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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. Rossmore
Chairman

Society for Industrial Microbiology Publications Committee

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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 anti-infective 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'*.

George A. Somkuti, Chairman, SIM Conference Committee
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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 unknown 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 microorganisms. 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, lipoxigenase 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.

Hamao Umezawa was a man of great vision and energy who worked hard both day and night in the laboratory. His humanistic character and broad scientific background enabled him to make great contributions to the industrialization of the production of antibiotics. His discovery of the first tetracycline in 1945 was followed by hundreds of discoveries of new antibiotics and their development in industry. Based on the royalties of his inventions, he was successful in establishing a large research institute. He effectively promoted the microbe's talent to provide useful antibiotics and other substances beneficial for mankind. He believed that original and creative results could be achieved when clear goals, and he always committed himself completely to his work.

There is an old proverb which says that one cannot have two hares in one time will not catch two. Professor Hamao Umezawa (Fig. 1) was an exceptional person in both academic and industry. In many ways, he was not only a legend but also a man of great endeavor.

Throughout his life, in 1985 he underwent a stroke. Recovering with some medical efforts, he attempted to return to his normal life. In 1986, he traveled overseas to give lectures. One year later, he was struck by pneumonia and hospitalized, the first of several repeated hospitalizations.

On December 3rd, 1986, Professor Umezawa was taken to the hospital in the Imperial Palace. He was decorated by Emperor Hirohito.

One and a half months later, on December 23rd, he passed away at the age of 72, leaving his colleagues in deep sorrow.

Hamao Umezawa was born in 1914, the second son of Dr. Junichi Umezawa, the medical director of the principal hospital in the city of Obama, Fukui Prefecture. Located north of Kyoto near the Sea of Japan, Obama is situated in an agricultural area of beautiful rice fields. Umezawa often remarked that he enjoyed his early childhood in that rural area, beautiful with nature.

The family moved several times, eventually settling in Tokyo. One of six sons, Umezawa and his brothers were all educated in natural science or medicine, continuing a family tradition. Umezawa's grandfather had been a physician, and Ume-

Contents

Foreword.	v
Preface.	vii
List of Contributors	ix
Introduction	xxv
 1. Hamao Umezawa, the man and his dream	 1
<i>Y. Okami (Tokyo, Japan)</i>	
 2. Use of the Plackett & Burman technique in a discovery program for new natural products	 25
<i>R.L. Monaghan and L.R. Koupoal (Rahway, NJ, U.S.A.)</i>	
Summary.	25
Introduction	25
Materials and Methods	25
Results	26
Formulation of screening media	26
Fermentations containing multiple activities	27
Similarity between complex fermentation ingredients.	28
Use to increase titers	29
Production of the same products by different microorganisms	30
Discussion	31
Acknowledgements	31
References	31
 3. Screening of cardiovascular agents	 33
<i>T. Andoh and K. Yoshida (Osaka, Japan)</i>	
Summary.	33
Introduction	33
Materials and Methods	34
Aorta-superfusion method	34
ACE assay.	34
Platelet aggregation assay	34
Blood pressure and heart rate measurement.	34
Antihypertensive action in conscious spontaneously hypertensive rats (SHR).	34
Results and Discussion	34
WS-1228A and B	34
Amauromine	35
WF-10129	37
FR-900452	38

Vinigrol	40
Conclusion	42
Acknowledgement	42
References	42
4. Screening of immunomodulating agents	45
<i>M. Asano, M. Kohsaka, H. Aoki and H. Imanaka (Ibaragi, Japan)</i>	
Summary	45
Introduction	45
Materials and Methods	45
Screening systems	45
Results	46
Structures	46
Biological Properties	46
FK-506	47
Conclusion	48
References	48
5. Enzymic synthesis of immunomodulators	49
<i>H. Kleinkauf, H. von Döhren, A. Billich, A. Lawen, H. Peeters and R. Zochner (Berlin, Fed. Rep. Germany)</i>	
Introduction	49
Peptide biosynthesis	49
Immunomodulators and their pathways	49
References	54
6. Microbial secondary metabolites inhibiting oncogene functions.	57
<i>K. Umezawa, M. Hori and T. Takeuchi (Tokyo, Japan)</i>	
Summary	57
Introduction	57
Erbstatin, a tyrosine kinase inhibitor	58
Herbimycin inhibits <i>src</i> oncogene expression	59
Oxanosine, an inhibitor of <i>ras</i> oncogene functions	59
Inhibitors of phosphatidylinositol turnover	60
References	61
7. Biosynthesis of rebeccamycin, a novel antitumor agent	63
<i>K.S. Lam, S. Forenza, D.R. Schroeder, T.W. Doyle and C.J. Pearce (Wallingford, CT, U.S.A.)</i>	
Summary	63
Introduction	63
Materials and Methods	63
Microorganism	63
Media and culture conditions	64
Preparation of rebeccamycin	64
Antitumor assay	64
Results and Discussion	64

