National Institutes of Health
Office of Science Policy

FIGHTING CANCER: USHERING IN A NEW ERA OF MOLECULAR MEDICINE

By unraveling the molecular causes of disease, biomedical research is paving the way for promising new therapeutics and ushering in the next era of medicine. This approach is known as molecular medicine and, in its most individualized form, precision medicine. Gleevec®, a drug used to treat chronic myelogenous leukemia (CML, a rare type of blood cancer), was among the first successful molecular medicines. This was achieved, in part, thanks to powerful scientific techniques and government efforts encouraging drug development for rare diseases. The NIH's National Cancer Institute (NCI), along with many other public and private organizations, played a vital role in developing Gleevec®.

ABOUT CHRONIC MYELOGENOUS LEUKEMIA (CML)

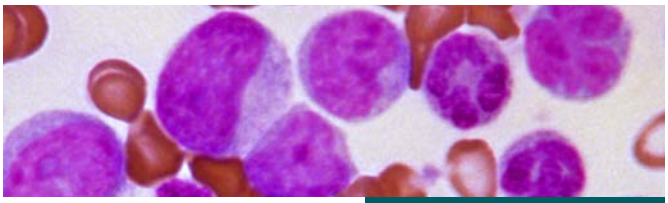
CML is a type of cancer caused by an abnormal chromosome, called the Philadelphia chromosome, which leads to uncontrolled growth of white blood cells that build up in the bone marrow and blood. The Philadelphia chromosome is created when two different chromosomes break and switch ends. When DNA sequences from both chromosomes are combined, it creates the cancer-causing gene *BCR-ABL*. Gleevec® is a targeted precision medicine therapy that blocks the protein kinase produced by the *BCR-ABL* gene, preventing the overproduction of white blood cells. In 2010, there were nearly 70,000 people in the U.S. with CML,[5] and about 6,000 people are newly diagnosed with CML each year.[6,7]

MOLECULAR MEDICINE: BEFORE AND AFTER GLEEVEC®

THEN

The five-year survival rate for CML patients was less than 30%.[1]

- In the 1950s, new techniques to study cells and the chromosomes within them were just starting to be developed; researchers began linking chromosomal abnormalities to specific human diseases.
- Until the 1990s, medications to treat cancer were limited to non-specific chemotherapy that killed many healthy cells in addition to cancerous cells.[3]
- The standard chemotherapy treatment for CML was not very effective and could cause serious side effects.
- Industry had little incentive to invest in therapeutic development for rare diseases.



NOW

CML patients treated with Gleevec® have an 89% five-year survival rate.[2]

- Gleevec® was FDA approved in 2001. Among the first precise cancer treatments, Gleevec® preferentially targets the growth of cancer cells.
- Gleevec® is standard therapy for CML patients.
- Patients with a new diagnosis of CML are now expected to live 30 years post-diagnosis, essentially a normal lifespan.[4]
- Building on Gleevec's® success, dozens of other drugs targeting the same class of molecules are now available to treat cancer and other diseases.

RESEARCH-TO-PRACTICE MILESTONES FOR GLEEVEC®

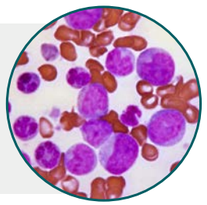
For more information on the supporting evidence and research sponsors for the following milestones, see the Web appendix table.

IDENTIFYING THE MOLECULAR TRIGGER OF CML (1914-1990)

1914 — Biologist Theodor Boveri first had the idea that chromosomal abnormalities might play a role in tumor development, but no tools existed at that time to test his hypothesis.[8]

1950s — New scientific techniques helped researchers link chromosomal abnormalities to specific diseases.[9]

1960 — The altered chromosome in CML cancer cells was discovered and named the "Philadelphia chromosome," after the city in which it was discovered.[10] NIH



1973 — The cause of the abnormal Philadelphia chromosome – a chromosomal translocation – was identified.[11]

1983-1984 — NCI researchers determined that ABL1, a gene that was known to be involved in some cancers, was altered by the chromosomal translocation.[12,13] NIH

1985 — The protein (BCR-ABL) created from the cancer-causing gene was determined to be a protein kinase, a class of cell-signaling molecules. The BCR-ABL protein constantly signals to a cell that it is time to divide, leading to cancer.[14] This finding inspired researchers to look for ways to inhibit BCR-ABL signaling as a treatment for CML. NIH

DEVELOPING A TARGETED BCR-ABL KINASE INHIBITOR (1990-1996)

1990 — NIH-funded researcher Dr. Brian Druker began developing model systems to study BCR-ABL kinase signaling and explore ways to inhibit it.[15] NIH

Scientists at the pharmaceutical company Ciba-Geigy (which later became Novartis) started to refine a compound that blocks the actions of the BCR-ABL kinase.[16]

1992 — Imatinib, the compound that would become Gleevec®, was first created, as part of a larger collection of compounds to test.[17]

1993 — Dr. Druker and his colleagues partnered with Ciba-Geigy to study their collection of compounds for signs of anti-cancer activity.[18] NIH

1996 — Imatinib (Gleevec®) was shown to kill cancerous cells without harming healthy ones by blocking BCR-ABL kinase signaling.[19] NIH

1997 — The Food and Drug Administration Modernization Act[20] allowed the FDA to create a "Fast Track" mechanism that makes important new drugs available to patients more quickly.[21]

