patient imaging studies from the MICCAI BraTS 2018 Challenge[1]. All patients underwent contouring of GD-enhancing tumor (C+), peritumoral T2 (pT2), necrotic and non-enhancing tumor core (NCR/NET). Images are co-registered to the anatomical template and skull-stripped. Our network consists of a GAN and a discriminative network. The generative model works to synthesize images from labels. Labels comprise the normal brain mask as well as the contoured C+, pT2 and NCR/NET. Normal brain mask is extracted from threshold segmentation on T2-weighted image (T2WI). A discriminative network compares the difference between synthetic and real patient image in both pixel and perceptual difference. The generative model is trained to minimize the difference from the discriminative network. This method was refined in the glioblastoma dataset and applied to BM MRI. RESULTS: Figure 1. Synthetic BM MRI images derived from human brain MRI studies using the GAN model with four modalities (T2, T2 FLAIR, T1 contrasted image, and T1 non-contrasted Image). CONCLUSION: Training DML in BM disease using GAN MRI models may overcome limitations in applying DML to healthcare, namely volume of high-quality data and patient privacy. GAN based modeling for BM needs to be further refined and validated.

### BSCI-15. METASTATIC BRAIN TUMOR TARGETING PEPTIDES ISOLATED THROUGH PHAGE DISPLAY BIOPANNING AGAINST BRAIN METASTASIS-INITIATING CELLS

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To effectively target metastatic brain tumors (MBTs), the paradigm of treating MBTs after visualization on clinical imaging needs to be shifted to an understanding of the mechanisms that drive the formation and maintenance of brain metastasis-initiating cells (BMICs). Targeting this tumor sub-population, which may form as a result from activation of epithelial-mesenchymal transition, may allow for more effective means of isolating and targeting brain metastasis. In order to isolate BMICs, we have harvested cells from patient derived MBTs originating from lung cancer and cultured the cells using serum-free media conditions. *In vivo* phage display biopanning was used to isolate 12-amino acid length peptides that specifically target BMICs. Of the peptides recovered, one peptide, LBM4, was tested for specificity of binding to MBTs through *in vitro* and *in vivo* binding assays. When comparing patient derived metastatic brain tumors cells against brain metastasis cell lines, we found that both types of cells demonstrated similar morphology when grown in serum media conditions, but when grown in serum-free media, both demonstrated a tumor sphere morphology, similar to a stem cell-like state. LBM4 demonstrated specific binding to MBT cells over primary lung cancer cells *in vitro* through flow cytometry analysis and immunocytochemistry. Fluorescent tagged LBM4 intravenously injected into mice harboring intracranial BM demonstrated peptide localization to the tumor within the intracranial cavity visualized with live animal imaging. *In vivo* phage display biopanning is an effective tool that is able to isolate cell specific targeting peptides. MBT targeting peptides can potentially result in a shifting of the clinical treatment paradigm of brain metastases, through the development of more effective targeted therapeutics aimed at BMICs, as well as improving detection of MBT cells which may result in earlier tumor visualization as well as delineation of tumor recurrence versus radiation effects.

### BSCI-16. HEMODYNAMIC SHEAR STRESS SELECTS A SUBPOPULATION OF LUNG ADENOCARCINOMA CELLS WITH HIGHER METASTATIC CAPACITY

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Patients with primary cancers often develop delayed brain metastases. One of the most common cancer types and sources of brain metastasis is lung cancer. For metastasis from lung cancer the 3-year survival is < 5%. Cancer cells in circulation are responsible for metastatic spread. The mechanical microenvironment plays an important role in cancer cells behavior. When cancer cells reach the bloodstream they are exposed to hemodynamic shear stress. It has been shown that most of the circulating tumor cells die once they reach the bloodstream, but the biology of the survival cells is poorly understood. We designed a microfluidics system that simulated the mechanical stress in the human circulating system such as turbulence, change in pressure (0.4-15dyn/cm2) and flow rate (1.06–106.1mm/s). Lung adenocarcinoma cells (A549) were put into circulation and collected after 72 hours. It was found that, 1.4±0.3% of the cells survived, and viability was evaluated by LDH and calcein. CD133, SOX2, and NANOG were downregulated and EMT genes were upregulated in the circulating cancer cells (CCCs) compared with cells in static-suspension or 2D. After re-seeding in 2D, CCCs overexpressed CD133. Female athymic nude rats (6-8weeks,n=16) received intracardiac injections of CCCs or 2D cells (GFP-LUC lentivirus traduced). Bioluminescence imaging was performed every week; the survival in of the CCCs group was lower than the 2D group. One-way ANOVA test was used to analyze survival and gene expression. Survival data was plotted on a Kaplan-Meier curve and compared using the Mantel-Cox logrank test, p=< 0.05. We have isolated a cellular subpopulation of lung adenocarcinoma with high resistance to hemodynamic shear stress that shows a higher metastatic capacity and genetic plasticity compared with cells growing in suspension or 2D. Targeting these cells would potentially allow us to develop personalized treatments to help to stop metastatic spread and improve actual therapeutical strategies.

### BSCI-17. YOUNG AGE PROMOTES BREAST CANCER METASTASIS TO THE BRAIN

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Younger women (< 40 years old) diagnosed with breast cancer often have a poorer outcome and a higher risk of developing brain metastases compared to women diagnosed at an older age. Multi-variate analyses have shown that even after accounting for differences in primary tumor characteristics, young age is still an independent predictor of poorer outcome. We therefore hypothesize that rather than intrinsic tumor properties, age-related changes to microenvironmental factors can affect breast cancer metastasis. To test this hypothesis, human and mouse breast cancer cells were injected into young (< 6 month) and old (> 13 month) mice and metastatic tumor burden was quantified. Young mice injected with brain-seeking breast cancer cells (MDA-MB-231BR, 4T1-BR, and 99LN-BrM) developed significantly more brain metastases compared to their older counterparts. In contrast, age had no effect on lung metastatic tumor burden in five breast cancer models. The effect of age is organ-specific, and the young brain is more permissive for breast cancer metastasis. To gain mechanistic insight, the transcriptome of young and old mouse brains were analyzed by RNAseq, the metastatic microenvironment was analyzed by laser capture microdissection and mass spectrometry, immune populations have been identified by flow cytometry, and functional immune contributions analyzed by immunodepleting antibodies. Multiple brain immune subsets were altered with age. In vivo depletion experiments showed no significant contribution of CD4+ T-cells and GR1+ myeloid cells to baseline brain metastatic colonization. A subpopulation of microglia in aged metastatic brains had a high side-scatter profile, which is consistent with published reports that aged microglia are in a "pro-inflammatory" state. Depletion of microglia reduced baseline brain metastatic colonization by 50% and experiments are underway to determine their contribution to an age effect.

### BSCI-18. ABLATION OF CSF2 MITIGATES RADIATION-INDUCED NEUROCOGNITIVE DECLINE INDEPENDENT OF HIPPOCAMPAL NEUROGENESIS

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**PURPOSE:** The results of the RTOG 0933 and NRG CC001 clinical trials have shown that physical sparing of the hippocampus during cranial irradiation (CI) is associated with preservation of memory functions at 4- and 6-months following therapy. Whereas the putative roles of protection of neural stem cells (NSCs) residing within the subgranular zone (SGZ) of the dentate gyrus are presently poorly defined, suppression of inflammation may be involved because ablation of microglia (MG) through blockade of the CSF-1R or selective targeting of CCR2$^+$ macrophages using an appropriate CCR2 inhibitor leads to the retention of hippocampal-dependent cognitive abilities following CI. Inhibition of Colony stimulating factor 2 (CSF-2), a proinflammatory cytokine causing the proliferation and activation of microglia, may be a suitable alternative strategy to alleviate inflammation. METHODS: Our studies have evaluated the effects of ablation of *Csf2* and also the inducible ablation of MG on the properties of neuroinflammation, neurogenesis and CI-associated cognitive impairments employing the requisite mouse models. RESULTS: We demonstrate that preservation of cognitive functions following CI does not require ablation of MG. In addition, the reduction in neuroinflammation following *Csf2*ablation was sufficient to prevent CI-induced cognitive decline. Moreover, *Csf2* ablation did not prevent the deficit in neurogenesis, thereby suggesting that NSC-mediated SGZ neurogenesis is not required for the prevention of radiation-induced cognitive dysfunction. CONCLUSION: We have previously shown that MG play seminal roles in neural development and adult homeostasis and plasticity. Our present study demonstrates that selective modulation of MG-associated neuroinflammatory signaling without MG ablation is a novel therapeutic strategy to preserve cognitive functions following CI. These experimental observations have seminal implications for patients undergoing radiation therapy for tumors of the brain or head and neck in which the hippocampus inevitably exposed to a high dose of radiation leading to potentially debilitating and possibly avoidable cognitive deficits.