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. PT3k/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 breast 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 is 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. противопоказаны 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.

**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. TNBC is the most common breast cancer type in women and 50% of patients with metastatic TNBC will develop brain metastases (BM). BM often occurs with concurrent progressive extracranial disease. While immunotherapy has shown promise in advanced TNBC, the immune profile of BM remains largely unknown. We used gene expression analysis of BM to determine the development of immunotherapy strategies in this aggressive disease. We characterized the tumor and immune landscape of TNBC BM and matched primary tumors. METHODS: Formalin-fixed, paraffin-embedded samples of BM 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: BM and BM tissues were confirmed by histology as a brain-intrinsic subtype. Compared to primary tumors, BM demonstrated higher tumor mutational burden. Neoantigen prediction showed elevated cancer tests 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 BM are warranted.

**BSCI-07**

**ACETYL-AMANTADINE AS A DIAGNOSTIC BIOMARKER IN PATIENTS WITH GLOBIOMA**

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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. Spermidin/spermine N1-acetyltransferase (SAT1) is a rate limiting enzyme in polyamine metabolism and has been reported to be upregulated in various cancer cells. We hypothesized that propofol effects of BM-GSCs 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-08**

**NEURELONAL MICYMICRO PROMOTES BREAST CANCER LEPTOMENEGIAL METASTASIS FROM BONE MARROW**

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Breast cancer (BC) patients diagnosed with leptomeningeal disease (LMD) have a median survival of less than 6 months. There has been limited therapeutical 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 ligating on the vascular basement membrane of
emissary vessels, mimicking an 06 integrin-dependent mechanism used by neural progenitors to migrate to the olfactory bulb. Once in the LM, BCCs co-localize with perivascular CSFIR+ meningeal macrophages which support BCC survival and the secretion of the neurotrophin GDNF. Pharmacologic depletion of these meningeal macrophages causes a marked reduction of GDNF concurrent with a decrease in LMD progression, which is rescued by intraventricular delivery of recombinant GDNF. Together these data suggest that BCC’s hijack neural migratory pathways and leptomenigeal macrophages to invade and survive in the LM niche. Finally, analysis of craniotomy samples from patients with breast cancer revealed a correlation between BCC integrin 06 expression and meningeal metastasis suggesting the potential of integrin 06 as a novel target to predict or treat LMD.

BSCI-10
TAPPING INTO GLIOMAS’ SECRETS: CSF PROTEOMICS FOR BIOMARKER DISCOVERY, GLIOMA MONITORING, AND THERAPEUTIC RESPONSE ASSESSMENT
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INTRODUCTION: Rapid, detailed feedback is needed to understand the individualized biological impacts of novel glioma therapies. We are performing glioma biomarker discovery by serum cerebrospinal fluid (CSF) sampling from Ommaya reservoirs to determine how the CSF proteome can reveal early longitudinal intelligence regarding glioma status, biology, and therapeutic response. METHODS: Global proteomic analysis was performed on the Somalogic platform – an aptamer-based technology for highly sensitive and specific analysis of over 7,000 proteins. Discovery analysis comprised of the top-500 ranked proteins in CSF from seven patients with high-grade gliomas (HGG) versus non-glioma controls. The top-500 HGG proteins were then preliminarily filtered to include only proteins that met two additional criteria of decrease with resection and increase with recurrence in individual paired patient samples. RESULTS: Proteomic enrichment analysis revealed a conserved HGG CSF proteomic signature defined by 79 proteins, including ones known to be over-expressed in solid tumor malignancies, such as retinoblastoma binding protein 4, heat shock protein 90, and sorcin. The HGG proteomic signature was consistently enriched in an independent validation cohort consisting of 13 gliomas diverse in primary versus recurrent status, subtype, and grade, when compared to control CSF samples. Encouragingly, proteins in the HGG signature decreased in the two patients for whom CSF was collected prior to and after resection (both at POD16 and POD18) with decreased tumor burden. CONCLUSIONS: Our preliminary data demonstrate the ability to gain detailed, individualized insights regarding glioma biology, tumor burden, and evolution through global CSF proteomics acquired from longitudinal neurosurgical access to unique gliomas.

BSCI-11
GB5121 IS A NOVEL, IRREVERSIBLE, COVALENT BTK INHIBITOR WITH HIGH SELECTIVITY AND CNS-PENETRANCE FOR TREATMENT OF CNS MALIGNANCIES
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Inhibitors of Bruton’s tyrrosine kinase (BTK) are approved treatments for several B cell lymphomas. However, they are characterized by modest selectivity and/or limited central nervous system (CNS) exposure which is important in instances of CNS disease. GB5121 is an orally available, selective, irreversible, covalent molecule BTK inhibitor that was designed to address these limitations. Here, GB5121 was profiled for selectivity, potency, inactivation kinetics and CNS penetration in comparison toibrutinib. GB5121 pharmacodynamic properties were evaluated using both cell-free enzymatic and cell-based functional assays showing nM potency for BTK inhibition and rapid BTK inactivation kinetics (Kinact/Ki) in both peripheral and CNS tissue, a critical parameter for irreversible inhibitors. In a kinome scan, GB5121 exhibited high kinase selectivity against 349 kinases with only TEC/TXK demonstrating >50% inhibition at 1 μM; GB5121 did not inhibit phosphorylation of EGF in a cell-based assay. When compared with other BTK inhibitors, GB5121 showed superior CNS target occupancy using a probe-based ELISA measuring free BTK in the brain of mice receiving 3 daily oral doses. GB5121 also demonstrated significantly higher brain to plasma ratio in mice with an intact blood brain barrier. In non-human primates, a 1:1 brain to plasma concentration ratio was demonstrated for GB5121 for up to 8 hours with both oral (30 mg/kg) and IV (2 mg/kg) doses. Together, these features differentiate GB5121 from both FDA-approved BTK inhibitors, as well as those currently under clinical investigation. Our data supports the use of GB5121 in clinical trials where BTK is a known driver of malignancies, including CNS lymphoma. This research has been previously presented at the AACR Annual Meeting 2022.

