1941

AACR Launches *Cancer Research*

JAMES B. MURPHY, MD, EDITOR, 1941-1944

A rare combination of administrator and scientist, Dr. Murphy made significant discoveries and led the principal cancer organizations of his time. He received his MD from Johns Hopkins in 1909, then worked with psychiatrist Adolf Meyer in New York. Dr. Florence Sabin recruited him to the Rockefeller Institute to work with Peyton Rous; he remained at Rockefeller for the rest of his career. Dr. Murray elucidated the role of lymphocytes in immunity to transplantable cancer, demonstrating that embryos do not reject transplanted tissue, and identified growth-stimulating and growth-inhibiting substances in normal tissue. In World War I, he helped develop mobile laboratories for field hospitals. He was AACR President in 1921 and served on the National Advisory Cancer Council.

CANCER RESEARCH

A MONTHLY JOURNAL OF ARTICLES AND ABSTRACTS REPORTING CANCER RESEARCH

VOLUME 1 JANUARY, 1941 NUMBER 1

Foreword

During the last two decades there has been a marked development of interest in the cancer problem as manifested by the number of workers now active in the field and the increased support which has become available for the work. The resultant significantly larger volume of reports of fundamental investigations has emphasized the need of improved facilities for prompt publication. In response to this need three Foundations which are contributing largely to the support of cancer investigation have accepted the responsibility of launching this new journal in cooperation with the American Association for Cancer Research. The start of this venture is being financed principally by these three organizations. An Advisory Board has been organized consisting of the Chairman of the Editorial Committee of the journal and one representative each from The International Cancer Research Foundation, The Jane Coffin Childs Memorial Fund for Medical Research, The Anna Fuller Fund, and The American Association for Cancer Research. The International Cancer Research Foundation has agreed to assign title to the journal and to hold the copyright in its name.

The members of CANCER RESEARCH will be in the hands of an Editorial Committee made up of representatives of the several fields which are involved in cancer research. The present policy is to publish original reports of laboratory and clinical investigations, abstracts of papers on cancer research appearing in other journals, and a bibliography with abstracts, of current clinical reports. The abstract section is a continuation of the valuable service which was rendered for a number of years by the American Journal of Cancer.

A number of articles which had been accepted for publication by the American Journal of Cancer have been transferred to CANCER RESEARCH with the consent of the authors except in a few instances where it has not been possible to establish contact with them under existing conditions. The date of the transfer is considered as the date of receipt by this journal.

It is hoped that the new publication will receive wide support from all of those interested in advancing knowledge of the cancer problem.

Population Study Shows UV Exposure Did NOT Cause More Skin Cancer

HIGHLY CITED ARTICLE

The Relation of Solar Radiation to Cancer Mortality in North America*

Frank L. Apperly, M.D.

The study by Apperly revealed statistical evidence for an inverse relationship between UV light exposure and non-skin cancer rates in North American populations. Since then, epidemiological studies describing the impact of geography and sun exposure on cancer incidence and so-called "cancer immunity" have attributed these effects to UV light-induced vitamin D production, a potential cancer prevention strategy currently undergoing clinical investigation.

TABLE I: MORTALITY FROM CANCER IN CITIES ACCORDING TO LATITUDE, 1908-12 *

Number of cities	Degrees of latitude	Deaths from cancer	Rate per 100,000 population
35	60 N—50 N	119,374	105.7
48	50 N—40 N	121,216	92.4
24	40 N—30 N	37,451	78.1
7	30 N—10 N	5,696	42.3
4	10 N—10 S	1,056	40.9
7	10 S —30 S	3,040	37.7
5	30 S —40 S	11,048	89.8

* Modified from Hoffman (5).

Metastatic Prostate Cancer Is Androgen Dependent

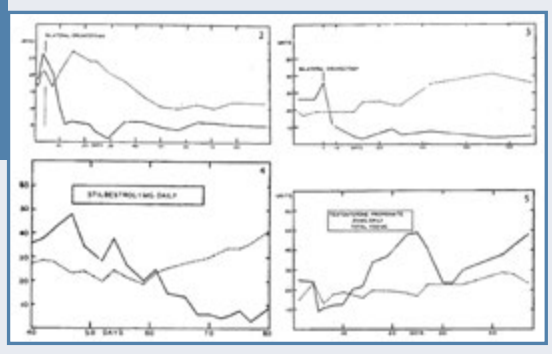
FIGURE 2. The effect of castration on serum phosphatases in metastatic carcinoma of the prostate in the case of P. R. Acid phosphatase ——; alkaline phosphatase - - - -.

FIGURE 3. The effect of castration on serum phosphatase values in metastatic carcinoma of the prostate in the case of J.R. Acid phosphatase ——; alkaline phosphatase - - - -.

FIGURE 4. The effect of estrogen injection, I mgm, stilbestrol for 23 days, on serum phosphatases in metastatic carcinoma of the prostate in the case of O. A. Acid phosphatase ——; alkaline phosphatase - - - -. Ordinates, units per 100 cc. of serum; abscissae, time in days.

FIGURE 5. The effect of androgen injection, testosterone propionate, 25 mgm. daily for 18 days, on serum phosphatases in metastatic carcinoma of the prostate in the case of O. A. Acid phosphatase ——; alkaline phosphatase - - - -.

Huggins and Hodges reported seminal findings demonstrating that metastatic prostate cancer is androgen-dependent and can be managed with hormonal treatments. This work paved the way for hormone-based therapeutic strategies, such as androgen-deprivation therapy, to become clinical standards for the treatment of advanced prostate cancer today.



HIGHLY CITED ARTICLE

Studies on Prostatic Cancer

I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate*

Charles Huggins, M.D., and Clarence V. Hodges, M.D.

Leukemia Retransplantable in Chickens

HIGHLY CITED ARTICLE

A Transmissible Lymphoid Tumor of the Chicken*

Carl Olson, Jr., D.V.M.

Carl Olson established a transmissible model of leukemia in which tumors could be faithfully recapitulated through serial transplantation into recipient chickens. These findings, among others in the avian tumor field, provided preliminary indications that viruses could cause human cancers, forming the basis for groundbreaking discoveries in tumor virology and the development of the first cancer vaccines.

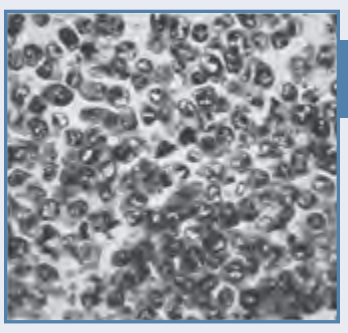


FIGURE 6. Section of tumor developed at site of implant in 10th serial passage. Magnification X710.

SCIENTIFIC PUBLISHING CENTENNIAL

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1943

Caloric Restriction May Reduce Cancer Incidence

HIGHLY CITED ARTICLE

Further Studies on the Tumor-Promoting Action of Fat*†

P. S. Lavik, Ph.D., and C. A. Baumann, Ph.D.

Associations between obesity and cancer incidence have long been recognized. Lavik and Baumann reported that the tumor-promoting effects of a high-fat diet could be directly attributed to caloric intake. Caloric restriction is now considered one of the most effective approaches to cancer prevention and continues to inspire drug discovery efforts in the tumor metabolism field.

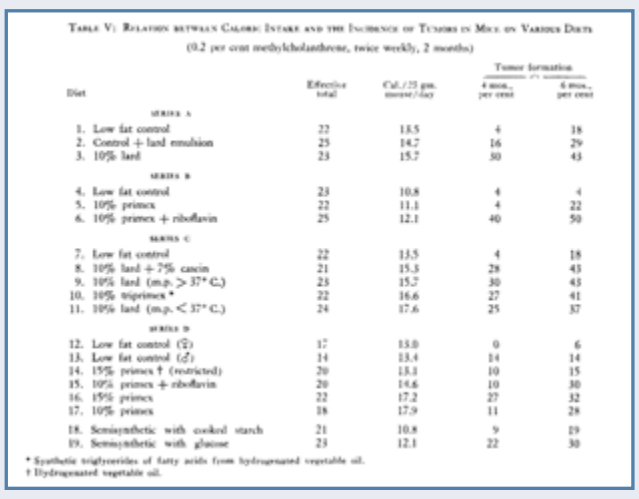


TABLE V: RELATION BETWEEN CALORIC INTAKE AND THE INCIDENCE OF TUMORS IN MICE ON VARIOUS DIETS

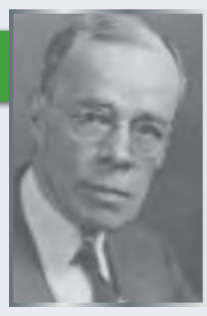
(0.2 per cent methylcholanthrene, twice weekly, 2 months)

Diet	Effective total	Cal./15 gm. mouse/day	Tumor formation: 4 mos., per cent	Tumor formation: 6 mos., per cent
SERIES A				
1. Low fat control	22	13.5	4	18
2. Control + lard emulsion	25	14.7	16	29
3. 10% lard	23	15.7	30	43
SERIES B				
4. Low fat control	23	10.8	4	4
5. 10% primex	22	11.1	4	22
6. 10% primex + riboflavin	25	12.1	40	50
SERIES C				
7. Low fat control	22	13.5	4	18
8. 10% lard + 7% casein	21	15.3	28	43
9. 10% lard (m.p. > 37° C.)	23	15.7	30	43
10. 10% triprimex *	22	16.6	27	41
11. 10% lard (m.p. < 37° C.)	24	17.6	25	37
SERIES D				
12. Low fat control (♀)	17	13.0	0	6
13. Low fat control (♂)	14	13.4	14	14
14. 15% primex † (restricted)	20	13.1	10	15
15. 10% primex + riboflavin	20	14.6	10	30
16. 15% primex	22	17.2	27	32
17. 10% primex	18	17.9	11	28
18. Semisynthetic with cooked starch	21	10.8	9	19
19. Semisynthetic with glucose	23	12.1	22	30

* Synthetic triglycerides of fatty acids from hydrogenated vegetable oil.
† Hydrogenated vegetable oil.

1945

In the Post-War Years, Several Editors Serve Short Terms

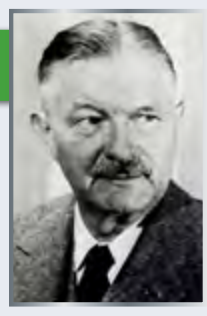


WILLIAM WOGLOM, MD, EDITOR, 1945-1946

A pioneer in the study of tumor transplantation, Dr. Woglom was known for his many thoughtful, scholarly treatises such as the 1913 review, "The Study of Experimental Tumors." Dr. Woglom received his MD from the College of Physicians and Surgeons of Columbia University in 1901 and worked in pathology and bacteriology in several New York hospitals before he joined Columbia's cancer research institute, which became the George Crocker Special Research Fund. The Crocker Fund provided financial aid to two early AACR journals. Dr. Woglom was AACR Secretary-Treasurer from 1917 to 1935 and President in 1936. His sustaining vision throughout his career was that "effectual interference with incessantly proliferating cells will become a reality."

STANHOPE BAYNE-JONES, MD, EDITOR, 1946-1947

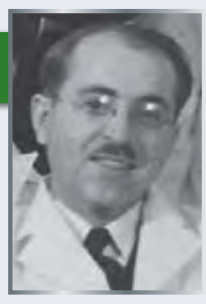
In both world wars, Dr. Bayne-Jones received the country's highest decorations, achieving the rank of brigadier general. He served as dean of Yale University School of Medicine between the wars and headed the Jane Coffin Childs Memorial Fund, which later supported *Cancer Research*. Soon after he became *Cancer Research* Editor he left to be president of the board of the New York Hospital Cornell Medical Center. He chaired the Surgeon General's committee that produced the first report on smoking and health in 1964.



BALDUIN H. LUCKÉ, MD, EDITOR, 1947-1948

A chair of pathology at the University of Pennsylvania Medical School, where he spent his career, Dr. Lucké studied tumor growth by transplanting adenocarcinoma cells from the kidney into the eyes of leopard frogs. After intensive study he concluded that the causative agent of kidney cancer was a virus. His laboratory would subsequently become a nexus of studies on the viral causes of cancer.

PAUL E. STEINER, MD, PHD, EDITOR-IN-CHIEF, 1949



Both pathologist and historian, Dr. Steiner received his MD and PhD from Northwestern Medical School and spent over 17 years at the University of Chicago School of Medicine, finishing his career at the Hospital of the University of Pensylvania. He was AACR President in 1951. He wrote several histories, including the highly praised Common Valor, which detailed civil war officers' reactions to wounds and disease. As *Cancer Research* Editor, Dr. Steiner noted that in order to maintain quality he was prepared for "receiving adverse criticism" and the "loss of all [his] friends."

