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GLADSTONE INSTITUTE OF CARDIOVASCULAR DISEASE NEWS

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GLADSTONE RESEARCHERS HONE IN ON DIFFERENTIATION OF HEART STEM CELLS

A team of scientists from the Gladstone Institute of Cardiovascular Disease (GICD) has identified a key factor in heart development that could help advance gene therapy for treating cardiac disorders.

Published in the current online edition of the *Proceedings of the National Academy of Sciences*, the study evaluates the role of short RNAs, also known as miRNAs, in the early stages of the developing heart. The study also will be reported in the December 27 issue of PNAS.

The findings could help cardiac stem cell researchers one day develop strategies for gene and cell-mediated cardiac therapies, according to Deepak Srivastava, MD, senior author and GICD director.

RNAs are nucleic acids found in all living cells that help transfer information from DNA to the protein-forming system of the cell. They also express--that is, instruct to turn on or off--genes within that transferred information. MiRNAs are short RNAs that repress gene expression to control a variety of developmental processes.

"Of all the medical disciplines that could potentially benefit from stem cell research, cardiology is among the most promising, but a better understanding of early heart development is crucial in order to move forward to stem cell-mediated therapies," says Srivastava, who holds appointments as professor in the Department of Pediatrics and the Wilma and Adeline Pirag Distinguished Professor in Pediatric Developmental Cardiology at UCSF.

In the study, which used *Drosophila* fly embryos as model systems, the research team demonstrated that a form of miRNA known as miR-1 helps in determination of heart progenitor cells (stem cells) in early embryonic stages. They also showed that miR-1 helps in maintenance of heart precursors in later embryonic stages.

In addition, researchers demonstrated that miR-1 can repress the ligand Delta, which otherwise binds to its receptor, Notch. The binding of Delta and Notch mediates development of many kinds of tissues and is involved in differentiation of cardiac stem cells into muscle cells.

"Given the importance of understanding cardiac progenitor determination and differentiation in current cardiac regenerative medicine, our study will contribute to the understanding of how heart progenitors differentiate to become mature heart cells in human heart development," explains Srivastava. "Finding the mechanism for how miR-1 regulates heart cell differentiation is very exciting. These insights into the fundamental questions of development may help us ultimately to harness the potential of stem cells for the treatment of heart disease and other afflictions."

"miRNAs bind to messenger RNAs and either degrade them or hinder their ability to make a protein," adds lead author Chulan Kwon, PhD, a GICD postdoctoral fellow. "miR-1 interferes with expression of a crucial gene that controls whether or not certain progenitor stem cells become heart

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cells. Thus it could be a target for future gene-mediated therapies to prevent early heart development problems.”

Other co-authors of the paper are Zhe Han and Eric N. Olson of the Department of Molecular Biology, University of Texas Southwestern Medical Center. This study was funded through grants from the National Heart, Lung and Blood Institutes/NIH, the March of Dimes Birth Defects Foundation, the American Heart Association, and the Donald W. Reynolds Clinical Cardiovascular Research Center.

GICD is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution. It is affiliated with UCSF, a leading university that consistently defines health care worldwide by conducting advanced biomedical research, educating graduate students in the life sciences, and providing complex patient care. For further information, visit www.gladstone.ucsf.edu and www.ucsf.edu.

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