BSCI-12
BREAST TO BRAIN METASTASIS IS EXACERBATED WITH CHEMOTHERAPY THROUGH BLOOD-CEREBRAL SPINAL FLUID-BARRIER AND INDUCES ALZHEIMER’S-LIKE PATHOLOGY
Ishu Nautiyal, Belmaa Saatani, Robert Herrera, Vahan Martirosyan, Rachel Eisenbarth, Mukund Iyer, Alex Julien, Allison Lowman, Pete LaViolette, Jan Remski, Adrienne Boire, E Sankey, Peter E Fecci, Mark Shrotri, Frances Chow, Kyle Hurtle, USC, Los Angeles, CA, USA. USAC, Los Angeles, CA, USA. Medical College of Wisconsin, Milwaukee, W, USA. Memorial Sloan Kettering Cancer Center, New York, NY, USA. Duke University, Durham, NC, USA

Control of breast to brain metastasis remains an urgent unmet clinical need. While chemotherapies are essential in reducing systemic tumor burden, they have also shown to promote non-brain metastatic invasiveness and drug-driven neurocognitive deficits through formation of neurofilbrillary tangles (NFT) independently. Now, in this study we investigated the effect of chemotherapy on brain metastatic progression and promoting tumor-mediated NFT. Results show chemotherapies promote increased brain-barrier permeability and facilitate enhanced tumor infiltration, particularly through the blood-cerebrospinal fluid-barrier (BCSB). This is attributed to increased expression of matrix metalloproteinase 9 (MMP9) which, in turn, mediates loss of Claudin-6 within the choroid plexus cells of the BCSFB. Importantly, increased MMP9 activity in the choroid epithelium following chemotherapy clearance in tissue of Tau released from breast cancer cells. This cleaved Tau forms tumor-derived NFT that further destabilize the BCSFB. Our results underline for the first time the importance of the BCSFB as a vulnerable point of entry for brain-seeking tumor cells post-chemotherapy and indicate that tumor cells themselves contribute to Alzheimer’s-like tauopathy.

BSCI-13
DEVELOPMENT OF NOVEL ANTI-BRAIN METASTASIS INHIBITORS
Agga Kielbassa, Daniel Mobillo, Blessing Bassey-Achibong, Jarrod Johnson, Dillon McKenna, Chitra Venugopak, Jakob Magolan, Sheila Singh; McMaster University, Hamilton, ON, Canada

The current standard of care (surgery and radiation) for brain metastases (BM) is inadequate as BM have a 90% mortality rate within one year of diagnosis, posing a large unmet clinical need. The Singh lab has generated a large in-house biobank of patient-derived BM cell lines that are established from BM patient tumor samples. We use these BM cell lines to generate murine orthotopic xenografts of BM and investigate the biological processes that lead to BM. These models have successfully recapitulated all the stages of their respective BM cascades and additionally captured a “pre-metastatic” population of BM cells that have just seeded the brains of mice before forming mature, clinically detectable tumors. Pre-metastatic cell populations are impossible to detect in human patients but represent a therapeutic window wherein metastasizing cells can be targeted and eradicated before establishing clinically detectable and difficult to treat brain tumors. BM rescuing of pre-metastatic BM cells revealed a distinct transcriptomic profile that is specific to pre-metastatic cells despite the origin of tumor. Connectivity Map analysis was applied to the gene expression signatures of pre-metastatic BM cells to identify a compound (Drug A) which selectively inhibits BM cell proliferation but is not blood-brain barrier (BBB) penetrant and has not been previously considered in the context of brain metastasis. We synthesized a BBB-penetrant analogue of Drug A and found, using our patient-derived xenograft (PDX) models, that it increased survival benefit relative to both placebo and Drug A. Beginning with this promising scaffold, we will conduct structure-activity hypothesis-driven medicinal chemistry campaigns to optimize this scaffold for brain permeation while maintaining selective anti-BM activity. Development of novel small molecules that target pre-metastatic BM cells could slow or prevent the formation of BM and dramatically improve the prognosis of at-risk cancer patients.

BSCI-14
THE ROLE OF ICAM1 IN GLOBLASTOMA TUMOUR ASSOCIATED MACROPHAGES UNDER HYPOXIC CONDITIONS
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BACKGROUND: Glioblastoma (GBM) is an aggressive and highly fatal brain cancer in adults. Existing treatment methods are ineffective and we are in need of new treatments that extend the overall survival and improve quality-of-life. Cell adhesion molecules (CAMs) are proteins that enable cells to communicate with one another and the surrounding environment. Intracellular adhesion molecule 1 (ICAM1) is a CAM expressed by TAMs in GBM. Tumour associated macrophages (TAMs) are thought to