

Understanding Cancer

One in two of us will develop cancer at some point in our lives and yet many of us don't understand how cancers arise. How many different kinds of cancer are there? What treatments are available? What does the future hold in terms of developing new therapies?

This book demystifies cancer by explaining the underlying cell and molecular biology in a clear and accessible style. It answers the questions commonly asked about cancer, such as what causes cancer and how cancer develops. It explains how DNA makes proteins and how mutations can corrupt those proteins. It also gives an overview of current therapies and how treatments may advance over the next decades, as well as explaining what actions we can take to help prevent cancer developing.

Understanding Cancer is an accessible and engaging introduction to cancer biology for any interested reader.

Robin Hesketh has been a member of the Department of Biochemistry at the University of Cambridge and a fellow of Selwyn College for over 40 years, working on cancer biology. He has published over 100 research papers, a textbook on cancer (*Introduction to Cancer Biology*, Cambridge University Press, 2013) and popular science books (*Betrayed by Nature*, Palgrave, 2012). He has spoken and written widely in the media on cancer and has run a blog on the topic of cancer for the general public since 2011.

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Robin Hesketh

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The *Understanding Life* series is for anyone wanting an engaging and concise way into a key biological topic. Offering a multidisciplinary perspective, these accessible guides address common misconceptions and misunderstandings in a thoughtful way to help stimulate debate and encourage a more in-depth understanding. Written by leading thinkers in each field, these books are for anyone wanting an expert overview that will enable clearer thinking on each topic.

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‘How often have we attended a lecture or opened a book to find that within minutes we are smothered by complicated facts that are way beyond our understanding? There has been no simple introduction. The speaker/author is so involved in the topic that they could no longer see out of the intellectual hole that they had dug for themselves. If ever a book was written to dispel this fault, then this is the one, as Robin Hesketh has managed to provide a remarkably clear and readable account of the science behind cellular behaviour and faults that lead to the development of cancer. We become convinced that the key to cancer is DNA mutation with chopping and changing of DNA strands, and the older you are the more likely this is to occur. Read why the tumour suppression protein (p53) can make cells commit suicide but does not always work.

The book reads like a novel, and I found that I could hardly put it down. The literary style is at times light-hearted with humorous analogies.’

Robert Whitaker, Anatomist, University of Cambridge

‘*Understanding Cancer* presents a carefully crafted, clear and concise book on aspects of cancer; a disease of importance to us all. Most readers will come to Robin Hesketh’s book with questions about cancer. *Understanding Cancer* will not disappoint. The most usual questions and answers are presented in the first chapter and ways of reducing the risk of some cancers are suggested later.

This book puts cancer into a historical and very interesting context; it then explores cancer, its biochemistry and functioning in an approachable way. Information is given about the latest treatments and the science behind them. This very readable book contains something for everyone. It is positioned in, and very adequately fills, the gap between personal accounts by patients of their experiences, and more advanced medical and cell biology texts. *Understanding Cancer* is well researched and greatly recommended.’

David Archer, Schools Liaison Officer, British Society for
Cell Biology

'Understanding Cancer is a fascinating and engaging perspective on the evolution of cancer research and treatment. Dr Hesketh provides insight into the key clinicians and scientists, following their discoveries in clinical care and research. It is clear that achievements in cancer treatments are rooted in basic research, and the book highlights the collaborations required between scientists and oncologists in order to make the next leap of advances in treating cancer. Dr Hesketh overviews the likely mutagenic causes of cancer spurring on the oncogenic transitions leading to a cancer cell that can replicate uncontrollably. He also highlights new avenues in cancer research, such as studies on components of the tumor microenvironment (i.e. blood vessel cells, immune cells), which can then lead to the development of additional 'ammunition' to battle cancer. Dr Hesketh conveys that preventive measures and advances in early cancer detection could make an impact on cancer incidence and patient outcomes/survival. This book is certainly a triumph and a must-read for all current and future scientists, physicians at any stage of their professional careers and anyone interested in cancer research and the quest for effective anti-cancer treatments.'

David Lyden, Cancer Researcher and Paediatric Oncologist,
Weill Cornell Medicine, Cornell University

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Without the limitless love and support of my wife, Jane, and my two sons, Robert and Richard, I could not have written this book nor indeed done much else in my life.

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Foreword

What causes cancer? This is a question that many people ask. The answer? There is no simple one. The term “cancer” is commonly used to describe a variety of diseases that share certain features such as uncontrolled cell proliferation. During the last several decades numerous researchers have tried to reveal the causes of cancer through the study of mutations and their impact on phenotypes. The main underlying idea has been that mutations, either caused by accident or by environmental factors, are responsible for the uncontrolled proliferation of cells in which they occur. In the present book, Robin Hesketh provides a detailed and informative account of what we know, as well as what we do not know, about the impact of mutations with respect to cancer. Readers will find a wealth of information, explained in a concise and clear manner.

