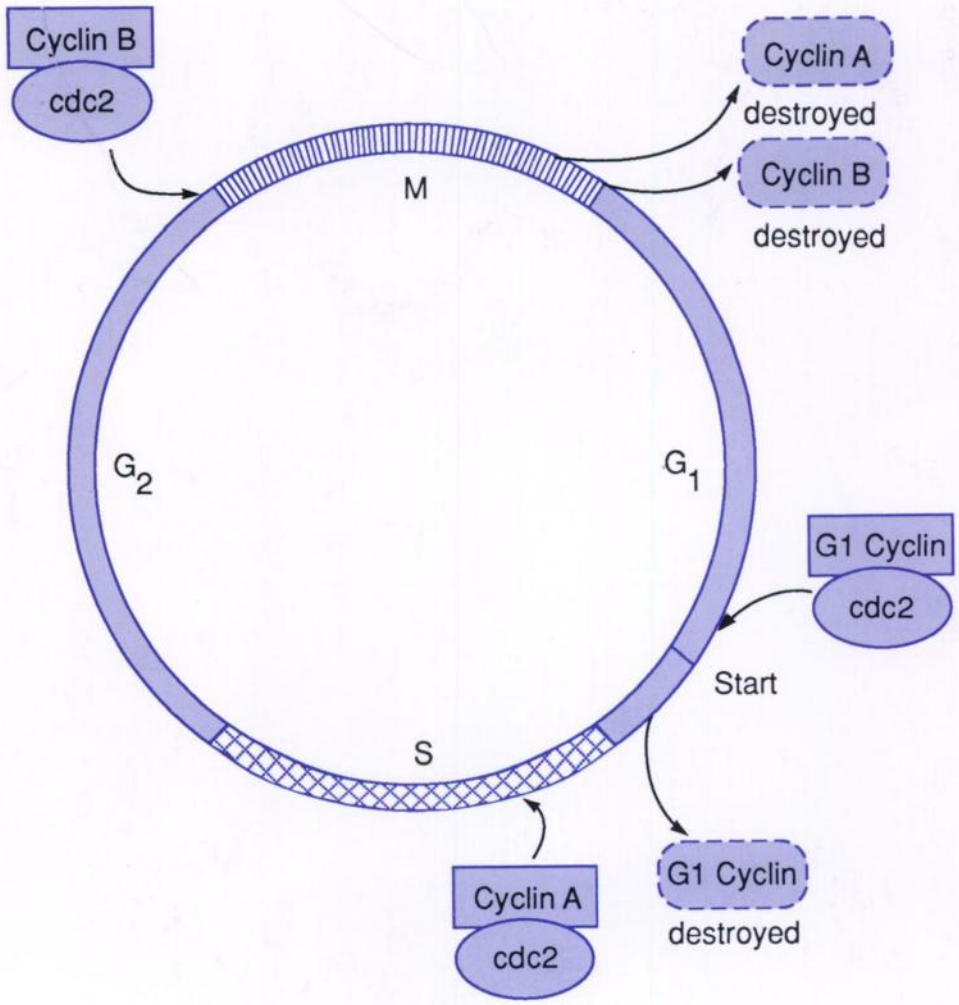
August 1, 1992

Cancer Research

OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

VOLUME 52 • NO. 15 • PP 4069–4296

ISSN 0008-5472 • CNREA 8



THE WENDY AND EMERY REVES INTERNATIONAL BREAST CANCER SYMPOSIUM

RECENT ADVANCES IN THE BIOLOGY AND TREATMENT OF BREAST CANCER AND OTHER MALIGNANCIES

OCTOBER 16-17, 1992

The University of Texas Southwestern Medical Center
5323 Harry Hines Boulevard, Dallas, Texas 75235-9060
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BRINGING TOGETHER EXPERTS IN THE FIELDS OF BASIC AND CLINICAL ONCOLOGY TO PRESENT RECENT ADVANCES IN THE MOLECULAR BIOLOGY, DIAGNOSIS, AND TREATMENT OF CANCER WITH PARTICULAR EMPHASIS ON BREAST CANCER.

SPEAKERS

SAMUEL BRODER, National Cancer Institute; PETER M. HOWLEY, National Cancer Institute; MARY-CLAIRE KING, University of California, Berkeley; MARC W. KIRSCHNER, University of California, San Francisco; GEORGE KLEIN, Karolinska Institute, Stockholm; PHILIP LEDER, Harvard Medical School, Howard Hughes Medical Institute; ARNOLD J. LEVINE, Princeton University; DAVID M. LIVINGSTON, Dana-Farber Cancer Institute; PAUL A. MARKS, Memorial Sloan-Kettering Cancer Center; STEVEN L. MCKNIGHT, Carnegie Institute of Washington; JOHN D. MINNA, University of Texas Southwestern Medical Center at Dallas; WILLIAM P. PETERS, Duke University Medical Center; JOSEPH SCHLESSINGER, New York University Medical Center; CHARLES J. SHERR, St. Jude Children's Research Hospital; PHILIP THORPE, UT Southwestern Medical Center; ELLEN S. VITETTA, UT Southwestern Medical Center.

