BLEOMYCIN

CURRENT STATUS AND NEW DEVELOPMENTS

Edited by

Stephen K. Carter
Northern California Cancer Program
Palo Alto, California
Stanford University Medical Center
Stanford, California
University of California
San Francisco, California

Stanley T. Crooke
Bristol Laboratories
Syracuse, New York
Baylor College of Medicine
Houston, Texas
Upstate Medical Center
Syracuse, New York

Hamao Umezawa
Institute of Microbial Chemistry
Tokyo, Japan

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CONTRIBUTORS

Numbers in parentheses indicate the pages on which authors' contributions begin.

FUMINORI ABE (311), *Research Laboratory, Pharmaceutical Division, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*

DAVID S. ALBERTS (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724*

NORIKO AMANO (35), *Research Laboratory, Pharmaceutical Division, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*

LAURENCE H. BAKER (173), *Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan 48201*

S. C. BARRANCO (81), *Division of Cell Biology, Department of Human Biological Chemistry and Genetics, University of Texas Medical Branch, Galveston, Texas 77550*

WILLIAM T. BRADNER (333), *Antitumor Biology, Bristol Laboratories, Thompson Road, Syracuse, New York 13201*

ALAN BROUGHTON (107, 131), *Department of Pathology and Laboratory Medicine, University of Texas Health Science Center, Houston, Texas 77025*

STEPHEN K. CARTER (9), *Northern California Cancer Program, 1801 Page Mill Road, Palo Alto, California 94304; Department of Medicine, Stanford University, Stanford, California; Department of Medicine, University of California, San Francisco, California*

HSIAO-SHENG CHEN (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona, Tucson, Arizona 85724*

JOSEPH CHEN (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724*

CHARLES A. COLTMAN, JR. (227), *Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78284*

ROBERT L. COMIS (279), *Hematology–Oncology Section, State University of New York, Upstate Medical Center, Syracuse, New York 13210*

STANLEY T. CROOKE (1, 117, 343, 357), *Bristol Laboratories, P.O. Box 657, Syracuse, New York 13201; Department of Pharmacology, Baylor College of Medicine, Houston, Texas 77025; Department of Pharmacology, Upstate Medical Center, Syracuse, New York 13210*

YERACH DASKAL (57), *Department of Pharmacology, Electron Microscopy Unit, Baylor College of Medicine, Houston, Texas 77030*

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EDWARD DEPERSIO (227), *Oklahoma Medical Research Foundation, 825 Northeast 13th, Oklahoma City, Oklahoma 73104*
KAZUO EBIHARA (299, 311), *Research Laboratory, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*
LAWRENCE H. EINHORN (201), *Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana 46202*
HISAO EKIMOTO (299, 311), *Research Laboratory, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*
MICHAEL A. FRIEDMAN (191), *Cancer Research Institute, University of California School of Medicine, San Francisco, California 94143*
ABRAHAM GOLDIN (91), *International Treatment Research, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014*
THEODORE E. GRAM (293), *Laboratory of Toxicology, National Cancer Institute, Bethesda, Maryland 20014*
JOSEPH GROSS (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724*
PETRE N. GROZEA (227), *Oklahoma Medical Research Foundation, 825 Northeast 13th, Oklahoma City, Oklahoma 73104*
FERENC GYORKEY (57), *Department of Laboratory Service, Veterans Administration Hospital, Houston, Texas 77030*
CHARLES W. HAIDLE (21), *University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, Texas 77030*
YOSHIMASA HASHIMOTO (311), *Research Laboratory, Pharmaceutical Division, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*
KLAUS HÖFFKEN (215), *Innere Universitätsklinik und Poliklinik (Tumorforschung), West German Tumor Center, Essen, Federal Republic of Germany*
DANIEL HOTH (243), *Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, Washington, D.C. 20007*
YUKIO INUYAMA (267), *Department of Otorhinolaryngology, School of Medicine, Keio University, 35 Shinano machi, Shinyu-ku-ku, Tokyo, Japan*
STEPHEN E. JONES (227), *Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724*
IRA KLINE (91), *International Treatment Research, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014*
MONTAGUE LANE (143), *Department of Pharmacology, Clinical Cancer Research, Baylor College of Medicine, Houston, Texas 77030*
DANIEL E. LEHANE (143), *Department of Pharmacology, Clinical Cancer Research, Baylor College of Medicine, Houston, Texas 77030*
ROSA LIU (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724*

