

# Scientists discover new method for regenerating heart muscle by direct reprogramming

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Scientists at the Gladstone Institute of Cardiovascular Disease (GICD) have found a new way to make beating heart cells from the body's own cells that could help regenerate damaged hearts. Over 5 million Americans suffer from heart failure because the heart has virtually no ability to repair itself after a heart attack. Only 2,000 hearts become available for heart transplant annually in the United States, leaving limited therapeutic options for the remaining millions.

In research published in the current issue of *Cell*, scientists in the laboratory of GICD director Deepak Srivastava, MD, directly reprogrammed structural cells called fibroblasts in the heart to become beating heart cells called cardiomyocytes. In doing so, they also found the first evidence that unrelated adult cells can be reprogrammed from one cell type to another without having to go all the way back to a stem cell state.

The researchers, led by Masaki Ieda, MD, PhD, started off with 14 [genetic factors](#) important for formation of the heart and found that together they could reprogram fibroblasts into cardiomyocyte-like cells. Remarkably, a combination of just three of the factors (Gata4, Mef2c, and Tbx5) was enough to efficiently convert fibroblasts into cells that could beat like cardiomyocytes and turned on most of the same [genes](#) expressed in cardiomyocytes. When transplanted into mouse hearts 1 day after the three factors were introduced, fibroblasts turned into

cardiomyocyte-like cells within the beating heart.

"Scientists have tried for 20 years to convert nonmuscle cells into [heart muscle](#), but it turns out we just needed the right combination of genes at the right dose," said Dr. Ieda.

"The ability to reprogram fibroblasts into cardiomyocytes has many therapeutic implications," explained Dr. Srivastava, senior author on the paper. "Half of the cells in the heart are fibroblasts, so the ability to call upon this reservoir of cells already in the organ to become beating [heart cells](#) has tremendous promise for cardiac regeneration. Introducing the defined factors, or factors that mimic their effect, directly into the heart to create new heart muscle would avoid the need to inject [stem cells](#) into the heart and all the obstacles that go along with such cell-based therapies." The study results imply that cells in multiple organs within an individual might be directed into necessary cell types to repair defects within the body.

This next generation of direct reprogramming builds on the reprogramming method discovered by Gladstone investigator Shinya Yamanaka, MD, PhD, who found that, by using four genetic factors, adult cells can be reprogrammed to pluripotent cells known as induced pluripotent stem (iPS) cells. Like embryonic stem cells, iPS cells can turn into any of the cell types of the human body.

However, direct cellular reprogramming that does not involve a stem cell state solves some of the safety concerns surrounding the use of stem cells. Going directly from one adult cell type to another would eliminate the risk that some stem cells might develop inappropriately to form tumors.

While direct reprogramming may offer some advantages over Yamanaka's original method, additional work will be necessary to refine

the method and bring it closer to a practical therapeutic strategy.

"Direct reprogramming has not yet been done in human cells," Dr. Srivastava explained. "And, the hope is still to find small molecules, rather than genetic factors, that can be used to direct the cell-fate switch."

**More information:** Srivastava et al.: "Direct Reprogramming of Fibroblasts into Functional Cardiomyocytes by Defined Factors." Publishing in *Cell* 142, 375-386, August 6, 2010.  
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