

Lowering the cost of heart cell therapies

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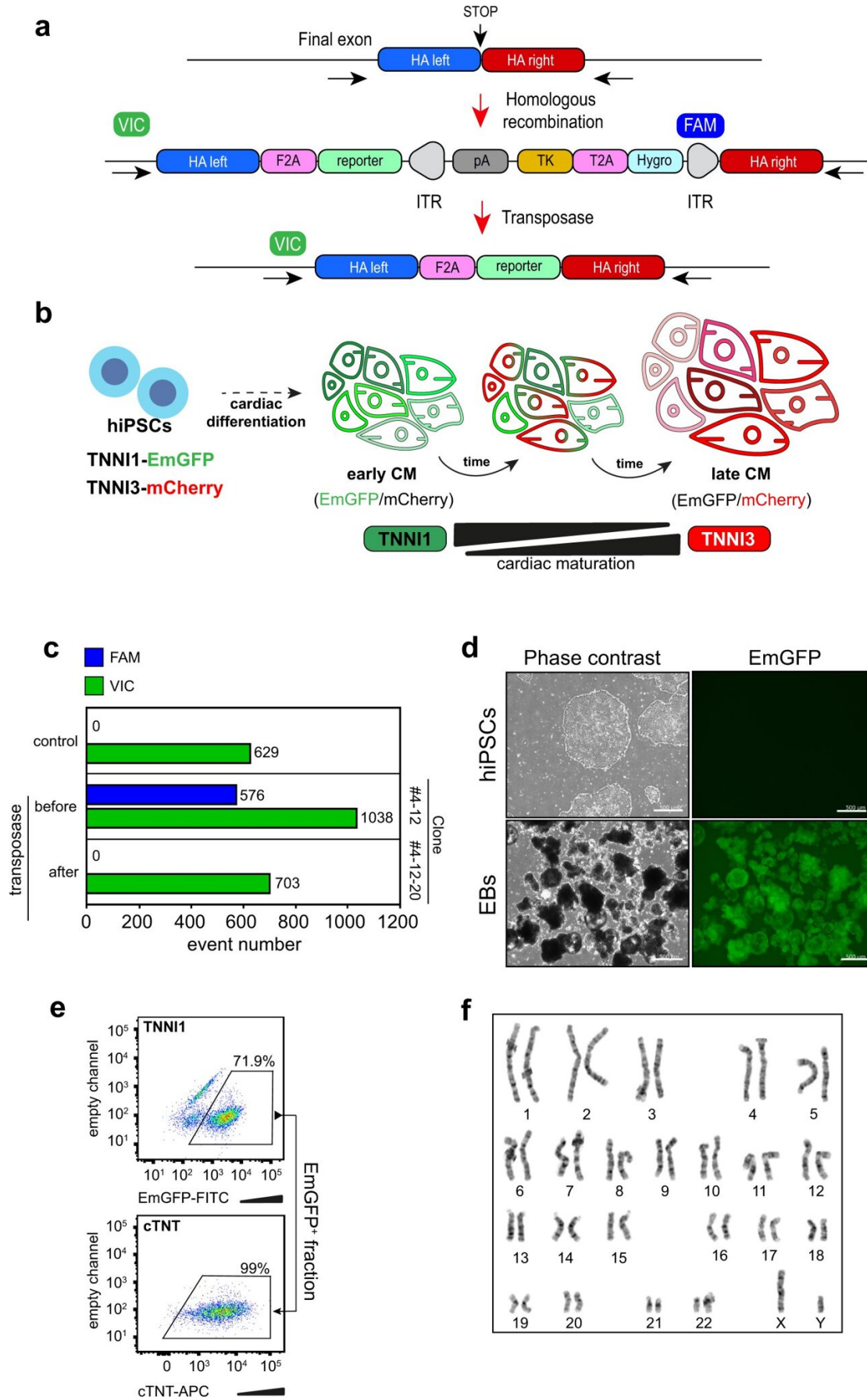


Fig. 1: Generation of the hiPSC TNNI1EmGFP and TNNI3mCherry dual reporter. From: ERR γ enhances cardiac maturation with T-tubule formation in human iPSC-derived cardiomyocytes

Suffering from the number one cause of death, patients with heart disease are in desperate need of new therapies. However, these new therapies rely on research using heart cells, which are not easy to access. In response, many scientists are investigating ways to generate heart cells from stem cells like iPSC cells. A new study led by researchers of Takeda-CiRA Joint Program for iPSC Cell Applications (T-CiRA) shows how mixing a single agonist for ERR γ , or estrogen-related receptor gamma, with iPSC cells can produce cardiomyocytes of good quality. The findings are expected to lower the cost and labor of future heart cell research.

One of the most exciting clinical applications of stem cell research is [heart](#) therapy. Among all cells in the body, [heart cells](#) are the least capable of regenerating, which is why [heart disease](#) or heart damage is usually permanent. Heart transplants and cell therapies are the only viable treatment options, but neither whole hearts nor heart cells are readily available. Stem cells, especially iPSC cells, offer a solution.

However, the heart cells made from [stem cells](#) are not equivalent to those in the heart.

"We can differentiate iPSC cells into cardiomyocytes, but the cells are structurally and functionally immature, resembling heart cells in the fetus but not the adult," explained Dr. Kenji Miki, one of the lead authors of the study.

This difference has important implications in the search for new drugs and new therapies.

The maturity of heart cells depends on a number of morphological and molecular events. One that scientists regularly rely on involves the protein troponin I.

"During the developmental transition from fetal to postnatal stages, troponin I undergoes an isoform switch from TNNI1 to TNNI3. This change is accompanied by electrophysiological changes in the heart," said CiRA Associate Professor Yoshinori Yoshida, who led the study. "We look for this switch when differentiating iPS cells into cardiomyocytes."

The study shows that a single $ERR\gamma$ agonist promotes the isoform switch in cardiomyocytes made from iPS cells and the formation of T-tubules, a key structural indicator of maturation. $ERR\gamma$ is a hormone receptor that switches the metabolism of mouse cells to [oxidative phosphorylation](#), but its role in humans is not as clear and requires more study.

Along with the structural and functional changes that are marked by the transition to TNNI3, cardiomyocytes undergo a change in metabolism during development. ATP is generated by one of two ways in all cells, glycolysis and oxidative phosphorylation. In the uterus, where [oxygen levels](#) are low, fetal cardiomyocytes depend on anaerobic glycolysis. However, the amount of ATP produced by aerobic oxidative phosphorylation is much higher, which is what adult cardiomyocytes primarily use.

The $ERR\gamma$ agonist supported this metabolic switch.

Maturation could be further promoted by adding to the agonist a chemical inhibitor of the cell cycle. The cell cycle is a natural process

that allows cells to replicate. Heart [cells](#), however, show cell cycle arrest, which is why they do not regenerate following injury.

"Our findings suggest that $ERR\gamma$ has an important role in cardiomyocyte maturation. This discovery will help in establishing protocols that produce high quality cardiomyocytes for disease modeling, drug discovery and cell therapies," said Yoshida.

More information: Kenji Miki et al, $ERR\gamma$ enhances cardiac maturation with T-tubule formation in human iPSC-derived cardiomyocytes, *Nature Communications* (2021). [DOI: 10.1038/s41467-021-23816-3](#)

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