in vivo, with no observable weight loss nor neurological deficits. Significant positive survival benefits from PLGA/PEG/TMZ/ETOP/therapy were observed in vivo compared to surgery alone, surgery with blank paste (49 vs. 14 days; p < 0.001) or oral TMZ (49 vs. 14 days; p < 0.001). These results suggest that S1P3-mediated permeabilization of BTB and enhancement of chemotherapeutic efficacy.

SCDT-13. PHASE I CLINICAL TRIAL ON SYSTEMIC PD-1 BLOCKADE IN COMBINATION WITH DIRECT INTRA-TUMORAL INJECTION OF CTLA-4/PD-1 IMMUNE CHECKPOINT INHIBITION FOLLOWING RESECTION OF RECURRENT GLOBLASTOMA

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Recurrent glioblastoma is a devastating disease for which no treatment has demonstrated to improve overall survival in a randomized clinical trial. Anti-tumor Cytotoxic T-cell ( CTL) activity is suppressed by the CTLA-4 and PD-1 immune-checkpoint receptors. Nivolumab (NIVO) is an IgG-4 mAb that blocks PD-1, and ipilimumab (IP) an IgG-1 mAb that blocks CTLA-4. In a clinical trial for recurrent glioblastoma (BMS CheckMate143), combination of NIVO and IP administered IV caused unacceptable toxicity. Animal and phase I clinical administration of NIVO at a ratio of [1:100] compared to IV-dosing had equivalent anti-tumor effect and was associated with improved tolerability. An ongoing phase I clinical trial for patients with recurrent glioblastoma (rGB) has recently recruited 5 patients, 3M, 2F, median age 60 (range 59-72). Study treatment consists of surgical resection of rGB with injection of IP (10mg:2ml) (cohort 1 = first 3 patients) or NIVO (10mg:1ml) (cohort 2 = 2 patients at present) in the walls of the resection cavity, concomitant with in vivo intratumoral administration of 10 mg of NIVO x6. Grade 3 AE consisted of epileptic seizures (1pt in cohort 2) and hemiplegia due to accumulation of serosanguinous fluid in the resection cavity (1pt in cohort 2). Additionally, 4/5 patients developed transient grade 1 pyrexia during the postoperative period (NIVO). Lympohocytosis up to 3 x 109/L was seen in 4/5 patients. All patients have persisting rim-enhancement on MRI. After 4 weeks, two patients have progression of disease (after respectively 13 and 19 weeks). All patients are alive. We conclude from these early results that surgical resection of rGB combined with direct intracerebral injection of IP alone/with NIVO followed by IV administration of NIVO at the doses administered in this trial is feasible and safe. Updated results of this ongoing clinical trial will be presented at the meeting.

SCDT-14. PAM-OBG: A MOAB SENSITIVE PRODRUG INHIBITOR OF MGMT POTENTIATES CHEMORADIOTHERAPY

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We have developed a prodrug version of the MGMT inhibitor, O\textsubscript{2}-benzylguanine, PAM-OBG. This prodrug is inert toward MGMT until oxidized by the enzyme MAOA. MAOA is highly elevated in glioma, and levels correlate with poor patient outcome, but is completely absent in human bone marrow. An examination of the enzyme kinetics of human recombinant MAOA and MAOB shows that PAM-OBG is only a good substrate for the latter. PAM-OBG has a K\textsubscript{M} of only 200 µM with respect to MAOA, whereas the K\textsubscript{M} is 575 µM for MAOB. PAM-OBG maturation, which gives rise to O\textsubscript{2}-benzylglycine, is therefore specific toward MAOB, with insignificant reactivity toward MAOA. The gliom MAOB maturation of the prodrug into the active MGMT inhibitor, O\textsubscript{2}-benzylguanine, can be observed in vitro and in vivo, using intracranial mouse models of primary glioblastoma multiforme. We have potentiated the anti-GMB activity of DNA alkylating chemotherapeutics Carmustine and Lomustine by six-fold via the pre-administration of PAM-OBG into animals (rat, mouse). This study suggests in vivo tumor selectivity of PAM-OBG. We have also demonstrated that PAM-OBG combined with direct intracerebral radiation in intracranial mouse models of glioma. Thus, we demonstrate that in addition to its use as an adjuvant in salvage therapy with alkylating agents PAM-OBG may also prove to be highly efficacious in the treatment of GBM alongside SUTT protocol as standard chemoradiation therapy.
cells bearing a targeted surface epitope, in vitro and in vivo. The nanovector is made from a hydrophobic, oxidized graphene core, with polyethylene glycol (PEG) tendrils attached via amide bonds. This targeted nanovector is unstable in blood, and has a large intracellular payload of hydrophobic drugs/dyes. Targeting the nanovectors toward specific epitopes is achieved by covalently linking targeting peptides to the PEG terminals, using peptides selected from phage-display libraries. The nanovector integrates into the clathrin-coated vesicle endosomal pathway, internalizing the nanovector into endosomes. When drugs such as doxorubicin are loaded into nanovectors, we observe internal transfer into cellular plasma/endosomal membranes, followed by diffusion into the cytosol and then the nucleus.

