Researchers overcome leukemia radiation resistance with an engineered precision medicine

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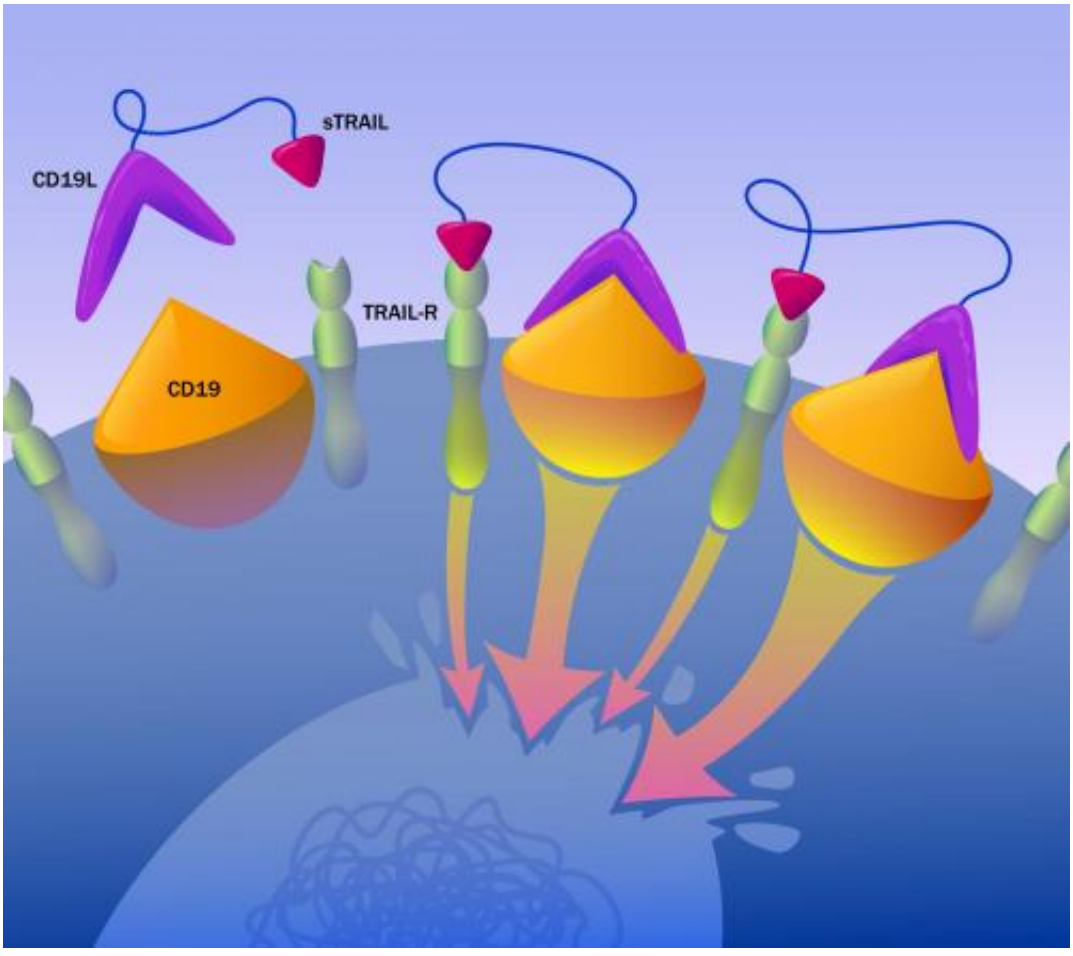

A team of researchers led by Fatih M. Uckun, MD, PhD, of The Saban Research Institute of Children's Hospital Los Angeles and Professor at the University of Southern California Keck School of Medicine has determined that radiation resistance in leukemia can be overcome by using an engineered protein they recently designed and developed as a new precision medicine against leukemia. This study has been published in open access journal *EBioMedicine*.

B-precursor acute lymphoblastic leukemia (ALL) is the most common cancer occurring in children and adolescents. Despite having received intensive chemotherapy, some patients experience a recurrence of their cancer, known as relapse. For these patients, the prospect of long-term survival is very poor..

The standard approach to treating relapsed patients has been intensive chemotherapy to achieve a second remission followed by very intensive treatment that could include "supralethal" chemotherapy, total-body irradiation (TBI), and hematopoietic stem cell transplantation. However, radiation resistance of leukemia cells hampers the success of these rigorous therapeutic approaches and results in poor survival.

"Despite advances in available therapies, unmet and urgent needs remain in the fight against leukemia. We still have children with disease that our drugs can't help enough. And for patients who relapse, their chances of long-term survival are less than 20 percent. We've got to do better." explained Dr. Uckun. "Therefore, discovering a way to overcome the radiation resistance of ALL has been one of the most urgent unmet challenges in cancer therapy," he added.

Uckun's research team has now provided the first proof-of-principle that radiation resistance of an aggressive leukemia can indeed be overcome using this rationally-designed specific protein-based medicine that markedly augments the potency of radiation therapy even against the

most aggressive and radiation-resistant forms of leukemia.

"Even very low doses of radiation were highly effective in mice challenged with aggressive human leukemia cells, when it was combined with the new precision medicine that was named CD19L-sTRAIL (short for CD19 Ligand - soluble TRAIL fusion protein)," said Dr. Uckun. CD19L-sTRAIL has been developed by genetic engineering as a fusion of the CD19 Ligand protein that seeks out and binds to leukemia cells with soluble TRAIL, a protein that that can amplify the potency of radiation if it can be anchored on the membrane of leukemia cells.

"Due to its ability to selectively anchor to the surface of leukemia cells via its CD19L portion, CD19L-sTRAIL was 100,000-fold more potent than sTRAIL, and consistently killed aggressive leukemia cells taken directly from children with ALL - not only in the test tube, but also in mice," commented Dr. Uckun. When total body irradiation alone failed to improve the survival of mice challenged with an otherwise invariably lethal dose of human leukemia cells taken directly from patients, adding only 1-3 doses of the new medicine to the radiation regimen improved its potency by 260% and resulted in long-term leukemia-free survival of mice without noticeable side effects.

"We are hopeful that the knowledge gained from this study will open a new range of effective treatment opportunities for children with recurrent leukemia," Dr. Uckun noted.

More information: "Low Dose Total Body Irradiation Combined With Recombinant CD19-Ligand × Soluble TRAIL Fusion Protein is Highly Effective Against Radiation-resistant B-precursor Acute Lymphoblastic Leukemia in Mice," *EBioMedicine*, DOI: dx.doi.org/10.1016/j.ebiom.2015.02.008