Antiangiogenic Agents in Cancer Therapy

CANCER DRUG DISCOVERY AND DEVELOPMENT
Beverly A. Teicher, Series Editor

6. **Apoptosis and Cancer Chemotherapy**, edited by *John A. Hickman and Caroline Dive,* 1999
5. **Signal Transduction and Cell Cycle Inhibitors in Cancer Therapy,** edited by *J. Silvio Gutkind,* 1999
4. **Antifolate Drugs in Cancer Therapy,** edited by *Ann L. Jackman,* 1999
3. **Antiangiogenic Agents in Cancer Therapy,** edited by *Beverly A. Teicher,* 1999
2. **Anticancer Drug Development Guide: *Preclinical Screening, Clinical Trials, and Approval,*** edited by *Beverly A. Teicher,* 1997
1. **Cancer Therapeutics: *Experimental and Clinical Agents,*** edited by *Beverly A. Teicher,* 1997

Antiangiogenic Agents in Cancer Therapy

Edited by

Beverly A. Teicher

Lilly Research Laboratories, Indianapolis, IN

SPRINGER SCIENCE+BUSINESS MEDIA, LLC

For the beautiful ones
Emily and Joseph

Originally published by Humana Press Inc. in 1999

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.

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

Library of Congress Cataloging-in-Publication Data

Antiangiogenic agents in cancer therapy/edited by Beverly A. Teicher.
p. cm.—(Cancer drug discovery and development)
Includes index.
ISBN 978-1-4757-4518-4 ISBN 978-1-59259-453-5 (eBook)
DOI 10.1007/978-1-59259-453-5
1. Neovascularization inhibitors. 2. Cancer—Chemotherapy. I. Teicher, Beverly A., 1952– . II. Series.
[DNLM: 1. Neoplasms—drug therapy. 2. Neovascularization, Pathologic—drug therapy. 3. Antineoplastic Agents—therapeutic use. QZ 267 A628 1999]
RC271.N46A58 1999
616.99'4061—dc21
DNLM/DLC
for Library of Congress 98-45812
CIP

PREFACE

The importance of normal cells and tissues to support the growth of tumors has been recognized for centuries. The observations of Van der Kolk *(1)*, Jones *(2)*, and Paget *(3)* more than 100 years ago documented this knowledge in the clinical science literature. Fifty years ago, Algire and Chalkey *(4)* reported that host vascular reactions could be elicited by growing tumors and described in exquisite detail the extent and tumor-specific nature of the induction of host capillaries by transplanted tumors. The central hypothesis of Algire and Chalkey was that vascular induction by solid tumors may be the major, and possibly, the only distinguishing factor leading to tumor growth beyond normal tissue control levels. By the late 1960s, Folkman and his colleagues *(5–7)* had begun the search for a tumor angiogenesis factor (TAF) and in 1971 in his landmark report in the *New England Journal of Medicine,* Folkman proposed "antiangiogenesis" as a means of holding tumors in a nonvascularized dormant state *(8)*.

Over the nearly 40 years since publication of that landmark paper, great strides have been made in understanding angiogenesis, blood flow, and tumor growth. Several angiogenic signaling molecules and angiogenic factors have been identified. Antiangiogenic agents from a wide variety of chemical classes, including steroids, polyanionic molecules, antibiotics, small molecule nutrients, synthetic small molecules, proteins, nucleic acid molecules (ribozymes and antisense DNA), and gene therapy agents have been identified. The significance of angiogenic activity as an important prognostic factor in many of the common solid tumors, and even in leukemia, is becoming more widely recognized.

Early clinical trials of antiangiogenic agents in cancer patients have been successful in that the toxicities observed with many of these new drugs have been mild. However, these early clinical trials have also highlighted the need to develop criteria by which to assess the clinical efficacy of these new agents. Finally, preclinical and early clinical studies have begun to incorporate antiangiogenic agents into combined modality regimens that are potentially curative.

Antiangiogenic Agents in Cancer Therapy describes our state of understanding of tumor growth and its dependence on vascular development as well as the present status of antiangiogenic agents on preclinical and clinical development and what is known about the mechanisms by which these molecules and treatment agents interfere with tumor vascular growth.

