Scientists create mimic of 'good' cholesterol to fight heart disease and stroke

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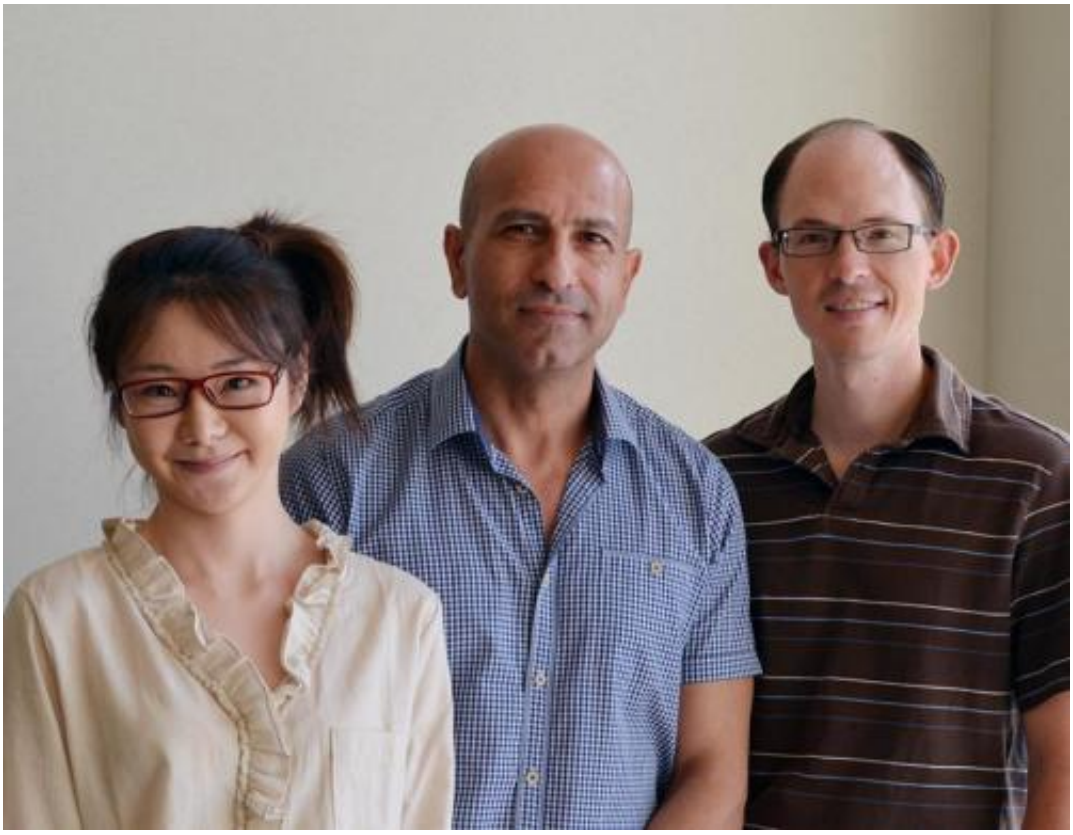

Authors of the new study include Scripps Research Institute Professor Reza Ghadiri (center), Assistant Professor of Chemistry Luke Leman (right) and Research Associate Yannan Zhao

Scientists at The Scripps Research Institute (TSRI) have created a synthetic molecule that mimics "good" cholesterol and have shown it can

reduce plaque buildup in the arteries of animal models. The molecule, taken orally, improved cholesterol in just two weeks.

This research, published in the October issue of *Journal of Lipid Research*, points scientists toward a new method for treating atherosclerosis, a condition where plaque buildup in the arteries can cause heart attacks and strokes.

"Atherosclerosis is the number one killer in the developed world," said TSRI Professor M. Reza Ghadiri, senior author of the new study with TSRI Assistant Professor of Chemistry Luke Leman. "This research clears a big step toward clinical implementation of new therapies."

Good vs. Bad Cholesterol

To combat atherosclerosis, researchers are looking for new ways to target and remove low-density lipoprotein (LDL) cholesterol (commonly known as "bad" cholesterol) from the body. Though the body needs some LDL to stay healthy, high levels lead to dangerous plaque buildups. In contrast, high-density lipoprotein (HDL) cholesterol ("good" cholesterol) is known for its protective effects.

"HDL is like a taxi in the bloodstream; it takes the LDL cholesterol out of the blood and delivers it to the liver," said Yannan Zhao, a postdoctoral researcher in Ghadiri's lab and first author of the new study. From the liver, the LDL is packaged for elimination from the body.

Using a method reported by the researchers last year in the *Journal of the American Chemical Society*, the team created a "nanopeptide" to have three arm-like structures that can wrap around cholesterol and fats in the blood.

Once the synthetic peptide wraps around LDL cholesterol, it removes it

by mimicking the behavior of apoA-1, a protein of HDL, and carrying it to the liver for elimination.

A Surprising Finding

In collaboration with Linda Curtiss, formerly a faculty member at TSRI, and Bruce Maryanoff, formerly at Johnson & Johnson and currently a visiting scholar at TSRI, the researchers tested this synthetic peptide in a mouse model prone to atherosclerosis.

The team originally used the synthetic peptide in an experiment the researchers thought was a gamble. They gave it to mice in their drinking water, but assumed their digestive acids might break down the peptide before it got a chance to interact with its target and modify LDL cholesterol. To their surprise, it worked.

After 10 weeks of treatment, the mice had a 40 percent reduction in potentially harmful cholesterol in their blood and a 50 percent reduction in the size of plaque lesions in their hearts.

"We were definitely surprised at the results in the oral feeding studies," said Leman. "We've repeated it many times."

Many cholesterol treatments currently in development rely on an injection, not a pill. With the option of an orally effective peptide, Ghadiri believes researchers are closer to developing an accessible new therapy for atherosclerosis.

The researchers also reported no signs of increased inflammation in the blood or toxicity after 10 weeks of the peptide treatment.

Future Studies Point to Gut

Ghadiri and his team are now investigating exactly how the synthetic peptide works in the intestines and the possibility that it interacts with beneficial microbes. The researchers believe that finding new targets in the gastrointestinal tract could lead to new therapies for many more diseases.

"That's one of the fun things in science—now we get to follow up on these different avenues," said Leman.

More information: "In vivo efficacy of HDL-like nanolipid particles containing multivalent peptide mimetics of apolipoprotein A-I" *J. Lipid Res.* 2014 55:(10) 2053-2063. DOI: 10.1194/jlr.M049262

"Mimetic peptides of human apoA-I helix 10 get together to lower lipids and ameliorate atherosclerosis: is the action in the gut?" *J. Lipid Res.* 2014 55:(10) 1983-1985. DOI: 10.1194/jlr.E053538

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