In lab study, researchers find molecule that disrupts Ewing's sarcoma oncogene

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Researchers at Georgetown University Medical Center have found a small molecule they say can block the action of the oncogene that causes Ewing's sarcoma, a rare cancer found in children and young adults. If further studies continue to prove beneficial, they say the novel agent could be the first targeted therapy to treat the disease, which can produce tumors anywhere in the body.

The findings, presented today at the annual meeting of the American Association for Cancer Research (AACR) in San Diego, suggest that the unique way in which this molecule works -- through a so-called protein-protein interaction -- could provide a model upon which to design other therapies, says the study's lead investigator, Jeffrey Toretsky, M.D., a pediatric oncology physician and researcher at Georgetown University's Lombardi Comprehensive Cancer Center.

"I think this holds really wonderful promise as a unique way of targeting fusion proteins," he says. "People thought it wasn't possible to have a small molecule that can bind between flexible proteins, but we have shown that it can be done."

This study was conducted in laboratory cells, so additional research is necessary before the novel agent can be tested in patients, Toretsky says. In vivo studies are now underway, he says.

Ewing's sarcoma is caused by the exchange of DNA between two chromosomes, a process known as a translocation. The new gene, known

as EWS-FLI1, is created when the EWS gene on chromosome 22 fuses to the FLI1 gene on chromosome 11, and its product is the fusion protein responsible for cancer formation.

In the United States, about 500 patients annually are diagnosed with the cancer, and they are treated with a combination of five different chemotherapy drugs. Between 60-70 percent of patients survive over time, but many have effects that linger from the therapy.

Toretsky has long led research into the causes of, and treatments for, Ewing's sarcoma. He and his laboratory colleagues were the first to make a recombinant EWS-FLI1 fusion protein. "We did this in order to find out if EWS-FLI1 might be binding with other cellular proteins," he says.

They found that, indeed, the fusion protein stuck to another protein, RNA helicase A (RHA), a molecule that forms protein complexes in order to control gene transcription. "We believe that when RHA binds to EWS-FLI1, the combination becomes more powerful at turning genes on and off," says the study's first author, Hayriye Verda Erkizan, Ph.D., a postdoctoral researcher in Toretsky's lab who is presenting the study results at AACR.

The researchers used a laboratory technique to keep RHA apart from the fusion protein, and found that both were important to cancer formation. Knowing that, they worked to identify the specific region on RHA that stuck to EWS-FLI1, and then collaborated with investigators in Georgetown's Drug Discovery Program to find a molecule that would keep the two proteins separated. In other words, such an agent would stick to EWS-FLI1 in the very place that RHA bound to the fusion molecule.

Using a library of small molecules loaned to Georgetown from the National Cancer Institute, the team of investigators tested 3,000

compounds to see if any would bind to immobilized EWS-FLI1 proteins. They found one that did, and very tightly.

This was a wonderful discovery, Erkizan says, because the notion long accepted among scientists is that it is not possible to block protein-protein interactions given that the surface of these proteins are slippery, and much too flexible for a drug to bind to.

"These are wiggly proteins yet this study shows that inhibition of protein-protein interactions with a small molecule is possible," Toretsky says. This possibility means that fusion proteins, such as those produced in other sarcomas as well as diverse disorders, might be inhibited, he says. This is a different process than other drugs that have been shown to work against fusion proteins, such as Gleevec, which blocks the enzyme produced by the chromosomal translocation responsible for chronic myelogenous leukemia (CML). "Gleevec inhibits a single protein, while we are trying to block the binding of two proteins, and we are very enthusiastic about the results so far," Toretsky says.

Toretsky recently received a $750,000 Clinical Scientist Award in Translational Research from the Burroughs Wellcome Fund (BWF), which he will use to accelerate these translational efforts to help treat Ewing's sarcoma, utilizing GUMC's drug discovery program.

Source: Georgetown University