NOVEL MICROBIAL PRODUCTS
FOR MEDICINE & AGRICULTURE

PT. 1

Topics in Industrial Microbiology

Novel Microbial Products for Medicine and Agriculture

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1989
ELSEVIER

Published by Elsevier Science Publishers
on behalf of the Society for Industrial Microbiology

ISBN 0-444-81066-8
ISSN 0923-2303

This book is printed on acid-free paper.

Published by:

Elsevier Science Publishers B.V. (Biomedical Division)
P.O. Box 211
1000 AE Amsterdam
The Netherlands

Sole distributors for the USA and Canada:
Elsevier Science Publishing Company, Inc.
655 Avenue of the Americas
New York, NY 10010
U.S.A.

Library of Congress Cataloging in Publication Data
Novel microbial products for medicine and agriculture / editors, A.L. Demain ... [et al.].
p. cm. — (Topics in industrial microbiology, ISSN 0923-2303)
Papers presented at the First International Conference on the Biotechnology of Microbial Products, held Mar. 13-16, 1988, in San Diego, Calif., under the sponsorship of the Society for Industrial Microbiology.
Includes bibliographies and index.
ISBN 0-444-81066-8 (U.S.)
1. Microbial products—Testing—Congresses. 2. Pharmaceutical microbiology—Congresses. I. Demain, A. L. (Arnold L.), 1927- II. International Conference on the Biotechnology of Microbial Products (1st : 1988 : San Diego, Calif.) III. Society for Industrial Microbiology (U.S.) IV. Series.
[DNLM: 1. Biological Products—congresses. 2. Industrial Microbiology—methods—congresses. QW 800 N937 1988]
QR53. N58 1989
660'.62—dc20
DNLM/DLC
for Library of Congress
89-1420
CIP

Printed in The Netherlands

Foreword

With this publication, the Society for Industrial Microbiology enters a new arena in service to the applied microbiological community. Future contributions will continue to focus on areas of topical interest to that community, bringing together wherever and whenever possible the interdisciplinary flavor so necessary to successfully treat the subject encompassed by our charter.

This volume and the conference that preceded it owe their genesis and nurturing to the tireless efforts and dedication of George Somkuti, Chair of the Society for Industrial Microbiology Conference Committee, and the members of the Program Committee: A.L. Demain (Chair), T. Beppu, R. Hamill, J.C. Hunter-Cevera, R. Monaghan, S. Ōmura, G.A. Somkuti, and M. Weinstein.

I hope that subsequent 'Topics in Industrial Microbiology' are favored with individuals of equal devotion, for this – above all – is a requirement for a successful venture.

Harold W. Rossmoore
Chairman
Society for Industrial Microbiology Publications Committee

Preface

The material in this volume was presented at the *'First International Conference on the Biotechnology of Microbial Products'*, held March 13–16, 1988, in San Diego, California, under the sponsorship of the Society for Industrial Microbiology, U.S.A. Attended by many of the scientific world's foremost authorities in the subject areas covered, the conference was dedicated to the memory of the late Professor Hamao Umezawa, the internationally recognized and respected investigator of bioactive microbial metabolites.

The establishment of this special and much-needed conference series reflects a rapidly increasing level of scientific inquiry worldwide in the search for useful microbial metabolites with other than antiinfective activities. The cases of confirmed applications and the anticipated impact of such microbial products in medicine and agriculture appear to signal the unfolding of an exciting and promising era in microbiological research that we are privileged to witness.

The new conference series, that will no doubt grow in recognition and stature, also represents the reaffirmation of the Society for Industrial Microbiology's mission, which is the *'advancement of the applied microbiological sciences'*.

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The contribution of the following organizations in the support of the conference and this publication is gratefully acknowledged:

Abbott Laboratories
Ajinomoto Company, Inc.
Allied-Signal Engineered Materials Research
American Cyanamid Company
AMGen
Bection Dickinson Microbiology Systems
Boehringer Ingelheim Pharmaceuticals, Inc.
Bristol Myers Company Industrial Division
Cetus Corporation
Eastman Kodak Company
Fujisawa Pharmaceutical Company, Inc.
Genencor, Inc.
Hoffmann-LaRoche, Inc.
Kerin Brewery Company, Ltd.
Kyowa Hakko Kogyo Company, Ltd.
Lab-Line Instruments, Inc.
Lilly Research Laboratories
Marcor Development Corporation
Meiji Seika Kaisha, Ltd.
Merck Sharp & Dohme Research Laboratories
Novo Laboratories, Inc.
Pfizer, Inc.
Pioneer Hi-Bred International, Inc.
Pitman-Moore, Inc.
Praxis Biologics, Inc.
Sankyo Company, Ltd.
Schering-Plough Corporation
Takeda Chemical Industries, Ltd.
Toyo Jozo Company, Ltd.
U.S. Department of Agriculture-Agricultural Research Service
The Upjohn Company
Xenova, Ltd.