We are entering a potentially very exciting period in anticancer agent discovery where the therapeutic focus is expanding to include not only agents cytotoxic toward malignant cells, but agents that may be growth controlling, growth inhibitory, or activating or deactivating toward stromal cells or malignant cells, as well as agents that may alter signaling cascades from one cell type to another. At this important time in the development of cancer treatment, this volume takes stock

of what has been accomplished in the area of angiogenesis, where the experimental therapeutics of antiangiogenic agents is going, and the continuing evolution of the means and methods of cancer treatment and new drug development.

Beverly A. Teicher

REFERENCES

1. Van der Kolk, S. (1826) in *Blood Supply of Tumors,* vol. 2 (Montagna, W. and Ellis, R., eds.), pp. 123–149.
2. Jones T. (1850) *Guy's Hospital Reports, 2nd Ser.* **7,** 1–94.
3. Paget, S. (1989) *Lancet* **March 23,** 571–573.
4. Algire, G. and Chalkey, H. (1945) *J. Natl. Cancer Inst.* **6,** 73–95.
5. Folkman, M. J., Merler, E., Abernathy, C., and Williams, G. (1971) *J. Exp. Med.* **133,** 275–288.
6. Folkman, M. J. (1974) *Adv. Cancer Res.* **19,** 331–358.
7. Folkman, M. J. and Cotran, R. (1976) *Int. Rev. Exp. Pathol.* **16,** 207–248.
8. Folkman, M. J. (1971) *New Engl. J. Med.* **285,** 1182–1186.

CONTENTS

CONTRIBUTORS

ACHIM AIGNER • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*

DIANE R. BIELENBERG • *Department of Cell Biology, University of Texas M. D. Anderson Cancer Center, Houston, TX*

NOËL BOUCK • *Department of Microbiology-Immunology and Robert H. Lurie Cancer Center, Northwestern University Medical School, Chicago, IL*

PETER D. BROWN • *Department of Clinical Research, British Biotech Pharmaceuticals, Ltd., Oxford, UK*

FEDERICO BUSSOLINO • *Department of Genetics, Biology, and Biochemistry, University of Torino, Italy*

VINCENT CASTRONOVO • *Metastasis Research Laboratory, University of Liege, Belgium*

GERHARD CHRISTOFORI • *Research Institute of Molecular Pathology, Vienna, Austria*

JOHN L. CLIFFORD • *Department of Clinical Cancer Prevention, University of Texas-M. D. Anderson Cancer Center, Houston, TX*

STEVEN K. CLINTON • *Dana-Farber Cancer Institute, Boston, MA*

FRANK CZUBAYKO • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*

ROBERT J. D'AMATO • *Department of Surgical Research, Children's Hospital, Harvard Medical School, Boston, MA*

DAVID W. DAWSON • *Department of Microbiology-Immunology and Robert H. Lurie Cancer Center, Northwestern University Medical School, Chicago, IL*

MARK W. DEWHIRST • *Department of Radiation Oncology, Duke University Medical Center, Durham, NC*

VIOLETTA DIMITRIADOU • *Æterna Laboratories, Inc., Ste-Foy, Quebec, Canada*

ERIC DUPONT • *Æterna Laboratories, Inc., Ste-Foy, Quebec, Canada*

JOHN J. FENG • *Department of Restorative Dentistry, University of California, San Francisco, CA*

NAPOLEONE FERRARA • *Department of Cardiovascular Research, Genetech, Inc., South San Francisco, CA*

ISAIAH J. FIDLER • *Department of Cell Biology, University of Texas M. D. Anderson Cancer Center, Houston, TX*

WILLIAM D. FIGG • *Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD*

GIAMPIETRO GASPARINI • *Bassano del Grappa, Italy*

Q. PERVEEN GHANI • *Department of Restorative Dentistry, University of California, San Francisco, CA*

WILLIAM J. GRADISHAR • *Department of Breast Medical Oncology, Robert H. Lurie Cancer Center, Northwestern University, Chicago, IL*

