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## Studies of Rare Blood Syndrome Uncover Novel Route to Cancer

By carefully studying why a rare blood disorder responds to the anti-cancer drug Gleevec, researchers have discovered an entirely new mechanism that generates cancer-causing genes.

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The study, published in the March 27, 2003, issue of the *New England Journal of Medicine*, shows that Gleevec is an effective treatment for hypereosinophilic syndrome (HES), a blood disorder that is nearly always fatal. According to the researchers, their studies suggest that HES should be reclassified by the World Health Organization from its current "gray-area" status as a "syndrome" to a form of cancer.

Senior authors of the article were D. Gary Gilliland, a Howard Hughes Medical Institute investigator at Brigham and Women's Hospital and Harvard Medical School, and Richard Stone at the Dana-Farber Cancer Institute (DFCI). Joint first authors on the paper were Jan Cools, a postdoctoral fellow in Gilliland's laboratory, and Daniel DeAngelo, who is also at DFCI and an instructor at Harvard Medical School.

HES is caused by overproliferation of a type of white blood cells called eosinophils. Physicians treat the syndrome with a combination of drugs and chemotherapy, said Gilliland, but eventually, the assault of eosinophils damages major organs, and causes the heart or lungs to fail, and ultimately results in death of most patients.

Recently, however, hints that the disorder might respond to Gleevec began to crop up in the medical literature. "There was a report of a single case of an HES patient treated with Gleevec and had what was described as a miraculous response," said Gilliland. "This anecdotal report was substantiated by a group of investigators that reported successful treatment in 4 of 5 additional HES patients, reported in the *The Lancet* (a British medical

journal) last year.

Gleevec works by inhibiting enzymes called tyrosine kinases. When the activity of tyrosine kinases is unregulated - which can occur when chromosomes improperly exchange chunks of genetic material, creating chromosomal rearrangements - cancer may develop.

With the apparent successes reported in the initial small case studies, Gilliland, Stone and their colleagues decided to conduct their own clinical trial and attempt a detailed study that they hoped would reveal the underlying mechanism of HES. They enlisted the aid of colleagues at eight medical centers who contributed 11 patients to the study.

“Nine of the eleven patients showed extraordinary and continuing responses to Gleevec treatment,” said Gilliland. “Their eosinophilia just went away. In one case, a patient with severe involvement of his central nervous system, in which he had lost bowel and bladder function, completely recovered. It's stunning to see such a recovery due to a simple pill that has minimal side effects compared to conventional chemotherapy.”

According to Gilliland, the initial group of patients is still responding to the drug, as have additional patients recruited after submission of the *New England Journal of Medicine* article. In an interesting twist, the researchers found that they could successfully treat HES patients with doses of Gleevec that were lower than those used to treat patients with chronic myelogenous leukemia. This is significant, Gilliland said, in part, because Gleevec is very expensive.

In the laboratory, the difficult work began when Gilliland and his colleagues tried to find a molecular explanation for why the patients responded to Gleevec therapy. “We didn't have any clues where to look,” Gilliland said. “This is not an inherited disease, so you cannot use the same strategies that one would use in familial breast or colon cancer. There are no recurring chromosome abnormalities that could reveal an underlying cause.”

Careful genetic analysis by Cools revealed some interesting information: His work showed that a small deletion of DNA in a region between two known genes could produce a tyrosine kinase that is essentially “turned on” in the absence of a normal activation signal. It appeared that in patients with HES, the absence of a small amount of DNA created a fusion between two genes, *FIP1L1* and *PDGFR alpha*, which switches on *PDGFR alpha*, a tyrosine kinase.

The researchers later confirmed that Gleevec did specifically block the activity of the wayward kinase. They did this by analyzing the genes of a patient who developed resistance to Gleevec due to an additional mutation in the *PDGR alpha* gen—as well as by analyzing the action of the drug in cell cultures.

“A key finding from this paper is this novel mechanism for generating a gain-of-function fusion gene,” said Gilliland. “This *FIP1L1-PDGFR alpha*

fusion is a constitutively activated tyrosine kinase, and it has all the hallmarks of a cancer-causing tyrosine kinase.”

Until now, said Gilliland, genetic deletions were associated with inactivation of tumor suppressor genes, an event that can also trigger cancers. Discovery of this new mechanism may prompt researchers to take a fresh look at whether it initiates other forms of cancer.

“These activated tyrosine kinases can act as gas pedals for the tumors, as in acute myelogenous leukemia, breast cancers and gastrointestinal stromal cell tumors,” said Gilliland. “Now that we have one example where small deletions can activate these kinases, we may find many more such examples of solid tumors with activated kinases.

“Such a finding would be especially important therapeutically because kinases are excellent drug targets. It's possible to make very specific lock-and-key inhibitors like Gleevec that selectively block kinase activity,” said Gilliland.

Although the broad range of standard analytical techniques now used to detect cancer-causing abnormalities will not uncover such deletions, said Gilliland, a screen of the 96 known tyrosine kinases in the human genome could readily identify such deletions.

According to Gilliland, the new study also suggests that Gleevec may be inhibiting other tyrosine kinases in some HES patients. While most of the patients who were successfully treated did show the characteristic gene fusion, four did not. Tracking down the causative genetic abnormalities in these patients—as well as in those with similar eosinophilic diseases—could yield additional insights into the basis of Gleevec's effects, he said. Gilliland and his colleagues are now exploring other kinase-inhibiting drugs to anticipate the Gleevec resistance that the patients might well develop.

In addition to the treatment implications for HES patients, added Gilliland, the findings offer an unequivocal diagnostic test for the Gleevec-sensitive gene fusion.