

Leukemia Drug Heralds Molecularly Targeted Era

(Posted 04/12/00) --When Brian Druker was a medical student, he envisioned destroying cancer without devastating the patient. "My most vivid memory was when we learned about chemotherapy. I thought, 'My God, this stuff works but it's horrible.' "

Nearly 20 years later, Druker the physician has helped a better way materialize in the form of STI571, a drug that selectively targets chronic myelogenous leukemia cells without any of the traditional chemotherapy side effects. The darling of two recent scientific conferences, STI571, which is owned by Novartis Pharmaceuticals Corp., East Hanover, N.J., passed phase I clinical testing with promising results and has entered phase II trials that will enroll several hundred patients in the United States and Europe.

If the drug continues to prove its worth against CML, which strikes 4,500 Americans annually, it will hit the market as one of the first representatives of a broad group of drugs called "cytostatics." Like monoclonal antibodies, another newer class of drug (the first, rituximab, was approved for non-Hodgkin's lymphoma in 1997), cytostatics are designed to home in on cancer cells without harming healthy ones. Traditional chemotherapy agents, or "cytotoxics," kill dividing cells with little regard for whether or not they are cancerous.

This is called "specificity" in drug development, where academics and industry are devoted to understanding, at the most basic molecular level, differences between cancer cells and non-cancer cells. This understanding, which National Cancer Institute director Richard Klausner, M.D., describes as "molecular credentialing," is offering scores of new targets to which drug developers can tailor -- sometimes atom by atom -- cancer-specific drugs. About two dozen cytostatics are in clinical trials, but "none are as elegant as this one," said Louise Grochow, M.D., chief of NCI's Investigational Drug Branch.

David Parkinson, M.D., vice president of research and development at Novartis, called STI571 "the first and best example of a molecularly targeted therapy." And Klausner singled the drug out for the same reason during his keynote address at an international cancer conference in Washington in November.

That STI571 fits this much-trumpeted specificity bill so well testifies to a long lineage of distinguished cancer researchers who studied CML, ending with Druker and beginning in Philadelphia 4 decades ago -- a mere handful of years after the discovery of the structure of DNA.

A String of Firsts

In 1960, University of Pennsylvania researchers Peter Nowell, M.D.,

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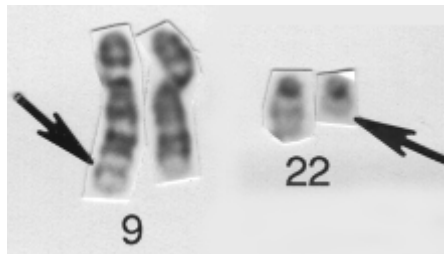
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and David Hungerford, M.D., noticed something strange in the chromosomes of certain blood cells of CML patients. One copy of a chromosome, which turned out to be chromosome 22 --technologies were too crude at the time to tell which it was for certain -- was shorter than normal; a whole chunk of DNA was missing. Nowell and Hungerford dubbed it the "Philadelphia chromosome" and it went down as the first chromosomal defect linked to a cancer. But the fate of the missing DNA remained a mystery.

Thirteen years later, a researcher from the University of Chicago, Janet Rowley, M.D., noticed in CML patients an extra clump of DNA on chromosome 9. Putting 9 and 22 together, she discovered that the missing piece of 22 had shifted, or "translocated" in genetics parlance, to chromosome 9. Another first, the elucidation of this translocation led to widespread acceptance that specific chromosomal defects cause specific types of leukemia. Today, dozens of translocations have been matched to various cancers. (In 1998, Rowley and Nowell were rewarded for their efforts against CML with the Albert Lasker Medical Research Award, sometimes called the "American Nobel Prize.")



When a section of chromosome 22 breaks off and translocates to chromosome 9, the resulting fusion protein causes white blood cells to divide rapidly, leading to CML. The broken 22 is called the Philadelphia chromosome after the city

where it was discovered. (Photo courtesy Gordon W. Dewald, Ph.D., Mayo Clinic.)

