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New Drug Sidesteps Gleevec Resistance in Human Trials

An experimental drug under development by Bristol-Myers Squibb is showing early promise in reversing the signs and symptoms of patients whose chronic myeloid leukemia failed to respond to Gleevec, which is considered the standard of treatment for the disorder.

In a study to be presented today at the 46th Annual Meeting of the American Society of Hematology in San Diego, Howard Hughes Medical Institute (HHMI) researchers at the University of California, Los Angeles, and colleagues at M.D. Anderson Cancer Center and Bristol-Myers Squibb in Princeton, NJ, report the first data from human clinical trials of the new compound, BMS-354825. Their studies indicate that the drug can successfully overcome Gleevec resistance in patients in the early stages of chronic myeloid leukemia. Patients enrolled in the study had experienced a worsening of the disease or intolerance when treated with Gleevec.

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— Charles L. Sawyers

Study leader, HHMI investigator Charles L. Sawyers, Neil P. Shah, and colleagues at UCLA's Jonsson Comprehensive Cancer Center, report that BMS-354825 successfully circumvented Gleevec (imatinib) resistance in 31 of the 36 patients treated with the drug during phase I clinical trials at UCLA and M.D. Anderson Cancer Center. Resistance to Gleevec develops when patients acquire mutations in an enzyme that is targeted by Gleevec. Phase I clinical trials evaluate drug safety and toxicity at different dose levels in a small number of volunteers.

"Our study examined patients in all phases of CML, including the chronic phase, the accelerated phase, and blast crisis. The patients responded quite well to this new compound, and we observed no side effects," said Sawyers. "In fact, the results of this clinical trial match very closely with what we would have predicted the outcome to be based on our earlier studies of this

drug in mice.”

The 36 patients treated by Sawyers and his colleagues were given BMS-354825 in doses ranging from 15 to 180 mg per day taken orally for five to seven days a week for a period of up to nine months. Dosing was fine-tuned for each patient based on detailed studies that examined how well the drug inhibited its target - a technique that was devised by Sawyers's group for use in earlier studies in mice. Another novel facet of the study, Sawyers said, is that each patient's resistance-enhancing mutation was sequenced by Bristol-Myers Squibb scientists. This provided a wealth of information about the type of mutation carried by each patient, and allowed the researchers to correlate how the drug responded to each type of mutation.

“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 BMS-354825 is one, are being 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.

In this case, the drug's target is the Abelson tyrosine kinase (ABL), an enzyme that 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 studies published earlier this year in the journal *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. In the case of both Gleevec and BMS-354825, there appears to be one particular mutation, known as T315I, which does not respond to either therapy. “That mutation will likely require a different drug, and researchers are working on that now,” said Sawyers.

Sawyers, who in addition to being a researcher, also sees cancer patients at UCLA, has long been hunting for an explanation of Gleevec resistance. The development of BMS-354825 is deeply rooted in scientific literature spanning several different fields, including molecular oncology and structural biology. 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.

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 all the way to FDA approval. Early signs are good, and phase II clinical trials are now being planned. “This is the first drug to get around kinase resistance, and that has broad implications,” Sawyers said. “If this drug continues to be safe and effective in the clinic, one can envision using this in a combination kinase inhibitor therapy for CML. This experience also teaches a lesson for what we might need to avoid similar problems with other kinase inhibitors, like the epidermal growth factor receptor inhibitors, Iressa and Tarceva, which were approved recently for lung cancer.”