cytosine methyltransferase. Human NSUN5 is located in chromosome 7 and is completely deleted in the Williams-Beurren syndrome, a complex neurodevelopmental disorder. However, RNA targets of NSUN5 in mammals and its role in cancer are unknown. The objective of this project is to determine whether elevated NSUN5 changes rRNA methylation pattern and thereby leads to pro-tumorigenic translational reprogramming and pro-tumorigenic phenotypes in glioblastoma. Western blotting showed that NSUN5 is expressed in 7 out of 9 established glioblastoma cell lines and in 8 out of 12 primary patient-derived glioblastoma cell lines. Bisulfite sequencing confirmed that NSUN5 methylates C3782 of human 28S rRNA in glioblastoma cells. Functionally, overexpression of NSUN5 increases, whereas NSUN5 knockout decreases global protein synthesis and sphere formation in glioblastoma cells. More importantly, mice bearing intracranial NSUN5-expressing U87 tumors survived for a shorter time than mice bearing tumors derived from U87 control cells. Our results suggest that NSUN5 methylates 28S rRNA and may enhance cancer stem cell phenotypes and tumor formation and/or progression in glioblastoma. Experiments are ongoing to determine whether NSUN5 promotes tumor formation and/or progression through translational reprogramming in glioblastoma. This study may help identify novel therapeutic targets for glioblastoma.

**62**

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**Improvement of hearing with bevacizumab in a patient with neurofibromatosis type 2 and bilateral acoustic schwannomas**

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BACKGROUND: Neurofibromatosis type 2 (NF2) is a rare genetic condition caused by mutations in the Merlin gene on chromosome 22. It results in acoustic neuromas (schwannomas) and other CNS tumors including meningiomas and ependymomas. Most patients develop hearing loss as a result of neuroma-driven destruction of auditory nerves. Surgery and radiation therapy remain the two most commonly recommended treatment options. However, there is a risk of further hearing loss with these procedures. There is emerging evidence that bevacizumab, a monoclonal antibody against VEGF-A, can shrink acoustic neuromas and mitigate hearing loss. CASE PRESENTATION: A 34-year-old female with bilateral acoustic neuromas from NF2 suffers partial hearing loss in the left ear and total hearing loss in the right ear after removal of the right-sided neuroma. Baseline MRI showed a left-sided acoustic neuroma (15 x 13 mm) and recurrence of the right-sided neuroma (18 x 14 mm). Bevacizumab was initiated at 5 mg/kg IV every 14 days. After 8 cycles, the patient reported marked improvement in hearing. At lower frequencies (< 1,000 Hz, the range of human voice), auditory thresholds improved by up to 60% of baseline, while at higher frequencies, improvements of up to 46% were seen. Repeat imaging showed no disease progression. CONCLUSIONS: Bevacizumab led to hearing improvement and prevention of disease progression after 8 cycles of therapy. This treatment should be considered in patients with NF2 and acoustic neuromas who wish to pursue a less-invasive treatment option with the potential of delaying progression and mitigating hearing loss.

# ORAL PRESENTATIONS
# 11 MAY 2018

## 1115 - 1200
## SESSION SIX ~ GLIOBLASTOMA

**25**

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**Durable complete responses observed in patients with recurrent high grade glioma treated with Toca 511 & Toca FC**

