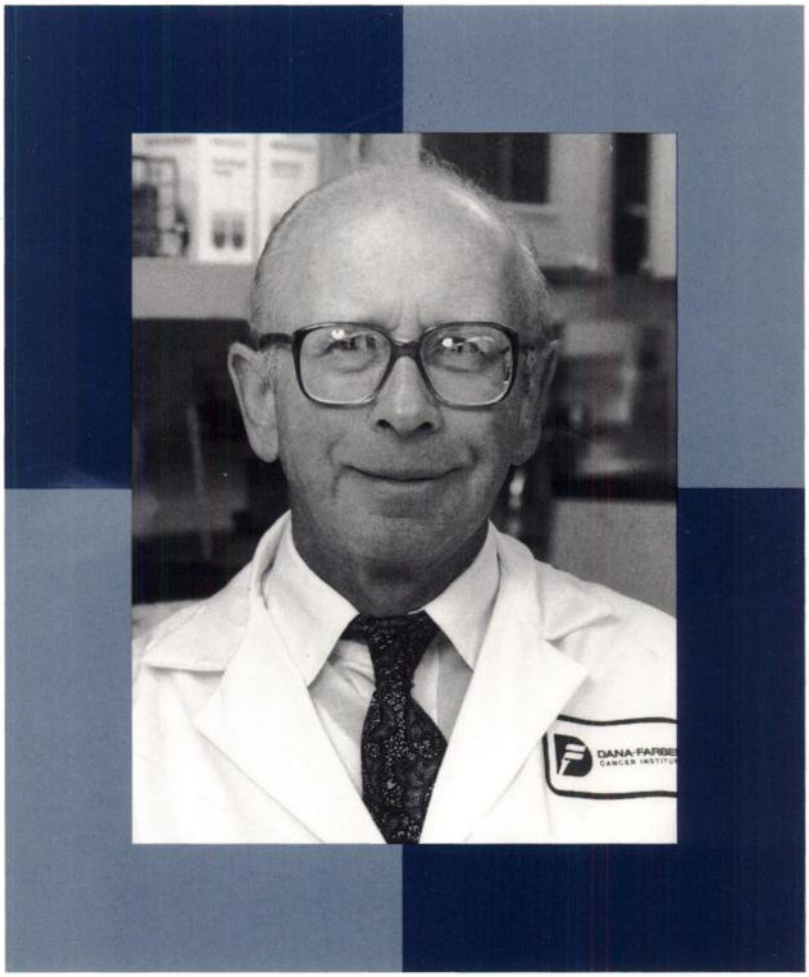
Cancer Research

AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH



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AACR SPECIAL CONFERENCE IN CANCER RESEARCH

Disrupted Transcription Factors in Cancer

January 17-21, 1997
Hotel Del Coronado
San Diego, CA

CONFERENCE CHAIRPERSONS
Peter K. Vogt / La Jolla, CA
Frank J. Rauscher, III / Philadelphia, PA

SCIENTIFIC PROGRAM

Keynote Address
Carlo M. Croce / Philadelphia, PA

Basic Transcriptional Mechanisms
Robert Tjian / Berkeley, CA
Danny F. Reinberg / Piscataway, NJ
Arnold J. Berk / Los Angeles, CA

Development, Negative Regulators
Peter Gruss / Gottingen, Germany
David M. Livingston / Boston, MA
Eric N. Olson / Dallas, TX
Stuart Orkin / Boston, MA
Jean Y. J. Wang / La Jolla, CA
Grace Gill / Boston, MA

Solid Tumors I
Gilles Thomas / Paris, France
Christopher T. Denny / Los Angeles, CA
David Ron / New York, NY
Cory Abate-Shen / Piscataway, NJ

Leukemias I
Terry H. Rabbitts / Cambridge, England
Michael L. Cleary / Stanford, CA
Thomas A. Look / Memphis, TN
Richard J. Baer / Dallas, TX
Gary Gilliland / Boston, MA
Mark P. Kamps / La Jolla, CA

Solid Tumors II
Riccardo Dalla Favera / New York, NY
Frederic G. Barr / Philadelphia, PA
Garrett M. Brodeur / Philadelphia, PA
Saraswati Sukumar / Baltimore, MD

Leukemias II
Janet D. Rowley / Chicago, IL
Ronald M. Evans / La Jolla, CA
Paul P. Liu / Ann Arbor, MI
Yoshiaki Ito / Kyoto, Japan
Laurie H. Glimcher / Boston, MA

Clinical Applications
Samuel Waxman / New York, NY
Pier Pellicci / Milan, Italy
Phil Koeffler / Los Angeles, CA

Applicants are encouraged to submit abstracts for poster presentation.

