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In vivo bioluminescence imaging of cord blood derived mesenchymal stem cell transplantation into rat myocardium

Jung-Joon Min,*[1,2] Youngkeun Ahn,*[3] Sungmin Moon,*[1,2] Yong Sook Kim,*[3] Jong Eun Park,*[5] Sung Mi Kim,*[1,2] Uyenchi N. Le,*[1,2,3] Joseph C. Wu,*[6] Soo Yeon Joo,*[3] Moon Hwa Hong,*[3] Deok Hwan Yang,*[7] Myung Ho Jeong,*[3] Chang Hun Song,*[4] Yun Hyeok Jeong,*[8] Kyung Yeon Yoo,*[9] Kyung-Sun Kang*[8] and Hee-Seung Bom*[1,2]

*[1]*Institute for Molecular Photonic Imaging Research, Chonnam National University Hospital*
*[2]*Department of Nuclear Medicine, Chonnam National University Medical School*
*[3]*Department of Cardiovascular Medicine, Chonnam National University Medical School*
*[4]*Department of Obstetrics and Gynecology, Chosun University College of Medicine*
*[5]*Research Institute for Clinical Medicine, Chonnam National University Hospital*
*[6]*Molecular Imaging Program at Stanford, Stanford University*
*[7]*Department of Hematooncology, Chonnam National University Medical School*
*[8]*Lab of Stem Cell and Tumor Biology, College of Veterinary Medicine, Seoul National University*
*[9]*Department of Anesthesiology, Chonnam National University Medical School*

Objective: The conventional method for the analysis of myocardial cell transplantation depends on postmortem histology. Here, we have sought to demonstrate the feasibility of a longitudinal monitoring of transplanted cell survival in living animals, accomplished with optical imaging techniques and pharmacological interventions. ***Methods:*** Human cord blood (50 m*l*) was donated with parental consent. After getting cord blood derived mesenchymal stem cells (CBMSCs), cells were transfected (MOI = 100) overnight with adenovirus encoding firefly luciferase gene (Ad-CMV-Fluc). Our experimental Sprague-Dawley rats (n = 12) were given intramyocardial injections containing 1×10^6 CBMSCs, which had been made to express the firefly luciferase (Fluc) reporter gene. Optical bioluminescence imaging was then conducted using a cooled charged-coupled device (CCD) camera (Xenogen), beginning on the day after the transplantation (day 1). Groups of mice were intraperitoneally injected with cyclosporine (5 mg/kg) or tacrolimus (1 mg/kg), in an attempt to determine the degree to which cell survival had been prolonged, and these values were then compared with the cell survival values of the negative control group. The presence of transplanted CBMSCs on *in vivo* images confirmed by *in situ* hybridization for human specific Alu in the myocardium. ***Results:*** Cardiac bioluminescence signals were determined to be present for 6 days after transplantation: day 1 ($97000 \pm 9100 \times 10^5$ p/s/cm^2/sr), day 3 (9600 ± 1110 p/s/cm^2/sr), and day 5 (3200 ± 550 p/s/cm^2/sr). The six mice that received either cyclosporine or tacrolimus displayed cardiac bioluminescence signals for a period of 8 days after transplantation. We observed significant differences between the treated group and the non-treated group, beginning on day 3 (tacrolimus; 26500 ± 4340 p/s/cm^2/sr, cyclosporine; 27200 ± 3340 p/s/cm^2/sr, non-treated; 9630 ± 1180 p/s/cm^2/sr, $p < 0.01$), and persisting until day 7 (tacrolimus; 12500 ± 2946 p/s/cm^2/sr, cyclosporine; 7310 ± 1258 p/s/cm^2/sr, non-treated; 2460 ± 160 p/s/cm^2/sr, $p < 0.01$). The human-derived CBMSCs were detected in the myocardium 3 days after transplantation by *in situ* hybridization. ***Conclusions:*** The locations, magnitude, and survival duration of the CBMSCs were noninvasively monitored with a bioluminescence optical imaging system. We determined that optical molecular imaging expedites the fast throughput screening of pharmaceutical agents, allowing for the noninvasive tracking of cell survival within animals. In rat cardiac CBMSC transplant models, transient immunosuppressive treatment with tacrolimus or cyclosporine was shown to improve donor cell survival.

Key words: cord blood, mesenchymal stem cell, bioluminescence, molecular imaging