Physiology of rebeccamycin production	64
Purification and biological activity	64
Labeled precursor experiments	64
Conclusion	66
References	66
8. New adenosine deaminase inhibitors, adechlorin and adecypenol	67
<i>H. Tanaka and S. Omura (Tokyo, Japan)</i>	
Summary	67
Introduction	67
Screening	68
Isolation and structure of adechlorin	68
ADA-inhibiting and biological activities of adechlorin	68
Isolation and structure of adecypenol	69
ADA-inhibiting and biological activities of adecypenol	70
Discussion	71
References	71
9. Trichostatin and leptomycin: specific inhibitors of the G1 and G2 phases of the eukaryotic cell cycle	73
<i>T. Beppu and M. Yoshida (Tokyo, Japan)</i>	
Summary	73
Introduction	73
Trichostatins	74
Leptomycins	75
Discussion	76
References	77
10. Rhizoxin, an inhibitor of tubulin assembly	79
<i>S. Iwasaki (Tokyo, Japan)</i>	
Summary	79
Introduction	79
Materials and Methods, Results	79
Effects of RZX and its homologs (<i>1a 3b</i>) on rice seedling roots	79
Antifungal activity of RZX	79
Antitumor activity of RZX and its homologs	81
Morphological changes and cell cycle analysis of tumor cells	83
Effects of RZX on cleavage of fertilized sea urchin eggs	84
Effects of RZX on the polymerization of tubulin and on polymerized microtubule proteins	84
Comparison of the effects of RZX, VLB, P-3 and CLC on tubulin polymerization	85
Effect of RZX homologs and derivatives on the polymerization of tubulin	86
Determination of RZX binding to tubulin	86
Determination of the RZX binding site on tubulin	87
Differential effect of RZX and benomyl on mutant strains of <i>Aspergillus nidulans</i>	87
Discussion	88
Acknowledgements	88
References	88

11. Reverse transcriptase inhibitors	91
<i>S. Nakamura and Y. Inouye (Hiroshima, Japan)</i>	
Summary	91
Materials and Methods	91
Assay methods for enzyme activities	91
Determination of cytotoxicity toward L5178Y cells	92
The in vitro replication of HIV	92
The in vivo replication of FLV	92
Results and discussion	92
Screening for AMV-RTase inhibitors	92
Inhibition of AMV-RTase by known antibiotics	93
Cytotoxicity of AMV-RTase inhibitors	93
Effect on the in vitro replication of HIV	93
Effect on the in vitro replication of FLV	95
Biological properties of STN derivatives	95
Inhibition of AMV-RTase by the quinones	97
References	99
12. Low molecular weight enzyme inhibitors produced by microorganisms	101
<i>T. Aoyagi and T. Takeuchi (Tokyo, Japan)</i>	
Summary	101
Introduction	101
Discussion	102
Endopeptidase inhibitors	102
Inhibitors of cell surface enzymes	103
Therapeutics applications of enzyme inhibitors	105
Acknowledgements	105
References	106
13. Chemistry, biochemistry and therapeutic potential of microbial α -glucosidase inhibitors	109
<i>L. Mueller (Leverkusen, Fed. Rep. Germany)</i>	
Summary	109
Introduction	109
Acarbose and homologs	110
Other pseudo-oligosaccharide inhibitors	113
Tendamistat	113
Monosaccharide inhibitors	114
α -Glucosidase inhibition as a new therapeutic principle	114
References	115
14. Trestatin: α -amylase inhibitor	117
<i>K. Yokose, T. Furumai, Y. Suhara and W. Pirson (Kanagawa, Japan and Basel, Switzerland)</i>	
Summary	117
Introduction	117
Taxonomic studies on the producing organism	118
Fermentation	118