SPONSORED BY THE SUSAN G. KOMEN FOUNDATION AND
THE UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER AT DALLAS

FOR GENERATIONS CANCER PLAGUED THIS FAMILY. THEN WE CAME INTO THE PICTURE.

It's a tragic coincidence that cancer has taken so many members of this family over the years.

It took Frank Domato in 1961. Patricia O'Hara Brown in 1974. And Serafino Gentile in 1982.

But the fact that the chain of tragedies has now been broken is no coincidence at all.

Over the last 40 years, research programs supported by the American Cancer Society have made increasing progress in the treatment, detection and prevention of cancer.

In 1985 alone, the Society funded over 700 projects conducted by the most distinguished scientists and research institutions in the country.

So it's no coincidence that in 1986, cancer did *not* take Debra Gentile—Frank Domato's great-granddaughter. Just as it didn't take hundreds of thousands of others who have been successfully treated for the disease.

You see, we are winning.
But we need you to help keep it that way.

AMERICAN CANCER SOCIETY
Help us keep winning.

AACR SPECIAL CONFERENCE IN CANCER RESEARCH

Genetics of Cancer

November 4-8, 1992
Marriott Hilton Head Resort, Hilton Head, South Carolina

Supported by a Generous Grant from the General Motors Cancer Research Foundation

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SCIENTIFIC PROGRAM

Keynote Address
Robert A. Weinberg / Cambridge, MA

Inherited Cancer Genes
Bruce A.J. Ponder / Cambridge, England
Raymond L. White / Salt Lake City, UT
Frank McCormick / Emeryville, CA
Arnold J. Levine / Princeton, NJ
Webster K. Cavenee / La Jolla, CA

Genetic Mechanisms
Carmen Sapienza / La Jolla, CA
Carlo M. Croce / Philadelphia, PA
Neal G. Copeland / Frederick, MD

Molecular Genetics of Mitosis
George F. Vande Woude / Frederick, MD
Carol Greider / Cold Spring Harbor, NY
Andrew Murray / San Francisco, CA
David Beach / Cold Spring Harbor, NY
Erich A. Nigg / Lausanne, Switzerland

Genetic Instability
Geoffrey Wahl / San Diego, CA
C. Thomas Caskey / Houston, TX
Walton Fangman / Seattle, WA

Application Deadline: August 10, 1992

Genetics and Cell Commitment
Stuart A. Aaronson / Bethesda, MD
Mariano Barbacid / Princeton, NJ
M. Geoffrey Rosenfeld / La Jolla, CA
David Anderson / Pasadena, CA
Leo Sachs / Rehovot, Israel

Animal Models
Mario Capecchi / Salt Lake City, UT
Douglas Hanahan / San Francisco, CA
Erwin Wagner / Vienna, Austria

Programmed Cell Death
Stanley J. Korsmeyer / St. Louis, MO
H. Robert Horvitz / Cambridge, MA
John T. Isaacs / Baltimore, MD
Peter Kramer / Heidelberg, Germany

Information and Application Forms

American Association for Cancer Research
Public Ledger Building
620 Chestnut Street, Suite 816
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AACR SPECIAL CONFERENCE IN CANCER RESEARCH

Molecular and Biochemical Methods in Cancer Epidemiology and Prevention - The Path Between the Laboratory and the Population

September 23-26, 1992
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SCIENTIFIC PROGRAM

Keynote Addresses
Paul A. Schulte / Cincinnati, OH
Mortimer L. Mendelsohn / Livermore, CA
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Assessment of Exposure to Genotoxic Agents
Stephen S. Hecht / Valhalla, NY
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Measurement of Endogenous Sex Steroid Hormones in Breast and Prostate Neoplasia
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Disorders of Immune Function in Human Carcinogenesis
Charles Rabkin / Bethesda, MD
Ian T. Magrath / Bethesda, MD
David T. Purtilo / Omaha, NE

Evaluation of the Applications of Biochemical and Molecular Markers in Epidemiological Studies
Barbara S. Hulka / Chapel Hill, NC
Neil E. Caporaso / Bethesda, MD
Nathaniel Rothman / Bethesda, MD
Arthur Schatzkin / Bethesda, MD
Mark Schiffman / Bethesda, MD

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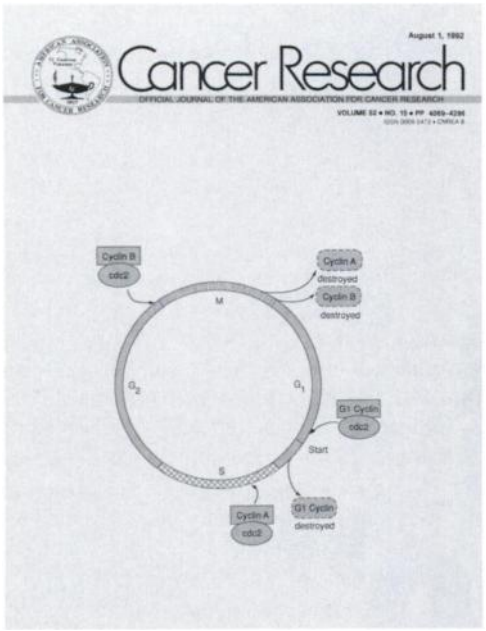
COVER LEGEND