ROBERT B. LIVINGSTON (165), *Department of Medicine, University of Texas Health Science Center, Audie Murphy Memorial Veterans Administration Hospital, San Antonio, Texas 78284*

R. STEPHEN LLOYD (21), *University of Texas Health Science Center, Graduate School of Biomedical Sciences, Houston, Texas 77030; University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77030*

AKIRA MATSUDA (35, 299, 311), *Research Laboratory, Pharmaceutical Division, Nippon Kayaku Company Ltd., 3–31, Shima, Kita-ku, Tokyo, Japan*

MICHAEL MAYERSOHN (131), *Section of Hematology–Oncology, Department of Internal Medicine University of Arizona Health Sciences Center, Tucson, Arizona 85724*

EDWARD G. MIMNAUGH (293), *Laboratory of Toxicology, National Cancer Institute, Bethesda, Maryland 20014*

TADAAKI MIYAMOTO (185), *Division of Hospitals, National Institute of Radiological Sciences 4-9-1, Anagawa, Chiba City, Japan*

THOMAS E. MOON* (131, 227), *Department of Biomathematics, The University of Texas System Cancer Center, M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77025*

FRANCO M. MUGGIA (151), *Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014*

RAINHARDT OSIEKA (215), *Innere Universitätsklinik und Poliklinik (Tumorforschung), West German Tumor Center, Essen, Federal Republic of Germany*

DONALD PERRIER (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona Health Sceinces Center, Tucson, Arizona 85724*

ARCHIE W. PRESTAYKO (117), *Bristol Laboratories, P.O. Box 657, Syracuse, New York 13201; Department of Pharmacology, Baylor College of Medicine, Houston, Texas 77025*

MARCEL ROZENCWEIG (151), *Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014*

SYDNEY SALMON (131), *Section of Hematology–Oncology, Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724*

PHILIP SCHEIN (243), *Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, Washington, D.C. 20007*

MAX E. SCHEULEN (215), *Innere Universitätsklinik und Poliklinik (Tumorforschung), West German Tumor Center, Essen, Federal Republic of Germany*

*Currently at Cancer Center Division, College of Medicine, University of Arizona Health Sciences Center, Tucson, Arizona 85724

CARL G. SCHMIDT (215), *Innere Universitätsklinik und Poliklinik (Tumorforschung), West German Tumor Center, Essen, Federal Republic of Germany*
SIEGFRIED SEEBER (215), *Innere Universitätsklinik und Poliklinik (Tumorforschung), West German Tumor Center, Essen, Federal Republic of Germany*
BRANIMIR IVAN SIKIC (293), *Laboratory of Toxicology, National Cancer Institute, Bethesda, Maryland 20014*
FREDERICK P. SMITH (243), *Division of Medical Oncology, Vincent T. Lombardi Cancer Research Center, Georgetown University School of Medicine, Washington, D.C. 20007*
JAMES E. STRONG (343), *Department of Pharmacology, Baylor College of Medicine, Houston, Texas 77025*
KATSUTOSHI TAKAHASHI (35, 311), *Research Laboratory, Pharmaceutical Division, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*
ANDREW T. TURRISI III (151), *Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Building 37, Room 6E12, Bethesda, Maryland 20014*
HAMAO UMEZAWA (15, 35, 299, 311), *Institute of Microbial Chemistry 4–23, Kamiosaki 3-Chome, Shinagawa-ku, Tokyo, Japan*
DANIEL D. VON HOFF (151), *Cancer Therapy Evaluation Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014*
TODD H. WASSERMAN (253), *Department of Radiation Oncology, University of California Medical Center, San Francisco, California 94143*
TAKUMI YAMASHITA (299, 311), *Research Laboratory, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*
OSAMU YOSHIOKA (35, 299, 311), *Research Laboratory, Pharmaceutical Division, Nippon Kayaku Company Ltd., 3–31, Shimo, Kita-ku, Tokyo, Japan*

PREFACE

Bleomycin is a drug with unique pharmacologic characteristics that plays an important role in the therapy of a wide range of human malignancies. This book reviews both the preclinical studies and the clinical role of this important compound and also gives data on analogs under development. The papers in this book were all presented at a symposium held in Oakland, California and jointly sponsored by the Northern California Cancer Program and Bristol Laboratories.

