

The Journal of the International Society for Oncology and BioMarkers

# Tumor Biology

Tumor Markers, Tumor Targeting and Translational Cancer Research

## The 36th Meeting of the International Society of Oncology and BioMarkers, ISOBM 2008

October 5-9, 2008, Tokyo, Japan



### Abstracts

### Development of New Molecular Tumor Markers for Diagnosis and Therapy

### Special Book Edition

This is not a free sample copy.  
Thank you for  
your order/purchase.

S. Karger  
Medical and Scientific Publishers  
Basel · Freiburg · Paris ·  
London · New York ·  
Bangalore · Bangkok · Shanghai ·  
Singapore · Tokyo · Sydney

**KARGER**

S. Karger AG, Basel

# Tumor Biology

**Tumor Markers, Tumor Targeting and Translational Cancer Research**

Founded 1980 as 'Oncodevelopmental Biology and Medicine'  
by the ISOBM, continued 1984–1986 as 'Tumour Biology'.  
Former Editors: W.H. Fishman 1980–1983, H. Hirai 1980–1993,  
A.M. Neville 1984–1994, S. von Kleist 1995–1999.

## Editor-in-Chief

T. Stigbrand, Umeå

## Managing Editor

P.D. Rye, Oslo

## Associate Editors

T.J. O'Brien, Little Rock, Ark.  
K. Imai, Sapporo

## Editorial Advisory Board

G. Abelev, Moscow  
V. Barak, Jerusalem  
R. Begent, London  
H. Biran, Tel Aviv  
E. Bombardieri, Milan  
O.P. Børmer, Oslo  
R.R. Brentani, São Paulo  
K. Chester, London  
E.P. Diamandis, Toronto  
A. Epenetos, London  
H.A. Fritsche, Houston, Tex.  
A. Fuks, Montreal  
P. Gold, Montreal  
S. Hammarström, Umeå  
F. Itoh, Kanagawa

J.M. Jessup, Washington, D.C.  
H. Kato, Ube  
Y.S. Kim, San Francisco, Calif.  
M. Kuroki, Fukuoka  
J.P. Mach, Epalinges s./Lausanne  
R. Molina, Barcelona  
B. Pedley, London  
M.F. Rajewsky, Essen  
J. Schlom, Bethesda, Md.  
J.E. Shively, Duarte, Calif.  
U.-H. Stenman, Helsinki  
M. Toyota, Sapporo  
J. Uriel, Paris  
C. Wittekind, Leipzig  
H. zur Hausen, Heidelberg



東大附一院 00158643

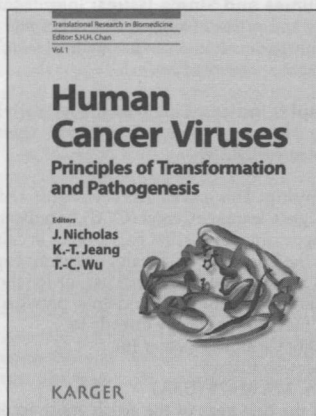
**KARGER**

Printed in Switzerland  
on acid-free and non-aging  
paper (ISO 9706) by  
Reinhardt Druck, Basel

Appears bimonthly:  
1 volume per year  
(6 issues)



Excellent reviews on the six major viruses by  
leading investigators



# Human Cancer Viruses

## Principles of Transformation and Pathogenesis

Editors

**John Nicholas**  
**Kuan-Teh Jeang**  
**T.-C. Wu**

The first identification of a tumor-causing virus, Rous sarcoma virus, occurred almost 100 years ago, but it was not until the 1970s that the genetic basis for oncogenesis by this and other acutely transforming retroviruses was appreciated. Since then, numerous viral oncogenes and their corresponding cellular proto-oncogene counterparts have been identified, and these studies have contributed much to our understanding of crucially important aspects of cell biology and transformation.

This book provides an up-to-date overview of the 6 major viruses that cause human cancers – HPV, HBV, HCV, EBV, KSHV and HTLV-1 – with respect to their molecular biology and epidemiology and to clinical aspects of disease, therapy and prevention. Contributed by over a dozen internationally renowned scientists, the chapters are comprehensively written and illustrated. The book is suitable for advanced students, postdoctoral researchers, scientists and clinicians who wish to understand the mechanisms leading to cellular transformation and oncogenesis by these viruses as a basis for the development of specific therapeutic and antiviral treatments.

