

## THE J. DAVID GLADSTONE INSTITUTES

1650 Owens Street, San Francisco, CA 94158 Telephone: 415.734.2000 [www.gladstone.ucsf.edu](http://www.gladstone.ucsf.edu)  
in affiliation with the University of California, San Francisco



## GLADSTONE INSTITUTE OF CARDIOVASCULAR DISEASE NEWS

### CONTACT:

Valerie Tucker, 415-734-2019

E-mail: [vtucker@gladstone.ucsf](mailto:vtucker@gladstone.ucsf)

Web: [www.gladstone.ucsf.edu](http://www.gladstone.ucsf.edu)

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### **GLADSTONE SCIENTISTS IDENTIFY GENETIC FACTORS THAT HOLD PROMISE FOR TREATMENT OF VASCULAR DISEASES**

SAN FRANCISCO, CA – July 5, 2009 --Researchers at the Gladstone Institute of Cardiovascular Disease (GICD) have discovered a key switch that makes stem cells turn into the type of muscle cells that reside in the wall of blood vessels. The same switch might be used in the future to limit growth of vascular muscle cells that cause narrowing of arteries leading to heart attacks and strokes, limit formation of blood vessels that feed cancers, or make new blood vessels for organs that are not getting enough blood flow.

In a study published in the current issue of the journal *Nature*, the researchers found that a tiny RNA molecule, called microRNA-145 (miR-145), not only had all the information necessary to turn a stem cell into a vascular smooth muscle cell (VSMC), but could also affect VSMCs in the adult artery. VSMCs have the unique property that they can start dividing when an artery is injured or during atherosclerosis, ultimately causing narrowing of the vessel leading to occlusion. miR-145 and its sister microRNA, miR-143, work together to stop the pathologic division of VSMCs. In the setting of vessel disease, their activity was turned down, allowing the VSMCs to divide and clog up the artery.

microRNAs are small RNA molecules that do not make protein, but instead affect that amount of protein synthesized by the cell from their target mRNAs—the blueprints for translating the genetic code into proteins. miR-145 and miR-143 together controlled the synthesis of a network of “master regulators” that control VSMCs, and thereby were able to function as a central “switch” for the behavior of these important cells.

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“The ability of miR-145 to efficiently direct the cell fate of vascular smooth muscle cells from stem cells represents the power of these tiny microRNAs to exert major effects on cells,” said Deepak Srivastava, MD, GICD director and senior author of the study. “We hope that we can use this knowledge to control when the body makes or does not make new blood vessels,” he added.

Previously, GICD researchers had shown that miR-143 is highly enriched when embryonic stem cells turned into cardiac stem cells. Here they found that miR-143 and miR-145 were both present as the heart was forming in mice, but became localized to the smooth muscle of blood vessels and of the gut after birth.

Further analysis revealed that miR-143 and miR-145 are directly controlled by a protein called myocardin, which itself is sufficient to “reprogram” an adult non-muscle cell into a VSMC. Furthermore, the activation of these microRNAs by myocardin was a necessary event for myocardin to induce the VSMC fate. In one type of stem cell, miR-145 by itself was enough to completely push the stem cell into a functioning VSMC.

These findings suggested that miR-143 and miR-145 are involved in the switch between the differentiation and proliferation of VSMCs—and thus contribute to vessel narrowing in heart disease. In a mouse model of this switch generated by collaborator Joseph Miano, PhD, a professor at the Cardiovascular Research Institute of the University of Rochester, expression of miR-143 and miR-145 was markedly reduced in injured arteries containing proliferating, less differentiated smooth muscle cells. Interestingly, miR-145 mRNA was also reduced to almost undetectable levels in atherosclerotic blood vessels with thickened walls.

“miR-145 was necessary and sufficient for differentiation of VSMCs, so it is possible that restoring its activity could prevent the vessel narrowing in atherosclerosis,” said Kimberly Cordes, PhD, a postdoctoral fellow in the Srivastava lab and lead author of the study.

Since the effects of miRNAs depend on their mRNA targets, the researchers looked for mRNA targets of miR-143 and miR-145. They found that miR-143 and miR-145 cooperate in targeting a network of transcription factors, including Klf4, myocardin, and Elk-1, to promote the differentiation and repress proliferation of smooth muscle cells. “The multiple targets we identified for miR-143 and miR-145 reveal an elegant mechanism by which these miRNAs promote differentiation and simultaneously repress proliferation of VSMCs” said Dr. Srivastava.

The targets miR-145 and miR-143 regulate are not only major regulators of VSMCs, but also control whether cells divide excessively in conditions such as cancer. According to Dr. Cordes, “the downregulation of miR-145 in numerous cancers and our findings in this study raise the possibility that miR-145 could function as a pro-differentiation factor in cancers also and could be a new therapeutic target.”

“Our findings in this study offer insights into regulatory mechanisms that govern the differentiation and proliferation of smooth muscle,” said Dr. Srivastava. “They have fundamental implications for the treatment of vessel diseases like atherosclerosis and also may be important for cancer.”

The research was supported the National Institutes of Health, the California Institute for Regenerative Medicine (CIRM) and the American Heart Association. Other authors on the study include Neil T. Sheehy, Mark White, Emily Berry, Sarah U. Morton, Alecia N. Muth, and Kathryn N. Ivey of Gladstone and UCSF and Ting-Hein Lee and Joseph M. Miano of the University of Rochester.

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Deepak Srivastava’s primary affiliation is with the Gladstone Institute of Cardiovascular Disease, where he is director and where his laboratory is located and all of his research is conducted. He is also a professor of medicine in the Departments of Pediatrics and Biochemistry and Biophysics at the University of California, San Francisco.

### **About the Gladstone Institutes**

The J. David Gladstone Institutes, an independent, nonprofit biomedical research organization, affiliated with the University of California, San Francisco, is dedicated to the health and welfare

of humankind through research into the causes and prevention of some of the world's most devastating diseases. Gladstone is comprised of the Gladstone Institute of Cardiovascular Disease, the Gladstone Institute of Virology and Immunology and the Gladstone Institute of Neurological Disease. More information can be found at [www.gladstone.ucsf.edu](http://www.gladstone.ucsf.edu).

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