

## A shot against heart attacks?

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Harvard Stem Cell Institute scientists, lead by Kiran Musunuru collaborating with researchers at the University of Pennsylvania have developed a "genome-editing" approach for permanently reducing cholesterol levels in mice through a single injection, a development that could reduce the risk of heart attacks in humans by 40 to 90 percent. Credit: B. D. Colen/Harvard University

Harvard Stem Cell Institute (HSCI) scientists collaborating with researchers at the University of Pennsylvania have developed a "genome-editing" approach for permanently reducing cholesterol levels in mice through a single injection, a development that could reduce the risk of

heart attacks in humans by 40 to 90 percent.

"For the first iteration of an experiment, this was pretty remarkable," said Kiran Musunuru of HSCI, an assistant professor in Harvard's Department of Stem Cell and Regenerative Biology (SCRB), and a cardiologist at Harvard-affiliated Brigham and Women's Hospital. Musunuru stressed, however, that it could take a decade of concerted effort to get this new approach for fighting heart disease from the laboratory to phase I clinical trials in humans.

The research was published online today by *Circulation Research*, a journal of the American Heart Association. Qiurong Ding, a postdoctoral fellow in Musunuru's laboratory, is first author on the paper.

The work by the Musunuru team and a Penn team led by Daniel J. Rader, an authority on cholesterol metabolism and a long-time collaborator of Musunuru, focused on altering the function of a liver gene called PCSK9.

In 2003, a group of researchers in France studying families with very high [cholesterol levels](#) and very early heart attacks discovered that PCSK9 was a cholesterol regulator, because they found that mutations in this gene seemed to be responsible for the [high cholesterol levels](#) and the heart attacks. These mutations are extremely rare and are limited to a few families.

But a research group in Texas discovered that about 3 percent of the population have mutations in PCSK9 that have the opposite effect. Those with the mutations have low-density lipoprotein (LDL, or bad) cholesterol levels about 15 to 28 percent lower than the average level. And the people with that "good" defect have heart attack risks that range from about 47 to 88 percent below average.

"Our reasoning was that nature has already done the experiment; you have people who have won the genetic lottery," said Musunuru. "They are protected from heart attack, and there are no known adverse consequences. So that led us to reason that if we could find a way to replicate this, we could significantly protect people from heart attack."

David T. Scadden, co-director of HSCI, co-chair of SCRB, and director of the Massachusetts General Hospital Center for Regenerative Medicine, said the work "is an outstanding example of how new approaches to disease can emerge when basic science and clinical care are creatively combined. It's a reminder of how important it is for all of us that research is supported if we are going to come up with disruptive new thinking to solve major health problems."

Musunuru and Rader's project to turn normal PCSK9 genes into those with the "good" defect came at an inflection point in genome editing, the refinement early last year of a technology called CRISPR/Cas9, first discovered in 2007. "The biological sciences as a field got really excited by this new technology, because it makes it far easier to edit the genome in every species you can think of, from fruit flies to fish, to mice, to monkeys, to human cells," said Musunuru, whose group was among the first to use it in stem cells.

"Cas9 is a protein that will create a break in DNA, and the CRISPR is an RNA component that will bind to a matching sequence and directs the Cas9 to that sequence in the DNA in which you are interested," he said. "This creates a break where you want it. The cell can then repair itself, though often with errors, which is useful if you want to disrupt a gene to create a 'knockout' of the gene," which is precisely what Musunuru's team did with PCSK9.

"The PCSK9 gene is expressed primarily in the liver," explained Musunuru, "and produces a protein that is active in the bloodstream and

prevents the removal of cholesterol from the blood. Several drug companies have been developing antibodies" to it, he said, but "the problem with antibody-based drugs is they don't last forever; you'd need an injection every few weeks. The main option for reducing cholesterol is statin drugs, such as Lipitor, but many people taking statin drugs every day still have heart attacks. So there is still a great need for other approaches," said the scientist.

"What we were thinking was that, with this genome-editing technology, we can do something we couldn't do before: make permanent changes in the genome at the level of the DNA. We can actually go to the source. So the question was whether we can use genome editing to make normal people like people born with the 'good' mutations." The answer, in mice, was yes.

"The first question was whether we could get CRISPR/Cas9 into the liver, and once we got it into the liver, would it function properly?" Musunuru asked. "And it did. It could have had no effect, but it turned out to have a dramatic effect. Within three to four days of delivering the system into the liver, the majority of the PCSK9 gene copies in all of the liver cells were disrupted, knocked out. And what we hoped to see was much less of the protein product in the bloodstream, which is what we saw.

"The other consequence that we saw was a 35 to 40 percent reduction in cholesterol levels in these mice," which would translate in humans to a heart attack risk-reduction of as high as 90 percent.

"Heart attack is the leading natural killer worldwide, with one in two men and one in three women past the age of 40 having heart attacks in their lifetimes," Musunuru continued. "If you had a therapy that targeted the liver, changed the genome, if you could do that, and if it were totally safe, then at least in theory you could think of this therapy as something

like a vaccination. It could be a onetime treatment, a permanent alteration. If you used this in a population, you could reduce the occurrence of heart attack by 30 percent, 50 percent, 90 percent.

"As a cardiologist, what I find most tragic is when a 55-year-old person, with a family, in the prime of life, still working, out of the blue has a [heart attack](#) and drops dead. The public health implications are not trivial. Heart attack is a killer of the elderly, but there are many 50-, 60-, 70-year-old men and women dying of heart attacks."

Provided by Harvard University

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