New Leads in Cancer Therapeutics

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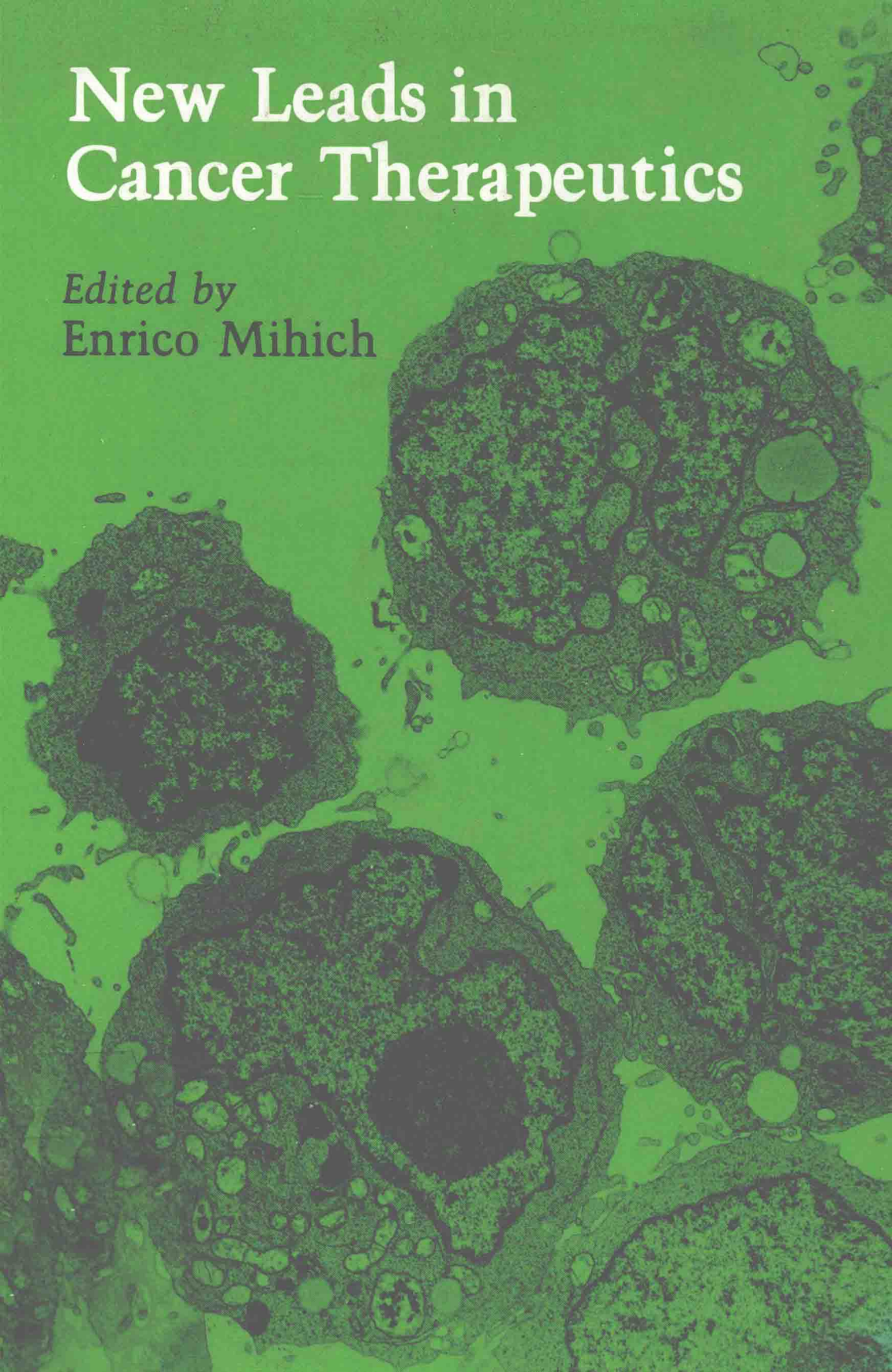

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Enrico Mihich, M.D.
Director, Department of Experimental Therapeutics and Grace Cancer Drug Center, Roswell Park Memorial Institute Buffalo, New York

