Preclinical tests shows agent stops 'slippery' proteins from binding, causing Ewing sarcoma

May 15 2013

Continuous infusion of a novel agent not only halted the progression of Ewing sarcoma in rats, while some tumors also regressed to the point that cancer cells could not be detected microscopically, say researchers at Georgetown Lombardi Comprehensive Cancer Center. Their study, which will be presented at the 2013 annual meeting of the American Society of Clinical Oncology, provides pre-clinical evidence necessary to initiate a clinical trial.

"This agent has the potential to be more effective, and considerably less toxic, than the current drugs now used to treat this rare cancer," says the study's lead investigator, Jeffrey Toretsky, MD, a pediatric oncologist and researcher at Georgetown Lombardi, part of Georgetown University Medical Center.

The agent, (S)-YK-4-279, was developed by Toretsky and his colleagues, including scientists in GUMC's Center for Drug Discovery. Based on early promising studies of the compound, Toretsky established TDP Biotherapeutics, Inc. to manufacture the agent. Toretsky says TDP Biotherapeutics, Inc. is preparing a U.S. Food and Drug Administration (FDA) investigational new drug (IND) application for (S)-YK-4-279 so that a clinical trial can be initiated.

In the United States, about 500 children and young adults are diagnosed with the cancer annually, and they are treated with a combination of five

different chemotherapy drugs. Between 60 to 70 percent of patients survive more than five years, but with many late effects from therapy. Few treatments lead to a cure for patients whose cancer progresses, Toretsky says.

Ewing sarcoma is caused by the exchange of DNA between two chromosomes. The resulting EWSR1-FLI1 gene produces a fusion protein, EWS-FLI1, responsible for development of the cancer. In 2006, Toretsky and his team discovered that the fusion protein binds to another protein, RNA helicase A (RHA), which is important for cancer progression.

The (S)-YK-4-279 agent they developed is considered unique because it stops the two proteins—EWS-FLI1 and RHA—from interacting. "Scientists have long thought it impossible to block protein-protein interaction because the surface of these proteins are too slippery and flexible for a drug to bind to," Toretsky says. "Our agent challenges that conventional thinking."

To test the agent, the researchers developed a rat model of Ewing sarcoma and figured out how to deliver a continuous drip of the drug to the animals. "We found that cancer cells need a continuous exposure at low concentrations for the drug to be of maximum effectiveness," Toretsky says. "And this strategy works extremely well in these animal models. The drug appears to be very successful."

Toretsky is an inventor on a patent application that has been filed by Georgetown University related to the technology described. He has an ownership interest in TDP Biotherapeutics, to which the technology has been licensed for research and development.

Provided by Georgetown University Medical Center