THE RETINOID REVOLUTION

Coordinated by Pierre Chambon, James A. Olson, and A. Catharine Ross
An Invitation....

FASEB SUMMER RESEARCH CONFERENCES

In 1980, FASEB began planning a new program for scientific communication to be at the cutting edge of research in a format entirely different from the annual meeting. The initiation of the FASEB Summer Research Conferences in 1982 spawned a continuing series of interdisciplinary exchanges that have become recognized as a valuable complement to the highly successful Society meetings. The conferences are divided into small groups of experimental biologists who meet intimately and without distractions to explore new approaches to those research areas undergoing rapid scientific change.

Conferences are currently convened at the Vermont Academy in Saxtons River, Vermont, Copper Mountain, Colorado and Snowmass Village, Colorado during the months of June, July and August. The topics for the conferences are approved by a scientific advisory committee. All conferences are scheduled at least two years in advance.

We invite you to submit a proposal for the 1998 FASEB Summer Research Conferences. To obtain a copy of the guidelines for submitting a proposal, please complete the information requested below and return to the FASEB Summer Research Conferences office.

FASEB SUMMER RESEARCH CONFERENCES
9650 Rockville Pike
Bethesda, MD 20814-3998

Tel. 301-530-7093    FAX 301-571-0650    E-mail: src@faseb.org

Please send me information and forms for submitting a proposal to schedule a conference on:

(Topic) ____________________________________________________________

Name ____________________________________________________________

Institute __________________________________________________________

Address __________________________________________________________

City/State/Zip ____________________________________________________

Telephone _________________________________________________________

Deadline for submission of proposals: September 20, 1996
Next Month

Serial Reviews

Liver regeneration B. Liver regeneration versus direct hyperplasia. A. Columbano and H. Shinozuka

State-of-the-art Reviews

The functional significance of brain metallothioneins. M. Aschner
From legumes to leukocytes: biological roles for sulfated carbohydrates. L. V. Hooper, S. M. Marzella, and J. U. Beersiger
Phospholipases: structural and functional motifs for working at an interface. M. F. Roberts
Chromatin and transcription. D. G. Edmondson and S. Y. Roth
Regulation of tumor growth and metastasis by thrombospondin-1. D. D. Roberts

In Press

Serial Reviews

Cytochromes P450 7. Role of the peroxisome proliferator activated receptor in cytochrome P450 4A gene regulation. E. F. Johnson, C. N. A. Palmer, K. J. Griffin, and M.-H. Hsu
Protein Motifs 9. The nicotinamide dinucleotide binding motif. C. R. Bellamacina

State-of-the-art Reviews

Sphingolipid metabolism and cell growth regulation. S. Spiegel and A. H. Merrill, Jr.
Interplay between Ras-related and heterotrimeric GTP binding proteins: Lifestyles of the BIG and little. G. M. Bokoch
Paneth cell defenses: endogenous peptide components of intestinal host defense. A. J. Quelle and M. E. Selsted
The elf-2α kinases and the control of protein synthesis. C. de Haro, R. Mendez, and J. Santosoy
Heparan sulfate — a piece of information. M. Salmivita, K. Lidholt, and U. Lindahl

The FASEB Journal publishes brief, definitive, original research communications and state-of-the-art reviews, as well as editorials, letters, a calendar, and public affairs. The views expressed in articles are those of the authors and not necessarily those of the Federation. All manuscripts are subject to review and approval by the Editors before publication. Copyright © 1996 by the Federation of American Societies for Experimental Biology. Printed at Lancaster Press, Lancaster, Pennsylvania.

Send manuscripts and proposals to the Editor-in-Chief, Dr. V. T. Marchesi, The FASEB Journal, Yale University School of Medicine, 295 Congress Ave., P.O. Box 9812, New Haven, CT 06530-0812, USA.