SHAWN GREEN • *Cancer Treatment Evaluation Program, National Cancer Institute, National Institutes of Health, Bethesda, MD*

CHARLES S. GREENBERG • *Department of Medicine, Duke University Medical Center, Durham, NC*

MARCELLE GUICHARD • *Laboratory of Radiobiology and Department of Radiotherapy, Institut Gustave Roussy, Villejuif, France*

ZISHAN A. HAROON • *Department of Pathology, Duke University Medical Center, Durham, NC*

ADRIAN L. HARRIS • *Molecular Oncology Laboratory, Imperial Cancer Research Fund, John Radcliffe Hospital, University of Oxford, UK*

THOMAS K. HUNT • *Department of Restorative Dentistry, University of California, San Francisco, CA*

M. ZAMIRUL HUSSAIN • *Department of Restorative Dentistry, University of California, San Francisco, CA*

ERIC LARTIGAU • *Laboratory of Radiobiology and Department of Radiotherapy, Institut Gustave Roussy, Villejuif, France*

SCOTT M. LIPPMAN • *Department of Clinical Cancer Prevention, University of Texas-M. D. Anderson Cancer Center, Houston, TX*

CLAUDIUS MALERCZYK • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*

DEBORAH M. MILKOWSKI • *TAP Holdings, Inc., Deerfield, IL*

ALBERTO MANTOVANI • *Mario Negri Institute for Pharmacological Research, Milano, Italy, and Department of Biomedical Sciences and Biotechnology, University of Brescia, Italy*

JOSEPH M. MIANO • *Department of Physiology, Cardiovascular Research Center, Medical College of Milwaukee, WI*

PURNA MUKHERJEE • *Dana-Farber Cancer Institute, Boston, MA*

HEONJOO PARK • *Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis, MN*

KEVIN G. PETERS • *Department of Medicine, Duke University Medical Center, Durham, NC*

JAMES M. PLUDA • *EntreMed Pharmaceutical, Inc., Rockville, MD*

PETER J. POLVERINI • *Laboratory of Molecular Pathology, Department of Oral Medicine, Pathology, and Surgery, University of Michigan School of Dentistry, Ann Arbor, MI*

HENRIK S. RASMUSSEN • *British Biotech, Inc., Annapolis, MD*

EDDIE REED • *Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, MD*

ANNA T. RIEGEL • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*

MARC RIVIÈRE • *Æterna Laboratories, Inc., Ste-Foy, Quebec, Canada*

BRIAN D. ROSS • *Radiology Department, University of Michigan Medical School, Ann Arbor, MI*

OLIVER SARTOR • *Department of Hematology and Oncology, Louisiana State University Medical Center, Shreveport, LA*

PIERRE SAVARD • *Neurosciences Research Unit, CHUL Research Center, University of Laval, Quebec, Canada*

ANKE M. SCHULTE • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*

B. KIM LEE SIM • *EntreMed, Inc., Rockville, MD*
CHANG W. SONG • *Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis, MN*
ALEXANDER V. SOTNIKOV • *Dana-Farber Cancer Institute, Boston, MA*
BEVERLY A. TEICHER • *Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN*
ANNE T. TUVESON • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*
TATURO UDAGAWA • *Department of Surgical Research, Children's Hospital, Harvard Medical School, Boston, MA*
HENK M. W. VERHEUL • *Department of Surgical Research, Children's Hospital, Harvard Medical School, Boston, MA*
ISRAEL VLODAVSKY • *Department of Oncology, Hadassah-Hebrew University Hospital, Jerusalem, Israel*
RACHELLE A. WEISS • *TAP Holdings, Inc., Deerfield, IL*
ANTON WELLSTEIN • *Lombardi Cancer Center and Department of Pharmacology, Georgetown University, Washington, DC*
MARK WHITTAKER • *Department of Medicinal Chemistry, British Biotech Pharmaceuticals, Ltd., Oxford, UK*
JON I. WILLIAMS • *Magainin Pharmaceuticals, Plymouth Meeting, PA*
JIN-RONG ZHOU • *Dana-Farber Cancer Institute, Boston, MA*