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New Drug Targets Three Kinds of Leukemia

Just three years after discovering a genetic mutation that causes a trio of leukemias, Howard Hughes Medical Institute (HHMI) researchers have helped move a new leukemia drug into clinical trials.

The Food and Drug Administration approved human clinical trials of the drug based on strong preclinical data and additional studies in mice showing that the drug eliminates clinical manifestation of the leukemias without any significant toxicity. Some of the data that laid the foundation for the clinical trials are now being reported in the April 7, 2008, issue of the journal *Cancer Cell* by D. Gary Gilliland and colleagues at Brigham and Women's Hospital and Harvard Medical School in Boston. Scientists at TargeGen Inc., in San Diego., and the Mayo Clinic are also coauthors of the article.

Phase I clinical trials of the drug began in March 2008 at the Dana Farber Cancer Institute, the Mayo Clinic, Stanford University Medical Center, MD Anderson Cancer Center, the University of California, San Diego (UCSD) School of Medicine, and the University of Michigan Medical Center. In this drug trial, small doses of the drug will be given to a few patients to see if any toxicities appear.

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"The amazing thing about this is that it normally takes eight to twelve years to move from the discovery of a gene to a clinical trial with a drug," says Gilliland. "This has been remarkably fast by conventional drug development standards. It speaks to the motivation of scientists in academia and industry to move drug development for cancer along at a more rapid pace."

The three leukemias, polycythemia vera, essential thrombocytosis, and primary myelofibrosis, affect about 80,000-100,000 people in the United States. The diseases are characterized by an overproduction of white blood cells, red blood cells and platelets. This surplus of blood cells can contribute to serious complications, such as blood clots and bleeding.

In 2005, Gilliland and his team, as well as several other laboratories, discovered that a mutation in the *JAK2* gene causes most of the cases of the three leukemias. *JAK2* produces an enzyme that drives proliferation of blood cells in the bone marrow. When the gene acquires a specific mutation, the enzyme - part of a family of enzymes called tyrosine kinases - gets stuck in the “on” position, and blood cell proliferation runs out of control.

The three leukemias are slow to develop, but may progress to acute myeloid leukemia, which is often a fatal complication. One standard treatment, hydroxyurea, can cause adverse effects and does not cure the diseases, Gilliland said.

After discovering the *JAK2* mutation, Gilliland and members of his research team began speaking with drug companies to see if they would be interested in developing drug therapies for the diseases. Gilliland figured the companies would be interested because of the success of Gleevec (imatinib), a drug that treats chronic myeloid leukemia (CML). Like the leukemias Gilliland was working on, CML is also caused by malfunction of a tyrosine kinase enzyme. Gleevec inhibits this enzyme, thereby squelching overproduction of certain white blood cells. Gleevec proved to be an early example of what is now called molecularly-targeted therapy for cancer. That is, instead of killing cancer cells - and causing all sorts of other toxicities - Gleevec inhibits cancer cells from dividing by exquisitely targeting a key molecule.

And, indeed, drug companies were interested when Gilliland knocked on their doors. He says that about a dozen companies, large and small, jumped at the opportunity to work with his group and collaborators at the Mayo Clinic and UCSD on this project. Due to the success of Gleevec, many companies already had their own libraries of molecules that inhibit various tyrosine kinases. After Gilliland provided the companies with reagents, the companies began screening tens of thousands of tyrosine kinase inhibitors against the *JAK2* mutation.

One of the most promising compounds, called TG101348, came from TargeGen, a privately held biopharmaceutical company in San Diego. “This compound has all the properties that we thought would be important in clinical trials,” says Gilliland. The compound specifically inhibits *JAK2* while leaving related enzymes untouched. In cell cultures, the compound does not show non-specific toxicity. It also is soluble in tissue, so it can distribute itself throughout the body, and can be taken as a pill rather than as an injection into blood vessels. And finally, the drug has a relatively long half-life, meaning that it will stay in the body long enough to do its work.

Gilliland and his team, led by Gerlinde Wernig, then tested the compound in mice. First, the researchers induced polycythemia vera in 168 mice. Then, for seven weeks the researchers gave 112 of the mice TG101348 daily, at either a high or a low dose. During the study, six animals in the placebo group and one animal in the low-dose drug group died. All of the animals receiving a higher dose of the drug survived.

“We saw that the compound alleviates and reverses the symptoms in the mice,” says Wernig. “The mice were healthy afterwards as their blood cell counts went down to normal.” Gilliland says that he could tell the compound was working simply by watching the animals' noses and paws turn from the ruddy color characteristic of the disease back to a normal color.

The researchers say that the drug did not suppress white blood cell production in the animals, a primary concern before the study began. Although it is still early, Gilliland is clearly pleased with the results thus far, but remains focused on a longer term goal. “Our goal is to get an efficacious drug into use for humans,” he says.