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New Drug Shows Promise Against Gleevec Resistance in Mice

One of the truly spectacular success stories in modern oncology is the development and implementation of Gleevec, a drug that virtually halts the progress of chronic myeloid leukemia. Yet for some patients who harbor particularly stubborn genetic mutations, Gleevec fails miserably.

Now, Howard Hughes Medical Institute (HHMI) researchers at the University of California, Los Angeles, and colleagues at Bristol-Myers Squibb Oncology in Princeton, NJ, are reporting the first description of a new compound that is designed to overcome Gleevec resistance in some of these individuals.

In an article published in the July 16, 2004, issue of the journal *Science*, HHMI investigator Charles L. Sawyers, Neil P. Shah and colleagues at UCLA's Jonsson Comprehensive Cancer Center, report that the compound BMS-354825, which is under development by Bristol-Myers Squibb, successfully sidesteps the vexing problem of Gleevec (imatinib) resistance.

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- Charles L. Sawyers

"The identification of this compound as a drug candidate is a direct byproduct of understanding why patients develop resistance to Gleevec," said Sawyers. He notes that just as Gleevec was developed as a "molecularly targeted" inhibitor, the next generations of Gleevec, of which is BMS-354825 is one, will be refined and improved by structural biology studies that show how the drugs "fit" with their target, and how mutations alter the shape of that target.

The all-important drug target in chronic myeloid leukemia (CML) is an enzyme called Abelson tyrosine kinase (ABL), which becomes overactivated by a chromosomal mix-up that occurs during blood cell development. The genes *ABL* and *BCR*, which are located on different chromosomes, become fused and express a hybrid BCR-ABL enzyme that is always active. The hyperactive BCR-ABL, in turn, drives the overproliferation of white blood cells that is the hallmark of CML.

In the studies published in *Science*, Sawyers and his colleagues demonstrated that BMS-354825 prolongs survival of mice with CML. In tests with cultured human bone marrow cells, the researchers showed that the drug inhibits the proliferation of bone marrow progenitor cells that are positive for BCR-ABL in patients who are resistant to Gleevec. “The bottom line is that our in vitro data indicate that this drug is active against all of the mutations except for one,” Sawyers said.

At the time Sawyers and his colleagues were writing their *Science* article, there were 17 reported Gleevec-resistance mutations. There are more known now. Each mutation hampers Gleevec's ability to bind to its target, the ABL kinase.

Sawyers, who in addition to being a researcher, also sees cancer patients at UCLA, has long been hunting for an explanation of Gleevec resistance. Deftly moving between the clinic and the research lab, Sawyers has been at the center of understanding why Gleevec works for some patients, but stops working for others.

In September 2000, HHMI investigator [John Kuriyan](#), a structural biologist then at The Rockefeller University, who had studied the regulation of Abl kinases for many years, made the [seminal discovery](#) that Gleevec, or STI-571, worked by binding to Abl when the enzyme was in its “off” position. If Abl was in the “on” position, the drug would not work.

In the arcane worlds of cellular signaling and structural biology, it was well known that Abl looks structurally quite similar to the Src family of oncogenes that also produce kinases. Yet, as Kuriyan's work demonstrated, STI-571 does not inhibit the Src proteins because they maintain a different shape when in their inactivated, or “off,” position. As Kuriyan prophetically stated at the time, “The puzzle of STI-571's extreme affinity and specificity is of broader interest because protein kinases are crucial elements in signal transduction pathways that control cell growth, cell death and other processes. Thus, understanding how kinases are turned on and off is a matter of extreme interest.”

Kuriyan's work caught the attention of Sawyers, who was examining how mutations in the ABL kinase could blunt the effect of Gleevec. Sawyers and Kuriyan began a collaboration to probe the problem, which culminated in a [publication](#) in the August 2002 issue of the journal *Cancer Cell*, reporting the

identification of 15 mutations in the *BCR-ABL* gene that caused resistance to Gleevec.

In that paper, Kuriyan's structural studies revealed that only a subset of patients bore a mutation right at the point where Gleevec would bind to BCR-ABL to inhibit it. Instead, most patients had mutations that impaired the flexibility of the kinase, preventing it from assuming the "off" position. To Sawyers and others, this raised the possibility that a second drug—a "sloppier inhibitor" than Gleevec that didn't hold the target to such tight structural constraints—might work against the mutations. In short, Sawyers wondered whether a drug that bound Abl in the "on" position, like a Src inhibitor, would be the model for Gleevec's second coming.

Over time, Sawyers's musings became more public. "I was giving scientific talks on the structural implications of Gleevec mutations and stating that I thought that a Src inhibitor would be a good idea," said Sawyers. "This was an informed guess based on what we were seeing in the crystallography data."

As fate would have it, Bristol-Myers Squibb had a dual Abl/Src inhibitor under development. Sawyers received a phone call from Bristol-Myers Squibb - and BMS-354825's reincarnation as a cancer drug was under way.

As Sawyers is quick to point out, only time - and further research - will tell whether the drug makes it into the clinic. Early signs are good. "This could be the first drug to get around kinase resistance, and that has broad implications," Sawyers said. "If this drug should prove to be safe and effective in the clinic, one can envision using this in a combination kinase inhibitor therapy for CML."

BMS-354825 is currently being evaluated at UCLA and MD Anderson Cancer Center in Houston in phase I clinical trials in CML patients with Gleevec resistance.