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## Foreword

Cancer pharmacotherapy has undergone dramatic changes. For centuries, trial and error attempts did not result in tangible success. From around 1945 through 1965, DNA damaging agents were generally used. However, their poisonous nature was dose limiting. The introduction of combination chemotherapy in 1965 led to improvements in reducing the serious adverse effects of this form of cancer chemotherapy. The approach to the drug treatment of cancer changed dramatically in the late 1990s, when molecularly targeted agents (predominantly small molecule kinase inhibitors and neutralizing antibodies) allowed the blockage of oncogene function, fairly selectively in cancer cells, as a first line of defense. This shift in treatment strategies rounded off 30 years of molecular cancer research that had been initiated with the discovery of the first endogenous oncogene, *src*, in 1976. The new therapeutic modalities demand a different approach to cancer diagnosis and classification than their predecessor treatments. The identification of a causative molecular defect, rather than the clinical presentation or histologic appearance, determines the most suitable drug therapy. Treatment in cycles of high dose chemotherapy followed by recovery phases has been the standard for classical chemotherapy. This is mandated by the need to reach near-toxic doses in order to eradicate most cancer cells, but the strain on the host cells makes breaks in the time lines unavoidable. For molecularly targeted drugs, treatment cycles are replaced by continuous (“metronomic”) therapy. Often, these agents are taken without interruption until disease progression or unacceptable adverse effects occur. Despite the progress molecular biology has introduced into cancer management, the conventional combination chemotherapy will likely have a durable role as a second or third line of defense against advanced cancers. Likewise, the new generation molecularly targeted drugs are projected to have some continued benefit whenever medical research progresses to better treatment modalities in the future. While a lot has been written about anti-cancer drugs in various forums, a book that comprehensively and systematically reviews their molecular actions is much needed.

The molecular structures, targets, and mechanisms of action of anti-cancer drugs as well as their grouping into drug classes are the topic of this book. There has long been a separation between basic molecular research and clinical applications. One of our goals is to explain the clinical use of specific anti-cancer treatment regimens (exemplified in the text boxes) on the basis of the underlying molecular drug actions (discussed in the sections). While it is impossible to cover all classes of drugs that are in development, reference is made to some of the up and coming drugs and treatment approaches that may find clinical applications down the road. This inclusion should give the current edition a longevity it would not otherwise have. Drugs are referred to in the text with the most commonly used chemical name. Alternative names and code names are listed on first mention in separate parentheses. Trade names are given thereafter in angle brackets. Bullet points marked by hyphens are listings of facts, bullet points marked by filled circles list structurally or functionally related drugs. The inclu-

sion of any compound in this book does not constitute a recommendation or endorsement. The administration of agents outside currently approved indications (off-label use) is considered experimental.

The history of cancer drug discovery and development is also the history of the people who participated in the process. It has highs and lows, bright and dark sides. The unique challenges of the subject have always attracted some of the most brilliant minds as well as some of the most self-absorbed egos. There are chapters in this history which are famous, others are infamous. To put the drug classes into the perspective of their origins, many of the descriptions in this book begin with a brief summary of the historical development that underlies the class of drugs to be discussed. Instead of reviewing the historical background in the first chapter, as I did in the predecessor book on molecular oncology [Georg F. Weber, *Molecular Mechanisms of Cancer*, Springer 2007], the stories are here woven into the main text. I tell them as they have been reported by public sources.

I am indebted to Drs. Jane Pruemmer and Victor Warner for critically reading and providing feedback on the treatment sections and the chemical structures respectively. In comparison to the mentioned book on molecular oncology, which meticulously referenced the literature, the reference lists here are much less extensive. This is not a disregard for prior research accomplishments. Rather, it reflects the circumstance that drug information is widely available online without attribution of authorship, so that detailed citation is not a requirement. The inclusion of select references that cite key sources or are representative for further reading seems to be consistent with the aims and scope of a textbook. So, why a textbook that to a large extent repeats what the internet already provides? Research takes place on all levels of inquiry. A comprehensive review of existing knowledge accomplishes innovation through systematic classification and the derivation of new paradigms. The capsules printed in bold italics at the end of each chapter summarize key information on the drug classes discussed, some of which has not been explicit in the literature. May this book actively contribute to scholarship and education in the drug treatment of cancer.

Molecular Therapies of Cancer

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2015, XV, 488 p. 120 illus., 86 illus. in color., Hardcover

ISBN: 978-3-319-13277-8