A multimodality imaging model to track viable breast cancer cells from cellular arrest to metastasis in the mouse brain

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**Purpose:** Cancer is the leading cause of death in Canada; however, the majority of deaths are due to metastasis rather than the presence of a primary tumour. Therefore, the clinical need to better understand and prevent metastasis is high. Cellular magnetic resonance imaging (MRI) is an emerging tool that aims to non-invasively visualize and quantify cells in living subjects. This technique uses iron oxide nanoparticles to label specific cells, enhancing their detectability by MRI. The presence of iron in cells causes a distortion in the magnetic field which leads to signal loss in iron-sensitive images. However, cellular MRI has limited ability to differentiate between dead and viable cells. Furthermore, when a cell dies the iron label may be transferred to phagocytic bystander cells leading to a false positive imaging result. Thus, complementary bioluminescence imaging (BLI) can provide a more holistic view of cell fate in living subjects by providing a direct readout of cell viability.

**Hypothesis:** Cellular MRI and bioluminescence imaging used together provide more sensitive and specific measurements of arrested cell number, cellular viability and brain tumour volume as compared to when these methods are used independently.

**Materials and Methods:** Human breast carcinoma cells (JIMT1) were engineered to express a luciferase reporter gene using a retroviral vector. Cells were incubated with micron-sized iron particles for 24h; then 175,000 cells/mouse were injected into the left cardiac ventricle of 4-week-old nude mice. Whole body BLI imaging was used to screen mice for successful intracardiac injection on an In Vivo FX PRO. Only mice with bioluminescence detected in the brain proceeded to MRI. On days 0, 8, 21 and 28, mice received 150uL of D-luciferin intraperitoneally and BLI images were captured for up to 30 minutes. 3T MRI was used to image the brain on days 0, 8, 21 and 28. A balanced steady state free precession (bSSFP) imaging pulse sequence was utilized, which has been optimized for iron detection. The volume of each brain metastasis and the number of signal voids were measured from MRI acquired at each timepoint. Bioluminescent signal was expressed as photons per second per square millimeter and was displayed as a signal intensity map. Photon flux was measured at each timepoint and compared to MRI findings.

**Results:** On day 0, iron labeled cells were visualized as signal voids by MRI, distributed throughout the brain. The number of signal voids in the brain correlated with the brain BLI signal intensity. On day 28, brain metastases appeared as regions of hyperintensity by MRI and BLI signal was detected in the brain and spinal cord. Total brain tumour burden measured by MRI showed a strong correlation with BLI signal intensity.

**Discussion and Conclusions:** Iron-labeled JIMT1 cells were readily detected in the brain and could be tracked to monitor the development of cancer metastasis. Using BLI to complement our current cellular MRI technology, we can screen animals for successful intracardiac injections prior to MRI as well as get a direct measure of cell viability. Furthermore, BLI can be used to track the fate of many different cell populations and will continue to be a valuable tool in monitoring cancer metastasis and treatment response in pre-clinical models of disease.