



FEATURE STORY

Timeline: Milestones in Cancer Treatment

EDITED BY LACEY MEYER

The current options for treating cancer were built upon successes of the past. The progress made in the past century has cleared the path for continued achievement. We highlight some of those triumphs here.

1882

The first mastectomy for breast cancer is performed.

1895

Wilhelm Conrad Röntgen discovers a new kind of radiation that he calls X-rays.

1896

Removal of the ovaries is performed for the first time as part of breast cancer treatment.

1897

Paul Ehrlich develops the side-chain theory—the root of his targeted therapy, or “magic bullet,” concept of drugs that go straight to their intended targets to treat disease. He later wins the Nobel Prize in 1908.

1898

Physicists Marie and Pierre Curie discover radium and later use it to effectively treat tumors.

1900

Thor Stenbeck cures a patient with skin cancer using small doses of daily radiation therapy. This technique is later referred to as fractionated radiation therapy, which is the basis of radiation treatment used today.

Early 1900s

George Papanicolaou finds that vaginal cell smears [the Pap smear] reveal the presence of cancer.

1941

Charles Huggins uses synthetic hormone to treat prostate cancer and shows that some breast and prostate cancer cells are hormone-dependent.

By demonstrating that metastatic prostate cancer responds to androgen ablation therapy, Huggins becomes the first to use a systematic approach to prostate cancer treatment. This leads to increased research in chemotherapy treatments. In 1966, Huggins wins the Nobel Prize for showing hormonal dependence of breast and prostate cancer cells. Androgen ablation remains a useful prostate cancer therapy today.

1943

The first electron linear accelerator designed for radiation therapy is developed. Today, the linear accelerator is the most widely used treatment device in the Western world.

1946

The beginning of chemotherapy as treatment for cancer can be traced to chemical warfare used during World War I. Louis Goodman and Alfred Gilman use nitrogen mustard, an agent derived from a deadly gas employed during the First World War, to treat a non-Hodgkin's lymphoma patient. The pair publish a report in 1946 that demonstrates for the first time that chemotherapy can induce tumor regression.

1947

Sydney Farber finds that a folic acid derivative inhibits acute leukemia and uses it to induce remissions in children with acute lymphocytic leukemia. This leads to a category of drugs that interfere with cell processes.

1949

Swedish neurosurgeon Lars Leksell invents a stereotactic apparatus exclusively for human functional neurosurgery. In the late 1960s, Leksell develops the Gamma Knife—today a popular radiosurgical tool that has the ability to eradicate cancerous tissue with a single high dose of radiation.

1951

Estrogen and testosterone are found to drive the growth of breast and prostate cancers, respectively.

1953

James Watson and Francis Crick publish their paper on the helical structure of DNA, the hereditary material that is the information archive of all cell activity.

Watson and Crick's discovery ushers in the genomics era, and techniques rapidly develop to sequence DNA and its inherent genetic material. Today researchers are using gene-analyzing techniques to examine everything about cancer cells, including the individual genes and the DNA that regulates their activity.

1957

Alick Isaacs and Jean Lindenmann discover interferon, which is used today to treat kidney cancer, melanoma, and bladder cancer.

Charles Heidelberger introduces 5-fluorouracil [5-FU], an anti-cancer drug used to treat colorectal, breast, stomach, and pancreatic cancers.

1958

Roy Hertz and Min Chiu Li demonstrate that methotrexate alone can cure choriocarcinoma, the first solid tumor in humans to be cured by drug therapy. Methotrexate is still used to treat patients with ALL, certain lymphomas, osteosarcoma, and choriocarcinoma.

1960

Peter Nowell and David Hungerford in Philadelphia discover the cytogenetic marker for chronic myeloid leukemia—the Philadelphia chromosome.

1962

Stanley Cohen discovers the epidermal growth factor.

The receptor for EGF was identified more than a decade later in 1978 and led to a class of agents known as EGFR inhibitors, which include colorectal cancer drugs Erbitux (cetuximab) and Vectibix (panitumumab).

1963

Vincent DeVita, George Canellos, and colleagues at the National Cancer Institute use combination chemotherapy to treat lymphomas. In the late 1960s, they cure patients with Hodgkin's disease and non-Hodgkin's lymphoma using nitrogen mustard, vincristine, procarbazine, and prednisone—the MOPP regimen.

1964

A virus—the Epstein-Barr virus—is linked to human cancer for the first time.

1965

James Holland, Emil Freireich, and Emil Frei show that a combination of methotrexate, vincristine, 6-MP, and prednisone—the POMP regimen—induces long-term remissions in children with ALL. This development initiates the move to combination chemotherapy to treat cancer.

1966

The receptor for estrogen is identified. A direct target now exists to stop growth of breast cancers fueled by estrogen.

1970s

Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) are developed. Revolution in computer technology throughout the '70s and '80s leads to improved treatment planning.

1971

Judah Folkman demonstrates the central role of angiogenesis—the formation of blood vessels—in tumor growth and metastasis in his landmark paper, “Tumor angiogenesis: therapeutic implications,” published in *The New England Journal of Medicine*. There is now a class of drugs called angiogenesis inhibitors that shut down a tumor’s blood supply to shrink the tumor.

Mid-1970s

The development of molecular cloning leads to important breakthroughs in many areas of research, including the genetics of cancer development and a better understanding of the signaling processes that direct cells’ behavior. These advances lead to the development of target-specific cancer drugs.