1947

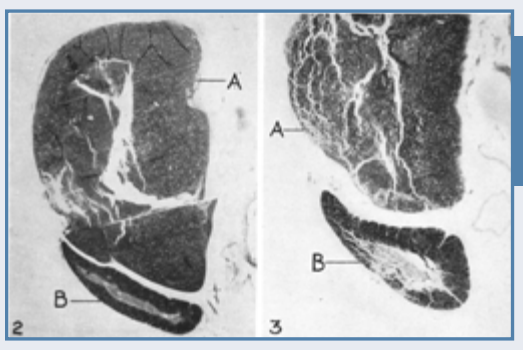
Radiation Studies Show Thymus Involved in Lymphoma Development

HIGHLY CITED ARTICLE

Observations on Radiation-Induced Lymphoid Tumors of Mice*

Henry S. Kaplan, M.D.

Henry Kaplan's report on the effects of age on radiation-induced lymphoid cancer brought to light the involvement of the thymus during lymphoma development. These findings helped to transform the field of radiation oncology, when years later, Kaplan made several groundbreaking medical contributions to the design of radiotherapy devices, the discovery of a leukemia-inducing virus, and the cure for Hodgkin's lymphoma.



FIGURES 2 AND 3. Sections through the thymus reveal, in each case, a normal lobe (B) and a greatly enlarged lobe (A) which is replaced by a lymphoid tumor. In both instances the other lymphoid and visceral tissues were not involved.

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1950 Founder of McArdle Laboratory Named Editor

HAROLD P. RUSCH, MD, EDITOR-IN-CHIEF, 1950-1964

A leader in cancer research, Dr. Rusch is best known for having launched, directed, and expanded the McArdle Laboratory for Cancer Research at the University of Wisconsin. In his 26 years at McArdle, he nurtured the ground-breaking research of outstanding faculty, including future members of the National Academy and a Nobel Laureate. In his own research, Dr. Rusch identified the wavelength of ultraviolet light that contributes to skin cancer and studied the influence of diet on hepatic cancer, the stages of tumor formation, and the biochemical aspects of cell growth and differentiation. He was the longest-serving Editor of *Cancer Research* and served as AACR President in 1953. Late in his career, he started and directed the University of Wisconsin Cancer Center. Dr. Rusch was ably assisted in his role as editor-in-chief by Elizabeth C. Miller, PhD, assistant editor from 1953 to 1963 and by Ilse L. Riegel, PhD, assistant, associate, or managing editor from 1955 to 1964.

Elizabeth C. Miller

Ilse L. Riegel

1953 Tar from a Smoking Machine Causes Cancer in Mice

HIGHLY CITED ARTICLE

Experimental Production of Carcinoma with Cigarette Tar*

Ernest L. Wynder,† Evarts A. Graham, and Adele B. Croninger

In a landmark study, Wynder and colleagues showed that laboratory mice directly exposed to cigarette tar developed cancer, establishing tobacco tar as a carcinogenic substance. These findings provided the critical link between cancer incidence and smoking, subsequently fueling numerous anti-tobacco initiatives whose impact is evident today and that continue to influence public policy, education campaigns, and healthcare.

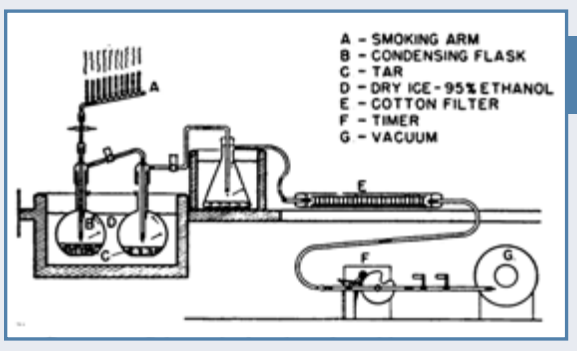

CHART 1. Schematic drawing of smoking apparatus.

Annual Meeting Proceedings Published as April Issue of Journal

1958 Toxicity Studies Help Establish Safe 5-fluorouracil Regimens

HIGHLY CITED ARTICLE

Clinical Studies with 5-Fluorouracil*

A. R. Curreri, Fred J. Ansfield, Forde A. McIver,† Harry A. Waisman, and Charles Heidelberger

In this early study on the toxicity of 5-fluorouracil (5-FU) in patients, Curreri and colleagues provided the framework for subsequent studies to establish a safe dose, formulation, and schedule of administration. Since then, the development of 5-FU prodrugs and combination chemotherapy regimens has helped maintain 5-FU as an important treatment for various malignancies.

TABLE 4

RESULTS IN 55 PATIENTS TREATED AT DOSAGES THAT PRODUCED TOXICITY

Type of neoplastic malignancy	Improved	Unimproved	Too early to evaluate
Adenocarcinoma of breast	3	1	1
Adenocarcinoma of stomach			2
Scirrhous carcinoma of stomach			1
Carcinoma of colon	1	1	3
Transitional-cell carcinoma of neck	1		
Carcinoma of pancreas			1
Carcinoma of thyroid			1
Carcinoma of cervix		2	2
Carcinoma of lung		1	2
Carcinoma of prostate			1
Squamous-cell carcinoma of tonsil		1	
Carcinoma of ovary	1	1	1
Reticulum-cell sarcoma, retroperitoneal	1		
Synovio-sarcoma	1		
Osteogenic sarcoma of skull			1
Malignant hepatoma	1		
Malignant melanoma		1	1
Glioblastoma multiforma			1
TOTAL:	9	8	18

SCIENTIFIC PUBLISHING CENTENNIAL

1916-2016

AACR American Association for Cancer Research

1958

Candidate Drugs Can Be Screened Using Cultured Human Cells

HIGHLY CITED ARTICLE

Cytotoxicity in Human Cell Cultures as a Primary Screen for the Detection of Anti-Tumor Agents*

HARRY EAGLE AND GEORGE E. FOLEY

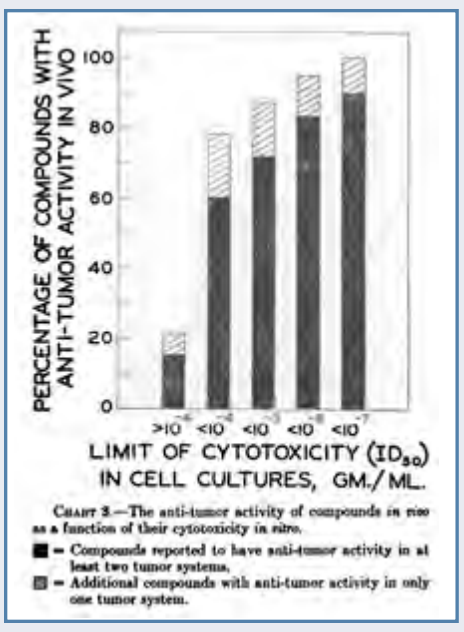

CHART 3.—The anti-tumor activity of compounds in vivo as a function of their cytotoxicity in vitro.
■ = Compounds reported to have anti-tumor activity in at least two tumor systems.
▩ = Additional compounds with anti-tumor activity in only one tumor system.

Eagle and Foley proposed that candidate anticancer agents could be initially screened in cultured human cells based on their finding that most drug-induced effects observed in vivo could be recapitulated in vitro. Consequently, the use of cell culture as a platform for the initial testing of new therapeutic strategies has become the cornerstone of all drug discovery and development programs.

1961

Chromosomal Abnormalities Described in Leukemias

HIGHLY CITED ARTICLE

The *in Vivo* Chromosome Constitution of Marrow from 14 Human Leukemias and 60 Nonleukemic Controls*

A. A. SANDBERG, T. ISHIHARA, T. MIWA, and T. S. HAUSCHKA

Sandberg and colleagues reported that a subset of leukemias exhibited chromosomal abnormalities compared with nonmalignant cells. The discovery of the human chromosome number a few years before this study followed by extensive karyotyping of neoplastic cells began to illuminate cancer as a genetic disease. Chromosomal aberrations remain crucial diagnostic and prognostic markers that continue to inform clinical decision making today.

FIGURE 7. Pseudodiploid karyotype with an atypical set of 46 chromosomes from the marrow of male patient #16 with acute myeloblastic leukemia. This karyotype lacks either the Y or one of the G22 chromosomes which may have been translocated. The C group contains one too many chromosomes for a male set.

FIGURE 8. Hypertetraploid metaphase with 99 chromosomes from the marrow of male patient #8 with acute lymphoblastic leukemia. The modal cell type of this leukemia had 97 chromosomes, X2500.

1962

Editorial Published on the Effects of Atomic Testing

1963

Non-Genetic Changes Affect Regulatory Circuits

HIGHLY CITED ARTICLE

Metabolic Regulatory Circuits and Carcinogenesis

HENRY C. PITOT AND CHARLES HEIDELBERGER*

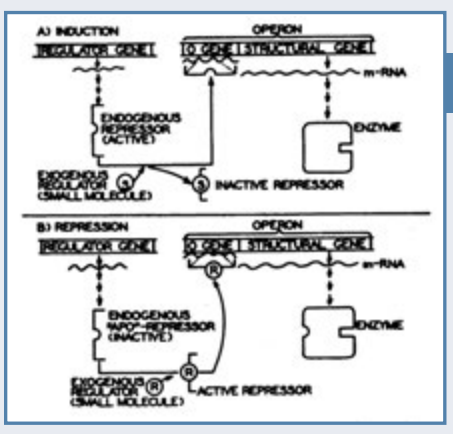

CHART 3. Basic regulatory circuit.

Cancer was historically thought to arise as a consequence of carcinogenic agents directly interacting with DNA. Pitot and Heidelberger proposed an alternative theory in which they presented multiple scenarios that demonstrated how regulatory circuits responsible for cell growth, division, and metabolism could be affected by non-genetic changes. Ultimately, this work contributed to the classification of carcinogens as genotoxic or non-genotoxic.

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1965

Fels Institute Head Named Editor

MICHAEL B. SHIMKIN, MD, EDITOR, 1965-1969

As early as the 1950s, Dr. Shimkin led studies that linked smoking to lung cancer and noted the influence of diet, drinking, and smoking on cancer development. He was a rigorous epidemiologist and believed in medical evidence, showing in several studies that mastectomy was no more effective than limited surgeries in some breast cancers. Dr. Shimkin earned his MD from the University of California, San Francisco, and was one of the first research fellows of the new National Cancer Institute. He subsequently had many NCI roles, including scientific editor of *JNCI*. A noted medical historian, Dr. Shimkin introduced historical covers for *Cancer Research* and continued as Cover Editor after moving to San Diego in 1969.

1966

Historical Covers First Appear

1967

Mantel Test Helps in Analyzing Cancer Clusters

HIGHLY CITED ARTICLE

Cancer Research

VOLUME 27 FEBRUARY 1967 NUMBER 2

The Detection of Disease Clustering and a Generalized Regression Approach

NATHAN MANTEL

Cancer clusters enable the identification of epidemiological factors underlying disease incidence within a defined geographical region and time period. Nathan Mantel developed a statistical model to explore the association between related disease characteristics and their spatio-temporal distribution. The Mantel test served as a foundation for population geneticists to develop and refine models that helped to explain genetic divergence among populations.

Hodgkin's Regimen Achieves 86% Remission

HIGHLY CITED ARTICLE

Intensive Combination Chemotherapy and X-irradiation in Hodgkin's Disease*

JOHN H. MOXLEY III, [1] VINCENT T. DeVITA, [2] KIRKLAND BRACE, [4] AND EMIL FREI III [2]

Moxley and colleagues reported their seminal finding that a regimen of four chemotherapeutic agents combined with radiotherapy could achieve 86% remission in patients with Hodgkin's lymphoma. This study aroused subsequent modifications to the dosage, composition, and duration of the treatment program, an outcome that was ultimately deemed as the cure for this type of lymphoma.

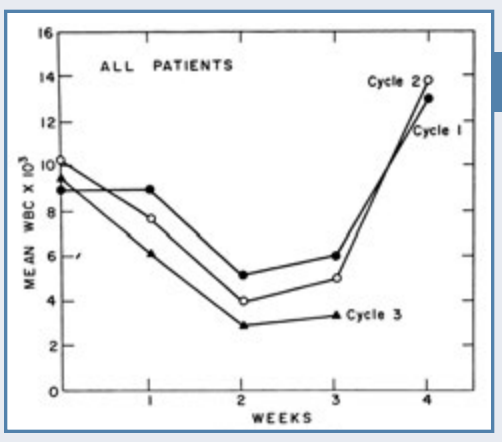


CHART 1. Mean weekly WBC for all patients.

