

# Gleevec: the Breakthrough in Cancer Treatment

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How do scientists develop new treatments for disease? With Gleevec, a remarkable cancer drug, the approach was to target the disease at the cellular and subcellular level.

Some say it's a miracle **drug**. Others call it a silver bullet. Gleevec, also marketed internationally as Glivec and sometimes referred to by its chemical name imatinib, entered the medical world with a bang. This medication was initially approved for use by the U.S. Food and Drug Administration (FDA) in 2001 for the **treatment** of chronic myelogenous leukemia (CML), a rare form of **cancer** that affects certain types of white blood cells. Since its initial approval, Gleevec has also been approved for use in patients with several types of gastrointestinal tumors. Currently, scientists continue to study the drug's effectiveness not only in various cancers, but also in other diseases, such as stroke (Su *et al.*, 2008). But just how effective is Gleevec, especially when it comes to CML, and what is its mechanism of action?

## Gleevec Statistics

When people say Gleevec is a miracle drug, they are usually referring to its phenomenal success rate. For instance, in one of the first clinical studies described in medical literature, oncologist Brian Druker and his colleagues reported that "[c]omplete hematologic responses were observed in 53 of 54 patients with CML treated with daily dosage of 300 mg or more and typically occurred in the first four weeks of therapy" (Druker *et al.*, 2001). Hematologic response is one of several ways to measure how well a patient is responding to therapy. In the case of CML, a **disease** in which patients have too many immature white blood cells in their bone marrow and blood, a complete hematologic response occurs when the patient's white blood cell count returns to within normal range.

More recently, the results of a five-year follow-up study were equally remarkable. In this study, Druker and his team found that, after 60 months of Gleevec therapy, 98% of patients had shown a complete hematologic response. Also at 60 months, the estimated overall survival rate for patients was 89%, with a relapse rate of only about 17% (Druker *et al.*, 2006).

These are impressive numbers. Given this success rate, many people say that Gleevec has transformed CML treatment. In the past, the only options patients had were either bone marrow transplantation, which had serious side effects and was often fatal (and only about 20% to 25% of patients were eligible for the procedure because of age or other factors), or daily interferon infusions. The latter also had serious side effects and, moreover, was not a cure but merely a way to prolong survival. Thus, before Gleevec, only 30% of patients with CML survived for even five years after being diagnosed. As previously mentioned, with Gleevec, that number rose to at least

89%.

## Understanding the Molecular Biology of CML

The dramatic nature of the Gleevec story has as much to do with how the drug was developed, and what researchers have learned from its **development**, as it does with the medication's truly remarkable effectiveness. In particular, the discovery and development of Gleevec taught scientists that by understanding the biology of a disease, it is possible to learn how to treat or cure that disease.

### Nowell and Hungerford's Discovery

The Gleevec story began in earnest in the late 1950s, when researcher Peter Nowell and graduate student David Hungerford were studying leukemias and lymphomas. As Nowell (2007) recounts:

I knew nothing about **cytogenetics** at this time but felt that the chromosomal preparations of the leukemic cells warranted investigation for any abnormalities . . . Hungerford and I, as well as other researchers around the world, began to use the new cytogenetic techniques to determine whether human leukemias could be characterized by specific **chromosome** abnormalities.

Of course, a great deal of **cancer** research had already occurred prior to Nowell and Hungerford's work, beginning in the late 1800s when scientists first speculated on "mitotic abnormalities" (i.e., chromosomal abnormalities) and their potential role in the formation of human tumors. Later, in 1914, biologist Theodor Boveri was among the first to articulate a series of hypotheses about the potential role of chromosomal abnormalities in tumor formation. These ideas were ignored by most of the scientific community for many years, mostly because researchers didn't have the tools to test them. Not until scientists had access to more sophisticated techniques, such as the use of colchicine in **chromosome preparations** (colchicine arrests the **cell** cycle in the middle of **mitosis**, at which time it is easiest to view and analyze chromosomes), were they even able to accurately count the **number of human chromosomes**. Indeed, during the 1950s, researchers continued to rely upon these techniques as they began finding connections between abnormal chromosome number and various human diseases, like an extra copy of **chromosome 21** and **Down syndrome**. This was also the period during which Nowell and Hungerford would be among the first researchers to identify a connection between a **chromosomal abnormality** and cancer.

