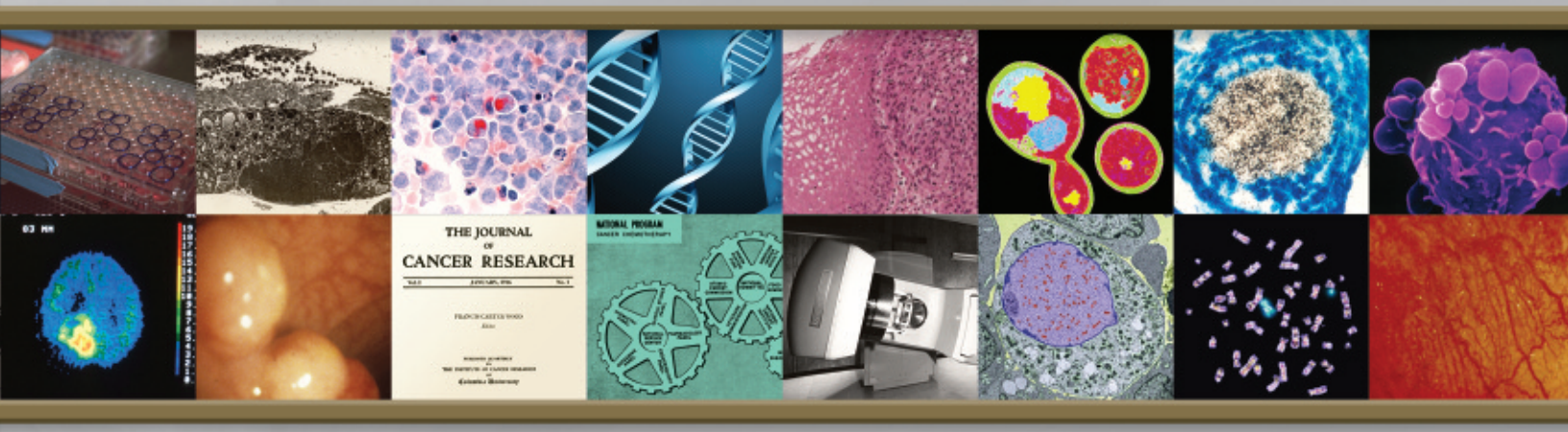


AACR CENTENNIAL 1907 - 2007

AMERICAN ASSOCIATION FOR CANCER RESEARCH

LANDMARKS

IN CANCER RESEARCH • 1907 - 2007

AACR CENTENNIAL 1907 - 2007

American Association for Cancer Research

Landmarks in Cancer Research

Much as there is no one disease called cancer, there is no single moment that truly defines the progress in cancer research made over the past 100 years. Instead, the Landmarks presented here offer a vantage point from which we can begin to understand the seminal discoveries and events that have unfolded since the founding of the American Association for Cancer Research in 1907.

As a centennial year tribute to the AACR's role in supporting the fight against cancer, these Landmarks represent the cumulative progress in the understanding and eradication of cancer by a global community of scientists, researchers, clinicians, and advocates.

The Landmarks before you are the result of more than two years of painstaking research and historical analysis by a committee of established cancer researchers and advocates with diverse expertise and areas of interest. By definition, the Landmarks are events or discoveries after 1907 that have had a profound effect on advancing our knowledge of the causes, mechanisms, diagnosis, treatment, and prevention of cancer. The final selections were based upon reviews of the scientific literature and historical reference works, debate and discussion among researchers in the field, and a rigorous system of review and prioritization by the committee, the senior editors of *Cancer Research,* and the AACR Board of Directors. Acknowledging the collaborative nature of scientific research and the emergence of discoveries over time, attribution to individuals or teams of researchers is not made.

These Landmarks are inherently incomplete. Indeed, they are intended as a living document: an ever-changing testament to human ingenuity and creativity in the scientific struggle to understand and eliminate the 200 diseases collectively known as cancer. Human knowledge, after all, does not advance merely by the passage of time, but by the integration of hypothesis and investigation. These Landmarks offer a perspective on the past that we believe will affect the future.

In the light of history, the science of the early 20th century seems crude, or even quaint, in contrast to our modern techniques and theories. Who knows, then, what opinions scientists in the future will have of the science we term "landmarks" today. Much like our counterparts in 1907, we can scarcely imagine the advances that will unfold over the next 100 years.

We invite you to consider these Landmarks as both a reminder of the past and a challenge for the future.

The Landmark events of the next 100 years are yours to discover.

1907

Sunlight exposure linked to skin cancer.

The first epidemiologic study of sunlight and skin cancer was reported; earlier observations had linked chronic skin conditions common in sailors to exposure to the radiation effects of the sun. Later work in animal models confirmed that skin cancer could be induced by ultraviolet light and sunlight. (1)

1907

American Association for Cancer Research founded on May 7 in Washington, D.C.

1907

Nine research papers presented at the first Annual Meeting of the AACR in New York City.

1907

First publication of the Japanese cancer journal, *Gann* (now titled *Cancer Science).*

1908

Cell-free extracts transmit cancer from one animal to another.

Cell-free agents were shown to transmit leukosis, a form of leukemia and lymphoma, and sarcomas in chickens. This finding would later be verified as evidence for viral initiation of cancer. (2)

1909

AACR writes President William H. Taft advocating funding for cancer research.

1910

Procedures for *in vitro* tissue culture developed.

The fundamental culture techniques, now ubiquitous in the laboratory, allowed researchers to study the evolution of tumor tissue under known conditions and to observe living cancer cells at every stage of growth. (3)

1911

First publication of the French journal, *Bulletin de l'Association Française pour l'Étude du Cancer,* and the Italian journal, *Tumori.*

1913

***Ladies' Home Journal* publishes "What Can We Do About Cancer," the first consumer-oriented article about cancer.**

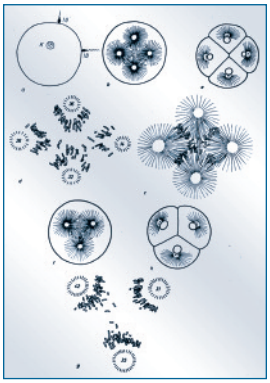
1913

Volunteers establish the American Society for the Control of Cancer, precursor to the American Cancer Society.

1914

Alterations in chromosomes postulated to cause tumor growth.

From earlier work on sea urchin eggs and association of inappropriate segregation of chromosomes and changes in cell growth characteristics came the hypothesis that cancer was caused by abnormal chromosomes. (4)



1915

The first experimental animal model of chemically induced cancer is developed.

Repeated tarring of rabbit skin caused tumors. The discovery added to early evidence for the theory of chemical carcinogenesis building upon the observation in 1775 of scrotal cancer in chimney sweeps. Later work would isolate and identify the specific components of coal tar responsible. (5)

1916

Oophorectomy decreases breast cancer in mice.

Removal of the ovaries from female mice of a strain with a high incidence of spontaneous breast cancer resulted in a decrease in tumors. Later work involving transplantation of ovaries into male mice showed an induction of mammary tumors supporting the suggestion that hormones from the ovary could promote breast tumors. (6)

1916

AACR first publishes *The Journal of Cancer Research*.

