# Researchers develop world's first human heart cell model

October 25 2012

Researchers at the National Heart Centre Singapore (NHCS) have successfully created a human heart cell model of arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited heart muscle disorder which puts one at high risk of developing life-threatening arrhythmias and sudden cardiac death. The NHCS research team discovered that key characteristics of the disease, such as abnormal "fatty changes" and altered distribution of proteins involved in cell-cell connections (called desmosomal proteins) are reproduced in the heart cells. This novel cellular model for studying the disease could help to improve understanding on how these mutations lead to arrhythmias and clinical manifestations of ARVC. The study, the first of its kind in the world, was published in the *European Heart Journal*, a top ranking international peer-reviewed journal, in July 2012.

The human heart cell model was developed using patient-specific induced pluripotent stem cell (iPSC) technology which converts skin samples from an ARVC patient into heart muscle cells on a petri dish outside the body. This technique is based on the revolutionary iPSC technology of transforming skin cells into stem cells, developed by Professor Shinya Yamanaka, winner of the 2012 Nobel Prize in Physiology/Medicine. The NHCS research team has taken a step further by developing a key clinical application of the iPSC technology by replicating one's own heart cells outside the body for the study of genetic cardiovascular diseases.

Associate Professor Philip Wong, Director, Research and Development

Unit, NHCS said, "For the first time, we have created a 'crystal ball' of the disease outside the body, to look into the patient's detailed genetic makeup and its relationship to the manifestation of disease. There would be significant opportunities now to safely study the effects of environmental factors and treatments, including gene and drug therapy, on such diseases as they do not have to be tested on patients in the first instance."

Genetic mutations in ARVC typically affect the function of desmosomes, which are structures that attach heart muscle cells to one another. Desmosomes provide strength to the heart muscle and play a signalling role between neighbouring cells. Without normal desmosomes, the heart muscle cells will detach from one another and die, particularly when the heart muscle is placed under stress (such as during vigorous exercise). The damaged heart muscle is gradually replaced by fat and scar tissue. These changes also disrupt the electrical signals that control the heartbeat, which can lead to dangerous arrhythmia and sudden cardiac death.

ARVC occurs in an estimated 1 in 2,000 to 1 in 5,000 people. The disorder may be under-diagnosed as it can be difficult to detect in people with mild or no symptoms. "Although ARVC is a rare condition, it is more commonly detected in younger individuals, in their 20s and 30s, particularly in males, and is more lethal in this age group," said Dr Reginald Liew, Deputy Director, Research and Development Unit, NHCS and principal investigator of the study. Dr Liew is also an Assistant Professor with the Duke-NUS Graduate Medical School Singapore (Duke-NUS). ARVC may not have any symptoms especially in the early stages. Common symptoms if they do occur include palpitations, light-headedness, and fainting. Those with family history of sudden cardiac death are at higher risk.

The team has also been successful in using the iPSC technology to

replicate other inherited heart rhythm diseases such as long QT syndrome (LQTS) and Brugada Syndrome. These diseases are caused by mutations in genes coding for proteins that control the electrical activity of the heart which can lead to ventricular arrhythmias, blackouts and sudden cardiac death.

"Our success in using iPSCs as a platform for the study of genetic cardiovascular diseases was made possible with the clear and cohesive networking between the research scientists, clinicians and bio-medical engineers. The collaborative efforts with other leading research institutions in Singapore, including Duke-NUS, NUS and A*STAR, has allowed NHCS to take a lead globally in this area and enhance Singapore's reputation as a leader in translational cardiovascular research," said Associate Professor Wong. The recognition has been followed with invitations for collaboration from other internationally recognised research centres working in this area.

The 10-member research team comprises six research scientists, two clinician scientists and two staff from the Electron Microscopy Unit, Yong Loo Lin School of Medicine, National University of Singapore. The three-year project which started in 2010, was supported with a research grant from Goh Foundation and administered through Duke-NUS.

"The next stage is for us to use this ARVC model to understand more about the disease and to specifically use such models to risk stratify patients with risk of cardiac arrhythmias. Such models will allow us to measure risk in individuals safely and tailor individual preventive programmes and treatments to patients in a more precise manner, i.e. the practice of 'stratified and personalised' medicine," said Associate Professor Wong.

Provided by SingHealth