and the expert user.

*In Situ Hybridization Protocols* is divided into 19 chapters, each of which constitutes one particular protocol. As with all volumes in the *Methods in Molecular Biology* series, each chapter is formatted into five sections: Introduction, Materials, Methods, Notes and References. This allows the user to easily and quickly assess from the Introduction whether the protocol is suitable for their requirements and, if so, which reagents will be required. The Methods sections all offer step-wise protocols, which are clear and simple to follow, and the associated indexed Notes sections offer many helpful insights with relevant background theory and useful practical tips from the expert authors.

The main focus of this third edition is performing ISH to detect mRNA on sectioned material. (Note that if you are after a resource that offers multiple detailed methods to detect DNA in situ, this is not the book for you.) Chapter 1 begins with a simple protocol for the preparation of either frozen or paraffin-embedded tissue sections for ISH by microwave oven treatment. The authors state that this novel approach is useful for denaturing target mRNA to allow easier probe access, replacing or enhancing the protease digestion of frozen or paraffin-sectioned samples, as well as denaturing endogenous phosphatases, thus lowering background signal.

The next two chapters cover the preparation of the other crucial reagent of the ISH experiment – the probe. Chapter 2 describes methods to prepare a DNA template fragment and to radioactively or non-radioactively label a DNA probe, whereas Chapter 3 summarises methods for generating complementary (c)RNA ISH probes, and provides protocols for both isotopic and non-isotopic labelling. Also included in Chapter 3 are complete protocols for mRNA ISH on sectioned material. These protocols cover specimen preparation and embedding, hybridisation and detection methods, including the amplification of signal using biotinylated tyramide chemistry. As tyramide signal amplification is perhaps the most significant advance in recent years for increasing the sensitivity of non-radioactive ISH, the next chapter is devoted entirely to the theory and practice of this technique. Protocols are given to apply the method to both DNA ISH and mRNA ISH on a variety of sample types, such as cell preparations and paraffin-embedded tissue sections.

**Despite being a commonly employed technique, ISH still retains its reputation of being notoriously difficult to perform. For the novice especially, it can be a daunting prospect to trouble-shoot**

The next three chapters are perhaps the most relevant ones for the readers of *Development*, as these list some tried-and-tested protocols specifically for assessing mRNA distribution by ISH in embryo specimens. The first of these chapters outlines protocols for assessing mRNA distribution in mouse embryos. Included are methods for cRNA probe synthesis (both radioactively and digoxigenin labelled), ISH on paraffin-embedded and frozen sections, and a method to perform whole-mount ISH. Associated with this excellent chapter are many notes that detail handy tips, covering everything from how to choose a suitable probe to lowering non-specific background in whole-mount samples. The second of this

group of chapters gives alternative protocols for carrying out non-radioactive ISH on both frozen sections and whole-mount mouse embryo samples, whereas the third chapter deals specifically with a method of ISH for whole-mount mouse embryos.

Most of the remaining chapters include other specialised and less-widely performed, yet potentially very useful, protocols. Chapter 10 details a method that combines electron microscopy and ISH, which allows ultra-structural examination of gene expression in situ. Chapter 11 outlines a protocol for ISH on free-floating sections (as opposed to the traditional approach of adhering the sections to a microscope slide), whereas Chapter 12 presents a protocol to detect low-abundance transcripts in adherent cultured cells. Chapter 13 discusses a protocol to identify xenotransplanted cells by DNA ISH (in this case, human cells transplanted into the mouse, identified by using a probe specific to a primate-specific repeat element), and Chapter 14 lists a set of protocols to perform DNA ISH on chromosome and extended fibre preparations from plant material, as well as mRNA ISH on paraffin-embedded plant specimens. Chapter 15 outlines a method to perform ISH to detect histone mRNA in order to identify cells in S-phase on paraffin-embedded sectioned material. This method offers an alternative to pulse-labelling samples with bromodeoxyuridine (BrdU) and can be applied to samples where BrdU labelling cannot be performed, such as human samples or archived sectioned material.

The book also covers methods for quantitatively and semi-quantitatively assessing differences in gene expression using ISH. The first of these (Chapter 18) covers a protocol for performing semi-quantitative ISH using radioactive probes. Details of probe and specimen preparation, hybridisation parameters and quantification of the data using image analysis software are discussed. The final chapter of the book gives a method that has been used to perform quantitative ISH on formalin-fixed, paraffin-embedded tissue microarrays using a phosphoimager.

