

brain tumor burden in vivo. These data offers compelling evidence that BiTE-mediated cytotoxicity against treatment-resistant CD133+ GBMs could provide a very potent, specific and can be a novel therapeutic strategy for GBM patients.

**PS2 – 174**

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**Hexokinase 2 Drives Radio-Resistance through ERK Signaling and Sensitizes Cells to Azole Compounds**

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Our ongoing work has demonstrated that hexokinase 2 (HK2) but not HK1 or HK3 is a critical mediator of tumour glycolysis and mitochondrial metabolism in Glioblastoma (GB). Furthermore, HK2 is highly expressed in GB but not in normal brain making it an attractive therapeutic target. Our current findings now support that loss of HK2 alters tumor vasculature, increases sensitivity to radiation, and confers a significant survival benefit in several GB xenograft-bearing mice. Using a genome wide transcript analysis, we identified that loss of HK2 attenuates several pro-growth signaling pathways in GB including ERK signaling. Mechanistically, ERK rescue experiments in HK2 depleted cells rescues cell sensitivity to radiation and reduces DNA damage. Furthermore using a systems biology approach and a rationale drug screen we identified several antifungal agents in the azole class as to inhibit tumor metabolism and growth in HK2 expressing GB cells. Loss of HK2 in GB cells dampened the effect of several azoles suggesting that the mechanism of action is mediated in part through HK2. Furthermore, we tested several azole compounds known to cross the blood brain barrier in vivo. Clinically achievable doses of azoles as single agents increased survival in several orthotopic xenograft GB mouse models. In summary, HK2 drives several oncogenic pathways associated with GB including ERK signaling and sensitizes tumour cells to the azole class of antifungals. Future work will determine whether azoles work synergistically with radiation and temozolomide and elucidate the mechanisms by which they inhibit GB growth in HK2 expressing cells.

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**Brevican-Specific Peptides for the Development of Next-Generation Targeted Theranostics for High Grade Gliomas**

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High-grade gliomas are deadly cancers, and current standard-of-care has demonstrated limited success. The ability to specifically target glioma cells can allow for the development of improved theranostic agents leading to better detection methods, as well as safer anti-cancer therapies. Brevican (Bcan), a CNS-specific protein is upregulated in glioma cells and correlates with tumor

progression. Particularly, a Bcan isoform lacking normal glycosylation, called B/bDg is a unique glioma marker and is not expressed in non-cancerous tissues. Therefore, B/bDg represents a valuable target for anti-cancer strategies. We describe here the discovery of novel high-affinity B/bDg-targeted peptides using rapid combinatorial library screening approaches and a microfluidic sorting device of our own design. Briefly, a one-bead-one-compound (OBOC) peptide library was screened against small magnetic particles decorated with B/bDg. Positive “hit” beads labeled with magnetic particles were isolated using an inexpensive but yet, accurate and high-throughput in-house microfluidic magnetic-activated sorter. These hits were exposed to cells expressing B/bDg, and beads with the highest cell association were isolated and sequenced. Seven novel peptides were identified. Cell uptake analyses and blocking studies revealed that 5 of these peptides displayed specific uptake in B/bDg-overexpressing cells. These candidates displayed nano-/micromolar binding affinity for recombinant B/bDg protein. Further analyses of these candidates using confocal microscopy revealed increased peptide binding/uptake in patient-derived glioma stem cells (GSCs) compared with primary human astrocytes. We plan to incorporate these onto multi-functional BBB-penetrating nanoparticles loaded with imaging agents or a drug payload to translate them into highly selective and efficacious brain cancer theranostic agents.

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**Bcl-2 Family Member Mcl-1 Expression is Reduced Under Hypoxia by the E3 Ligase FBW7 Contributing to BNIP3 Induced Cell Death In Glioma Cells**

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Mcl-1 is an anti-apoptotic Bcl-2 family member that is often over-expressed in the malignant brain tumour glioblastoma (GBM). It has been previously shown that epidermal growth factor receptors (EGFR) up-regulate Mcl-1 expression contributing to a cell survival response. Hypoxia is a poor prognostic marker in glioblastoma despite the fact that hypoxic regions have areas of necrosis. Hypoxic regions of GBM also highly express the pro-cell death Bcl-2 family member BNIP3, yet when BNIP3 is over-expressed in glioma cells, it induces cell death. The reasons for this discrepancy are unclear. METHODS: Using malignant glioma cell lines +/- hypoxia, gain and/or loss of function assays of BNIP3 or Mcl-1 were performed. BNIP3 and MCL-1 expression was assessed in GBM tumours from adult patients and human gliomas grown as xenografts in immunocompromised mice. RESULTS: Mcl-1 expression is reduced under hypoxia due to degradation by the E3 ligase FBW7 leading to increased hypoxia-induced cell death. This cell death is augmented by EGFR activation leading to increased Mcl-1 expression under hypoxia. Conversely, BNIP3 is over-expressed in hypoxia at times when Mcl-1 expression is decreased. Knocking down BNIP3 expression reduces hypoxia cell death and Mcl-1 expression effectively blocks BNIP3-induced cell death. Of significance, BNIP3 and Mcl-1 are co-localized under hypoxia in glioma cells, GBM tumours and in xenograft glioma tumours expressing mutant EGFR (EGFRvIII). CONCLUSION: These results support that Mcl-1 can block the ability of BNIP3 to induce cell death under hypoxia in GBM tumours