anaphase. Using an independent cohort of patients with BMs, we demonstrated that high protein expression of UBE2C was associated with worse survival. UBE2C-driven cancer cells promoted migration and invasion in vitro and induced an aggressive phenotype and decreased survival in mouse orthotopic xenografts. PI3K/mTOR inhibition effectively blocked cancer cell signaling and prevented the development of leptomeningeal metastases. Therefore, we have identified UBE2C as a molecular marker of worse outcome in BMs patients and pre-clinically validated an effective therapy against UBE2C-driven brain metastatic disease.

BSCI-05

REPURPOSING PROPOFOL FOR THE TREATMENT OF BRAIN METASTASES

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BACKGROUND: Recent clinical studies suggest beneficial effects of propofol anesthesia on tumor progression and patient survival in solid tumors but reported benefits are modest. One potential reason is the relatively short, single exposure to propofol, limited to the surgical period. Brain metastases (BM) are the most common brain tumors in adults. Metastatic tumors develop following infiltration of the brain from primary tumors such as lung, breast, melanoma, and colorectal cancers. BM are treated with combination therapies, including surgery, radiotherapy, chemotherapy, and immunotherapy, however the prognosis of most patients with BM remains dismal. In this report we investigated the effects of propofol plus radiation on cancer stem cells derived from human lung cancer brain metastases (BM-CSCs) and their cross-talk with microglia. OBJECTIVES: Our hypothesis is that propofol can be repurposed as a treatment of BM in addition to its anesthetic uses. To test this, we first examined the cytotoxic effects of propofol on cancer stem cells established from BM-CSCs alone and with radiation. Also, we studied the effects of propofol on the cross-talk of BM-CSCs and microglia. RESULTS: We found that propofol 1) exerted inhibitory effect on BM-CSCs self-renewal, stemness and cell proliferation; 2) increased cell death of cancer cells but not normal neural elements; 3) sensitized BM-CSCs to radiation; 4) inhibited the pro-tumorigenic BM-CSCs/microglia cross-talk by promoting M1 phenotypes of co-cultured microglia. CONCLUSIONS: Propofol exerted anti-tumor effects on BM-CSCs including inhibition of cell renewal, proliferation, and mesenchymal transition. Propofol at sensitized BM-GSCs to radiation and at higher concentrations induced cell death. Propofol exerted anti-tumor cytotoxicity also by inhibiting the pro-tumorigenic CSC-microglia cross-talk via secreted extracellular vesicles (EVs). Propofol effects can be exploited as a general anesthetic of choice during tumor resection and should be examined as an anti-tumor agent in sub-anesthetic doses either alone or in combination with radiation.

BSCI-06

COMPREHENSIVE ANALYSIS OF THE IMMUNOGENOMICS OF TRIPLE NEGATIVE BREAST CANCER BRAIN METASTASES FROM LCCC1419

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BACKGROUND: Triple negative breast cancer (TNBC) lacks expression of hormone receptors (estrogen and progesterone receptors, ER and PR) and HER2. Almost 50% of patients with metastatic TNBC will develop brain metastases (BrM), often with concurrent progressive extracranial disease. While immunotherapy has shown promise in the treatment of advanced TNBC, the immune profile of BrM remains largely unknown. To inform the development of immunotherapy strategies in this aggressive disease, we characterized the genomic and immune landscape of TNBC BrM and matched primary tumors. METHODS: Formalin-fixed, paraffin-embedded samples of BrM and primary tumors of patients with clinical TNBC (n=25, n=9 matched pairs) from the LCCC1419 biobank at UNC-Chapel Hill were analyzed by whole exome (WES) and RNA sequencing, with matched blood DNA sequenced for identification of somatic variants. Mutational and copy number alteration analyses, neoantigen prediction, and transcriptomic analysis of the tumor immune microenvironment were performed. RESULTS: Primary and BrM tissues were confirmed as TNBC and of the basal intrinsic subtype. Compared to primary tumors, BrM demonstrated higher tumor mutational burden. Neoantigen prediction showed elevated cancer

testis antigen- and endogenous retrovirus-derived MHC class I-binding peptides in both primary tumors and BrM, and predicted single nucleotide variants (SNV)-derived peptides were significantly higher in BrM. BrM demonstrated reduced immune gene signature expression, although a signature associated with fibroblast-associated wound healing was elevated in BrM. Metrics of T and B cell receptor diversity were also reduced in BrM. CONCLUSIONS: BrM harbored higher mutational burden and SNV-derived neoantigen expression along with reduced immune gene signature expression relative to primary TNBC. Further research will expand these findings to other breast cancer subtypes. Exploration of immunomodulatory approaches including vaccine applications and immune checkpoint inhibition to enhance anti-tumor immunity in TNBC BrM are warranted.

BSCI-07

ACETYL-AMANTADINE AS A DIAGNOSTIC BIOMARKER IN PATIENTS WITH GLIOBLASTOMA

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AIM: Glioblastoma (GB) is the most common malignant primary brain tumor in adults, with a prognosis as poor as 12-15 months with standard treatment. Spermidine/spermine N1-acetyltransferase (SAT1) is a rate limiting enzyme in polyamine metabolism and has been reported to be upregulated in various cancers, including GB. Amantadine is a Health Canada approved drug that is acetylated by SAT1. We established a clinical trial in GB patients to determine if plasma and urine acetyl amantadine (Ac-Am) can be used to measure SAT1 activity and whether levels correlate with their tumor burden. METHODS: A clinical trial was established that is currently active and recruiting patients with GB who receive care at CancerCare Manitoba. A total of n=8 participants have been recruited thus far. Participants' blood and urine were collected two hours after ingesting amantadine (200 mg). Levels of serum and urine Ac-Am were measured using liquid chromatography-tandem mass spectrometry. Acetyl-amantadine levels were correlated with tumour bidimensional diameter and volume measured on MRI. In addition, expression of SAT1 was examined in various cultured GB cells (both cell lines and patient-derived cells) and correlated with Ac-Am. RESULTS: Preliminary results indicate that the levels of plasma Ac-Am in study participants positively correlate with their initial tumor burden (r = 0.41). While transient increases in plasma and urine Ac-Am above baseline levels were observed, the clinical significance of these findings is undergoing further analysis. SAT1 was detected in all the GB tumor cells examined. The production of Ac-Am in cultured GB cells varied as a function of SAT1 expression. SIGNIFICANCE: A diagnostic biomarker, such as Ac-Am, that could effectively and reliably detect tumor progression and recurrence would be an invaluable adjunct to MRI imaging and could significantly impact the timing of appropriate treatment and reduce patients' morbidity and mortality.

BSCI-08

NEURONAL MIMICRY PROMOTES BREAST CANCER LEPTOMENINGEAL METASTASIS FROM BONE MARROW

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Breast cancer (BC) patients diagnosed with leptomeningeal disease (LMD) have a median survival of less than six months. There has been limited therapeutic innovation in treating LMD due to our poor understanding of the molecular mechanisms governing breast cancer cell (BCC) invasion and survival within the leptomeninges (LM). Here we show that BCCs can invade the LM by migrating along the outer surface of emissary vessels that passage from the skull and vertebral bone marrow through cortical bone fenestrations, emerging as LM vasculature in the sub-arachnoid space. This process requires BCC integrin α6 engaging laminin on the vascular basement membrane of