Maintaining Blood-Brain Barrier Integrity in Translational Brain Tumor Models

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Introduction

Brain tumors and brain metastases remain among the most challenging cancers to treat, with many therapeutic candidates failing in clinical trials due in part to inadequate modeling of the blood–brain barrier (BBB) in preclinical studies. Widely used intracranial models disrupt BBB integrity, limiting their utility for accurately predicting drug delivery and therapeutic efficacy. Conversely, intravenous and intracardiac tumor cell inoculation preserve BBB function but often result in widespread systemic metastases, constraining study duration and interpretability.

To overcome these limitations, we developed an intra-carotid implantation strategy that selectively targets tumor cells to the brain, enabling localized tumor growth while preserving BBB integrity. Tumor establishment and growth kinetics were assessed longitudinally using magnetic resonance imaging (MRI) and bioluminescence imaging (BLI), allowing noninvasive and precise monitoring of tumor burden over time.

Our intra-carotid model provides a more physiologically relevant platform for studying both primary brain tumors, including glioblastoma, and brain metastases arising from systemic malignancies. By maintaining BBB function and supporting reliable longitudinal assessment, this approach enhances the translational relevance of preclinical studies and may improve the predictive power of BBB-penetrant therapeutic development in neuroscience and oncology.

Materials & Methods

MDA-MB-231_luc is a highly aggressive, invasive and poorly differentiated triple-negative breast cancer (TNBC) cell line as it lacks estrogen receptor (ER) and progesterone receptor (PR) expression, as well as HER2 (human epidermal growth factor receptor 2) amplification.

Mice were anaesthetized with IP injection of ketamine/xylazine cocktail. After surgical site prep, a small incision was made in the skin, and dissection of the surrounding tissue was performed to reach the CCA. After preparation of the CCA, the MDA-MB-231_luc cells were then injected into the CCA. The mouse was sutured, placed into a heating pad until fully conscious, and then returned to its cage.

Starting on Day 5 post inoculation, mice were assessed at multiple timepoints for the presence of tumor cells in the brain via IVIS bioluminescent imaging (BLI).

Starting on Day 7 post inoculation, mice were assessed at multiple timepoints for the integrity of the BBB and presence of tumor in the brain via magnetic resonance imaging (MRI) with a 7 tesla Bruker Biospec 70/20as small animal imaging system.

Mice were terminated based on signs of clinical disease and were on study for median of 30 days.

References

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In Vivo Performance of Intra-Carotid Brain Tumor Models

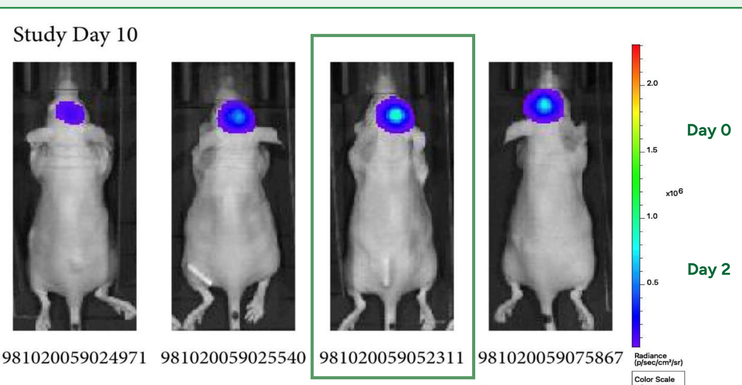


Figure 1: Individual Animal In vivo Bioluminescence (Total Flux [p/s]) for **intra-cranial** MDA-MB-231_luc on Day 10 post inoculation.

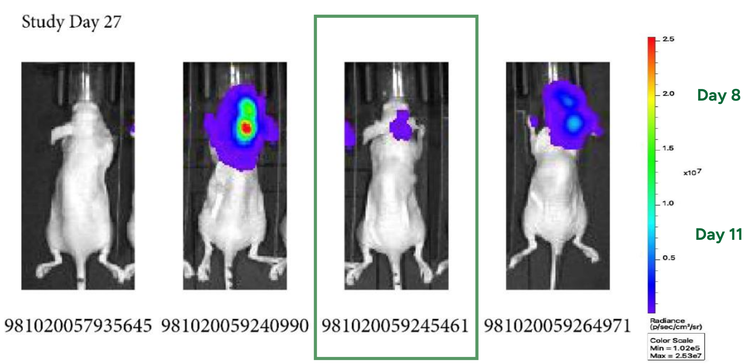


Figure 2: Individual Animal In vivo Bioluminescence (Total Flux [p/s]) for **intra-carotid** MDA-MB-231_luc on Day 27 post inoculation.

