# Anticancer Drug Development Guide

# CANCER DRUG DISCOVERY AND DEVELOPMENT

1. **Cancer Therapeutics:** *Experimental and Clinical Agents,* edited by Beverly A. Teicher, *1997*
2. **Anticancer Drug Development Guide:** *Preclinical Screening, Clinical Trials, and Approval,* edited by Beverly A. Teicher, *1997*

# Anticancer Drug Development Guide

*Preclinical Screening, Clinical Trials, and Approval*

Edited by

Beverly A. Teicher

*Dana-Farber Cancer Institute, Boston, MA*

SPRINGER SCIENCE+BUSINESS MEDIA, LLC

*For the beautiful ones*
*Emily and Joseph*


Originally published by Humana Press Inc. in 1997
Softcover reprint of the hardcover 1st edition 1997



This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

Cover illustration: From Fig. 1 in Chapter 14, "Discovery of TNP-470 and Other Angiogenesis Inhibitors," by Donald E. Ingber, in *Cancer Therapeutics: Experimental and Clinical Agents*, Edited by Beverly A. Teicher, Humana Press, 1997.

Cover design by Patricia F. Cleary.



Library of Congress Cataloging-in-Publication Data

Anticancer drug development guide: preclinical screening, clinical trials, and approval / edited by Beverly A. Teicher.
p. cm. -- (Cancer drug discovery and development)
Includes index.
ISBN 978-1-4615-8154-3 ISBN 978-1-4615-8152-9 (eBook)
DOI 10.1007/978-1-4615-8152-9
1. Antineoplastic agents--Testing. I. Teicher, Beverly A., 1952–
II. Series.
[DNLM: 1. Antineoplastic Agents--standards. 2. Drug Approval. 3. Drug Screening. QV 269 A62953 1997]
RC271.C5A6722 1997
616.99'4061--dc21
DNLM/DLC
for Library of Congress 96-38113
CIP

# SERIES PREFACE

Cancer drug discovery has been, and continues to be, a process of ingenuity, serendipity, and dogged determination. In an effort to develop and discover better therapies against cancer, investigators all over the world have increased our knowledge of cell biology, biochemistry, and molecular biology. The goal has been to define therapeutically exploitable differences between normal and malignant cells. The result has been an increased understanding of cellular and whole-organism biology and an increased respect for the flexibility and resiliency of biologically systems. Thus, as some new therapeutic targets have been defined and new therapeutic strategies have been attempted, so have some new biological hurdles resulting from tumor evasion of the intended therapeutic attack been discovered.

Historically, anticancer drugs have originated from all available chemical sources. Synthetic molecules from the chemical industry, especially dyestuffs and warfare agents, and natural products from plants, microbes, and fungi have all been potential sources of pharmaceuticals, including anticancer agents. There is no shortage of molecules; the challenge has been and continues to be methods of identifying molecules that have the potential to be therapeutically important in human malignant disease. "Screening" remains the most important and most controversial method in cancer drug discovery. In vitro screens have generally focused on cytotoxicity and have identified several highly cytotoxic molecules. Other endpoints available in vitro are inhibition of proliferation, inhibition of [$^3$H]thymidine incorporation into DNA and various viability assays, based most frequently on dye exclusion or metabolism. The current National Cancer Institute in vitro screen attempts to take into account both cytotoxic potency and histological selectivity. In vitro screens may be viewed as limited to the discovery of only directly cytotoxic agents, thereby neglecting the fact that cancer is a disease occurring in a host organism.

The discovery of cancer drugs by in vivo screening has traditionally utilized syngeneic transplantable murine tumors. The earliest in vivo screens were the fast-growing murine leukemias (L1210 and/or P388) implanted intraperitoneally and growing as ascites. These tumors, with survival as an endpoint, provided a rapid, reproducible means for identifying potential anticancer drugs. It became evident more than 10 years ago that there were marked similarities in the drugs emerging from the murine leukemia screen. Panels of murine solid tumors and panels of human tumor xenografts were added to or have replaced the murine leukemias as anticancer drug screens. Each of these models has strengths and limitations. Most obviously, xenograft systems are not suitable for testing immunologically active agents or species-specific agents that involve host cell signaling cascades. The endpoints most frequently used with in vivo screens include tumor growth inhibition, tumor growth delay, increase in lifespan, and tumor cell survival.

In vivo systems also allow the opportunity to assess normal tissue damage by prospective agents. Murine dose-limiting toxicities are frequently useful, but studies in larger animals are often done to provide more definitive information on the potential clinically important toxicities of new anticancer agents. Spontaneous tumors in pets (dogs and cats) can provide useful populations in which to test new agents where efficacy and toxicity can be examined.

Once a new agent has demonstrated activity, and a toxicity profile has been documented, clinical testing can begin. Initial trials test the tolerance of patients to the drug and try to establish an appropriate dose for the drug in humans. The second phase of clinical testing seeks to demonstrate the efficacy of a new drug as a single agent. The third phase of clinical testing incorporates the new agent into current therapeutic regimens and seeks to demonstrate that the addition of the new agent to the combinations leads to better treatment outcomes than the conventional regimen. Final passage into medical use requires approval from the FDA in the United States and similar regulatory agencies in other countries.