### Contents

Foreword: **Chan, S.H.H.**  
Preface: **Nicholas, J.; Jeang, K.-T.; Wu, T.-C.**  
Molecular Epidemiology of Human Papillomavirus Infection: **Gillison, M.L.**  
Molecular Pathogenesis of the Human Papillomavirus: **Mao, C.-P.; Wu, T.-C.**  
Human Papillomavirus Vaccines: **Roden, R.; Hung, C.-F.; Monie, A.; Wu, T.-C.**  
Hepatitis C Virus Genetics and the Discovery of Mechanism-Based Inhibitors of the NS3/4A Protease and NS5B Polymerase: **LaFemina, R.L.**  
Role of the Hepatitis B Virus in Hepatocellular Carcinoma: **Toh, S.-T.; Lee, C.G.**  
Carcinogenesis Induced by Hepatitis B Virus: **Cougot, D.; Buendia, M.-A.; Neuveut, C.**  
Disease and Pathogenesis Associated with Epstein-Barr Virus: **Ambinder, R.F.**

The Biology and Molecular Biology Underlying Epstein-Barr Virus Oncogenesis: **Martin, H.J.; Hayward, S.D.**  
Kaposi-Sarcoma-Associated Herpesvirus. Clinical Diseases and Viral Pathogenesis: **Damania, B.; Dittmer, D.P.**  
Molecular Biology of Human Herpesvirus 8 Neoplasia: **Chaudhary, P.M.; Nicholas, J.**  
Human Cancer Viruses. Human T Cell Leukemia Virus Type 1 and 2: Mechanisms of Pathogenesis: **Arnold, J.; Green, P.L.**  
Chromosomal Instability and Human T Cell Leukemia Virus 1 Transformation: **Chi, Y.-H.; Jeang, K.-T.**

Author Index  
Subject Index

[www.karger.com/trebi](http://www.karger.com/trebi)

Translational Research in Biomedicine, Vol. 1  
Series Editor: Chan, S.H.H. (Kaohsiung)  
ISSN 1662-405X / e-ISSN 1662-4068

**Human Cancer Viruses**  
Principles of Transformation and Pathogenesis  
Editors: Nicholas, J. (Baltimore, Md.); Jeang, K.-T. (Bethesda, Md.); Wu, T.-C. (Baltimore, Md.)  
XII + 244 p., 35 fig., 9 in color, 9 tab., hard cover, 2008  
CHF 212.- / EUR 151.50 / USD 212.00  
Prices subject to change  
EUR price for Germany, USD price for USA only  
ISBN 978-3-8055-8576-7  
e-ISBN 978-3-8055-8577-4

Please send: \_\_\_\_\_ copy/ies

Postage and handling free with prepayment

#### Payment:

Please charge to my credit card  
☐ American Express ☐ Diners ☐ Eurocard  
☐ MasterCard ☐ Visa

Card No.: \_\_\_\_\_

Exp. date: \_\_\_\_\_

#### CW/CVC

(3 digits in the signature field on the back of VISA and Mastercard)

☐ Check enclosed ☐ Please bill me

Orders may be placed with any bookshop, subscription agency, directly with the publisher or through a Karger distributor.

Fax: +41 61 306 12 34

S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)  
E-Mail orders@karger.ch, [www.karger.com](http://www.karger.com)

Name/Address: \_\_\_\_\_

Date: \_\_\_\_\_

Signature: \_\_\_\_\_

**KARGER**

### Introduction

'Tumor Biology' is an international journal publishing original research and reviews in experimental and clinical cancer research. Translational research with a focus on tumor markers and tumor targeting are major interests, but studies in other areas of basic or clinical cancer research are also welcome. Manuscript categories include Research Articles, Reviews, Workshop Reports, Editorials, and Research Commentaries.

### Submission

Only original papers written in English are considered and should be submitted **online**. For specific instructions on how to prepare a manuscript for submission, you are encouraged to view the guidelines at [www.karger.com/tbi](http://www.karger.com/tbi), where you will also find a link to the **Submission Website**. Should you have any problems with your submission, please contact the editorial office:

Dr. Phil D. Rye  
Managing Editor 'Tumor Biology'  
Fax +47 23 24 8959  
E-mail [phil.rye@diagenic.com](mailto:phil.rye@diagenic.com)

**Reviews:** Review articles are usually by invitation only. However, proposals clearly outlining a theme including a probable submission date are welcome. Suggestions for articles can be submitted by e-mail to the Editor-in-Chief:

Prof. Torgny Stigbrand  
[torgny.stigbrand@climi.umu.se](mailto:torgny.stigbrand@climi.umu.se)

**Research commentaries:** Research commentaries are usually initiated by the editorial board, although unsolicited submissions are welcome. Prospective authors should contact the Managing Editor ([phil.rye@no.axis-shield.com](mailto:phil.rye@no.axis-shield.com)).

### Conditions

All manuscripts are subject to peer review. Manuscripts are received with the explicit understanding that they are not under simultaneous consideration by any other publication. A cover letter with the name, address, and telephone and fax numbers of the corresponding author must accompany each manuscript. This letter must include a statement that affirms that all authors agree with the submission. Submission of an article for publication implies transfer of the copyright from the author to the publisher upon acceptance. Accepted papers become the permanent property of 'Tumor Biology' and may not be reproduced by any means, in whole or in part, without the written consent of the publisher and the Editor-in-Chief. It is the author's responsibility to obtain permission to reproduce illustrations, tables, etc. from other publications.

