中文題目：異體骨髓間質幹細胞於心肌梗塞治療之應用

英文題目：Allogeneic bone marrow mesenchymal stromal cells in the treatment of myocardial infarction

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Background: The infarcted heart has limited ability to repair itself. Bone marrow mesenchymal stromal cells could favorably impact the infarcted heart. It remains unknown, however, whether clinical scale bone marrow stromal cell therapy is feasible and effective to repair the infarcted heart. Therefore, we aimed to investigate the therapeutic potential of bone marrow stromal cell transplantation for myocardial infarction (MI) and its possible mechanism(s). Here we used a canine MI model to test effect of bone marrow mesenchymal stromal cell treatment.

Methods: We induced MI in inbred canine (weight 15~20 kgw) by balloon occlusion of the middle part of left anterior descending coronary artery (LAD) for 90 minutes. MI was documented by increased serum cardiac troponin levels and ST segment elevation of electrocardiograms. At 2 weeks post-MI, either vehicle (as control) or allogeneic, clonal c-kit negative, CD34 negative, CD146 positive canine bone marrow mesenchymal stromal cells (designated DS1 cells [$10x10^6$/kg]) was intravenously infused. To assess left ventricular (LV) function, we performed serial echocardiographic studies (prior to MI, 2 weeks after MI, and 4 weeks after treatment) and cardiac magnetic resonance imaging (CMR) at 2 weeks after MI (prior to vehicle or DS1 cell infusion) and 4 weeks after treatment. The canine was euthanized at post-treatment 4 weeks and the heart was harvested for histological studies.

Results: $Indium^{111}$ labeled DS1 cells showed the cells are sequestered in the lung and then disappear in less than 48 hours. Polymerase chain reaction (PCR)-based analysis failed to detect DS1 cells in the blood but we detected increased numbers of circulatory endothelial progenitor cells within days of DS1 cell infusion. At post-MI 2 weeks (prior to treatment), there was no significant difference of LV systolic and diastolic function between the controls and DS1 cell-treated dogs. However, at 4 weeks post treatment, compared to the control group, the DS1 cell-treated group had better LV diastolic function, presenting with tissue Doppler mitral e' (control *vs*. DS1 cell-treated: 3.0 ± 0.2 *vs*. 4.8 ± 0.3, $p = 0.007$), E/e' (control *vs*. DS1 cell-treated: 14.3 ± 1.4 *vs*. 10.2 ± 1.7, $p = 0.03$) and left atrial volume index (control *vs*. DS1 cell-treated: 23.0 ± 1.0 *vs*. 15.2 ± 1.2, $p < 0.001$). LVEF measured by CMR was not deteriorated in the DS1 cell-treated group (post-MI 2 weeks *vs*. post-MI 6 weeks:

55.0 ± 6.3 vs. 54.2 ± 1.2, p = 0.61), despite further significant deterioration in the vehicle controls (post-MI 2 weeks *v*s. post-MI 6 weeks: 54.3 ± 2.6 vs. 47.6 ± 2.3, p = 0.01). Furthermore, 2-dimensional speckle-tracking strain echocardiography also revealed that there was no significant difference of LV global peak systolic longitudinal strain (GLS) between the controls and the DS1 cell-treated dogs at the baseline (prior to MI) and post-MI 2 weeks (prior to treatment). Nevertheless, at 4 weeks after treatment, compared to the controls, the DS1 cell-treated dogs had better GLS (control *vs*. DS1 cell-treated: -13.6 ± 1.7 *vs*. -16.0 ± 0.8, p = 0.04). CMR and speckle-tracking strain echocardiographic studies indicated that the DS1 cell-treated dogs had better LV systolic function at 4 weeks after treatment. Although we observed no significant difference of infarct size and arteriole density between the control group and the DS1 cell-treated group, importantly, the nonuniformity of collagen orientation was increased in the vehicle group.

Conclusions: These data suggested that single intravenous infusion of DS1 cells at 2 weeks after MI may ameliorate the deterioration of LV systolic function and improve LV diastolic function by preventing post-MI collagen fiber disarrangement.