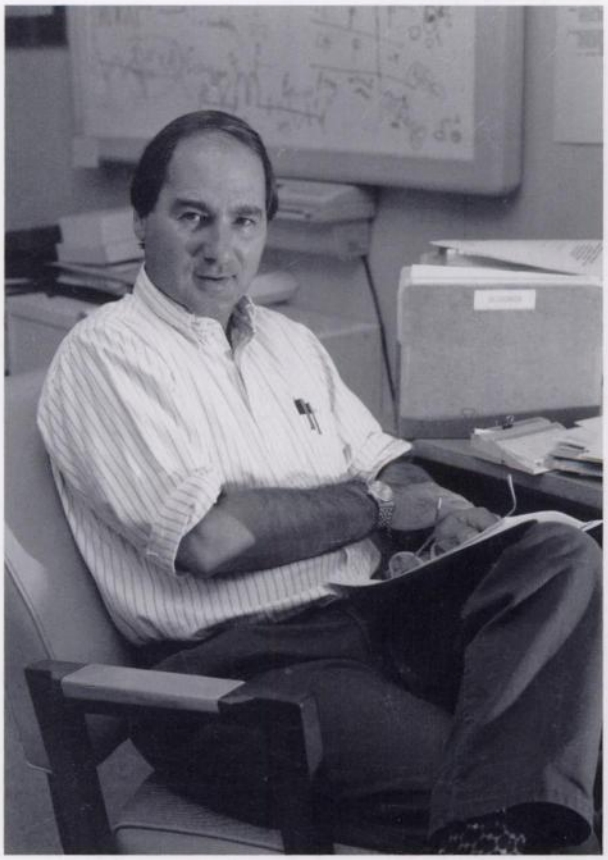
Cancer Research

AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH



May 1, 1995
Volume 55 • Number 9
PP. 1811–2005
ISSN 0008-5472 • CNREA 8

AACR SPECIAL CONFERENCE IN CANCER RESEARCH

Cytokines and Cytokine Receptors

October 14-18, 1995
The Sagamore, Bolton Landing (Lake George), New York

CONFERENCE CHAIRPERSONS

Steven Gillis / Seattle, WA
Douglas E. Williams / Seattle, WA

SCIENTIFIC PROGRAM

Keynote Address
Joost J. Oppenheim / Frederick, MD

Cytokines and Hematopoiesis
Manfred R. Keller / Ann Arbor, MI
Stewart D. Lyman / Seattle, WA
William P. Sheridan / Thousand Oaks, CA
Pamela Hunt / Thousand Oaks, CA
Connie J. Eaves / Vancouver, B.C, Canada
Katherine J. Turner / Cambridge, MA

Cytokines and Lymphopoiesis
Michael I. Lotze / Pittsburgh, PA
David H. Lynch / Seattle, WA
Mary K. Kennedy / Seattle, WA
Teresa M. Foy / Lebanon, NH

Cytokines and Infectious Disease
Steven A. Miles / Los Angeles, CA

Cytokine Receptors - Biological and Clinical Implications
Marc Feldmann / London, England
Thomas A. Waldmann / Bethesda, MD

Cytokine Signal Transduction
Tadamitsu Kishimoto / Osaka, Japan
Klaus Pfizenmaier / Stuttgart, Germany
Melanie K. Spriggs / Seattle, WA

Inhibition of Cytokine Procession as a Means of Therapeutic Intervention
Roy A. Black / Seattle, WA
David J. Pickup / Durham, NC

Additional Speakers to be Announced

Applicants are encouraged to submit abstracts for poster presentation.

