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# Designer RNA fights high cholesterol, researchers find

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Small, specially designed bits of ribonucleic acid (RNA) can interfere with cholesterol metabolism, reducing harmful cholesterol by two-thirds in pre-clinical tests, according to a new study by researchers at UT Southwestern Medical Center in collaboration with Alnylam Pharmaceuticals and the Massachusetts Institute of Technology.

In a study that appears online today and in an upcoming issue of the *Proceedings of the National Academy of Sciences*, researchers found that a single dose of a small interfering RNA (siRNA), a chemical cousin of DNA, lowered cholesterol levels up to 60 percent in rodents, with the effects lasting for weeks.

This result indicated that the RNA interference, or RNAi, mechanism could provide a new tactic for treating high cholesterol. Similar treatments in four nonhuman primates, conducted off-site by a certified contract research organization, produced an average 56 percent drop in low-density lipoprotein cholesterol levels in the animals' blood.

The siRNA works by jamming the production of PCSK9 (proprotein convertase subtilisin/kexin type 9), a protein that normally raises the level of LDL cholesterol, the "bad" cholesterol that tends to create fatty deposits inside blood vessels.

Studies by other UT Southwestern researchers have found that people with mutations in the PCSK9 gene, which prevented them from making normal levels of the PCSK9 protein, had LDL cholesterol levels 28

percent lower than individuals without the mutation and were protected from developing coronary heart disease.

“It’s very clear that eliminating this protein has cardiovascular benefits,” said Dr. Jay Horton, professor of internal medicine and molecular genetics at UT Southwestern and the study’s co-senior author.

The RNAi method also performed as well as cholesterol-lowering drugs currently on the market or in clinical trials, Dr. Horton said. Those medicines can provide about 20 percent to 50 percent drops in LDL cholesterol, but patients usually have to take maximum doses over prolonged periods.

“RNA-based drugs might provide a course of treatment for people whose cholesterol levels are resistant to current drugs, or they might be combined with current drugs,” said Dr. Horton.

Working with scientists at MIT and at Alnylam, an RNAi therapeutics company in Cambridge, Mass., Dr. Horton and his colleagues designed siRNAs to block the process by which DNA creates the PCSK9 protein. Normally, to make a protein, DNA’s genetic code is translated to form a correspondingly coded RNA, which carries out instructions that tell the cell to make the protein.

But in the study, the lab-designed siRNA latched onto the cell’s much larger RNA, preventing it from completing the PCSK9 protein-creation process.

The scientists made versions of siRNA that blocked the forms of PCSK9 found in mice, rats, nonhuman primates and humans. Those siRNAs were then injected into normal rodents and non-human primates, as well as into mice that had been genetically engineered to produce human PCSK9.

The siRNAs caused the levels of PCSK9 to drop up to 70 percent in mice livers and 60 percent in rat livers, where the protein is primarily produced. The non-human primates also showed a significant drop in blood levels of PCSK9.

In conjunction with the drop in PCSK9, the levels of cholesterol in the blood dropped by about one-third in mice and nearly two-thirds in rats.

The nonhuman primates' LDL cholesterol dropped an average of 56 percent, with one animal showing a nearly 70 percent reduction.

Source: UT Southwestern Medical Center