All rights reserved. Requests for any reproduction of copyrighted material except the first page of a regular article should be made in writing to the Assistant Executive Editor, The FASEB Journal, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA, and should include an explicit statement of intended use and detailed specification of the material to be reproduced. Telephone 301-530-7100. COPYRIGHT: An individual may make a single copy of an article for personal use. The code at the bottom of the first page of an article indicates the copyright owner's consent that additional copies of the article may be made provided that the stated fee is paid. Received 301-530-7100. EXECUTIVE BOARD

Kari Altalalou
Leonard J. Banaszak
Carl G. Becker
Káro Berg
Robert M. Berne
Piet Borst
Henry R. Bourne
Mario R. Capocchi
C. Thomas Caskey
Pierre Chambon
Gwen V. Childs
Bryan F. C. Clarke
Walter Colli
R. John Collier
Robert J. Cousins
David Drubin
Thomas S. Edgington
Anthony S. Fauci
Ray W. Fuller
John W. Funder
Paul Greengard
Sarah Hitchcock-DeGregori
Ann L. Hubbard
Bernard Jeanrenaud
Thomas J. Kindt
Tadamitsu Kishimoto
George Klein
Hynda K. Kleinman
Hans L. Komberg

EDITORIAL ASSOCIATE
Claire L. Bien
203-737-2785
COPY EDITOR
Kendall Sites
301-530-7102
OFFICE OF MARKETING SERVICES
301-530-7159
fax 301-571-0883
email: adner@faselb.org
SUBSCRIPTION MANAGER
Eleanor B. Peabody
301-730-7026
fax 301-530-7001
COMPTROLLER
John R. Rice
301-530-7080
fax 301-530-7014
FASEB MAILING ADDRESS:
9650 Rockville Pike
Bethesda, MD 20814-3998, USA

EDITORIAL BOARD

Kari Altalalou
Leonard J. Banaszak
Carl G. Becker
Káro Berg
Robert M. Berne
Piet Borst
Henry R. Bourne
Mario R. Capocchi
C. Thomas Caskey
Pierre Chambon
Gwen V. Childs
Bryan F. C. Clarke
Walter Colli
R. John Collier
Robert J. Cousins
David Drubin
Thomas S. Edgington
Anthony S. Fauci
Ray W. Fuller
John W. Funder
Paul Greengard
Sarah Hitchcock-DeGregori
Ann L. Hubbard
Bernard Jeanrenaud
Thomas J. Kindt
Tadamitsu Kishimoto
George Klein
Hynda K. Kleinman
Hans L. Komberg

EDITOR-IN-CHIEF
Vincent T. Marchesi
203-737-2283
fax 203-737-2287
email: vincent.marchesi@yale.edu

EXECUTIVE EDITOR
Levis I. Glodez
301-530-7100
fax 301-530-7115
email: lglodez@pubs.faseb.org

ASSISTANT EXECUTIVE EDITOR
Sandra W. Jacobson
301-530-7104
email: sjaobson@pubs.faseb.org

The FASEB Journal is published 14 times a year (monthly except bi-monthly in March and April) by FASEB, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA. Subscriptions price U.S. and its possessions: members of Corporate Societies, $47 per year; nonmembers (personal), $110 per year; institutional, $310 per year; students, $25 per year with certification. Mexico/ Canada add $20 postage; rest of world add $48 (expected delivery). All subscriptions entered on a calendar-year basis only and payable in advance. Single issues, except Abstract issues, $27. Subscriptions and orders should be sent to The FASEB Journal, Subscription Department, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA; 301-530-7027. In Japan, contact USA COC, Corp., 13-12 Shinbashi 1-Chome, Minato-ku, Tokyo. Japa; telex J28274; fax 03-593-2708. Periodicals postage paid at Bethesda, Maryland, and at additional mailing offices. Postmaster: Send address changes to The FASEB Journal, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA. Designed to report on rapidly changing developments in biological sciences,

The FASEB Journal publishes brief, definitive, original research communications and state-of-the-art reviews, as well as editorials, letters, a calendar, and public affairs. The views expressed in articles are those of the authors and not necessarily those of the Federation. All manuscripts are subject to review and approval by the Editors before publication. Copyright © 1996 by the Federation of American Societies for Experimental Biology. Printed at Lancaster Press, Lancaster, Pennsylvania.

