New drug stops aggressive form of childhood leukemia

May 24 2011

In a significant breakthrough, investigators at Weill Cornell Medical College and the University of California, San Francisco, have been able to overcome resistance of a form of leukemia to targeted therapy, demonstrating complete eradication of the cancer in cell and animal studies.

Their study, published in the May 19 issue of *Nature*, shows that an investigational drug, RI-BPI, developed at Weill Cornell, in combination with the drug Gleevec shut down stem cells responsible for about one-third of acute lymphoblastic leukemia (ALL), a cancer of white blood cells that affects young children as well as older adults.

This form of ALL has the so-called Philadelphia chromosome, which is also found in chronic myelogenous leukemia (CML). But while Gleevec has greatly improved survival in CML, it has had a less dramatic effect in ALL, and most patients still die within a relatively short timeframe.

That desperate prognosis may radically change given these results, says co-senior investigator Dr. Ari Melnick, associate professor of medicine and director of the Raymond and Beverly Sackler Center for Biomedical and Physical Sciences at Weill Cornell Medical College, and a hematologist-oncologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center.

"I am surprised, and extremely glad, to see that RI-BPI has such strong activity in a leukemia. This opens up the possibility that the agent will

have similar beneficial effects in other tumor types," says Dr. Melnick.

Dr. Melnick and his colleagues developed RI-BPI and they have shown its potent effects in non-Hodgkin's lymphoma (NHL) with no toxicity to normal cells. The drug targets the transcription factor BCL6, a master regulator of hundreds of genes that provides strong growth signals to NHL cells.

The new study demonstrated that BCL6 is also active in ALL driven by the Philadelphia chromosome (Ph+ ALL), and that a combination of RI-BPI and Gleevec virtually shuts the cancer down, says Dr. Melnick. After a long search for the source of Gleevec resistance in this form of ALL by the team at the University of California, San Francisco (UCSF), it appears that BCL6 is the fundamental mediator of that resistance, he explains. "This gives us an opportunity to target Gleevec resistance, something that has the potential to substantially improve outcomes for patients with this disease."

The UCSF research team discovered that production of BCL6 is turned on after administration of Gleevec in Ph+ ALL. UCSF investigators then initiated collaborative research with Dr. Melnick, who provided RI-BPI and conducted experiments on how BCL6 regulates genes in leukemia cells.

The UCSF team also conducted animal tests and discovered that BCL6 hits the stem cells that give rise to ALL. "These stem cells continually repopulate disease cells by making copies of themselves," Dr. Melnick says. "We believe RI-BPI counteracts the BCL6 gene regulatory program that these stem cells need to survive.

"BCL6 turns off the brakes that normally limit cancer growth, which is why Gleevec does not work in this cancer, but RI-BPI puts those brakes back on," he says.

The study also suggests that transcription factors like BCL6 may be less impervious than once thought to targeted treatment, Dr. Melnick says. BCL6 is a protein, and it "mediates its cancer-causing actions by attaching to other proteins. Traditionally, however, protein-protein interactions have been viewed as being too difficult to block with small-molecule drugs."

Although it has yet to be tested in refractory CML -- CML that has become resistant to Gleevec, which occurs in most patients over time -- it makes sense that RI-BPI could restore Gleevec sensitivity, Dr. Melnick adds.

"From this study and from the others in my lab, I have become very impressed with how reliant tumor cells are on certain proteins for their survival," he says. "If we can hit several of these brittle and dependent processes, we have the chance to eradicate cancer."

Based on this study, a clinical trial is being developed to treat children with Ph+ ALL with a combination of RI-BPI.

Provided by New York- Presbyterian Hospital