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Researchers discover why Gleevec-type drugs control, but do not eradicate leukemia

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Oregon Health & Science University Knight Cancer Institute researchers are closer to understanding why certain chronic myeloid leukemia mutations are not stopped by the revolutionary targeted cancer pill, Gleevec, or similar therapies in that drug family.

The research will be presented Monday, Dec. 8, at the 50th Annual American Society of Hematology conference in San Francisco.

Gleevec, also called imatinib, works by shutting down a critical protein, BCR-ABL, which causes leukemia cells to grow uncontrollably. However, Gleevec also affects other proteins, specifically the KIT protein, which exists on the surface of certain cells and binds to a substance that causes them to grow. Researchers wanted to find out if Gleevec's ability to inhibit KIT in addition to BCR-ABL is an important component in its success in stopping this cancer.

"What we found is that only simultaneous inhibition of both proteins effectively suppresses leukemia cell growth, suggesting that the reason imatinib is so clinically successful may be due to its capacity to inhibit both the cancer-causing BCR-ABL and the complementary protein KIT," said Amie Corbin, OHSU Knight Cancer Institute senior research scientist.

"Most of the time we consider 'off-target effects' such as those seen with imatinib against KIT as detrimental because they may cause side effects. Our study indicates that things are a little more complicated: some off-

target effects may actually be critical for the efficacy of the drug," said Michael Deininger, M.D., Ph.D., associate professor of medicine (hematology/medical oncology), OHSU School of Medicine; head of the Hematologic Malignancies Section, OHSU Knight Cancer Institute; and Scholar of the Leukemia & Lymphoma Society.

Corbin stresses that this finding should not impact patients currently taking the drugs imatinib or the related drugs dasatini or nilotinib. However, patients should check with their physicians if they have any concerns. All three of the drugs target both BCR-ABL and KIT. However, novel drugs against multidrug resistant mutants of BCR-ABL may not be as effective if they don't also target KIT and this should be considered in pre-clinical drug development.

Researchers also found that while dual BCR-ABL/KIT inhibition was important to suppress the majority of CML cell types that rely on both BCR-ABL and KIT activity, the most primitive CML stem cells that are resistant to imatinib treatment and cause long-term residual disease in imatinib-treated patients were not sensitive to the effects of KIT inhibition.

"This suggests that CML stem cell survival depends on different proteins that are not targets of imatinib and presents a possible explanation for why these cells survive therapy," Corbin said.

Source: Oregon Health & Science University