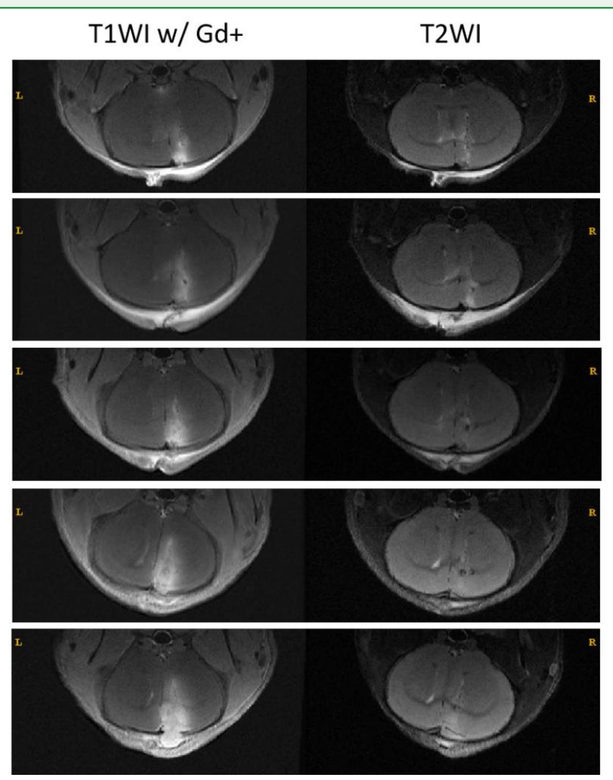
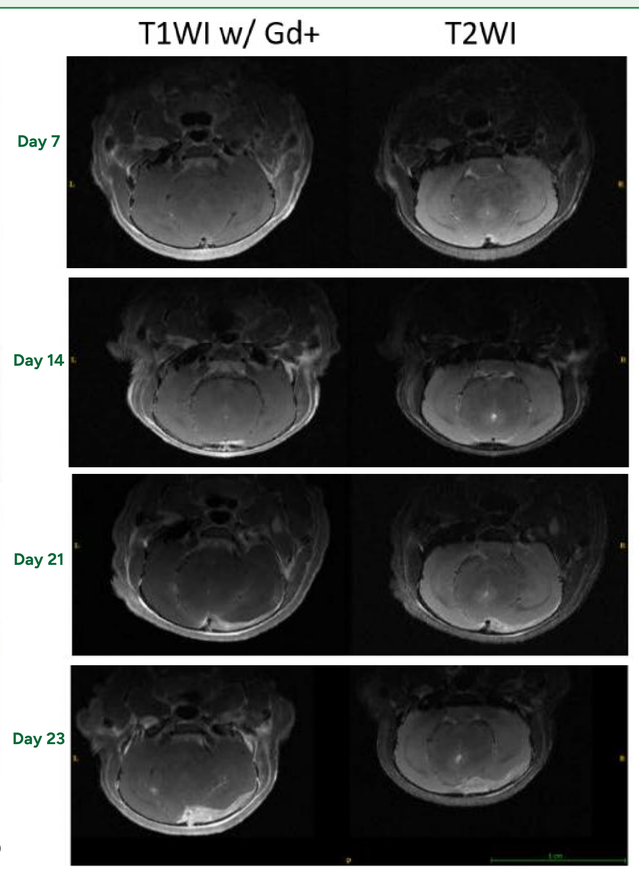


Figure 3 (above): MRI images* for Mouse #052311 (MDA-MB-231 intra-cranial) taken on Day 0 (4hr post inoculation), 2, 4, 8, 11.

Figure 4 (right): MRI images* for Mouse #2454561 (MDA-MB-231 intra-carotid) taken on Day 7, 14, 21, and 23.



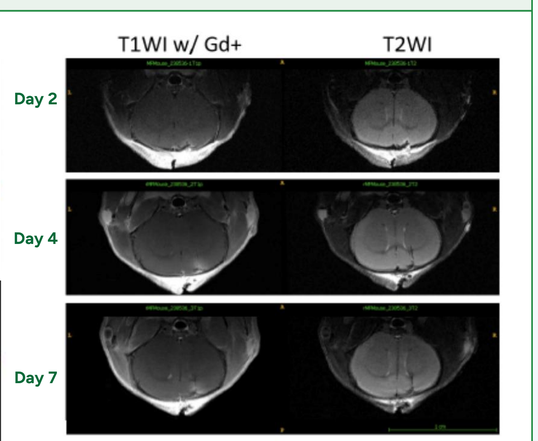


Figure 5: Sham intra-cranial inoculation mouse MRI images* taken on Day 2, 4, and 7 post inoculation. NOTE: The injection site's long T2 signal was significantly reduced on Day 4 and not visible on Day 7, which indicates the recovery of damaged tissue. However, the injection site and surrounding area was significantly enhanced in post-contrast T1WI on all three scan days, which indicates the damage of brain blood barrier related to the injection.

***MRI data includes:** T2-weighted image (T2WI), pre-contrast T1-weighted image (T1WI), and T1WI 10 minutes post-contrast enhancement. All MRI images were acquired axially in 32 0.5 mm-thick axial slices covering the whole brain with an in-plane spatial resolution of 0.078 mm × 0.078 mm.