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Contributors

Ralph J. Bernacki, Ph.D.
Cancer Research Scientist IV, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

John S. Bertram, Ph.D.
Cancer Research Scientist V, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Alexander Bloch, Ph.D.
Associate Chief Cancer Research Scientist, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Chi-Hsiung Chang, Ph.D.,
Research Affiliate, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Yung-Chi Cheng, Ph.D.,
University of North Carolina Medical School, Department of Pharmacology, Chapel Hill, North Carolina

Patrick J. Creaven, M.B.B.S., Ph.D.
Chief, Department of Clinical Pharmacology and Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Lynn Danhauser
Research Affiliate, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Gerald B. Grindey, Ph.D.
Cancer Research Scientist V, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Debora Kramer
Research Affiliate, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Elihu Ledezma, M.D.
Clinician I, Department of Surgical Oncology, Roswell Park Memorial Institute, Buffalo, New York

Enrico Mihich, M.D., Editor
Director, Department of Experimental Therapeutics and Grace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, New York

Fredika Mikles-Robertson, Ph.D.
Postdoctoral Fellow, University of Southern California Medical Center, Los Angeles, California

Arnold Mittelman, M.D.
Program Director, Colon and Rectal Service, Department of Surgical Oncology, Roswell Park Memorial Institute, Buffalo, New York

Michael J. Morin, Ph.D.
Research Affiliate, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Carl W. Porter, Ph.D.
Cancer Research Scientist IV, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Harvey Preisler, M.D.
Deputy Chief of Medical Oncology, Department of Medical Oncology, Roswell Park Memorial Institute, Buffalo, New York

Fred Rosen, Ph.D.
Associate Chief Cancer Research Scientist, Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

Youcef M. Rustum, Ph.D.
Cancer Research Scientist V, Departments of Experimental Therapeutics and Clinical Pharmacology and Therapeutics, Roswell Park Memorial Institute, Buffalo, New York

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Introduction

Enrico Mihich, M.D.

Considerable progress in cancer therapeutics has been achieved since the mid-forties, when the initial trials of antifolates, steroids, and alkylating agents marked the beginning of cancer chemotherapy as we know it today. Advances have increased the options available in treating the patient with a specific tumor type or with a tumor at a specific stage, as well as in terms of the types of cancer for which effective treatments can be instituted.

Despite obvious advances, particularly in the treatment of leukemias, lymphomas, Hodgkin's disease, certain types of choriocarcinoma, Wilms's tumor, and certain skin tumors, many limitations must be overcome before chemotherapy by itself can be widely and generally used as the primary treatment in the management of the solid tumors. The primary limitation is that most of the anticancer drugs developed to date are also toxic to normal tissues and have limited selectivity for the tumors they are meant to treat. Consequently, in many cases even a limited degree of natural or acquired resistance to a drug cannot be overcome without incurring unacceptable toxicity. Attempts to overcome these limitations and to further improve the effectiveness of cancer therapeutics should focus on multiple approaches.

The development of new drugs with improved selectivity of action against tumor cells is a primary goal based on 1) acquisition of new information about the biological and biochemical characteristics of cancer cells that may result in new types of drugs affecting these cells through selective action upon newly identified targets; 2) development of analogs of known active agents that have more favorable pharmacological charac-

teristics than their parent compounds and, consequently, improved selectivity of antitumor action; 3) careful study of new chemical structures that derive from semiempirical or even empirical approaches in screening; and 4) the development of agents and treatments that act against tumors indirectly by augmenting the physiological responses of the host against the tumor or by mimicking these responses.

Clarification of the biochemical and pharmacological basis of the selective toxicity of known drugs and treatments is another important goal, since in many cases available agents may not be used under conditions that maximize selectivity of antitumor action or are not used against tumors which may be unrecognized targets of their action. Improvements in the clinical utilization of the well-known antimetabolite methotrexate during the past 30 years provides a convincing example of the opportunities open to the chemotherapist for identifying new target tumors and designing new regimens with increased therapeutic advantages.