Application deadline: November 1, 1996

Information and Application Forms

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Philadelphia, PA 19106-3483

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CARCINOGENESIS FROM ENVIRONMENTAL POLLUTION: ASSESSMENT OF HUMAN RISK AND STRATEGIES FOR PREVENTION

Joint Meeting Organized by the American Association for Cancer Research (AACR) and the International Agency for Research on Cancer (IARC)

With the Collaboration of the Hungarian Cancer Society

October 6-9, 1996
Hotel Gellért
Budapest, Hungary

CONFERENCE CHAIRPERSONS
Frederica Perera / New York, USA
Paul Kleihues / Lyon, France

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Alán Pintér / Budapest, Hungary
Manfred F. Rajewsky / Essen, Germany
David Zaridze / Moscow, Russia

SCIENTIFIC PROGRAM

Keynote Address
Curtis C. Harris / Bethesda, USA

Cancer Incidence and Etiology
Witold A. Zatoński / Warsaw, Poland
Frederica Perera / New York, USA
J. Carl Barrett / Research Triangle Park, USA
Helmut Bartsch / Heidelberg, Germany

Air, Water, Food, and Soil Contamination
Radim J. Šrám / Prague, Czech Republic
Joellen Lewtas / Research Triangle Park, USA
Wieslaw Jedrychowski / Cracow, Poland
Olav Axelson / Linköping, Sweden

Ambient, Environmental, and Occupation Exposure and Cancer Risk
Mieczyslaw R. Chorąży / Gliwice, Poland
Alán Pintér / Budapest, Hungary
Kimmo Peltonen / Helsinki, Finland
Monica C. Hollstein / Heidelberg, Germany
Kari Hemminki / Stockholm, Sweden

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Paolo L. Vineis / Turin, Italy
Stephen S. Hecht / Valhalla, USA
Krystyna Frenkel / New York, USA
Bernadette Schoket / Budapest, Hungary

Strategies for Prevention
Waun Ki Hong / Houston, USA
I. Bernard Weinstein / New York, USA
Anna Tompa / Budapest, Hungary

Roundtable Discussion
Paul Kleihues / Lyon, France
Hans-Olov Adami / Uppsala, Sweden
Paolo Boffetta / Lyon, France
Edward Bresnick / Worcester, USA
Andrew E. Czeizel / Budapest, Hungary
Terri Damstra / Research Triangle Park, USA
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Kenneth Olden / Research Triangle Park, USA
Manfred F. Rajewsky / Essen, Germany
William A. Suk / Research Triangle Park, USA
David Zaridze / Moscow, Russia

Applicants are encouraged to submit abstracts for poster presentation.

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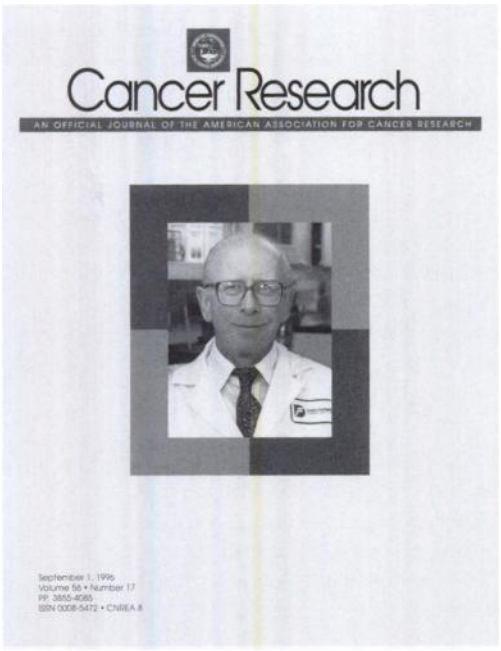
COVER LEGEND



Featured on this issue's cover is Arthur B. Pardee, a distinguished molecular biologist, who has been the recipient of many honors for his pioneering investigations on regulatory mechanisms, initially with bacteria and then with mammalian cells (summarized in Adv. Cancer Res., *65:* 213–228, 1994; Protein Science, *3:* 1136–1139, 1994).

In his studies with *Escherichia coli*, Dr. Pardee discovered numerous major mechanisms for regulating enzyme activity, synthesis, and cell proliferation. One such mechanism is feedback inhibition of biochemical sequences, in which a product made after a half-dozen steps of the pathway of pyrimidine synthesis inhibits the first enzyme in the sequence. When overproduced, this product shuts down the whole pathway at its start, thereby providing a very tight control that avoids waste. Remarkably, the inhibitor and substrate do not look at all alike. A solution to this problem of apparent nonspecificity is that the enzyme comprises interacting proteins. The substrate binds to the catalytic partner and the inhibitor to the regulatory one, an initial example of allostery.

