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# Researchers Discover Why Some Leukemia Drugs Are Not Sufficiently Effective

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By Jim Stallard, Thursday, September 6, 2012

## Summary

Memorial Sloan Kettering researchers have found why certain drugs are not sufficiently effective in treating leukemias called myeloproliferative neoplasms.

Memorial Sloan Kettering researchers have discovered why a class of drugs called JAK2 inhibitors has not been sufficiently effective to treat blood cancers known as myeloproliferative neoplasms (MPNs). Armed with this insight, they also demonstrated that these drugs could successfully treat such blood diseases if combined with a different type of therapy.

The findings, reported in the [September 6 issue of \*Nature\*](#) by medical oncologist [Ross Levine](#) and colleagues, are guiding researchers as they plan clinical trials to improve therapies for patients with these types of [leukemias](#), which affect more than 200,000 people in the United States.



Medical oncologist Ross Levine

## An Unyielding Target

MPNs are diseases in which several types of blood cells are excessively produced by the bone marrow. Earlier research by Dr. Levine and others found that cancer cells in many people with MPNs have a mutation in a gene called *JAK2*, which makes the JAK2 kinase — a protein that helps regulate a number of basic cell functions.

Identifying the *JAK2* mutation offered a potential target for therapeutic drugs. However, clinical trials testing therapies that inhibit the mutated form of *JAK2* have been less successful in patients than targeted therapies for other blood cancers. Although disease-related symptoms are alleviated — swollen spleens get smaller and patients report feeling better — the cancerous cells in the blood remain.

Until now, it was not known why the drugs fail to bring about the strong responses seen with other targeted therapies — most notably imatinib (Gleevec®), which is very effective against [chronic myelogenous leukemia](#), another blood cancer.

“It isn’t a case of the patients becoming resistant to the drug over time, it is a lack of a response from the beginning,” Dr. Levine says. “Something is allowing the cancer cells to endure despite ongoing treatment. It’s a case of persistence rather than resistance.”

In the *Nature* study, researchers discovered that the cancer cells can use an alternate means of maintaining the function of the mutated JAK2 kinase, even when the cells are exposed to JAK2 inhibitors. When the mutated JAK2 protein comes in contact with an inhibitor, the protein enters an altered state that allows it to remain activated by other JAK kinases.

“The mutated JAK2 normally functions by activating itself,” Dr. Levine says. “But it turns out that when you put the drug on the cells, the mutated JAK2 suddenly can be activated by other proteins. Exposure to the inhibitor causes mutated JAK2 to rely on this alternative activation mechanism to avoid the drug’s effects and stay active.”

The molecular persistence of JAK2 enables the cancer cells to stay alive and continue proliferating. The researchers demonstrated this characteristic in human cell lines, in mouse models, and in samples taken from people with MPN.

“The cancer cell’s persistent reliance on JAK2 told us that it is still the best target. We just need to find a better way to inhibit it,” Dr. Levine says.

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## Adding New Weapons

In 2010, Dr. Levine and colleagues showed that the JAK2 protein could be targeted indirectly by inhibiting another protein, HSP90, which helps keep JAK2 stable. When HSP90 is inactivated, JAK2 becomes degraded inside the cell. In the new study, the researchers combined HSP90 inhibitors with JAK2 inhibitors in human cell lines and demonstrated that this approach is effective in killing the MPN cells.

“Understanding why the disease persists provides a potentially new avenue to achieve better responses, and there are several options that could prove effective,” Dr. Levine says. “The new therapies are in late-stage preclinical testing, and we hope to move into the clinic soon. This could have a significant impact on these diseases.”

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This research was supported by the National Cancer Institute of the National Institutes of Health under award number CA151949-0, as well as by the Starr Cancer Consortium, the Leukemia and Lymphoma Society, and the Myeloproliferative Neoplasms Foundation.

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