Genetically reprogrammed HSV given systemically shrinks distant sarcomas

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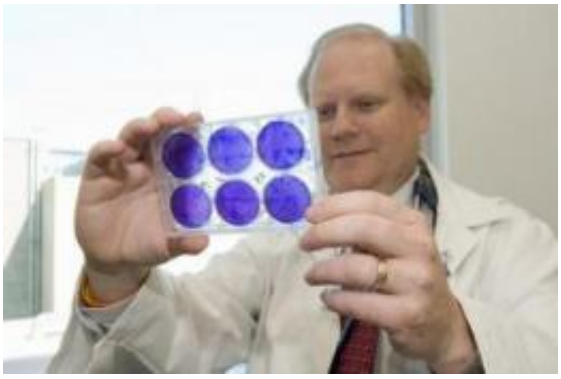

Timothy Cripe, M.D., Ph.D., an oncologist and researcher at Cincinnati Children's Hospital Medical Center, inspects cell cultures in his laboratory. Cripe and his research colleagues are investigating oncolytic viruses as a new strategy for fighting hard-to-treat childhood cancers. Credit: Cincinnati Children's Hospital Medical Center

Scientists have used a genetically reprogrammed herpes virus and an anti-vascular drug to shrink spreading distant sarcomas designed to model metastatic disease in mice - still an elusive goal when treating humans with cancer, according to a study in the July 8 *Gene Therapy*.

Less than 30 percent of patients with metastatic cancer survive beyond five years, despite the aggressive use of modern combination therapies, including chemotherapy. This creates a significant need for new sarcoma therapies to treat metastatic disease, said Timothy Cripe, M.D., Ph.D., a

physician/researcher in the division of Hematology/Oncology at Cincinnati Children's Hospital Medical Center and the study's senior investigator.

The study results are even more significant because the oncolytic herpes virus, HSV-rRp450, was given to the mice systemically to attack tumors via the blood stream instead of being injected directly into tumors.

"Systemic bio-distribution has been a major stumbling block for using virus vectors in gene transfer and virotherapy to treat cancer, but we show that viruses can be used systemically by giving them intravenously to get an anti-tumor effect," Dr. Cripe said.

Also important to results of the current study was using the virus in conjunction with a drug (bevacizumab) that blocks the growth of tumor feeding-blood vessels. In the current study, researchers focused on spreading Ewing sarcoma and Rhabdomyosarcoma - cancers that form in muscle, bone and connective tissue.

Anti-angiogenic agents like bevacizumab are usually given first in combination cancer therapies because they help enlarge intercellular openings to tumor cells and ease the delivery of drugs, such as chemotherapies. In this study, however, the researchers discovered that bevacizumab has to be given after the virus to maximize the anti-tumor effect of the combined therapy. In fact, giving bevacizumab first lowered the virus's uptake in cancer cells.

The rRp450 oncolytic virus used in the study was derived from herpes simplex type 1. The virus was genetically modified by scientists by removing a gene that makes the virus unable to replicate efficiently in dormant cells. This causes the virus to selectively target and replicate in rapidly growing cancer cells while leaving normally dormant healthy tissue cells alone.

After removing the one gene from the virus, researchers replaced it with a gene that encodes an enzyme that activates a class of anti-tumor chemotherapies called oxazaphosphorines. The overall therapeutic approach is for the virus to infect and degrade the cancer cells and then activate chemotherapy agents as anti-angiogenic agents cut off vascular growth and blood supply to the tumors.

In the current study, however, researchers treated the mice only with rRp450 and the anti-angiogenic drug bevacizumab. This allowed them to test whether the virus could be given systemically, how anti-angiogenic drugs affected virus tumor uptake and the impact this had on tumor growth.

In mice receiving bevacizumab prior to the rRp450, overall tumor shrinkage averaged 40 percent. In mice receiving rRp450 before bevacizumab, tumor size was reduced by an average of 75 percent. The researchers also reported that mice treated with rRp450 before bevacizumab had longer survival rates.

Results of the current study could be used immediately to help design subsequent research into treatment protocols for oncolytic viruses, particularly clinical trials involving combination therapeutic strategies, Dr. Cripe said. Clinical trials are underway in the United States and Europe using oncolytic herpes viruses similar to the one used in the current study.

Provided by Cincinnati Children's Hospital Medical Center