Introduction to Cancer Biology

From basic principles to insights into pioneering research, this introductory textbook provides the fundamentals of cancer biology that will enable students of biology and medicine to enter the field with confidence. It opens with a discussion of global cancer patterns, how cancers arise and the risk factors involved. A description of the normal signalling pathways within cells then explains how DNA mutations affect proteins and what this means for the development and behaviour of tumours. Later chapters discuss methods for tumour detection, biomarker identification and the impact of genome sequencing, before reviewing the development of anti-cancer drugs and exciting current advances in treatment. With 50% new material, including two new chapters on genetic analysis of cancer and cancer chemotherapy, improved pedagogy, examples of revolutionising technologies in drug design and delivery, and useful online resources, this textbook offers an accessible and engaging account of cancer biology for undergraduate and graduate students.

Robin Hesketh is Emeritus Professor in the Department of Biochemistry, University of Cambridge. He is also a Fellow of Selwyn College. His major research area is anti-angiogenic strategies for cancer therapy. He has lectured in undergraduate and post-graduate courses on cell and molecular biology and cancer, and has published over 100 research papers and seven books, including the 1st edition of *Introduction to Cancer Biology* (2012) and *Understanding Cancer* (2022) for Cambridge University Press.

"A comprehensive, engagingly written, accurate overview of a topic that has continued to rapidly evolve in recent years. As our knowledge of cancer's molecular underpinnings advances, it is essential to remain up-to-date and this book delivers. Each chapter is full of concise explanations and wonderful illustrations that convey complex concepts in a straightforward way. I highly recommend this valuable resource to all students of biology and medicine."

Dr Andrew Lam, M.D., *University of Massachusetts Medical School*

"The new edition of *Introduction to Cancer Biology* has been well worth waiting for. It develops logically from the previous edition and brings our current understanding of all aspects of the nature of cancer biology up to date. Central to the book are chapters dealing with DNA, oncogenes, tumour suppressor genes and signalling pathways. The chapters convey the historical development of these ideas into our current understanding. Thus, the book is suitable for students, undergraduates and postgraduates with an interest or need, to develop an overview of cancer research."

Dr Tony Bradshaw, *Oxford Brookes University*

"This textbook has easy to understand figures and clearly laid out chapters. My favourite is the logical roadmap describing how one should teach using this textbook. I never saw that before. I think the students will appreciate the 'pause and recap' throughout the book; what a great way to check your knowledge one step at a time."

Professor Luiza Nogaj, *Mount Saint Mary's University, Los Angeles*

"A comprehensive look at cancer biology and treatment with chemical-level precision."

Professor John Schmidt, *Villanova University, Pennsylvania*

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SECOND EDITION

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Preface

The 1st edition of this book, published in 2012, was written to introduce the science of cancer for those coming to the topic for the first time – be they undergraduate students, graduates, postdoctoral scientists or medical practitioners moving into the field of oncology. Its aim was to paint a picture of what we think happens to cells and molecules in the making of cancers, how this bears on diagnosis and prognosis, and where the science is taking us in terms of treatment.

This new edition pursues the same aims, but it is greatly expanded and substantially reorganised. This in part reflects the amazing advances in the intervening 10 years, most notably in the areas of epidemiology, genome sequencing and analysis, cancer detection and chemotherapy. These have emphasised the fact that cancers are still the most daunting of subjects – the most complex of diseases with no two cases being identical. Nevertheless, it remains true that the underlying processes by which cancers arise are remarkably consistent and conceptually straightforward. Moreover, as we shall see, the extraordinary diversity of cancers offers opportunities for therapeutic treatment.

The fact that this book is up to date, particularly in the areas of epidemiology, genome sequencing and analysis, cancer detection and chemotherapy, places it in a separate category to all others currently available.

To help keep readers up to date, the author writes a regular blog at: https://cancerforall.wordpress.com/. This explains clearly and simply how recently published work has provided new data, insights and advances in the general field of cancer biology and therapy. It is designed to take up themes described in *Introduction to Cancer Biology* and can therefore be viewed as a continuous update, albeit with a selectivity that reflects the author's interests – what has caught his eye and for which a short, illustrated synopsis might be useful for readers of this textbook.

New to this edition

- Two new chapters: Chapter 3 covers Genetic Analysis of Cancer and Chapter 9 covers Cancer Chemotherapy.
- Now fully in colour, with new and revised illustrations throughout.
- Updated statistics providing a comprehensive picture of cancer patterns worldwide.
- A discussion of the Fukushima nuclear disaster (Chapter 2) and the emerging importance of the microbiome and mycobiome in cancer development and treatment.
- An exploration of all the relevant findings from the Human Genome Project, as well as contemporary methods of extracting DNA sequence data (Chapter 3).