Information and Application Forms

American Association for Cancer Research
Public Ledger Building, Suite 816
150 South Independence Mall West
Philadelphia, PA 19106-3483
215-440-9300 215-440-9313 (FAX)

AACR SPECIAL CONFERENCE IN CANCER RESEARCH

The Molecular Basis of Gene Transcription

December 2-6, 1995
Hotel Del Coronado
San Diego, CA

CONFERENCE CHAIRPERSON

Tom Curran / Nutley, NJ

PROGRAM COMMITTEE

Anjana Rao / Boston, MA

Danny F. Reinberg / Piscataway, NJ

CONFERENCE PROGRAM

Keynote Address
James E. Darnell / New York, NY

Signaling
Ronald M. Evans / La Jolla, CA
Anjana Rao / Boston, MA
Tom Curran / Nutley, NJ

Basic Mechanisms
Danny F. Reinberg / Piscataway, NJ
Robert Tjian / Berkeley, CA
Robert G. Roeder / New York, NY
Richard A. Young / Cambridge, MA

Structure
Alanna Schepartz / New Haven, CT
Stephen K. Burley / New York, NY
Nikola P. Pavletich / New York, NY

Higher Order Organization
James T. Kadonaga / La Jolla, CA
Nouria Hernandez / Cold Spring Harbor, NY

Repression
Jasper D. Rine / Berkeley, CA
Frank J. Rauscher, III / Philadelphia, PA
Michael S. Levine / La Jolla, CA

Activation
Bernard F. Mach / Geneva, Switzerland
Robert N. Eisenman / Seattle, WA
Michael R. Green / Worcester, MA

Cell Cycle
Joseph R. Nevins / Durham, NC
Brian Dynlacht / Charlestown, MA

Additional Speakers to be Announced

Application Deadline: September 18, 1995

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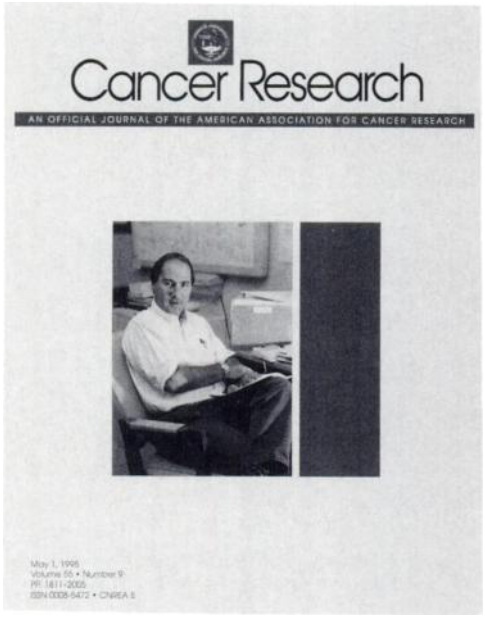
COVER LEGEND



Hormonally active xenobiotics exhibit estrogen-like activities that have both developmental and physiological actions most clearly related to controlling reproduction in females. Their source can be dietary, such as phytoestrogens (*e.g.*, coumestrol and genestein), or environmental (*e.g.*, *o,p*-dichlorodiphenyltrichloroethane and polychlorinated biphenyl) (Am. J. Clin. Nutr., *40:* 569–578, 1984; Toxicol. Appl. Pharmacol., *14:* 358–367, 1969; Mol. Pharmacol., *33:* 120–126, 1988), produced as pesticides or from manufacturing processes. A noticeable feature in evaluating the chemical properties of estrogenic agents is their structural diversity. Estrogen elicits its biological actions by interacting with a receptor protein contained within the nucleus of target cells. The estrogen receptor has been characterized as a member of the steroid retinoid nuclear receptor superfamily. These proteins act as ligand-inducible transcription factors stimulating gene regulation in responsive cells. The level of activity is dependent on the binding affinity of the receptor for a particular compound. Weakly active compounds are bound by the receptor with the lowest affinities. Receptor-mediated estrogen action also can be stimulated by other signaling mechanisms, such as growth factors. This could broaden the mechanistic possibilities to include the action of xenobiotics on other signaling pathways in addition to direct interactions with the estrogen receptor.