Another mechanism, discovered while Dr. Pardee was on sabbatical with Jacques Monod and Francois Jacob, is repression, in which a negatively regulating repressor protein binds to an enzyme's DNA and shuts down its transcription. This binding is released when a substrate-like molecule combines with the repressor and transcription starts.

Dr. Pardee also found links between macromolecular syntheses, such as stringent control, in which nucleic acid synthesis (as well as protein synthesis) depends upon available amino acids. Conversely, protein synthesis requires continual nucleic acid synthesis, a concept that was a forerunner of the discovery of mRNA. He discovered ribosomes in bacteria and isolated and crystallized the first active transmembrane transport protein.

In the 1960s, Dr. Pardee began to investigate deranged regulation in cancer, particularly the question of what goes wrong in cancers so that mammalian cells grow when and where they should not. A central idea is that proliferation depends upon switches between resting and growing states. His suggestion in 1964 that interactions of extracellular factors with membrane are important in the growth of cancer was far ahead of its time because growth factor receptors had not yet been discovered. Much evidence now supports his early hypothesis (done while on sabbatical with Sir Michael Stoker) that the restriction (R) point mechanism located in late G_1 phase of the cell cycle, which limits onset of DNA synthesis, is the major subsequent intracellular control of cell proliferation. The cell cycle is not tightly controlled after a cell has passed the R point of no return. Dr. Pardee showed that this R point process requires a protein in sufficient quantity for DNA synthesis to be initiated. This protein has a short half-life in normal cells and is stabilized in tumor cells. A cancer cell thereby more easily proceeds beyond R than does a normal cell.

Dr. Pardee and colleagues studied control of the R protein by using transcription of mouse thymidine kinase (TK) as a marker for transition from G_1 to S. TK, like DNA-related events, is under the same general control by growth factors and inhibitors as is DNA synthesis itself. Because TK mRNA appears at the restriction point, one can apply molecular genetics. A minimal promoter DNA sequence determines turning on G_1-S-phase specific transcription of TK. A promoter-binding protein complex appears strikingly at this time, which includes retinoblastoma-related p107 protein, E2F, cyclin E, and cdk2 kinase. In transformed tumor-forming cells, a very different picture emerges, *i.e.*, TK controls and complexes are deranged.

Cyclins, particularly D and E, are major contributors to growth control. Alterations of cyclins in tumor cells allow G_1-S transcriptions more readily. Cyclins can appear at inappropriate times in cancer cells, so that one cyclin replacing another could signal faulty initiation of cell proliferation. Dr. Pardee concluded that cyclin E is most probably the R point protein. It is a single protein in normal cells, but it is grossly altered in size, amount, and activity in cancer cells. Changed cyclin E protein was seen in all the cancer tissues examined *in vivo versus* normal adjacent biopsy material. It may provide diagnostic and prognostic cancer markers.

Recently, Dr. Pardee has invented a general method, differential display, to detect the mRNAs expressed in a given cell type. Comparisons of displays of mRNA markers from different cells permit isolation of genes that are expressed differently in normal *versus* tumor cells. Hundreds of researchers are now using this method, and they have isolated numerous genes of interest.

Dr. Pardee received his B.S. in Chemistry from the University of California, Berkeley, in 1942, and his Ph.D. in Chemistry from the California Institute of Technology in 1947. While at Cal Tech, he worked with Nobel Laureate Linus Pauling. His postdoctoral studies with Van R. Potter, on one of the first Merck Fellowships, were in the area of cancer enzymology.

Dr. Pardee has authored nearly 400 original articles, reviews, and chapters, and he has received many honors throughout his distinguished career, including his election to membership in the prestigious National Academy of Sciences. His other achievements include his receipt of the Paul Lewis Award of the American Chemical Society (1960), the Sir H. A. Krebs Medal (1973), and the Rosensteil Medal (1975).

He has been a member of the American Association for Cancer Research (AACR) since 1979. He served on its Board of Directors from 1983–86 (*ex officio* from 1986–88) and on the Policy Committee from 1984–88, acting as its Chairperson in 1986–87. In addition, he has been active on the Awards Committee, chairing it in 1986–87, and he served on the Rhoads Award Committee in 1983–84 and the Clowes Award Committee in 1988–89. Most significantly, Dr. Pardee served as AACR President from 1985–86. Under his leadership, the first efforts to strengthen the Association's programs in molecular biology and genetics were launched. Now, the AACR membership includes thousands of molecular cancer researchers, and advances in molecular biology permeate all of the Association's scientific programs.

Sidney Weinhouse