The current volume traces the discovery, preclinical, and clinical testing of anticancer agents currently available for routine use, as well as the discovery, rationale for, and current status of potentially exciting new agents for cancer therapy. Current screening methods for cancer drug discovery and for determination of the activity of rationally designed agents are discussed, with a focus on the strengths and limitations of the methods. The phases of clinical testing of new agents are discussed with a view toward presenting the strengths and limitations of that process. Finally, the requirements for approval of new anticancer drugs are presented.

The time from discovery to the time of approval for a new anticancer agent can be 10 years or more. The survival rate for compounds through this process is small.

We are entering a potentially very exciting period in anticancer agent discovery where the therapeutic focus may expand to include not only agents cytotoxic toward malignant cells, but agents that may be growth controlling, growth inhibitory, activating or deactivating toward stromal or malignant cells, or may alter signaling cascades from one cell type to another. At this important time in the development of cancer treatment, *Cancer Drug Discovery and Development* takes stock of what has been accomplished, where experimental cancer therapeutics are going, and the continuing evolution of the means and methods of cancer drug discovery.

***Beverly A. Teicher***

# PREFACE

This unique volume traces the critically important pathway by which a "molecule" becomes an "anticancer agent." The recognition following World War I that the administration of toxic chemicals such as nitrogen mustards in a controlled manner could shrink malignant tumor masses for relatively substantial periods of time gave great impetus to the search for molecules that would be specifically lethal to cancer cells. We are all today still actively engaged in that search. The question is how to discover these "anticancer" molecules. The current volume describes the evolution to the present of preclinical screening methods. The National Cancer Institute's high throughput, in vitro disease-specific screen of 60 or more human tumor cell lines searching of molecules selectively toxic toward cells of a specific histology. The Human Tumor Colony-forming Assay (HTCA) uses fresh tumor biopsies as sources of cells that are more nearly the human disease.

There is no doubt that the greatest successes of traditional chemotherapy have been in the leukemias and lymphomas. Since the earliest widely used in vivo drug screening models were the murine L1210 and P388 leukemias, the community came to assume that these murine tumor models were appropriate to discovering "antileukemia" agents, but that other tumor models would be needed to discover drugs active against solid tumors. Several solid tumor models were developed in mice that are still widely used today and have the advantage of a tumor growing in a syngenic host. In the meantime, a cohort of immunodeficient mice were developed, including nude, beige, and SCID mice, allowing the growth of human tumor cell lines and human tumor biopsies as xenografts in the mice. Through the great advances in our knowledge of intracellular communication by secreted growth factors, cytokines, chemokines, and small molecules, the importance of the normal cellular environment, both stromal and organal to the growth of malignant tumors, has come to the fore. Now preclinical tumors in which malignant cells are implanted into the organ of origin, that is, in the orthotopic site, add this additional level of sophistication to drug discovery. In addition, new endpoints for preclinical testing, such as quantified tumor cell killing and detection of tumor cells in sanctuary sites, have been developed.

Of the hundreds of thousands of molecules passing through the in vitro screens, few reach clinical testing. In the United States, the FDA must grant permission to proceed with each phase of drug development in patients whether the clinical testing is through the NCI or industry. Patient safety is the foremost concern. The Phase I clinical trial allows study of a drug candidate's pharmacokinetics, pharmacodynamics, and tolerated dose. In Phase II clinical trials, therapeutic benefit becomes the goal, and in Phase III clinical trials, therapeutic benefit over and above the current best therapy is required for success and FDA approval. Much of the world community of physicians and investigators now participate in the clinical trial of potential new anticancer agents; however, the goal of nearly one century of discovering molecules specifically lethal to cancer cells remains elusive.

The systems for finding such molecules are in place worldwide and our knowledge of cell growth and regulation is increasing daily; thus one remains optimistic of success in cancer drug discovery.

***Beverly A. Teicher***

# CONTENTS

Series Preface ..... *v*

Preface ..... *vii*

Contributors ..... *xi*

## PART I. IN VITRO METHODS

**1** High-Volume Screening ..... *3*
*Michel Pagé*

**2** The NCI In Vitro Anticancer Drug Discovery Screen: *Concept, Implementation, and Operation, 1985–1995* ..... 23
*Michael R. Boyd*

**3** Human Tumor Screening ..... 43
*Axel-R. Hanauske, Susan G. Hilsenbeck, and Daniel D. Von Hoff*

## PART II. IN VIVO METHODS

**4** Murine L1210 and P388 Leukemias ..... 59
*William R. Waud*

**5** In Vivo Methods for Screening and Preclinical Testing: *Use of Rodent Solid Tumors for Drug Discovery* ..... 75
*Thomas Corbett, Fred Valeriote, Patricia LoRusso, Lisa Polin, Chiab Panchapor, Susan Pugh, Kathryn White, Juiwanna Knight, Lisa Demchik, Julie Jones, Lynne Jones, and Loretta Lisow*