1968

AACR Bans Smoking in Annual Meeting Rooms

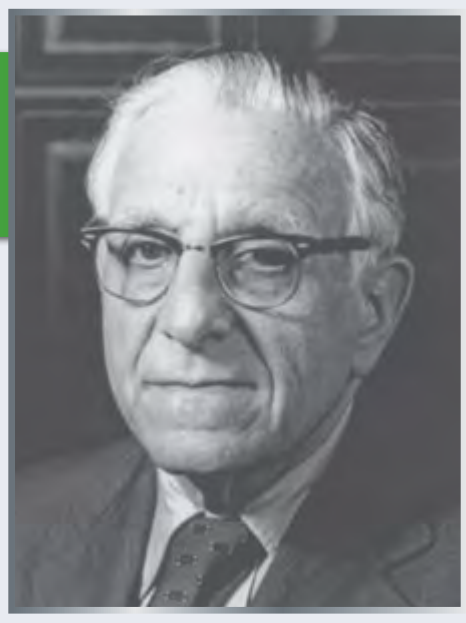
SCIENTIFIC PUBLISHING CENTENNIAL

1916-2016

AACR American Association for Cancer Research

1969

Biochemist Named Editor



SIDNEY WEINHOUSE, PHD, EDITOR, 1969-1979

The first basic scientist to become Editor, Dr. Weinhouse received his PhD in organic chemistry from the University of Chicago. Early in his career he pioneered the use of radioactive isotopes in research. Later at the Institute for Cancer Research and then at the Fels Institute of Temple University in Philadelphia, he was known for elucidating isoenzyme expression in cancer tissues and for major advances to the understanding of metabolism and cancer as well as his pioneering advocacy of more biochemical research to advance the cancer field. Dr. Weinhouse conducted some of the first detailed studies on glucose turnover in mammals, which had important implications for diabetes. After completing his last term as Editor, he continued as Cover Editor for 12 years.

1972

Editorial Supports the War on Cancer

1974

Vasculature Important to Tumor Angiogenesis

HIGHLY CITED ARTICLE

Tumor Angiogenesis Factor[1]

Judah Folkman

Judah Folkman presented evidence supporting the importance of the vasculature to tumor growth, yet the identity of the diffusible factor responsible for promoting tumor angiogenesis remained unknown at the time. The eventual discovery of VEGF was instrumental to understanding the nature of a tumor's lifeline, and the ensuing development of antiangiogenic therapies significantly altered the course of cancer treatment.

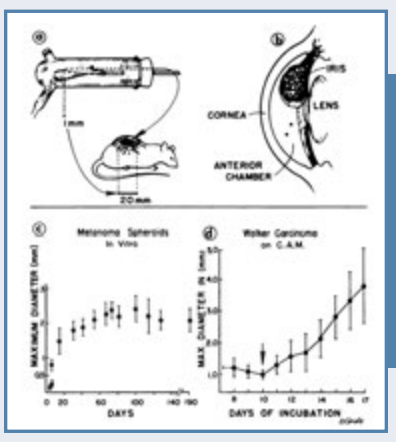


CHART 1. Summary of 4 experiments in which lack of angiogenesis leads to tumor dormancy. In a, tumor grown in isolated perfused organ remains avascular and stops growing at about 1 mm diameter. When reimplanted into the host animal, the tumor is vascularized and grows rapidly to a much larger size. In b, tumors floating in the anterior chamber of the rabbit eye become dormant at about 0.9 cu mm but, when placed against the iris, new vessels penetrate the tumor; rapid tumor growth follows. In c, tumor spheroids grown in soft agar in which the medium is continually renewed also reach a dormant phase and will not expand beyond a mean diameter of 2 to 3 mm. In d, tumors grown in the chorioallantoic membrane (*C.A.M.*) of the chick embryo are not vascularized for 3 days after implantation. During the avascular phase, the mean diameter is approximately 1 mm. After new capillaries penetrate the tumor nodule (*arrow*), rapid tumor growth begins.

Errors in DNA Replication Lead to Malignant Transformation

HIGHLY CITED ARTICLE

Errors in DNA Replication as a Basis of Malignant Changes[1]

Loeb and colleagues proposed that malignant transformation occurs due to errors in DNA replication, leading to oncogenic mutations. Subsequent studies elucidated the concept of driver, mutator, and passenger mutations, which accumulate in tandem to generate cell variants with selective growth advantages. The systematic cataloguing of cancer mutations now offers an unprecedented opportunity to investigate the genetic mechanisms underlying malignant phenotypes.

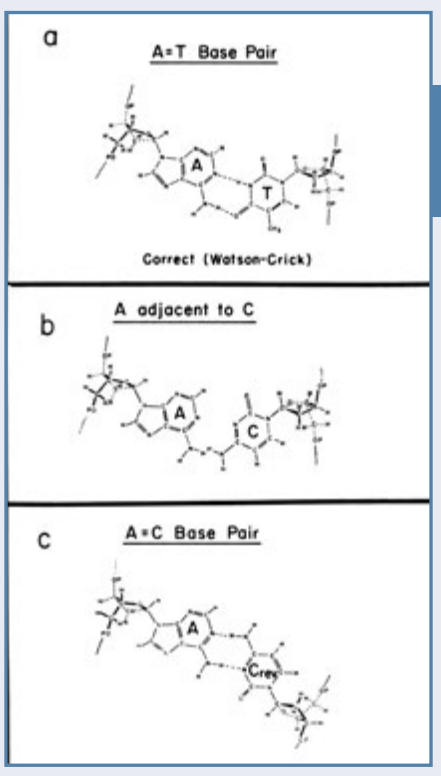


CHART 1. Complementary and noncomplementary base pairing. A, Watson-Crick A-T base pair; B, substitution of cytidine for thymidine without changing molecular coordinates; C, rotation of cytidine as proposed by Donohue (13).

SCIENTIFIC PUBLISHING CENTENNIAL

1916-2016

AACR American Association for Cancer Research

1975

Journal Receives Its First Impact Factor (3.391)

1977

ER-Negative Breast Cancer More Likely to Recur

HIGHLY CITED ARTICLE

Estrogen Receptor as an Independent Prognostic Factor for Early Recurrence in Breast Cancer[1]

William A. Knight, III,[2] Robert B. Livingston, Ernest J. Gregory, and William L. McGuire

Department of Medicine, University of Texas Health Science Center, San Antonio, Texas 78284

SUMMARY

The usefulness of estrogen receptor measurements in primary breast tumors in the prediction of early recurrence was examined in a series of 145 patients. The absence of estrogen receptor in such tumors was associated with early recurrence independent of other known prognostic factors such as axillary lymph node status and tumor size.

INTRODUCTION

It is now established that patients with metastatic breast cancer are more likely to respond to endocrine therapy if their tumors contain ER+ (4). In addition, a survival advantage has been reported for those patients with ER+ tumors (7). We therefore inquired whether this survival advantage might be reflected in a longer interval between primary mastectomy and first recurrence. We now report that those breast cancer patients whose tumors are determined to be ER− at the time of primary mastectomy recur early and constitute a very high risk group.

MATERIALS AND METHODS

From September 1973 until September 1976, 145 women underwent modified or radical mastectomy for potentially curable breast cancer. All patients were operated on by the same group of San Antonio surgeons and had their tumors analyzed for ER by a Dextran-coated charcoal assay in the same laboratory (3). Tumors with levels less than 10 biochemically cytosol protein were considered ER−; those with greater than 10 fmoles were ER+. Clinical information was obtained from the patient records and pathology reports. Recurrence of disease was documented by liver, bone, and brain scans, chest X-rays, and biopsy, if lesions were accessible. Statistical significance between groups was determined by the χ^2 test.

RESULTS

Chart 1 presents the recurrence data in 145 breast cancer patients. We found a statistically significant increase in early recurrence in those patients with ER− primary tumors. The median follow-up was 16 months in ER− and 18 months in ER+ patients.

We next considered whether the early recurrence in ER− patients might be due to a maldistribution of patients with positive axillary nodes, tumor size or location, etc. Table 1 presents the patient characteristics, ER distribution, and recurrence rate at 18 months. The majority of the patients were over 50 years old; these were less frequently ER−. However, regardless of age, early recurrence was more frequent in the ER− group.

ER− tumors were distributed evenly in all categories of axillary node status. Recurrence was clearly related to ER− status in each case, although only in the group of 4 or more positive nodes were the results statistically significant at $p < 0.05$. The higher overall recurrence rate among positive-node patients emphasizes the predominance of ER− recurrences, as seen in Chart 2. Some positive-node patients received additional postoperative radiotherapy and/or a variety of adjuvant therapies including chemotherapy and endocrine therapy. ER− tumors were distributed similarly in these groups, and again the recurrences were found predominantly in the ER− patients. Tumor size and location of the primary lesion are also considered in Table 1. Although ER− tumors were equally distributed among these subgroups, recurrences once again predominated in the ER− patients.

DISCUSSION

Watt et al. (7) have reported that ER− patients are more likely to develop visceral metastases and have a shorter survival. We have examined the prognostic implication of an ER− tumor determined at primary mastectomy and have found that recurrence is higher in ER− patients regardless of primary size, location of the tumor, number of involved axillary nodes, age, or adjuvant therapy.

The distribution of ER− tumors was similar in all of the above groups, except for age, wherein a significantly larger percentage of ER− patients were under 50 years old, and as a group ER− patients had a median age that was 5 years younger than that of ER+ patients. Nevertheless, within both age groups recurrence was higher in ER− patients.

Meyer and Bauer (5) have reported that primary breast tumors with a high growth fraction, as represented by a high thymidine-labeling index, are more subject to early recurrence, and it has been suggested that such tumors

Knight and colleagues demonstrated that early recurrence of breast cancer was more likely in patients with ER-negative rather than ER-positive breast tumors, triggering the early classification of breast cancer and providing a basis for the molecular guidelines routinely used today to inform clinical strategy. The quest for new prognostic markers continues, especially for those tumor subtypes still lacking targeted therapies.

Table 1

Prognostic factors, estrogen receptors, and recurrences in breast cancer patients

	No. of patients	ER distribution (% ER−)	% recurrence at 18 mos. ER−	ER+
Total no. of patients	145	37 (54)[a]	34 (14)	14 (13)[b]
Age				
<50	48	48 (23)	35 (8)	8 (2)[c]
>50	97	32 (31)	36 (11)	17 (11)[c]
Tumor-infiltrated axillary nodes				
0	71	35 (25)	12 (3)	6.5 (3)
1–3	24	33 (8)	38 (3)	12.5 (2)
≥4	50	42 (21)	62 (13)	27 (8)[c]
Postoperative radiation	57	40 (23)	43 (10)	21 (7)
Adjuvant therapies[d]	41	34 (14)	43 (6)	19 (5)
No adjuvant therapy[d]	33	46 (15)	67 (10)	28 (5)[c]
Size of tumor				
<2 cm	27	33 (9)	33 (3)	0 (0)[b]
2–5 cm	79	37 (29)	31 (9)	14 (7)
Location of tumor				
Inner and central	28	32 (9)	56 (5)	26 (5)
Outer	79	41 (32)	28 (9)	4 (2)[b]

[a] Numbers in parentheses, number of patients in each group.
[b] Horizontal comparison, $p = 0.01$.
[c] Horizontal comparison, $p = 0.05$.
[d] Node-positive patients only.

1978

Photoradiation Therapy Deemed Safe and Effective

HIGHLY CITED ARTICLE

Photoradiation Therapy for the Treatment of Malignant Tumors[1]

Thomas J. Dougherty,[2] Jerome E. Kaufman, Abraham Goldfarb, Kenneth R. Weishaupt, Donn Boyle, and Arnold Mittleman

Department of Radiation Medicine (T. J. D., K. R. W., D. B.) and Surgical Oncology (J. E. K., A. G., A. M.), Roswell Park Memorial Institute, Buffalo, New York 14263

ABSTRACT

Administration of hematoporphyrin derivative i.v. followed by local exposure to red light has resulted in complete or partial response in 111 of 113 cutaneous or s.c. malignant lesions. Tumors treated have included carcinomas of the breast, colon, prostate, squamous cell, basal cell, and endometrium; malignant melanoma, myxoma fungoides; chondrosarcoma; and angiosarcoma. No type has been found to be unresponsive. In several cases complete clearing of chest wall metastasis has been achieved in treated areas. Deep-seated and pigmented tumors required a higher dose of drug for effective treatment than did the more superficial and nonpigmented lesions. A high therapeutic ratio between tumor and skin response has been obtained by allowing at least 3 days between drug injection and exposure to the therapeutic light for 2.5 mg/kg doses and at least a 5-day interval for 5.0 mg/kg doses.

INTRODUCTION

The combination of HPD[3] and red light (photoradiation therapy) is curative for a number of experimental tumor systems. For example we have reported previously nearly 50% long-term cures in the syngeneic DBA/2 Ha SMT mammary tumor system in mice (5). The success of this technique is due to the ability of HPD to accumulate (and/or be retained) to a higher degree in malignant tissue than in most other tissues and its ability to produce the cytotoxic agent, singlet oxygen, when activated by red light (photodynamic process) (16). These properties of HPD have been known for some time. Hematoporphyrin and HPD have been used extensively to aid in identification and localization of human cancers since their red fluorescence can be observed readily upon activation with blue light. Apparent selective HPD uptake has been demonstrated in a wide range of human and animal tumors (7, 12, 17). The ability of hematoporphyrin and HPD to act as photodynamic agents has been demonstrated in several systems (13). We have shown recently that the cytotoxicity of activated HPD probably results from intracellular formation of singlet oxygen (a short-lived, highly reactive state of the oxygen molecule) when cells containing the dye are exposed to visible light (16).

