Oncogenic Viruses and Host Cell Genes

Edited by

Yoji Ikawa and Takeshi Odaka

Oncogenic Viruses and Host Cell Genes

edited by

YOJI IKAWA
Department of Viral Oncology
Cancer Institute, Tokyo

TAKESHI ODAKA
Department of Cell Genetics
Institute of Medical Science
University of Tokyo, Tokyo

ACADEMIC PRESS New York San Francisco London 1979
A Subsidiary of Harcourt Brace Jovanovich, Publishers

ACADEMIC PRESS, INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS, INC. (LONDON) LTD.
24/28 Oval Road, London NW1 7DX

Library of Congress Cataloging in Publication Data

Oji International Seminar on Genetic Aspects of Friend Viruses and Friend Cells, 5th, Yamanakako-mura, Japan, 1977.
Oncogenic viruses and host cell genes.

Held Sept. 4-8 1977, at Lake Yamanaka under the sponsorship of the Japan Society for the Promotion of Science and the Fujihara Foundation of Science.
Includes index
1. Mouse leukemia complex—Genetic aspects—Congresses. 2. Oncogenic viruses—Congresses. 3. Friend virus—Congresses. 4. Host-virus relationships—Congresses. 5. Molecular genetics—Congresses. I. Ikawa, Yoji. II. Odaka, Takeshi, Date III. Nippon Gakujutsu Shinkokai. IV. Fujihara Kagaku Zaidan. V. Title.
RC643.038 1977 616.1'55'071 78-31253
ISBN 0-12-370650-5

PRINTED IN THE UNITED STATES OF AMERICA
79 80 81 82 9 8 7 6 5 4 3 2 1

Participants

Toshio Andoh Department of Virology, Institute of Medical Science, University of Tokyo, Shirokanedai, 4-6-1, Minato-ku, 108, Tokyo

Thomas August Department of Pharmacology and Experimental Therapeutics, The Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, Maryland 21205

Haim Aviv Department of Virology, The Weizmann Institute of Science, Rehovot, Israel

Robert H. Bassin Laboratory of Tumor Virus Genetics, National Cancer Institute, NIH, Bldg. 37, Rm. 1B17, Bethesda, Maryland 20014

Peter H. Duesberg Department of Molecular Biology, University of California, Berkeley, Berkeley, California 94720

Charlotte Friend Center for Experimental Cell Biology, Mount Sinai School of Medicine of the City University of New York, Fifth Avenue and 100th Street, New York, New York 10029

Mitsuru Furusawa Department of Biology, Laboratory of Embryology, Faculty of Science, Osaka City University, Sugimoto-cho Sumiyoshi-ku, 558, Osaka

Sataro Goto Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, 7-3-1, Bunkyo-ku, 113, Tokyo

Fumio Harada Biology Division, National Cancer Center Research Institute, Tsukiji, 5-1-1, Chuo-ku, 104, Tokyo

Paul R. Harrison The Beatson Institute for Cancer Research, Garscube Estate, Bearsden Road, Glasgow G61 1BD, Scotland, United Kingdom

Toru Higachinakagawa Department of Developmental Biology, Mitsubishi–Kasei Institute of Life Sciences, 11 Minamiooya, Machida, 194, Tokyo

Tasuku Honjo Department of Physiological Chemistry and Nutrition, Faculty of Medicine, University of Tokyo, Hongo, 7-3-1, Bunkyo-ku, 113, Tokyo

Motoo Hozumi Chemotherapy Division, Saitama Cancer Center Research Institute, 18 Komuro Inamachi, Kitaadachi-gun, 362 Saitama

Yoji Ikawa Laboratory of Viral Oncology, Cancer Institute, Kami-Ikebukuro, 1-37-1, Toshima-ku, 170, Tokyo

Akira Inoue Department of Biochemistry, Osaka City University Medical School, Asahi-machi, 1-4-54, Abeno-ku, 545, Osaka

Yoshio Inoue Laboratory of Viral Oncology, Cancer Institute, Kami-Ikebukuro, 1-37-1, Toshima-ku, 170, Tokyo

Claude Jasmin Department of Virology, Institute of Cancerology and Immunogenetics, Groupe Hospitalier Paul-Brousse, 14 & 16 Avenue Paul-Vaillant-Couturier, 94800 Villejuif France

Richard P. Junghans Department of Chemistry, California Institute of Technology, Pasadena, California 91125