As technologies improved in the 1980s, other researchers mapped the breaks in the two chromosomes, and found that they occur in particularly bad spots, smack in the middle of two genes. On chromosome 22, the broken gene is called *bcr*; on chromosome 9, the broken gene is *abl*. When these genes fuse as *Bcr-Abl* on chromosome 9, they produce an abnormal protein.

In 1986 and 1987, a research team led by Nobel laureate David Baltimore, Ph.D., then at the Whitehead Institute for Biomedical Research in Cambridge, Mass., published a pair of articles in *Science* that pegged the *Bcr-Abl* protein as a tyrosine kinase, a class of enzymes that play an important role in regulating cell growth and division.

And that's about the time that Druker was getting fed up with the state of cancer care and moving back to the lab, where he geared up to study tyrosine kinases.

Homing In

"As I gained experience working with tyrosine kinases, I wanted to apply it to a human disease. And clearly, CML was the best case of a tyrosine-kinase-causing disease," said Druker at the American Society

of Hematology meeting, held in early December in New Orleans.

He went to work figuring out how Bcr-Abl causes the hallmark of CML, an over production of white blood cells. His focus was finding and describing where Bcr-Abl fits into the complex cellular puzzle of cell signaling — which is how cells know when to start dividing and when to commit cellular hari-kari. An important paper Druker published in *Blood* in 1992 linked the mutant Bcr-Abl enzyme to a specific chain of signals that command cells to divide.

In normal cells, this chain gets stimulated periodically by various so-called growth factors outside the cell. But in cells with the Philadelphia chromosome, Bcr-Abl (the enzyme) jams the signal from the inside. Like a stuck throttle, Bcr-Abl revs up the cell, causing it to divide wildly. Each daughter cell itself carries the Philadelphia chromosome, which makes *it* divide over and over. During the chronic phase of CML, the daughter cells can still die through normal programmed cell death. But when Philadelphia chromosome cells develop a second mutation in their cell-division machinery -- and inevitably some of them will -- patients enter a crisis phase where the number of white blood cells skyrockets, eventually to an overwhelming number. Treatments include interferon therapy and bone marrow transplants, but many patients do not respond well; the 5-year survival rate for CML is 32%; 20 years ago it was 31%.

Druker knew these grim odds in the late 1980s when he forged relationships with scientists at Ciba-Geigy, which 3 years ago was acquired by Novartis. These industry scientists had started a drug discovery program aimed more broadly at tyrosine kinases. Druker suggested that they check out Bcr-Abl as a target for their efforts.

A few years passed without much contact between Druker and Ciba-Geigy. Druker continued characterizing how Bcr-Abl causes cellular havoc, developing tests to detect tyrosine kinase activity. In 1993, he moved from Dana-Farber Cancer Institute, Boston, to Oregon Health Sciences University, Portland. "When I arrived in Oregon, I had one goal: to identify a company that had the best inhibitor for Bcr-Abl, and bring it into clinical trials," recalled Druker.

He got back in touch with the scientists at Ciba-Geigy. "They had the idea to make compounds to inhibit tyrosine kinases, and we had the experience in reagents for detecting activity of tyrosine kinases. It was the perfect marriage," he said.

Led by Nick Leyden, Ph.D., and Alex Matter, Ph.D., the Ciba-Geigy group had produced libraries of small molecules they wanted to test against various tyrosine kinases. The first go-around produced "weak compounds that had a lack of specificity," according to Druker. In other words, they inhibited Bcr-Abl poorly while mucking up other intra-cellular processes. Ciba-Geigy refined the candidate drugs, learning what atomic arrangements would make them more specific against Bcr-Abl; each iteration was more potent than the last. At the end of 1993, they delivered a half-dozen compounds to Druker, where he had his screening tests ready to go.