1974

Lawrence Einhorn cures advanced testicular cancer with cisplatin. The introduction of cisplatin-containing regimens in the mid-1970s for metastatic testicular cancer changes the cure rate from 5 percent to 60 percent.

1975

Methods are developed to sequence DNA. This technology makes it possible to identify and target mutated genes and DNA abnormalities that cause cancer.

Georges Kohler and Cesar Milstein develop the technique (hybridoma technology) for producing monoclonal antibodies against defined proteins. The pair win the Nobel Prize in 1984.

1976

Michael Bishop and Harold Varmus discover oncogenes, genes that control normal cell growth and division and can transform a normal cell into a malignant cell. The pair win the Nobel Prize in 1989.

Clinical trials begin to show that lumpectomy with radiation can be as effective as mastectomy.

Research by Bishop and Varmus influenced contemporary knowledge about tumor development. Today, there are many types of drug therapies that target oncogenic proteins, including small molecules such as Gleevec and monoclonal antibodies such as Herceptin.

1979

The most frequently mutated gene in human cancer, named p53, is discovered.

1970s to 1980s

Studies link specific cancers to infectious diseases, such as human papillomavirus to cervical cancer and hepatitis B to liver cancer. The first viral vaccine to prevent cancer—hepatitis B virus vaccine for liver cancer—is introduced in 1981. The FDA later approves the HPV vaccine Gardasil in 2006 to prevent cervical cancer.

1980s

The first highly effective anti-nausea drugs are developed to alleviate this chemotherapy side effect.

1981

C-erbB2 cancer-causing gene is discovered in mice; the human version of the gene (HER2) is later discovered in 1985.

1986

Nerve-sparing prostatectomy, designed to preserve potency and urinary continence, is introduced.

1987

Dennis Slamon and his colleagues publish data showing a link between HER2 gene amplification and an aggressive type of breast cancer.

Approximately 20 to 25 percent of breast cancer patients have HER2-positive cancer, which is associated with reduced survival and time to relapse. Slamon's discovery provides an important opportunity to evaluate the concept of targeted cancer therapy, including the development of highly specific monoclonal antibodies that target HER2.

1988

Intensity-modulated radiation therapy is developed. This high-precision radiation conforms to the three-dimensional shape of the tumor using multiple beams of radiation with varying intensity from different angles.

1989

The gene for vascular endothelial growth factor (VEGF) is identified. VEGF is an important protein molecule involved in angiogenesis, and discovery of the growth factor leads to a new class of drugs that cut off the tumor's blood supply by targeting VEGF.

1991

First human gene therapy for cancer [melanoma] is attempted.

1994

BRCA1 is the first discovered breast cancer susceptibility gene.

1997

The FDA approves Rituxan (rituximab), the first monoclonal antibody, to treat non-Hodgkin's lymphoma.

1998

Tamoxifen is approved based on its ability to reduce the risk of breast cancer by half in high-risk women participating in the Breast Cancer Prevention Trial.

Herceptin (trastuzumab), the first humanized antibody targeting a cancer-related molecular marker, receives

FDA approval for HER2-positive metastatic breast cancer. HercepTest, a diagnostic kit to screen breast cancer patients for HER2 overexpression, is also approved; this is the first time the FDA requires a diagnostic lab test be made available with a drug to predict the likelihood of a response.

2000

The da Vinci robotic surgery system becomes the first robotic system approved by the FDA for general laparoscopic surgery. Use of robot-assisted surgery was first documented in 1985 and is now used for prostatectomy to treat prostate cancer, hysterectomy to treat cervical and endometrial cancers, as well as surgery to treat bladder and kidney cancers.

2001

The FDA grants accelerated approval to Gleevec (imatinib) to treat chronic myeloid leukemia, making it the first anticancer drug specifically developed to target the molecular problem that causes a particular type of cancer.

Brian Druker's groundbreaking work with Gleevec leads to the drug's accelerated approval for CML in May 2001—only a few years after it entered clinical testing in 1998. Gleevec, a milestone in the development of molecularly targeted small-molecule drugs, makes the cover of Time magazine, which touts it as “new ammunition in the war against cancer.”

2004

The FDA approves Avastin (bevacizumab) for the treatment of metastatic colorectal cancer. Avastin, a humanized monoclonal antibody that targets VEGF, becomes the first antiangiogenic agent approved by the FDA. It is later approved for non-small cell lung cancer and breast cancer, and has shown benefit with chemotherapy in clinical studies for a variety of other cancers.

2005

Data presented at the San Antonio Breast Cancer Symposium show Oncotype DX, a 21-gene profiling test, successfully predicts whether chemotherapy is needed based on a recurrence risk score.

2006

The FDA approves adjuvant (post-surgery) Herceptin for early-stage HER2-positive breast cancer based on data that show the drug results in a 52 percent improvement in preventing recurrence.

2007

The FDA approves Nexavar (sorafenib) for primary liver cancer, making it the only drug approved for liver cancer. Nexavar's first approval came in 2005 for kidney cancer.

2008

Data presented at the American Society of Clinical Oncology's annual meeting validates KRAS as the first molecular marker to determine targeted treatment in metastatic colorectal cancer. Studies show that patients with cancer expressing the wild-type (normal) gene respond better to Erbitux plus chemotherapy than patients with certain mutant forms of KRAS.