00477 Generation of Clinically Safe and Efficacious Cardiovascular Progenitors in a Chemically Defined and Xeno-free Laminin-221 Based System

Lynn Yap[1], *Wang Jiong-wei*[2], *Aida Moreno-Moral*[1], *Chong Li Yen*[1], *Miina Ohman*[1], *Stuart Cook*[1], *Enrico Petretto*[1], *Karl Tryggvason*[1]

[1]Duke-NUS Medical School, [2]National University of Singapore

Aims: The aim of this project is to investigate the efficacy of cardiovascular progenitors differentiated from a chemically defined and xeno-free laminin-221 based system.

Methodology: We investigated the aims using RNA sequencing, transplantation of CVPs into ischemic reperfused injury model in mice, echocardiography and histology and imaging to observe human muscle fibres.

Result: Here, we show that laminin 221 (LN-221) is the most abundant laminin in the human heart by deep RNA sequencing using human control patients. We then synthesized LN-221 as a recombinant human protein and it was found to drive pluripotent human embryonic stem cells (hESCs) to the cardiovascular lineage under fully defined human conditions. LN-221 induces specific biological effects in hESCs by downregulating genes involved in pluripotency and teratoma development, while upregulating genes for cardiac development. We have also identified a highly reproducible expression signatures during differentiation of two separate hESCs to cardiovascular progenitors (CVPs) that become beating cardiomyocytes (CMs).

Transplantation of CVPs into ischemic reperfused injury model in mice resulted in the formation of human muscle bundles. These bundles were formed from single CVPs cell suspension and later organized itself in vivointo well-organized CMs with normal sarcomeres and gap junctions.

Transplanted hearts also showed improved cardiac function by echocardiogram. Moving towards a clinically safe therapy, we investigated the safety of these CVPs using teratoma assay and in vivoimaging.

Conclusion: We propose that LN-221-mediated differentiation of hESCs to CVPs may be developed as a new and fully human methodology for regenerative cardiology.