As can be seen from these chapters, this book contains both a set of relatively standard mRNA ISH protocols, which will be of interest to the first-time user, and an impressive number of lesser-known applications of ISH, which will be useful to many developmental biology labs. This provision of a variety of ISH protocols – written independently by separate expert authors with an abundance of useful notes and helpful tips – is a distinct advantage of the book; however, one unfortunate drawback of this approach is that continuity between the chapters is somewhat lacking. For example, information is often repeated between chapters (such as methods of in vitro transcription for generating riboprobes) and is not cross-referenced, making it difficult to compare and contrast the methods. The book would also benefit from a general introductory chapter to outline the theory of ISH and give a comprehensive grounding of the technique for the first-time user. This would be very useful should trouble-shooting be required. It could discuss, for example, features to include or avoid when designing a fragment for use as a probe, the theory of how different tissue treatments can affect probe accessibility in a sample, and the pros and cons of radio-labelled probes versus non-radiolabelled probes. Most of this information is present in the book, but it can be rather difficult to find and can be hidden in a chapter that is not of immediate relevance to the reader. It is also a pity that all three chapters devoted to ISH on embryos focus on the mouse. Although each chapter mentions that the protocols can be modified for use in other organisms, suggestions as to how this can be achieved are not given and could thus prove challenging for the novice, especially without another protocol to compare to and contrast with.

Despite these drawbacks, this book does contain a lot of useful information, drawn from many experts in the field. As such, it would be a useful addition to the ISH methods already present on the lab bookshelf.

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# Basic recipes for the molecular biologist

**Steven Russell**

Department of Genetics, University of Cambridge, Downing Street, Cambridge CB2 3EH, UK
e-mail: s.russell@gejn.cam.ac.uk

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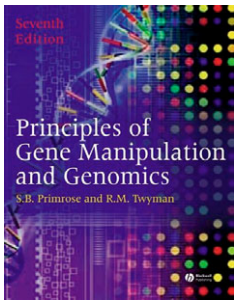


## Principles of Gene Manipulation and Genomics, Seventh Edn

**By Sandy B. Primrose and Richard M. Twyman**

Blackwell Publishing (2006) 644 pages
ISBN 1-4051-3544-1
£29.99 (paperback)

"When *I* was a student I had to make my own *Eco*RI" my PhD supervisor would declare, in a manner akin to the gents in the four Yorkshiremen sketch that was popularised by Monty Python, as I reached into the freezer for a bit of the said enzyme. Skip forward two decades and my own graduate students are treated to similar reminiscences regarding the re-distilling of phenol or the making of sequencing gels, particularly when they are clutching requisitions for some molecular biology 'kit' that need my authorisation. Are these trips down memory lane simply the irrelevant ravings of grumpy middle-aged men or is there a point to these 'when I were a lad' stories? Molecular biology is a bit of an art; I mean art in its broadest sense of course, much in the same way that cooking is an art. After all, almost anyone can follow a recipe, but turning out a gourmet meal is a different matter, requiring an understanding of the individual ingredients and how they blend together to provide a result greater than the sum of the parts. Similarly with molecular biology: you can follow a protocol, but will that genomic library contain all the sequences you want (tasty) or be a collection of useless scrambled clones because you didn't do the partial digests properly (unpalatable). Thus, good molecular biology is built upon a sound understanding of the underlying biochemistry. Obviously, we old hands like

to think we can rustle up a decent plate of food without the aid of a Nigel Slater cookbook – hence our enthusiasm for recounting our past experimental exploits.