The combined properties of tumor localization and photoactivated toxicity of certain porphyrins provide the possibility of achieving a relatively localized tumoricidal effect with sparing of surrounding normal tissue.

The earliest attempt to use the photodynamic effect for treatment of human tumors was by Tappeiner and Jesionek in 1903 (14). Although favorable results were reported with eosin as the photosensitizing dye, no further reports were forthcoming. Diamond et al. (1) reported in 1972 that the crude hematoporphyrin, activated by white light, caused regression of an experimental glioma in rats.

At about the same time, we reported that fluorescein, activated by 488 nm light, could be used in a similar fashion to treat an experimental mammary tumor in mice (2, 3). Later we reported that cures could be obtained in experimental tumor systems with the use of HPD activated by red light (5). Tomioh et al. (15) reported in 1975 that acridine orange, activated by an argon laser, caused destruction of a mouse epithelial tumor. Kelly et al. (10) showed, in the next year, that specific destruction of a heterotransplant of human bladder carcinoma in mice could be obtained by local exposure to white light following HPD injection.

Because of the success in experimental animal tumor systems, we have initiated a clinical study of the efficacy of photoradiation in the treatment of various human tumors. We report here our results in the first group of 25 patients with cutaneous and s.c. tumors. A recent report of treatment of a single patient with bladder carcinoma by a method similar to ours has been reported by Kelly and Snell (9).

MATERIALS AND METHODS

HPD was prepared by a method similar to that of Lipson et al. (11). Hematoporphyrin hydrochloride (Roussel Corp., New York, N. Y.), 1 part, was dissolved in glacial acetic acid-sulfuric acid (19:1, by volume) and allowed to stand overnight at room temperature. The mixture was filtered by gravity through a Whatman No. 1 filter paper (1 to 5 ml depending on total volume) and neutralized to approximately pH 6.0 by addition of 3% sodium acetate solution. The precipitated material was recovered by filtration and washed extensively with distilled water until the washings were neutral. The solid was then dried in a vacuum to remove all traces of acetic acid and water and was stored in the dark in the solid state at −20°. This material had 3 components detectable by thin-layer chromatography (Brinkman Polygram SIL-N-HR plates, benzene-methanol-4:1, by volume) in a ratio of 15, 30, and 55% in increasing R_f. The material with the lowest R_f (10%) corresponds to a major peak in the crude hematoporphyrin hydrochloride. The other 2 components have been identified as a monoacetate (30%) and diacetate (55%) by using ^{14}C-labeled acid to

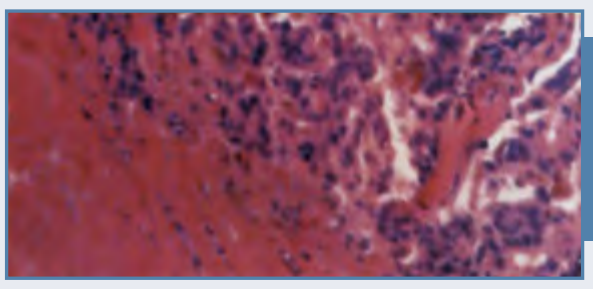


FIGURE 4. Case 2. Biopsy section taken across treatment field and into adjacent nontreated area, 7 days after treatment. Complete coagulation necrosis is apparent within treatment field (approximately 2 cm deep), and apparent viable melanoma cells are outside field.

Metastasis Shown as a Complex, Multistep Process

HIGHLY CITED ARTICLE

Tumor Heterogeneity and the Biology of Cancer Invasion and Metastasis[1]

Isaiah J. Fidler

Cancer Biology Program, National Cancer Institute Frederick Cancer Research Center, Frederick, Maryland 21701

Abstract

The development of a metastasis is dependent on an interplay between host factors and intrinsic characteristics of malignant tumor cells. The process of metastasis is highly selective, and the metastatic lesion represents the end point of many destructive events that only a few cells can survive. Neoplasms, which are predominantly heterogeneous, contain a variety of subpopulations of cells with differing metastatic potential. Furthermore, metastatic cell variants have been shown to preexist in murine neoplasms of old and recent origin. The possible existence of highly metastatic variant cells within a primary tumor suggests that we no longer should consider a neoplasm to be a uniform entity. Efforts to design effective therapeutic agents and procedures against malignant tumors should be directed toward the few but fatal metastatic subpopulations of cells.

Introduction

Metastasis is defined by Durland (6) as the transfer of disease from one organ or part to another not directly connected with it. The metastasis of cancer cells is one of the most devastating aspects of neoplasia; it is responsible for most therapeutic failures because patients succumb to multiple secondary tumor growths and not necessarily to the primary tumor. Major advances in surgical techniques, coupled with advances in general patient care, have increased the success of the resection of primary neoplasms. However, in the majority of patients with clinical cancer, excluding those with skin tumors, metastasis has already occurred at the time of diagnosis (50, 56, 58). Therefore, even the most extensive surgical procedures cannot hope to bring about a high "cure" rate. Short of the complete prevention of cancer, the urgent goal of the oncologist should be the prevention or the successful treatment of micrometastases.

Additional approaches to the therapy of disseminated disease may be forthcoming if the underlying pathogenesis of cancer metastasis can be clearly understood. The outcome of the metastatic process depends on the properties of both host and tumors, and the balance of these contributions probably varies in tumor systems (15, 58).

Animal models have proven invaluable in the elucidation of the host and tumor factors involved in determining the outcome of cancer metastasis. The proper utilization of such models may advance considerably our understanding of the biology of the phenomenon and, therefore, allow the development of new approaches to the therapy of disseminated disease.

We have recently developed one such animal model for quantitative studies of metastasis. Mice are given i.d. injections, in the external ear, of 0.05 ml of tumor cell suspension. Three to 4 weeks later, when the tumors are established, the ear is amputated at its base and the mice are allowed to survive. Six to 8 weeks later, the mice are killed and examined for the presence of lymph node or visceral metastases. In the model shown in Fig. 1a, 20,000 viable cells of the B16 melanoma, syngeneic to the C57BL/6 mouse, were injected into the medial surface of the external ear. The ear and growing tumor were amputated 3 weeks after i.d. injection. If the tumor mass contained no metastatic cells, the amputation of the ear would be curative. Alternatively, if the growing tumor contained some metastatic cells, which invaded blood vessels and lymphatics prior to amputation of the ear, the mice would eventually die of distant tumor growths. As seen in Fig. 1b, in some mice growth of tumor occurred in the lymph nodes regional to the ear, i.e., the cervical and submandibular nodes, and in the lungs. The components of this qualitative assay for the metastatic potential of murine neoplasms are shown in Fig. 1c. This model or procedure may also be useful for determining the metastatic potential of murine neoplasms or in studies that evaluate the therapy of spontaneous metastases.

Pathogenesis of Metastasis

The first steps in the pathogenesis of metastasis (Chart 1) are the local invasion of normal host tissues, penetration into lymphatics or blood vessels by malignant cells, and detachment. The actual mechanism for tumor cell invasion remains unclear. It probably depends on both tumor and host factors.

Tumor cells can spread by three major routes. The first involves spread by direct extension in which a tumor growing in a body cavity releases cells or fragments that can seed serosal and/or mucosal surfaces and develop into new growths. Two examples are lung metastatic tumors that enter the pleural cavity and malignant ovarian tumors that shed cells into the peritoneal cavity. Primary tumors of the central nervous system, although highly invasive, rarely produce metastases in organs outside the nervous system. The mode of their spread appears to be by direct extension or via the cerebrospinal fluid. The second and third modes of spread, which are the subject of this lecture, are via the lymphatic and hematogenous compartments of the circulatory system.

Clinical observations have suggested that carcinomas frequently spread and grow in the lymphatic system, whereas malignant tumors of mesenchymal origin spread

Isaiah Fidler presented evidence favoring the view that tumor cell subpopulations are highly heterogeneous in regards to their metastatic potential, only capable of executing successful dissemination after thriving under strong selection pressures exerted by the harsh tumor microenvironment. These observations continue to potentiate the perspective of metastasis as a complex, multistep process, requiring further characterization to enable successful therapeutic intervention.

Table 1

Heterogeneity of the B16 melanoma parent tumor for experimental metastasis

Source of cells[a]	Median no. of pulmonary metastases		No. of animals with extrapulmonary metastases
B16 parent line (60)[b]	40.5	(8–131)[c]	8/60 ovary, 11/60 lymph nodes, 6/60 liver, 4/60 kidney, 3/60 gut, 2/60 adrenal
Clone 16 (10)	3.5	(2–15)	0/10
Clone 15 (11)	5	(2–20)	1/11 lymph node
Clone 12 (9)	6	(0–34)	0/9
Clone 24 (9)	10	(5–29)	1/9 ovary, 1/9 liver, 1/9 lymph node
Clone 19 (10)	13	(0–42)	0/10
Clone 7 (10)	17	(0–43)	0/10
Clone 21 (8)	18	(1–48)	1/8 lymph node
Clone 18 (11)	36	(0–91)	0/11
Clone 5 (10)	45.5	(2–171)	0/10
Clone 6 (9)	99	(5–232)	0/9
Clone 17 (9)	150	(104–210)	0/9
Clone 3 (9)	214	(160–450)	1/9 lymph node
Clone 1 (9)	237	(73–321)	0/9
Clone 2(10)	254.5	(7–450)	0/10
Clone 13 (9)	260	(50–350)	2/9 ovary, 1/9 liver
Clone 14 (9)	>500		2/9 ovary
Clone 9 (10)	>500		6/10 lymph node, 2/10 adrenal, 1/10 kidney, 2/10 liver

[a] C57BL/6 mice were given injections in the tail vein of 50,000 viable single cells and killed 18 days later. The number of pulmonary tumor colonies was determined with the aid of a dissecting microscope.
[b] Numbers in parentheses, number of mice per group.
[c] Numbers in parentheses, range.

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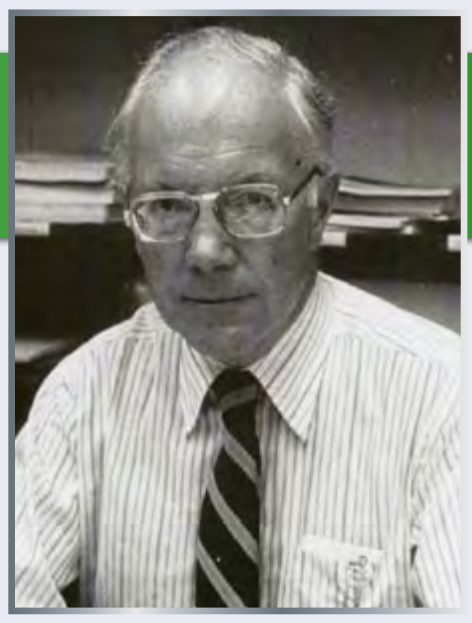
1980

Carcinogenesis Expert Named Editor



PETER N. MAGEE, MD, EDITOR, 1980-1989

Known for his pioneering discovery of the carcinogenic potential of N-nitrosamines and their mechanism of action, Dr. Magee conducted research that led to the first demonstration of carcinogen-DNA interactions. Others later showed that some DNA mutations and cancer types may be due to alkylation of the 6-oxygen of guanine, a fundamental finding that has since been extended worldwide. Nitrosamines can be formed in many foods treated with nitrite, and their potential carcinogenic effects often incite controversies about food safety and links to specific malignancies such as gastric cancer. The presence of nitrosamines in tobacco products has also added to the body of evidence linking smoking to cancer onset. Dr. Magee was the second director of the Fels Institute to serve as Editor.

Melanoma Cells Have Different Metastatic Potential

HIGHLY CITED ARTICLE

In Vitro Selection of Murine B16 Melanoma Variants with Enhanced Tissue-invasive Properties

FIGURE 4. Tumor cell suspension (0.3 to 0.4 ml) has been injected into the ductus deferens, and the urinary bladder is filled by retrograde flow. Hemostat occludes the penile urethra and ligature is 2-0 catgut.

The finding by Poste and colleagues that highly invasive subpopulations of melanoma cells could be isolated from a single tumor strengthened the concept that tumor cells are heterogeneous with varying metastatic potentials. Their methods for in vitro selection and propagation of invasive cell variants offered the opportunity to investigate metastatic behavior in an accessible and tractable manner.

1985

Foundation Laid for the Two-Hit Theory of Cancer Genetics

HIGHLY CITED ARTICLE

Perspectives in Cancer Research

Hereditary Cancer, Oncogenes, and Antioncogenes

Alfred G. Knudson, Jr.

During his studies on hereditary cancers, Alfred Knudson alluded to the idea that cancer is caused not only by activating mutations in oncogenes, but also by the loss or inactivation of "antioncogenes.x" Soon after, the discovery of tumor suppressor genes, particularly RB1, gave further credence to Knudson's famous "two-hit" theory, the genetic basis for understanding cancer etiology.

