TRACKING CELL TRANSPLANTS IN VIVO USING A DUAL MODALITY MRI/BIOLUMINESCENCE TOMOGRAPHY PLATFORM

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Target Audience: Clinicians and researchers who are investigating cell transplant therapies *in vivo* at the pre-clinical stage

Purpose

A persistent challenge in the development of cell transplantation therapies is the need to monitor cell targeting, survival, and tumorigenicity in pre-clinical models. In the past years several *in vivo* imaging techniques have been developed for this purpose, the most popular of which leverage MRI or optical imaging. MR-based cell tracking using iron oxide labeling can localize single cells along with high anatomical detail. Techniques to quantify cell viability or count using ^{19}F labeling or MR reporter genes, however, are limited to a minimum number of roughly 10^4 detectable cells[1]. Conversely, an optical method such as bioluminescent imaging (BLI) is capable of detecting and quantifying down to 10^2-10^3 cells *in vivo*[2], as well as provide the 3D cell distribution using BLI tomography (BLIT), but with a limited spatial resolution on the order of mm. Combining the strengths of both modalities, we have developed a method to track cell transplants in small animal models using a specialized holder and an *a priori* determined transformation to co-register MRI and BLIT images.

Methods

A holder was designed for the immobilization and transport of mice between a combination BLI-CT imager and an 11.7T Bruker MR scanner, with a phased-array surface coil which is removed during BLI imaging (Fig. 1). A coordinate transformation between the BLI-CT and MRI imagers was determined by imaging an air-water phantom. Luciferase-expressing murine ES cells were tagged with superparamagnetic iron oxide (SPIO) nanoparticles and transplanted into the right hemisphere in three immunosuppressed mice. The mice were imaged the next day after transplantation and after 1, 2, and 4 weeks: imaging sessions included CT and spectrally-resolved BLI, followed by T1- and T2-weighted MR sequences to visualize the growing cells. BLIT reconstruction was performed on the acquired BLI-CT datasets and the apparent tumor volume was computed from the T2-weighted images using a level set segmentation.

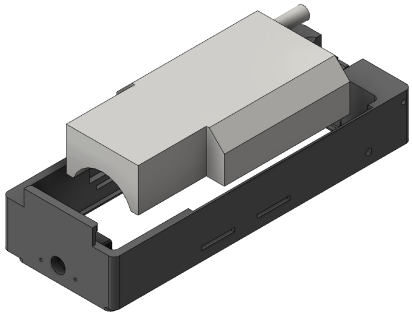

Figure 1. Animal holder with removable coil

Results

Imaging tests using the phantom and live mice showed repeatable alignment between MR and CT images when using the animal holder. Superposition of the co-registered BLIT and MR data (Fig. 2b) indicated cell depth estimation errors by BLIT as large as 8 mm relative to MRI; lateral positions were correctly estimated by BLIT to within ±1 mm. BLIT showed a significant ($p<0.05$) increase in luminescence by the second imaging session by nearly 100x, indicating rapid proliferation of the ES cells and the formation of tumors (Fig. 3). The apparent tumor volume did not change appreciably in the MR images between days 1 to 13, with significant growth visible only by the final imaging session (Fig. 3).

Discussion

These findings suggest a benefit to combining the two modalities, with MRI providing more accurate localization of the cells and BLI offering a more sensitive measure of cell proliferation. Therefore, the information obtained from dual-modality imaging may help with the understanding of stem cell and/or tumor dynamics by providing a more accurate representation of cell fate *in vivo*. The technique we have developed can also be leveraged as a platform for more advanced BLIT reconstruction algorithms in the future that use anatomical information obtained from MRI.

References

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2. Rabinovich, B. A. *et al.* Visualizing fewer than 10 mouse T cells with an enhanced firefly luciferase in immunocompetent mouse models of cancer. *Proc. Natl. Acad. Sci. U. S. A.* **105,** 14342–14346 (2008).

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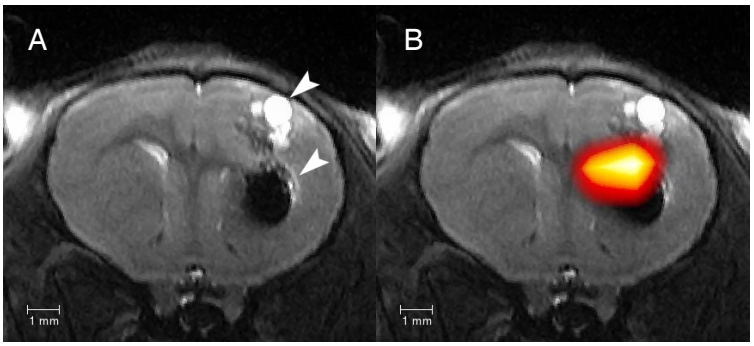

Figure 2. T2-weighted coronal section at week 4 showing A) tumor formation and hypointense region indicating original SPIO-labeled cells and B) superimposed BLIT reconstruction of Luc+ cells over the same MRI slice.

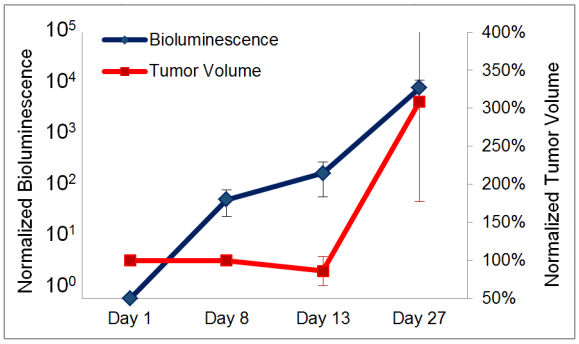

Figure 3. Plot of total cell luminescence and segmented tumor volume, both normalized to day 1 (n=3).