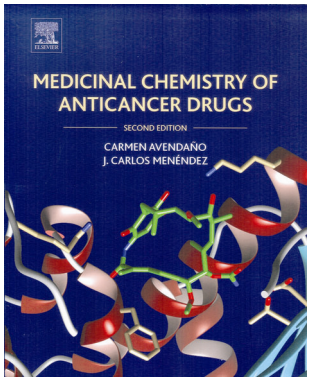

Medicinal Chemistry of Anticancer Drugs, 2nd Edition. Carmen Avendaño and J. Carlos Menéndez. Elsevier, Radarweg 29, P.O. Box 211, 1000 AE Amsterdam, The Netherlands. 2015. xxvi + 740 pages. Price: US$ 200.

Influential ideas are always simple. Since natural phenomena need not be simple, we master them, if at all, by formulating simple ideas and exploring their limitations.

—Al Hershey

The topic of disease mitigation and eradication of associated sufferings has kept alive the human inquiry into underlying principles in search for novel therapies and cures of diseases. Cancer, a clinical term referring to about 200 different malignancies, has emerged as mankind's gravest health burden vis-à-vis morbidity and mortality. The book under review unique in its concept, context and contents, presents an in-depth account of various non-biological, biological and synthetic approaches to halt initiation, development, progression and metastasis of cancer. Guided by an approach of chemical decoding of various atomic and molecular interactions within/outside the cell, determining and shaping its trajectory to full blown cancer, the book is a comprehensive topical overview of the central principles and contemporary clinical practices in cancer treatment using anticancer drugs, bringing underlying chemistry to the fore. As a standard and lasting 'cure' for cancer is still elusive, the theme and contents of the book seem to resonate the aforementioned statement of Al Hershey from the perspective of undying hopes and persistent global efforts to consolidate the incremental gains in pursuit of that goal.

While 20th century saw the emergence and establishment of cancer chemotherapy ultimately culminating in the birth of 'medical/clinical oncology' with anticancer drugs as the tools of its trade[1], the state-of-the-art in deeper molecular understanding of cellular and system-level processes assisted by latest technology undoubtedly point to paradigm shift in basic and applied biological research vis-à-vis focus, opportunities and reach in the present millenium. It is increasingly being felt that biology will eventually morph into a sort of 'chemical science'. In line with this notion of chemical decoding of life at the molecular level, this book is built – perhaps rightly so – on the idea that all cellular processes are result of some type of chemical interaction(s) between two or more components of the cellular machinery and/or its surrounding environment. Indeed, decoding of these biological principles in cancer versus normal healthy cells/tissues has also brightened prospects to tackle cancer in the beginning itself.

Individually organized on the basis of 'mechanism of action' of anticancer drugs, each chapter of the book starts with a brief but highly informative introduction to the topic followed by the main stories on drugs and their targets, illustrating the chemical interctions. The book begins with an excellent introduction to the overall subject (chapter 1) providing a ringside view of various cellular factors and processes responsible for cancer initiation and subsequent progression and spread; history of cancer chemotherapy; role of natural products in cancer chemotherapy to the latest concepts of personalized medicine and nanotechnology. The chapter ends with a useful list of FDA approved anticancer drugs.

The precisely regulated process of the duplication and distribution of genetic material, the DNA, is central to the normal cellular division. As such, it is the most attractive target of the anticancer drugs, preferentially affecting the fast-dividing cancer cells over normal cells. Interestingly, mechanistic studies on the very first generation of anticancer drugs discovered in the 20th century revealed them to do just that. It is no surprise then that most of the first half of the book is devoted to anticancer drugs targeting DNA or related processes either as antimetabolites interfering in DNA biosynthesis (chapter 2; focus here is on enzyme inhibition in the initial and later steps of DNA biosynthesis); free radical generators such as antibiotics bleomycins, anthracyclines and actinomycin D including drugs based on radioactive isotopes to induce DNA damage and apoptosis (chapter 4); DNA alkylating agents including nitrogen mustards (chapter 5); DNA minor groove binding agents including distamycin A, mitomycins, tetrahydroisoquinoline alkaloids and their derivatives, etc. (chapter 6); DNA intercalating drugs and other agents targeting topoisomerases 1 and 2 including camptothecin and derivatives (chapter 7); and finally the latest buzz in this field – drugs modulating the chromatin status and gene expression through effectors of epigenetic processes such as HDACs, DNMTS, HMTs, etc. (chapter 8). Additionally, molecular components of the DNA damage repair process have been discussed as anticancer drug targets in various sections of the book particularly in chapter 12.

Sex hormones had long been suspected to play important roles in male and female specific cancers. Several clinical observations of the past and present have corroborated this notion. Chapter 3 highlights the central role played by sex hormones in selective cancers of men and women, such as breast and prostate cancers. The chapter highlights the effectiveness and role and scope of hormone therapy in these cancers through the modulation of the male and female sex hormone biosynthesis and/or their receptors.