### Arrangement

The complete manuscript (including table legends, figure legends and references) should be typed double-spaced using a 12 point font on one side of the paper (A4 size or 8½ × 11 inches) with 2.5 cm (1 inch) margins on all sides and with page numbers. Articles should contain: Title page, Key Words, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgements, References, Tables and figure legends.

**Title page:** The first page of each paper should indicate the title, the authors' names, the institute where the work was conducted, and a short title for use as running head.

**NB:** Authors wishing to preserve the phonetic meaning of diacritics (PubMed reduces diacritics to their root characters) must spell their names accordingly when submitting manuscripts (e.g. Müller should be Mueller).

**Full address:** The exact postal address of the corresponding author complete with postal code must be given at the bottom of the title page. Please also supply phone and fax numbers, as well as e-mail address.

**Key words:** For indexing purposes, a list of 3–10 key words in English is essential.

**Abstract:** Each paper requires an abstract of up to 200 words clearly outlining the objective(s), methods, results, and conclusion(s).

**Footnotes:** Avoid footnotes.

**Tables and illustrations:** Tables and illustrations (both numbered in Arabic numerals) should be prepared on separate pages. Tables require a heading and figures a legend, also prepared on a separate page. For the reproduction of illustrations, only good drawings and original photographs can be accepted; negatives or photocopies cannot be used. Due to technical reasons, figures with a screen background should not be submitted. When possible, group several illustrations in one block for reproduction (max. size 180 × 223 mm) or provide crop marks. Electronically submitted b/w half-tone and color illustrations must have a final resolution of 300 dpi after scaling, line drawings one of 800–1,200 dpi.

### Color illustrations

**Online edition:** Color illustrations are reproduced free of charge. In the print version, the illustrations are reproduced in black and white. Please avoid referring to the colors in the text and figure legends.

**Print edition:** Up to 6 color illustrations per page can be integrated within the text at CHF 760.– per page.

**References:** In the text identify references by Arabic numerals [in square brackets]. The number of references should not normally exceed 40 for Research Articles, and 80 for Reviews. Material submitted for publication but not yet accepted should be noted as 'unpublished data' and not be included in the reference list. The list of references should include only those publications which are cited in the text. Do not alphabetize; number references in the order in which they are first mentioned in the text. The surnames of the authors followed by initials should be given. There should be no punctuation other than a comma to separate the authors. Preferably, please cite all authors. Abbreviate journal names according to the Index Medicus system. (Also see International Committee of Medical Journal Editors: Uniform requirements for manuscripts submitted to biomedical journals. *N Engl J Med* 1997;336:309–315. [www.icmje.org](http://www.icmje.org)).

### Digital Object Identifier (DOI)

S. Karger Publishers supports DOIs as unique identifiers for articles. A DOI number will be printed on the title page of each article. DOIs can be useful in the future for identifying and citing articles published online without volume or issue information. More information can be found at [www.doi.org](http://www.doi.org).

### Examples

(a) *Papers published in periodicals:* Sun J, Koto H, Chung KF: Interaction of ozone and allergen challenges on bronchial responsiveness and inflammation in sensitised guinea pigs. *Int Arch Allergy Immunol* 1997;112:191–195.

(b) *Papers published only with DOI numbers:*

Theoharides TC, Boucher W, Spear K: Serum interleukin-6 reflects disease severity and osteoporosis in mastocytosis patients. *Int Arch Allergy Immunol* DOI: 10.1159/000063858.

(c) *Monographs:* Matthews DE, Farewell VT: Using and Understanding Medical Statistics, ed 3, revised. Basel, Karger, 1996.

(d) *Edited books:* Parren PWHI, Burton DR: Antibodies against HIV-1 from phage display libraries: Mapping of an immune response and progress towards antiviral immunotherapy; in Capra JD (ed): *Antibody Engineering*. Chem Immunol. Basel, Karger, 1997, vol 65, pp 18–56.

### Author's Choice™

With this option the author can choose to make his article freely available online against a one-time fee of CHF 2750.–. This fee is independent of any standard charges for supplementary pages, color images etc. which may apply. More information can be found at [www.karger.com/authors\\_choice](http://www.karger.com/authors_choice).

### Page Charges

There are no page charges for articles of 3 (ISOBM members and 'Tumor Biology' subscribers: 5) or fewer printed pages (including tables, illustrations and references). Each additional complete or partial page is charged to the author at CHF 290.–. One printed page is equal to approximately 3 manuscript pages (including tables, illustrations and references).

### Proofs

Unless otherwise indicated, proofs are sent to the first-named author and should be returned with the least possible delay. Alterations made in proofs, other than the correction of printer's errors, are charged to the author. No page proofs are supplied.

### Reprints

Order forms and a price list are sent with the proofs. Orders submitted after the issue is printed are subject to considerably higher prices.



