

An apparent overnight success,  
this new leukemia drug has decades  
of research behind it. **By Jill Waalen**

# Gleevec's Glory Days

**Gleevec seemed to spring up overnight.**

“Powerful Anti-Cancer Drug Emerges from Basic Biology,” trumpeted *The New York Times* on May 8. Two days later, the Food and Drug Administration (fda) announced its approval after a record-breaking review period of only two and a half months. With words such as “fantastic” and “incredibly important,” an impressive array of scientists welcomed the new drug as the first demonstrable success among a new generation of cancer weapons targeting aberrant signaling molecules within cells. Before the month was out, *Newsweek* was luring readers with a headline that teased “A Cure for Cancer?”

Gleevec, a.k.a. compound STI-571, is not a sure cure for any cancer, and in fact has shown clear benefit in only two diseases so far: a



rare blood cancer, chronic myelogenous leukemia (CML), and an equally rare stomach malignancy, gastrointestinal stromal tumors. Aside from that important qualifier, however, most researchers believe that the compound—and, more important, the biological rationale behind its development—holds enormous promise.

Taken as a simple daily pill, it causes few side effects and has brought dramatic remissions, with up to double the effectiveness of other treatments. This is largely because the underlying treatment strategy—to halt the cancer right where it starts—is so specific and efficient. By targeting a particular rogue molecule, STI-571 prevents a signaling cascade inside cells that would otherwise turn cells cancerous. Most cancer treatments, in contrast, target more general processes of cell division, often damaging normal cells and causing intolerable side effects. With Gleevec's meteoric clinical success, researchers probing the molecular origins of cancer are more excited than ever about designing comparable drugs that offer hope to a broader range of patients.

Neither the strategy nor the treatment sprang up overnight, however. Last May's splashy headlines notwithstanding, the accomplishment took nearly four decades, more than a few odd coincidences and convergences, and one gloomy period near the end when market limitations seemed likely to scuttle it all.

## TWO PATHS CONVERGE

When you're a basic scientist, of course, a few decades can still seem a relatively short time. It did for Owen N. Witte, a key player since the early days of the Gleevec story and now an hhmi investigator at the University of California, Los Angeles: "In one scientific lifetime, to see the fruits of your basic science evolve and end up in a therapeutic that actually makes a major difference in people's lives is an extremely rewarding feeling."

When Witte started his career in the 1970s as a postdoc at the Massachusetts Institute of Technology (MIT), he joined a crowd of junior researchers jostling for lab space and face-time with the boss. Last May he joined his former boss, David Baltimore, now president of the California Institute of Technology, and three other researchers, Brian Druker of Oregon Health Sciences University, Nicholas Lydon of Amgen, Inc., and Alex Matter of Novartis, to receive Harvard Medical School's prestigious Warren Alpert Foundation Prize for their discoveries leading to the development of STI-571.

At the outset, Witte had no idea his work would play a role in CML. He and Baltimore were studying the Abelson murine leukemia virus,

which was known to trigger another type of leukemia in mice. Their research built on what was then a recent discovery by the Nobel Prize-winning team of J. Michael Bishop and Harold Varmus at the University of California, San Francisco. Bishop and Varmus had found that another cancer-causing virus, one that produced sarcomas in chickens, worked by commandeering a normal gene from the chicken genome and changing it into a cancer-causing gene called *src*. At MIT, Witte, Baltimore and colleagues found that the Abelson virus seemed to work in the same way in mice, seizing a normal mouse gene, named *Abl*, and adding its own genetic material. The hijacked gene caused the resulting ABL protein to overstimulate cell growth.

On a seemingly unrelated front, other scientists had been gathering clues about the origins of CML, a type of leukemia characterized by white blood cell counts up to 50 times higher than normal. CML strikes up to 8,000 people in the United States each year, most of whom are in their 50s and 60s. While studying chromosomal "snapshots," or karyotypes, in the 1960s, Peter Nowell and David Hungerford of the University of Pennsylvania School of Medicine and the Institute of Cancer Research (now Fox-Chase Cancer Center) in Philadelphia had noticed that chromosome 22, which is short to begin with, was almost invariably even shorter in the white blood cells of CML patients.

The significance of that stubby fragment, which came to be known



Owen Witte watched with excitement as his basic research from the 1970s resulted in a viable cancer therapy.

as the Philadelphia chromosome, remained a mystery for another decade. Then, in 1973, new techniques for staining chromosomes with barcode-like patterns enabled Janet Rowley of the University of Chicago to discover that the piece from the shortened chromosome 22 was not missing but in fact had jumped to chromosome 9—and, in exchange, a shorter piece of chromosome 9 had shifted to chromosome 22.