1921

American Society for the Control of Cancer creates the first National Cancer Week as an extensive public education campaign.

1922

U.S. Public Health Service opens Office of Cancer Investigations at Harvard Medical School.

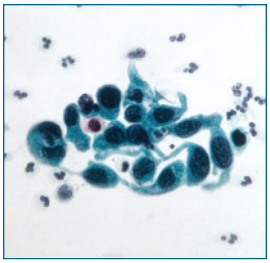
1924

Metabolic studies show that tumors exhibit anaerobic respiration.

Whereas normal tissues use oxygen to break down nutrients for growth as their primary mode of respiration, it was observed that within tumors, cells respire anaerobically, fermenting sugars without oxygen. It will take several decades before hypoxia is revisited as a marker for tumors. (7)

1927

Cancer named one of the top three causes of death in America by U.S. Census Bureau.



1928

Genetic mutation proposed as the origin of cancer.

As an alternative to the infection theory of cancer, popular at the time because of the expansion of microbiology as a field of study, came the proposal that somatic mutation was the cause of cancer. As Mendel's works were rediscovered in 1928, the field of genetics grew. The term "somatic mutation" had been coined in 1916. (8)

1928

Cervical cancer cells visible in smears of exfoliated vaginal cells.

Findings of cervical cancer cells in smears were met with skepticism, and it would take until the 1960's before the "Pap" smear would become widely accepted as an effective method of screening and cancer prevention. (9)

1928

X-rays shown to be mutagenic.

X-rays are shown to be mutagenic in the common fruit fly. This discovery formed the basis for thinking about how carcinogens participate in tumorigenesis. (10)

1930

The first pure carcinogen, benzopyrene, isolated from coal tar.

The known cancer-causing environmental substance, coal tar, was fractionated into components and assayed in mouse models to identify the individual chemicals responsible for carcinogenesis. (11)

1930

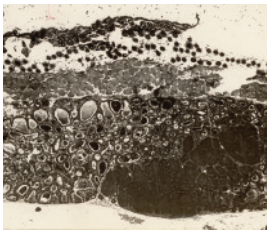
***The American Journal of Cancer* replaces *The Journal of Cancer Research* as the official AACR publication.**

1930

The Ransdell Act establishes the National Institute of Health.

1932

Injected synthetic hormones induce breast cancer in mice.



Building on work on endogenous hormones, it was demonstrated that addition of synthetic exogenous hormones such as folliculin (and in 1952, diethylstilbestrol) can induce cancer. (12)

1932

Electron microscope invented.

The electron microscope permitted the visualization of minute subcellular structures, allowing observation of detailed differences between malignant and normal tissues. (13)

1937

Transplantation of a single leukemic cell transmits leukemia in mice.

Studies showed that not all cancer cells behaved in an identical manner; some were uniquely capable of initiating and maintaining a tumor. This work laid the foundation for the later search for a cancer stem cell. (14)

1937

The National Cancer Institute Act establishes the NCI as an independent research institution.

1938

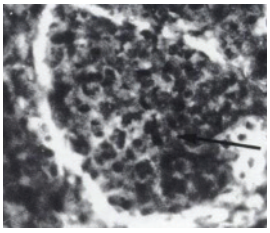
Telomeres identified.

The ends of chromosomes were shown to be protected by a structure that prevented their fusion. Later, it was shown that telomeres are repeated simple sequence elements that are added by an enzyme, telomerase, which is not normally expressed in somatic cells. In each cell division, telomeres shorten. When they become sufficiently truncated they cause the cells to enter into senescence and die, limiting the number of divisions a cell can undergo and suppressing tumor development. (15)

1938

The discovery of antigens explains why tumors can be transplanted within inbred strains.

Previous work to transplant tumors had been successful in some instances but failed in others. The discovery of major histocompatibility antigens later led to an immunologic explanation that applied to grafts of normal tissue as well as to malignant tissue. (16)



1938

Chemicals induce cancer in two distinct steps of initiation and promotion.

Tumorigenesis is identified as a multistage disease, and it is shown that chemicals induce cancer in two distinct steps of initiation and promotion. A nonspecific irritant (wounding) was shown to promote tumorigenesis after initiation with a suboptimal dose of carcinogen (tarring or application of Shope papillomavirus to rabbit ears). (17)

1939

Transplanted animal tumors shown to grow blood vessels.

Tumors transplanted into the ears of rabbits elicited a vascular network. This was early evidence of the phenomenon of angiogenesis, or new blood vessel growth, which would later become a target for antiangiogenesis cancer therapies. (18)

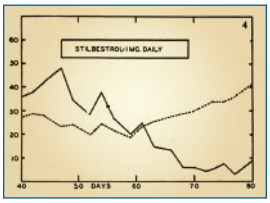
1940

Caloric restriction reduces tumors in mice.

Caloric intake was shown to be proportional to the incidence of tumors of several kinds, including spontaneous mammary carcinomas and hepatomas in susceptible mouse strains and benzopyrene-induced skin tumors. Only recently, with the increasing prevalence of overweight and obesity in the global population, have the implications of the work been revisited. (19)

1941

Hormone dependence of prostate cancer demonstrated.



The therapeutic use of physical castration or chemical castration by treatment with estrogens was shown to decrease disease burden in metastatic prostate cancer whereas injection of androgens increased metastases. (20)

1941

Cancer Research replaces *The American Journal of Cancer* as AACR's official journal.

1944

DNA identified as the active material in the genes of bacteria.

It was not known whether the protein or DNA components of the chromosomes contained the information necessary for inheritance. This work showed that DNA contained the heritable information and set the stage for many important works and techniques. (21)

1944

The American Society for the Control of Cancer becomes the American Cancer Society.

1944

The Public Health Services Act designates NCI as a division of the National Institutes of Health.

1945

The Atomic Bomb Casualty Commission established to monitor the effects of radiation exposure.

1946

Nitrogen mustard established as the first chemotherapeutic agent.

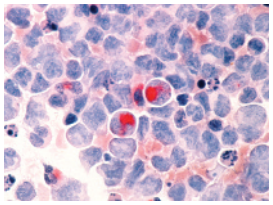
Observational reports that soldiers exposed to nitrogen mustard during wartime had low white blood cell counts led to testing of nitrogen mustard as chemotherapy for cancer. Intravenous nitrogen mustard was shown to slow the growth of lymphomas and leukemias in patients refractory to radiation therapy and it achieved remissions of a few months. Nitrogen mustard was approved for cancer treatment in 1949. (22)

1947

The Nuremberg Code establishes the legal principle of voluntary consent for human subjects of research.

1948

First successful chemotherapy for childhood leukemia.



A synthetic folate antagonist achieved a 3-month remission in 10 of 16 children with leukemia. Although not successful by today's standards, this was an important result that would lead to further work on antimetabolites and the first generation of effective chemotherapeutic agents. (23)

1948

The United Nations establishes the World Health Organization.

1950

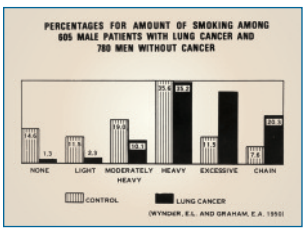
First rationally conceived nucleotide analog chemotherapeutic agents developed.