**ISSN Print Edition:** 1010-4283  
**ISSN Online Edition:** 1423-0380

**Journal Homepage:** [www.karger.com/tbi](http://www.karger.com/tbi)

**Publication Data:** 'Tumor Biology' is published 6 times a year. Volume 29 with 6 issues appears in 2008.

**Copyright:** © 2008 S. Karger AG, Basel (Switzerland). All rights reserved. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher or, in the case of photocopying, direct payment of a specified fee to the Copyright Clearance Center.

**Disclaimer:** The statements, opinions and data contained in this publication are solely those of the individual authors and contributors and not of the publisher and the editor(s). The appearance of advertisements in the journal is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality or safety. The publisher and the editor(s) disclaim responsibility for any injury to persons or property resulting from any ideas, methods, instructions or products referred to in the content or advertisements.

**Subscription Rates:** Subscriptions run for a full calendar year. Prices are given per year.

**Personal subscription:**

Print or Online	Print+Online combined
CHF 672.-	CHF 717.-
EUR 480.-	EUR 512.-
USD 611.00	USD 652.00
<b>postage and handling</b>	(added to print and print+online)
CHF 36.- Europe, CHF 54.- Overseas	
EUR 25.80	
USD 49.50	

**Institutional subscription:**

Print or Online	Print+Online combined
CHF 1344.-	CHF 1478.-
EUR 960.-	EUR 1056.-
USD 1222.00	USD 1344.00
<b>postage and handling</b>	(added to print and print+online)
CHF 45.- Europe, CHF 67.50 Overseas	
EUR 32.40	
USD 61.80	

**Airmail surcharge:** CHF 45.60 / USD 41.40

**Discount subscription prices:**

- American Association for Cancer Research
  - European Association for Cancer Research
  - Japanese Cancer Association.
- Tumor Biology is included in
- 'International Society for Oncology and BioMarkers (ISOBM)' membership fee, for information: <http://www.med.uio.no/isobm>

**Back Volumes and Single Issues:** Information on availability and prices of single print issues and print or electronic back volumes can be obtained from Customer Service at [service@karger.ch](mailto:service@karger.ch).

**Bibliographic Indices:** This journal is regularly listed in bibliographic services, including *Current Contents®* and PubMed/MEDLINE.

**Photocopying:** This journal has been registered with the Copyright Clearance Center (CCC), as indicated by the code appearing on the first page of each article. For readers in the US, this code signals consent for copying of articles for personal or internal use, or for the personal or internal use of specific clients, provided that the stated fee is paid per copy directly to

Copyright Clearance Center Inc.  
222 Rosewood Drive  
Danvers, MA 01923 (USA)

A copy of the first page of the article must accompany payment. Consent does not extend to copying for general distribution, for promotion, for creating new works, or for resale. In these cases, specific written permission must be obtained from the copyright owner,

S. Karger AG, P.O. Box  
CH-4009 Basel (Switzerland).

### Subscription Orders:

Orders can be placed at agencies, bookstores, directly with the Publisher

S. Karger AG  
Medical and Scientific Publishers  
P.O. Box  
CH-4009 Basel  
Switzerland  
(for courier services only:  
Allschwilerstrasse 10  
CH-4055 Basel)  
Tel. +41 61 306 11 11  
Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

or further Karger offices  
or representatives:

**France:**  
Librairie Medi-Sciences Sarl  
36, bd de Latour-Maubourg  
75007 Paris  
France  
Tél. +33 (0) 1 45 51 42 58  
Fax +33 (0) 1 45 56 07 80  
E-Mail [librairie@medi-sciences.fr](mailto:librairie@medi-sciences.fr)  
[www.medi-sciences.fr](http://www.medi-sciences.fr)

**Germany:**  
S. Karger GmbH  
Postfach  
79095 Freiburg  
Deutschland  
(Hausadresse: Lörracher Strasse 16A  
79115 Freiburg)  
Tel. +49 761 45 20 70  
Fax +49 761 45 20 714  
E-Mail [information@karger.de](mailto:information@karger.de)  
[www.karger.de](http://www.karger.de)

**India, Bangladesh, Sri Lanka:**  
Panther Publishers Private Ltd.  
33, First Main  
Koramangala First Block  
Bangalore 560 034  
India  
Tel. +91 80 25505 836  
Tel. +91 80 25505 837  
Fax +91 80 25505 981  
E-Mail [panther\\_publishers@vsnl.com](mailto:panther_publishers@vsnl.com)  
[www.pantherpublishers.com](http://www.pantherpublishers.com)

**Japan:**  
Karger Japan, Inc.  
Yushima S Bld. 3F  
4-2-3, Yushima, Bunkyo-ku  
Tokyo 113-0034  
Japan  
Tel. +81 3 3815 1800  
Fax +81 3 3815 1802  
E-Mail [publisher@karger.jp](mailto:publisher@karger.jp)

**China, Taiwan and Malaysia:**  
Karger China  
Suite 409, Apollo Building  
1440 Central Yan An Road  
Shanghai 200040  
China  
Tel. +86-21-6133 1861  
Fax +86-21-6133 1862  
E-Mail [karger.ray@gmail.com](mailto:karger.ray@gmail.com)

