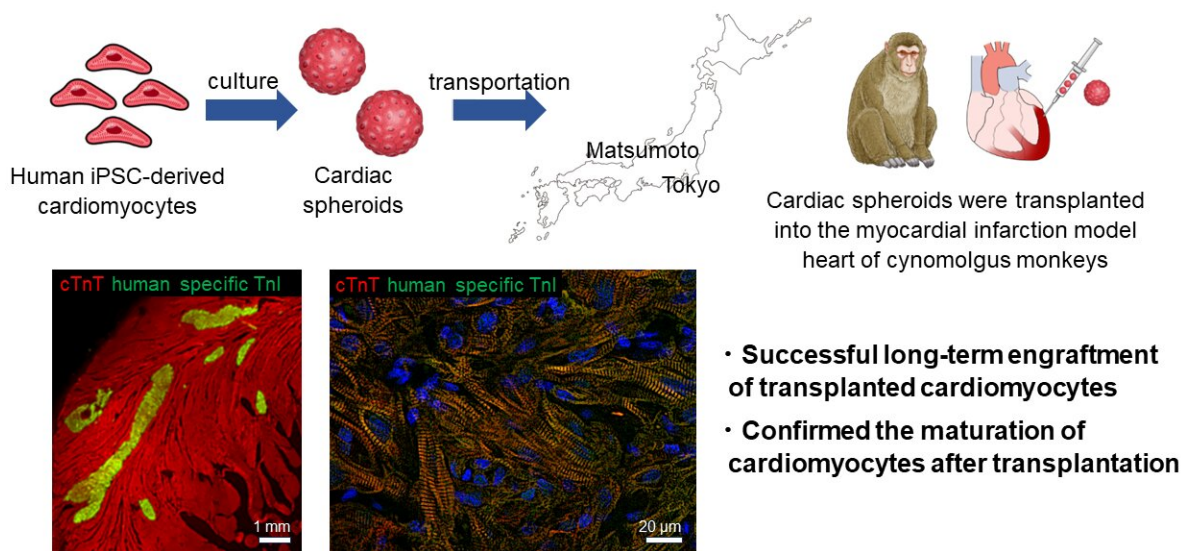


Using stem cell-derived heart muscle cells to advance heart regenerative therapy

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Study shows that cardiac spheroids, derived from human induced pluripotent stem cells, can be easily transported and injected into damaged areas of the heart to promote its regeneration and recovery of function. Credit: Hideki Kobayashi, Shinshu University

Regenerative heart therapies involve transplanting cardiac muscle cells into damaged areas of the heart to recover lost function. However, the risk of arrhythmias following this procedure is reportedly high.

In a recent study, researchers from Japan tested a novel approach that involves injecting "cardiac spheroids," cultured from [human stem cells](#), directly into damaged ventricles. The highly positive outcomes observed in primate models highlight the potential of this strategy.

Cardiovascular diseases are still among the top causes of death worldwide, and especially prevalent in developed countries. Myocardial infarctions, commonly known as "heart attacks," are on the rise, resulting in a significant number of deaths each year.

Heart attacks typically kill millions of [cardiac muscle cells](#), leaving the heart in a weakened state. Since mammals cannot regenerate cardiac muscle cells on their own, heart transplants are currently the only clinically viable option for patients suffering (or likely to suffer) [heart failure](#). Given that full [heart transplants](#) are expensive and donors difficult to come by, it is no surprise that alternative therapies are highly sought after by the medical community.

One promising strategy that has been steadily gaining traction is using human induced [pluripotent stem cells](#) (HiPSCs) for regenerative heart therapy. Simply put, HiPSCs are cells derived from mature cells that can be effectively "reprogrammed" into a completely different cell type, such as cardiac muscle cells (cardiomyocytes).

By transplanting or injecting cardiomyocytes derived from HiPSCs into damaged areas of the heart, it is possible to recover some lost functionality. Unfortunately, studies have reported that this approach can increase the risk of arrhythmias, posing a major hurdle to [clinical trials](#).

In their recent study, the Japanese research team from Shinshu University and Keio University School of Medicine, tested a new strategy for regenerative heart therapy that involves injecting "cardiac spheroids" derived from HiPSCs into monkeys with myocardial

infarction. This study, published on April 26, 2024, in the journal [Circulation](#), was led by Professor Yuji Shiba from the Department of Regenerative Science and Medicine, Shinshu University.

The team included Hideki Kobayashi, the first author, and Koichiro Kuwahara from the Department of Cardiovascular Medicine, Shinshu University School of Medicine, as well as Shugo Tohyama, and Keiichi Fukuda from the Department of Cardiology, Keio University School of Medicine, among others.

In their novel approach, the researchers cultivated HiPSCs in a medium that led to their differentiation into cardiomyocytes. After carefully extracting and purifying cardiac spheroids (three-dimensional clusters of cardiac cells) from the cultures, they injected approximately 6×10^7 cells into the damaged hearts of crab-eating macaques (*Macaca fascicularis*).

They monitored the condition of the animals for twelve weeks, taking regular measurements of cardiac function. Following this, they analyzed the monkeys' hearts at the tissue level to assess whether cardiac spheroids could regenerate the damaged heart muscles.

First, the team verified the correct reprogramming of HiPSCs into cardiomyocytes. They observed, via cellular-level electrical measurements, that the cultured cells exhibited potential patterns typical of ventricular cells. The cells also responded as expected to various known drugs.

Most importantly, they found that the cells abundantly expressed adhesive proteins such as connexin 43 and N-cadherin, which would promote their vascular integration into an existing heart.

Afterwards, the cells were transported from the [production facility](#) at

Keio University to Shinshu University, located 230 km away. The cardiac spheroids, which were preserved at 4°C in standard containers, withstood the four-hour journey without problem. This means that no extreme cryogenic measures would be needed when transporting the cells to clinics, which would make the proposed approach less expensive and easier to adopt.

Finally, the monkeys received injections of either cardiac spheroids or a placebo directly into the damaged heart ventricle. During the observation period, the researchers noted that arrhythmias were very uncommon, with only two individuals experiencing transient tachycardia (fast pulse) in the first two weeks among the treatment group.

Through echocardiography and computed tomography exams, the team confirmed that the hearts of monkeys that received treatment had better left ventricular ejection after four weeks compared to the control group, indicating a superior blood pumping capability.

Histological analysis ultimately revealed that the cardiac grafts were mature and properly connected to pre-existing existing tissue, cementing the results of previous observations. "HiPSC-derived cardiac spheroids could potentially serve as an optimal form of cardiomyocyte products for heart regeneration, given their straightforward generation process and effectiveness," says Assistant Professor Kobayashi.

"We believe that the results of this research will help solve the major issue of ventricular arrhythmia that occurs after cell transplantation and will greatly accelerate the realization of cardiac regenerative therapy."

Although tested in monkeys, it is worth noting that the cardiac [spheroid](#) production protocol used in this study was designed for clinical application in humans.

"The favorable results obtained thus far are sufficient to provide a green light for our clinical trial, called the LAPiS trial. We are already employing the same cardiac spheroids on patients with ischemic cardiomyopathy," says Asst. Prof. Kobayashi.

More information: Hideki Kobayashi et al, Regeneration of Nonhuman Primate Hearts With Human Induced Pluripotent Stem Cell–Derived Cardiac Spheroids, *Circulation* (2024). [DOI: 10.1161/CIRCULATIONAHA.123.064876](https://doi.org/10.1161/CIRCULATIONAHA.123.064876)

Provided by Shinshu University

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