PRINCIPLES OF MOLECULAR ONCOLOGY

SECOND EDITION

EDITED BY

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Foreword

At the midpoint of the 20th century, our knowledge of cancer was based on epidemiology and pathology, and treatment consisted of surgery and radiation therapy. At mid-century, Medawar and colleagues initiated the understanding of transplantation immunology, Farber described the first use of an antifolic drug to treat leukemia, and Jacobson and coworkers described the irradiation-protection effect of spleen cells. These observations opened the door to the development of chemotherapy and transplantation in the treatment of cancer. Despite the rapid development of these new disciplines, progress was usually based on empiric observations and clinical trials.

The rapid advances in molecular biology at the end of the 20th century mark a new era in our knowledge of cancer. Molecular immunology, molecular genetics, molecular pharmacology, and the Human Genome Project are in the process of providing a level of understanding of cancer undreamed of in the past. Optimism is based on the firm belief that understanding at the molecular level will lead to better and earlier diagnosis, to new forms of treatment, and, most importantly, eventually to prevention of many types of cancer.

Principles of Molecular Oncology provides a bold new look at the evolution of our knowledge of cancer. Authors from many disciplines are bringing together the facets that provide a comprehensive view of the whole. In a field progressing as rapidly as the understanding of cancer at the molecular level, any book must be regarded as a report of work in progress. The reader will enjoy the opportunity to pause and look at the whole field as it stands today. This book will prove both informative and intellectually satisfying.

E. Donnall Thomas, *MD*
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Foreword

A famous London surgeon is quoted as saying that a cure for cancer would not be discovered by people in white coats working in laboratories, but rather by somebody leaning over a fence watching workmen digging a hole in the ground. Indeed, the idea that malignant disease might have a single cause was rife until quite recently. But until the era of molecular biology, and the remarkable insights into cell biology that followed, the cancer field was in the doldrums. Viruses as the cause of human cancer had come and gone, chemical carcinogens and exposure to ionizing radiation seemed to be unlikely causes of the bulk of human cancers, and it was not at all clear where to turn in cancer research. However, in the 1960s, two fields of investigation started to yield results that at least held some promise. Epidemiological studies showed quite unequivocally that there is a relationship between the development of certain cancers and cigaret smoking. And at least some forms of leukemia appeared to be associated with specific chromosomal changes. However, until the advent of recombinant DNA technology, there was no indication as to how these observations might be connected or about the cellular mechanisms of malignant transformation.

When historians of science look back on the close of the 20th century and try to evaluate the fruits of the application of molecular and cell biology to the study of human disease, it is likely that they will pinpoint the better understanding of the biology of cancer as one of the highlights of this period. The discovery of oncogenes, together with improvements in cytogenetics, resulted in an amalgamation of these two fields of research and led to the dawning of an understanding of how cancers might result from the breakdown of normal cellular homeostatic mechanisms. Subsequently, the elucidation of the genetic control of the cell cycle, and how certain oncogenes monitor different aspects of cellular activity, allowing cells to go into cycle or directing them toward apoptosis, has started to provide some insights into the cellular mechanisms of malignant disease. Almost overnight, cancer has become less mysterious. It is clear that in many cases it results from the acquisition of mutations in one or more oncogenes that we acquire during our lifetime. Since at least some of these may result from specific chromosomal changes, or from the action of environmental carcinogens, these observations provide an elegant synthesis of several different fields of research. So although the final details of how a cell becomes cancerous still remain to be worked out, at last we have a blueprint of where to go in the future.

Although it is true to say that the clinical impact of the remarkable advances in molecular medicine of the last few years may still be some time in the future, and that their immediate benefits have been oversold to the public, there seems little doubt that

these new discoveries will play a major role in the cancer field in the future. The molecular approach is likely to provide a wide range of extremely valuable diagnostic agents for both the early recognition and assessment of the prognosis of different forms of cancer. It also seems likely that gene therapy, something that has been "just around the corner" for far too long, will find some of its early applications in cancer treatment. Thus, although molecular biology has shown us that cancer is an extremely complex disease, and that there are multiple routes to the neoplastic phenotype, there is little doubt that much of this work will find application in the clinic in the not too distant future.