Drug design had been primarily by trial and error. The design of molecules similar to the bases of DNA, but sufficiently different to prevent replication, proved an effective drug targeting approach that led to several chemotherapeutic drugs for cancer such as 6-mercaptopurine and 5-fluorouracil, which are still in use today. (24)

1950

Epidemiological work links tobacco smoking to lung cancer.

A retrospective analysis of the smoking habits of patients with lung cancer showed an association with tobacco. This was followed by a prospective study of male doctors that showed a clear relationship between smoking and lung cancer deaths. Tobacco exposure is now a known risk factor for many cancer types, accounting for an estimated 30% of all cancer mortality. (25)



1951

Leukemia in mice shown to be transmissible by a virus.

Leukemia had been considered an inherited disease before it was shown that it could be transmitted from one mouse strain to another by a virus and then passed from one generation to another via vertical transmission. These findings laid the groundwork for later research on other mouse tumor viruses and those in other species. (26)

1951

Cobalt-60 irradiator developed.

Radiotherapy previously had been carried out using radium, which was in limited supply and needed to be used in close proximity to the tumor. Radioactive cobalt provided a continuous source with greater ability to treat internal tumors, with less damage to the intervening tissue. Clinical cobalt-60 is still used in much of the developing world. (27)

1951

Ultrasound imaging developed for detecting tumors.

Although earlier studies had used ultrasound as a therapy and had examined its use as an imaging tool, research showed that ultrasound could detect differences in density between malignant and normal tissues. (28).

1953

Structure of DNA described.

Not only was the global structure of DNA identified but how the bases pair and possible implications for methods of replication were elucidated. (29)

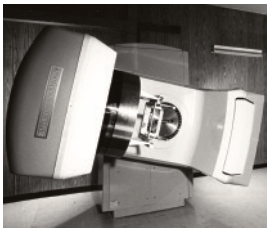
1953

Human carcinoma cell line, HeLa, established.

The HeLa epithelial cell line is readily grown in laboratories worldwide and has become a fundamental tool for studying many aspects of molecular biology. Stable cell lines such as HeLa allow researchers to use genetically identical cells for experiments over long-term courses of repeated culturing in a manner not possible with primary cells. (30)

1953

Medical linear accelerator developed for radiotherapy.



Unlike early radiotherapy machines that used a radioactive source to generate X-rays, the linear accelerator produces a beam of electrons. This eliminated the need to replace the radioactive source and is limited in power by the length of the accelerator tube. (31)

1953

First publication of AACR Annual Meeting abstracts as *Proceedings of the American Association for Cancer Research* (154 abstracts).

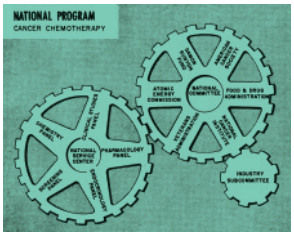
1955

Tumor clonogenic assay developed.

Although human cells had been cultured before, these new methods allowed cultures to be propagated from single human cells, enabling the kind of detailed genetic studies previously only possible for bacterial cells. (32)

1955

U.S. Congress funds National Chemotherapy Program to test compounds that might be effective against cancer.



1956

First successful chemotherapy for solid tumors.

Building on earlier work on folate and aminopterin, another anti-folate, methotrexate, was developed. The drug was shown to be effective in a small group of three patients with metastatic choriocarcinoma and chorioadenoma. (33)

1958

Food Additives Amendment prohibits food additives shown to induce cancer in humans or animals.

1959

In vitro viral carcinogenesis demonstrated.

Earlier work had shown that viruses could be used to transmit cancer from one organism to another. New studies showed that chick embryo cells infected with Rous sarcoma virus continued to grow in culture and produce more virus. The infected cells had changes in morphology and rapid, disordered growth characteristic of cancer cells. (34)

1959

DNA repair after radiation demonstrated.

Chinese hamster ovary cells subjected to X-irradiation and surviving did not display heritable damage but repaired the damage prior to cell division. This finding confirmed the presence of DNA repair mechanisms, later shown to be defective in some cancers. (35)

1959

Dose-response relationship shown in radiation leukemia.

Radiation carcinogenesis was unequivocally established in human populations, and the nature of the dose-response relationship was described. (36)

1959

Radioimmunoassay developed.

The radioimmunoassay uses antibodies to detect the amounts of specific proteins in a solution. Originally developed to measure insulin levels in the blood of diabetics, this technique is now the basis for diagnostic tests to measure serum proteins and biomarkers, such as prostate-specific antigen, although now the detection mechanism often uses fluorescent rather than radioactive labeling. (37)

1959

AACR membership passes 1,000.

1960

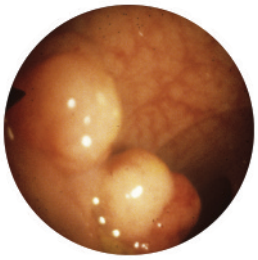
Growth factors are purified and identified.

The fact that growth factors were necessary for cells to survive and replicate had long been known, but the individual components of serum responsible had not been identified. The purification of nerve-growth factor (NGF) led to the identification of other growth factors, their cognate receptors, and their complex signaling pathways. These pathways have emerged as novel targets for therapies such as those targeting the epidermal growth factor receptor. (38)

1960

Screening techniques for prevention of colon cancer adopted.

The sigmoidoscope permitted early identification of colorectal cancer as well as precancerous polyps, leading to increased survival rates. Today, it is estimated that screening, by sigmoidoscopy, colonoscopy, barium enema, or fecal occult blood testing, may result in a 20% decrease in colorectal cancer mortality. (39)



1960

American Cancer Society urges widespread use of Pap smear to detect cervical and uterine cancers.

1960

First AACR award established: G.H.A. Clowes Memorial Award.

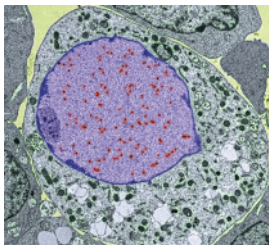
1961

Triplet code for amino acid translation deciphered.

A synthetic RNA molecule consisting entirely of uracil is shown to produce a polypeptide of repeating phenylalanine amino acids. Researchers went on to show how triplets of DNA bases transcribed to RNA are then translated into the individual amino acids of peptides, with different triplets representing the different amino acids, providing the mechanism in which DNA encodes proteins. (40)

1963

Chemotherapy cures Burkitt's lymphoma.



The geographical distribution of Burkitt's lymphoma in parts of sub-Saharan Africa, described in the early 1960s, suggested that it was caused by a vector-transmitted virus. The first successful treatment of a human cancer thought to be caused by a virus, later shown to be Epstein Barr virus, was reported. (41)

1964

U.S. Surgeon General Luther L. Terry publicly affirms that smoking leads to lung cancer.

1964

The World Medical Association adopts the Declaration of Helsinki for governing research on human subjects.

1965

Chemoprevention demonstrated in animal models of chemical carcinogenesis.

A variety of chemicals are shown to prevent cancer induced by chemicals by activating the detoxification system, competitively inhibiting the carcinogen, preventing initiation of carcinogenesis and other unknown mechanisms. The term chemoprevention was later coined as a new area of focus in cancer research. (42)

1965

Federal Cigarette Labeling and Advertising Act requires printing of warnings on cigarette packs.

