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Isl1 Gene Therapy For the Ifarcted Heart – Preservation of Cardiac Function through Enhancement of Angiogenesi

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The LIM-homeobox transcription factor isl1 plays a crucial role during heart embryogenesis. Embryonic isl1+ precursors give rise to over two-thirds of the heart and to its subsequent lineages: cardiac muscle, smooth muscle and endothelium. Interestingly, a subset of Isl1+ progenitors remains embedded in the postnatal heart. We have previously shown that isl1 forced expression in endothelial cells and mesenchymal stem cells enhances their angiogenic and vasculogenic properties.

In the current study, we investigated whether isl1 is expressed in progenitors of adult bone marrow stem cells (BMSCs) and spleen, and whether isl1 expression varies after acute myocardial infarction (MI). Additionally, we examined whether intramyocardial gene transfer of naked DNA encoding isl1 could promote a functional recovery after MI.

We used the transgenic mice isl1/cre/Z/EG, in order to detect isl1 expression in BMSCs and spleen of adult mice. At 4 and 14 days after MI induction, isl1 expression was assessed in heart, bone marrow and spleen of FVB mice by qRT-PCR and immunostaining. Furthermore, intramyocardial injection of plasmid encoding isl1 to mice after ligation of the LAD has been performed. We report for the first time, that Isl1 gives rise to sub populations of progenitors in the bone marrow and spleen, and that Isl1 is reexpressed in the spleen and left ventricle following MI. Moreover, intramyocardial gene transfer of Isl1 to the borderzone of infarcted heart resulted in partial salvage of left ventricular function, enhanced vascularization, and reduced myocardial fibrosis.

Thus, the isl1 gene appears as an attractive target for future gene therapy for regenerative myocardial dysfunction.