It is still debated whether estrogens act as initiators, promoters, or both, with regard to breast cancer; in any case, many breast cancers, as well as nonmalignant reproductive tract conditions such as endometriosis, are hormonally responsive, which makes estrogenic exposure an important component of their etiology. Prenatal estrogen exposure is known to produce hypospadias and cryptorchidism. Recent reports have hypothesized a link between the observed increase in testicular tumors and lower sperm counts in humans and possible prenatal and neonatal estrogen exposure (Lancet, *341:* 1392–1395, 1993). Part of the difficulty in evaluating a possible link is the lack of understanding of the role(s) for estrogen in males.

There are also reported estrogenic effects on wildlife populations related to fertility and sexual development. Wildlife exposed to the pesticide DDT have exhibited hypospadias and male infertility resulting from low sperm counts. Experimental studies in rats and mice with *o,p*-DDT have shown *in vivo* estrogenic activity. Other types of simple alkyl-substituted phenols (*e.g.*, 4-octylphenol and 4-nonylphenol), which are nonionic surfactants present in detergents, are environmentally persistent, affecting fish populations in contaminated waters (Chem. and Ecol., *8:* 275–285, 1994).

Estrogenic xenobiotics (*e.g.*, nonylphenol and bisphenol A) are also contaminants of laboratory plasticware, and materials used in the plastic manufacturing process have been found to alter the growth of MCF-7 breast cancer cells due to their estrogenic activity (Endocrinology, *132:* 2279–2286, 1993; Environ. Health. Perspect., *92:* 167–173, 1991). The biological activities are weak but potentially significant considering that 300,000 tons of alkylphenol polyethoxylates are introduced into the environment each year.

A major unresolved question is the impact of environmental estrogens on human disease, as well as the mechanisms of the associated link between estrogens and cancer. Although wildlife populations have been affected, there is no analysis of tumors or cancers in the exposed populations. Additionally, identifying and evaluating exposed human populations is much more difficult. Epidemiological studies will be required to critically evaluate and establish the relevance of these exposures. Both human and experimental studies must be done before the causative role of environmental estrogens and various hormonally dependent cancers can be assessed. It should at least be considered, however, that the effects that are seen in wildlife may be an early indication of the consequences of human exposures (*Chemically Induced Alteration in Sexual and Functional Development: Wildlife Human Connection.* Princeton, NJ: Princeton Scientific Publ. Co., 1992).

Evaluating the hormonal activity of these environmental xenoestrogens requires consideration of their bioavailability, lipophobicity, metabolism, and pharmacokinetics, which are not yet totally understood and most likely will be different from those of steroidal estrogens. Studies need to be conducted to evaluate these parameters relevant to those of established estrogenic agents. In addition to the above-mentioned chemical and pharmacological properties of the xenoestrogens, the hormonal activities of compound mixtures and the effect of persistent dosing need to be determined. A single agent or chemical may be weak and have a low threshold of activity, but mixtures of environmental compounds could produce a noticeable effect by synergism. In fact, it has been reported that some drinking water sources have as many as 20 chemically related alkylphenolic compounds (J. Environ. Anal. Chem., *47:* 167–180, 1992).

Kenneth S. Korach (*cover*) is Chief of the Receptor Biology Section at the National Institute of Environmental Health Sciences (NIEHS). He received his Ph.D. degree in Endocrinology from the Medical College of Georgia and was a Postdoctoral Fellow in Biological Chemistry at Harvard Medical School. Since joining the NIEHS in 1976, he has been investigating basic mechanisms of environmental estrogen action in the reproductive tract and bone tissues. During this time, he has studied the role of the estrogen receptor in mediating hormonal responses in uterine tissue; characterized estrogen receptor and hormonal responsiveness during early development; described coupling of growth factor and nuclear receptor signaling pathways; investigated estrogen carcinogenesis and toxicity; and created mouse lines using transgenic technologies for evaluating the estrogen receptor in endocrine regulation and hormonal carcinogenesis.

We are indebted to Dr. Korach for the information and photograph used for this cover feature.

Sidney Weinhouse