madridge CONFERENCES
International Conference on
Stem Cells and Cell Biology
December 6-7, 2018 Valencia, Spain

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

Karl Tryggvason[1,9]*, Lynn Yap[1], Jiong-Wei Wang[2,3], Aida Moreno-Moral[1], Li Yen Chong[1], Yi Sun[4], Miina Öhman[1], Stuart Cook[1,5,6], Outi Hovatta[7], Dominique P.V. de Kleijn[3,8] and **Enrico Petretto[1]**

[1]Duke-NUS Medical School, National University of Singapore, Singapore
[2]Department of Surgery, National University of Singapore, Singapore
[3]Cardiovascular Research Institute, National University Heart Centre Singapore, Singapore
[4]BioLamina AB, Sweden
[5]National Heart Research Institute Singapore, National Heart Centre Singapore, Singapore
[6]National Heart Lung Institute, Imperial College London, UK
[7]Department of Clinical Sciences, Karolinska Institute and Karolinska University Hospital, Sweden
[8]University Medical Center Utrecht, The Netherlands
[9]Department of Medical Biochemistry and Biophysics, Karolinska Institute, Sweden

The human heart has limited regeneration capacity after birth and methods for safe and reproducible generation of stem cell-derived therapy for use in patients have not been successful. These include culturing of the stem cells or its products in undefined conditions and on xenogenic materials like Matrigel™ that render the cells unsuitable for human therapy and extensive variations in the differentiation protocols. In order to replace the xenogenic Matrigel™ and the use of ROCK inhibitor for a fully defined protocol, we have explored the extracellular matrix (ECM) components in the heart and found that a cardiomyocyte laminin protein is a highly biologically culture matrix. Here, we show based on deep RNA sequencing human heart muscle, that laminin 221 (LN-221) is the most abundantly expressed laminin in the human heart. We synthesized LN-221 as a recombinant human protein and found it 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 down regulating genes involved in pluripotency and teratoma development, while up regulating 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). Cardiac transplantation of CVPs into ischemic reperfusion heart in farction region in mice resulted in the formation of human muscle bundles. These bundles were formed from single troponin negative CVPs which later organized itself *in vivo* into 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 a teratoma assay and *in vivo* imaging. We propose that LN-221-mediated differentiation of hESCs to CVPs may be developed as a new and fully human methodology for regenerative cardiology.

Biography:

Karl Tryggvason, MD, PhD is Professor at Duke-NUS Medical School, Singapore and Duke University, North Carolina, as well as Senior Professor at Karolinska Institutet in Stockholm. His research concerns the molecular nature, biology and diseases of basement membranes (BM), a special compartment of the extracellular matrix. His group has cloned almost all human BM proteins and clarified genetic causes of many BM-associated diseases, such as Alport and congenital nephrotic syndromes, junctional epidermolysis bullosa and congenital muscular dystrophy, as well as studied matrix metalloproteinases, including the discovery and crystal structure of MMP-2. His group has produced most laminins as recombinant human proteins and currently the group mainly studies how different laminin isoforms influence cell growth and stem cell differentiation. Tryggvason has published over 400 research articles. He is a member of the Finnish Academy of Sciences and the Swedish Royal Academy of Sciences, and has served for 18 years as a member of the Nobel Assembly and Committee for Physiology or Medicine at the Karolinska Institute. He has received several international awards, and he is co-founder of Bio Lamina AB, Stockholm, that produces laminins for cell biology and cell therapy purposes.