Introduction

Hamao Umezawa and the Second Coming of Microbial Secondary Metabolites

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With great vision, Hamao Umezawa began in the 1960's his pioneering efforts to broaden the scope of industrial microbiology to low molecular weight secondary metabolites which had activities other than, or in addition to, antibacterial, antifungal and antitumor potency. He and his colleagues at the Institute of Microbial Chemistry focused on enzyme inhibitors and over the years have discovered, isolated, purified and studied the *in vitro* and *in vivo* activity of many of these novel compounds. We are fortunate that a number of antibiotic companies, research institutes and academic laboratories throughout the world interpreted this effort in a positive way and began similar programs. Today we see on the market microbial metabolites with activities such as β-lactamase inhibition, immunostimulation, immunodepression, hypocholesteremic, anthelmintic, insecticidal, herbicidal, coccidiostatal, plant growth stimulation and animal growth promotion.

The above successes came about in two ways: (1) broad screening of known compounds with antibiotic and/or toxic activities and (2) screening of unknown compounds in fermentation broths for enzyme inhibition or inhibition of a target pest. Both strategies had one important concept in common, i.e. that microbial metabolites have activities other than, or in addition to, inhibition of other microbes. The outmoded concept that microbial products could only be used for curing microbial diseases was very popular during the early days of the antibiotic era and it has taken a long time to discredit this narrow view. One reason for its unfortunate perpetuation was the hesitancy of pharmacologists to inject crude (dark and ugly? microbial broths into their animal model systems. Fortunately some enlightened (and adventurous) companies and laboratories refused to take the narrow path and broadly screened known antibiotics (which had failed as commercially important products) and mycotoxins for new activities. This led to the development of ergot alkaloids for various medical uses, monensin as a coccidiostat, gibberellin as a plant growth stimulator, zearelanone as an animal growth promotant, phosphinothricins as herbicides, and cyclosporin as an immunodepressant, the last-named virtually revolutionizing the practice of organ transplantation in medicine. The testing of inknown compounds as enzyme inhibitors in Tokyo and other places complemented the above efforts and soon resulted in the discovery of many potent inhibitors. Enzyme inhibitors which have been well accepted include those for research (antipain, pepstatin, leupeptin, cerulenin), medicine (clavulanic acid, lovastatin) and agriculture (polyoxins, phosphinothricins). Direct *in vivo* screening of fermentation broths against nematodes led to the major discovery of the potent activity of the avermectins against helminths causing disease in animals and humans.

The above successes have brought about a major change in our concepts of the potential of the microbe for the improvement of human welfare. Realization of this development led the Society for Industrial Microbiology to organize the *First International Conference on the Biotechnology of Microbial Products: 'Novel Pharmacological and Agrobiological Activities'* Indeed, it was the first special conference organized by the Society for Industrial Microbiology in recent times and most of the credit goes to the foresight, enthusiasm and energy of former President and Conference Committee Chairman, George A. Somkuti.

This book offers to the reader the flavor of the field today as an ever-increasing number of companies pursue the activities of a virtually limitless feast of secondary metabolites from microorganims. Today's screens are searching for better immunomodulating agents, anticholesterol compounds, antitumor agents, insecticides, anthelmintics, herbicides, plant and animal growth regulators as well as receptor antagonists and agonists, antiviral agents, antiinflammatory drugs, carbohydrase, inhibitors, cardiovascular drugs, lipoxygenase inhibitors, antiulcer agents, aldose reductase inhibitors, antidiabetes agents and adenosine deaminase inhibitors, among others.

I know that the visions of Hamao Umezawa and other pioneers in this worldwide effort are reaching fruition and will continue to provide products of benefit to humankind. I know that fermentation research and development will continue to expand beyond its previous narrow focus, aided by new technologies of molecular biology and genetic engineering. I regret that Hamao Umezawa passed away before he could see the fruits of his ideas come together in San Diego in 1988. However, I am pleased that his work was presented at the Conference by his colleagues and his son and that his concepts will be advanced and spread throughout the world by publication of this volume.

Contents