All these aspects of this complex and rapidly moving field are covered in this excellent book, *Principles of Molecular Oncology*. Clinical oncologists will find a series of balanced reviews of the current state-of-the-art of the diagnosis and treatment of cancer based on molecular technology, and, since cancer touches almost every field of clinical practice, specialists in other disciplines will find a very lucid and readable account of what is happening in one of the genuine success stories of today's molecular medicine.

Writing a foreword for a book for one of one's former students, while a constant reminder of the closeness of personal dissolution, is still an enormous pleasure. If nothing else, it is reassuring to see that at least a few resistant human lines can survive all the potential damage of medical education and emerge relatively unscathed. I wish the editors and the excellent team of authors that they have brought together all the success with this book that it deserves. In a field that is moving so rapidly it is vital to have a bird's eye view of the state of the art: I am sure that readers will obtain a balanced view of the potential and limitations of this exciting field.

Professor Sir David J. Weatherall, *MD, FRS*
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Foreword

The second edition of *Principles of Molecular Oncology* is published 200 years after the exposition of Dalton's atomic theory of matter and 50 years after Watson and Crick described the basic structure of DNA. This edition comes less than four years after the first and is a consequence of the pace of discovery in such an exciting field of research. In the first edition it was anticipated that the publication of the sequenced human genome would appear in the middle of the first decade of the 21st century. It was published in 2001 and already sequenced genomes for several viruses, bacteria, plants, and animals are available. In 1844 Darwin wrote to a friend, "at last gleams of light have come and I am almost convinced (quite contrary to the opinion I started with) that species are not (it is like confessing a murder) immutable". His *The Origin of Species* issued in 1859 provided evidence for the evolutionary theory of life and represented one of the most important discoveries in biology.

The controversy surrounding Darwin's theory resulted in the famous debate between Bishop Wilberforce and Thomas Huxley. When Wilberforce finished his long tirade against the theory, Huxley replied tersely "I have come here in the cause of science only" and went on to demolish the Bishop's argument. The two men had very different backgrounds in education. Scientific method has continued to be the cornerstone in the study of life and human disease. The discovery of the structure and chemistry of DNA and the subsequent genetic research by many scientists have led to a much better understanding of the mechanisms of human biology and evolution and of the function of genes. The last 50 years has been a golden era in this important field with enormous consequences for applied medicine. Darwin of course knew nothing of genes; the processes he described were those of trial and error taking place over a vast time scale.

Recent discoveries in human genetics have not been without controversy, but clinical research has benefited from the move away from trial and error to a more rational approach in the development of new patient management techniques for many medical conditions. The techniques involved are being applied in the study of human cancer and the molecular discoveries relating to the diagnosis, prevention, early detection, and new treatments are the subject of this book. Progress in the field of molecular oncology has been much faster than previously imagined because of the abundance of innovative technology. High throughput technology for gene sequencing and expression, including comparative genomic hybridization, proteomics, and proteoglycan research, has already allowed the study of biologic function using sequenced DNA, RNA, protein, and oligosaccharide molecules. We are already awash with data and the new subject of bioinformatics has been developed to bring some order to the problem.

Poincaré, the famous French mathematician, knew from the work of Newton that the behavior of 2 bodies acting in a gravitational field could be explained with reasonable accuracy using simple mathematics but the behavior of 3 bodies was much more difficult to describe. He spent an important part of his working life on this problem and his eventual model was inaccurate. Understanding the function of genes is the key to the rational development of new treatments, but though some cancers are the result of an altered function of a single dominant gene, many arise from a more complex interaction between genes. New mathematics is being developed to help understand the complexity of these biologic systems.