In intracranial mouse models of glioma, when drugs are loaded into EFRG-targeted nanovectors, we observe both enhanced efficacy of chemotherapeutics and lower off-target toxicity.

In GBM, highly effective chemotherapeutics such as Vinblastine and Doxorubicin are seldom used clinically because of their off-target toxicity. When comparing native and nanovector-loaded chemotherapy in an aggressive intracranial glioma mouse model we observe a huge enhancement (>7-fold) in animal survival, and a lower off-target toxicity. 85% of vinblastine and 90% of doxorubicin treated animals out survived the empty vector controls by more than a year.

SCDT-16. ENHANCING THE EFFICACY OF CHEMOTHERAPY BY FOCUSED ULTRASOUND MEDIATED SONOCHEMICAL INTERNALIZATION (SCI) Henry Hirschberg1; 2 and Steven Madtes1; 2 Beckman laser Institute, Irvine, CA, USA, 1. 2 UNLV, Las Vegas NV, USA Systemically administered chemotherapeutic agents are, firstly limited by their inability to penetrate across the blood brain barrier (BBB). Site-specific disruption of the BBB using focused ultrasound (FUS) has been demonstrated in experimental animal glioma models and in a small number of patients. Secondly, many highly effective chemotherapeutic agents are large and hydrophobic and are actively transferred into tumor cells by endocytosis. Their poor ability to escape from the resulting intracellular endosomes leads to their inactivation via lysosomal-endosome fusion. Activation of sonosensitizers via focused ultrasound (FUS), i.e. sonodynamic therapy (SDT) has been proposed as an extension to light activated photodynamic therapy for the treatment of brain as well as other tumors. The use of focused FUS, as opposed to light, allows treatment to tumor sites buried deep within tissues as well as through the intact skull. We have examined ultrasonic activation of sonosensitizers to enhance the efficacy of the anti-cancer agent bleomycin (BD). The coapplication of sonosensitizers drug and FUS is termed sonochemical internalization (SCI), as an extension of light based photochemical internalization (PCI). SCI is a technique which utilizes FUS for the enhanced delivery of endo-lysosomal trapped macromolecules into the cell cytoplasm. The released agents thus exert their full therapeutic potential, as opposed to being degraded by lysosomal hydrolases. Our results indicate that, compared to drug or FUS treatment alone, FUS activation of the sonosensitizer AlPcS2a together with BLM significantly inhibits glioma growth. SCI is a promising new technology that, like PCI, may potentiate the efficacy of a wide variety of therapeutic compounds. However, unlike PCI, SCI is not limited by the poor tissue penetration inherent to light-based approaches and, as such, this ultrasound-based technology is ideally suited for the treatment of deep seated or intracranial lesions like gliomas.

SCDT-17. DECREASED OPERATIVE COMPLICATIONS WITH IMAGE-GUIDED OMMAYA RESERVOIR INSERTION: SYSTEMATIC REVIEW AND META-ANALYSIS Jonathan Lau1, 2, Suzanne Kostenuik1, Tom Walker1, Alla Iansavichene1, 4, David Macdonald1, 4, and Joseph Meyers1, 5; 1 London Health Sciences Centre, Western University, London, ON, Canada, 2 Imaging Research Laboratories, Robarts Research Institute, Western University, London, ON, Canada, 3 London Regional Cancer Program, London, ON, Canada OBJECTIVE: One of the classic technologies facilitating therapeutic drug delivery to the central nervous system (CNS) is the Ommaya reservoir. Subcutaneous Ommaya reservoir insertion (ORI) has been available as a treatment option for targeted intraventricular pharmacotherapy since the 1960’s. The percutaneous catheter has conventionally been inserted freestanding. However, advancements in image-guidance (IG) over the past two decades has enabled IG-ORI as a viable, and arguably preferred, alternative to blind insertion. In this study, we sought to compile evidence from the literature about surgical outcome in ORI to assess the impact of IG on safety and efficacy. METHODS: A systematic review and meta-analysis of operative outcomes from ORI was performed using Medline and Embase databases in compliance with standard guidelines. Patient demographics, surgical details, and peri-operative outcomes (hemorrhage, infection, malposition, malfunction, mortality, overall morbidity) were extracted from the full text of included articles. Study quality was assessed via MINORS criteria. Random effects and heterogeneity analysis were performed. RESULTS: 45 studies met study criteria, for a total of 2075 independent ORIs. Pooled IG ORI versus non-IG ORI was associated with lower overall complications: 2.1% compared to 2.9% for catheter malfunction; 1.7% compared to 3.0% for catheter malposition; 0.8% compared to 4.2% for early post-operative infection; 0.4% compared to 1.4% for mortality. Interestingly, post-operative hemorrhage was increased at 3.8% compared to 2.3%. There was an overall trend towards decreased complications with date of publication (Pearson correlation = -0.606). The reported analyses all met the threshold for statistical significance (p-value < 0.05). CONCLUSION: IG was associated with decreased overall complication, catheter malfunction/malposition, and early post-operative infection but increased hemorrhage rates are likely the result of increased routine post-operative imaging concurrent with the IG era. Although the overall quality of evidence is low, this meta-analysis provides objective support for IG-ORI.