Kostas Kampourakis, Series Editor

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Preface

Cancer is unique. No other human condition is quite so two-faced in being, on the one hand, easy to grasp in terms of its basic cause, while, on the other hand, confronting us with overwhelming complexity when we get down to details. Highly appropriate, then, that if you delve into the huge toolbox of cancer drivers you'll find a gene called *Janus* – after the mythological god of beginnings and transitions, usually depicted as having two faces, one looking to the past and the other towards the future.

Cancer's past is immense: we know it has afflicted animals for millions of years. However, a cancer biologist might argue that some 60-odd years ago it turned its face to the future. The critical event was, of course, the revelation of the structure of DNA and all that followed. Henceforth cancer biology became the science of molecules – genes and proteins and how they cause cancers – that continues to build the foundations of an understanding of cancer and rational approaches to therapy.

If this sounds as though I am casting aside the heroic efforts of numerous great scientists and physicians who, starting with the ancient Egyptians and Chinese, attempted to grapple with the cancer challenge, rest assured that this is not the case, and Chapter 2 surveys the major events that preceded the age of molecular biology.

After that we look at cancer numbers worldwide and how their sheer scale begins to tell us something about underlying causes. Then, on to DNA and how the code it carries was worked out and the picture we now have of cells turning its message into a limitless number of proteins that define each species and enable all living things to function. Chapter 5 reveals how cells work – in particular how one cell becomes two – and that leads to how

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disruptions in DNA compromise the delicate machinery of replication to give rise to cancers.

We then turn to the causes of cancer, familiar – tobacco, alcohol, etc. – and less well-known – bacteria, fungi, etc. – and, most importantly, what, if anything, can be done about them.

Cancers may be treated by surgery, radiotherapy or drugs (chemotherapy), often in combinations. Chapter 9 considers the current state of play with the emphasis on chemotherapy and molecular approaches to treatment. This leads to the final chapter which looks to the future by reviewing the astonishing range of innovative strategies that are under development. Some of these are relatively advanced (e.g., immunotherapy), others are embryonic. Some will fall by the wayside but, collectively, they represent extraordinary science and offer great promise that, after so many millennia, mankind may at last be able to control these dreaded yet fascinating diseases.

We begin, however, by answering a dozen or so of the most likely questions a newcomer to cancer might ask or indeed that children often do ask. This should clear up misunderstandings that are common in the general perception of cancer and set the stage for the exciting voyage to come.

Acknowledgements

In writing a story of cancer for non-specialists I owe a massive amount to countless people I've been fortunate to meet in the course of my career. Scientific colleagues, clinicians, patients, students, and members of the public who've been kind enough to come to my talks or read my blogs and books – so many that I've been privileged to encounter and to learn from. Enormous thanks to Katrina Halliday of Cambridge University Press, without whom this book would not have happened, and also to Jessica Papworth and Kostas Kampourakis for brilliant editing. Many thanks also to my colleague Thomas Shafee who drew the originals for several figures. I am also very appreciative of the work of Olivia Boulton, Sam Fearnley, Gary Smith, Judith Reading, Gayathri Tamilselvan and Vigneswaran Viswanathan in the production stages.

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Gene Names

The HUGO Gene Nomenclature Committee (HGNC: www.genenames.org/index.html) assigns unique symbols to human genes. Gene names are written in italicized capitals: the protein that they encode is non-italicized: *EGFR* (gene)/EGFR (protein). They are pronounced phonetically when possible (SRC is *sarc*, MYC is *mick*, ABL is *able*). Viral forms are prefixed by *v-* (e.g., *v-src*). For some genes that have commonly used informative names both are shown (e.g., *SLC2A1*/GLUT1 and *SLC2A5*/GLUT3).

Chemical and Trade Names of Drugs

Throughout the text chemical names of drugs are used. This list provides corresponding trade names.

- 5-fluorouracil (Adrucil and others)
- Azacitidine (Vidaza)
- Cetuximab (Erbix)
- Docetaxel (Taxotere and others)
- Enasidenib (Idhifa)
- Erlotinib (Tarceva)
- Fulvestrant (Faslodex and others)
- Gefitinib (Iressa)
- Gemcitabine (Gemzar)
- Imatinib (Gleevec)
- Larotrectinib (Vitrakvi)

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Methotrexate, formerly amethopterin (Trexall, Rheumatrex, Otrexup and others)

Olaparib (Lynparza)

Paclitaxel (Taxol and others)

Palbociclib (Ibrance and others)

Pembrolizumab, formerly lambrolizumab (Keytruda)

Raloxifene (Evista and others)

Rituximab (Rituxan and others)

Tamoxifen (Nolvadex and others)

Toremifene (Fareston)

Trastuzumab (Herceptin)

Vemurafenib (Zelboraf)