In spite of the complexity, important information has been provided using molecular techniques, allowing substantial improvement in management of patients with cancer. Improvements have included the identification of predisposition to some forms of cancer, more accurate diagnostic and prognostic information, new markers for analyzing tumor progression, a quantified assessment of minimal residual disease, and the rational development of new treatments and methods of prevention. Information on all these aspects of cancer care has been updated in this new edition. It is gratifying to see that a collaborative approach between scientists in many fields is being rewarded by so much progress in the field of human cancer care. As an undergraduate at Cambridge in the 1950s, I had the advantage of contact with Crick, Brenner, Sanger, and Perutz, each of whom provided some insight into what was to come. Although since this time progress has been logarithmic, there is a great deal that remains a challenge for future editions of this book. *Principles of Molecular Oncology* provides valuable information for the continuing education of all oncologists.

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Charles Darwin "Recapitulation and Conclusion," from *The Origin of Species* (1859): Appleton-Century-Crofts Inc.

John Dewey "The Influence of Darwinism on Philosophy," from *The Influence of Darwinism on Philosophy and Other Essays* (1910), reprinted from the Popular Science Monthly (July 1909), Henry Holt & Co.

Preface

Thomas Hodgkin's (1796–1866) criteria for determining a cancer's malignancy would still stand today: appearance of the tumor, tendency to spread, enlargement of neighboring lymph nodes, general symptoms of wasting. Until the late 18th century, medicine was symptom oriented. Toward the early 19th century, the French clinicopathological school stressed symptoms of diagnostic significance and the primacy of physical signs. Louis Pasteur (1822–1895) did much to solve the problem of correlating microbes and disease, and Robert Koch formulated the now famous postulates to prove the pathogenicity of microorganisms. In spite of extremely important therapeutic advances (such as antimicrobials, endocrine agents, and drugs based on receptor–ligand interactions or inhibition of enzyme catalytic sites), our diagnostic skills today appear to be more potent than our ability to cure. X-rays, CT scans, NMR, ultrasounds, radioisotopes, PET scans, endoscopies, and other high-tech procedures have gradually increased our diagnostic abilities and have decreased our strict dependence on the skilled elucidation of clinical physical signs. After the important discoveries of molecular biology and genetics in the second half of the 20th century, molecular medicine is seen as the main promise for medical progress in the coming century, but it will probably come at the inevitable price of increasing complexity.

Leibniz (1646–1716) argued that Nature obeys a principle of "simplicity" or "least action." This concept has been often associated with "positivism," to the effect that one should choose the "simplest hypothesis" fitting the facts. Simplicity, however, has been criticized on the grounds that for any given problem there can still be several possible explanations of equal simplicity. In other words, simplicity is elegant, but it can also be deceiving. The history of science reveals progressively more complex, rather than simpler, laws and theories. In some of the most advanced sciences (for example, physics), the 20th century has brought us extremely complex theories, such as quantum mechanics or the general theory of relativity, fully understandable only to a few gifted minds.

Similarly, cancer is also turning out to be a more complex phenomenon than originally thought by many. This is why a realistic approach is a common denominator to all of the chapters of this book. Nevertheless, the search for esthetic formal simplicity and a general model pervades most of the text, together with a firm belief that even cancer can be understood and eventually defeated. The book is written by a combination of basic scientists and clinical researchers, and it is meant for practicing clinicians (such as medical oncologists, radiotherapists, hematologists, internists, general surgeons, urologists, gynecologists, thoracic surgeons, orthopedic surgeons), pharmacolo-

gists, and advanced medical students. The emphasis is not on biological mechanisms or pathology, but on prevention, early diagnosis, prognosis, and treatment.

