Lasker–DeBakey Clinical Medical Research Award

Award Description

Brian Druker, Nicholas Lydon, and Charles Sawyers
For the development of molecularly-targeted treatments for chronic myeloid leukemia, converting a fatal cancer into a manageable chronic condition.

The 2009 Lasker–DeBakey Clinical Medical Research Award honors three scientists who developed novel treatments for chronic myeloid leukemia (CML) that converted this fatal cancer into a manageable chronic condition. By targeting the molecular underpinnings of this disease, Brian J. Druker (Oregon Health & Science University), Nicholas B. Lydon (formerly, Novartis), and Charles L. Sawyers (Memorial Sloan-Kettering Cancer Center) broke new ground in cancer therapy and radically altered the prognosis of CML patients.

ABL to cause cancer
In 1960, Peter Nowell (Lasker Clinical Medical Research Award, 1998) and the late David Hungerford, working in Philadelphia, noticed an abnormally small chromosome in cells from patients with CML. The consistent presence of this so-called “Philadelphia chromosome” prompted them to propose that the genetic lesion causes the disease. Thirteen years later, Janet Rowley (Lasker Clinical Medical Research Award, 1998), showed that the shortened chromosome—chromosome 22—resulted from a swap between chromosomes 9 and 22.

Several world-class molecular biology groups then figured out that the Philadelphia chromosome generates an enzyme that promotes aberrant cell division. The chromosomal rearrangement places the tail of a gene called Abelson (ABL) from chromosome 9 onto the head of a gene called the breakpoint cluster region (BCR) from chromosome 22. The product of the resulting BCR-ABL fusion oncogene possesses ABL's so-called tyrosine kinase activity—the ability to add phosphate chemical groups to the amino acid tyrosine—but fails to turn off appropriately. BCR-ABL's continuous activity stimulates cell-growth pathways and transforms normal cells into ones that proliferate without restraint.

As these results emerged in the mid-1980s, Druker, who was training to be an oncologist at the Dana-Farber Cancer Institute, and Lydon, a biochemist at Ciba-Geigy (now Novartis) realized that blocking BCR-ABL might obliterate a CML cell's ability to stir trouble. Until then, oncology drugs had relied on the fact that cancer cells reproduce faster than normal ones. Because chemotherapeutic agents targeted cell division in general, treatments killed not only cancer cells, but also healthy cells that must divide to perform their jobs. Perhaps by targeting BCR-ABL, a drug would strike only the misbehaving cells—the malignant ones—that depended on it to duplicate.

Although the idea held enormous appeal, many scientists thought it would not work. Hundreds of kinases operate in mammalian cells and any compound that quelled one would thwart them all, the skeptics argued, thus causing toxic side effects. Furthermore, although BCR-ABL by itself can cause CML, the diseased cells accumulate additional genetic flaws. Some of these anomalies might also spark cell division, in which case focusing on only the original one would not stifle disease.
By the early 1980s, the field of oncogenes had implicated unruly kinases in cancer, and Ciba-Geigy had begun to explore these proteins as potential drug targets. Lydon set up the company's tyrosine kinase inhibitor program in 1986, under the direction of Alex Matter. Their team, which included cell biologist Elizabeth Buchdunger and chemist Jürg Zimmermann, was screening large chemical collections for compounds that hamper tyrosine kinases in test tubes and inside cells. They then chemically tweaked promising compounds, hoping to improve potency and selectivity. Along the way, Lydon began using a molecular tool that Druker made while studying kinases in the laboratory of Thomas Roberts (Dana-Farber Cancer Institute). This reagent, an antibody that detects the phosphotyrosine product of the tyrosine kinase reaction, proved crucial to Lydon's enzyme-activity measurements in cells.

In 1993, Druker set up his own laboratory with a single goal in mind: Find a company that had a BCR-ABL kinase inhibitor and develop it for clinical use in CML patients. He contacted Lydon, who sent several compounds for Druker to test. In 1996, Druker and Lydon reported that one of these substances, imatinib (now widely known as Gleevec), killed cultured cells that required BCR-ABL activity to survive, but did not affect a cell line that depended on a different tyrosine kinase, v-SRC. These same cell lines form tumors when injected into mice, and similarly, the compound quashed tumor formation of the BCR-ABL-producing cells, but not the v-SRC-producing cells. Patient samples provided especially exciting results. The compound did not harm normal cells, but it blocked multiplication of cells that carried BCR-ABL. Based on these studies, Gleevec emerged as the best compound to pursue.

**Astonishing results**

Ciba-Geigy and Druker assembled a team to design the clinical trials. A key member was Charles Sawyers, who was studying BCR-ABL at the University of California, Los Angeles. The study they conceived differed in several important ways from the norm. Crucially, rather than measuring only a clinical response—in this case, reducing white blood cell counts—they decided to track activity of BCR-ABL in remaining blood cells. Doing so would allow them to assess whether the drug was working as predicted—by blocking the enzyme's activity. To perform the first clinical trials, they enlisted the collaboration of Moshe Talpaz, an oncologist at MD Anderson Cancer Center.

But before they could conduct the study, the enterprise hit some bumps. Ciba-Geigy merged with Sandoz to form Novartis, and Lydon left the company soon afterward. Toxicity concerns arose, although Druker thought they could easily be handled in the clinic. Passionate in his belief that Gleevec showed tremendous promise and eager to offer patients a potentially life-saving therapy, he lobbied Novartis to move the project forward.