It is hoped that this book will be of interest to all scientists involved in both the preclinical and clinical aspects of drug development since the papers on bleomycin also explore the critical broad flow of steps that any drug must pass through in its evaluation. This volume will look at chemistry, mechanism of action, bioassay pharmacology, toxicology, pathology, and clinical evaluation in relation to the bleomycins.

CONTENTS

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Chapter 1

BLEOMYCIN: A BRIEF REVIEW

Stanley T. Crooke

Bleomycin will be discussed in detail in subsequent papers. Thus, the purpose of this paper is to provide a brief overview of bleomycin and analogs, and to introduce the papers that will follow.

I. CHEMISTRY

The bleomycins are a group of complex glycopeptides extracted from a strain of *Streptomyces verticillus*. Figure 1 shows the general structure of the bleomycins, and the terminal amines of several of the analogs, which may be purified by ion-exchange chromatography. Most of the bleomycin species are soluble in water and methanol, and insoluble in other organic solvents (Umezawa *et al.*, 1966). A closely related group of compounds, the phleomycins, also has antitumor activity (Bradner and Pindell, 1971).

Bleomycin analogs can be divided into three groups. First generation analogs include the 13 analogs comprising the clinically employed bleomycin, Blenoxane . Second generation bleomycin analogs are those prepared since the original 13 were

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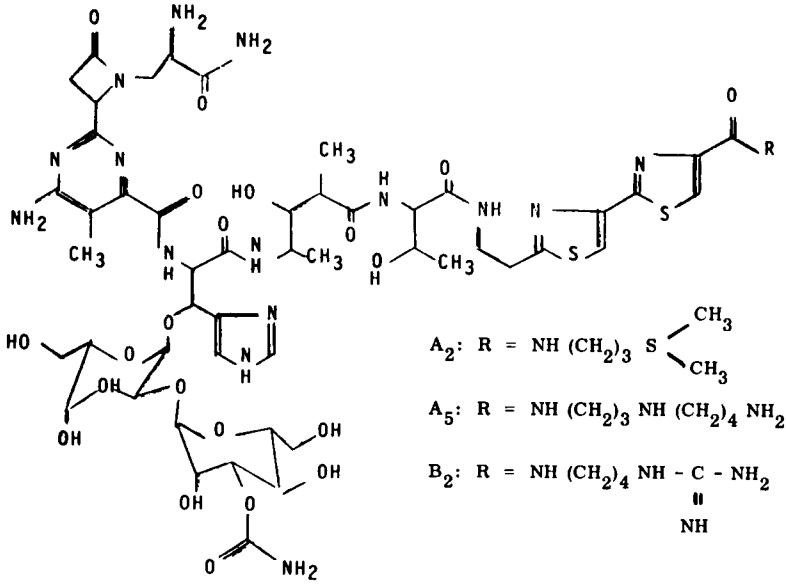

Fig. 1. The structure of bleomycin.

isolated, which differ from others only by differences in the terminal amine. Third generation analogs are those which differ from other analogs in the bleomycinic acid nucleus.

II. MECHANISM OF ACTION

That bleomycin binds to DNA has been demonstrated by studies with tritiated bleomycin (Umezawa, 1974) and by studies on circular dichroism. The circular dichroism studies suggested that bleomycin binds to DNA without causing extensive changes in secondary structure (Krueger *et al.*, 1973). Binding of bleomycin is thought to be a partial intercalation in the major groove, and the inhibiting effect of copper ions is suggested to be due to an alteration in the secondary structure of bleomycin such that binding to DNA is not efficient (Murokami *et al.*, 1973).