SCDT-18. EXPRESSION OF ABC TRANSPORTERS AS PROGNOSTIC BIOMARKERS FOR GLOBLASTOMA Laurent Guiver Bay; Myriam Lemelin, Marie-Belle Poirier, Marie Blanchette, and David Fortin; Université de Sherbrooke, Sherbrooke, QC, Canada INTRODUCTION. Glioblastoma (GBM) is the most common and aggressive malignant primary brain tumour in adults. Standard therapy, consisting in surgery followed by concomitant radio- and chemotherapy, only offers palliative benefits. Indeed, recurrence is inevitable and this disease remains incurable with a median survival of 14 months. We hypothesized that the chemoresistant phenotype of GBM is supported by their expression of several efflux pumps (ABC transporters). We thus hypothesized that gene expression of these transporters could correlate with patients clinical surrogates such as overall survival and progression-free survival (PFS).

We investigated the expression of ABCB1, ABCG1, ABCG2 and ABCG2 by qPCR in 159 GBM specimens collected during surgery and 22 non-tumoral brain tissue. With the exception of ABCB1, all three efflux pumps were significantly overexpressed in GBM. While ABCB1 had no effect on clinical surrogates, ABCG1 and ABCG2 expression correlated with drastically shorter overall survival (OS) and progression-free survival (PFS) in newly diagnosed patients. Moreover, our multivariate analysis showed that patients with high and moderate levels of ABCG2 had a considerably poorer prognosis than patients with low expressing tumours (hazard ratio [95% CI]: 2.424 [1.340 - 4.531]; p<0.001). However, in recurrent tumours, these transporters showed no correlation with clinical outcome. Interestingly, high ABCG2 expression correlated with better prognosis in both newly diagnosed and recurrent tumours (hazard ratio for high vs. low [95% CI]: 0.323 [0.207-0.598]; p=0.044). CONCLUSION. This study shows that ABCB1, ABCG1 and ABCG2 transporters are upregulated in GBM tumours. Moreover, our data suggest that expression of these efflux pumps could be quantified upon diagnosis and serve as prognostic markers for GBM. Therefore, we truly feel that ABCG1, ABCG2 and ABCG2 expression levels could be used to influence treatment and clinical management of patients.

SCDT-19. DELIVERY OF ISPINESIB IS LIMITED BY EFFLUX TRANSPORT AT THE BLOOD-BRAIN BARRIER (BBB) Gaurahm Gampa1, James Crish2, Karen Parrish3, Nicholas Cook-Rostie3, Minjoo Kim1, Janice Laramy1, Steven Rosenfeld2, and William Elmore3; 1 University of Minnesota, Minneapolis MN, USA, 2 Mayo Clinic, Jacksonville FL, USA, 3 Cleveland Clinic, Cleveland OH, USA PURPOSE: A challenge in developing therapies for GBM is the inability of drugs to cross the BBB. Ispinesib, an inhibitor of kinesin spindle protein, has potent anti-cancer activity by causing mitotic arrest and growth inhibition. The objective was to determine the distribution of ispinesib across the BBB, and determine transporters for ispinesib. METHODS: Brain distribution studies were conducted in FVB wild-type (WT), triple-knockout (TKO; Mdr1a/b(-/-) Bcrp1(-/-)), and P-gp knockout (PKO; Mdr1a/b(-/-) and Bcrp knockout (BKO; Bcrp1(-/-)) mice. In a separate study, WT mice administered with and without elacridar (n=5) were co-administered with ispinesib. The released agent can therefore exert its full biological activity, in contrast to drug or FUS treatment alone, FUS activation of the sonosensitizer AlPcS2a together with BLM significantly inhibits glioma growth. SCI is a promising new technology that, like PCI, may potentiate the efficacy of a wide variety of therapeutic compounds. However, unlike PCI, SCI is not limited by the poor tissue penetration inherent to light-based approaches and, as such, this ultrasound-based technology is ideally suited for the treatment of deep seated or intracranial lesions like gliomas.

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