ies revealed **BTP-7** as the lead candidate for B/bΔg binding. BTP-7 displayed 260 nanomolar affinity for recombinant B/bΔg protein, and had little association with the fully glycosylated isoform of BCAN. Scrambling of the BTP-7 sequence led to complete abrogation of B/bΔg binding. For *in vivo* evaluation, GBM-6 tumors derived from human patients were established intracranially in nude mice, and tumor formation was verified by MRI. Upon systemic administration, BTP-7 displayed approximately 10x greater binding to GBM-6 tumors than the control, as well as 4x higher tumor uptake compared to normal brain tissue. We are currently working on conjugating BTP-7 to a variety of toxic payload to selectively target gliomas, with the goal of improving brain cancer therapeutic efficacy that can ultimately benefit patient.

DDIS-20. FASN INHIBITION AS A POTENTIAL TREATMENT TO PREVENT METABOLIC ADAPTATION IN GBM

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INTRODUCTION: Response to antiangiogenic therapy (ie bevacizumab) in glioblastoma is mostly transient and without proven survival benefit. Acquired resistance to antiangiogenics is felt to be substantially driven by the hypoxic microenvironment. **METHODS:** Tumor and matching sera from 12 patients having failed bevacizumab was performed by LCMS and NMR. Patient derived GBM neurosphere cultures were established using previously described methods and exposed to fatty acid synthase (FASN) inhibitor TVB-3166 at varying concentration in the presence of 20% or 2% oxygen. **RESULTS:** Evaluation of metabolic profiles from serum and tumor showed significant changes of number of fatty acids (including tricosanoic acid, carboceric acid, phosphatidylinositol 20:4, nonacosanoic acid, n-palmitoyl valine, ceramide 18:1/12:20), which was correlated with degree of hypoxic change. Continuous incubation in the presence of 200–800 nM TVB-3166 for 7–14 days leads to dose dependent inhibition of neurospheres formation and tumor cell death of patient derived GBM short term cultures. Given these findings, a pilot phase 2 study which evaluate the potential effectiveness and safety of TVB-2640 in combination with bevacizumab for patients with relapsed high-grade glioblastoma. This study will include an exploratory phase where patients will be randomized to either antiangiogenic therapy alone with bevacizumab, or the combination of bevacizumab and TVB-2640 for the first 28 days followed serum sampling and MRI. **CONCLUSION:** Fatty acid synthase inhibition is a potential strategy to overcome metabolic adaptation to antiangiogenics which will be explored in a recently initiated phase 2 study.

DDIS-21. APPLICATION OF A FUNCTIONAL GENETICS APPROACH TO IDENTIFY PHARMACOLOGICAL INHIBITORS OF HIF-1α

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Two phase III clinical trials with temozolomide (TMZ) in combination with bevacizumab for newly diagnosed glioblastoma multiforme (GBM) failed to demonstrate any survival benefit when compared to TMZ alone. Previous studies have shown that bevacizumab treatment increases intratumoral hypoxia followed by up-regulation of hypoxia-inducible factor 1 alpha (HIF-1α), a key mediator of tumor cell survival under hypoxic conditions. As such, inhibition of HIF-1α might be a promising therapeutic strategy in GBM. The aim of this study was to identify new pharmacological inhibitors of HIF-1α by combining functional genomics data with the Connectivity Map (cMap) database. First, a genome-wide lentiviral short hairpin RNA (shRNA) synthetic lethality screen was performed using a pool of 27,290 shRNAs targeting 5,046 known human genes to identify genes essential for GBM cell survival under hypoxia. The cMap database was subsequently interrogated using these results to identify drugs that would induce corresponding changes in gene expression. By applying this approach, we identified albendazole (ABZ), a widely used anti-helmintic drug, as a potent inhibitor of HIF-1α. ABZ treatment of GBM cells induced a broad-spectrum down-regulation of pro-angiogenic-factors, such as vascular endothelial growth factor (VEGF). Furthermore, ABZ induced a G2/M cell cycle arrest followed by apoptotic cell death. Mechanistically, we showed that ABZ disrupts microtubule polymerization leading to impaired translation of HIF-1α mRNA. The therapeutic potential of ABZ and concomitant bevacizumab is currently being assessed in vivo and the data will be presented. In conclusion, ABZ is a potent pharmacological inhibitor of HIF-1α. Considering that HIF-1α is a key mediator of resistance to anti-angiogenic therapy, a combined approach with ABZ and bevacizumab might be a promising treatment strategy for GBM patients.