The clinical development of chemotherapeutic regimens utilizing known active drugs in multiple combinations received major impulse in the 1960s and has radically changed the outlook on cancer chemotherapy by demonstrating the [possibility of inducing] long-term survival without detectable disease. The development of new combination chemotherapeutic regimens represents a continuing effort and has the potential for additional significant improvements based on novel approaches. Indeed, as more knowledge is acquired on the determinants of the selectivity of action of known drugs, opportunities increase to develop new combination therapies. These can be based not only on synergisms among active agents, but also on such mechanisms as the potentiation of active agents by compounds affecting their rate of activation or inactivation, or their potentiation by compounds augmenting the response of target tumor cells through a favorable modification of the biochemical and pharmacological determinants of their action.

While chemotherapy has become recognized as an effective modality in the management of certain types of cancer, it is apparent that additional therapeutic advantages may be achieved through its combination with other treatment modalities. Increased attention is being given to chemotherapy as a potentially curative adjunct to presumed radical surgery and radiotherapeutic treatments. Moreover, the possibility is being explored that modifiers of biological responses of the host against the tumor may provide an effective and probably relatively nontoxic means to eliminate residual tumor cells after cytoreductive treatment with antiproliferative or cytocidal chemotherapy is given alone or in combination with radiotherapy or surgery. If judiciously applied, this multimodality approach in cancer therapeutics may turn out to be at least as profitable as

the systematic introduction of combination chemotherapy was in the 1960s.

The approaches already mentioned are all directed toward the improved elimination of tumor cells in patients with a given clinically defined tumor type. Increased attention is also being given to the possibility that chemotherapy may be designed for the individual patient, based on the identification of his or her key pharmacological and biochemical determinants of drug action. Initial steps are being taken in this direction particularly with certain antimetabolites and the anthracyclines, and the results obtained to date seem to encourage further efforts in this difficult area of clinical biochemical pharmacology.

Several of the approaches mentioned here are being pursued in the Department of Experimental Therapeutics and the Grace Cancer Drug Center of Roswell Park Memorial Institute, in cooperation with the Institute's clinical departments. Some of the directions pursued were selected as representative and discussed during a one-day seminar held in the fall of 1978 as part of the Institute's continuing medical education program. Updated versions of these presentations are the subject of this volume.

The topics discussed include 1) the basic process of developing new drugs for clinical use, with acquisition of maximal information and consequent optimal evaluation in human beings; 2) the study of the pharmacological and biochemical determinants of antimetabolite action in individual patients as a prerequisite for the potential design of individualized chemotherapy; 3) the design of novel therapies with antifolates, based on the augmentation of antitumor effectiveness, with decreased toxicity as an example of the therapeutic modulation of antimetabolite action by metabolites; 4) the role that steroid receptors and their regulation might have in determining responsiveness of tumors to hormones and related agents; 5) the basis for the development of new nucleosides as a family of compounds with potential antitumor activity; 6) the biochemical basis for the design of new compounds and treatments selectively affecting deoxynucleotide metabolism in tumor cells; 7) the possible advantages offered by the plasma membrane of cancer cells as a site for therapeutic intervention; 8) new ideas stemming from studies of cell-to-cell contact and growth control in cell populations that may lead to the design of new types of treatments; and 9) the opportunities offered by electron microscopy in identifying ultrastructural changes in cells affected by drugs and in providing insights leading to the design of new treatments. The emphasis in this volume is on providing a few examples of the kinds of approaches that are being pursued to provide new leads toward the development of improved cancer chemotherapy.

Contents

Chapter 1

Preclinical and Clinical Pharmacology in Drug Development

Patrick J. Creaven, M.B.B.S., Ph.D.
and Enrico Mihich, M.D.

The emphasis in this book is, rightly, on novel approaches to cancer treatment in both the development of new therapies and the development of ways in which established drugs and therapies can be used more effectively. It must be recognized, however, that much of the advance in the drug treatment of cancer over the past 30 years has come from the introduction of new antineoplastic agents, and there remains an acute need for the development of drugs which are more effective, more selective, and less toxic than those currently available. This chapter will deal with some aspects of the development of new agents, with particular reference to the role which preclinical and clinical pharmacology can play in this process, and with specific emphasis on the program of drug development of the Grace Cancer Drug Center, the drug development arm of Roswell Park Memorial Institute. We shall first attempt to summarize the broad general principles of new drug development and then give three examples of current studies with antineoplastic agents under development in the Grace Cancer Drug Center.

