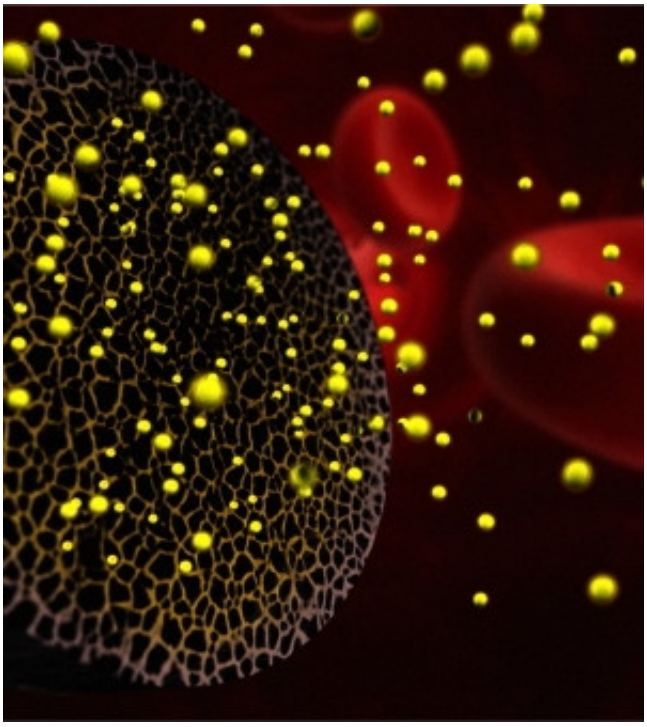
Nanotech'ed RNA drug reduces ovarian cancer tumors by 83 percent

February 14 2013



In this rendering, RNA-carrying "nanoliposomes" (yellow) are released from a silicon nanoparticle (grey) near targeted ovarian cancer cells (not pictured). Intravenous injections of the microscopic drug delivery system in animal models appear to have resulted in anywhere from a 36 to 83 reduction in ovarian tumor weight, depending on the dose administered.

By loading fragile RNA into silicon nanoparticles, researchers from The Methodist Hospital and two other institutions found a new drug delivery system can reduce the size of ovarian tumors by as much as 83

percent—and stop tumor growth in chemotherapy-resistant ovarian cancer tissue.

The study, conducted in animal models, is published in an upcoming issue of *Clinical Cancer Research* (now online).

"Drug resistance is a huge problem in the clinic," said Mauro Ferrari, Ph.D., one of the senior authors of the paper. "Our work shows that protecting the RNA longer so that it can get to where it must go and do its work inside cancer cells not only increases the RNA's impact, but also makes drug-resistant cancer cells once again sensitive to commonly used chemotherapy drugs."

The National Cancer Institute estimates that 1 in 72 women born today will be diagnosed with ovarian cancer at some point during their lives. Mortality is highly dependent on how early the cancer is detected, ranging from 8.5 to 78 percent. Drug resistance is a major reason for drug therapy failure in ovarian cancer patients.

The present work combines nanoparticle technologies developed separately at TMHRI and The University of Texas MD Anderson Cancer Center.

"New approaches to overcome drug resistance are urgently needed to improve the survival of cancer patients, and small inhibitory RNA is a promising approach," said co-senior author Anil Sood, M.D., of MD Anderson's Department of Gynecologic Oncology and Reproductive Medicine.

Sood and co-senior author Gabriel Lopez-Berestein, M.D., of MD Anderson's Department of Experimental Therapeutics developed the siRNA approach to ovarian cancer.

Small inhibitory RNA, or siRNA, is a snippet of genetic material that interferes with the expression of genes, in this case, a crucial ovarian cancer gene called ephA2. Here, siRNA is being used as a drug to stop the cancer cells from growing—and eventually kill them.

While safe, the siRNA can't simply be injected into a patient. There are enzymes in the blood and inside cells that would destroy the siRNA before it gets close to its target cancer cells. MD Anderson researchers developed a protective shield for the siRNA, a lipid carrier nanoparticle called a nanoliposome.

The researchers learned the liposome-clad siRNA were more likely to make it to cancer cells (where the liposome would be absorbed), but the liposomes don't usually last very long in the blood, and for any cancer therapy to be effective, they decided a more sustained drug delivery method was needed.

"The use of siRNA is an attractive strategy for cancer treatment by targeting essential genes for cancer cell survival," said Haifa Shen, M.D., Ph.D., a lead author. "But it needs an effective delivery vector to overcome many biological barriers. Our multistage vector delivery system serves as a bridge from bench to clinic."

Ferrari's group has developed silicon, disc-shaped nanoparticles (actually 1 micrometer in diameter) that are designed to bind to tumor cells. Past studies by Ferrari and his colleagues have helped them perfect the shape of the particles, their size, and their surface chemistry, so that they bind specifically to overexpressed proteins dotting the outside of cancer cells.

Combining these two things—liposome-clad siRNA, inserted into the perforations of silicon nanoparticles—had a remarkable impact on ovarian cancer in mouse models.

"Loading liposomes into the nanoparticle system not only allows tumor-specific delivery, but also adds another layer of protection for the siRNA," Shen said.

Twelve injections of 5, 10, or 15 micrograms of the nanoparticles over 6 weeks appear to have caused reductions of 36 percent, 64 percent, and 83 percent in ovarian cancer tumor weight, respectively, in each of the three treatment groups, compared to controls that received a placebo. The scientists also saw a reduction in the number of tumor nodules in each of the three treatment groups, relative to the control.

When the nanoparticles were injected with the common first- and second-line chemotherapy drug paclitaxel, the researchers saw zero tumor growth.

The research team also looked at how the siRNA-loaded nanoparticles, in combination with the later-stage chemotherapy drug docetaxel, impacted multidrug-resistant ovarian cancer tissue. Cancer cells in this group were otherwise resistant to docetaxel treatment alone—one of the controls in this round of experiments. Past studies suggest overexpression of the gene ephA2 indirectly confers resistance to ovarian cancer cells.

"We can completely eliminate tumor nodules, which means the patients—mice—can achieve long-term survival," Shen said.

To assess the safety of the liposome-clad siRNA nanoparticles, the researchers compared body weight loss/gain in different treatment groups, and found the nanoparticles were no more toxic to the animals than treatment with paclitaxel or docetaxel alone at clinically relevant doses.

The next steps, of course, are moving the therapy to humans, a multistep

process. "We will be contacting the FDA to work out a road map to clinic," Shen said.

More information: Enhancing chemotherapy response with sustained EphA2 silencing using multistage vector delivery, *Clinical Cancer Research*, doi:10.1158/1078-0432.CCR-12-2764

Provided by The Methodist Hospital System