New and improved RNA interference

Researchers use RNA interference to silence multiple genes at once. The advance, which one expert calls a 'substantial breakthrough,' could lead to new treatments for liver diseases.

Anne Trafton, MIT News Office

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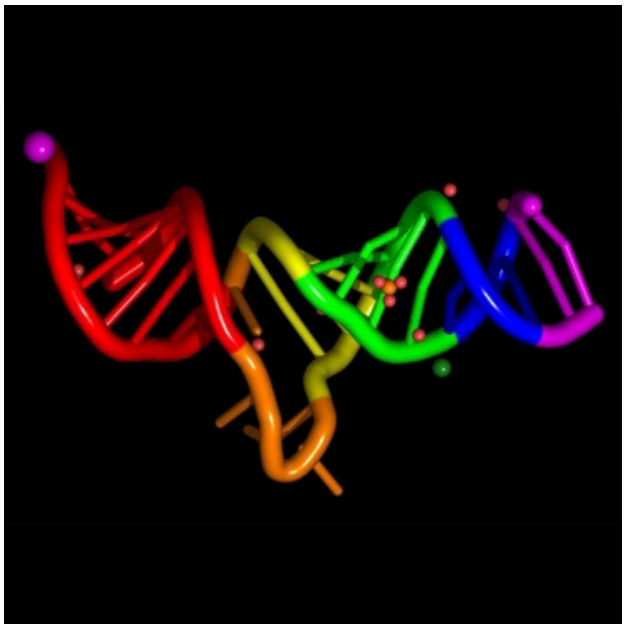

Ever since RNA interference was discovered, in 1998, scientists have been pursuing the tantalizing ability to shut off any gene in the body — in particular, malfunctioning genes that cause diseases such as cancer.

This week, researchers at MIT and Alnylam Pharmaceuticals report that they have successfully used RNA interference to turn off multiple genes in the livers of mice, an advance that could lead to new treatments for diseases of the liver and other organs.

The new delivery method, described in the *Proceedings of the National Academy of Sciences*, is orders of magnitude more effective than previous methods, says Daniel Anderson, senior author of the paper and a biomedical engineer at the David H. Koch Institute for Integrative Cancer Research at MIT. It's also the first method that can deliver as many as five genes — previous delivery vehicles could carry only one or two genes.

"This greatly improved efficacy allows us to dramatically decrease the dose levels, and also opens the door to formulations that can simultaneously inhibit multiple genes or pathways," says Anderson.

Gene silencing

RNA interference works by disrupting the flow of genetic information from a cell's nucleus to the protein-building machinery of the cell. The key to success is finding a safe and effective way to deliver the short strands of RNA that can bind with and destroy messenger RNA, which carries instructions from the nucleus.

Anderson and his colleagues believe the best way to do that is to wrap short interfering RNA (siRNA) in a layer of fat-like molecules called lipidoids, which can cross cells' fatty outer membrane. Anderson and others in Institute Professor Robert Langer's lab at MIT, along with Alnylam researchers, have developed methods to rapidly produce, assemble and screen a variety of different lipidoids, allowing them to pick out the most effective ones.

In a previous study, the researchers created more than 1,000 lipidoids. For their latest study, they picked out one of the most effective and used a novel chemical reaction to

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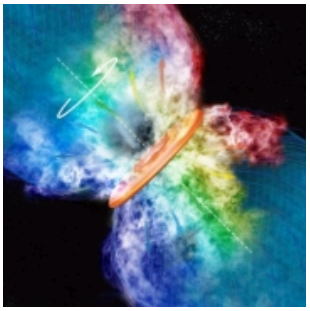

Artist's conception of the rotating disk of hot, ionized gas surrounding Orion Source I, blocking the star from our view. A cool wind of gas is driven from the upper and lower surfaces of the disk and is sculpted into an hourglass shape by tangled magnetic field lines.
Image: Bill Saxton, National Radio Astronomy Observatory/Associated Universities, Incorporated/National Science Foundation

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create a new library of 126 similar molecules. The team focused on one that appeared the most promising, dubbed C12-200.

Using C12-200, the researchers achieved effective gene silencing with a dose of less than 0.01 milligrams of siRNA per kilogram of solution, and 0.01 milligrams per kilogram in non-human primates. If the same dosing were translated to humans, a potential therapy would only require an injection of less than 1 milliliter — about a fifth of a teaspoon — to specifically inhibit a gene, compared with previous formulations that would have required hundreds of milliliters, says Anderson.

In studies with mice, the researchers were able to successfully deliver five snippets of RNA at once, and Anderson believes the lipidoids have the potential to deliver as many as 20. That could be a huge advantage in treating diseases such as cancer that result from multiple malfunctioning genes.

Four of the genes shut off in the mouse study are involved in metabolic pathways regulating cholesterol homeostasis; mutations in those genes have been linked to altered cholesterol levels. In a study of non-human primates, the researchers successfully turned off a gene for the protein TTR (transthyretin), which has been implicated in several diseases including senile systemic amyloidosis, familial amyloid polyneuropathy and familial amyloid cardiomyopathy, with very low doses of RNA.

The liver is a natural starting point for studies of RNA interference delivered by nanoparticles, according to Anderson, because such particles are often carried to the liver and spleen, which filter the blood. Because of that, the some of the earliest targets for potential treatments will likely be liver diseases such as cancer or hepatitis.

John Rossi, a molecular biologist at the Beckman Research Institute in Duarte, Calif., says the ability to achieve gene silencing with such low doses of siRNA represents a “substantial breakthrough,” for several reasons: It reduces the cost of producing siRNA; offers potentially improved safety for patients who may receive injections over a long period of time; and could lead to new treatments for liver disease that would eliminate the need for liver transplantation.

“It will be of interest to see what other tissues the lipidoids penetrate with siRNA cargo, since this approach could have broad-based applications in the RNAi therapy world,” adds Rossi, who is working on RNAi therapies for AIDS and cancer.

The MIT/Alnylam team is conducting further pre-clinical studies to determine optimal doses for the siRNA-lipidoid complex.