Table 2

Comparison of oncogenes and antioncogenes in human cancer

Oncogenes	Antioncogenes
Gene active	Gene inactive
Specific translocations	Deletions or invisible mutations
Translocations not hereditary	Mutations hereditary and nonhereditary
Dominant	Recessive
Tissue specificity may be broad	Considerable tissue specificity
Especially leukemias and lymphomas	Solid tumors

1986

Extracellular Matrix Linked to Invasion and Metastasis

HIGHLY CITED ARTICLE

Tumor Invasion and Metastases—Role of the Extracellular Matrix: Rhoads Memorial Award Lecture

Lance A. Liotta

CHART 1. Three-step hypothesis of tumor cell invasion of extracellular matrix. Schematic diagram (not to scale) of tumor cell invasion of the basement membrane. Step 1 is tumor cell attachment to the matrix. This process may be mediated by specific attachment factors such as laminin, which form a bridge between the cell surface laminin receptor and type IV collagen. Step 2 is local degradation of the matrix by tumor cell-associated proteases. Such proteases may degrade both the attachment proteins as well as the structural collagenous proteins of the matrix. Type IV collagenase makes a single cleavage 25% of the distance from the amino terminus of type IV collagen. Proteolysis may be localized at the tumor cell surface where the amount of active enzyme outbalances the natural protease inhibitors present in the matrix. Step 3 is tumor cell locomotion into the region of the matrix modified by proteolysis. The direction of locomotion may be influenced by chemotactic factors. Continued invasion of the extracellular matrix may take place by cyclic repetition of these three steps.

Lance Liotta presented the accumulating evidence that linked the extracellular matrix (ECM) to cancer cell invasion and metastasis. His three-step model underlying tumor invasion, discovery of various ECM components, and invention of laser capture microdissection launched a new era of cancer research that began to consider how extrinsic cues within the tumor microenvironment could promote malignant progression and eventual metastasis.

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1986

Tumor Angiogenesis Factors Described

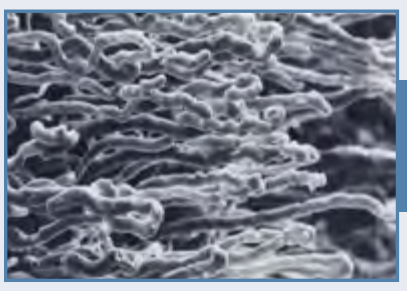
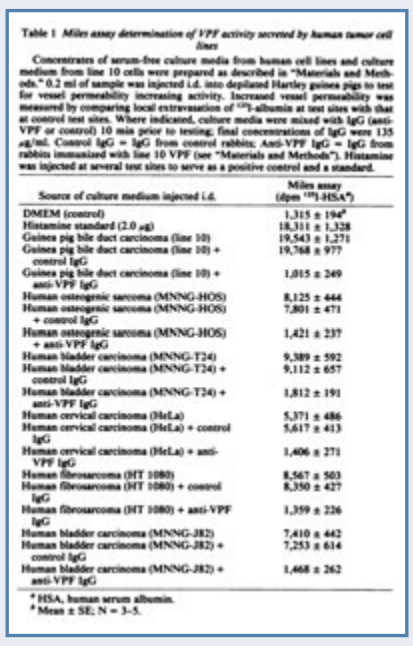


FIGURE 2. Final stages of capillary formation. Each capillary loop has formed by the anastomosis of two sprouts. The capillary loops in this scanning electron micrograph are growing into a human carcinoma of the larynx. Original magnification, x 192. From Miodonski et al., with permission.

Judah Folkman chronicled the period of research devoted to the discovery of tumor angiogenesis factors. Observations that such factors could be purified based on their affinity for heparin spawned a new era in vascular medicine. Folkman's ultimate ambition to incorporate angiogenesis inhibitors into cancer treatment was eventually fulfilled, and development of the next generation of antiangiogenic therapy is already underway.

Cancer Cells Secrete Elevated Levels of VEGF

Three years after the discovery of vascular permeability factor (VPF or VEGF) in guinea pig tumor cells, Senger and colleagues went on to demonstrate that human cancer cells also secreted elevated levels of VEGF compared to their nonmalignant counterparts. These pivotal findings laid the groundwork for the eventual development and FDA approval of the first VEGF-targeted antiangiogenesis therapy for cancer treatment, bevacizumab.



1987

New Methods to Measure Cell Viability After Radiotherapy

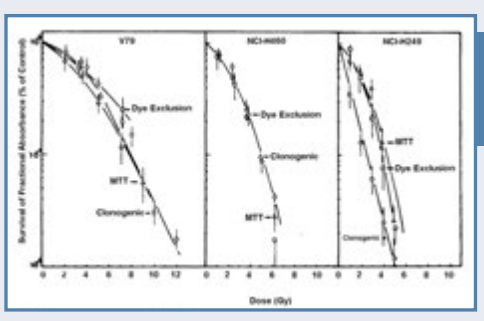


FIGURE 1. Assessment of survival (percentage of control) using clonogenic, MTT, and dye exclusion assays for three different cell lines as a function of radiation dose. *Bars*, SE.

The advent of cell culture as a tractable model for testing anticancer efficacy was met by a large effort to develop suitable bioassays that could quickly yet reliably assess cancer cell behavior. Carmichael and colleagues optimized the MTT assay in nonclonogenic cancer cells to measure cell viability following radiotherapy, a popular in vitro technique still heavily used in cancer research.

Chemoinvasion Assay Developed

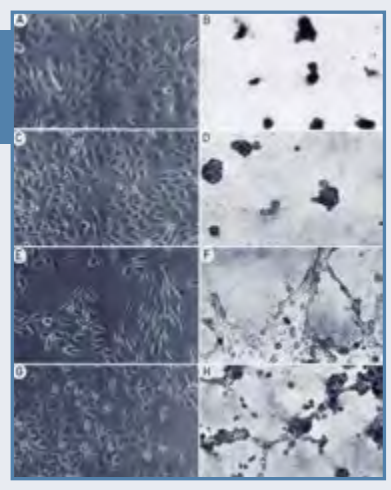


FIGURE 4. Appearance of prostate cells on plastic (left) and on matrix (right). A and B, benign prostate hyperplasia; C and D, low metastatic carcinoma Du 145; E and F, high metastatic carcinoma (PC 3); G and H, high metastatic carcinoma line (Du LM).

A critical step during the metastatic cascade involves the invasion of tumor cells through the extracellular matrix. Using a basement membrane-like matrix, Albini and colleagues developed an in vitro procedure, known as the chemoinvasion assay, to evaluate the invasive and metastatic potential of cancer cells. Still frequently used, many variations of invasion assays have uncovered key characteristics of metastatic cells.

Journal Moves to Twice Monthly Publication

SCIENTIFIC PUBLISHING CENTENNIAL
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1988

Overexpression of HER2 in Breast Cancer Described

HIGHLY CITED ARTICLE

Correlation of *c-erbB-2* Gene Amplification and Protein Expression in Human Breast Carcinoma with Nodal Status and Nuclear Grading

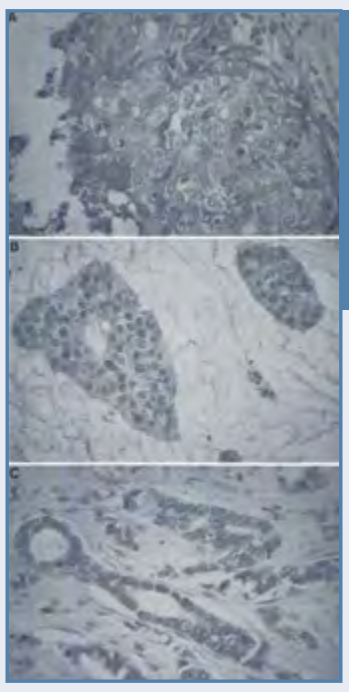
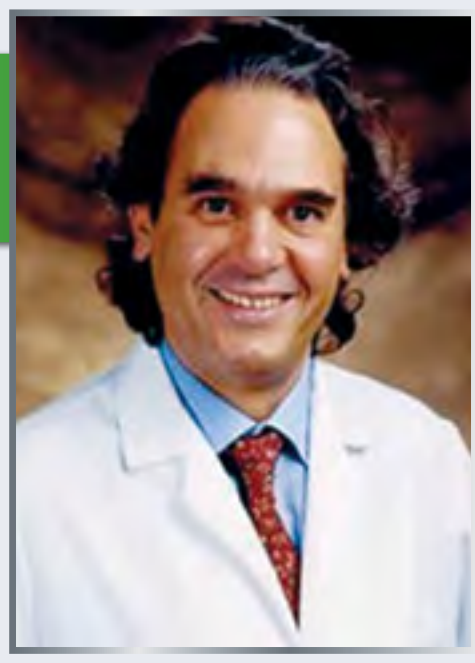


FIGURE 2. Immunohistochemical assay for the *c-erbB-2* protein. Tumor sections were stained with the *c-erbB-2* specific antiserum, 20N, as described in "Materials and Methods." The nuclei were counterstained with hematoxylin. A, section from tumor 49, whose DNA contains heavily amplified *c-erbB-2* gene copies (Fig 1A, lane 3). Histologically, the tumor was classified as invasive ductal with a predominant intraductal component. The tumor displays a nuclear grade 3 and was taken from an estrogen receptor-positive patient with nodal involvement. The 20N staining is strongly positive (++). B, section from a mucinous carcinoma which does not contain amplified *c-erbB-2* gene copies. The tumor has a nuclear grade of 1 and was taken from an estrogen receptor-positive patient with no nodal involvement. The 20N staining is moderate (+). C, section from an invasive ductal carcinoma which does not contain amplieif *c-erbB-2* gene copies. The nuclear grade is 2, and the patient was estrogen receptor positive, node negative. 20N staining is negative (–). Original magnification, X832.

Berger and colleagues reported the clinical observation that about a quarter of breast tumors exhibited amplification and overexpression of ERBB2 (HER2). These seminal findings led to the establishment of this oncogene as a prognostic biomarker and the subsequent generation of targeted therapies, which have significantly improved outcomes in patients with aggressive HER2-positive breast cancers.

1990

Geneticist Appointed Editor-in-Chief



CARLO M. CROCE, MD, EDITOR-IN-CHIEF, 1990-1999

Recognized for having revolutionized the understanding of the genetic basis of cancer, Dr. Croce was the first to show that chromosomal translocations involving the Ig loci are common in patients with Burkett's lymphoma and that T-cell receptor genes play a role in the pathogenesis of leukemia and lymphoma. He was the first investigator to discover and sequence bcl-1 and bcl-2, and characterize them as oncogenes. His studies have persistently shown that various chromosomal abnormalities are capable of contributing to both cancer initiation and progression. In Philadelphia, he was at the Wistar Institute for over 20 years, was director of the Fels Institute at Temple, and subsequently was director of the Thomas Jefferson Cancer Institute; he is currently director of the Institute of Genetics at Ohio State University School of Medicine.

HER2 Overexpressed in Ovarian Cancer

HIGHLY CITED ARTICLE

Overexpression of *HER-2/neu* Is Associated with Poor Survival in Advanced Epithelial Ovarian Cancer

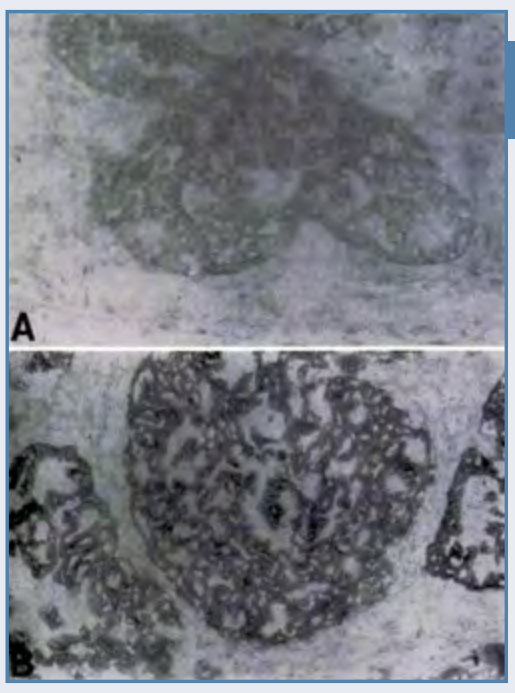


FIGURE 2. *HER-2/neu* expression in ovarian cancer. A. light (1+) staining for *HER-2/neu*: B. heavy (3+) staining for *HER-2/neu*.

Berchuck and colleagues found that HER2 (ERBB2) overexpression occurred in about one-third of ovarian cancers and was associated with poor outcome. The true frequency of overexpression remains under debate, but has prompted studies to elucidate the role of HER2 in ovarian cancer and investigate the efficacy of the targeted therapies that have proved highly beneficial in HER2-positive breast cancers.