The Philadelphia chromosome discoveries were part of “a complete sea change in our understanding of cancer at the time,” says Witte. “They made us realize that cancer did not necessarily result from random chromosome changes and that it could be caused not only by a loss or gain of information, but also by a rearrangement of information.” Understanding how the swap between chromosomes 9 and 22 might lead to CML, however, required knowing which genes were disrupted in the process. Another new technique at the time enabled scientists to pinpoint genes on chromosomes, which led in 1982 to the unexpected convergence of Witte’s work and the Philadelphia chromosome: As it turned out, the piece of chromosome 9 that shifted to chromosome 22 in CML contained the human version of the *ABL* gene.

Now able to pinpoint genes involved in the chromosomal exchange, Witte and others found that just as the Abelson virus’ genetic material had increased the ABL protein’s activity in mice, genes near the site where the *Abl* gene landed on the Philadelphia chromosome (called the breakpoint cluster region, or BCR) combined with *Abl* to encode a protein that was an overactive switch for cell division. Although it would take several more years to demonstrate that the *Bcr-Abl* gene could cause CML in animal models, “we knew then

that we had our molecular target for CML,” says Witte.

### NEW MOLECULAR M.O.

It was now clear that stopping CML would require stopping the hyperactive BCR-ABL protein. Important clues about the workings of the *Bcr-Abl* gene and proteins coded by similar cancer genes were emerging from experiments conducted in the late 1970s and early 1980s in, among others, the laboratory of molecular biologist and hhmi Medical Advisory Board member Tony Hunter at The Salk Institute in San Diego.

Many signaling proteins, including ABL and SRC, were already known to work by triggering cascades of chemical reactions that drive cell division. They set off the chain of reactions by “tagging” certain proteins with phosphate groups, a process called phosphorylation. At the time, researchers knew of only two amino acids that could accept phosphate tags: serine and threonine. Then, in 1979, while Hunter was running a routine experiment on SRC and other signaling proteins, he found a phosphate-tagged form of a third amino acid, tyrosine. At about the same time, Witte found that a viral protein, later identified as the functional part of BCR-ABL, also worked by phosphorylating tyrosine. Signaling proteins had another means of flipping the switch for cell division.

The discovery that tyrosine could be phosphorylated led to a flurry of retesting other important cell signalers thought to tag only serine and threonine. “Within about a year, many tyrosine kinases [the signaling proteins that phosphorylate tyrosine] came out of the woodwork,” Hunter says. The number is now estimated to be more than 90, including not only SRC and ABL, but also other important regulators of cell division, such as receptors for epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF).

### BLOCKING SIGNALS

By the mid-1980s, Witte had taken to the road to try to stir interest in developing drugs to jam BCR-ABL’s signals, which triggered CML. “I gave a lot of seminars and kept telling people this would be a great target,” says Witte. Because CML does not affect large numbers of people, it was very hard to interest drug companies in developing inhibitors specifically for BCR-ABL, he explains.

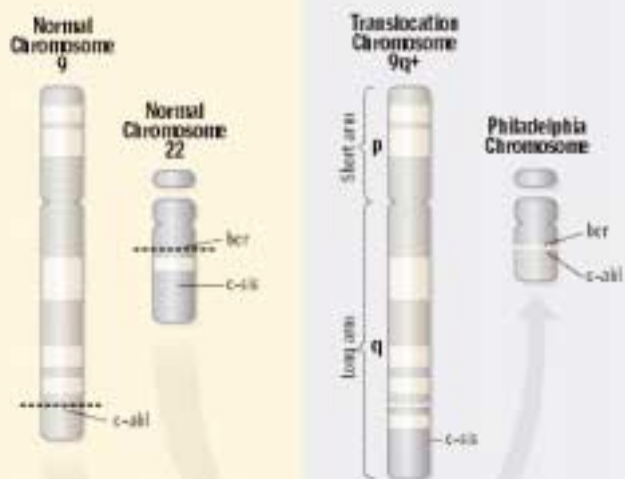


Owen Witte, Nicholas Lydon, Brian Druker, Alex Matter and David Baltimore shared the 2000 Warren Alpert Foundation Award for their work leading to the development of Gleevec.

KATHY TARANTOLA

## Chromosome Swap in Chronic Myelogenous Leukemia

In chronic myelogenous leukemia, segments of chromosome 9 and chromosome 22 switch places. The shortened chromosome 22, called the Philadelphia chromosome, forms a gene called *BCR-ABL*, which causes overactive white blood cell division.