1966

Combination chemotherapy and maintenance treatment prolong remission.

Preliminary studies of pediatric leukemia had shown synergistic effects of dual-drug treatments. By selecting agents with different side effects, it was proposed that it might be possible to combine several chemotherapy drugs to give greater efficacy without prohibitive toxicity. One of the first of these was MOPP (nitrogen mustard, vincristine, prednisone and procarbazine), a successful treatment for Hodgkin's disease. Other combination chemotherapies followed. (43)

1966

The first dedicated mammography machine developed.

For several decades prior to the invention of this machine, breast images had been obtained using standard x-ray technology. Subsequent developments allowed for reduced exposure and, eventually, digital mammograms.

1966

U.S. Surgeon General requires institutional review of clinical research, leading to the establishment of institutional review boards.

1967

Estrogen receptor identified.

Targets in uterine tissue are identified that interact specifically with estrogen. This finding was the first step that led to the detection of estrogen receptors in breast cancers and design of specific and effective therapies for hormone-dependent breast cancer. (44)

1968

AACR issues its first policy statement on tobacco.

1969

Rhabdomyosarcoma is an inherited familial cancer syndrome.

A study of children with rhabdomyosarcoma who had relatives who developed other organ-site cancers at an early age led to the identification of a familial cancer syndrome later shown to be primarily influenced by inherited mutations in p53. (45)

1969

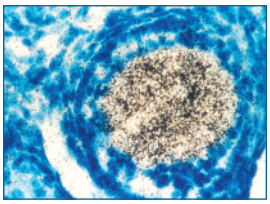
Tumors successfully heterotransplanted into athymic "nude" mice.

Heterotransplantation had only been possible in certain immune privileged sites in the mouse, such as the eye chamber, and eventually those grafts were rejected. The removal of the thymus, and thus the T-cell immune response, from young mice permitted transplantation of human tumors into mice for their characterization in a whole organism. (46)

1969

In situ hybridization introduced.

This method enabled detection of the location of specific genes within chromosomes. Today, a wide variety of probes ranging from whole chromosome fluorescent paints to probes for individual genes and gene segments can be used to detect changes in genome copy number, structure or nuclear location. Combining these with image analysis techniques and multiplex labeling strategies enables today's multicolor cytogenetics assays termed SKY or M-FISH in which all human chromosomes can separately visualized. (47)



1970

Multidrug resistant (MDR) cell lines described.

Resistance to multiple cytotoxic agents is one of the major causes of chemotherapy failure. Research would lead to the identification of drug transporters present in the cell membranes that control entry of drugs in and out of the cell and are important for the pharmacokinetics of drug action. (48)

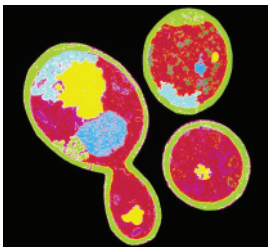
1970

Reverse transcriptase identified.

The discovery of reverse transcriptase had implications for how viruses caused cancer and also challenged the "central dogma" that the transfer of cellular information passed from DNA to RNA to protein, and not in reverse. (49)

1970

Cell cycle is an ordered process.



By fusing mammalian tissue culture cells at different stages of the cell division cycle and by observing the division of mutant yeast cells under the microscope, it was determined that the order of the cell division cycle is regulated and genes involved in cell cycle regulation were identified and ordered. This work laid the groundwork for the discovery of checkpoint proteins and how cancer cells derail checkpoints. (50)

1970

Chromosome banding technique developed.

Q-banding using alkylating fluorochromes allowed individual chromosomes and aberrations therein to be identified with high accuracy. This technique was followed by a large number of different banding chemistries. (51)

1970

DNA restriction enzymes discovered.

Restriction enzymes cut DNA at specific and reproducible locations. They would become an important tool in molecular biology, enabling basic characterization of genomes through early mapping techniques prior to sequencing. Once it was determined that they recognized specific sequence motifs surrounding cleavage sites, they would be used for many functions including cloning, transfer, and testing of genes and genotyping. (52)

1970

U.S. Public Health Cigarette Smoking Act bans advertisements for cigarettes.

1970

The U.S. Environmental Protection Agency forms and provides regulatory enforcement against environmental carcinogens, such as asbestos.

1971

Two-hit hypothesis proposed.

Using retinoblastoma as a model and observing patients with one or both eyes affected and those with and without a family history of disease, it was shown how cancer can be caused by two mutational events. In the inherited form of the disease the first mutation or "hit" occurs in the germline cells and the second in the somatic cells. In the non-hereditary form of the cancer, both "hits" occur in somatic cells over time. (53)

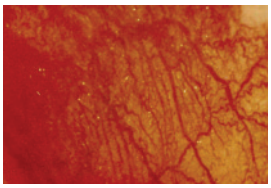
1971

Daughters of mothers who used diethylstilbestrol during pregnancy can develop vaginal cancer.

Vaginal cancer is rare, particularly in young women. A small group of women aged 14-25 with vaginal cancer showed a highly significant association with treatment of their mothers during the first trimester of pregnancy with diethylstilbestrol (DES). In 1971, the FDA issued a warning against prescribing DES for pregnant women. Between the time that DES was first manufactured in 1938 and the discovery of health problems in 1971, an estimated 5-10 million pregnant women and their children were exposed to the drug. (54)

1971

Tumor growth dependent on angiogenesis.



Starting from the observation that transplanted tumors that did not grow blood vessels were unable to increase in size, serial experiments demonstrated that tumors secreted factors that encourage new blood vessels to grow into and feed the tumor. Eventually, the genes for these factors would be identified and would become a target for molecular therapies. (55)

1971

Taxol, a natural plant product, developed for chemotherapy.

A component of the Pacific Yew tree, Taxol was shown to actively inhibit leukemia cell lines *in vitro*. The isolated molecule was later produced by chemical synthesis allowing the increased production necessary for it to be used as a drug treatment. Taxol was approved by the FDA in 1992 for treating ovarian cancer and, subsequently, for breast cancer. (56)

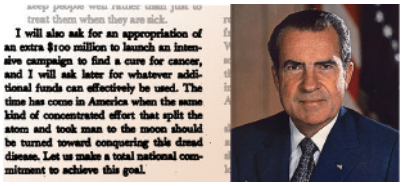
1971

Cells within a tumor can be differentiated into benign cells.

Shown previously with teratomas (tumors that contain differentiated tissues), it was also demonstrated with squamous cell carcinomas that some cells within a tumor are capable of differentiating into benign cells incapable of forming a tumor when transplanted. This finding supported the idea of a cancer stem cell. (57)

1971

President Richard Nixon declares a "War on Cancer" in State of the Union address.



treat them when they are sick.

I will also ask for an appropriation of an extra $100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal.

1971

National Cancer Act of 1971 enables NCI Director to expand and designate Cancer Centers and Comprehensive Cancer Centers.

1972

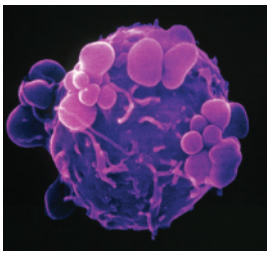
Bone marrow transplantation established as a cancer treatment.