Croce Introduces Advances in Brief (Now Called Priority Reports)

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1991

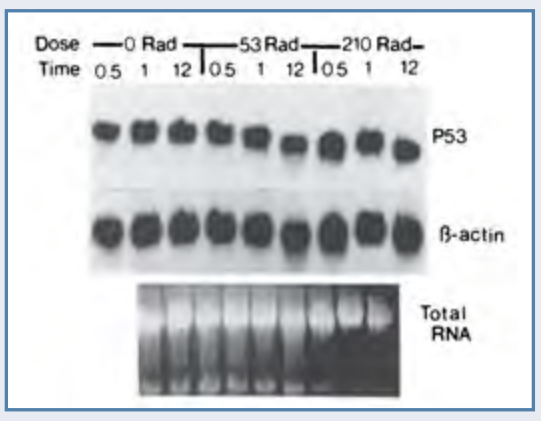
Malignant Cells Exhibit a Mutator Phenotype

The notion that mutation rate accounts for the numerous alterations found in cancer cells was challenged by Lawrence Loeb, who argued that malignant cells exhibit a mutator phenotype in which mutations compromising genome stability facilitate increased mutagenesis during tumor progression. Cancer genome sequencing efforts have enabled the identification of mutations in DNA synthesis and repair genes, thus reinforcing this hypothesis.

1991

Link Established Between p53 Induction and Cell Cycle Arrest

Kastan and colleagues demonstrated that upregulation of p53 in response to DNA-damaging agents occurred concomitantly with stalled DNA synthesis, an effect not observed in cells exhibiting p53 mutations or loss. Subsequent studies confirmed the direct link between p53 induction and cell cycle arrest, reinvigorating a research field that would proceed to exhaustively catalog the many multifaceted functions of p53.



1993

Hereditary Colorectal Cancer Linked to Germline Mutations

Peltomäki and colleagues reported that tumors associated with hereditary non-polyposis colorectal cancer were characterized by a unique microsatellite instability phenotype. During the same month these findings were published, a separate study determined that mutations to a DNA mismatch repair gene accounted for the mutator phenotype. Subsequently, several additional germline mutations affecting genome stability were discovered to predispose individuals to malignancy.

Table 1 *Microsatellite instability in different types of cancer*

Organ	% of tumors showing the RER alteration/Locus								% of RER+ tumors (*N*)* with no. of affected loci	
	D5S404	*D17S787*	*D8S255*	*D13S216*	*D13S904*	*D18S197*	*D13S175*	*D3S1266*	≥2	≥1
Colon and rectum[b]	8	8	5	5	7	7	10		10 (226)	17 (243)
Stomach	24	13	10	9	12	11	17		18 (33)	18 (33)
Endometrium	11	12	6	15	7	21	21		22 (18)	22 (18)
Breast[b]	0	0	0	0	0	0	0		0 (84)	0 (84)
Testis[b]	0	0	0	0	0	0	0		0 (86)	0 (86)
Lung	0	0	0	2	0	0		0	0 (85)	2 (87)

* *N* = number of scorable tumors, *i.e.*, the added number of RER+ in that group and RER− tumors. In RER− cases information was obtained from 5 loci on the average (a successful study of a minimum of 3 loci was required and that should provide no evidence of the RER alteration).
[b] From the report of Lothe *et al.* (9).

1994

p53/p21 Growth Control Pathway Described

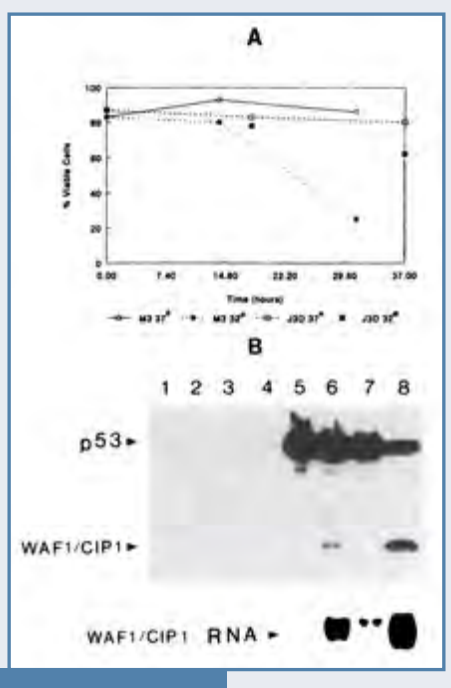


FIGURE 3. WAF1/CIP1 is induced in p53-mediated apoptosis. In A, the viability of parental J3D and daughter M3 (containing an exogenous temperature sensitive Val 135 p53 mutant) T-cell lymphoma cell lines is shown as a function of incubation time at 37°C or 32°C. The plotted values represent the mean of triplicate determinations, with a range within 10% of the mean. B. Western blot analysis of J3D cells (Lanes 1, 2 at 17 h and Lanes 3, 4 at 37 h) and M3 cells (Lanes 5, 6 at 14 h and Lanes 7, 8 at 31 h), correlating WAF1/CIP1 expression with apoptosis induction at 32°C (Lanes 2,4,6,8) or the control temperature (Lanes 1, 3, 5, 7). Northern blot analysis (bottom) was performed on lysates obtained from M3 cells, demonstrating that WAF1/CIP1 induction was regulated at the mRNA level.

El-Deiry and colleagues showed that in cells exposed to DNA-damaging agents, p53 induces the expression of WAF1/CIP1 (p21) to promote G1 arrest, establishing the first connections within the p53/p21 growth control pathway. The ability of p21 to stall cell growth through both p53-dependent and independent mechanisms was later deciphered, highlighting the wide-ranging functions of p21 in cell cycle regulation.

SCIENTIFIC PUBLISHING CENTENNIAL
1916-2016
AACR American Association for Cancer Research

1995

Helicobacter Infection Increases Risk of Stomach Cancer

HIGHLY CITED ARTICLE

Infection with *Helicobacter pylori* Strains Possessing cagA Is Associated with an Increased Risk of Developing Adenocarcinoma of the Stomach[1]

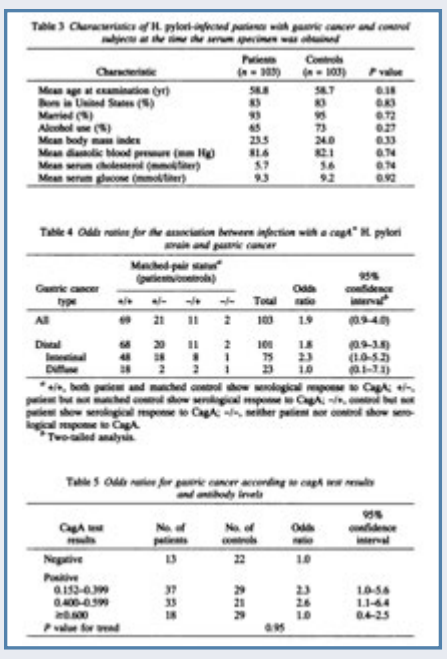


Table 3 *Characteristics of* H. pylori*-infected patients with gastric cancer and control subjects at the time the serum specimen was obtained*

Characteristic	Patients (n = 103)	Controls (n = 103)	P value
Mean age at examination (yr)	58.8	58.7	0.18
Born in United States (%)	83	83	0.83
Married (%)	93	95	0.72
Alcohol use (%)	65	73	0.27
Mean body mass index	23.5	24.0	0.33
Mean diastolic blood pressure (mm Hg)	81.6	82.1	0.74
Mean serum cholesterol (mmol/liter)	5.7	5.6	0.74
Mean serum glucose (mmol/liter)	9.3	9.2	0.92

Table 4 *Odds ratios for the association between infection with a cagA*[a] H. pylori *strain and gastric cancer*

Gastric cancer type	Matched-pair status[a] (patients/controls) +/+	+/−	−/+	−/−	Total	Odds ratio	95% confidence interval[b]
All	69	21	11	2	103	1.9	(0.9–4.0)
Distal	68	20	11	2	101	1.8	(0.9–3.8)
Intestinal	48	18	8	1	75	2.3	(1.0–5.2)
Diffuse	18	2	2	1	23	1.0	(0.1–7.1)

[a] +/+, both patient and matched control show serological response to CagA; +/−, patient but not matched control show serological response to CagA; −/+, control but not patient show serological response to CagA; −/−, neither patient nor control show serological response to CagA.
[b] Two-tailed analysis.

Table 5 *Odds ratios for gastric cancer according to cagA test results and antibody levels*

CagA test results	No. of patients	No. of controls	Odds ratio	95% confidence interval
Negative	13	22	1.0	
Positive				
0.153–0.399	37	29	2.3	1.0–5.6
0.400–0.599	35	21	2.6	1.1–6.4
≥0.600	18	29	1.0	0.4–2.5
P value for trend			0.95	

In a nested case-control study of Japanese-American men, Blaser and colleagues found that infection with *Helicobacter pylori* cagA-positive strain was associated with an increased risk of stomach cancer. These findings helped reveal how *H. pylori* enhances cancer risk in only a subset of infected individuals, highlighting the importance of strain difference, inflammatory response, and host-microbiota interactions in determining pathogenic potential.

p21 Is Critical for p53 Blockade of Cell Cycle

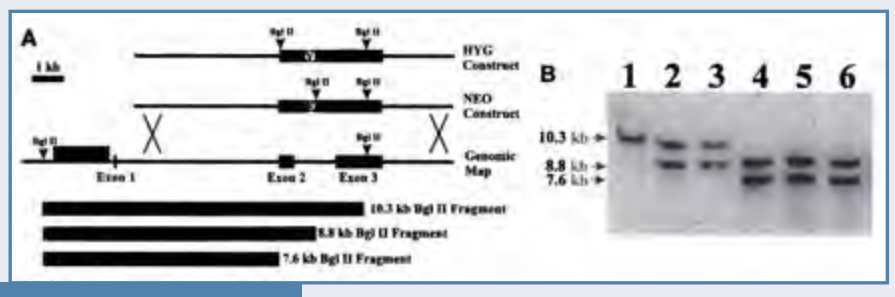


FIGURE 1. Targeting p21 by homologous recombination. A. map of the genomic region encompassing the p21 gene is shown, along with a diagram of the constructs used for gene targeting. The sizes of the BglII fragments expected from the wild-type and targeted alleles are also indicated. B, Southern blots of BglII-digested DNA from drug-selected clones are shown. Only the wild-type 10.3-kb allele is present in HCT116 cells (Lane 1), while the wild-type plus an 8.8-kb NEO-targeted allele is present in the clones shown in Lanes 2 and 3, and the 8.8-kb NEO and 7.6-kb HYG-targeted alleles and no wild-type allele are present in the clones shown in Lanes 4–6.

The generation of a p21-deficient colon adenocarcinoma cell line allowed Waldman and colleagues to provide the definitive evidence that p53-induced cell cycle arrest was directly mediated by p21. These findings laid the groundwork needed to discover additional p53 tumor suppressor functions, elucidate the mechanisms underlying cell cycle regulation, and therapeutically exploit cyclin-dependent kinases for cancer treatment.

HIGHLY CITED ARTICLE

p21 Is Necessary for the p53-mediated G_1 Arrest in Human Cancer Cells[1]

1996

Mouse Model Developed for Metastatic Prostate Cancer

HIGHLY CITED ARTICLE

Metastatic Prostate Cancer in a Transgenic Mouse[1]

Gingrich and colleagues described a mouse model of metastatic prostate cancer in which prostate epithelium-specific regulatory elements drive transgenic expression of the SV40 tumor antigen. The TRAMP mouse remains one of the best characterized models of prostate cancer today and has deepened our understanding of disease prevention, treatment, and metastatic progression.

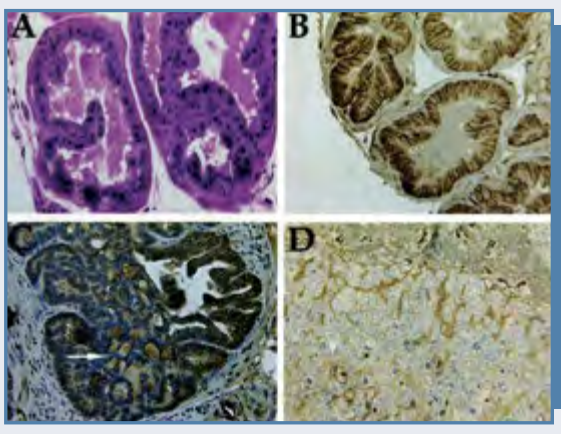


FIGURE 4. Immunohistological analysis of E-cadherin expression in metastatic prostate cancer in TRAMP mice. A, normal 8-week nontransgenic dorsolateral prostatic acinus. H&E; 40X. B, E-cadherin staining at the basolateral cell-cell borders of the epithelia of a 24-week nontransgenic mouse; 40X. C, an 18-week TRAMP mouse prostatic acinus displays profound cribriform structures and neoplastic changes. Normal E-cadherin expression is maintained in the relatively normal epithelium basolaterally and on the right portion of the acinus, in contrast to the more hyperplastic areas and cells forming the cribriform structures (arrow). D, immunohistochemistry of a metastatic lymph node deposit of tumor demonstrates abnormal, poorly localized expression of E-cadherin.