**South America and Central America:**  
Cranbury International LLC  
7 Clarendon Ave., Suite 2  
Montpelier, VT 05602  
USA  
Tel. +1 802 223 6565  
Fax +1 802 223 6824  
E-Mail  
[eatkin@cranburyinternational.com](mailto:eatkin@cranburyinternational.com)  
[www.cranburyinternational.com](http://www.cranburyinternational.com)

**United Kingdom, Ireland:**  
S. Karger AG  
c/o London Liaison Office  
4 Rickett Street  
London SW6 1RU  
United Kingdom  
Tel. +44 (0) 20 7386 0500  
Fax +44 (0) 20 7610 3337  
E-Mail [uk@karger.ch](mailto:uk@karger.ch)

**USA:**  
S. Karger Publishers, Inc.  
26 West Avon Road  
P.O. Box 529  
Unionville, CT 06085  
USA  
Toll free: +1 800 828 5479  
Tel. +1 860 675-7834  
Fax +1 860 675-7302  
E-Mail [karger@snet.net](mailto:karger@snet.net)

### Change of Address:

Both old and new address should be sent to the subscription source.

# Development of New Molecular Tumor Markers for Diagnosis and Therapy

## Abstracts

**The 36th Meeting of the International Society of Oncology and BioMarkers, ISOBM 2008**

October 5–9, 2008, Tokyo, Japan

Organizers

*K. Imai, Sapporo*

*F. Itoh, Kawasaki*

**KARGER**

Basel • Freiburg • Paris • London • New York • Bangalore •  
Bangkok • Shanghai • Singapore • Tokyo • Sydney



S. Karger  
Medical and Scientific Publishers  
Basel • Freiburg • Paris • London  
New York • Bangalore • Bangkok  
Shanghai • Singapore • Tokyo • Sydney

#### Disclaimer

The statements, opinions and data contained in this publication are solely those of the individual authors and contributors and not of the publisher and the editor(s). The appearance of advertisements in the journal is not a warranty, endorsement, or approval of the products or services advertised or of their effectiveness, quality or safety. The publisher and the editor(s) disclaim responsibility for any injury to persons or property resulting from any ideas, methods, instructions or products referred to in the content or advertisements.

#### Drug Dosage

The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

#### All rights reserved.

No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means, electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher or, in the case of photocopying, direct payment of a specified fee to the Copyright Clearance Center (see 'General Information').

© Copyright 2008 by S. Karger AG,  
P.O. Box, CH-4009 Basel (Switzerland)  
Printed in Japan by Hokuetsu Co., Ltd., Tokyo  
ISBN 978-3-8055-8997-0  
e-ISBN 978-3-8055-8998-7

**KARGER**

Fax +41 61 306 12 34  
E-Mail [karger@karger.ch](mailto:karger@karger.ch)  
[www.karger.com](http://www.karger.com)

## Epigenetic Profiling and Epigenetic Therapy in Cancer: A Promising New Era

Jean-Pierre Issa

University of Texas MD Anderson Cancer Center

Yoshitake Hayashida

Institute of Health Sciences, University of Tokyo, Japan

Epigenetics refers to stable changes in gene expression that cannot be accounted for by mutations or other genetic events. Epigenetic changes, such as DNA methylation and histone modification, are reversible and can be targeted by drugs. The epigenetic changes in cancer are closely related to the development of the disease. In this review, we discuss the role of epigenetics in cancer and the potential of epigenetic therapy in cancer treatment. We also discuss the role of epigenetics in cancer diagnosis and prognosis. The epigenetic changes in cancer are closely related to the development of the disease. In this review, we discuss the role of epigenetics in cancer and the potential of epigenetic therapy in cancer treatment. We also discuss the role of epigenetics in cancer diagnosis and prognosis.

# Plenary Lecture

are several microRNAs, and we found that miR-124 is frequently hypermethylated in MDS, which results in increased expression of its target, CDK6. The DNA methylation inhibitor decitabine leads to hypomethylation of miR-124 in patients with MDS, along with upregulation of the miRNA and downregulation of CDK6. This suggests that expression of miR-124 correlates with response to decitabine in MDS. We conclude that epigenetic therapy is a promising approach in MDS, which may explain in part responsiveness of this disease to epigenetic therapy. These principles are now being translated in other leukemias and in solid tumors.

