MRI and PET dual detection of embryonic stem cells grafted in the myocardium

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Introduction There are a number of methods available to visualize cells and can be divided into two categories: 1) direct labeling method, and 2) reporter gene approach (1). The former utilizes an imaging-detectable probe which can be loaded into cells and would remain intracellular during tracking. It has two inherent limitations: labels may be diluted upon cell division making these cells invisible; labels may efflux from cells or may be degraded over time, both leading to inability to detect grafted cells. The reporter gene approach involves inserting into stem cells a reporter gene(s) whose expression could be detected by imaging. This approach can potentially overcome the limitations of direct cell labeling when the reporter is integrated into cellular genome via stable transfection. However, comparing to direct labeling method, in which a high intracellular probe concentration is achieved, the concentration of reporter protein expressed in each cell is relatively low and an imaging modality with high sensitivity is required.

Methods In this study, murine embryonic stem cells (ESCs) were stably transfected with a PET reporter gene, a mutant version of HSV1-tk, and were also labeled with SPIO particles (Feridex). After 1 or 5 millions of ESCs were grafted directly into myocardium of athymic nude rats, detection of these cells was achieved by both MR and PET imaging over the time course of 6 weeks. The animal was under isoflurane anesthesia during both MRI and PET scan. For MRI detection, cardiac and respiratory gating was applied during acquisition of short and long axis cine images of the heart using a fast gradient echo sequence with flip angle =20°, TE=10 ms and effective TR is one cardiac cycle (about 150 ms). [N-13]ammonia of 1.5 mCi was injected intravenously and N-13 images were acquired immediately (15 minute scan) on an animal PET (2). After decay of [N-13], which has a short half life of 10 min, [F-18]9-[4-Fluoro-3-(hydoxymethyl)butyl]guanine (FHBG) of 1-1.5 mCi was injected and acquisition of [F-18] images was started 1 h after injection and lasted for 30 min.

Results Both 1 million and 5 million cells were readily detected by MR imaging at day 1 post injection as a region of hypointense. The hypointensive area decreases overtime, so does the contrast between the cells and the surrounding myocardium (Fig 1 panel E-H, 1 million cells injected). In contrast, [F-18] PET was not able to detect 5 million cells until day 4 nor 1 million cells until day 12 after injection; [F-18] signal expanded and increased over time (especially from week 2 to 3) indicating the proliferation of cells in the heart (Fig 1) leading to formation of teratoma shown as wall thickening in panel D and was confirmed by histological analysis. The size of teratoma is dependent on the cell dose.

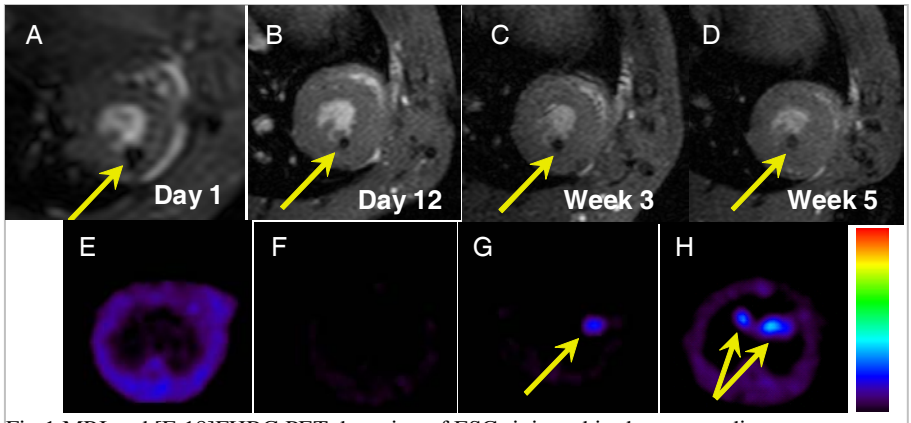

Fig.1.MRI and [F-18]FHBG PET detection of ESCs injected in the myocardium.

Discussion Double labeling method provides complementary information from different imaging modality: MRI for short term cell distribution and PET for long term cell survival / proliferation.

References 1. Journal of American College of Cardiology, 2006. **48**: p. 2094-106.
2. IEEE Transactions on Nuclear Science, 2003. **50**: p. 1357-63.