**6** Human Tumor Xenograft Models in NCI Drug Development ... 101
*Jaqueline Plowman, Donald J. Dykes, Melinda Hollingshead, Linda Simpson-Herren, and Michael C. Alley*

**7** Fertile Seed and Rich Soil: *The Development of Clinically Relevant Models of Human Cancer by Surgical Orthotopic Implantation of Intact Tissue* ..... 127
*Robert M. Hoffman*

**8** Preclinical Models for High-Dose Therapy ..... 145
*Beverly A. Teicher*

**9** Models for Minimal Residual Tumor ..... 183
*Beverly A. Teicher*

**10** Spontaneously Occurring Tumors in Companion Animals as Models for Drug Development ..... 197
*David M. Vail and E. Gregory MacEwen*

## PART III. CLINICAL TESTING

**11** Working with the National Cancer Institute ..... 217
*Edward A. Sausville*

**12** Phase I Trial Design and Methodology ..... 227
*Deborah L. Toppmeyer*

**13** Phase II Clinical Trials in Oncology ..... 249
*Christine Khater, Paul Laub, James M. Gallo, André Rogatko, and Peter J. O'Dwyer*

**14** Drug Development in Europe ..... 271
*Thomas Anthony Connors and Herbert M. Pinedo*

**15** The Phase III Cancer Clinical Trial ..... 289
*Emil Frei III*

**16** FDA Role in Cancer Drug Development and Requirements for Approval ..... 293
*Robert L. Justice*

Index ..... 305

# CONTRIBUTORS

MICHAEL C. ALLEY, PhD • *Biological Testing Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Birmingham, AL*

MICHAEL R. BOYD, MD, PhD • *Laboratory of Drug Discovery and Research and Development, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Frederick Cancer Research and Development Center, Frederick, MD*

THOMAS A. CONNORS, PhD, DSc • *The School of Pharmacy, Centre for Polymer Therapeutics, Brunswick Square, London, UK*

THOMAS CORBETT, PhD • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

LISA DEMCHIK, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

DONALD J. DYKES, BS • *Southern Research Institute, Birmingham, AL*

EMIL FREI III, MD • *Dana-Farber Cancer Institute, Boston, MA*

JAMES M. GALLO, PharmD, PhD • *Fox Chase Cancer Center, Philadelphia, PA*

AXEL-R. HANAUSKE, MD, PhD • *Division of Hematology and Oncology, I. Medizinische Klinik und Poliklinik, Klinikum rechts der Isar der Technischen Universität München, Germany*

SUSAN G. HILSENBECK, PhD • *Section of Biostatistics, Division of Medical Oncology, Department of Medicine, University of Texas Health Science Center, San Antonio, TX*

ROBERT M. HOFFMAN, PhD • *AntiCancer, Inc., San Diego, CA; Laboratory of Cancer Biology, University of California at San Diego, La Jolla, CA*

MELINDA HOLLINGSHEAD, PhD • *Biological Testing Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Birmingham, AL*

JULIE JONES, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

LYNNE JONES, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

ROBERT L. JUSTICE, MD • *Division of Oncology and Pulmonary Products, Food and Drug Administration, Rockville, MD*

CHRISTINE KHATER, MD • *Fox Chase Cancer Center, Philadelphia, PA*

JUIWANNA KNIGHT, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

PAUL LAUB, BS • *Fox Chase Cancer Center, Philadelphia, PA*

LORETTA LISOW, BA • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

PATRICIA LORUSSO, DO • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*

E. GREGORY MACEWEN, VMD • *Department of Medicine/Oncology, University of Wisconsin, Madison, WI*

PETER J. O'DWYER, MD • *Fox Chase Cancer Center, Philadelphia, PA*
MICHEL PAGÉ, PHD • *Cancerology Laboratory, Department of Biochemistry, University of Laval Faculty of Medicine, Ste-Foy, Quebec, Canada*
CHIAB PANCHAPOR, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*
H. M. PINEDO, MD, PHD • *Department of Medical Oncology, Amsterdam, The Netherlands*
JAQUELINE PLOWMAN, PHD • *Biological Testing Branch, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Birmingham, AL*
LISA POLIN, PHD • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*
SUSAN PUGH, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*
ANDRÉ ROGATKO, PHD • *Fox Chase Cancer Center, Philadelphia, PA*
EDWARD A. SAUSVILLE, MD, PHD • *Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD*
LINDA SIMPSON-HERREN, BS • *Southern Research Institute, Birmingham, AL*
BEVERLY A. TEICHER, PHD • *Division of Cancer Pharmacology, Dana-Farber Cancer Institute, Boston, MA*
DEBORAH L. TOPPMEYER, MD • *34 Manor Dr., Princeton, NJ*
DAVID M. VAIL, DVM • *Department of Medicine/Oncology, University of Wisconsin, Madison, WI*
FRED VALERIOTE, PHD • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*
DANIEL D. VON HOFF, MD • *Research Department, Cancer Therapy and Research Center, San Antonio, TX*
WILLIAM R. WAUD, PHD • *Chemotherapy Division, Southern Research Institute, Birmingham, AL*
KATHRYN WHITE, BS • *Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI*