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Glioblastoma multiforme (GBM) is the deadliest brain tumor with an approximate 14 month survival rate after diagnosis and treatment. Temozolomide (TMZ), the chemotherapeutic drug of choice for GBM, is an alkylating agent that causes DNA damage. TMZ treatment results in the induction of apoptosis in GBM cells, however, it induces autophagy and consequently chemoresistance. Statins are mevalonate (MEV) cascade inhibitors with beneficial effects on the enhancement of the survival rate of patients with different types of cancer. Here, we determined the effect of simvastatin (Simva), a blood brain barrier permeable statin, on the sensitization of GBM cells to TMZ induced apoptosis through inhibition of autophagy flux. We pretreated two GMB cell lines, U251 and U87 cells, with low doses of Simva (1 and 2.5 M, respectively) with or without different intermediates of the mevalonate cascade and then treated cells with TMZ (100 M) for 48-96 hrs. A signficiantly reduced viability and increased in the population of apoptotic dead cells were observed in GBM cells treated with the Simva-TMZ compared to cells treated with TMZ alone. Addition of MEV, Farnesyl pyrophosphate, Geranylgeranyl pyrophosphate and cholesterol did not attenuate these effects significantly. Sima-TMZ treatment did not alter the total cholesterol pool in U87 and U251 cells compared to controls. Western blot analysis, immunocytochemistry and transmission electron microscopy revealed that Simva-TMZ inhibited autophagic flux. Overall, the results suggest that sensitization of GBM cells to TMZ-induced apoptosis by Simva is independent on the cholesterol biosynthetic pathway but may involve inhibition of autophagy.

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Toca 5: Toca 511 combined with Toca FC versus standard of care in patients undergoing planned resection for recurrent glioblastoma or anaplastic astrocytoma

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Toca 511 (vocimagene amiretrorepvec) is an investigational, conditionally lytic, retroviral replicating vector (RRV). RRVs selectively infect cancer cells due to innate and adaptive immune response defects in cancers that allow virus replication, and the requirement for cell division for virus integration into the genome. Toca 511 spreads through tumors, stably delivering an optimized yeast cytosine deaminase gene that converts the prodrug Toca FC (investigational, extended-release 5-FC) into 5-FU within the tumor microenvironment. 5-FU kills infected dividing cancer cells and surrounding tumor, myeloid derived suppressor cells, and tumor associated macrophages, resulting in long-term tumor immunity in preclinical models. Data from a Phase 1 resection trial showed six durable CRs and extended mOS compared to historical controls. The FDA granted Breakthrough Therapy Designation for Toca 511 & Toca FC in the treatment of patients with rHGG. Toca 5 is an international, randomized, open-label Phase 3 trial (NCT02414165) of Toca 511 & Toca FC versus SOC in patients undergoing resection for first or second recurrence of rHGG. Patients will be stratified by IDH1 status, KPS, and geographic region. Primary endpoint is OS, and secondary endpoints are durable response rate, durable clinical benefit rate, duration of durable response, and 12-month survival rate. Key inclusion criteria are histologically proven GBM or AA, tumor size ≥1cm and ≤5cm, and KPS ≥70. Immune monitoring and molecular profiling will be performed. Approximately 380 patients will be randomized. An IDMC is commissioned to review the safety and efficacy data which includes 2 interim analyses. Enrollment is ongoing.

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Study of Polynucleotide Kinase/Phosphatase (PNKP) Mutations Found in a Patient with Microcephaly, Seizures, and Developmental Delay (MCSZ) and Glioblastoma

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The enzyme polynucleotide kinase/phosphatase (PNKP) plays a key role in DNA repair by resolving the chemistry at DNA strand breaks. Mutations in PNKP (chromosome 19q13.4) are known to cause MCSZ, a serious neurodevelopmental disorder, but to date there has been no link to cancer initiation or progression. However, a child with MCSZ recently presented at Seattle Children's Hospital with a 3-cm glioblastoma. The child was shown to have two germline mutations in PNKP. To study the effects of the PNKP mutations found in this patient, we generated mutant PNKP cDNAs carrying either the individual mutations or the double mutation using site directed mutagenesis. These cDNAs were incorporated into bacterial and mammalian expression vectors. The bacterially expressed mutant proteins as well as the wild type have been purified and are undergoing testing for PNKP DNA kinase and phosphatase activity. The PNKP cDNAs, fused to GFP, were expressed in Hela and HCT116 human cancer cell lines. High-content analysis and micro-irradiation techniques are being used to determine PNKP localization within the cells and recruitment to damaged DNA. Our preliminary results indicate that the mutations alter the ratio of nuclear to cytoplasmic PNKP compared to the wild-type protein.