TESTING AND APPROVING A LIFE-CHANGING DRUG (1997-2015)

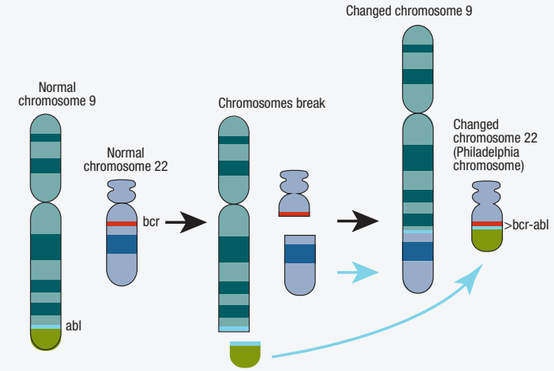
1998 — The pharmaceutical company Ciba-Geigy prepared Gleevec® for use in patients, and the first NIH-funded Phase I clinical trial began. The trial yielded an astounding positive response rate of 98%, as all 31 patients experienced remission with limited side effects.[22] NIH

2001 — FDA granted "Fast Track" designation for Gleevec®, speeding up the review process because Gleevec® treated a serious condition with no known cure. FDA approved it only 10 weeks after the New Drug Application was submitted by Novartis.[23]

2006 — A follow-up clinical study found that after five years of continuous treatment, the vast majority of CML patients receiving Gleevec® remained cancer-free.[24]

NIH *indicates NIH-funded milestones*

SCHEMATIC OF THE PHILADELPHIA CHROMOSOME FORMATION



IMPACTS OF GLEEVEC®

Gleevec® is a "first-in-class" drug that many consider to be a forerunner of molecular medicines. Its success was proof that knowledge about the underlying biological mechanism of a disease could help scientists design powerful, targeted strategies to kill cancer cells without harming healthy cells.

KNOWLEDGE

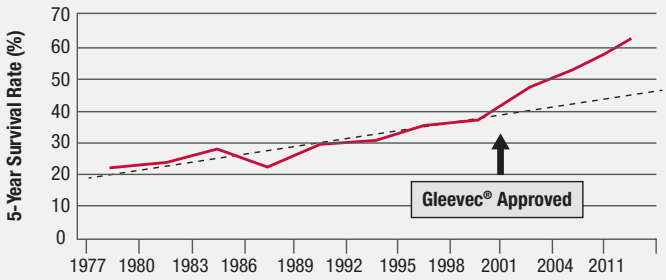
- Gleevec® was the first cancer drug approved by the FDA that directly targeted a signaling molecule inside the cell.[25]
- The dramatic effectiveness of Gleevec® stimulated an ongoing surge of new research into the treatment potential of kinase inhibitors. For imatinib alone, more than 12,000 scientific articles have been published in the last 15 years.[26]
- The success of Gleevec® spurred the development of other kinase inhibitors for CML and for other types of cancer. These newer kinase inhibitors, many based on the structure of Gleevec®, are improving survival rates for patients with CML and other diseases.[27]

HEALTH

Five-year survival rates for CML patients treated with Gleevec® currently top 89%.[28]

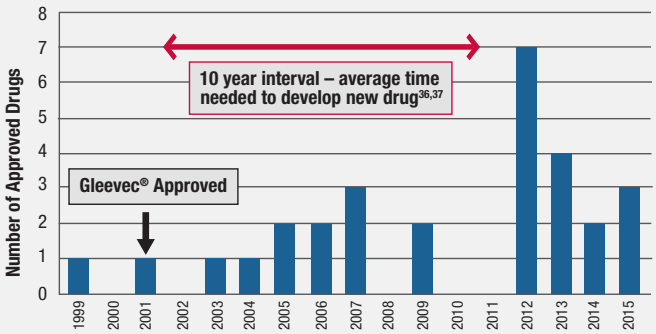
- Patients with a new diagnosis of CML are now expected to live 30 years post-diagnosis, essentially a normal lifespan.[29]
- Worldwide, more than 600 clinical trials have been undertaken on Gleevec® for new disease indications and drug formulations.[30]
- Gleevec® is now approved to treat multiple cancers, including gastrointestinal stromal tumors (GIST), in adults and children.[31]

CML Survival Rates Increased Dramatically after the Introduction of Gleevec®



Above: Five-year survival rates for patients with CML (including some patients not treated with Gleevec®) have doubled since Gleevec® was introduced, from about 30% in the early 1990s to over 60% today. The dotted line indicates the expected survival rate without Gleevec®. Source: NCI's Surveillance, Epidemiology, and End Results (SEER) database.[32]

Gleevec® Stimulated New Drug Development: Number of FDA-approved Kinase Inhibitors by Year



Above: The approval of Gleevec® in 2001 initiated a flood of activity in drug discovery and development related to protein kinases. In 2012, roughly 10 years after Gleevec® came to market, a record number of kinase inhibitors were approved.[36,37]

SOCIETY

- Far beyond its impact on CML, Gleevec® helped to pave the way for a new industry of medications that are tailored to the specific genetic changes that cause a disease.
- More than 15 major pharmaceutical companies have pursued kinases as viable targets for new product development.[34]
- By the end of 2014, more than 39 drugs targeting different kinds of kinases were approved by the FDA (see Figure).[35]

By the late 2000s, more than 100,000 CML patients worldwide had been treated with Gleevec®.[33]

For references, supplementary information, and more on the impact of NIH, please visit **http://www.nih.gov/impact**