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Embryonic stem cell derived cardiovascular progenitors for heart regeneration

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Abstract

Stem cell-based therapies are considered a potential solution for myocardial infarction (MI) despite several recent failures. Thus, cell therapy trials with bone marrow-derived cells have been deemed futile, pluripotent stem cell (hPSC) derived cardiomyocytes (CM) most often lead to arrhythmias and inconsistencies in protocols and poor reproducibility and sadly large-scale falsifications of data on adult heart stem cells have decreased the credibility of regenerative cardiology. Cardiovascular progenitors (CVPs) are considered a promising source for hPSC-derived cardiac cells that have shown improvements in animal models of MI and some early-phase clinical trials. A highly reproducible differentiation protocol for generation of CVPs from hESCs in a fully-defined and xeno-free system has been developed. Multi-potent CVPs that enabled generation of human MI heart tissue in infarcted mice have been identified. The studies are entering an experimental phase studies in pigs and monkeys via intra-cardial transplantation of CVPs into permanently ligated hearts for a proof of concept. The hypothesis is that the non-beating troponin T negative CVPs allows survival, maturation and functional regeneration of heart tissue after myocardial infarction. The CVPs were generated from hESCs on a novel heart laminin (LN-221) matrix under reproducible, xeno-free and chemically defined conditions. In the pigs, the animals are subjected to permanent ligation on the left coronary artery and first branch of the left circumflex. This gives a scar size of 10% of the left ventricular anterior wall. One hundred million progenitor cells are intra-myocardially injected into the infarcted and per-infarcted myocardium at several locations. Whole body CT scan for any associated tumour in any organs at week 4 are performed to determine the safety of the CVPs. Cardiac function is measured by MRI at 1 and 4 weeks post treatment assessing the left ventricular ejection fraction, regional wall motion and thickness and infarct size. At week 4, hearts are harvested for histology analysis using human nuclei antibody, human cardiac markers (cTNT, alpha-actinin) to visualise human cells retention, organisation and retention in the swine. Data on the fate of transplanted CVPs under these conditions as well as data on potential arrhythmia will be presented.

Biography

Karl Tryggvason MD, PhD is Professor at Duke-NUS (Singapore) and Duke University (USA) and Professor Emeritus at the Karolinska Institute, Stockholm. His research concerns the molecular nature, biology and diseases of basement membranes (BM). Currently his main projects involve the role of BM laminins in stem cell differentiation and cell therapy of regenerative medicine. He has published over 450 research articles. He is a member of the Finnish Academy of Sciences and the Swedish Royal Academy of Sciences and he has served for 18 years as a member of the Nobel Assembly and Committee at the Karolinska Institute. He has received several International awards, and he is co-founder of BioLamina AB, Stockholm, that produces laminins for cell biology and cell therapy purposes.

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