The pharmaceutical companies had their sights set on bigger markets. Novartis (then Ciba Geigy), taking the lead in the search for inhibitors of tyrosine kinases, focused on the PDGF receptor, which was not only implicated in many different cancers, but also was considered a good target for preventing reblockage of coronary arteries following angioplasty. A number of researchers persisted in their efforts to find an inhibitor for BCR-ABL, however, including oncologist Brian J. Druker of the Oregon Health Sciences University in Portland, who was supplying reagents for Novartis' tests. In 1993, Druker heard that Novartis had generated one inhibitor, known as STI-571, which was only moderately active against the PDGF receptor but was active and specific for stopping ABL.

For the next few years, he worked to convince the company that CML was a worthwhile market. Druker collected preclinical results showing that STI-571 could stop proliferation of leukemia cells without harming normal cells, both in animal models and in blood samples from CML patients.

"The question was whether STI-571 was going to be any better than tumor necrosis factor or other compounds that look extremely potent in mice but aren't as good in clinical trials," Druker says. The answer came quickly when phase I clinical trials began in June 1998. Remissions occurred in 100 percent of the first 31 patients who participated in the trial, with remarkably few side effects. These patients and the majority of other patients treated since have maintained their normal white blood cell counts for more than one year, according to Druker.

Anticipating increased patient and physician demand for the drug when the results were unveiled at an American Society of Hematology meeting in December 1999, Druker and other investigators lobbied the company to make more of the drug available for the next phase of patient studies. Their efforts, backed by a petition sent to the Novartis CEO from 4,000 members of the Leukemia and Lymphoma Society of America, led to rapid expansion of clinical trials, from 100 patients to 1,000 within a year and to 6,000 within two years.

## Bullets With Limited Magic

**It's remarkably potent** against two cancers so far, but will the same targeted strategy work with other malignancies? Researchers are hopeful but are keeping their expectations in check.

With Gleevec's dramatic success in muzzling the tyrosine kinases underlying chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors (GISTs), the search is on for compounds that inhibit other cancer-causing tyrosine kinases. One such drug, Herceptin, for patients with metastatic breast cancer and excess levels of the growth factor receptor Her2, was approved in 1998. Other inhibitors are in patient studies, including several that target tyrosine kinases serving as receptors for epidermal growth factor or vascular endothelial

growth factor (VEGF). The VEGF receptor is of particular interest because it promotes growth of new blood vessels that feed tumors.

None of these inhibitors, however, are likely to match Gleevec's knockout performance against CML and GISTs, predicts Brian J. Druker, at Oregon Health Sciences University in Portland. Although they could be at least as effective as other cancer chemotherapies directed toward general growth processes, most will not squelch the cancer at its molecular source, Druker says. Even if they inhibit tyrosine kinases that are expressed in many cancers, expression is not enough. For inhibitors to strike with power and precision, their targeted molecules must be part of the cancer's root cause.

Indeed, Gleevec itself—now being tested in lung cancer patients—is unlikely to match its earlier successes. That's because although the

If Novartis' early efforts in developing STI-571 could be characterized as slow, says Druker, "they more than made up for lost time by responding quite remarkably when the demand was there." After the spectacular initial results held up in the later trials, STI-571 sailed through the drug approval process faster than any other cancer drug in the history of the FDA.

Even while STI-571 triumphed in clinical trials, its specificity for ABL—the key to its success against CML—remained unexplained. Why, researchers wondered, did the drug inhibit ABL while leaving other tyrosine kinases essentially unaffected? "Tyrosine kinases share similar active sites because they catalyze the same reaction. When they're in the active conformation, they all look the same, like soldiers at attention," says John Kuriyan, an HHMI investigator who recently moved from The Rockefeller University to the University of California, Berkeley. Thus, most inhibitors that bind to active forms of the enzymes are fairly nonspecific, able to short-circuit multiple cellular processes, which could lead to a generalized meltdown of cells, including normal ones.

By contrast, inactive tyrosine kinases assume their own unique shapes, like soldiers standing at ease, Kuriyan explains. Using x-ray crystallography to visualize the interaction between STI-571 and the active site of ABL, Kuriyan and colleagues found unexpectedly that STI-571 binds to ABL in its inactive—and therefore more unique—conformation. "The result is that STI-571 specifically blocks ABL, but not serine/threonine kinases or other tyrosine kinases," Kuriyan says.

Although the explanation lies in the molecular realm, the difference that specificity makes is palpable to patients. Before STI-571, CML patients faced two main treatment options: bone marrow transplant, available only to the one-third of patients for whom a donor could be found, or daily injections of interferon, which often resulted in side effects likened to having the worst case of the flu every day for a lifetime.

