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What composes the human heart? Researchers crunch the numbers

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A foundational study published in the journal *PNAS* (*Proceedings of the National Academy of Sciences*) this week by researchers at the University of Toronto's Institute of Biomaterials & Biomedical Engineering (IBBME) and the McEwen Centre for Regenerative Medicine have identified the optimal structure and cell ratio associated with heart function – and the discovery has already led the team to another research first: the engineering of the first-ever living, three-dimensional human arrhythmic tissue.

The study marks the first time that researchers have tried to define and formulate the precise type and ratio of cell types that produce highly functional cardiac tissue.

"Hearts are not just composed of one type of cell," explained fourth-year IBBME PhD Student Nimalan Thavandiran and first author of the *PNAS* study. But until now, scientists have not known how to mix different cell types in engineered heart tissue in such a way that the tissue achieves the composition and maturity level of the native human heart.

Thavandiran solved this mystery by methodically separating out different cell types derived from human pluripotent stem cells and precisely mixing them back together. Using scoring metrics associated with functional hearts - contraction, electrical activity and cell alignment – Thavandiran was able to develop a formula for engineering highly functional heart tissue.

The composition of the cells is vital," stated Thavandiran. "We discovered that a mixture of 25% cardiac fibroblasts (skin-like cells) to 75% cardiomyoctes (heart cells) worked best." The carefully composed cell ratios were then grown in three-dimensional "wires" that mimic the structure of human heart tissue.

"An exciting result of our study is our ability to miniaturize the tissues into human heart micro-tissues that can be used to measure normal and diseased human heart responses to drugs," emphasized Professor Peter Zandstra, corresponding author of the study and Canada Research Chair in Stem Cell Bioengineering at IBBME and the McEwen Centre for Regenerative Medicine.

From discovering the right composition of heart cells, the researchers next designed the first-ever three-dimensional arrhythmia tissue model.

Millions of people experience arrhythmia each year, a condition in which the feedback of electrical pulses of the heart is interrupted, leaving the heart unable to contract and pump blood effectively.

With the right cellular composition, though, the researchers were able to engineer the circular tissue model associated with arrhythmia. The team then applied electrical pulses to the arrhythmic tissues, 'zapping' the irregularly beating tissue into a state of regular contractions.

Since human heart cells aren't easily grown, being able to engineer highly functional heart tissue from human stem cells is a vital concern for cardiac researchers.

"We can now combine this compositional knowledge with electrical stimulation and mechanical stimulation to obtain a truly biomimetic system necessary for cardiac research," cited corresponding author Associate Professor Milica Radisic, core faculty at IBBME and the

Department of Chemical Engineering and Applied Science, and Canada Research Chair in Functional Cardiovascular Tissue Engineering.

Stressing the urgent need for highly functional heart tissue to perform important drug screening research, Thavandiran added, "We're making a really big push to bring this model to the marketplace."

The team has been working with the Centre for the Commercialization of Regenerative Medicine (CCRM) to commercialize their tissue modeling platform.

More information: Design and formulation of functional pluripotent stem cell-derived cardiac microtissues, www.pnas.org/cgi/doi/10.1073/pnas.1311120110

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