1997

Anti-VEGF Monoclonal Antibodies Work in Humans

HIGHLY CITED ARTICLE

Humanization of an Anti-Vascular Endothelial Growth Factor Monoclonal Antibody for the Therapy of Solid Tumors and Other Disorders

Presta and colleagues humanized the murine anti-VEGF monoclonal antibody, thus triggering the first generation of clinical angiogenesis inhibitors. Since then, bevacizumab has been approved in combination with chemotherapy for the treatment of multiple solid malignancies. However, the continual introduction of next-generation anti-VEGF agents, VEGF receptor inhibitors, and other antiangiogenic compounds demonstrates that the tumor vasculature requires new therapeutic opponents.

FIGURE 2. Ribbon diagram of the model of humanized F(ab)-12 VL and VH domains. VL domain is shown in brown with CDRs in tan. The side chain of residue L46 is shown in yellow. VH domain is shown in purple with CDRs in pink. Side chains of VH residues changed from human to murine are shown in yellow.

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1998

APC/Beta-catenin Pathway Important in Colorectal Cancer

HIGHLY CITED ARTICLE

Mutational analyses of colorectal tumors, undertaken by Sparks and colleagues, revealed that alterations to APC and β-catenin were frequent, but mutually exclusive, and occurred during early adenoma stage. These findings established the basis for the APC/β-catenin pathway as an early driver of colorectal tumorigenesis, the progression of which continues upon sequential accumulation of mutations in other key pathways.

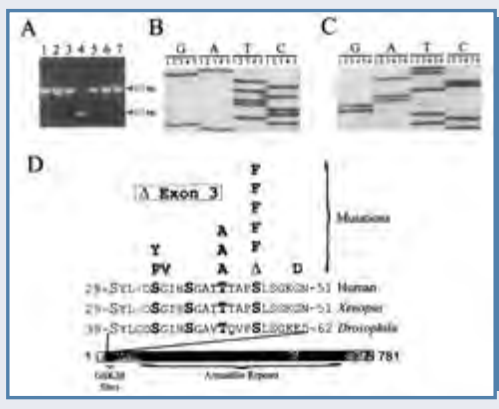

FIGURE 1. β-catenin mutations in CR tumors. A, PCR of genomic DNA revealing a deletion of exon 3 in adenoma A14. B, nucleotide sequencing of the regulatory domain of β-catenin revealed a C → T (S45Y) transition in adenoma A13. Lanes 1-5 correspond to samples C3, C2, C1, A15, and A13, respectively. Nucleotides 126-139 of β-catenin, as derived from an antisense primer, are shown. The film was flipped to allow the sequence to be read in the sense direction. C, nucleotide sequencing of the regulatory domain of β-catenin reveals a G → T (G34V) transversion in Carcinoma C17. Lanes 1-6 correspond to samples C15, C17, C5, C7, C9, and C23, respectively. Nucleotides 96-109 of β-catenin are shown in the sense direction. D, summary of the β-catenin mutations. The regions encompassing the β-catenin regulatory domains from human, frog (*Xenopus*), and fly (*Drosophila*) are shown with the identified mutations indicated above.

Combinatorial Treatment Effective in HER2-Positive Breast Cancer

The striking findings of Baselga and colleagues demonstrated that a high rate of tumor regression could be achieved through the combination of anti-HER2 antibodies and chemotherapy in preclinical models. Subsequent work to optimize the chemotherapy regimens resulted in improved formulations of this combinatorial treatment approach, which are now frequently prescribed to patients with HER2-positive breast cancer.

Table 1 *Pooled data for complete tumor regressions in the different treatment groups of BT-474 xenografts*

Treatment	Initial no. of mice	No. of mice alive at 5 weeks	No. of mice tumor-free at 5 weeks[a]	P^b
Control	31	31	2 (6.4%)	—
RhuMAb HER2	30	29	9 (31%)	0.013
Doxorubicin	25	23	3 (13%)	0.38
Doxorubicin + rhuMAb HER2[c]	23	21	7 (33.3%)	0.01
Paclitaxel	26	23	4 (17.3%)	0.2
Paclitaxel + rhuMAb HER2[d]	25	22	13 (59%)	0.004

[a] Additional complete tumor regressions were observed after 5 weeks in one mouse in the control group, one mouse in the rhuMAb HER2 alone group, one mouse in the rhuMAbHER2 + doxorubicin group, and two mice in the rhuMAbHER2 + paclitaxel group.
[b] Two-sided *P*s for Pearson χ^2 comparison of complete tumor regression rates of each treated group *versus* control animals.
[c] Doxorubicin + rhuMAb HER2 *versus* rhuMAb HER2 alone, $P = 0.8$; *versus* doxorubicin alone, $P = 0.09$.
[d] Paclitaxel + rhuMAb HER2 *versus* rhuMAb HER2 alone, $P = 0.04$; *versus* paclitaxel alone, $P = 0.004$.

HIGHLY CITED ARTICLE

1999

Mutations in Apoptotic Genes Not Only Cause of Drug Resistance

HIGHLY CITED ARTICLE

It was conventionally held that anticancer agents exerted their cytotoxic effects by inducing apoptosis in tumor cells, with mutations in p53 or apoptotic genes thus conferring drug resistance. Brown and Wouters put forth the experimental evidence against this viewpoint, leading to the adoption of a broader perspective regarding anticancer drug mechanisms of action and the factors underlying therapeutic resistance.

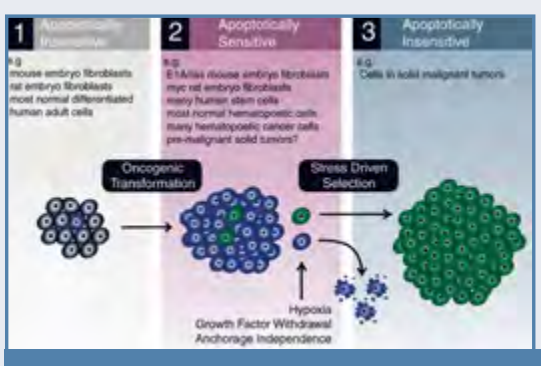

FIGURE 5. Malignant evolution and apoptotic sensitivity. Most differentiated adult cells, as well as normal mouse and human fibroblast cell lines, are resistant to the induction of apoptosis by genotoxic agents (panel 1). These cells typically undergo permanent arrest or senescence after treatment. Initial oncogenic transformation increases the proliferative potential and can dramatically sensitize these cells to apoptosis (panel 2). In general, these cells are more sensitive to apoptosis induced by both genotoxic and nongenotoxic stress (e.g., hypoxia, growth factor withdrawal, or anchorage independence). Cells in this state have also been shown to be hypersensitive to overall cell killing as assessed by clonogenic assay. Examples of cells that can be classified within this apoptotically sensitive state include the E1A- and ras-transformed MEFs, the myc-expressing Rat-1 cells, many human stem cells, and hematopoietic tumor cells. Most solid human tumors and tumor-derived cell lines have evolved past this apoptotically hypersensitive state due to the selective pressure arising from various forms of nongenotoxic stress found within the tumor microenvironment (panel 3). In response to genotoxic stress, the predominant mode of cell death for cells in this state may or may not be apoptosis. Manipulations in the levels of apoptosis by means of genetic changes has only been shown to affect cells that are apoptotically sensitive (middle panel). Dramatic changes in the level of apoptosis in cells from human tumors often have no effect on overall survival.

Proteasome Inhibitors Developed as Antitumor Agents

HIGHLY CITED ARTICLE

Adams and colleagues generated and preclinically characterized one of the first proteasome inhibitors to be used for cancer treatment, paving the way for subsequent clinical trials. PS-341, more notably known as bortezomib, was FDA-approved for the treatment of multiple myeloma and mantle cell lymphoma, and continues to serve as the basis for new therapeutic strategies targeting the ubiquitin-proteasome pathway.

Table 1 *Structure-activity relationships of 13 boronic acid proteasome inhibitors against purified proteasome activity (K_i) and their ability to inhibit cell growth across 60 tumor cell lines (average GI_{50}) from the National Cancer Institute*

Compound (NSC no./PS no.)	Structure	K_i (nM)	Average GI_{50} (nM)
681226/PS-273	MorphCONH(CHNaphthyl)CONH(CHisobutyl)B(OH)$_2$	0.2	6.3
681227/PS-293	Enantio-PS-273	2,300	56,000
681228/PS-296	8-Quinolyl sulfonylCONH(CHNaphthyl)CONH(CHisobutyl)B(OH)$_2$	3.5	17
681229/PS-303	NH$_2$(CHNaphthyl)CONH(CHisobutyl)B(OH)$_2$	12	68
681231/PS-305	MorphCONH(CHNaphthyl)CONH(CHisobutyl)B(OH)$_2$	189	4,700
681234/PS-313	NaphthylCH$_2$CH$_2$CONH(CHisobutyl)B(OH)$_2$	58	1,300
681236/PS-321	MorphCONH(CHNaphthyl)CONH(CHPhe)B(OH)$_2$	0.5	6.6
681237/PS-334	CH$_3$NH(CHNaphthyl)CONH(CHisobutyl)B(OH)$_2$	3.5	13
681239/PS-341	PyrazylCONH(CHPhe)CONH(CHisobutyl)B(OH)$_2$	0.6	3.9
681242/PS-364	PheCH$_2$CH$_2$CONH(CHisobutyl)B(OH)$_2$	1,500	10,000
683086/PS-325	2-QuinolylCONH(CHHomoPhe)CONH(CHisobutyl)B(OH)$_2$	2	34
683094/PS-352	PheCH$_2$CH$_2$CONH(CHPhe)CONH(CHisobutyl)B(OH)$_2$	0.1	10
683098/PS-383	PyridylCONH(CH$_2$)$_4$PheCONH(CHisobutyl)B(OH)$_2$	0.6	10

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2000 Molecular Geneticist Named Editor-in-Chief

FRANK J. RAUSCHER, III, PHD, EDITOR-IN-CHIEF, 2000-2009

A specialist in the molecular genetics of cancer, Dr. Rauscher studies tumor suppressor and oncogene proteins, mechanisms of transcription regulation, and transcriptional control of cellular differentiation and organogenesis. He identified the association between the oncogenes fos and jun and highlighted their DNA-binding activity in vivo. He discovered the role of the WT1 gene in Wilms' tumor and discovered the BAP1 tumor suppressor gene and its role in regulating BRCA1 function and breast and lung cancer development. He studies proteins that directly recognize and target histone tail modifications that lead to gene silencing. A professor in the Gene Expression and Regulation Program at the Wistar Institute, Dr. Rauscher is deputy director of the Institute's Cancer Center.

2001 Tyrosine Kinase Key Factor in GIST

Rubin and colleagues reported that more than 90% of gastrointestinal stromal tumors (GISTs) harbored activating mutations in the KIT receptor tyrosine kinase, revealing a critical oncogenic event underlying tumorigenesis. These and subsequent findings initiated a pivotal shift in the therapeutic management of GIST that now opts for the incorporation of highly effective tyrosine kinase inhibitors in place of conventional chemotherapy.

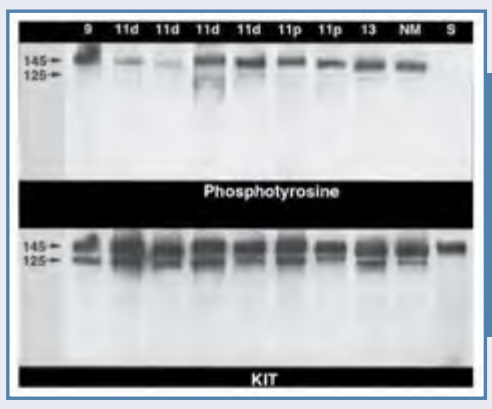

FIGURE 2. Primary GIST cell lysates were immunoprecipitated with polyclonal anti-KIT, Western blotted, stained for phosphotyrosine (top), and then stripped and restained for KIT (bottom). Lanes 9, 11d, 11p, 13, and NM, GISTs with exon 9 mutation, exon 11 deletion mutation, exon 11 point mutation, exon 13 mutation, and no detectable mutation, respectively. Lane S, a non-GIST control (seminoma) that expresses nonphosphorylated KIT. Arrows, Mr 125,000 and Mr 145,000 KIT proteins, the Mr 145,000 form being the mature KIT protein that is fully glycosylated. Only the Mr 145,000 mature form is substantially tyrosine phosphorylated.

Full Text of Journal Is Launched Online

2005 Multi-Kinase Inhibitors Effective in Imatinib-Resistant CML

Resistance to the Abl kinase inhibitor imatinib limits the successful treatment of chronic myeloid leukemia (CML). O'Hare and colleagues provided the preclinical rationale for the investigation of two multi-kinase inhibitors with potent effects against imatinib-resistant CML. Although approved as second-line therapy in refractory AML, the efficacy of these inhibitors, dasatinib and nilotinib, as first-line treatment remains under clinical evaluation.