Kazushige Kai Department of Genetics, Institute of Medical Science, University of Tokyo, Shirokanedai, 4-6-1, Minato-ku, 108, Tokyo

Sadaaki Kawai Department of Oncology, Institute of Medical Science, University of Tokyo, Shirokanedai, 4-6-1, Minato-ku, 108, Tokyo

Richard A. Lerner Department of Immunopathology, Scripps Clinic & Research Foundation, Kenney Park, 10666 North Torrey Pines Road, La Jolla, California 92037

Stuart B. Levy Department of Medicine, Hematology Service, Tufts University School of Medicine, New England Medical Center Hospital, 171 Harrison Ave., Boston, Massachusetts 02111

Frank Lilly Department of Genetics, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, New York 10461

Tak W. Mak Department of Medical Biophysics, University of Toronto, 500 Sherbourne Street, Toronto, M4X 1K9, Canada

Masanao Miwa Department of Virology, National Cancer Center Research Institute, Tsukiji, 5–1–1, Chuo-ku, 104, Tokyo

Masami Muramatsu Department of Biochemistry, Cancer Institute, Kami-Ikebukuro, 1–37–1, Toshima-ku, 170, Tokyo

Kazuya Nakakuki Department of Pathology, Mie University School of Medicine, Edobashi, 2–174, Tsu Mie 514, Japan

Ohtsura Niwa Department of Radiology, Faculty of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, 606, Japan

Akio Nomoto Department of Public Health, Kitasato University, Shirokane, 5–9–1, Minato-ku, 108, Tokyo

Kiyoshi Nose Department of Biochemistry, Toyama Medical and Pharmaceutical University School of Medicine, Sugitani, Toyama 930–01, Japan

Masuo Obinata Laboratory of Viral Oncology, Cancer Institute, Kami-Ikebukeero, 1–37–1 Tokyo

Takeshi Odaka Department of Genetics, Institute of Medical Science, University of Tokyo Shirokanedai, 4–6–1, Minato-ku, 108, Tokyo

Tetsuo Ono Department of Biochemistry, The Tokyo Metropolitan Institute of Medical Science Honkomagome, 3–18–22, Bunkyo-ku, 103, Tokyo

Stuart H. Orkin Division of Hematology–Oncology, The Children's Hospital Medical Center, 300 Longwood Avenue, Boston, Massachusetts 02115

Wolfram Ostertag Department of Molecular Biology, Max–Planck Institute for Experimental Medicine, 400 Goettingen, Hermann Rein Strasse 3, West Germany

Ian B. Pragnell The Beatson Institute for Cancer Research, Garscube Estate, Bearsden Road, Glasgow G61 1BD, Scotland, United Kingdom

Roberta C. Reuben Department of Human Genetics and Development, College of Physicians and Surgeons of Columbia University, 701 West 168th Street, New York, New York 10032

Giovanni B. Rossi Department of Virology, Istituto Superiore di Sanita, Viale Regina Elena 299, Rome 00161, Italy

Keiko Sakuma Department of Physiology, Kagawa Nutrition College, Komagome, 3–24–3, Toshima-ku, 171, Tokyo

Deborah H. Spector Department of Microbiology, University of California, San Francisco, San Francisco, California 94143

Natalie M. Teich Department of Viral Oncology, Imperial Cancer Research Fund, P.O. Box 123, Lincoln's Inn Fields, London, WC2A 3PX, United Kingdom

Raymond W. Tennant Tumor Virus Unit, Biology Division, Oak Ridge National Laboratory, P.O. Box Y, Oak Ridge, Tennessee 37830

Kumao Toyoshima Department of Tumor Virus, Research Institute for Microbial Diseases, Osaka University, Yamada-Kami, Suita, Osaka, 565, Japan

David H. Troxler Tumor Virus Genetics Laboratory, National Cancer Institute, NIH, c/o Meloy Laboratories, 2501 Research Boulevard, Rockville, Maryland 20850

Takashi Tsuruo Division of Experimental Chemotherapy, Cancer Chemotherapy Center, Kami-Ikebukuro, 1–37–1, Toshima-ku, 170, Tokyo

Peter K. Vogt Department of Microbiology, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, California 90033

Samuel D. Waksal Tufts Cancer Research Center, Tufts University School of Medicine, Boston, Massachusetts 02111

Robert A. Weinberg Center for Cancer Research, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, Massachusetts 02139

