ISSN 2644-2345
MARCH - 2021

STARTUPCITY

STARTUPCITY.COM

APAC SPECIAL

JAPANESE STARTUPS EDITION

HEARTSEED INC.

EN ROUTE TO CLINICAL TRIALS OF FUNCTIONAL CARDIOMYOCYTES

KIKUO YASUI, COO

DR. KEIICHI FUKUDA, FOUNDING SCIENTIST, CEO

$15

STARTUP CITY TOP 10 JAPANESE STARTUPS - 2021

TAIJI EDOGAWA

AKIRA FUJIYOSHI

KIKUO YASUI, COO

DR. KEIICHI FUKUDA, FOUNDING SCIENTIST, CEO

KAY DEGUCHI

MUTSUKI TAKANO

TOMOYUKI KIKUGAWA

TAKEHIKO KANEKO

YUTARO KASAI

EN ROUTE TO CLINICAL TRIALS OF FUNCTIONAL CARDIOMYOCYTES

HEARTSEED INC.

A Professor and Chair of the Department of Cardiology at Keio University School of Medicine in Tokyo, Vice President of the Japanese Society of Internal Medicine, and former president of the Japanese Pulmonary Hypertension Society – these are the titles of Dr. Keiichi Fukuda. He is one of the pioneers of cardiac regeneration and has worked extensively in the field of stem cells. It is not very common that a highly accomplished scholar like Dr. Fukuda will lead a technology company. Dr. Fukuda wanted to develop an innovative technology to cater to the unmet demand for effective therapies for cellular and functional damage associated with heart failure. Since each company has its

focus and priorities, he established his own company called Heartseed.

"Heartseed's key technology is to make functional cardiomyocytes that are purified, safe, and efficacious," says Kikuo Yasui, COO, Heartseed. Cardiomyocytes are the cells that make up the heart muscle. After a heart failure, these cells are dead, and transplanting regenerated cardiomyocytes can be a better solution than heart transplant, which is not widely available due to lack of donors. Through his initial research, Dr. Fukuda had reported that cardiomyocytes could be derived from bone marrow mesenchymal stem cells in 1999, and stem cell research for heart disease gained momentum around the world.

> THROUGH THE YEARS OF DISCUSSIONS WITH JAPAN'S PMDA, OUR PHASE I/II CLINICAL TRIAL OF IPSC-DERIVED CARDIOMYOCYTE SPHEROID FOR HEART FAILURE, NAMED LAPIS STUDY, IS ALLOWED TO BE INITIATED

Stem-cell possesses the ability of self-renewal and differentiation by virtue of being pluripotent. The induced Pluripotent Stem Cells (iPSCs) and Embryonic Stem Cells (ESCs) proved to have the greatest multilineage capability than other cell-based therapies; however these also possess the greatest risks. The clinical trials of ESC or iPSC-derived cardiomyocytes therapy are slow because of concerns of ventricular arrhythmia and a risk of teratoma formation, which is a severe health concern.

Heartseed has successfully addressed the arrhythmia issue and minimized the formation of teratoma using their innovative regenerative technology, and that enables the next generation cardiac cell therapy – Remuscularization.

'REMUSCULARIZATION'

As the name suggests, Remuscularization aims to build the lost muscles – cardiomyocytes – by producing a large number of ventricular type cardiomyocytes from iPSCs and transplanting outside the mass of the weakened cardiomyocytes. These are beating cardiomyocytes that help in the long-term improvement of cardiac function. When a person suffers from a heart attack or myocardial infarction, the blood flow is hampered due to damaged cardiomyocytes resulting in weak pumping and systolic functions. These cells are beyond repair, and to rejuvenate the heart, the blood flow needs to improve by standard technology or surgery. "The patient can be rescued by newly transplanting beating cardiomyocytes," says Yasui.

DR. KEIICHI FUKUDA,
FOUNDING SCIENTIST,
CEO

To generate beating cardiomyocytes that overcome all the apprehensions and concerns of the stem-cell-based therapy, Heartseed developed a four step Remuscularization technology. These steps are carefully executed to ensure that regenerated cardiomyocytes are efficiently engrafted in the patient's heart and contribute to its long-term cardiac functions.

In the first step of Remuscularization – iPSC production, the company has their patented methodology to generate iPSCs with enhanced efficiency. The conventional method of iPSC production follows a collection of skin tissue of the patient and direct insertion of reprogrammed genes into the patient's genome, which can result in rupturing of the genome. Heartseed does away with this method and produces iPSC from a single drop of patients' blood. That being said, Heartseed uses Kyoto University's iPSCs for the first clinical study because making iPSCs from the patient takes time at this moment.

Once the iPSCs are in place, Heartseed proceeds to its second stage called Differentiation. Here, the company proceeds to differentiate iPSC into ventricular-type cardiomyocytes. Heart is composed of atria and ventricles, and each cardiomyocyte differ in electronic activity. Ventricular-specific cardiomyocytes differentiation is considered to be important to reduce the risk of arrhythmia.

To ensure that tumorigenic residual iPSC does not reach the cell culture environment, Heartseed has a patented methodology used in their third step called Purification. This methodology helps in identifying tumorigenic iPSC using the difference of energy metabolism of iPSC and cardiomyocytes in detail. "We added a selection method using lactate which cardiomyocytes use to survive while the undifferentiated stem cells cannot," says Yasui. "The surviving cardiomyocytes can then be safely transported to the cells into the patient's heart."

Though there exists a method of engrafting cardiomyocytes into a patient's heart, the process is not efficient in the sense that only a few cardiomyocytes are retained after transplantation. The fourth stage of the process ensures that as many as one thousand cardiomyocytes are aggregated and form a micro tissue. This is possible via a breakthrough technology developed by Heartseed where they can create a Spheroid in which 1000 cardiomyocytes can be aggregated to transplant in the heart tissue, thereby drastically improving the engrafting rate. The technology has enabled cardiomyocytes to grow further after engraftment and significantly improve cardiac function. This cardiomyocyte spheroid serves as the seed of the heart that helps it rejuvenate after a myocardial infarction, and this is where the company derives its name.

ROAD TO CLINICAL TRIALS

In the pre-clinical trials, Remuscularization has been efficacious in monkeys, and the company is gearing up for clinical trials. Though the data of the pre-clinical trial on monkeys is confidential, Heartseed has given an essential impact of the trial. "Usually in monkeys, arrhythmia occurs in 10-15 hours per day for the first month but it didn't happen here," says Yasui. "The cardiac function is improving significantly without safety concerns."

The numbers must surely be encouraging as Heartseed is gaining investor confidence significantly. Heartseed has raised approximately $40million in total by its Series B held until early 2020, which is the highest in Japan for any company at the pre-clinical stage. Heartseed is now entering the clinical stage, and aims to complete its Series C round in 2021for further organic growth.

In terms of technological development, the company will be coming up with special transplantation devices for cardiomyocytes spheroids and establishing a cell transplantation system that does not require skilled operators. The company is also collaborating with key players across the value chain for manufacturing and transportation.

"We want to change the world with regenerative medicine," ends Yasui.

APAC SPECIAL

MARCH - 2021

STARTUPCITY

BIOTECH STARTUPS EDITION

STARTUPCITY.COM

HEARTSEED INC.

Top JAPANESE STARTUPS 2021

Awarded by STARTUPCITY

HEARTSEED INC.

Top JAPANESE STARTUPS 2021

Awarded by STARTUPCITY

In appreciation of their relentless pursuit of excellence and innovation in Japanese Startups technology

Kenneth Thomas
Managing Editor