- An expanded and updated discussion of diagnosis methods, the efficacy of screening and tumour detection, therapeutic vaccines and the problem of drug resistance.
- The latest in sequence data and examples of modern technologies that are revolutionising drug design and delivery (Chapter 10).
- Enhanced and updated pedagogical features, including:
  - 'Pause and Recap' boxes. These are placed at the end of the main sections within each chapter, highlighting the key concepts covered up to that point and connecting them to what will come next and why. This feature will help students to retain the main concepts covered as they progress through the chapters and instructors to facilitate their decision about what chapters or parts to assign to their students, based on the nature and level of their course.
  - Revised and updated Review Questions at the end of each chapter, to help students assess their knowledge of the topics discussed.
  - Key terms highlighted in bold throughout the manuscript, and their definitions provided in a Glossary at the end of the book.
  - Four revised appendices provide supporting reference sources: Appendix A describes how tumours are graded and staged; Appendices B and C summarise the main classes of oncoproteins and tumour suppressor genes; and Appendix D reviews the principal features of the 10 types of cancer that predominate in terms of global mortality.
  - Enhanced cross-referencing across topics within the book to help students tackling or revisiting them as they go through the text.

Readership

This book is aimed at undergraduate and graduate students in cancer biology, molecular and cellular biology, genetics, biochemistry and oncology. The aim of this book is to provide an ideal companion to most student courses on cancer. The starting level is no more than knowing what a molecule is and having a general concept of a cell. The emphasis is on the critical principles with numerous diagrams and photographs to convey the key points without becoming submerged in detail.

In this edition, we also provide online resources to support the reader's learning experience. Instructors' resources will include the JPEG and PowerPoint slides of the figures within the book as well as a testbank made up of both multiple-choice questions and essays that can be used to evaluate their students' knowledge as they progress through the textbook. These can be found at www.cambridge.org/hesketh2e.

How to teach from this book

The diagram below provides a visual walk-through of how instructors can teach from this textbook and the main topics covered:

This layout offers a logical pathway from cancer statistics through causes to a summary of DNA sequencing methods and cumulative sequence data that now forms a foundation to the science of cancer. A summary of the major pathways that control proliferation in normal cells leads to a discussion of 'cancer genes' – genes in which acquired mutations yield oncogenes or ablate the actions of tumour suppressors, creating 'drivers' of abnormal proliferation.

Chapter 6 considers the distinction between benign and malignant cancers and reviews the established hallmarks of cancer. The following chapter overlays this phenotypic picture with the key signalling pathways that promote cancer development. Chapter 8 summarises screening and the problem of biomarkers. This sequence sets up the last two chapters. The first reviews highlights in the history of chemotherapy and discusses the continuing problem of drug resistance. The book ends with a summary of a selection of the astonishing range of drug treatments currently under development and illustrates the extraordinary confluence of scientific disciplines now being brought to bear on this problem. Some of these methods have already moved to clinical trials, while others are at a more embryonic stage.

This book is therefore designed so that the sequence of Chapters from 1 to 10 can be followed without deviation. However, depending on specific course requirements, individual chapters or part chapters may be selected and combined.

Book organisation

The book advances through the story of cancer in 10 chapters that clearly separate key areas:

Chapter 1 reviews the global patterns of incidence and mortality, and discusses what they tell us about the underlying causes. This includes an expanded comment on socioeconomic factors, with a focus on the USA, although the critical issues apply worldwide. The chapter ends with a summary of progress in terms of treatment efficacy.

Chapter 2 considers causes of cancer – those beyond our control (e.g. arising from normal metabolic processes) and those susceptible to regulation (e.g. diet, smoking, use of mobile phones). The extensive survey of the evidence for the involvement of dietary factors in cancers leads to the new but rapidly expanding field of the microbiome and its role in obesity and cancer. There is an up-to-date summary of the impact of radiation on cancers, including comment on unethical human experimentation in the USA, and the long-term effects of nuclear disasters (Hiroshima and Nagasaki, Chernobyl, Fukushima). This chapter concludes with a discussion of ultraviolet radiation, low- and high-frequency magnetic fields and radon.

Chapter 3 traces the story of the project to sequence the entire human genome – one of the greatest undertakings in the history of science – and the subsequent technical revolution that now permits whole-genome sequencing on a massive scale. This is generating a global database of normal and tumour genomes, one aim of which is to identify specific mutational signatures. Surveys of major projects are included (e.g. The Pan-Cancer Project and The Genome Aggregation Database), together with comment on bioinformatics and the growing impact of machine learning.

