To prevent leukemia's dreaded return, go for the stem cells

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Researchers reporting in the April *Cell Stem Cell*, a Cell Press publication, have found a way to stop leukemia stem cells in their tracks. The advance in mice suggests that a combination approach to therapy might stamp out chronic myeloid leukemia (CML) for good.

That's in contrast to the vast majority of CML patients taking drugs like imatinib (aka Gleevec) today, who often go into remission only to see their cancer return again. It is those lingering leukemia stem cells, which stubbornly resist existing therapies, that fuel the cancer's comeback.

"Imatinib inhibits the oncoprotein [that drives CML] and it is incredibly effective at putting patients into remission," said Scott Armstrong of Harvard Medical School. "But there is growing evidence that this doesn't rid the body of the most immature cancer cells. The question is: How can we eradicate those cells?"

The *Cell Stem Cell* study focused on a pathway known to be important in blood stem cells during development but not in adulthood. The new findings in mice suggest that leukemia stem cells revert back to their dependence on that early developmental pathway.

That leaves leukemia stem cells vulnerable to treatments aimed at the so-called β-catenin pathway in a way that normal blood stem cells aren't. The evidence shows that imatinib plus the loss of β-catenin can help to prevent recurrence of the disease. β-catenin inhibitors given to mice also helped to eliminate leukemia stem cells, as did a pain-relieving drug

already in use that lowers β-catenin levels, if indirectly.

Armstrong says there is more work to do to ensure that β-catenin blockers would work in the same way in humans that they do in the mice. If so, it's likely CML patients won't be the only or even the first to gain from the new treatment strategy.

"It will take time because people with CML already do pretty well," he says. But β-catenin inhibitors might be just what the doctor ordered in the case of some other, harder-to-treat forms of leukemia, in colon cancer, or perhaps in patients who have entered an acute stage of CML.

"The appeal is that this pathway is important for the leukemia, but not for normal cells," Armstrong says. "It gives us an angle for therapy." A drug targeted at β-catenin might just get rid of leukemia and its stem cells once and for all, while leaving healthy blood stem cells unscathed.

More information: Heidel et al.: "Genetic and Pharmacologic Inhibition of β-Catenin Targets Imatinib-Resistant Leukemia Stem Cells in CML." *Cell Stem Cell* - April 6, 2012 print issue. DOI:10.1016/j.stem.2012.02.017

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