Now these patients take STI-571 almost as if it were a daily vitamin. The lack of major side effects was a surprise, even to the scientists who designed it that way. "It really is remarkably without side effects," Witte says. Although these results are encouraging, says Druker, follow-up is

drug's specific targets, ABL and c-KIT tyrosine kinases, may participate in the growth pathways of other cancers, they are less likely to be the root cause in those diseases, Druker explains.

Owen N. Witte, an HHMI investigator at the University of California, Los Angeles, is enthusiastic about testing Gleevec in other cancers, but he thinks the drug will prove most useful as part of combination chemotherapy. "When you have a drug that has limited side effects and can have efficacy in different settings, it should be tried," Witte says. "You may need to combine it with other drugs, but that's the history of chemotherapy for cancer—combinations of drugs work better for certain tumors." Likewise, inhibitors of the majority of other tyrosine kinases are expected to be most helpful as part of a multipronged treatment approach, stemming a cancer's growth while leaving its roots intact. —JW



CHRISTOPHER DENNEY

John Kuriyan showed that STI-571 is so specific because it binds to ABL's more unique, inactive form.

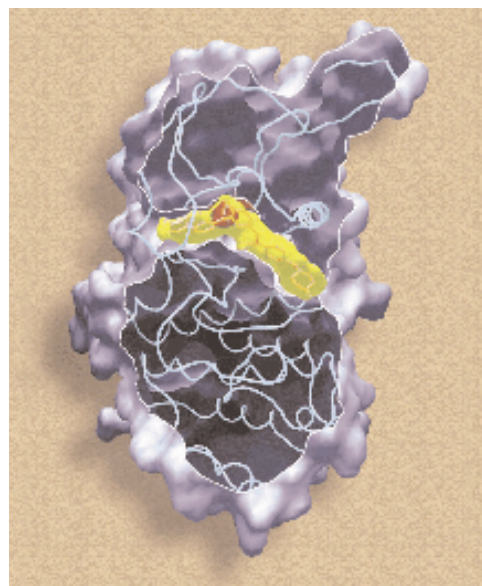
needed to see how long the response lasts and whether STI-571 prolongs survival compared with standard treatments.

## RESISTANCE TO STI-571

Although STI-571 remains effective in treating most patients with CML, the drug has proven less active, and eventually fails, in patients in blast crisis, the rapidly progressing end stage of the disease. Many researchers have attributed this resistance to an accumulation of molecular abnormalities that occur late in the disease and are altogether separate from BCR-ABL.

However, another and more surprising story is emerging from studies of blood cells from patients in blast crisis by oncologist Charles Sawyers, a former Witte trainee, and his colleagues at ucl a. Those findings, reported in the August 3, 2001, *Science*, suggest that end-stage resistance results from a change in the ABL protein's active site, which Kuriyan had found to be important for STI-571 binding.

"These results suggested that BCR-ABL is still the right target" even in late-stage blast crisis, Druker says. "The remarkable finding is that STI-571 as a single agent has any effect at all on blast crisis," Witte notes. Exper-



LORE LEIGHTON, KURIYAN LAB

## Resistance in Late-Stage Disease

STI-571 (orange) can shut down the overactive BCR-ABL protein (purple), except during blast crisis, when a mutation (red circle) changes the shape of the protein's active site. The drug can no longer bind tightly and is less effective.

iments show that BCR-ABL continues to drive the cancer at that stage, suggesting that STI-571 could still be used in combination with other drugs to treat blast crisis, a common strategy in cancer treatments, he adds.

## GIST REWARDS

On the heels of its dramatic success in CML, STI-571 held one more surprise. David A. Tuveson, an oncologist working as an hhmi postdoctoral fellow in the laboratory of hhmi investigator Tyler Jacks at mit, heard about the drug's success against the BCR-ABL protein. He wondered whether it would work against another defective protein called c-KIT, which is the central cause of solid (non-blood-cell) tumors known as gastrointestinal stromal tumors, or GISTs. This relatively rare cancer, which strikes up to 5,000 adults in the United States each year, is notoriously resistant to chemotherapy. Tuveson, Jacks and colleagues found that the drug blocked the growth of GIST cells in the lab. Follow-up studies in patients have shown that tumors shrink in 60 percent of those treated—a victory similar to that over CML.

Ironically, the key to STI-571's effectiveness against CML and GISTs—its specificity—is also the reason the drug is not likely to work against other cancers, Druker says. In CML and GISTs, STI-571 strikes the root cause, the defective BCR-ABL and c-KIT proteins (see box). For other cancers, although STI-571 may help stop processes that contribute to cell growth, other specific inhibitors aimed at the root causes of the cancers still need to be developed. That prospect has scientists searching for all kinds of molecular triggers and their inhibitors, hoping to discover a drug like STI-571 during their lifetimes—a rare and inspiring event. ■