Bone marrow transplants were used to replace blood-cell-generating hematopoetic cells in patients with leukemia who had radiation therapy. Initially, transplants were from twin donors and later from donors matched by cell surface antigens. More recently, culturing stem cells extracted from the patient's blood before treatment has been the method. (58)

1972

Apoptosis, programmed cell death, triggered by cancer therapies.

Apoptosis is the process of controlled destruction of unwanted cells, the opposite of cell replication. Cells exhibit characteristic stages of DNA and cytoplasmic condensation, followed by the breaking of the cell into apoptotic bodies and their degradation. Apoptosis can also be triggered by cytotoxic drugs. It would later be shown that tumors can arise from mutations in the apoptosis machinery, making cells resistant to death signals. (59)



1972

CAT scanner invented.

Previous imaging techniques had been unable to distinguish between tissues of similar density. The development of the computerized axial tomography (CAT) system, which uses a series of sectional X-rays, allowed a greater sensitivity of imaging, particularly for detecting abnormalities in soft tissue. (60)

1972

Regression models and life tables applied.

The Cox regression model and its generalizations represented an important biostatistical advance with application to cancer research as well as many other areas. It affected the conceptualization of follow-up studies in a manner that led to nested case-control and case-cohort sampling methods and other applications relevant to clinical trial design. (61)

1973

NCI begins the Surveillance, Epidemiology and End Results Program, a model for large-scale cancer registries worldwide.

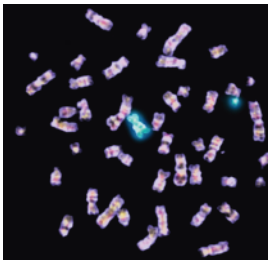
1974

Errors in DNA replication responsible for tumor oncogenesis.

It was proposed that as DNA was synthesized the polymerase might make errors in which bases were incorporated either during replication or repair. These mutations might be the consequence of an error-prone polymerase or the presence of carcinogens. (62)

1974

Specific chromosome rearrangements are characteristic of types of leukemia.



Cytogenetics and the evolution of molecular diagnostics for leukemia and lymphoma lay the groundwork for future targeted therapies. The Philadelphia chromosome of chronic myelogenous leukemia, with its characteristic translocation from chromosome 22 to 9, will later be shown to generate the fusion protein Bcr-Abl, against which the molecular treatment imatinib (Gleevec) acts. (63)

1974

DNA cloning methods developed.

A method for isolating DNA fragments and introducing them into autonomously replicating bacterial plasmids provided the ability to isolate, identify, and amplify DNA fragments from any organism. The availability of pure and abundant sources of specific DNA fragments enabled the determination of the sequence of bases they contain, and the detection of mutations that cause cancer and heritable diseases. Ultimately, the ability to clone DNA was the basis for determining the sequence of the human and other genomes. (64)

1974

First Lady Betty Ford undergoes a mastectomy and speaks publicly about breast cancer.

1975

Method developed to detect specific DNA fragments in mammalian genomes (Southern blotting).

A method to detect unique sequence genes in complex genomes enabled more precise study of the genetic basis of inherited diseases and cancer. Modifications to the original technique made in 1979 substantially shortened the time needed to do the nucleic acid hybridization and increased the sensitivity to the point that single copy genes in the human genome could be detected within a few days. (65)

1975

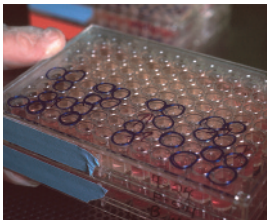
BrdUrd labeling techniques introduced.

Immunochemical techniques were developed to detect incorporation of BrdUrd labeled nucleotides. This was enabled by development of an antibody against BrdUrd labeled DNA, and later by development of a flow cytometric technique that simultaneously measured DNA content and incorporated BrdUrd. (66)

1975

Monoclonal antibodies produced.

By fusing an antibody-deficient myeloma cell with a B-cell it was possible to create a line of cells or hybridoma that would produce large quantities of identical or monoclonal antibodies that all recognize the same part of a molecule. Monoclonal antibodies are used in a wide range of applications, diagnostics as well as drug therapies such as trastuzumab (Herceptin). (67)



1976

Viral oncogenes exist in a related proto-oncogene form in normal cells.

By using hybridization techniques (because this work was before the advent of DNA sequencing), researchers showed that there were forms of cancer-causing viral oncogenes in chicken cells. These were later shown in other species, including mice and humans. (68)

1976

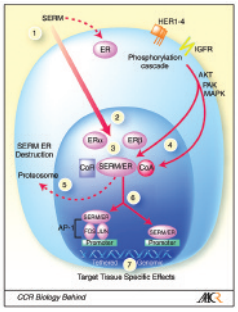
Combination chemotherapy regimen cures pediatric leukemia.

By applying the previously proved theory of combining chemotherapies in different phases and based on different toxicities, and including radiotherapy, a regimen was developed that prolonged remission in 80% of patients with acute lymphocytic leukemia. (69)

1977

Tamoxifen approved for treatment of breast cancer.

Building on earlier work on oophorectomy and estrogen removal as a treatment for breast cancer, tamoxifen was shown to inhibit growth of mammary tumors in mice, leading to its approval for treatment of breast cancer. It was also shown that tamoxifen was a selective estrogen receptor modulator (SERM), acting in opposition to estrogen in some tissues but acting like estrogen in others. (70)



1977

Individual cells within a tumor have different potential for metastasis.

Taking individual cells from a tumor and transplanting them into mice showed that not all cells are capable of forming new tumors and only some cells within a tumor may be capable of metastasis. (71)

1977

RNA splicing demonstrated.

That the linear sequence of bases in mRNA results from transcription of a corresponding sequence of DNA had been accepted. New work, first done in viruses and later extended to the cellular genome, showed that mRNA is made from much larger precursors, from which segments are removed by a process called RNA splicing. Alternative splicing patterns are found in many genes to produce different protein products, such as in the p16-ARF locus, which encodes two important tumor suppressors. (72)

1977

Medical MRI scanner developed.

The medical magnetic resonance imager (MRI) allowed sensitive visualization of internal structures without the use of X-rays. MRI provides more clear and detailed images of the soft tissue structure than other imaging methods, making it an invaluable tool in early diagnosis and evaluation of tumors. (73)

1977

DNA sequencing developed.

The introduction of DNA sequencing led to many advances. Over time, sequencing techniques have been refined and improved to use fluorescent dyes rather than radiolabeling, reduce sample volumes, increase the lengths of sequence read, and use automated robotic systems. (74)

1977

American Cancer Society sponsors first "Great American Smokeout" to curb tobacco use.

1978

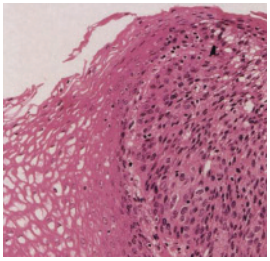
Tobacco-specific nitrosamines identified as carcinogenic components of cigarette smoke.