Druker, Sawyers, and Talpaz finally got the go ahead to begin a clinical trial, which started in June 1998. The first study aimed primarily to assess Gleevec's safety in chronic-phase CML patients who had not responded to interferon-based therapy or could not tolerate its side effects. Every month, a single patient at each institution began receiving the drug. As long as the patients experienced no severe side effects, a new set of three patients would receive the next higher dose the following month. At 300 milligrams, the patients' white blood cell counts plunged over the first few weeks of therapy, returning to normal in 53 of the 54 patients treated with this or higher doses. Presumably, Gleevec was cutting off creation of new BCR-ABL-carrying white blood cells. Furthermore, the drug impeded activity of the enzyme in cells from patients—and in a third of the patients, the number of bone marrow cells with the Philadelphia chromosome plummeted after about six months of treatment. The patients experienced only mild side effects. These results were astonishing for a cancer drug. Typically, researchers hoped that about 10-20 percent of patients would respond in a clinical trial; in this study, 98 percent of the patients showed dramatic improvements.

Subsequent large-scale trials bore out the earlier results and, once the researchers knew the drug was working in chronic-phase patients, they offered it to those in blast crisis, the late stage of disease. At that point, Druker, Sawyers, and Talpaz saw something no oncologist had seen before. Patients on the edge of death were climbing out of bed and leaving the hospital within a week of their first Gleevec dose. In May of 2001, less than three years after the beginning of the first clinical study, the US Food and Drug Administration (FDA) approved the drug.

In the meantime, the researchers had organized an international study that compared interferon-based therapy with Gleevec in more than 1000 chronic-phase patients. After a year and a half, Gleevec was
so outperforming interferon-based therapy that the researchers closed the trial and switched almost everyone to Gleevec. Five years after diagnosis, overall survival of patients treated with Gleevec was 89 percent, the researchers reported in 2006. The comparable statistic for interferon-treated patients (from other studies) was about 60 percent (see Graph).

Survival of CML Patients

![Graph showing survival rates for CML patients treated with Gleevec, interferon, and chemotherapy.](image)

During the 2006 study, the scientists realized that Gleevec, as remarkable as it was, did not "cure" patients in the strictest sense. Sensitive detection methods uncovered BCR-ABL-containing cells even when the usual laboratory tests did not reveal the Philadelphia chromosome, and individuals who discontinued Gleevec relapsed. Fortunately, because patients tolerate the drug well, they can take it long term.

Combating resistance
But another challenge was simmering. Some patients were developing resistance to the drug and Sawyers wanted to figure out why. Perhaps some substance in the bloodstream was soaking up the drug, or maybe CML cells no longer depended on BCR-ABL to duplicate, given the many other genetic perturbations in blast-stage cells. By assessing enzyme activity from patients over the course of their treatment, Sawyers discovered that a different scenario was at play. In patients who relapsed, Gleevec no longer dampened BCR-ABL activity: The enzyme itself had changed during therapy.
Initial analysis of the $BCR-ABL$ gene revealed a sequence alteration that caused one amino acid to replace another at a particular spot in the protein. John Kuriyan (University of California, Berkeley) had recently deduced the structure of the BCR-ABL enzyme bound to Gleevec using X-ray crystallography, and the picture he produced explained what Sawyers observed. The amino acid change placed a large chemical group in the pocket where Gleevec normally grabs hold of the enzyme, which blocked the drug from binding.

Subsequent studies by Sawyers and others identified more than 50 genetic perturbations in BCR-ABL that confer resistance to Gleevec. Unlike the first mutation, they map mostly to locations other than points of contact between the drug and the enzyme. Many of these alterations likely prevent the enzyme from assuming its inactive form—the structure bound by Gleevec.

Sawyers proposed to find agents that block the resistant enzyme’s activity by fastening to BCR-ABL’s active form, yet barring it from performing its reaction. He pursued this tactic in record time with scientists at Bristol Myers Squibb to create a drug called Sprycel (desatinib) that binds BCR-ABL in its active as well as its inactive shape. Sprycel progressed rapidly through clinical trials and is FDA approved for patients with resistance to Gleevec. Scientists are exploring the possibility of treating people with combinations of Gleevec and second-generation medications such as Sprycel, with the hope of delaying or preventing the emergence of drug resistance.

Sawyers’ success has driven home the notion that even cells with multiple genetic flaws still rely on BCR-ABL to multiply and cause disease. If scientists can keep that enzyme in check, they can control the cancer.

**Spreading success**

Gleevec has helped not only CML patients, but those with other illnesses as well. The drug inhibits two tyrosine kinases in addition to BCR-ABL, and it has benefited individuals who suffer from cancers in which these other enzymes foster disease. In particular, Gleevec provides an effective therapy for patients with gastrointestinal stromal tumor (GIST) and hypereosinophilic syndrome (HES), caused by activated forms of c-Kit and PDGFR, respectively. Approximately 120,000 CML patients and 28,000 GIST patients are currently being treated with Gleevec worldwide.

Druker, Lydon, and Sawyers seized upon the known molecular defect that underlies CML, formulated the idea of tackling this root cause of the disease, crafted a specific kinase inhibitor, and designed a second-generation inhibitor when drug resistance developed. Their work has provided a model that extends well beyond CML. Now, hundreds of drugs for cancer that target specific molecules are in development and dozens have been approved. Druker, Lydon, and Sawyers have provided a stunningly successful treatment for CML and a new paradigm for cancer therapy.

by Evelyn Strauss, Ph.D.