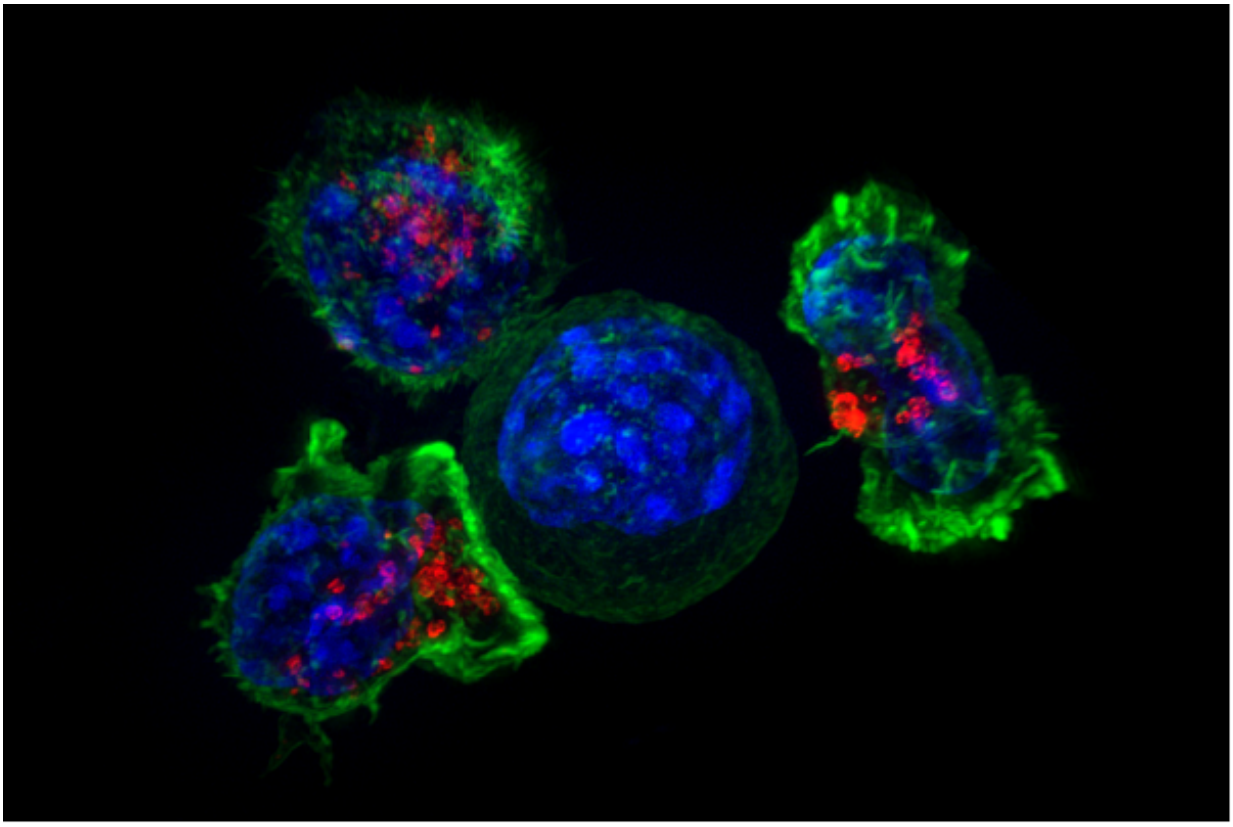
MedicalXpress

Chemical screening suggests a two-pronged treatment for pediatric Ewing sarcoma

August 15 2019



Killer T cells surround a cancer cell. Credit: NIH

For children with Ewing sarcoma, an aggressive bone cancer, a combination of two different classes of drugs may work synergistically to turn off the drivers fueling this disease, finds a new study. The

combination appears to be more powerful than relying on either treatment alone.

The study, published online last month in *Clinical Cancer Research*, is the latest in a series of investigations performed by researchers at Dana Farber/Boston Children's Cancer and Blood Disorders Center and their collaborators from other leading cancer centers. Their efforts are shedding new light on the biology that fuels the aggressive nature of Ewing sarcoma cells and is leading to new drug targets for this and other forms of pediatric cancer.

A challenging disease to tackle

While current treatment methods have been found to cure about 70 percent of children with a localized form of Ewing sarcoma, they often involve a combination of aggressive chemotherapy, radiation, and surgery that can be difficult for young patients to tolerate. For children with metastatic disease or those who relapse after completing first-line therapy, treatment options are limited and rarely result in a cure.

Further compounding matters is that children face long delays in accessing clinical trials of less toxic medications that target the mutations that drive their cancer, says Kimberly Stegmaier, MD, co-director of the pediatric hematologic malignancy program at Dana-Farber/Boston Children's Cancer and Blood Disorders Center and a member of the Broad Institute.

Identifying a two-pronged treatment approach

Stegmaier and Dana Farber/Boston Children's colleague Brian Crompton, MD, are both corresponding authors of the latest study. In previous work, they demonstrated that Ewing sarcoma is dependent on the activity of a protein called focal adhesion kinase (FAK), and that

inhibition of FAK activity slows Ewing tumor growth. However, numerous studies have demonstrated that treatment with a single drug is insufficient. Rather than combining FAK inhibitors with chemotherapy, Stegmaier and Crompton set out to find other less toxic targeted therapies that could be paired with FAK inhibitors to more effectively kill Ewing sarcoma cells.

In their new study, Stegmaier and Crompton screened a large collection of cancer drugs to identify agents that would synergize with FAK inhibition to kill Ewing sarcoma cells. They found that combining FAK inhibitors with drugs targeting a protein required for cells to divide, aurora kinase B, resulted in more Ewing sarcoma cell death and significantly inhibited tumor progression more than either treatment did on its own.

Building on past findings

The discovery comes on the heels of two other published studies on Ewing sarcoma that identify novel treatment approaches for this disease.

Stegmaier was senior author on a study published in *Cancer Cell* in early 2018, which explored how to target challenging cancers such as Ewing sarcoma that are driven by oncogenic transcription factors (proteins that turn genes on or off). The researchers discovered that CDK12 inhibitors, when combined with a PARP inhibitor drug, can have a dramatic impact on Ewing sarcoma cells, a combination expected to be less toxic to patients than chemotherapy.

Another recently published study used a CRISPR-Cas9 editing screen to probe for genetic weaknesses. The researchers were able to identify genes whose activity promotes proliferation of Ewing sarcoma cells in which p53, a protective gene that is mutated in most adult cancers, is

intact. By targeting these genes, they were able to kill Ewing sarcoma cells in a dish and slow tumor growth in mouse models. These findings, published last summer, have also led to a clinical trial in patients with Ewing sarcoma and several other types of cancer.

Offering new hope for pediatric cancer patients

"These studies are beginning to pave the way for the development of new and more effective treatments for patients with Ewing sarcoma that are expected to have less toxicity than the current standard treatment for this disease," Crompton says.

They may also provide much-needed therapeutic options for patients who relapse after receiving front-line therapy, offering new hope for children and their families.

Provided by Children's Hospital Boston

Citation: Chemical screening suggests a two-pronged treatment for pediatric Ewing sarcoma (2019, August 15) retrieved 6 February 2023 from https://medicalxpress.com/news/2019-08-chemical-screening-two-pronged-treatment-pediatric.html