DDIS-22. ANTI-DEPRESSANT, SSRI IDENTIFIED BY DRUG REPOSITIONING SYSTEM, BLOCKED GLIOBLASTOMA INVASION WITH TARGETING TO INHIBIT ACTIN POLYMERIZATION

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Invasion of Glioblastoma (GBM) cells into normal brain is the major cause of poor prognosis and requires dynamic reorganization of the actin cytoskeleton, which includes lamellipodial protrusions, focal adhesions, and stress fibers at the leading edge of GBM cells. Therefore, we hypothesized that inhibitors of actin polymerization can suppress GBM migration and invasion. We adopted a drug repositioning system for screening with a pyrene-actin-based actin polymerization assay and identified fluvoxamine, a clinically used antidepressant. Fluvoxamine, selective serotonin reuptake inhibitor, was a potent inhibitor of actin polymerization and confirmed as drug penetration through the blood–brain barrier (BBB) and accumulation of whole brain including brain tumor with no drug toxicity. Fluvoxamine inhibited serum-induced ruffle formation, cell migration, and invasion of human GBM and glioma stem cells *in vitro* by suppressing FAK signaling. Fluvoxamine showed no drug toxicity. Daily treatment of athymic mice bearing human glioma-initiating cells with fluvoxamine blocked tumor cell invasion and prolonged the survival with almost same doze of anti-depressant effect. In conclusion, Fluvoxamine is a promising anti-invasive treatment against GBM with reliable approach. Key words, glioma, invasion, actin-polymerization, SSRI, Drug repositioning

DDIS-23. A COMBINATORIAL TREATMENT USING A CK2 INHIBITOR, CX-4945, AND TMZ DECREASED MEDULLOBLASTOMA TUMORIGENESIS

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Medulloblastoma (MB) is the most common malignant pediatric brain tumor. While surgery, craniospinal irradiation, and chemotherapy have resulted in a cure rate of 70–75%, the surviving patients are afflicted with neurocognitive impairment, endocrine dysfunction, and a severe decrease in quality of life. Consequently, better and more effective treatments are needed to treat these young patients. Casein kinase 2 (CK2) is an intriguing therapeutic target for MB because it is dysregulated in all the MB molecular subgroups and patients with high CK2 expression have a significantly worse prognosis. To elucidate the role of CK2 in MB we transduced multiple MB cell lines with CK2 isoforms. We discovered that a CK2 isoform, CK2alpha, increased MB tumorigenesis in both the SHH and Grade 3 molecular subgroups, while knocking down its expression ameliorated MB growth. We also found that CK2 can regulate MB tumorigenesis through beta-catenin and potentially GLI1. We extended our analysis to a CK2 inhibitor, CX-4945, which is currently undergoing phase I/II clinical trials. Treatment with CX-4945 reduced MB cell growth and tumor growth in mice that were intracranially injected with MB cells. Consistent with previous research we found that CX-4945 specifically inhibited CK2 and has the ability to cross the blood-brain-barrier. Treatment with CX-4945 also reduced expression of MGMT, a well-known regulator of temozolomide (TMZ) efficacy. Combinatorial treatments with CX-4945 and TMZ had a synergistic effect on MB tumor reduction. Our findings were corroborated when we screened 4,000 FDA approved compounds to identify molecules that work synergistically with CX-4945. TMZ was one of the major compounds that were identified in the screen suggesting that CX-4945 treatment can sensitize MB cells to TMZ by dysregulating MGMT. Together, our findings suggest that CK2 is a novel MB therapeutic target and combining CX-4945 and TMZ can lead to a promising new MB therapy.

DRUG RESISTANCE

DRES-01. ROLE OF HISTONE LYSINE DEMETHYLASE KDM2B IN GLIOBLASTOMA TUMOR CELL MAINTENANCE AND CHEMORESISTANCE

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Glioblastoma (GBM) is the most deadly and malignant of all brain tumors in adults partly due to acquired resistance to conventional drugs leading to recurrence. Emerging evidence indicate that aberrant expression of epigenetic enzymes, resulting in altered gene transcription, may be responsible for cell maintenance and drug resistance in several cancers including GBM.