Nitrosamines derived from nicotine are shown to cause cancer in animal models. These substances will later be shown to contribute to human lung and oral cancers. (75)

1979

p53 discovered.

Discovered as a cellular protein bound by the monkey oncogenic virus SV40, or as a transformation associated protein in chemically induced tumors, p53 was originally thought to be an oncogene. Later studies showed that it is a tumor suppressor gene that is mutated in the germline of individuals with the Li-Fraumeni cancer pre-disposition syndrome and in 50% of diverse human tumors. (76)



1979

DNA damage products detected in human DNA.

DNA adducts were detected in cells incubated with the carcinogen benzo(a)pyrene. The adducts were more common in cells from older persons. The detection of DNA damage products would be useful for identification of carcinogens and in epidemiologic studies. (77)

1979

Tyrosine phosphorylation and protein tyrosine kinases discovered.

The discovery of a new type of protein kinase that phosphorylates tyrosine residues in proteins, associated with the polyomavirus middle T antigen transforming protein and the Rous sarcoma virus v-Src oncoprotein, led to the conclusion that dysregulated tyrosine phosphorylation by an activated tyrosine kinase can cause malignant transformation. In later years, inhibitors that target disease-causing tyrosine kinases would be approved for treatment. (78)

1979

Method developed to detect gene transcripts (Northern blotting).

Identification of the RNA products of transcription is essential for addressing many biological problems. The ability to separate RNA by size on gels, transfer it to a solid support, and then detect specific molecules by nucleic acid hybridization provided a critical technical link to enable detection of the transcripts produced by any gene. (79)

1979

Method developed to detect specific proteins (Western blotting).

Establishing how particular genes elicit specific phenotypes requires detection of the protein products encoded by their transcripts. A rapid and sensitive method combining gel electrophoresis for fractionation, and electrophoretic transfer to a solid support for subsequent detection by specific antibodies enabled this detection. Now, proteins can also be detected using mass spectrometry. (80)

1979

U.S. Department of Health, Education and Welfare creates The Belmont Report, ethical guidelines for research on humans.

1980

Degradation of collagen in tumor environment promotes metastasis.

For tumors to metastasize they must pass through the epithelial and endothelial basement membranes and gain access to the blood stream. Studies showed that tumors secrete proteases that degrade collagen and that cell lines with the highest levels of collagenase had the highest potential for metastasis. (81)

1980

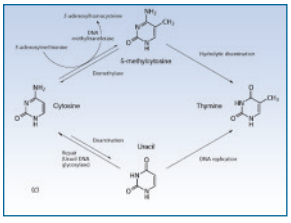
Prostate specific antigen is a marker for prostate cancer.

The association of levels of prostate specific antigen (PSA) with risk for prostate cancer led to the first routine protein biomarker test used in cancer screening and prevention. (82)

1980

DNA methylation shown to be important in cancer.

Methylation of DNA can prevent a gene from being switched on. Chemotherapy drugs were shown to affect methylation and activate genes, suggesting that targeting methylation of specific genes may provide a way of controlling gene expression and lead to future therapies. It was later demonstrated that the methylation patterns of some genes were different in tumors compared with cells in the same tissue that were not part of the tumor. (83)



1980

NCI commissions National Research Council to review data linking diet and cancer.

1981

Cell surface antigens of lymphocyte subtypes aid further classification of leukemias and lymphomas.

Development of monoclonal antibodies that recognized specific cell surface receptors characteristic of stages of differentiation of lymphoctyes allowed subclassification of different diseases and more accurate prognosis. (84)

1981

Ubiquitin system for protein degradation identified.

How ubiquitin act as a tagging system to mark proteins that need to be destroyed by the proteosome was demonstrated. Ubiquitination controls proteins involved in many fundamental cell processes important for cancer such as cell cycle, DNA repair and apoptosis. Later work involved targeting drugs to this pathway as a mechanism to promote apoptosis. (85)

1981

First mouse ES cell line established.

This technology allows the generation of mouse embryos with directed mutations such as transgenics or knockouts. (86)

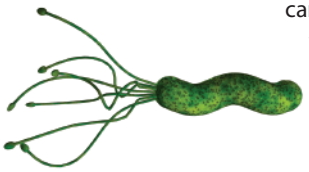
1982

Proto-oncogenes are involved in cancer.

Building on earlier work, research showed that the endogenous proto-oncogenes of normal cells could become mutated, becoming oncogenes and causing cancer. (87)

1982

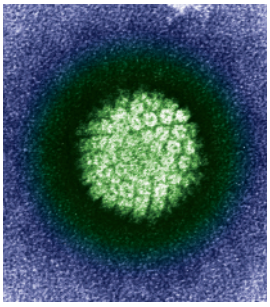
***Helicobacter pylori* isolated from human stomach ulcers.**



Many decades previously, work had shown viruses involved in causing cancer, but it took years for it to be widely accepted that infection with *H. pylori* could cause stomach ulcers and that continuous infection and inflammation could result in cancer. (88)

1983

Human papillomavirus identified as the causative agent of cervical cancer.



Early epidemiological work documenting the low incidence of cervical cancer in nuns suggested that the disease might be caused by an infectious agent transmissible by sexual contact. The isolation of human papillomavirus (HPV) DNA from biopsy samples identified the HPV 16 and 18 strains as highly associated with cervical cancer. This work would lead to the development of vaccines to prevent cervical cancer. (89)

1983

Oncogene cooperation demonstrated.

The observations that normal cells required multiple genetic events to become oncogenically transformed provided a model for the molecular basis for the multistep nature of cancer. (90)

1983

Polymerase chain reaction developed.

The polymerase chain reaction (PCR) uses a heat-stable DNA polymerase from thermophilic bacteria, allowing replication of multiple copies of a DNA sequence *in vitro*. This technique permitted an explosion of new methods for cloning, sequencing, and diagnostics and is used in virtually every genetics and molecular biology laboratory. (91)

1983

National Academy of Sciences issues report, "Diet, Nutrition and Cancer," leading NCI to introduce dietary guidelines to reduce cancer.

1984

Bcl-2 links apoptosis and cancer.

Links between Bcl-2 and apoptosis provided the first evidence of a role for programmed cell death in cancer development. (92)

1985

Lumpectomy is a viable alternative to mastectomy.

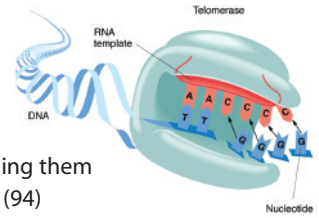
Clinical studies showed that lumpectomy plus radiation therapy resulted in improved survival compared with radical mastectomy for women with early-stage breast cancer. (93)

1985

Health Research Extension Act expands the NCI mission to include research on the continuing care of patients and their families.

1986

Telomerase discovered.



The mechanism of replication at the ends of chromosomes, or telomeres, had been unclear. The discovery of an enzyme capable of synthesizing telomeric DNA onto chromosome ends, thus replenishing them as cells divided, had implications for aging and cancer. (94)

1986

Retinoblastoma gene, RB, identified.

The retinoblastoma gene, RB, was identified in children with hereditary retinoblastoma and shown to be a tumor suppressor gene. (95)

1987

Her-2/neu receptor overexpressed in some breast cancers.