"STI571 was clearly the winner, in terms of its potency and selectivity," said Druker. "STI571 was the best at killing cells that had Bcr-Abl and the best at sparing normal cells." For the next 4 years, Ciba-Geigy and then Novartis jumped through all the hoops needed to start clinical trials: drug formulation, pharmacokinetic studies, initial toxicology screening.

"It could have happened more quickly, but it still went pretty well," said Druker. Pretty well considering that CML, with so few patients annually, does not present a lucrative market for a profit-driven drug company to invest millions in. Still, somehow there was enough inertia inside the company to keep the STI571 ball rolling toward patient trials.

At one point in this process, Druker and Leyden had a long talk about how patients might need to take the drug for the rest of their lives. As the name states, CML is chronic, and the two researchers did not know if STI571 would kill the progenitor, or bone marrow stem cells, that originally carry the Philadelphia chromosome and spawn the flood of daughter cells. Even if one stem cell remained after therapy, it could geometrically generate the countless white blood cells that cause symptoms and eventually death.

But if patients stayed on the drug, it might suppress the disease, keeping the number of errant cells in check. Druker and Leyden agreed that STI571 should be reformulated from injection to pill form, and they engaged the Novartis chemists to this task.

A Prototype Drug

With the pill form of STI571 ready, phase I clinical trials began in June 1998, on a traditional dose-escalating study design. Fifty-four patients in the chronic phase of the disease, who had not responded to interferon, took between 25 mg and 500mg of the drug daily. Druker and his colleagues reported the study in an abstract presented at the December hematology meeting, where it warranted a press conference and coverage from CNN and others.

All patients treated with 140 mg and above had at least a 50% decrease in white cell counts, a sign that Philadelphia chromosome cells were dying. At the 300 mg level and above, 23 out of 24 (96%) patients had normal white blood cell counts -- an even better sign of effectiveness. The responses were sustained for up to 8 months while patients stayed on the drug. (It is unclear whether patients will relapse if they stop taking it.) When the authors used more specific genetic measures of whether Philadelphia chromosome cells were present, they counted fewer patient responses -- 33% of those taking 300 mg or more.

In patients with late, or crisis phase CML, the drug appears to be less effective, because, somehow, many late phase CML cells do not have the same bcr-abl mutation. So while single-drug STI-571 regimens may work for early or chronic phase CML, some other strategy would be necessary for late phase disease, said Novartis' Parkinson. He added that the company was exploring additional studies, one using a

combination of STI571 and other drugs and another with previously untreated patients. Both Parkinson and Druker said that if STI571 pans out for CML, it may be tested for glioblastomas and sarcomas, as the drug showed pre-clinical activity against both.

"Side effects of therapy have been minimal, and no dose limited toxicities have been encountered," Druker's abstract reports. Encouraging news for sure. But if patients need to stay on the drug for years, toxicities or even drug resistance problems not yet seen could surface. Grochow, who has been watching the STI571 story unfold, said that preclinical data showed some liver toxicity. She's concerned that this could be a long-term problem. And in a review article in the March/April 1999 *CancerJournal*, Druker pointed out that wound healing and bone marrow suppression are other possible side effects.

The early success of STI571 also raises a host of questions about the design of clinical studies with molecularly targeted drugs. Traditional phase I trials operate under a "more is better" mentality, increasing the dose of a chemotherapy agent until patients can no longer tolerate it. But if the effective dose is well below the toxicity threshold, as it appears to be for STI571 and other cytostatic drugs, new standards will be needed.

But for now, STI571 is seen by many as a prototype for molecularly targeted drugs of the near-future. Druker said he is the first to admit that the long history of interest in the Philadelphia chromosome gave him and his collaborators a huge head start. But that doesn't diminish his delight: "Words can't describe how gratifying this has been for me. I've dreamed of doing something like this since I was a medical student. I've worked on the project for 10 years, on this drug for 6, and now I get to see it work in patients."

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