Masaru Yamaizumi Department of Animal Virology, Research Institute for Microbial Diseases, Osaka University, Yamada-Kami, Suita, Osaka, 565, Japan

Hiroshi Yamasaki Institute of Cancer Research, College of Physicians & Surgeons of Columbia University, 701 West 168th Street, New York, New York, 10032

Mitsuaki Yoshida Laboratory of Viral Oncology, Cancer Institute, Kami-Ikebukuro, 1–37–1 Toshima-ku, 170, Tokyo

Hiroshi Yoshikura Department of Genetics, Institute of Medical Science, University of Tokyo, Shirokanedai, 4–6–1, Minato-ku, 108, Tokyo

GUEST PARTICIPANTS

Takashi Fujii Emeritus Professor, Department of Zoology, Faculty of Science, University of Tokyo, Hongo, 7–3–1, Bunkyo-ku, 113, Tokyo

Yohei Ito Professor, Department of Microbiology, Faculty of Medicine, Kyoto University, Yoshida-Konoe-cho, Sakyo-ku, Kyoto, 606, Japan

Yoshio Sakurai Director, Cancer Chemotherapy Center, Japanese Foundation for Cancer Research, Kami-Ikebukuro, 1–37–1, Toshima-ku, 170, Tokyo

Hiroto Shimojoo Director, Institute of Medical Science, University of Tokyo, Shirokanedai, 4–6–1, Minato-ku, 108, Tokyo

Haruo Sugano Director, Cancer Institute, Japanese Foundation for Cancer Research, Kami-Ikebukuro, 1–37–1, Toshima-ku, 170, Tokyo

Takashi Sugimura Director, National Cancer Center Research Institute, Tsukiji, 5–1–1, Chuo-ku, 104, Tokyo

Tadashi Yamamoto Ex-Director, Institute of Medical Science, University of Tokyo, Shirokanedai, 4–6–1, Minato-ku, 108, Tokyo

Saburo Kasagi Executive Director, Japan Society for the Promotion of Science, Kooji-machi, 5–3–1, Chiyoda-ku, 102, Tokyo

Yoshiichi Fukuda Domestic Program Division, Japan Society for the Promotion of Science, Kooji-machi, 5–3–1, Chiyoda-ku, 102, Tokyo

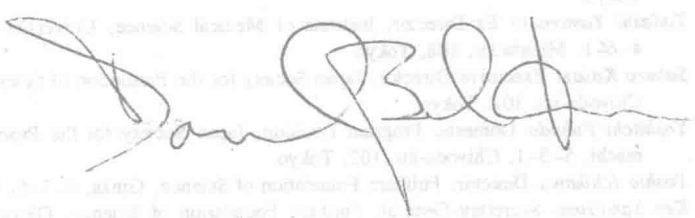
Yoshio Ichikawa Director, Fujihara Foundation of Science, Ginza, 4–7–5, Chuo-ku, 104, Tokyo

Ken Sakaizumi Secretary-General, Fujihara Foundation of Science, Ginza, 4–7–5, Chuo-ku, 104, Tokyo

Michiya Konno Treasurer, Fujihara Foundation of Science, Ginza, 4–7–5, Chuo-ku, 104, Tokyo

Foreword

In spite of the monumental advances in molecular biology and biochemistry that have occurred over the last 30 years, genetics remains the most precise tool the biologist has for the investigation of complex phenomena. It is therefore very appropriate that the Oji International Seminar focus on the genetic aspects of Friend virus and Friend cells. One of the great strengths of the meeting was to integrate the general biology of RNA tumor viruses with the more specific questions about the Friend cell system. As we learn more about how oncornaviruses are able to affect cellular control and differentiation, we will at once understand more about cancer and also about the normal processes of development.