The first chapter of *Principles of Molecular Oncology* presents the conceptual framework applicable to the rest of the book. Cancer is approached not from a specific disease-oriented point of view (e.g., lung cancer, breast cancer) nor from a selective therapeutic point of view (e.g., surgery, radiotherapy, chemotherapy). Instead, we have focused the problem starting from the hypothesis that cancer can be regarded as a "disease of key regulatory pathways." Pathways involved, for example, in the homeostatic regulation of cell growth, differentiation, and death. Carcinogenesis, as it is understood today, involves several cumulative genetic changes that, in at least some instances, can lead to the acquisition of a malignant phenotype. At the same time, these successive molecular changes can provide us with "markers" of malignant or premalignant lesions at genetic or cellular levels or circulating in the extracellular fluids. Some can even be inherited, leading to a genetic predisposition to malignant disease. The picture is still incomplete, but it seems reasonable to propose that each individual cancer has its own natural history, genetic makeup, and clonal evolution. Each individual cancer, therefore, may provide a particular "matrix of targets" for therapeutic intervention, conditioned by the regulatory networks of the tissue of origin. Moreover, even transformed cells are liable to modulation by their own microenvironment and the immune system of the host, and therapies can be directed not only to the cancer cells themselves, but also to the immune system of the patient and the specific microenvironment (e.g., to delay or prevent angiogenesis, tissue invasion, and metastasis).

There are still many gaps in our knowledge, both in terms of biological mechanisms and new effector molecules. These "blank spaces" in the matrix will eventually be filled by rapidly accumulating knowledge, just as new atoms gradually filled the chemical periodic table at the turn of the century. It seems likely that most of these key regulatory cascades will converge into a limited number of key regulatory events: the coordinated expression or suppression of a battery of genes, the initiation of normal DNA replication at multiple different sites in the genome, the culmination of the developmental history, and cell fate, of any given clone.

The future of molecular oncology is exciting. It will have profound implications in the prevention, early detection, and treatment of cancer. It might also help us exchange some of our unhealthy life habits for healthier ones, estimate individual vulnerability to environmental carcinogens, or allow the development of effective anticarcinogenic diets. Cancers do not happen overnight, and the often protracted lag periods of cancer growth should allow opportunities for chemoprevention or new methods of screening and early detection. Nuclear magnetic devices of the future might help to detect "in vivo" areas of genomic instability or chromosomal "disorder" by focusing on abnormal DNA patterns. The ultimate outcomes of basic research (and early clinical research) are seldom identifiable while the research is in progress. Better coordination of all research efforts by university, government agencies, pharmaceutical corporations, and international scientific societies will lead to success. Medicine is evolving at a more rapid pace than ever before, with the increasing specialization and integration of parts, learning through the association of ideas and the natural equilibration of interests.

Principles of Molecular Oncology, and the preceding *Principles of Molecular Medicine* by Larry Jameson et al. (Humana Press, 1998) are good examples of what has already been achieved.

I am indebted to the generous contribution of all authors, from both sides of the Atlantic; and to the constant support of the other editors, and MaryAnn Foote, in particular.

Since different perspectives allow readers to arrive at their own conclusions and serve to stimulate scientific thought, we have not removed areas of controversy or overlap among chapters. We hope that this book proves useful and we invite your comments. We have tried to acquire the necessary permissions and authorizations before publication, and great care has been taken in the preparation of the chapters. Nevertheless, errors cannot always be avoided. The editors and publishers, therefore, cannot accept responsibility for any errors or omissions that have inadvertently occurred. The views and opinions expressed in the book are those of the participating individuals and do not necessarily reflect the views of the editors, the publisher, or any other manufacturer of pharmaceutical products named herein. The package insert should be consulted before administration of any pharmaceutical product.

Miguel H. Bronchud, *MD, PhD*

Color Illustrations

The following color illustrations follow p. 362:

Color Plate 1: Figure 3 from Chapter 6; full caption appears on p. 221.
Color Plate 2: Figure 4 from Chapter 6; full caption appears on p. 225.
Color Plate 3: Figure 5 from Chapter 6; full caption appears on p. 227.
Color Plate 4: Figure 5 from Chapter 11; full caption appears on p. 367.
Color Plate 5: Figure 6 from Chapter 11; full caption appears on p. 367.
Color Plate 6: Figure 9A,B from Chapter 11; full caption appears on p. 370.
Color Plate 7: Figure 14 from Chapter 11; full caption appears on p. 395.
Color Plate 8: Figure 2A,B from Chapter 12; full caption appears on p. 420.
Color Plate 9: Figure 1 from Chapter 18; full caption appears on p. 572.

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