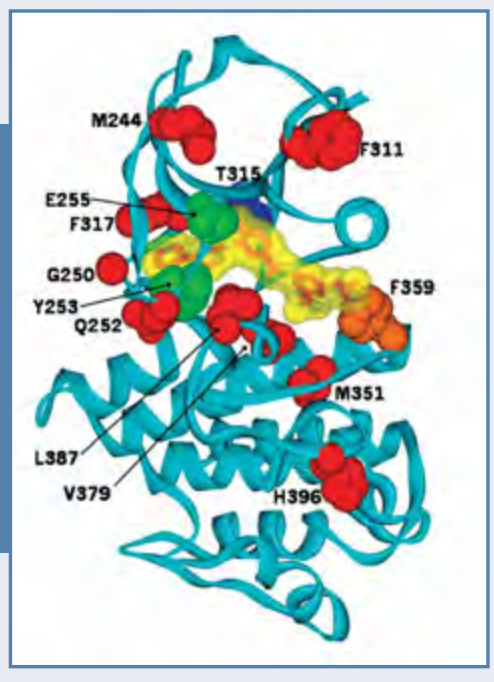

FIGURE 2. AMN107 in complex with kinase domain of Abl mutant M351T. Schematic diagram showing the locations of residues on Abl kinase corresponding to imatinib-resistant mutant forms of Bcr-Abl detected in patients. The residues are color coded according to their sensitivity to inhibition by AMN107, which is shown as a tube representation with a transparent yellow surface, as bound in a crystal structure of M351T Abl kinase (light blue). Mutations of residues shaded in red are highly sensitive to AMN107 (IC50 ≤ 70 nmol/L: M244V, G250E, Q252H, F3IIL, F317L, M351T, V379I, L387M, H396P, H396R), residues in orange show medium sensitivity (IC50 ≤ 200 nmol/L: Y253F, E255K, F359V), residues in green show low sensitivity (IC50 ≤ 450 nmol/L: Y253H, E255V), and the blue residue (T315I) is insensitive to AMN107 (IC50 > 2 μmol/L). Note that the level of AMN107 sensitivity at positions 253 and 255 (green) is dependent on the specific amino acid substitution. Thus, mutants Y253F and E255K fall in the medium (orange) classification, whereas Y253H and E255V comprise the low (green) category.

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2006

Tumor-Associated Macrophages Play Key Roles in Malignancies

Lewis and Pollard presented the mounting evidence that tumor-associated macrophages (TAMs) carry out a diverse repertoire of protumorigenic functions, including tumor invasion, growth, angiogenesis, metastasis, and immunosuppression. The steady increase in TAM-related publications over the last decade has only further solidified the perception of TAMs as pivotal contributors to malignancy and has heightened interest in the development of targeted therapies.

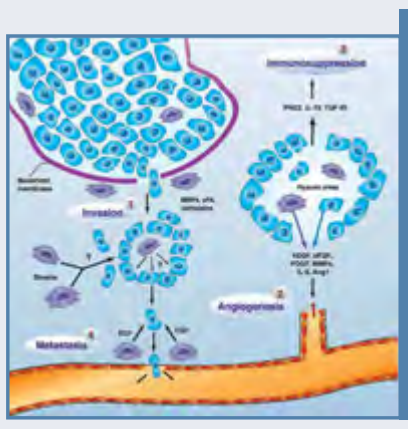

FIGURE 2. The roles of different subpopulations of TAMs in tumor progression. 1, invasion: TAMs secrete a variety of proteases to breakdown the basement membrane around areas of proliferating tumor cells (e.g., ductal carcinoma in situ in the breast), thereby prompting their escape into the surrounding stroma where they show deregulated growth. 2, angiogenesis: In areas of transient (avascular) and chronic (perinecrotic) tumor hypoxia, macrophages cooperate with tumor cells to induce a vascular supply for the area by up-regulating a number of angiogenic growth factors and enzymes. These diffuse away from the hypoxic area and, together with other proangiogenic stimuli in the tumor microenvironment, stimulate endothelial cells in neighboring, vascularized areas to migrate, proliferate, and differentiate into new vessels. 3, immunosuppression: Macrophages in hypoxic areas secrete factors that suppress the antitumor functions of immune effectors within the tumor. 4, metastasis: A subpopulation of TAMs associated with tumor vessels secretes factors like EGF to guide tumor cells in the stroma toward blood vessels where they then escape into the circulation. In the stromal compartment (both the acellular regions and others where they are in close contact with tumor cells), TAMs secrete growth factors to stimulate tumor cell division and/or undefined factors that promote tumor cell motility.

Cetuximab Non-Response Attributed to *KRAS* Mutation

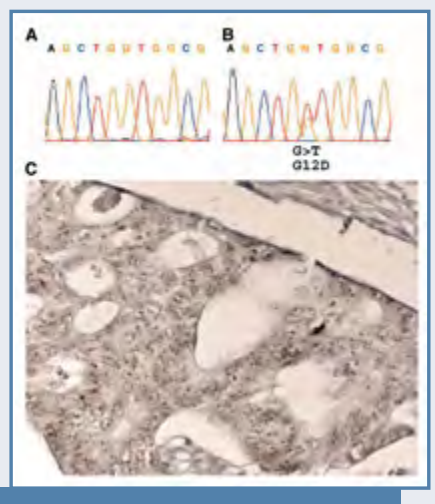

FIGURE 1. Example of different genetic alterations studied. A and B, electrophoregram from normal (A) and tumor tissue (B). A G12D *KRAS* mutation is observed in tumor tissue compared with normal tissue. C, an example of high EGFR amplification by chromogenic in situ hybridization. Original magnification, X100. One brown spot corresponds to one EGFR gene copy.

The EGFR inhibitor cetuximab significantly improved the survival rate of a subset of patients with metastatic colorectal cancer, but remained ineffective in others. Lièvre and colleagues demonstrated that about two-thirds of patients harboring *KRAS* mutations failed to respond to cetuximab. These findings established the framework for treatment stratification of colorectal cancer patients based on routine *KRAS* mutation testing.

2007

MicroRNAs Have a Role in Oncogenesis

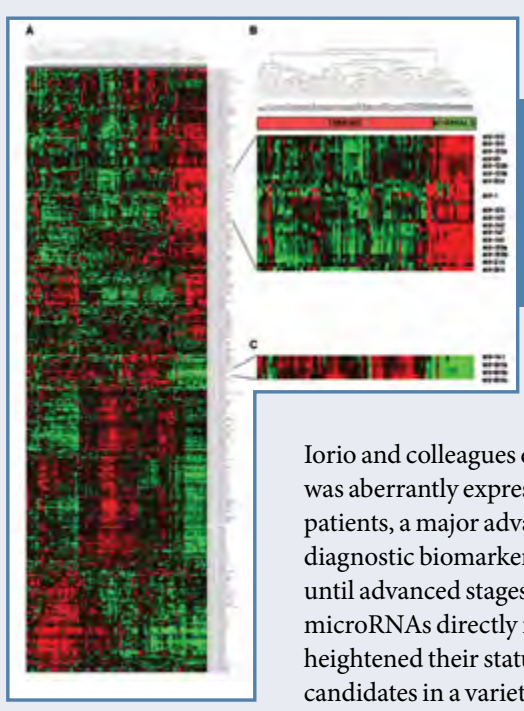

FIGURE 1. Cluster analysis of ovarian carcinomas and normal ovarian tissues. A, tree generated by the hierarchical cluster analysis showing the separation of normal tissues from ovarian cancers on the bases of all human miRNAs spotted on the chip. Some of the miRNAs most significantly down-modulated in tumors versus normal ovary (B) and the four miRNAs most significantly up-modulated in tumors versus normal ovary (C).

Iorio and colleagues determined that a set of microRNAs was aberrantly expressed in ovarian tumors from human patients, a major advance towards the identification of diagnostic biomarkers for a cancer difficult to detect until advanced stages. Subsequent findings implicating microRNAs directly in the tumorigenic process further heightened their status as promising therapeutic candidates in a variety of malignancies.

2009

Epithelial-to-Mesenchymal Transition Drives Multidrug Resistance

Arumugam and colleagues revealed that a molecular signature associated with epithelial-to-mesenchymal transition (EMT) was a common feature of chemotherapy-resistant pancreatic cancer cells, establishing this biological process as a major mechanism driving multidrug resistance. Consequently, targeting EMT-associated factors sensitized tumor cells to therapy, and thus strategies to therapeutically exploit these pathways in pancreatic cancer remain under preclinical and clinical investigation.

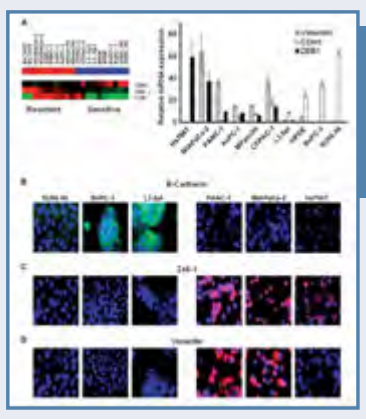

FIGURE 3. Expression of EMT markers in pancreatic cancer cells. A, expression patterns of E-cadherin, ZEB-1, and vimentin in the array data were generated via heat map and confirmed by quantitative real-time PCR. An inverse correlation between E-cadherin and Zeb-1 was observed across the cell lines. Columns, mean of triplicate samples; bars , SE. B to D, immunofluorescence localization of E-cadherin, Zeb-1, and vimentin confirms the association of epithelial and mesenchymal phenotype in drug sensitivity and resistance.

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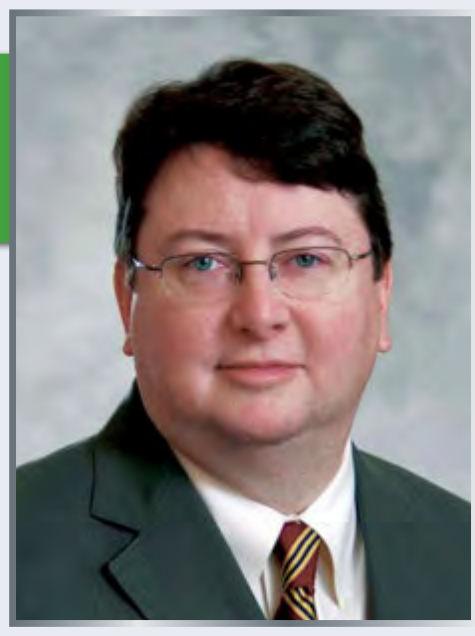
2010

Research Institute President Named Editor-in-Chief



GEORGE C. PRENDERGAST, PHD, EDITOR-IN-CHIEF, 2010-PRESENT

In the quest to develop new principles for treating cancer, Dr. Prendergast and his research group study disease modifier pathways that determine disease severity, with a specific focus on modifiers of inflammatory processes. They have developed a new class of drugs termed IDO (indoleamine 2,3-dioxygenase) inhibitors, which utilize the immune system to counteract inflammation-driven cancers. His laboratory also studies RhoB, a member of the Ras/Rho superfamily, in cancer cell signaling and the role of Bin1 in modifying inflammation. Dr. Prendergast is President and CEO of the Lankenau Institute for Medical Research in Wynnewood, PA, and serves as co-director of the Program in Cell Biology & Signaling at the Kimmel Cancer Center of Thomas Jefferson University in Philadelphia.

2013

Immune Checkpoint Blockade and Vaccine Therapy Are Effective

HIGHLY CITED ARTICLE

Development of immune checkpoint inhibitors has re-energized the field of cancer immunotherapy, but only a subset of patients responds to treatment. Duraiswamy and colleagues demonstrated that significant tumor rejection was achieved through dual blockade of PD-1 and CTLA-4, further enhanced by combined therapy with a cancer vaccine. Clinical implementation of this and newer immunotherapies cautiously awaits clinical trial results.

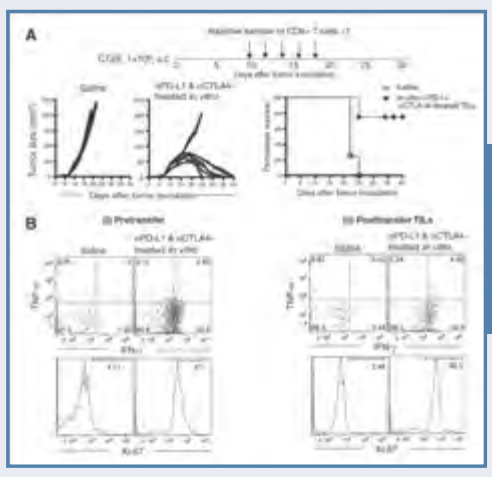


FIGURE 4. Therapeutic adoptive transfer of in vitro αPD-1 and αCTLA-4 pretreated TILs cause regression of CT26 tumors in mice. A, tumor regression in mice transferred with in vitro expanded CT26 antigen-specific CD8+CTLA-4+PD-1+ CT26 TILs. B, the percentage of IFN-γ+ and Ki-67+ of in vitro pretreated CD8+ T cells just before adoptive transfer (left) and the TILs recovered from tumor one week after the final transfer (right) are shown. i.t., intratumorally.

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