Cancer Drug Discovery

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Preface

This book was written with the aim to provide a comprehensive and multifaceted overview of the history of the development of anticancer drugs and to present future directions for the development of new anticancer drugs. First, this book examines the scientific progress in biological science periodically and the influence such progress had in cancer research. Furthermore, this book outlines the development process of anticancer drugs with a focus on the characteristic drug groups of each era, in relation with the advancements in the relevant fields of chemistry and biological science and also presents a brief mechanism of the drugs. After examining the side effects of each anticancer drug and the treatments for alleviating the effects, this book finally sums up the limitations of the current anticancer drugs and seeks new directions for the development of anticancer drugs.

During the last 60 years, research in biological science has centered on the cell, and cellular molecules, with an emphasis on the activities and functions of various genes. Accordingly, cancer research has also focused on cancer cells; the differences between normal cells and cancer cells, including their genetic variations, were discovered and corresponding molecule-targeted anticancer drugs developed.

The development process of anticancer drugs indicates that leukemia, which can be easily observed through the microscope, served as the model during the early days of cancer research and that the rapid proliferation of the leukemia cells was accepted as the general characteristic of cancer cells. As a result, development of anticancer drugs that have anti-proliferative effects began, starting with the alkylating agent in 1946, based on the unity assumption that all cancer cells characteristically grows abnormally. The search for a standard treatment for all cancers was launched through the development of such cytotoxic anticancer drugs.

Alkylating agents, which are one of the first types of anticancer drugs developed during this process, inhibit persistent cell proliferation, which is the representative feature of cancers, by causing DNA damage, and was developed especially during the 1940s to the early 1970s. The second type, antimetabolites, have been developed since the late 1940s and display structural mimicry with precursors of DNA synthesis, thus inhibiting cell proliferation by inhibiting activities of various enzymes contributing to DNA replication. In addition, as a result of a large-scale drug screen-

ing that began in 1954, plant alkaloids and anticancer antibiotics were developed from the 1960s and continued to be developed until the 1990s. Anticancer drug screenings on chemical molecules also proceeded at the same time, leading to the development of various chemical anticancer drugs from the mid-1960s which continued to be developed until the mid-2000s. These drugs form the third type of anticancer drugs. The fourth type of anticancer drugs, consisting of immunotherapy and miscellaneous anticancer drugs, were developed in the mid-1960s, proceeded to be developed from the 1980s to the 1990s and are still consistently being developed. Immunotherapy anticancer drugs, which activate the immune system to eliminate cancer cells, include cytokines such as interferons, humanized antibodies, and dendritic cells, while asparaginase and others were developed as miscellaneous type of anticancer drugs. Before the molecule-targeted anticancer drugs were developed, the fifth type of anticancer drugs, hormonal cancer drugs were developed for treating several cancers based on the understanding of the biological characteristics of cancers. Hormonal anticancer drugs for treating testosterone- or estrogen-dependent cancers such as diethylstilbestrol or tamoxifen were developed from the 1940s and are continued to be used today. Beginning from the 1990s, new types of molecule-targeted anticancer drugs were rapidly developed, forming the sixth type of anticancer drugs. Molecule-targeted anticancer drugs are products of in-depth biological research on cancers that was intensified from the 1980s. In other words, molecular mechanisms of tumorigenesis and malignancy were better understood by extensive research which used molecular biology as its major research technologies. In particular, various factors that play important roles in various types of cancers were discovered, facilitating the development of new drugs targeting the discovered factors. These molecule-targeted anticancer drugs are forming a major anticancer drug group starting from the 2000s.

Accordingly, this book presents an overview of the scientific discoveries and history of the development of anticancer drugs in the following order. Chapter 1 summarizes the characteristics of cancer in accordance to the development of science. This chapter describes the characteristics of the cancer cells based on the research that focused exclusively on cancer cells, similarly to biological science which mainly focuses on cells. Moreover, this chapter provided characteristics of cancer which interacts with its surrounding microenvironment. In particular, this chapter provides a systematic explanation of cancer in relation with the vascular system, lymphatic system, and immune system, which also relates to the new research prospects presented in the final chapter of this book. Chapter 2 examined the relation between the development of biological science since the advent of the cell theory in 1838 with the corresponding history of cancer research and development of anticancer drugs and summarized the relation through a chronological table. Chapter 3 provided images that explain a historical background of cancer chemotherapy and describe chronologically the developmental history of screening systems of anticancer drugs. Chapters 4–9 classified the characteristics and effects of approximately 160 anticancer drugs, which used the screening system described in Chapter 3 for development, into 6 groups and provided a comprehensive account of the development process and history of each group. Chapter 10 provided details on the side

effects of the clinical use of the anticancer drugs introduced in Chapters 4–9, along with the drugs that can alleviate such side effects. Finally, in Chapter 11, this book provided new anticancer drugs that will be researched and developed, based on research focusing on the difference between cancer cells and normal cells which has been conducted since the 1980s. This book also suggested a cell network research for a next research methodology, based on the perspective that cancer is related with various systemic characteristics of the human body. In other words, this book emphasizes that the research on cell network of the tissue level is necessary.

This book, in short, is a review of the past and current research conducted on anticancer drugs and a proposal for a new direction of cancer research for the future. I would like to express my gratitude to Professor Jae Kyung Roh, Dr. Hee-Jun Wee, and Dr. Chan Kim for joining me as co-authors to write this book. I also thank my graduate students at the research center who helped me with the images and tables included in this book. I also extend my gratitude to Professor Seishi Murakami at the Cancer Research Institute of Kanazawa University, Japan, who has always been a source of advice and encouragement throughout the past 35 years of research on cancer. Lastly, I thank Dr. Jeong Hun Kim at Seoul National University Hospital who helped me throughout my personal ailment. This book would not have been published without their help.

Seoul, Korea Kyu-Won Kim
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