Novel gene-silencing nanoparticles shown to inhibit Ewing's sarcoma

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A novel delivery system that transports gene silencing nanoparticles into tumor cells has been shown to inhibit Ewing's sarcoma in an animal model of the disease.
In this classic "Trojan horse" approach, a protein called transferrin that normally delivers iron into cells is modified to also smuggle into tumor cells siRNA (short interfering RNA) encased in nano-sized sugar polymers. The siRNA was designed to target a specific growth-promoting gene called EWS-FLI1 that's active only in Ewing's sarcoma tumors.

Once inside these cells, the genetic machinery of the tumor cells are effectively silenced or shut down, preventing further growth.

"This is the first study to show that systemic administration of siRNA can inhibit disseminated tumor growth," said Siwen Hu, a postdoctoral fellow at Children's Hospital of Los Angeles and the University of Southern California, and one of the study's lead investigators.

"We conclude that this novel delivery system is a powerful and simple method to induce gene silencing, with the potential to move to clinical trials," said Hu, who presented the results at the 96th Annual Meeting here of the American Association for Cancer Research.

In recent years, scientists have been intrigued by the potential of siRNA to block the activity of genes that promote the growth of tumors. Harnessing the power of this new technology, however, has proved

daunting for a variety of reasons, including the ability to deliver these bits of genetic material in high concentrations to specific tumor sites, while avoiding degradation.

To overcome these hurdles, the scientists employed a sugar-containing polymer invented by chemical engineers at the California Institute of Technology. For this experiment, the polymer binds to and condenses the engineered siRNA into nanoparticles that, in effect, form a protective shield around their precious genetic cargo. These nanoparticles, in turn, are attached to transferrin, a protein that typically carries iron molecules through the bloodstream until it meets up with a transferrin receptor on the surface of another cell. The transferrin binds tightly to a receptor on the cell's surface, where it is drawn inside and surrounded by a small vesicle. The vessels are acidified, causing the nanoparticles to release its contents – the siRNA.

"Since transferrin receptors are upregulated in tumor cells, this delivery system will home in on tumor cells, leaving normal cells in tact," Hu said.

To test their new delivery system, the scientists targeted tumor cells from the patients of Ewing's sarcoma, a rare and often deadly bone cancer that generally strikes young adults. Despite aggressive therapy, about 40 percent of patients with Ewing's family tumors and 95 percent with metastases die as a result of their disease.

Scientists now recognize that Ewing's sarcoma results when two chromosomes break and trade their genetic content in what's technically called a "translocation," activating the oncogene EWS-FLI1 which triggers the tumor growth characteristic for this cancer.

In their experiment, siRNA was delivered to this growth-promoting region of the tumor cell, effectively reducing cell replication by 80

percent.

The scientists then tried their novel technology in laboratory mice grafted with human Ewing's sarcoma tumors. Following three consecutive days of treatment, the scientists observed strong, but transient, inhibition of tumor growth.

However, when used over longer durations (twice-weekly injections up to four weeks), the results were striking.

"Long-term treatments with this delivery system markedly inhibited tumor growth, with little or no tumor growth in many animals," said Hu.

Future experiments will combine the novel delivery system with small molecular anti-tumor agents, with hopes of creating a new and effective way to treat Ewing's sarcoma and other tumors in the clinic.

"Clinically, Ewing's patients are treated with combination of chemotherapeutic agents, but despite aggressive treatments, the patient outcomes are poor," said Hu.

"The delivery system we're developing can shield the drugs from degradation before reaching the target sites, while delivering siRNA for more specificity and potency so as to lower the required dose for efficacy."

The study was a collaborative effort between the laboratory of Timothy J. Triche, at Children's Hospital of Los Angeles; and the laboratory of Mark E. Davis, at the Caltech. Also participating in the study were Jeremy D. Heidel and Derek W. Barlett, both at Caltech.

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