Similar to DNA duplication, the role played by spindle apparatus in equal distribution of the genetic material across daughter cells marks its special relevance as an anticancer drug target. The microtubule targeting agents (MTAs) such as the Taxol®, vinca alkaloids, epothilones, colchicin, podophyllotoxin and their derivatives modulate the spindle microtubule dynamics leading to the cell division arrest (chapter 9). Interestingly, this class of anticancer drugs is almost exclusively represented by natural products or their derivatives, thus highlighting the extraordinary evolutionary significance of this biological target vis-à-vis its chemical modulation as a defensive strategy in natural ecosystems.

Cancer is a multifactorial disease often involving multiple deregulated cellular processes arising either during normal cellular physiology or induced by external environmental factors. The book especially highlights the significance of

deregulated cellular signal transduction networks in initiation, progression and spread of cancer. These networks which relay the intra- and intercellular signals from the cell surface to the interior to readjust the cellular biochemistry, physiology and homeostasis play critical roles in maintaining the normal health. Indeed, the vast amount of data from the recent past clearly implicates the defects in these signal transduction networks and their individual molecular components such as receptor tyrosine kinases (RTKs) and their ligands, phosphatases, MAPKs, etc. in cancer initiation, progression and metastasis. This obviously points to the relevance of signal transduction targets in anticancer drug design and discovery. Anticancer agents targeting abnormal cellular signaling, in particular a reduced apoptotic or an enhanced survival and proliferation signaling have been beautifully illustrated in chapter 10 which focuses on a range of receptor tyrosine kinases, non-receptor kinases and other components of these pathways. Incidentally, chapter 10, the largest chapter of the book is the flag bearer of its thematic message, highlighting some of the latest stories in anticancer drug discovery and development. Recently, an interesting report on the prediction, development and validation of an allosteric inhibitor, SHP099 of the cellular phosphatase SHP2 has been published in *Nature*[2]. Difficult to target, this enzyme has been widely known to be involved in several cancers with deregulated RTK-mediated MAPK signaling. In continuation of this signal transduction theme, chapter 11 also covers inhibitors of targets from diverse signaling pathways, including proteolytic enzymes and other enzymes/factors with role(s) in tumour angiogenesis and metastasis as well as those regulating cancer stem cells (e.g. targets in Wnt/β-catenin, Notch and Hedgehog signalling pathways). Chemical strategies to target components of signal transduction involved in apoptosis induction and regulation are special features of this chapter.

Immune response and control of cancer is a well-known biological phenomenon and an active area of research. Targeting of the important molecular and cellular components of this highly regulated process has profound applications in cancer treatment. Manipulation of the tumour microenvironment by the application of monoclonal antibodies targeting cancer cells to elicit immune response or deliver some therapeutic cargo; use of engineered killer T-cells to seek[3] and destroy cancer cells; various forms of cancer vaccines; and gene and antisense oligonucleotide therapies have been discussed in chapter 12.

The book largely succeeds in projecting the special significance of anticancer drugs in the treatment of cancer, highlighting their seminal contribution and future scope in clinical management of cancer. However, the two major issues of drug resistance and unwanted side effects due to non-specificity remain as the foremost challenges in chemotherapy's ultimate success. Chapters 13 and 14 deal with strategies directed at addressing these challenges. Improved drug design as inactive prodrugs which get activated at their desired target site by utilizing unique tumour microenvironment such as hypoxia, acidic pH, etc. is one such approach to increase specificity to tackle the issue of side effects (chapter 13). Further, targeted drug delivery to cancer cells by applications of nanotechnology such as drug-polymer conjugates and liposome-based delivery systems exploiting the highly permeable tumour vasculature increase drug specificity and minimize toxicity (chapter 13). A similar effort in addressing the issue of drug resistance through chemical modulation of the molecular players and processes involved therein is the focus of chapter 14. In particular, inhibitors of ABC efflux pumps and the P-glycoprotein; cellular detoxifying molecules such as glutathione and GST; chemosensitizers affecting the outcome of DNA repair processes; inhibitors of tumour-associated carbonic anhydrase IX responsible for acidic tumour microenvironment; etc. are discussed from this viewpoint. Finally, the idea of cancer prevention by dietary and other chemical agents, an approach known as chemoprevention, is highlighted with a range of synthetic and natural molecules in chapter 15. The chapter also touches upon the topic of genomics-based personalized medicine.

Currently, a whirlwind of activity and reports on the precise genome editing CRISPR technology with potential applications in cancer biology research and treatment[4–8] combined with wider paradigm shifts, unprecedented focus and pace in cancer research and therapeutics seem to suggest that a new and updated edition of this book will arrive in the near future.

This book has the potential to become a one-of-a-kind study material on a galaxy of anticancer drugs and their molecular mechanisms of action. We strongly believe that the book will benefit a host of scientific and clinical R&D personnel from across diverse disciplines especially instructors and students of medicinal chemistry, cancer biology, pharmacology, clinical oncology, biochemistry and research community from structural biology, bioinformatics and pharma industry engaged in anticancer drug design and development. Most importantly, it is hoped to motivate all the stakeholders to appreciate the molecular and chemical principles underlying the discovery, design and development of highly efficient and targeted anticancer molecular therapies with minimal or no side effects. It is thus a must read for anyone with an interest in cancer biology and treatment.

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