# New approach to treating B-cell acute lymphoblastic leukemia shows promise

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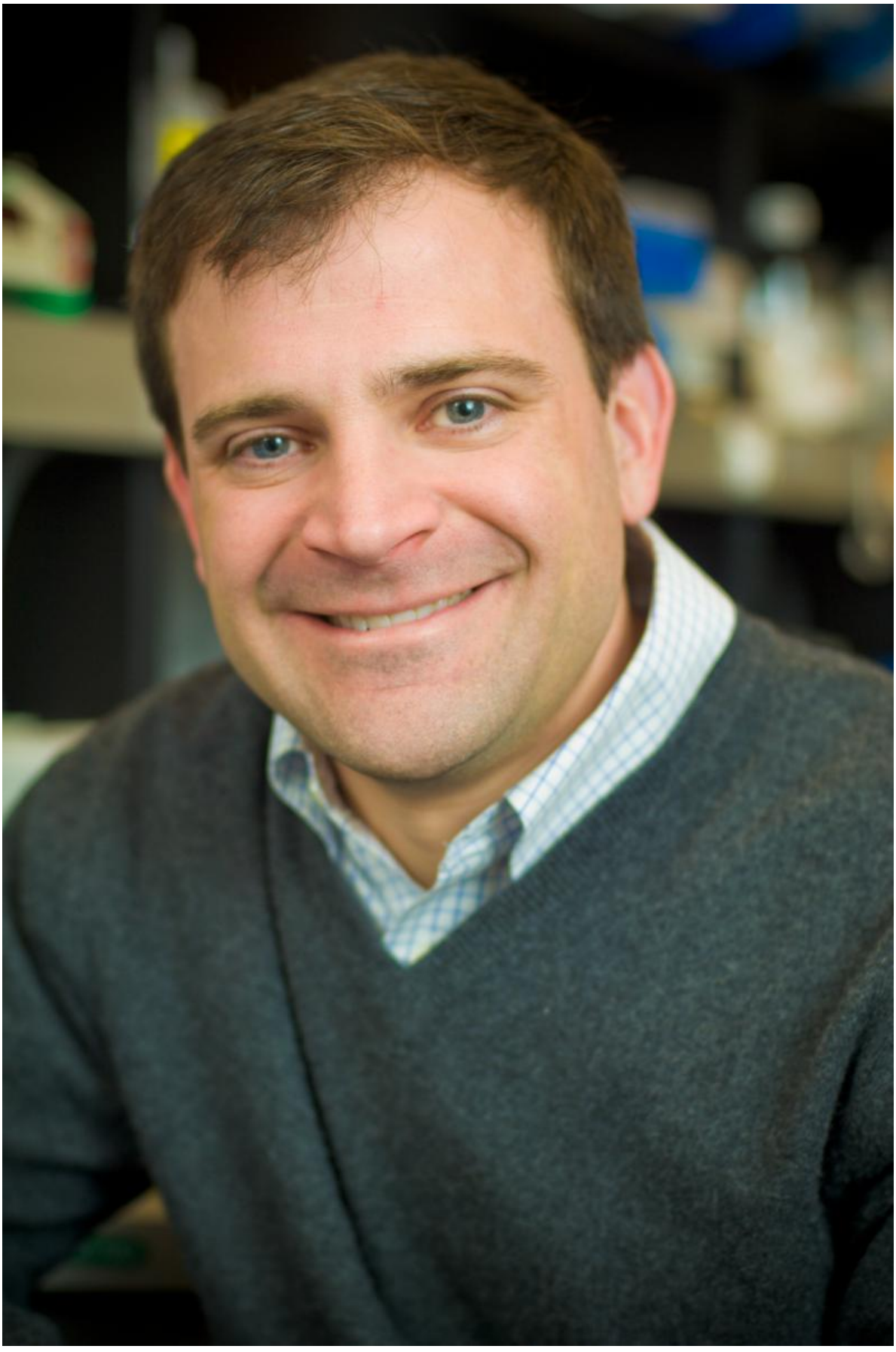

David Weinstock, M.D. Credit: Sam Ogden, Dana-Farber

A new compound that locks a disease-related protein into an inactive position stifled the growth of an aggressive form of leukemia in laboratory and animal tests, researchers at Dana-Farber Cancer Institute and other institutions report. When the compound was combined with a steroid, the leukemia was reduced even further and the animals lived longer than they did when treated with the compound alone.

The results, published online July 13 by the journal *Cancer Cell*, demonstrate that the technique - in which a drug compound shuts down the protein by snapping it closed, preventing it from functioning - can be especially effective in some cancers. "Our results were achieved in an aggressive type of B-cell acute lymphoblastic leukemia [B-ALL], the most common cancer in children and a highly fatal disease in adults," said David Weinstock, MD, of Dana-Farber, the co-senior author of the study with Christoph Gaul, PhD, of Novartis Institute for Biomedical Research. "But because the same protein is found in an abnormal form in other cancers, this approach holds promise for treating them as well."

The study involved a variety of B-ALL in which the cancer cells carry a rearrangement of the gene CRLF2. (Such rearrangements occur when DNA damage causes certain genes to be out of their proper order in a chromosome.) While most children with B-ALL can be successfully treated, those with this genetic variant often do not fare as well.

One of the most inviting targets on B-ALL cells with CRLF2 rearrangements is a signaling protein called JAK2, which the cells rely on to grow and survive. Drugs that block JAK2 have received Food and

Drug Administration approval for treating diseases such as myeloproliferative disorders (which affect blood cell growth in the bone marrow) and rheumatoid arthritis, but they have not been successful in cancer. "While these drugs can reduce the symptoms associated with certain cancers, they don't alter the natural course of the disease," Weinstock said.

Researchers have shown that such "type I" JAK2 inhibitors fail in cancer because the tumor cells manage to re-route the chemical signals that usually pass through JAK2. This allows the cells to resume their hectic growth and division.

In the new study, Weinstock and his colleagues tested a type II JAK2 inhibitor, which uses a different strategy against the errant protein. Made by Novartis, the inhibitor, called CHZ868, binds JAK2 into a tightly clenched position that prevents it from functioning.

Weinstock's team tested the agent in laboratory samples of B-ALL with CRLF2 rearrangement, in mice with the disease, and in mice implanted with human B-ALL tissue. "In each case, we saw good activity: leukemia cells died, JAK2 signaling was suspended, and survival rates increased," Weinstock said. "When we combined CHZ868 with the steroid dexamethasone, the killing of leukemia cells was much more extensive and the animals lived longer than they did with CHZ868 alone."

Especially encouraging was the lack of bone marrow problems in the treated mice, a possible side effect of JAK2 inhibitors, Weinstock added.

"JAK2 abnormalities are found in some cases of triple-negative breast cancer and Hodgkin lymphoma," he continued. "The success of CHZ868 in B-ALL suggests that it, or a compound that works by a similar mechanism, may also be effective in these cancers."

Provided by Dana-Farber Cancer Institute