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The potential role of exercise in the supportive care of neurological cancer survivors: delivering effective and appropriate programming through the Alberta cancer exercise (ACE) study

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BACKGROUND: Exercise has been shown to benefit health-related fitness, psychosocial health, and disease outcomes in cancer survivors. PURPOSE: To review the evidence on exercise for individuals diagnosed with Neurological Cancer (NC); present data on NC participants in the ACE pilot and ongoing implementation study; and propose a framework to incorporate exercise into the

care of NC survivors in Alberta. METHODS: The ACE program is open to survivors with any cancer diagnosis at any stage of treatment. Exercise programming consists of two training sessions per week, with the pilot and implementation studies being 8 and 12 weeks in duration respectively. Outcomes are assessed at study baseline, post-exercise intervention, and 24-week follow-up, and include recruitment and follow-up rates, health-related fitness, psychosocial outcomes, and cancer symptoms. RESULTS: NC survivors represented 7 of 80 participants in the ACE pilot; however, only 3 of the 7 (43%) completed the study. Findings suggested a need for consideration of supervised exercise for some survivors with NC. To date, 14 NC survivors have enrolled in the ACE implementation study. Participants are screened and then referred to either supervised clinic-based or community-based exercise. Seven of 9 participants have completed the ACE intervention, and 5 of 5 have completed the 24-week follow-up. NC participants improved or maintained health-related physical fitness, and reported reduced symptom burden and fatigue. CONCLUSION: Preliminary results suggest exercise training is feasible and beneficial for NC survivors. To optimize recruitment and outcomes, efforts are needed to better identify, screen, and refer survivors to appropriate exercise programming.

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Combining an oncolytic vaccinia virus with image-guided radiotherapy: a multi-modal therapeutic approach for treating glioma

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Malignant gliomas (MG) are highly invasive and aggressive brain tumors. Despite the current standard of care, the prognosis for patients with MG is abysmal– highlighting the need for novel, more effective treatment options to combat this aggressive disease. Oncolytic virus (OV) therapy is an advancing treatment option that harnesses tumor-selective viruses to kill cancer cells while simultaneously facilitating a systemic anti-tumor immune response. Many studies have noted synergistic effects when OV"s are combined with radiotherapy in preclinical cancer models, warranting further investigation of this multi-modal approach. Image-guided radiotherapy (IGRT) uses computer-modulated imaging techniques to precisely deliver ionizing radiation to treat cancer. Despite the precision IGRT offers, cancer cells can still be „missed" due to tumor microextensions or radioresistant cell populations– such as glioma stem cells or therapy-induced senescent cancer cells –and may contribute to recurrence or progression. Here we propose to combine our mCherry-tagged mutant vaccinia virus (deltaF4L-deltaJ2R-mCherry), which exhibits tumor-selectivity due to mutations in key viral nucleotide biosynthesis genes, with IGRT executed using state-of-the-art Small Animal Radiation Research Platform (SARRP) technology. We hypothesize that combining deltaF4L-deltaJ2R-mCherry with IGRT will produce better tumor control than either modality alone, by generating additive or synergistic effects in which IGRT destroys the majority of the tumor mass while our OV seeks out and targets any remaining cancer cells that have been missed or are resistant to radiotherapy.

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Tailored exercise for survivors with brain tumours: A case series

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Purpose: Exercise has been shown to be beneficial for the physical and psychological health of cancer survivors, however, little research has been conducted on the effects of exercise in the brain tumour population. Survivors with brain tumours present with unique challenges in terms of mobility and function that may compromise their ability to safety take part in community-based exercise. Methods: Three survivors with primary brain tumours will be profiled in this case series presentation. Participants were screened using a cancer specific intake questionnaire and the Physical Activity Readiness Questionnaire, and triaged to supervised clinic-based or community-based exercise. All participants completed the 12-week intervention for the Alberta Cancer Exercise (ACE) study. Measurements were taken at baseline, and post-intervention including measures of body composition, aerobic fitness, musculoskeletal fitness, balance and flexibility. Self-reported measures included questionnaires to assess impact on physical functioning, symptoms and quality of life, and to evaluate satisfaction with programming. Results: One participant was referred to supervised clinic-based exercise programming due to a high risk of falls, and two participants were deemed safe and approved for community-based supported exercise programming at a preferred location closer to their home. Preliminary results suggest high program satisfaction, maintenance and/or benefit of physical fitness, balance, and symptom control. Conclusions: Further efforts are needed to better tailor programming to the needs of the survivor and consideration given to the advantages of the supervised clinic-based environment when compared to the survivor preference for a "closer to home" community-based setting.

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Autophagy related metals in IDH1 mutant glioma: Chloroquine and TMZ as a potential novel strategy to treat IDH1 mt gliomas

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Glioblastoma is considered among the most aggressive cancers, dismal prognosis and overall survival is only 14 months, 80% of primary low grade gliomas and seccondary GBMs that progress from low grade to grade II or III WHO classification have isocitrate dehydrogenase, (IDH1) or IDH2, mutations [1]. IDH1 mutant glioma is characterized by impaired glycolysis activity resulting in an abnormal production of 2-hydroxyglutarate (2-HG) [2] resulting in an undifferentiated phenotype with permanent hyper-methylation status and enhanced proliferation and invasion[3]. Interestingly, the IDH1 mutant phenotype of U87MG glioma cells shows resistance to autophagy induced cell death even in starving and low oxygen conditions [4]. Recent evidence has demonstrated increased autophagy activity on IDH1 mt cytotoxic