Discovery of New Drugs

Development of new anticancer drugs starts with the demonstration of antitumor activity. Some of the approaches that have been used for the discovery of new antineoplastic agents are listed here:

1. Random screening
2. Screening of compounds from specific sources (e.g., fermentation broths)

3. Synthesis and testing of analogs of known antineoplastic agents
4. Rational synthesis employing biochemical principles or other scientific rationales
5. Serendipity

Random Screening

Random screening has been an accepted method for searching for new antineoplastic agents since the establishment of the Cancer Chemotherapy National Service Center (CCNSC) in the mid-fifties. Since that time, the CCNSC and its successors have been responsible for the screening of approximately 15,000 compounds a year from diverse sources (1). As a method of identifying new agents, screening is a procedure with low yield and high cost, and for this reason it is currently undergoing some reevaluation. Its potential advantage is that it has the capability of identifying totally novel structures which could interfere with as yet unrecognized mechanisms for cell growth peculiar to tumor cells, thus providing us with the long-awaited non-cytotoxic antitumor agent. So far this has not occurred, and the number of compounds currently used for the clinical treatment of cancer whose antitumor activity was identified by purely random screening is relatively small. It seems reasonable to predict that random screening will become relatively less important in the overall program for the identification of antitumor agents in the future (2).

Screening Compounds From Specific Sources

The screening of compounds from specific sources is more efficient than random screening. For example, a number of clinically active antitumor agents including daunorubicin, adriamycin, bleomycin, streptonigrin, mitomycin-C, and mithramycin are all derived from different species of Streptomyces. Screening of products isolated from members of this genus would, therefore, be potentially much more fruitful than random screening as the starting point for an attempt to isolate new antitumor agents.

Analog Development

Analogs constitute another high-yield source of new active agents. Once a compound has proved to have clinical activity against tumors, it is customary to attempt to develop analogs designed either to increase antitumor efficacy or to decrease or eliminate unwanted features of the compound such as specific target organ toxicities. An analog may turn out to have a somewhat different spectrum of antitumor activity or toxicity than the parent compound. This may be an advantage, as happened in the

case of adriamycin, an analog of daunorubicin whose antitumor spectrum for solid tumors is broader than that of the parent compound.

Rational Synthesis

Many of the antimetabolites in current use are antitumor agents of rational chemical design, although, as in the case of cytosine arabinoside (ara-C), the original rationale may prove to be erroneous. Because it differs from cytidine in the stereochemistry of the 2-position of the sugar, and because this position is the site of reduction of ribose to deoxyribose, it was felt that ara-C would be an effective inhibitor of the reduction step of deoxyribonucleotide biosynthesis (3), whereas it was found that the compound acts by inhibiting DNA polymerase (4). Cyclophosphamide is an example of a rationally synthesized alkylating agent precursor that turned out to be effective for the "wrong" reasons. Designed as a pro-drug which would release nor-nitrogen mustard inside the tumor cell (5), it was found to be activated in the liver without giving rise to substantial amounts of nor-nitrogen mustard (6, 7).

Since compounds developed by rational chemical design are among the compounds most likely to have antitumor efficacy, their development is a logical and relatively economical approach and is the one being pursued in the Grace Cancer Drug Center.

Serendipity

Serendipitous discovery of a compound's antitumor activity is of importance because it may, as in the case of cis-diamminedichloroplatinum-II (cisplatin), lead to a new class of antitumor agents (8) that can then form the starting point for analog development.

Stages of Preclinical Drug Development

Table 1.1 lists the stages in preclinical drug development. Listed in the left column are those procedures which form part of a routine drug development program. On the right are a series of procedures which, while not strictly required in order to introduce an antitumor drug into the clinic, are of considerable importance and should be included as part of the regular development of all drugs. Although it is not essential to perform in vitro tests of antitumor activity (essentially tests of cytotoxicity), in vitro tests are normally included for economic reasons, since large numbers of compounds can undergo initial screening relatively cheaply by this means. The Grace Cancer Drug Center approach to the identification of antitumor activity in vitro and in vivo will be discussed briefly later in this chapter.