The growth factor receptor gene Her-2/neu is shown to be amplified in approximately 15% of stage I breast cancers. The degree of amplification is associated with decreased survival. This biomarker would later become the target of the highly successful molecular therapy, trastuzumab (Herceptin), improving survival in Her-2/neu-positive patients. (96)

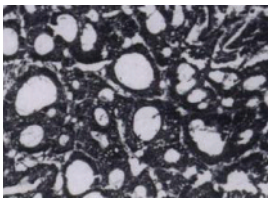
1987

Technique developed to use homologous recombination in mouse ES cells to create genetically engineered mouse strains.

Technology to generate mice lacking specific genes, or containing specific mutations, has provided insights into the function of genes involved in development that underlies many inherited diseases and contributes to cancer. Generation of strains with mutations found in human cancers enables modeling of the initiation and progression of cancers in mice that resemble their human counterparts. Such models should prove useful for testing of biologically targeted therapies. (97)

1988

Tumor suppressor genes are mutated in cancer and are the targets of tumor viruses.



Mutations in tumor suppressor genes have been shown to be responsible for several familial cancers such as retinoblastoma (Rb) and Li-Fraumeni syndrome (p53) as well as spontaneously mutated in many types of non-inherited cancer. They are also the targets of viral oncogenes such as the E1A proteins of adenovirus and E7 of human papillomavirus, which bind and inactivate Rb. (98)

1988

In response to rapidly growing research needs, AACR hosts its first special conference, "Gene Regulation and Cancer."

1990

Specific molecular alterations correlated with stages of cancer progression.

Expanding on the two-hit hypothesis of carcinogenesis in colorectal tumors, researchers showed that a number of events occurred, including activation of oncogenes and inactivation of tumor suppressor genes, totaling mutations in at least four to five genes, which influenced progression from a benign polyp to a large metastatic malignant tumor. (99)

1990

BRCA1 mutations are associated with breast cancer.

The identification of gene variants associated with a family history of breast cancer allowed screening of high-risk women and the choice for those with known increased risk to take preventive measures such as tamoxifen therapy or mastectomy. (100)

1990

Americans with Disabilities Act protects cancer survivors against discrimination in the workplace.

1990

Breast and Cervical Cancer Mortality Prevention Act provides grants to improve programs for breast and cervical cancer prevention.

1990

San Luis Obispo, California, becomes the first city in the world to ban smoking in all public buildings.

1990

NIH and the U.S. Department of Energy formally begin the Human Genome Project.

1991

Specific mutation in p53 in liver cancer associated with exposure to environmental carcinogen, aflatoxin.

Mutations in codon 249 of p53 in hepatocellular carcinoma, a cancer endemic in locations in southern Africa and Asia, are shown to be associated with aflatoxin exposure. (101)

1991

Fifteen U.S. departments and agencies join to create the Federal Policy for the Protection of Human Subjects, informally known as the "Common Rule."

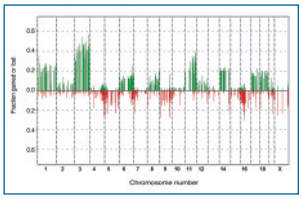
1991

AACR publishes first issue of *Cancer Epidemiology, Biomarkers & Prevention.*

1992

Comparative genomic hybridization developed.

A new technique allows changes in genome copy number to be mapped onto normal representations of the human genome. Initial mapping representations were metaphase chromosomes but these have now been supplanted by a wide range of microarray technologies including some that allow allele-specific analysis. (102)



1992

The U.S. Department of Defense mandated to fund the Breast Cancer Research Program.

1992

American Cancer Society recommends widespread use of prostate-specific antigen test for prostate cancer.

1992

Mammography Quality Standards Act regulates mammography screening facilities, providers and equipment.

1994

Carcinomas originate from normal stem cells that become a cancer stem cell.

Investigations show that a determined stem cell required for normal tissue renewal is the most likely cell of origin of carcinomas. (103)

1994

AACR membership passes 10,000.

1995

Microarray technology developed for molecular profiling.

A chip that can assay the expression of thousands of genes from one sample rapidly expands the generation of data on molecular targets and diagnostics and drives the need for computational analysis methods. This hardware and software can be applied to gene expression, measuring genetic variation at SNPs and gene copy number and examining alternative splicing to measure biomarkers for individual cancers, which ultimately can lead to personalized therapies. (104)

1995

Computer-guided technology improves delivery of radiation therapy.

Computerized systems improve the accuracy of radiation therapy with better focusing on the tumor, reducing damage to surrounding healthy tissue. (105)

1995

AACR publishes first issue of *Clinical Cancer Research*.

1998

Use of a monoclonal antibody (trastuzumab, Herceptin) significantly improves survival in advanced Her-2/neu breast cancer.

Patients with Her-2/neu-positive metastatic breast cancer who were treated with chemotherapy plus trastuzumab (Herceptin) lived longer and their tumors showed a greater decrease in size compared with those in patients who received chemotherapy alone. (106)

1998

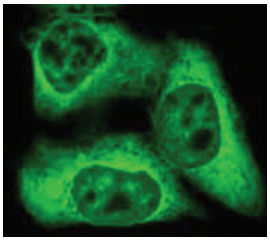
Selective estrogen receptor modulators prevent breast cancer in high-risk women.

A study showed reduction of breast cancer incidence by 44% in women at high risk for developing breast cancer who were treated with selective estrogen receptor modulators, leading to FDA approval of tamoxifen for prevention of breast cancer. (107)

1998

PTEN is a lipid phosphatase.

This observation focused attention on the PI3K pathway in cancer development, which is currently an important area of drug development. (108)



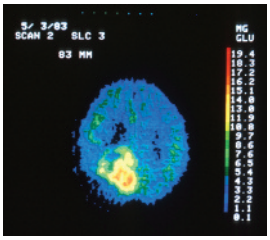
1998

RNAi knockdown demonstrated.

RNA interference provides a method to switch off the actions of genes and can be performed in a high-throughput manner, unlike the creation of knockout mice, which is very time-consuming. Researchers are using RNAi to identify genes that might be involved in cancer by switching them off and examining the consequences. It is hoped that therapies might one day be enhanced through RNAi, for example, using RNAi to switch off genes involved in drug resistance to make chemotherapy more effective. (109)

1998

PET scanner approved for functional imaging.



Positron emission tomography (PET) uses an injected dye to view tissues that are highly metabolically active. PET can identify tumors that are fast growing and active. It is more sensitive at detecting small tumors and metastatic tumors than CT or MRI and so may aid in early diagnosis. (110)

1998

Human embryonic stem cells grown for the first time.

Embryonic stem cells have the capacity to become any cell type. Various possible applications have been suggested for how stem cells might be used to cure cancer, from generating host-identical replacement cells for tissues that have been surgically removed or destroyed by radiation therapy to generating immune cells that recognize tumors and can enhance the body's own defense system to kill cancers. (111)

1998

Master Settlement Agreement forces tobacco companies to pay $246 billion to U.S. states over next 25 years as restitution for violating antitrust and consumer protection laws.

1998

250,000 people take part in the Cancer March on Washington, D.C., in support of increased cancer research funding.