After binding, bleomycin excises free bases, resulting in single-strand breaks (Haidle *et al.*, 1972; Koyama *et al.*, 1968; Muller *et al.*, 1972; Saunders *et al.*, 1975; Suzuki *et al.*, 1969). Double-stranded scission occurs at higher concentrations of bleomycin, and is thought to occur when a number of single-strand breaks occur proximally enough to result in double-strand breaks (Saunders *et al.*, 1975). An active center, similar to esterase active centers, in which the threonine hydroxyl and the histidine imidazole groups participate in the reaction with DNA has been proposed. The pH optima suggest that the α-amino group of the β-amino-alanine

moiety of bleomycin is involved in the reaction, and studies on enzymatically inactivated bleomycin have suggested that the carboxyamide portion of the β-aminoalanine moiety is also involved (Umezawa, 1974).

Bleomycin has been observed to inhibit the replication of viruses, bacteria, and mammalian cells, and a broad range of tumor cells (Crooke and Bradner, 1977).

Bleomycin treatment of sensitive cells *in vitro* has resulted in degradation of preformed DNA (Cox *et al.*, 1974; Miyaki *et al.*, 1975), and inhibition of DNA synthesis (Suzuki *et al.*, 1968; Muller *et al.*, 1975). Inhibition of RNA and protein synthesis have been reported to be somewhat less sensitive to bleomycin than DNA synthesis (Crooke *et al.*, 1975; Watanabe *et al.*, 1973).

Eukaryotic cells are reported to be most sensitive to bleomycin during the G_2 and M in phases of the cell cycle (Barranco and Humphrey, 1971; Terasima and Umezawa, 1970). Whether cycling or noncycling cells are more sensitive to bleomycin is unclear, but most studies suggest that noncycling cells are more sensitive (Twentyman and Bleehen, 1973; Terasima *et al.*, 1972).

III. CLINICAL PHARMACOLOGY

Bleomycin is absorbed rapidly after intramuscular administration, resulting in peak plasma concentrations approximately one-third to one-half of those obtained after rapid intravenous administration (Fujita, 1971). Bleomycin is also absorbed following subcutaneous administration, but the extent of absorption is imprecisely defined. Only minute quantities of bleomycin are absorbed after intravesical administration of as much as 120 u (Johnson *et al.*, 1976).

Plasma clearance of bleomycin following rapid intravenous administration is rapid. The $t_{1/2}\,\beta$ in patients with normal renal function is approximately 115 min. In patients with creatinine clearances less than 25-35 ml/min the $t_{1/2}\beta$ of bleomycin increases exponentially as the creatinine clearance decreases (Crooke *et al.*, 1977b; Crooke *et al.*, 1977a).

Although the principal mechanism of detoxification of bleomycin is renal excretion, a bleomycin inactivating enzyme has been described (Umezawa *et al.*, 1972). It is possible that this enzyme accounts for intracellular inactivation and perhaps a portion of the total detoxification in patients with compromised renal function.

IV. CLINICAL TOXICOLOGY

A. Pulmonary

The usual dose-limiting toxicity of bleomycin is pulmonary fibrosis. Although the reported incidence of pulmonary toxicities has varied from 0–40% with 0–6% toxicity-related deaths, the incidence of clinically significant pulmonary toxicities is approximately 10%. The incidence and severity of pulmonary toxicities are related to age and total dose. Patients >70 years old, or those receiving >400 u are clearly

at greater risk than younger patients treated with lower doses (Blum *et al.*, 1973). Radiotherapy to the thorax probably increases the incidence of bleomycin pulmonary toxicities.

The development of pulmonary toxicities is ususally delayed, typically occurring between 4 and 10 weeks after initiation of therapy. Physical findings, rales and rhonchi and occasionally pleural friction rubs, usually precede radiographic changes, and may progress to signs and symptoms of respiratory failure. The radiographic presentation is typical of interstitial pneumonitis which may progress to pulmonary fibrosis (Agre, 1974; Blum *et al.*, 1975; Blum *et al.*, 1973; E.O.R.T.C., 1970; Yagoda *et al.*, 1972). It has been suggested that patients with bleomycin pulmonary toxicity may present in one of two ways: a minimal form with exertional dyspnea, minimal radiographic changes, and a normal resting arterial partial pressure of oxygen; and a severe form with prominent roentgenographic findings and hypoxemia at rest (Samuels *et al.*, 1976).