Nowell and Hungerford started their search by investigating cells from individuals with acute myelogenous leukemia (AML). They found no consistent chromosomal abnormalities in these patients. This trend continued until the duo began to work with patients with CML. At this time, Hungerford noticed an atypical small chromosome in cancer cells from two patients with this disease. Expanding their search, the scientists also found the same unusual small chromosome in five other CML patients. This chromosome was soon dubbed the "Philadelphia chromosome," named after the city in which it had been discovered. Thereafter, the finding that nearly all cancer cells from patients with CML carried the Philadelphia chromosome was strong evidence that the researchers were onto something significant.

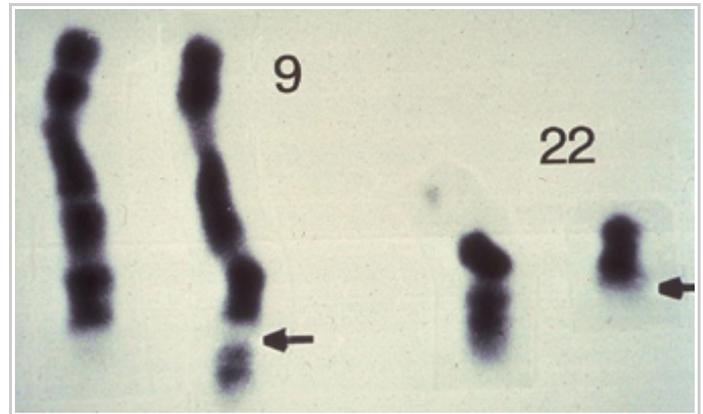
Indeed, while later scientists would go on to discover that nearly all cancer cells have some kind

of abnormal chromosome pattern, no other pattern displays the same consistency as CML does with the Philadelphia chromosome. Thus, scientists now believe that in many cancers other than CML, chromosomal abnormalities are a consequence rather than a cause of the disease.

## Details of the Philadelphia Chromosome Begin to Emerge

In the decades following Nowell and Hungerford's discovery, cytogenetic techniques were refined even further. For example, scientists developed new ways to treat and dye chromosomes so that their organization and substructure were clearly visible when examined through a light microscope. This allowed researchers to be able to home in on the actual genetic event that gave rise to the Philadelphia chromosome.

Janet Rowley, a biologist at the University of Chicago, was among the first scientists to use some of these new techniques to study the Philadelphia chromosome. Rowley examined cells from nine CML patients and discovered that the Philadelphia chromosome looks the way it does because it is actually a **translocated chromosome**, or a fusion of parts from two different chromosomes (Rowley, 1973). Specifically, the Philadelphia chromosome is a variant of chromosome 22 that is missing its long arm and, instead, has the long arm of chromosome 9. The transfer between the long arms of chromosomes 9 and 22 is called a reciprocal **translocation**. In Figure 1, the arrows indicate the translocation breakpoints for each of the involved chromosomes. The smaller chromosome 22 on the right is the Philadelphia chromosome.



 **Figure 1: The Philadelphia chromosome**

Discovered in 1960, the diagnostic karyotypic abnormality for chronic myelogenous leukemia is shown in this picture of the banded chromosomes 9 and 22. Shown is the result of the reciprocal translocation of 22q to the lower arm of 9 and 9q (c-abl to a specific breakpoint cluster region [bcr] of chromosome 22 indicated by the arrows).

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Following Rowley's work, it took another 10 years before scientists were able to determine the actual **genes** involved in the Philadelphia chromosome translocation. This milestone took place in 1983, when researchers from the National Cancer Institute and Erasmus University demonstrated that the human *c-abl* **oncogene** is located in the region of chromosome 9 that translocates to become part of the Philadelphia chromosome (Heisterkamp *et al.*, 1983). Then, in 1984, the same group of researchers identified what they called the breakpoint cluster region (*bcr*), or the 5.8-kilobase region in which all the chromosome 22 breakpoints seemed to occur in CML patients with the Philadelphia chromosome (Groffen *et al.*, 1984). The researchers thus concluded that these two genes, together known as the *bcr-abl* fusion, were likely the molecular culprits responsible for CML. Their suspicions were confirmed in 1990, when scientists from the

Whitehead Institute in Cambridge, Massachusetts, infected bone marrow cells with a **retrovirus** encoding the fusion **gene** and demonstrated that, indeed, the presence of an active *bcr-abl* gene initiates CML or CML-like symptoms (Daley *et al.*, 1990).

