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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 joining 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 "effective interference with incessantly proliferating cells will become a reality." 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, and subsequently, 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.

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 metastasis field.

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.

A chair of pathology at the University of Pennsylvania Medical School, where he spent his career, Dr. Stein received numerous honors 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.

In both world wars, 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 Pennsylvania. He was AACR President in 1951. He wrote several histories, including the highly praised "Common Valor," which detailed civil officers' reactions to wounds and diseases. As Cancer Research Editor, Dr. Steiner noted that in order to maintain quality he was prepared to "suffering adverse criticism" and the "loss of all [his] friends."
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.

**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 24 years at this facility, he nurtured the groundbreaking 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 inaugural serving Editor of Cancer Research and served as AACR President in 1953. Late in his career, he initiated 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 1964 and by Ilse L. Riegel, PhD, assistant, associate, or managing editor from 1955 to 1964.

**1953**

**Tar from a Smoking Machine Causes Cancer in Mice**

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.

**1958**

**Toxicity Studies Help Establish Safe 5-fluorouracil Regimens**

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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.

Candidate Drugs Can Be Screened Using Cultured Human Cells

Eagle and Sidney 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.

Chromosomal Abnormalities Described in Leukemias

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.

Non-Genetic Changes Affect Regulatory Circuits

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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, drawing in several studies that mainstream was not as 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.

1965
Fels Institute Head Named Editor

1966
Historical Covers First Appear

1967
Mantel Test Helps in Analyzing Cancer Clusters

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.

1968
AACR Bans Smoking in Annual Meeting Rooms

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.
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 in 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.

J. 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.

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 accumulated 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.
1975
Journal Receives Its First Impact Factor (3.391)

1977
ER-Negative Breast Cancer More Likely to Recur

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 these tumor subtypes still lacking targeted therapies.

1978
Photoradiation Therapy Deemed Safe and Effective

The study by Dougherty and colleagues represented one of the first clinical demonstrations that photoradiation therapy could be used safely and effectively to treat various recurrent and metastatic tumors. These findings paved the road for further advances in photosensitizing agents and optical devices, culminating in photodynamic therapy, a potent, minimally invasive treatment modality for both malignant and nonmalignant diseases.

Metastasis Shown as a Complex, Multistep Process

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.
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.

Carcinogenesis Expert Named Editor


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 carcinogenicity in laboratory animals. Others later showed that some DNA mutations and cancer types may be due to the expression of the enzyme or-guanine N-methyltransferase. Although his work was soon extended to other systems, N-nitrosamines remain a major public health concern, with many foods treated with nitrite forming potential carcinogens. Dr. Magee was the second director of the Fels Institute to serve as Editor.

Melanoma Cells Have Different Metastatic Potential

Foundation Laid for the Two-Hit Theory of Cancer Genetics

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 of function inactivating “antioncogenes.” 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.

1980

1985

1986

Extracellular Matrix Linked to Invasion and Metastasis
1986

Tumor Angiogenesis Factors Described

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, Benger and colleagues went on to demonstrate that human cancer cells also secreted identical levels of VEGF compared to their normal counterparts. These pivotal findings laid the groundwork for the eventual development and FDA approval of the first VEGF-targeted angiogenesis therapy for cancer treatment, bevacizumab.

1987

New Methods to Measure Cell Viability After Radiotherapy

The advent of cell culture as an attainable model for testing anticancer efficacy was met by a large effort to develop suitable biomarkers 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

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. This assay is frequently used, and many variations of invasion assays have uncovered key characteristics of metastatic cells.

Journal Moves to Twice Monthly Publication
Overexpression of HER2 in Breast Cancer Described

1988

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

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)

1999

Croce introduced advances in brief (now called priority reports) as a way to disseminate important findings rapidly.
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.

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 untangle the many multifaceted functions of p53.

Polakis 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.

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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 mutations during tumor progression. Cancer genome sequencing efforts have enabled the identification of mutations in DNA synthesis and repair genes, thus reinforcing this hypothesis.

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In a nested case-control study of Japanese-American men, Blaser and colleagues found that infection with *Helicobacter pylori* cagA-positive strains is 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 differences, inflammatory response, and host-microbiota interactions in determining pathogenic potential.

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.

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 continued introduction of next-generation anti-VEGF agents, VEGF receptor inhibitors, and other antiangiogenic compounds demonstrate that the tumor vasculature requires new therapeutic antagonists.
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.

Mutational analysis of colorectal tumors, undertaken by Sparks and colleagues, revealed that alterations in 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.

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 combinational treatment approach, which are now frequently prescribed to patients with HER2-positive breast cancer.

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.

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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.

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.
Arumugam and colleagues revealed that a molecular signature associated with epithelial-to-mesenchymal transition (EMT) carry out a diverse repertoire of pro-malignant 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.

**Cetuximab Non-Response Attributed to KRAS Mutation**

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.

**MicroRNAs Have a Role in Oncogenesis**

Iorio and colleagues determined that a set of microRNAs was aberrantly expressed in ovarian cancers from human patients, a major advance toward the identification of diagnostic biomarkers for a cancer disease 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.

**Epithelial-to-Mesenchymal Transition Drives Multidrug Resistance**

Stromal and colleagues revealed that molecular signatures associated with epithelial-to-mesenchymal transition (EMT) were a common feature of chemotherapy-resistant pancreatic cancer cells, establishing this biological process as a major mediator 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.

**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 pro-malignant 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.
In the quest to develop new principles for treating cancer, Dr. Prendergast and his research group study modified pathways that determine disease severity, with a specific focus on modifiers of inflammatory processes. They have developed a new class of drug termed IDO (indoleamine 2,3-dioxygenase) inhibitors, which utilize the immune system to counteract inflammation-driven cancers. His laboratory also studies Bifl, a member of the Ras/Rho superfamily, in cancer cell signaling and the role of Bifl 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.

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.