## Large-scale Metagenomic Analyses of Human Cancers: Lessons Learned from Sequencing Cancer Genomes

DW Parsons<sup>1,2</sup>, S Jones<sup>1</sup>, R Li<sup>1</sup>, J Lin<sup>1</sup>, X Zhang<sup>1</sup>, LD Wood<sup>1</sup>, T Sjöblom<sup>1</sup>, N Papadopoulos<sup>1</sup>, G Parmigiani<sup>1</sup>, KW Kinzler<sup>1</sup>, VE Velculescu<sup>1</sup>, and B Vogelstein<sup>1</sup>

<sup>1</sup>Shirley Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital, Baltimore, MD, USA

<sup>2</sup>Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA

<sup>3</sup>Department of Genetics and Pathology, Uppsala University, SE-751 83 Uppsala, Sweden

Human cancer is caused by the accumulation of mutations in oncogenes and tumor suppressor genes. In an attempt to comprehensively catalog the genetic changes that occur during tumorigenesis, we have developed techniques for genome-wide sequencing-based mutational analysis. These methodologies have been applied to a panel of 11 breast and 11 colorectal cancers. Based on analysis of exons representing ~30,000 transcripts from ~18,000 genes, we conclude that the genomic landscapes of breast and colorectal cancers are composed of a handful of commonly-mutated genes "mountains" and a much larger number of genes "hills" that are mutated at low frequency. We have developed statistical and bioinformatic tools that help to identify single genes with a role in tumorigenesis, as well as to implicate pathways and enriched for genetic alterations. These genome-wide analyses have provided us an unprecedented view of the spectrum and extent of somatic mutations in human tumors of similar and different histologic types. The results of these studies have profound implications for understanding the nature and heterogeneity of human cancers and for using personal genomics for tumor diagnosis and therapy.



## PL1

### Epigenetic Profiling and Epigenetic Therapy in Cancer

Jean-Pierre Issa

*University of Texas MD Anderson Cancer Center*

Epigenetics refers to stable changes in gene expression that cannot be accounted for by mutations or other genetic events. Epigenetic reprogramming, an essential component of embryogenesis, also has the potential to reverse the malignant phenotype in some cases. The myelodysplastic syndrome (MDS) has been used as a proof of principle disease for this approach. Preliminary studies using a panel of genes methylated in myeloid malignancies revealed frequent abnormal methylation in MDS, and classification of the disease into methylation high/low groups that correspond to shorter survival. In an effort to understand epigenetics of MDS in a global way, we have applied MCAM, a methylation microarray method that represents ~7,000 genes to several patients with MDS, including patients treated with the DNA methylation inhibitor decitabine. Overall, we identified hundreds of genes hypermethylated in MDS, with a rate of anomalies ranging from 5-15% of detectable loci. We identified ~200 genes concordantly methylated in the poor prognosis subset of MDS earlier described. Turning to therapy, we and others have shown that a certain degree of epigenetic reprogramming can be achieved by drugs that inhibit DNA methylation, and this leads to significant responses and prolongation of life in this disease. Using MCAM, we identified ~100 genes commonly hypomethylated after decitabine. Among the modified genes are several microRNAs, and we found that mir124a is frequently hypermethylated in MDS, which results in increased expression of its target, CDK6. The DNA methylation inhibitor decitabine leads to hypomethylation of mir124a in patients with MDS, along with upregulation of the miRNA and down-regulation of CDK6. Increased expression of mir124a correlates with response to decitabine in MDS. We conclude that aberrant methylation is very common in MDS, which may explain in part responsiveness of this disease to epigenetic therapy. These principles are now being translated in other leukemias and in solid tumors.

## PL2

### Large-scale Mutational Analyses of Human Cancers: Lessons Learned from Sequencing Cancer Genomes

DW Parsons<sup>1,2</sup>, S Jones<sup>1</sup>, RJ Leary<sup>1</sup>, J Lin<sup>1</sup>, X Zhang<sup>1</sup>, LD Wood<sup>1</sup>, T Sjöblom<sup>3</sup>, N Papadopoulos<sup>1</sup>, G Parmigiani<sup>1</sup>, KW Kinzler<sup>1</sup>, VE Velculescu<sup>1</sup>, and B Vogelstein<sup>1</sup>

<sup>1</sup>*Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Hospital, Baltimore, MD, USA*

<sup>2</sup>*Texas Children's Cancer Center, Baylor College of Medicine, Houston, TX, USA*

<sup>3</sup>*Department of Genetics and Pathology, Uppsala University, SE-751 85 Uppsala, Sweden*

Human cancer is caused by the accumulation of mutations in oncogenes and tumor suppressor genes. In an attempt to comprehensively catalog the genetic changes that occur during tumorigenesis, we have developed techniques for genome-wide sequencing-based mutational analysis. These methodologies have been applied to a panel of 11 breast and 11 colorectal cancers. Based on analysis of exons representing ~20,000 transcripts from ~18,000 genes, we conclude that the genomic landscapes of breast and colorectal cancers are composed of a handful of commonly-mutated gene "mountains" and a much large number of gene "hills" that are mutated at low frequency. We have developed statistical and bioinformatic tools that help to identify single genes with a role in tumorigenesis, as well as to implicate pathways enriched for genetic alterations. These genome-wide analyses have provided us an unprecedented view of the spectrum and extent of somatic mutations in human tumors of similar and different histologic types. The results of these studies have profound implications for understanding the nature and heterogeneity of human cancers and for using personal genomics for tumor diagnosis and therapy.