Also in 1990, researchers from the University of California, Los Angeles, identified the **function** of the *bcr-abl* fusion gene: production of an abnormal tyrosine kinase **protein** that is not properly regulated (Lugo *et al.*, 1990). Tyrosine kinase is a common signaling **molecule** that, when activated, triggers cells to divide. In patients with CML, the mutated tyrosine kinase is active for far too long, causing cells to proliferate at an abnormally high rate. This proliferation results in the overproduction and accumulation of immature white blood cells, which is the hallmark of CML. In fact, whereas a milliliter of blood from a healthy person contains about 4,000 to 10,000 white blood cells, the same volume of blood from a person with CML contains 10 to 25 times that amount.

Thus, after 30 years of basic scientific research, the stage was finally set for the development of a drug that countered CML. The fact that this disease was caused by only a single aberrant protein meant that drug developers had just one easy-to-see target. Their next step was to figure out how to hit that target—in other words, to determine how to stop the aberrant tyrosine kinase molecules from driving uncontrolled cell growth.

## From Basic Science to Drug Discovery and Development

Up until the 1990s, most pharmaceutical companies were not interested in developing drugs that could block kinases (so-called "kinase inhibitors"). After all, there are many different kinases in cells, and each one functions by binding **ATP** and transferring phosphates to other molecules. Given the large number of kinases in the human body, the general consensus had been that it would be too difficult, if not impossible, to develop a compound that targeted a specific ATP-binding pocket on a particular kinase (e.g., the kinase implicated in CML). Furthermore, if patients were treated with a drug that blocked multiple ATP-binding pockets rather than only one specific pocket, these patients would certainly experience devastating side effects. Such a general assault on the human body would not make for a useful drug.

However, as scientists started learning more about kinase structure, they began to realize that there is considerable variation among the different kinases with respect to the structure of their ATP-binding pockets. This discovery meant that specificity might be possible after all. Oncologist Brian Druker, the researcher at Oregon Health and Science University who would eventually conduct the pivotal clinical trials leading to FDA approval of Gleevec, was one of the first scientists to recognize this possibility. Prior to this period, Druker had already been heavily involved with CML genetics research. As he later recounted, "I had one goal at the time: to find a company that had an inhibitor for *bcr-abl* and to bring it into the clinic" (Cameron, 2007).

This company ended up being Ciba-Geigy (which later became Novartis), one of the few pharmaceutical firms in which scientists were conducting tyrosine kinase inhibitor research. In fact, company scientists had already synthesized some kinase-blocking inhibitor compounds, using computer models to predict which molecular structures might fit the ATP-binding site of the **fusion protein**. Druker collaborated with Ciba-Geigy, screening their collection of synthesized

compounds in human bone marrow cells for signs of anticancer activity. One compound in particular looked promising. In **cell culture**, this chemical caused a 92%–98% decrease in the number of *bcr-abl* colonies formed, suggesting that it was effective, while simultaneously causing no decrease in normal colony formation, suggesting that the chemical was safe and did not harm healthy cells (Druker *et al.*, 1996).

Two years later, this chemical, which was called ST1571 and eventually renamed Gleevec, entered its first **clinical trial**: a small phase I trial involving just 31 patients. Remarkably, all 31 individuals experienced complete remission; in other words, their blood counts returned to normal. In some of these patients, there was also cytogenetic remission, meaning that the Philadelphia chromosome was no longer found in their blood cells. As Druker noted, "That was virtually unheard of in a phase I clinical trial. Usually in a phase I clinical trial, if you see a 20% response rate, that's remarkable. We had a drug that was extremely well-tolerated and had a 100% response rate. It was absolutely incredible to see this unfold" (Taubes, 2003). Subsequent clinical trials produced results just as astonishing.

## The “Moral” of the Gleevec Story

In a way, Gleevec is an exceptional case, and the same success is not likely to be achieved with other cancers any time soon. Unlike most other cancers, which are caused by a multitude of complex interacting genetic and environmental factors and therefore have many targets, CML is caused by a single aberrant protein related to a consistent chromosomal translocation. Scientists were thus able to focus all of their efforts on this single target. Nonetheless, the Gleevec story is no less an excellent and, some would say, beautiful example of how knowledge of the biological functioning of a cell can lead to life-saving **medical treatment**.

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