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GLADSTONE INSTITUTE OF CARDIOVASCULAR DISEASE
NEWS

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GLADSTONE SCIENTISTS IDENTIFY SINGLE microRNA THAT CONTROLS HOW HEART CHAMBERS FORM

SAN FRANCISCO, CA – October 27, 2008 – Scientists at the Gladstone Institute of Cardiovascular Disease (GICD) and the University of California San Francisco (UCSF) have identified a genetic factor critical to the formation of chambers in the developing heart. The discovery of the role of a microRNA called miR-138, could offer strategies for the treatment of congenital heart defects.

The heart is one of the first and most important organs to develop. In fact, embryos cannot survive long without a functioning heart. In vertebrates (animals with backbones), special cells form a heart tube; that tube loops back on itself to form the atrium and ventricle and the canal and valve that separates them. This requires a complicated sequence of genes turning on and off. MicroRNAs are very small RNAs of 20 to 25 nucleotides that regulate numerous gene functions. Approximately 650 human miRNAs are known, but only a few have yet been studied to determine what they actually do in a cell.

Researchers, led by Sarah Morton, an MD/PhD student at UCSF and GICD Director Deepak Srivastava MD, examined zebrafish, which are an ideal model system for understanding genetic functions. Zebrafish are small, reproduce fast, and are essentially transparent so that that events of heart formation can be studied

while they are still alive. Yet many of their systems are quite similar to those of humans. For example, miR-138 is exactly the same in zebrafish and humans.

"What's interesting is that a single microRNA is responsible for setting up the distinct patterning of a developing heart into separate chambers," said Dr. Srivastava, senior author of the study. "Since many congenital heart defects involve abnormalities in the formation of the chambers, this is important information in finding ways of treating or avoiding those defects."

The GICD scientists reported in today's issue of the *Proceedings of the National Academy of Science USA*, that miR-138 is present in the zebrafish heart at specific times and in specific places in the developing heart. Furthermore, they showed that it is required to insure that the cardiac chambers develop properly. When the scientists used genetic engineering techniques to eliminate miR-138, cardiac function was disrupted, and the ventricles did not develop correctly, with the muscle precursor cells failing to mature properly.

"The miR-138 function was required during a discrete developmental window that occurred 24-34 hours after fertilization," said Sarah Morton. The team also showed that the miRNA controlled development by regulating numerous factors that function jointly to define the chambers, including a key enzyme that makes retinoic acid.

Dr. Paul Scherz co-led this study, which involved close interactions with Dr.Didier Stainier, a Professor at UCSF, Dr. Kimberly Cordes and Dr. Kathryn Ivey. It was supported by grants from the National Institutes of Health and the California Institute of Regenerative Medicine.

About the Gladstone Institutes

The J. David Gladstone Institutes, affiliated with the University of California, San Francisco (UCSF), 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*.

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