Although the cell cycle is known to proceed via well-defined sequential events between successive mitoses, the underlying details have remained an enigma until the past few years. Now a flood of exciting new findings is clarifying molecular mechanisms and is beginning to reveal long-suspected relationships between disturbances of cell cycle control and cancer development. Major advances are the recognition that the molecular control of specific stages of the cycle is fundamentally similar in all eukaryotes from yeast to humans and that competitive interplay between certain oncogenes and suppressor genes and their encoded proteins may be involved in the lack of control of cell proliferation in cancer. It now appears that protein complexes act by protein phosphorylation to advance cells at possibly three sites: at start, when cells are committed to divide; at S, the DNA synthesis phase; and at the initiation of mitosis. These new findings are discussed in several recent articles and reports [Science (Washington DC) *245:* 252, 1990; *252:* 1253, 1490, 1991; Trends Biol. Sci., 10/90, pp. 378; and Cell, *60:* 487, 1990].

Current conceptions got their start some 20 years ago when Masui and Markert and, independently, Smith and Ecker discovered the maturation promoting factor, a substance that caused oocytes of *Xenopus laevis* to undergo premature cell division and to promote mitosis of ordinary somatic cells. The next advance occurred with the discovery by Hunt and Rosenthal of a protein that increased greatly in sea urchin eggs after fertilization and the content of which fluctuated between cell divisions. They named it cyclin. In the meantime, Nurse and colleagues [Nature (Lond.), *292:* 558, 1976] isolated a gene from the yeast, *Schizosaccharomyces pombe* (called *cdc2* for cell division cycle) which on mutation caused interruption of cell division. Further key events were the discovery that the *cdc2* gene protein product (p34cdc2) was required at two points in the yeast cell cycle, that similar gene products regulate division in other cell types including human, and that these proteins have protein kinase activity toward many diverse substrates and are activated at multiple stages of the cell cycle.

Parallel studies revealed that the cyclins are a family of proteins which periodically accumulate during the cell cycle and are abruptly destroyed at mitosis (as depicted on the cover); they bind to p34cdc2 and this complex comprises the maturation promoting factor. The cyclins are probably regulatory subunits for the p34cdc2 and similar protein kinases. According to Draetta *et al.* (Trends Biol. Sci., 10/90, pp. 378), the initiation of DNA synthesis is activated by protein kinase activity of the p34cdc2 protein by combination with an as yet unidentified cyclin X. Similar activation for the S-G_2 transition occurs by complexing of p34cdc2 with cyclin A and that for G_2-M occurs by combination of p34cdc2 with cyclin B. The basic process appears to be similar in a wide range of cell types.

The cancer connection is becoming clearer. Vande Woude and coworkers have shown that the *mos* protooncogene product is required for maturation promoting factor activation during meiotic maturation of frog and mouse oocytes [Sagata *et al.*, Nature (Lond.), *335:* 519, 1988; Paules *et al.*, Proc. Natl. Acad. Sci. USA, *86:* 5395, 1989]. In addition, the mos protein was shown to be an active component of cytostatic factor, an activity responsible for the arrest of vertebrate eggs at metaphase of meiosis II [Sagata *et al.*, Nature (Lond.), *342:* 512, 1989]. This arrest is believed to result from the stabilization of maturation promoting factor by cytostatic factor. This led to the hypothesis that the transforming activity of certain oncogenes in somatic cells is due to the expression of their M-phase activities during interphase [Sagata *et al.*, Nature (Lond.), *333:* 519, 1988].

Further recent evidence implicates the retinoblastoma (*Rb*) gene, a tumor suppressor gene in cell cycle function, as reported at the 1991 Cold Spring Harbor Symposium [May 29–June 30, 1991, Science (Washington DC), *252:* 1492, 1991]. In addition to its involvement in cancer of the eye, loss or inactivation of this gene has been observed in cases of breast and lung cancer. Several investigators have shown that Rb protein can bind to cell cycle components and can be phosphorylated by cdc2 kinases. This protein also binds to several transcription factors and to the *myc* oncogene protein, which is involved in gene transcription. The picture that emerges is that the Rb protein inhibits cell division by binding to transcription factors, but this "brake" is released when Rb protein is phosphorylated and transcription factors are activated by release from Rb binding. If these findings are verified by further work, the control of cell division will be enormously simplified, to be dependent on the competitive actions of phosphorylated and dephosphorylated proteins.

The assistance of George Vande Woude is gratefully acknowledged.

Sidney Weinhouse