1998

U.S. Congress enacts a plan to double the 1998 National Institutes of Health budget by 2003.

1999

AACR launches the Scientist ↔ Survivor Program to unite scientific, cancer survivor, and patient advocacy communities worldwide.

2000

Breast and Cervical Cancer Treatment Act passes to provide treatment for low-income women diagnosed with cancer.

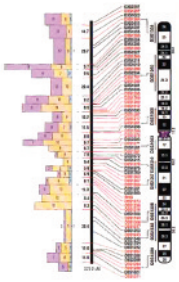
2001

Bcr-Abl inhibitor ST1571 (imatinib, Gleevec) effective for treating chronic myelogenous leukemia.

Earlier work established that the Bcr-Abl fusion protein, a result of the Philadelphia chromosome translocation event, was characteristic and causative of chronic myelogenous leukemia (CML). The molecular targeted therapy, kinase inhibitor imatinib (Gleevec) selectively kills Bcr-Abl-containing cells and is successful in achieving remission. (112)

2001

Draft sequence of the human genome published.



A public, free access, complete human genomic sequence allows researchers to perform many experiments including but not limited to studies of comparison with other organisms, predictions of gene functions, identification of new genes involved in cancer, and design of new diagnostics and therapeutics. The race to sequence the genome advanced technologies for sequencing and analysis, and it is believed that the $1000 genome sequence may be possible within a few years. This opens up the possibility that patients might sequence and store their full genetic information and that it might be used for personalized medicine, such as determining customized drug treatments and preventive measures. (113)

2001

AACR publishes first issue of *Molecular Cancer Therapeutics*.

2002

AACR publishes first issue of *Molecular Cancer Research* (successor to *Cell Growth & Differentiation*, first published in 1990).

2002

AACR holds first Frontiers in Cancer Prevention Research conference.

2003

Ubiquitin-proteosome pathway inhibitor bortezomib (Velcade) receives accelerated approval.

Bortezomib (Velcade), a member of a new class of anticancer drugs that target the ubiquitin protein degradation system, was shown to be active in patients with relapsed multiple myeloma that was refractory to conventional chemotherapy. (114)

2003

AACR membership passes 20,000.

2004

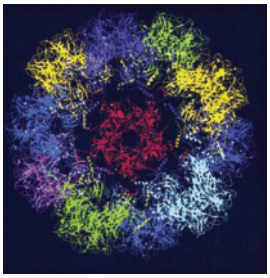
The antiangiogenesis antibody bevacizumab (Avastin) approved for treating advanced colon cancer.

Building on earlier work identifying the need of new blood vessel networks to feed tumor growth, therapies were designed to antagonize VEGF, a key molecule in angiogenesis. The addition of bevacizumab (Avastin) to conventional fluorouracil-based combination chemotherapy resulted in improved survival in patients with metastatic colorectal cancer. (115)

2004

Vaccines against human papillomavirus (HPV) developed to prevent cervical cancer.

Vaccination against the most common oncogenic human papillomavirus types, HPV 16 and HPV 18, could prevent up to 70% of cervical cancer cases worldwide. (116)



2004

According to the American Cancer Society, the absolute number of cancer deaths in the United States declines for the second year in a row, confirming a trend in cancer-related mortality.

2005

Small non-coding RNAs have a role in oncogenesis.

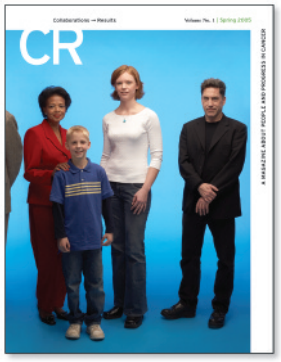
Traditionally, much of the focus of genomic research had concentrated on genes that code for proteins. Work showing that small, non-coding RNAs may play a role in the development of cancer has challenged the long-standing belief that proteins were the principal functional products of the genome. (117)

2005

Proffered abstracts at the AACR Annual Meeting set a new record of over 6,500.

2006

AACR publishes *CR*, the association's first magazine specifically for cancer survivors and advocates.



2006

There are over 10 million cancer survivors in the United States alone.

2007

AACR celebrates 100 years of uniting the cancer community in a shared mission to conquer cancer.

Sources Consulted

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AACR Staff Contributions

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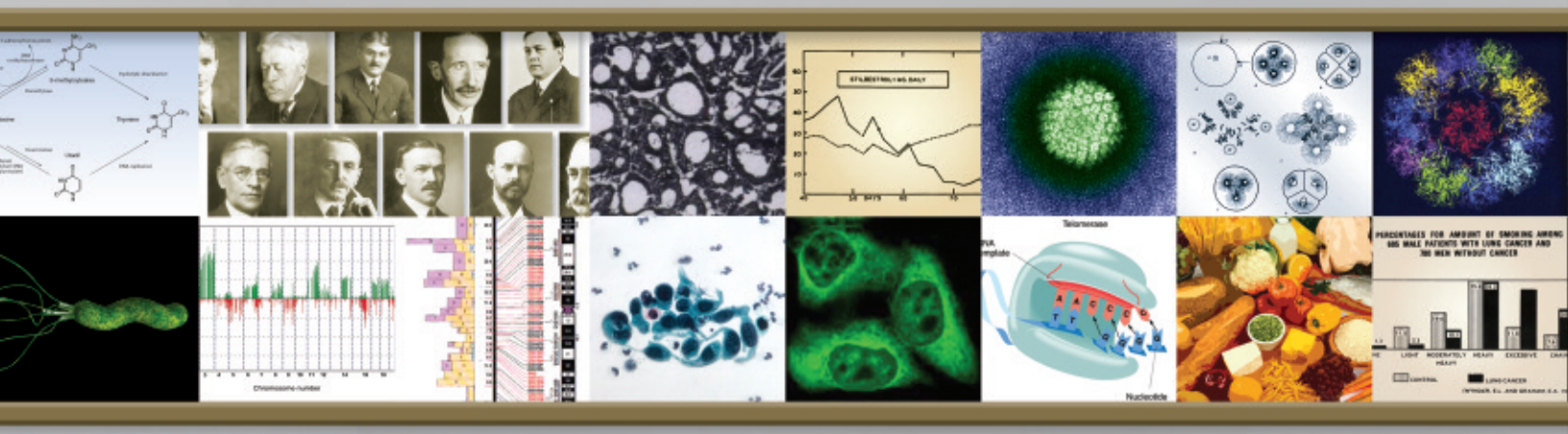
Were Dr. Shimkin still with us, he would be the first to note that any such list is necessarily limited and subjective and that a history of cancer research must have continuing input from the cancer community. Throughout our centennial year and beyond, AACR will be seeking that input.

A special project starting in late 2007 will be a series of articles published in *Cancer Research,* reviewing and offering perspectives on advances in cancer research in the past 100 years. We gratefully acknowledge the vision and the efforts of I. Bernard Weinstein, who is serving as series editor. We invite you to share your views with us by contacting AACR through the *Cancer Research* editorial office: cancerres@aacr.org.



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615 Chestnut Street, 17th Floor
Philadelphia, PA 19106-4404
215-440-9300 • Fax: 215-440-9319
communications@aacr.org • www.aacr.org