

S. Shojaei, J. Alizadeh, J. Thliveris, N. Koleini, E. Kardami, G.M. Hatch, Fr. Xu, S. Hombach-Klonisch, T. Klonisch, S. Ghavami.
shahla.shojaei@umanitoba.ca

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 GBM 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 significantly 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. Simva-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

Zadeh G, Walbert T, Perry J, Zhu J, Salacz M, Bota D, Kim L, Iwamoto F, Petrecca K, Sully S, Montellano T, Kheoh T, Das A, Cloughesy TF. tmontellano@tocagen.com

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-FU) 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 ≥ 1 cm and ≤ 5 cm, 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

Mr. Bingcheng Jiang, Dr. Chibawanye I. Ene, Dr. Bonnie Cole, Dr. Jeff Ojemann, Dr. Sarah Leary, Mr. Mesfin Fanta, Mr. Sudip Subedi, Dr. Michael Weinfeld. bj@ualberta.ca

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

C.M. Sellar, R.A. Spsychka, T. Williamson, S.N. Culos-Reed, M.L. McNeely. csellar@ualberta.ca

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