David Baltimore

Foreword

The Friend virus-infected cell lines are now being extensively employed in laboratories around the world as a model system for studying mechanisms in controlling cell differentiation. These cell lines originally established by Charlotte Friend in 1965 were recognized early as a valuable experimental model for studying normal and abnormal differentiation of eukaryotic cells. The workers in Japan, in particular Dr. T. Odaka, working on the genetics of host susceptibility to Friend virus complex, and Drs. H. Sugano and Y. Ikawa, establishing Friend cell lines independently, and studying the biological and biochemical aspects of erythroleukemia differentiation, have contributed and continue to contribute much to the elucidation of these important problems. Therefore, it seems particularly appropriate that this international seminar on the genetic aspects of Friend virus and Friend cells was organized in Japan. As is apparent from the scientific presentations, this appears to be a particularly timely seminar because of the significant recent advances in our understanding of many aspects of induced erythroleukemia differentiation. A variety of chemicals are now known to be active as inducers of MELC differentiation. The program of expression of differentiation has many similarities to normal erythropoietin regulated differentiation. The characteristics of this program appear to be expressed in a sequential fashion, the steps of which are partially defined. Our laboratory has been particularly interested in the relationship between the characteristics of the program expressed early, during a period when differentiation is still reversible as indicated by the continued capacity for unlimited proliferation and those characteristics which are expressed later, including the commitment to terminal differentiation, limited capacity for cell division, and the accumulation of mRNA for globin and globin synthesis. The current evidence suggests that these latter characteristics are related to cell cycle dependent effects of the inducer. Inducers of murine erythrodifferentiated changes in other cell systems, e.g., neuroblastoma and teratocarcinoma. Taken together these findings suggest that the under-

standing of the mechanism of induced murine erythroleukemia cell differentiation will provide important clues to the elucidation of regulatory mechanisms of eukaryotic cell differentiation—a critical biological problem.

Paul A. Marks

Paul A. Marks, M.D.
Director, Cancer Center

Foreword

I have known the two young medical scientists, Takeshi Odaka and Yoji Ikawa, since their postgraduate days. They applied to the Japan Society for the Promotion of Science to sponsor an Oji International Seminar, and succeeded in obtaining the approval to hold the Oji International Seminar for 1977. This Seminar on Friend Leukemia Virus and Friend Cells was held in the Yamanakako Hotel, at the foot of Mount Fuji, on September 4–8, 1977. This seminar was planned to invite more young active scientists from the world and to discuss a new direction in tumor virology and eukaryote genetics. I was highly pleased with the successful outcome of this seminar and would like to express my appreciation of their efforts.

Takashi Odaka, M.D., D.M.Sc., joined our group as a postgraduate researcher when the Department of Oncology was newly set up in the Institute of Medical Science (then known as the Institute for Infectious Diseases), University of Tokyo, in 1960. At that time, he started the work of examining the sensitivity of various strains of mice, maintained as inbred strains in the animal breeding unit laboratory of our Institute, to Friend leukemia virus (FLV) which had been sent by Dr. Charlotte Friend to Dr. Waro Nakahara. He found that, when splenomegaly was taken as an index, C57BL/6 mice showed an extremely strong resistance. Examination made with the hybrids between C57BL/6 and FLV-sensitive RF mice indicated that this sensitivity mainly depended on a single dominant gene, irrespective of sex or hair color of the animals. The paper describing these results on the first discovery of 'Fv gene,' once rejected by nature, was published in the Japanese Journal of Experimental Medicine as early as 1962. After returning from 2 years of postdoctoral training at the Max–Planck Institute in Tübingen, Takeshi Odaka took up the same work again with C57BL/6 mice and DDD mice, which has been established as an inbred line by Drs. K. Suzuki and M. Okugi in the above mentioned Breeding Unit. Later, congenic mice were produced by Dr. Odaka and his work finally led to the naming of the Friend virus locus. Our Institute intended to start inbreeding of experimental animals soon after cessation of the war, when research

work itself was difficult, and contributed to the development of research works in Japan by securing important research materials.

Yoji Ikawa, M.D., D.M.Sc., is in the Department of Pathology, Cancer Institute, Tokyo as a postgraduate Pathologist. He worked with the Friend leukemia virus passaged through dd mice, established as a closed colony in our Institute. (dd signifying Deutschland-Denken, Denken being the acronym of Japanese words for Institute of Infectious Disease, i.e., *Den*senbyo *Ken*kyujo. This strain of mice is of an European origin and is known to have characteristics akin to Swiss mice.) Later, the virus has passaged through DDD mice by which this virus has luckily retained the N tropic nature, because of the low endogenous virus background of DDD mice.

In the electron microscopic and autoradiographic analyses in 1966 of early splenic lesions of Friend virus-induced leukemia, he suggested that Friend cells appearing in the spleen were erythroid cells, and this was later confirmed by him and his colleagues by the capacity to synthesize heme and the presence of erythrocyte membrane antigens. He also established in the same year an ascites Friend cell line which showed erythrocytic differentiation *in vivo*. He also established *in vitro* cultured lines. He observed that these cultured Friend cells differentiated into erythrocytes by redifferentiation. The fact that Friend cell lines established by him and others in Japan have been propagating potent FLV for many years has been noted by the American scientists.

