Gold nanoparticles could improve antisense cancer drugs

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In the fight against cancer, antisense drugs, which prevent genes from producing harmful proteins such as those that cause cancer, have the promise to be more effective than conventional drugs, but the pace of development of these new drugs has been slow.

Using gold nanoparticles combined with DNA, scientists at Northwestern University now have demonstrated a new method for developing antisense drugs that outperform conventional antisense agents. The findings will be published May 19 in the journal *Science*.

A major challenge has been delivering antisense drugs to cells inside the body while avoiding their break down along the way. The Northwestern team shows that by attaching multiple strands of antisense DNA to the surface of a gold nanoparticle (forming an "antisense nanoparticle") the DNA becomes more stable and can bind to the target messenger RNA (mRNA) more effectively than DNA that is not attached to a nanoparticle surface (as in commercial agents).

When compared to antisense DNA complexed with commercial agents such as Lipofectamine and Cytofectin, the antisense nanoparticles were more effective in gene knockdown (decreasing gene expression and protein production), were less susceptible to degradation resulting in longer lifetimes, exhibited lower toxicity and were more readily absorbed by cells, exhibiting a greater than 99 percent uptake.

"When mutations in the body's genetic material cause too many copies

of certain proteins, cancer and other diseases can result," said Chad A. Mirkin, director of Northwestern's Center for Cancer Nanotechnology Excellence, who led the study. "Whereas typical drugs target the proteins, it is possible through gene therapy to target the genetic material itself before it is ever made into copies of harmful proteins. One way to target the genetic material is to block the messenger RNA by using 'antisense DNA,' which prevents the message from ever becoming a protein."

Once inside cells, the DNA-modified nanoparticles act as messenger RNA "sponges" that bind to their targets and prevent them from being converted into proteins.

In their experiments the researchers targeted mRNA sequences that code for enhanced green fluorescent protein (EGFP) expressed in a mouse cell. The antisense sequence of the DNA attached to the nanoparticles was complementary to the mRNA for EGFP expression. When the nanoparticles were introduced to the cells the fluorescence dimmed -- a result of the nanoparticles binding to the mRNA and shutting down the protein's expression, or fluorescence.

"In the future, this exciting new class of antisense material could be used for the treatment of cancer and other diseases that have a genetic basis," said Mirkin, who is George B. Rathmann Professor of Chemistry, professor of medicine and professor of materials science and engineering.

In addition to Mirkin, other authors on the *Science* paper are Nathaniel L. Rosi (co-first author), David A. Giljohann (co-first author), C. Shad Thaxton, Abigail K. R. Lytton-Jean and Min Su Han, all from Northwestern University.

Source: Northwestern University