Chapter 4 turns to signalling in normal cells and discusses how information is transmitted across cell membranes to stimulate intracellular pathways that regulate gene transcription. Key examples focus on enzyme-coupled receptors (receptor tyrosine kinases), the RAS/MAPK pathway, and the role of MYC as a central regulator of cell growth and proliferation. Cytokine receptors, G-protein-coupled receptors, ligand-gated ion channels and steroid hormones are also discussed.

Chapter 5 distinguishes the two major classes of 'cancer genes' – oncogenes and tumour suppressor genes – and how the acquisition of mutations can result in cancer 'drivers'. These processes are illustrated with major examples (e.g. RAS, phosphatidylinositol 3-kinases (PI3Ks), the epidermal growth factor receptor (EGFR) family, gene amplification (MYC), and chimeric proteins (BCR-ABL1, PML-RARA and ETV6-RUNX1). Chromothripsis is explained, and there is an extensive discussion of tumour suppressor genes (retinoblastoma and tumour protein 53 (TP53)), DNA repair and hereditary cancers, polymorphisms and microRNAs.

Chapter 6 explains the concept of a tumour, the benign/malignant boundary and the characteristics that make a cancer cell (the 'hallmarks of cancer'). There is extensive discussion of angiogenesis, metabolic perturbation in cancer cells, inflammation and the immune system, and the tumour cell environment. This leads to a review of metastasis, the endothelial-to-mesenchymal transition and the role of stem cells.

Chapter 7 describes the effect of mutations on critical signalling pathways that create the transformed phenotype (i.e. a cancer cell). These emerge in the form of a central axis (ARF, MDM2, TP53, INK4, RB1, MYC and RAS), mutations that promote survival and resistance to apoptosis. Other pathways that may contribute to tumour development are also discussed: JAK–STAT, WNT and GPCR signalling, cadherin signalling, integrin signalling, BCR-ABL1, the hedgehog pathway and GLI signalling, transforming growth factor-β (TGFβ), vascular endothelial growth factors (VEGFs) and Notch signalling.

Chapter 8 is set against the foregoing cellular and molecular background and evaluates the current position regarding cancer detection, diagnosis and radiotherapy. This covers screening (with comment on mammography), staging, diagnosis, grading and monitoring of cancers. A summary of radiotherapy leads to the concept of tumour biomarkers, tumour imaging and molecular imaging (positron emission tomography (PET)), magnetic resonance imaging (MRI), smart contrast agents, ^{13}C hyperpolarisation, superparamagnetic iron oxide nanoparticles (SPIONs) and optical imaging. This chapter concludes with sections on proteomics, metabolomics, gene expression profiling and protein imaging.

Chapter 9 assesses the development of anti-cancer drugs (chemotherapy) from its earliest days. The layout takes the 'hallmarks of cancer' as targets and describes the progress that has been made in the development of agents designed, for example, to inhibit proliferation, modulate metabolism or block metastasis. This leads to the field of cancer vaccines and the recent concept of tumour-agnostic drugs. Drug resistance remains a problem, however, and the chapter concludes with a consideration of this critical issue.

Chapter 10 reviews the astonishing developments in chemotherapy that are going to shape cancer treatment over the next decades. It is, perforce, somewhat selective but includes an extensive discussion of immunotherapy and checkpoint inhibitors that leads to gene therapy and CRISPR-Cas. Other exciting approaches mentioned that are in various stages of development include liquid biopsies, breath biopsies, Cytosponge and the range of nano-oncology approaches for drug delivery. There is a broad review of epigenetics and epigenetic drugs and of drug delivery from inert capsules. The controversial topic of personal versus what could be called impersonal medicine is broached through examples showing the

possibility of targetting mutant RAS or MYC as central signalling nodes in tumour cells. The emerging message is one of real optimism that being able to bring the major cancers under control is a realistic objective. However, enthusiasm must be tempered by the evidence that we are still in the preliminary stages of understanding cancer – a point exemplified by recent data revealing the extraordinary, dynamic heterogeneity of the breast tumour microenvironment.

Gene nomenclature

The HUGO Gene Nomenclature Committee (HGNC: www.genenames.org/index.html) assigns unique symbols to human genes. Gene names are written in italicised capitals; the proteins that they encode are non-italicised: *EGFR* (gene) and EGFR (protein). They are pronounced phonetically when possible (SRC is *sarc*, MYC *mick*, ABL *able*). Viral forms are prefixed by v- (e.g. v-*src*). For some genes that have commonly used informative names, the gene is first shown followed by the protein name, e.g. *SLC2A1* (GLUT1), *TGFB1* (TGFβ), *PIK3CA* (PI3K), *TP53* (p53).