Ikawa worked for some time in the National Cancer Institute, N.I.H., U.S.A., and cooperated with molecular biologists, and this fact must have contributed greatly to his later work. He and his American collaborators were also the first to report that the globin gene in Friend cells was suppressed at a transcription level. One of the cultured Friend cell systems that he established is currently very useful for the analysis of oncogenic nucleic acids in FLV and much will be anticipated for its future development.

山 本 正

Tadashi Yamamoto

Tadashi Yamamoto

Preface

Recent progress in technological aspects of molecular biology has enabled analyses of specific sequences in oncogenic viruses and molecular mechanisms of host cell restriction on their expression, and also elucidation on a molecular level of the cancerous or decancerized state of the cells.

It is our great pleasure that we could organize the Fifth Oji International Seminar on Genetic Aspects of Friend Virus and Friend Cells, sponsored by the Japan Society for the Promotion of Science (JSPS) and the Fujihara Foundation of Science. Stated as the subtitle of the meeting, the major accent was placed on the expression of exogenous or viral and endogenous or cellular genetic materials in the cells infected with Friend leukemia virus or other oncorna viruses.

Topics specifically treated in this volume are sarcomogenic or leukemogenic RNA sequences in RNA tumor viruses, virological and molecular mechanisms of host cell restriction on viral genes, difference between primary leukemia virus-infected cells and cells established as transplantable or cultured cell lines, and molecular mechanisms of viral leukemogenesis and induction of differentiation of leukemia cells.

Although this volume is the proceedings of the above meeting, we have tried to rearrange the contents so as to make it complete as an independent monograph. We hope that readers would be satisfied with the articles in this volume including latest accomplishments of the leading scientists in this fast progressing scientific field of viral oncology and eukaryotic genetics that developed through viral systems.

Two lectures were featured in the Oji Seminar; one by Dr. Charlotte Friend, Mount Sinai School of Medicine of the City University of New York, and the other by Dr. Peter K. Vogt, University of Southern California, School of Medicine, but their manuscripts were treated similarly as those from other speakers. We have also included a few papers which were not presented in the seminar.

In the Oji Seminar, Dr. T. Odaka and myself as organizers have made efforts to include a larger number of young active scientists, and we had a favorable age distribution of the participants, which made the meeting quite active in every re-

spect. The committee for Oji Seminars within JSPS has responded to this organizers' idea by increasing the budget.

We are indebted to the following scientists for their suggestions and cooperation in the meeting; Drs. David Baltimore, J. Michael Bishop, Bayard Clarkson, Norman Davidson, Paul Marks, John B. Moloney, Walfram Ostertag, Wallace P. Rowe, I. Bernard Weinstein, Robert McAllister, Yohei Ito, and Haruo Sugano. We are also grateful to the JSPS and the Fujihara Foundation of Science for sponsoring the meeting. Oji Seminars have been based on the donation to the Foundation from such major paper manufacturing companies in Japan as Oji, Jujo, and Honshu Seishi Co. Ltd.

Secretarial assistance in the Oji Seminar by Ms. H. Ishino, M. Aida, and Mr. S. Kagari, and technical assistance of Ms. M. Kimura for editing the articles are also gratefully acknowledged.

Yoji Ikawa

CONTENTS

II *Nucleic Acid Analyses of Oncovirus Genomes*

III *Avian Oncoviruses and Origin and Function of Their Specific Transforming Genes*

IV *Friend Murine Leukemia Virus and Its Transforming RNA Sequences*

V *Viral Leukemogenesis and Virus-Induced Proteins*

PART II
FRIEND LEUKEMIA CELL SYSTEM AS A MODEL FOR MOLECULAR ANALYSES OF GENE EXPRESSION

VI *Induction* in Vitro *of Differentiation of Friend Leukemia Cells*

VII *Influences of Tumor-Promoting Agent, Interferon, Cell Cycle, Histone on Erythrodifferentiation of Friend Leukemia Cells*

VIII *Induction of Globin and other Genes during Erythrodifferentiation of Friend Leukemia Cells*

IX *Molecular Analyses of Gene Expression in other Cell Systems*