Stan Cohen and Herb Boyer introduced the world to DNA cloning in 1973 by reporting the first recombinant plasmid propagated in *E. coli*; 33 years later we can now manipulate virtually any DNA sequence in vitro and even sequence entire eukaryotic genomes. However, despite these considerable advances, most of molecular biology still involves the same basic principals of combining DNA and enzymes in appropriate buffers to generate a desired output, be it a mutagenised gene, a bit of nucleotide sequence or a construct capable of expressing high levels of a recombinant protein. Thus, I would argue, the basic principals of molecular biology have changed little over the past three decades: they have just become more sophisticated. DNA microarrays, despite the hype, are not new revolutionary molecular biology techniques – they are simply adaptations of the methods developed by Ed Southern in the mid 70s. Particularly clever adaptations that need a fair degree of technical ability to implement and quite sophisticated techniques to analyse, but nevertheless they are very much based on the original Southern blotting technique. Of course, more sophisticated generally means more complex: more steps in a cloning scheme, more enzymes, more buffers – more ways to go wrong. Thus, many molecular biologists now rely heavily on manufactured kits for everything from cloning a PCR product to making a cDNA library. Kits are not necessarily a bad thing when everything works out well and the desired product is generated; quality controlled reagents and validated recipes can save a considerable amount of time. However, when things don't work or there is not a kit for the particular reaction you want to perform, it's back to basics. To successfully and painlessly use molecular biology to make a transgenic mouse or to carry out a large-scale, yeast two-hybrid screen, it pays to know what you are doing. It pays to understand the basic principals behind the reactions being performed and the rational behind particular ways of doing things. At least then, when it doesn't quite go as expected, you have a chance of troubleshooting the procedure and getting what you want.

This book, the seventh revision of a textbook first published in 1980, brings together two previously separate volumes – *Principles of Gene Manipulation* and *Principles of Genetic Analysis and Genomics* – into a single comprehensive text that attempts to summarise the doctrine of molecular biology as it is currently applied in modern biology. By comprehensive, I mean comprehensive. From the principals behind basic DNA cloning, through sequencing an entire genome, to the large-scale analysis of protein-protein interactions, the authors provide a Cook's tour through the molecular analysis of genomes and their products. The book is divided into four major parts. Part 1 covers the basics of molecular biology: how to clone, sequence and manipulate DNA, as well as an introduction to bioinformatics and sequence analysis. Part 2 covers the manipulation of DNA in different organisms (various bacteria, fungi, plants and animals), including chapters on the increasingly sophisticated possibilities for gene manipulation in transgenic mammals. Part 3 covers the 'omics (at least the ones I know about – there may have been some new 'omics invented since I wrote this review), including genome analysis, transcriptomics, proteomics and metabolomics. Part 4 introduces some of the biomedical and biotechnological applications of 'omics, such as approaches to deciphering complex polygenic traits in humans or agricultural species, pharmaco-genomics and the industrial production of useful biomolecules. One should not underestimate the breadth of this book, it genuinely attempts, successfully in my view, to cover the range of topics that encompass virtually all of the types of molecular analysis a biologist may contemplate these days, and it does this very well indeed. Each chapter is prefaced by an introduction to the technique or problem, including a historical perspective. The reader is then led through the subject with the emphasis on explaining why particular steps or reactions are performed, what the problems are, and how variations have been devised to overcome limitations. In addition, each chapter contains several explanatory boxes that cover some principals or techniques in greater depth. The illustrative figures are generally informative without being over-complex. Although there are a few details that I might not necessarily agree with (as with different cuisines – there's more than one way to cook a fish – there are also many ways to clone a gene), and despite the fact that on multiple occasions we are told that a bit of DNA can be 'transformed into *E. coli*' (a particularly annoying grammatical construction that was beaten out of me as a student), these minor personal quibbles in no way detract from my very positive view of the book's quality.

It is important to emphasise that this is not a laboratory manual and, consequently, does not contain detailed protocols, rather it's a textbook designed to explain the biochemical or biophysical basis that underpins particular experimental manipulations. Having said that, it would sit very comfortably alongside the methods books found in most molecular biology labs, acting as a first port of call before a particular line of experimentation is initiated. At £30, it costs less than a few units of most restriction enzymes and will pay for itself many times over if it helps researchers troubleshoot the molecular biology they are doing. Therefore, I believe this book makes not only a superb advanced undergraduate level textbook, but an excellent addition to the research lab – it should be required reading for any graduate student embarking upon laboratory research and will also be useful for more experienced researchers starting a new line of investigation. With the pervasive 'buy a kit for it' mentality that is prominent in laboratories these days, it is even more essential that bench researchers have a source other than the kit instructions for understanding each step in a particular protocol. Perhaps with such an understanding they may even attempt experiments without expensive pre-packaged reagents! When I was a graduate student, I made a few cDNA libraries: no kits, just the principals of the enzymology taken from the literature that guides the molecular biology. 'You try and tell the young people of today that, and they won't believe you'.

**[This book] genuinely attempts to cover the range of topics that encompass virtually all of the types of molecular analysis a biologist may contemplate these days, and it does this very well indeed**

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