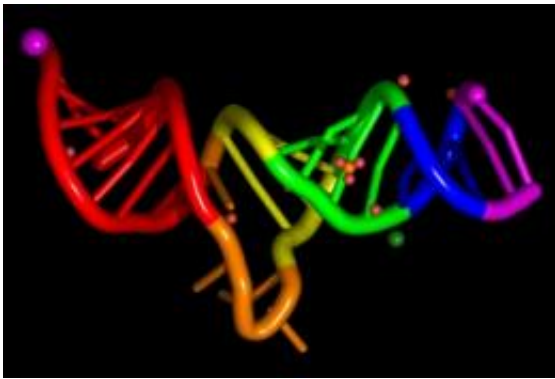


New RNA interference technique can silence up to five genes

December 28 2009, by Anne Trafton



Researchers at MIT and Alnylam Pharmaceuticals report this week 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.

Since the 1998 discovery of RNA interference — the naturally occurring phenomenon in which the flow of [genetic information](#) from a cell's [nucleus](#) to the protein-building machinery of the cell is disrupted — scientists have been pursuing the tantalizing ability to shut off any gene in the body. Specifically, they have been trying to silence malfunctioning genes that cause diseases such as cancer.

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.

"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.

The key to success with [RNA interference](#) 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](#). Using one such lipidoid, 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.

The team 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 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 to specifically inhibit a gene, compared with previous formulations that would have required hundreds of milliliters, says Anderson.

Other authors from MIT include Kevin T. Love, Kerry P. Mahon, Christopher G. Levins, Kathryn A. Whitehead and Institute Professor Robert Langer.

The MIT/Alnylam team hopes to start clinical trials within the next couple of years, after figuring out optimal doses and scaling up the manufacturing capability so they can produce large amounts of the siRNA-lipidoid complex.

More information: "Lipid-Like Materials for Low Dose, in vivo Gene Silencing," Kevin T. Love, Kerry P. Mahon et al. Proceedings of the National Academy of Sciences, week of Dec. 28, 2009.

Provided by Massachusetts Institute of Technology

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