## The New Phase of Transcriptome Analysis

Yoshihide Hayashizaki

*1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, 230-0045, Japan*

### **Aim:**

The international FANTOM consortium was organized in 2000 and established the *de facto* standard of the full-length cDNA banks of mouse, human and several other species. Now, it is entering a new scientific phase dealing with functional genomics of the gene networks.

### **Method:**

A human monoblast cell line, THP-1, is used as a model for the development of a general-purpose pipeline for the elucidation of the gene expression regulatory network which consists of transcriptional factor proteins and functional RNA molecules. Large amounts of data such as promoter activities and RNA profiling by CAGE, chromatin structures and protein-DNA interaction by ChIP-Chip, small RNA profiling by sequencing and so on was obtained through PMA stimulation time course of THP-1, followed by extensive computational analysis.

### **Results:**

The analysis has showed that the differentiation of the cell was precisely controlled by concerted regulation of gene expressions.

### **Conclusion:**

We have recently introduced a new concept called "basin" for understanding cell function. The basin is defined as a steady state of a cell with specific gene expression profile to autonomously maintain the cell function.









## SPF1

### **From Analbuminemic Rats to Pierisin, An Apoptogenic Peptide from Butterflies**

Takashi Sugimura, Keiji Wakabayashi

*National Cancer Center*

In the 1980's, I was fortunate in having opportunities to attend ISOBM meetings, or their precursors, and to interact with Prof. Hidematsu Hirai, who was once my mentor at University of Tokyo and a founder of the ISOBM. As I recall the meetings, I would like to start with one or three slides for each subject which I had the pleasure to present. The areas covered were: 1) analbuminemic rats and splicing infidelities induced in hepatic cells by treatment with carcinogens; 2) disdifferentiation and decarcinogenesis concepts deduced from findings of changes in isozyme patterns in tumors; and 3) the likely importance for carcinogenesis of epigenetic changes, in addition to genetic alterations, inferred from the modification of chromatin proteins by many carcinogens also producing DNA base adducts. I would like to also present our current and exciting information concerning an apoptogenic peptide, pierisin, isolated from the cabbage butterfly. Pierisin is rich in late phase larvae and pupae in the early phases of the cabbage butterfly life cycle. It exerts potent apoptogenic activity in cancer cells, and is able to ADP-ribosylate guanine bases of DNA. Pierisin seems to be important for metamorphosis of this species of butterfly and might be effective as a protective agent against natural enemies. The molecular biology, and phylogenetic and ontogenic aspects of this compound are attracting increasing attention, and pierisin clearly could be a promising candidate for development as a lead compound for cancer drugs.

## SPF2

### **From "Placental Alkaline Phosphatase" to "Oncodevelopmental Biology" to the "Burnham Institute for Medical Research" - A Success Story**

José Luis Millán

*Professor and Sanford Investigator, Sanford Children's Health Research Center, Burnham Institute for Medical Research, La Jolla, CA 92037 - USA*

It started with a biochemical observation: a male patient with lung cancer had elevated plasma levels of placental-type alkaline phosphatase, an enzyme usually found in pregnant women. This discovery led William H. Fishman, Tufts University, Boston, to begin to formulate the concept that the re-expression of embryonic and/or developmental genes might be a mechanism evoked by cancer cells to gain a competitive advantage over neighboring normal cells in their quest to proliferate. Simultaneous and independent studies by Phil Gold on the expression of carcino-embryonic antigen and by Gary Abelev on alpha-fetoprotein, led to coining the term "Oncodevelopmental Biology" to define this new paradigm in cancer research. These scientists shared their views at the annual meetings of the "International Research Group for Carcinoembryonic Proteins", led by Prof. Hidematsu Hirai, Sapporo, Japan, and together decided to focus on this new paradigm and re-named that research group the "International Society for Oncodevelopmental Biology and Medicine" (ISOBM). Prof. Hirai, furthermore, encouraged Dr. Fishman to create an institution in the USA to sharply focus research at the interface of oncology and developmental biology. Thus, at the 4<sup>th</sup> ISOBM meeting organized by Bill Fishman at the Hotel del Coronado, San Diego, May 1976, the creation of the La Jolla Cancer Research Foundation, La Jolla, CA was announced. I had the privilege to join Bill Fishman's research group shortly after, in August 1977, when that new Foundation had less than 10 employees and I've had the unique opportunity to grow with and to contribute to the growth of that Institute that currently, known as the Burnham Institute for Medical Research (BIMR), counts with ~900 employees, ~70 principal investigators, NIH funding in the order of 90 million USD and conducts bicoastal operations with campuses in La Jolla and Santa Barbara in California and Orlando in Florida. BIMR has been ranked among the 10 most influential research institutes world-wide based on the impact of its research. Its motto is "From Research, the Power to Cure". It all started with an experimental observation, a supportive society, a dreamer like Bill Fishman and the will and perseverance to see that dream come true.