Send manuscripts and proposals to the Editor-in-Chief, Dr. V. T. Marchesi, The FASEB Journal, Yale University School of Medicine, 295 Congress Ave., P.O. Box 9812, New Haven, CT 06530-0812, USA.

All rights reserved. Requests for any reproduction of copyrighted material except the first page of a regular article should be made in writing to the Assistant Executive Editor, The FASEB Journal, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA, and should include an explicit statement of intended use and detailed specification of the material to be reproduced. Telephone 301-530-7100. COPYRIGHT: An individual may make a single copy of an article for personal use. The code at the bottom of the first page of an article indicates the copyright owner's consent that additional copies of the article may be made provided that the stated fee is paid. Telephone 301-530-7100.

EDITOR-IN-CHIEF
Vincent T. Marchesi
203-737-2283
fax 203-737-2287
email: vincent.marchesi@yale.edu

EXECUTIVE EDITOR
Levis I. Glodez
301-530-7100
fax 301-530-7115
email: lglodez@pubs.faseb.org

ASSISTANT EXECUTIVE EDITOR
Sandra W. Jacobson
301-530-7104
email: sjaobson@pubs.faseb.org

The FASEB Journal is published 14 times a year (monthly except bi-monthly in March and April) by FASEB, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA. Subscriptions price U.S. and its possessions: members of Corporate Societies, $47 per year; nonmembers (personal), $110 per year; institutional, $310 per year; students, $25 per year with certification. Mexico/ Canada add $20 postage; rest of world add $48 (expected delivery). All subscriptions entered on a calendar-year basis only and payable in advance. Single issues, except Abstract issues, $27. Subscriptions and orders should be sent to The FASEB Journal, Subscription Department, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA; 301-530-7027. In Japan, contact USA COC, Corp., 13-12 Shinbashi 1-Chome, Minato-ku, Tokyo, Japan; telex J28274; fax 03-593-2708. Periodicals postage paid at Bethesda, Maryland, and at additional mailing offices. Postmaster: Send address changes to The FASEB Journal, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA.

Designed to report on rapidly changing developments in biological sciences,
ETHANOL INHIBITION OF RETINOIC ACID SYNTHESIS

Retinol, the alcohol form of vitamin A, is oxidized to retinoic acid, the active form of vitamin A, needed for growth and development. The role of ethanol in the pathogenesis of fetal alcohol syndrome has been proposed to involve ethanol inhibition of retinol oxidation catalyzed by alcohol dehydrogenase. Deltour et al. (pages 1050-1057) report that treatment of mouse embryos with ethanol led to a significant decrease in retinoic acid. Furthermore, mRNA for class IV alcohol dehydrogenase was detected in mouse embryos. These findings suggest that embryos use alcohol dehydrogenase for retinoic acid synthesis, thus supporting the postulated mechanism of fetal alcohol syndrome.

VITAMIN A, ANDROGEN AND CYP2C11

Dietary vitamin A deficiency leads to decreased hepatic drug oxidation catalyzed by cytochrome P450 (CYP) enzymes. Previous studies have established that the male-specific CYP2C11 is down regulated at a pretranslational level in dietary deficiency, but the mechanism of this effect is unclear. Murray et al. (pages 1058-1063) now report that treatment of vitamin A-deficient male rats with exogenous androgen restores CYP2C11 expression without influencing vitamin A status. Thus, androgen deficiency mediates the down regulation of CYP2C11 in vitamin A-deficient male rat liver.