The histopathologic manifestations of bleomycin lung toxicity in humans are comparable to those noted in animals, and do not differ significantly from interstitial pneumonitis and fibrosis associated with many other lung toxins. The lesions are found more frequently in the lower lobes and subpleural areas and consist of a fibrinous exudate, atypical proliferation of alveolar cells, hyaline membranes, interstitial and intraalveolar fibrosis and squamous metaplasia of the distal air spaces (Blum, 1974; Daskal *et al.*, 1976; Livingston *et al.*, 1973). Electron microscopic studies suggest Type I alveolar cell destruction followed by Type II cellular proliferation (Bedrossian, 1974). In addition, nucleolar fibrillar centers and granular nuclear bodies have been shown in Type I and Type II alveolar epithelial cells and fibroblasts (Daskal *et al.*, 1976).

It is clear that bleomycin pulmonary toxicity is associated with changes in pulmonary function tests. It has not been established, however, that pulmonary functions tests are predictive, i.e., that by performing serial pulmonary function tests on a patient it is possible to detect early bleomycin toxicity, and discontinue the drug in time to avoid progressive pulmonary involvement.

In a study of 150 patients vital capacity was noted to be decreased in patients with bleomycin lung toxicity, but it was felt that clinical parameters provided a better index of toxicity than pulmonary function tests in many patients (Blum *et al.*, 1973). A decrease in total lung capacity and vital capacity was noted in approximately 20, and a decrease in diffusion capacity was found in 7 of 40 patients in another study. However, no correlation between changes in pulmonary functions and advent of pulmonary toxicity or dose of bleomycin could be ascertained (Yagoda *et al.*, 1972).

A statistically significant decrease in forced vital capacity was found in five of six patients treated with bleomycin who had abnormal chest x rays at the initiation of the study, but the change in forced vital capacity noted in eight patients with normal chest x rays was not statistically significant, and no correlation between the total dose of bleomycin and pulmonary function tests could be determined (Pasqual *et al.*, 1973). Similarly, a decrease in total lung capacity was found in a series of 26 patients, but the nature and extent of the changes seemed to correlate best with the type of tumor rather than the developments of toxicity (Rudders, 1973).

Recently, it has been suggested by two groups that serial determinations of carbon monoxide diffusion capacity may allow earlier detection of pulmonary toxicities than other methods (Baker, personal communication; Comis *et al.*, 1978).

B. Other Toxicities

Bleomycin induces a febrile response in 20-50% of patients treated. Hyperpyrexia is more common in patients with lymphomas (Agre, 1974). Moreover, in approximately 6% of these patients acute fulminant reactions (hypotensive response) are reported in association with hyperpyrexia (Agre, 1974).

Mucocutaneous toxicities are common in patients treated with bleomycin. These toxicities include alopecia, hyperpigmentation of skin, erythema, hyperkeratosis, and muscositis, and are total-dose related. The incidence and severity of mucositis are increased when bleomycin is employed in combination with radiotherapy to the head and neck (Crooke and Bradner, 1977).

Neither clinically significant myelosuppression nor immunosuppression has been reported to be associated with bleomycin. However, subclinical myelosuppression induced by bleomycin may contribute to the myelosupression in markedly marrow-toxic regimens (Baker *et al.*, 1975).

V. CLINICAL ACTIVITY

As a single agent bleomycin has demonstrated activity against the tumors indicated in Table I. Response rates $\geqslant$15% in 40 or more patients have been reported for these tumors.

TABLE I. Tumors Responsive to Bleomycin As a Single Agent

Squamous cell carcinoma
Head and neck
Larynx
Cervix
Vulvo-vaginal
Skin
Penis
Lymphomas
Mycoses fungoides
Testicular carcinomas

In general, combinations in which bleomycin is employed are active against a spectrum of tumors similar to those sensitive to bleomycin as a single agent. In squamous cell carcinoma of the head and neck bleomycin-containing combinations are definitely active, and most active regimens employ both bleomycin and methotrexate (Crooke and Bradner, 1977). In squamous cell carcinoma of the cervix, mitomycin C, vincristine, and bleomycin is one of the more active regimens (Baker *et al.*, 1975).

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