Title: Characterizing the fate of a brain trophic metastatic breast cancer cell line in the severely immune-compromised NSG mouse with MRI

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Structured Abstract:

Introduction: Metastasis is the leading cause of death in breast cancer patients, with brain metastasis occurring in up to 30% of cases. Previously, our group has used iron-based cellular MRI technologies to track the fate of cancer cells in vivo, primarily using human mammary carcinoma cell lines (such as 231BR) in nude mice. Recently, there is strong momentum to use patient derived xenografts (PDX) that better represent the tumour heterogeneity observed clinically and are recognized as a critical element for developing personalized treatments. NOD/SCID/IL2rg^-/- (NSG) mice are essential for successful engraftment of these PDX models, however, there are no studies characterizing breast cancer brain metastases in NSG mice. To transition from cell lines to PDX models, our objective is to understand differences that may exist in NSG and nuce mice with cellular MRI, first with human cell lines.

Methods: NSG (n=10) and nude mice (n=10) received intracardiac injections of 1.5x10^5 iron-labeled GFP expressing 231BR cells. Images of the mouse brain andbody were acquired with a clinical GE 3T MR system at Day 0, Day 21 (NSG endpoint), and Day 32 (nude endpoint). Day 0 brain images were assessed for signal voids, representing arrested iron-labeled 231BR cells; the % of black pixels was determined. Endpoint images were assessed for retained signal voids and brain metastases. Brain metastases were counted, and the % of brain occupied by metastases was determined, representing brain tumour burden. Body images were assessed for metastases.

Results: On day 0, iron-labeled cells were visualized throughout the brain in all mice as signal voids. The % of these signal voids decreased significantly between day 0 and endpoint for both strains, indicating that the clearance and retention of cells in the brain is similar between strains. At endpoint, brain metastases were evident in all mice as regions of hyperintensity. There was no difference in the number of brain metastases in NSG mice (M=69.00±15.12) compared to nudes (M=58.33±33.70), however, tumour volumes in nude mice (M=0.38mm^3±0.50) were significantly larger than in NSGs (M=0.033mm^3±0.036, p<0.0001). The brain tumour burden (% of the brain with metastases at endpoint) was higher in nude mice; although not statistically significantly. Body images indicated that the NSG mice had numerous metastases located in the liver, lungs, and lymph nodes.

Discussion: Characterization of the NSG mouse as a preclinical platform is needed to successfully implement PDX models for studying breast cancer metastasis. Here we show that the 231BR cell line grew differently in NSG mice compared to nude mice. While both are immune-compromised strains, NSG mice are more severely deficient. Interestingly, brain metastases were much smaller in NSG mice. The burden of liver and lung metastases in NSG mice led to an early endpoint for this model which prevented further development of brain metastasis. This work demonstrates the valuable role that imaging can play towards credentialing these important models.