ABERRANT RETINOID SIGNALING IN CANCER

Retinoic acid (RA) is a negative growth regulator and differentiation inducer in epithelial tissues. Recent findings have suggested that underexpression of nuclear RA receptors (RAR), such as RARα1 and RARβ2, contribute to deregulated breast cancer cell growth. In support of this concept, Jing et al., (pages 1064-1070) show that two other receptors, RARα2 and RARγ2, are underexpressed in breast cancer cells relative to breast fibroblasts, and present evidence that at least in the case of RARβ2, underexpression is tumor-specific since RARβ2 is expressed in immortalized but non-tumorigenic luminal breast epithelial cells. Also, the mRNA for the cytosolic cellular retinol binding protein I is expressed in normal breast epithelial cells but not breast cancer cells suggesting impairment of both cytosolic and nuclear retinoid signaling in this disease.

THE ROLE OF RXR SELECTIVE RETINOIDS IN APOPTOSIS AND DIFFERENTIATION

V. Horn et al. (pages 1071-1077) report that RAR and RXR selective retinoids act in concert to induce apoptosis and neuronal differentiation in P19 embryonal carcinoma cells. These findings favor a model in which RXR, heterodimerized with RAR, plays an active role in mediating retinoid signals, rather than acting as a silent partner.

3,4-DIDETHYDRORETINOIC ACID AND NEURONAL DEVELOPMENT

All-trans 3,4-didehydroretinoic acid (ddRA) is a vitamin A metabolite that has been found in avian, but not mammalian embryos. Repa et al. (pages 1078-1084) demonstrate that ddRA is as effective as all-trans retinoic acid in supporting the survival and differentiation of NGF-treated embryonic chick sympathetic neurons. It is concluded that ddRA functions through a retinoic acid receptor (RAR)-mediated pathway, and that chick and murine RARs are functionally equivalent.

AGE, DIETARY RESTRICTION AND RETINOL ABSORPTION

Hepatic stores of retinoids accumulate with age in rodents and humans. Chevalier et al. (pages 1085-1090) present evidence that the accumulation of retinoids seen in ad libitum-fed rats is not associated with an increase in retinol absorption. However, an enhanced retinol absorption was found in rats subjected to dietary restriction without malnutrition, as a result both of high lymph flow rate and long-term vitamin A intake per body weight. Furthermore, dietary restriction results in decreased plasma retinol levels, indicating that this dietary manipulation may influence various aspects of retinoid metabolism.

RARβ2, FURTHER EVIDENCE OF TUMOR SUPPRESSOR ACTIVITY

The retinoic acid receptor RARβ is located in a region of the short arm of human chromosome 3p, frequently deleted in lung cancer cells and has been shown to be generally inactivated in epidermoid lung cancer cell lines. Earlier work demonstrated that the RARβ isoform shows tumor suppressive activity upon de novo expression in epidermoid cancer cell lines. However, definitive proof that disruption of the RARβ pathway leads to lung carcinogenesis was needed. By the use of a transgenic mouse model expressing antisense RNA, Bérard et al. (pages 1091-1097) present evidence that reduction of the expression of the RARβ isoform positively correlates with high incidence of lung tumors.

ELECTROSpray LC-MIcS OF RETINOIDS

In this first application of electrospray liquid chromatography-mass spectrometry to retinoid analysis, vitamin A retinoids, including retinol, retinal, retinyl acetate and retinoic acid, were separated by using HPLC with a C30 reversed phase column and analyzed on-line using electrospray mass spectrometry. Limits of detection were 23 pg, 1.0 ng, 0.5 ng and 10 ng, for retinoic acid, retinal, retinol, and retinyl acetate, respectively. Retinoic acid formed predominantly deprotonated molecules; retinal formed abundant protonated molecules. Retinyl acetate and retinol fragmented extensively during electrospray ionization with loss of acetic acid or water, respectively, so that no molecular ion species were detected. (See van Breemen and Huang, pages 1098-1101).