Isolation of trestatin	118
Isolation of trestatin complex (Ro 09-0154)	118
Isolation of trestatins A, B and C	119
Isolation of minor components (Ro-09766, Ro 09-767 and Ro 09-0768)	119
Physicochemical properties of trestatins A, B and C, Ro 09-0766, Ro 09-0767 and Ro 09-0768	119
Structure determination of trestatins, A, B and C	120
Structure of trestatin B	120
Structure of trestatins A and C	121
Structure determination of Ro 09-0766, Ro 09-0767 and Ro 09-0768	122
Structure determination of Ro 09-0765, Ro 09-0896 and Ro 09-0897	123
Biological properties	123
Toxicity	124
Antidiabetic properties of trestatin (Ro 09-0154)	124
Animal studies	124
Healthy volunteer studies	124
Patient studies	125
Acknowledgements	125
References	125
15. Aldostatin, a novel aldose reductase inhibitor	127
<i>S. Yaginuma, A. Asahi, M. Takada, M. Hayashi, M. Tsujino and K. Mizuno (Shizuoka, Japan)</i>	
Summary	127
Introduction	127
Materials and Methods	127
Materials	127
Microorganism	128
Aldose reductase preparation	128
Enzymatic activity	128
Rat lens preparation and incubation	128
Determination of sorbitol content in lens	128
Production of aldostatin	128
Assay of aldostatin	129
Hydrolysis of aldostatin	129
Preparation of LL-bityrosine	129
Results	129
Production	129
Isolation procedure	129
Physico-chemical properties	129
Biological properties	129
Discussion	131
References	133
16. Emeriamine: a new inhibitor of long chain fatty acid oxidation and its antidiabetic activity.	135
<i>T. Kimura and H. Okazaki Osaka, Japan</i>	
Summary	135
Introduction	135

Materials and Methods	136
Materials	136
Microorganisms	136
Assay of mitochondrial oxidation of long chain fatty acids	136
Assay of carnitine palmitoyltransferase I	136
Assay of carnitine acetyltransferase	136
Measurements of hypoglycemic and antiketogenic activities in rats	136
Determination of protein	137
Statistics	137
Results	137
Screening for inhibitors of long chain fatty acid oxidation in culture filtrates of microorganisms	137
Fermentation, isolation, and structures of emericedins A, B and C	137
Inhibition of long chain fatty acid oxidation in rat liver mitochondria by emeriamine and the inhibition site	139
Effect of emeriamine, acetyleriamine and palmitoylemeriamine on carnitine acetyltransferase and carnitine palmitoyltransferase	139
Effect of emeriamine on glucoeogenesis in hepatocytes	141
In vivo hypoglycemic and antiketogenic activity of emeriamine	141
Tissue specificity of inhibition of fatty acid oxidation by emeriamine	142
Discussion	143
Acknowledgements	143
References	143
17. Lipoxygenase inhibitors	145
<i>S. Kitamura, K. Hashizume, T. Iida, K. Ohmori and H. Kase (Shizuoka, Japan)</i>	
Summary	145
Introduction	145
Materials and Methods	146
5-Lipoxygenase inhibitors from microbial metabolites	146
Characterization of 5-lipoxygenase inhibitors	146
12-Lipoxygenase inhibitors from microbial metabolites	149
Discussion	149
References	149
18. A Specific bacterial inhibitor of the extracellular polygalacturonase of <i>Geotrichum candidum</i>	151
<i>Y. Aharonowitz, S. Bauer, S. Loya, R. Schreiber, I. Barash and D.L. Gutnick (Ramat Aviv, Israel)</i>	
Summary	151
Introduction	151
Materials and Methods	152
Microbial strains	152
Media	152
Culture conditions	152
Preparation of polygalacturonase from <i>G. candidum</i> culture broth	152
Phosphate determination	153
Reducing group determination	153