**From the Study of Carcinoembryonic Proteins to Molecular Medicine**Sabine von Kleist*Univ. Freiburg, Germany*

Not only anniversaries lend themselves for reflections and critical evaluations of the years that have passed. A change of name of a scientific society existing now for 36 years under the same name provides also a welcome opportunity to have a look on its past and to dare a look into the future. If it needs to count the milestones of success of this society, the first is surely its foundation as International Society of Oncodevelopmental Biology and Medicine (ISOBM) by the eminent and farsighted researcher Prof. H. Hirai, whose wisdom, reputation and outstanding leadership attracted right from the start (Oct. 23, 1972) a rapidly growing audience around renowned colleagues from all over the world. They all were highly interested in this new field of research of fetal proteins and a phenomenon already observed by Hirszfeld in 1932 of common traits between embryonal and tumor tissues. In less than ten years purely basic fetal research had developed into molecular biology and medicine. Clinical implications were found most everywhere thanks to a close collaboration between basic scientists and clinical oncologists fostered since the beginning by ISOBM's president. He was also at the origin of many life-long friendships beyond any what so ever boundaries. Let us henceforth revive the thought that a society is made of human beings, who -although having common interests- still need personal attention and individual contacts testifying the esteem of the presidency for the members of the society.





# Clinical Aspects of $\alpha$ -fetoprotein and Its Sugar Chain

Kazuhisa Taketa

Emeritus Professor Okayama University, Japan

Serum  $\alpha$ -fetoprotein (AFP) has been widely used for the early detection of hepatocellular carcinoma (HCC) and its follow-up after intervention. The positive rate of AFP in HCC in the period of 1980-1981 was 63.1% for cases with AFP > 200 ng/ml and 25.1% for those with AFP > 10,000 ng/ml and the rate in the period of 2002-2003 decreased to 27.1% for those with AFP > 200 ng/ml and to 15.7% for those with AFP > 10,000 ng/ml. The decrease in positive rate of AFP was correlated with the decrease in tumor size. This is probably related to the fact that HCC became detected

## ISOBM Abbott Award

phytohemagglutinin (E-PHA) had a monosialylated biantennary oligosaccharide with an exposed  $\beta$ -D-galactose of the  $\alpha$ -D-mannose at  $\alpha$ -6 antenna and increased in HCC even in cases with negative AFP-L3. Therefore, the combined use of different glycoforms of AFP increases both the specificity and sensitivity in diagnosing HCC. Two-dimensional isoelectric focusing and lectin affinity electrophoresis with E-PHA further revealed additional microheterogeneity forms of AFP in HCC. This new separation technique would facilitate the marker diagnosis of HCC in view of the fact that the microheterogeneity of antigenic expression is the fundamental feature of malignancy in addition to dedifferentiation.

## **Clinical Aspects of $\alpha$ -fetoprotein and Its Sugar Chain**

Kazuhisa Taketa

*Emeritus Professor Okayama University, Japan*

Serum  $\alpha$ -fetoprotein (AFP) has been widely used for the early detection of hepatocellular carcinoma (HCC) and its follow-up after intervention. The positive rate of AFP in HCC in the period of 1980-1981 was 63.1% for cases with AFP>200 ng/ml and 25.1% for those with AFP>10,000 ng/ml and the rate in the period of 2002-2003 decreased to 27.1% for those with AFP>200 ng/ml and to 15.7% for those with AFP>10,000 ng/ml. The decrease in positive rate of AFP was correlated with the decrease in tumor size. This is probably related to the fact that HCC became detected earlier while the tumor size was small as a result of the development of imaging modalities. Thus, the setting of cut-off level for AFP is less meaningful. Another difficulty in interpreting the rise in serum AFP level lies in the fact that serum AFP level rises not only in HCC but also in hepatitis and cirrhosis, which are the underlying pathogenetic conditions of HCC. In order to circumvent the difficulty in differentiating benign and malignant conditions, microheterogeneity of AFP sugar chain was determined in HCC and compared with that in hepatitis and cirrhosis. AFP having sugar chains with fucosylated core *N*-acetylglucosamine, namely, AFP-L3, was more specific to HCC when it was expressed by the percentage of total AFP. AFP-P4, which was separated by affinity electrophoresis with erythroagglutinating phytohemagglutinin (E-PHA), had a monosialylated biantennary oligosaccharide with an exposed  $\beta$ -D-galactose of the  $\alpha$ -D-mannose  $\alpha 1 \rightarrow 6$  antenna and increased in HCC even in cases with negative AFP-L3. Therefore, the combined use of different glycoforms of AFP increases both the specificity and sensitivity in diagnosing HCC. Two-dimensional isoelectric focusing and lectin affinity electrophoresis with E-PHA further revealed additional microheterogeneity forms of AFP in HCC. This new separation technique would facilitate the marker diagnosis of HCC in view of the fact that the microheterogeneity of epigenetic expression is the fundamental feature of malignancy in addition to dedifferentiation.