Cholesterol Controlled for Good by Gene Therapy in Mice

By Angela Zimm Jun 10, 2014 9:01 PM PT

By altering how a liver gene works, scientists say they've developed a way to cut cholesterol permanently with a single injection, eliminating the need for daily pills to reduce the risk of heart attack.

In a test in mice, scientists at the **Harvard Stem Cell Institute** and the **University of Pennsylvania** disrupted the activity of a gene, called PCSK9, that regulates cholesterol, the fatty material that builds up in veins, hindering blood flow. The process permanently dropped levels of the lipid by 35 to 40 percent, said **Kiran Musunuru**, the lead researcher.

"That's the same amount of cholesterol you'll get with a cholesterol drug," said Musunuru, who is a cardiologist and assistant professor at Harvard. "The kicker is we were able to do that with a single injection, permanently changing the genome. Once that changes, it's there forever."

Pfizer Inc. (PFE)'s Lipitor and **AstraZeneca Plc (AZN)**'s Crestor, both of which target so-called bad cholesterol, are pills that are designed to be taken daily. The prospect of replacing them with the newly tested procedure may be 5 to 10 years away, Musunuru said in a telephone interview.

The PCSK9 gene is the same one now being targeted by Amgen Inc., **Sanofi (SAN)** and**Regeneron Pharmaceuticals Inc. (REGN)** with experimental compounds designed to suppress the protein the gene produces. Certain rare PCSK9 mutations are found to cause high cholesterol and heart attacks. Good mutations also exist, and people with them have a heart attack risk that ranges from 47 to 88 percent below average, the researchers said.

'Good Mutations'

“It’s not too much of a leap to think that if it works as well in mice, it will work as well in humans,” said Musunuru, who works in the Cambridge, Massachusetts school’s Department of Stem Cell and Regenerative Biology. With one shot, a patient “would be like those people born with the good mutations.”

The research was published yesterday in **Circulation Research**, a journal of the **American Heart Association**.

The approach used a two-part genome-engineering technique that first targets the DNA sequence where the gene sits, and then creates a break in the system. The therapy was carried to the liver using an injected adenovirus.

The genome-editing technique used in the experiment has only been around for about a year and a half, Musunuru said.

The next step is to see how effective the therapy is in human cells, by using mice whose liver cells are replaced with human-derived liver cells, he said. Assessing safety will be the primary concern.