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Toca 511 (vocimagene amiretrorepvec) is an investigational retroviral replicating vector that selectively infects dividing cancer cells, integrates into the genome and replicates due to immune defects in tumors. Toca 511 spreads through tumors and stably delivers the gene encoding an optimized yeast cytosine deaminase that converts the prodrug Toca FC (investigational, extended-release of 5-fluorocytosine) into 5-fluorouracil. In preclinical models, 5-fluorouracil kills infected dividing cancer cells, myeloid derived suppressor cells and tumor associated macrophages, enabling immune activation against the tumor. In this dose ascending Ph1 trial (NCT01470794), Toca 511 was injected into the resection cavity wall of patients with rHGG, followed by courses of oral Toca FC. Additional cohorts included combination with bevacizumab or lomustine. Across the Ph1 program, the safety profile remains favorable. Objective responses (ORs) were assessed by IRR using MRI scans prior to Toca FC treatment as baseline. ORs occurred 6-19 months after Toca 511 administration, suggesting an immunologic mechanism. The ORs were observed in 4 patients with IDH1-wildtype and 2 patients with IDH1-mutant tumors, including 5 complete responses (CRs) with the investigational therapy alone, and 1 CR in combination with bevacizumab. The median duration of response (mDoR) was 35.1+ months. As of AUG2017, all responders were CR and remain alive. In a 23-patient subgroup who received high doses of Toca 511 and met Ph3 trial criteria, mOS was 14.4 months, 3-year survival rate was 26.1%, and mDoR was 35.7+ months with a durable response rate of 21.7%. Data suggest a positive association of durable response with OS.

**51**

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**Timing of adjuvant treatments on glioblastoma survival: A retrospective cohort analysis based on the national cancer database**

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Few studies investigated the associations between intervention modalities, timing, and survival in glioblastoma (GBM) patients. A total of 20511 eligible GBM patients underwent biopsy and

craniotomy surgeries followed by adjuvant treatments (2005-2014) were derived from the National Cancer Database (NCDB). The time intervals (days) from the date of diagnosis to the initiation date of adjuvant treatment [radiation therapy only (RT), chemotherapy only, concurrent chemoradiation (CRT), or non-concurrent RT and chemotherapy] were categorized into quartiles (Q1-Q4). Kaplan-Meier method and Cox proportional hazards regression were applied for survival analysis. Multivariate logistic regression was performed to compare differences in treatment timing, intervention modalities, and secondary outcomes. The patients underwent biopsy obtained significant survival benefit by having delayed adjuvant treatment [comparing to Q1, Q2: HR (hazard ratio), 0.88, Q3: HR, 0.86]. For patients underwent resection, the prolonged waiting time of adjuvant treatment had 5-6% reduced risk of death [comparing to Q1, Q2: HR, 0.95; Q3: HR, 0.94]. Patients received more RT fractions [comparing to 10-29 fractions, 30-33 fractions: HR: 0.62 (biopsy), 0.62 (resection); ≥34 fractions: HR: 0.53 (biopsy), 0.62 (resection)] and high-dose RT [comparing to 34-46 Gy, 50-60 Gy: HR: 0.91 (biopsy), 0.95 (resection); ≥ 60 Gy: HR: 0.77 (biopsy), 0.88 (resection)] experienced significantly superior survival in both biopsy and resection groups. The impact of timing to adjuvant treatment on GBM survival varied by surgery procedures. Having adjuvant treatment initiated within 21 days for both biopsy and craniotomy groups may not guarantee a significant survival benefit. More RT fractions and high-dose RT are associated with better GBM survival.

**53**

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**Alterations in the epigenetic profile of glioblastoma tumors within hypoxic tumor regions**

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Glioblastomas are the most frequent and aggressive primary brain tumor in adults and despite recent therapeutic advances, they are resistant to treatment. Increasing malignancy of gliomas correlates with an increase in cellularity and a poorly organized tumor vasculature, leading to insufficient blood supply, hypoxic areas, and ultimately to the formation of necrosis. Hypoxia induces direct or indirect changes in the biology of solid tumor and their microenvironment through the activation of HIF transcription factors, leading to increased aggressiveness and tumor resistance to therapy. Not much is known about the epigenetic alterations induced by hypoxia and how they could alter tumor biology. In the present study, we have utilized PIMO as a specific marker of hypoxia in glioblastoma patients, treated with PIMO preoperatively. We have estimated PIMO positivity in each tumor (5-45%) and determined that it positively correlates with the hypoxia marker CA IX (r=0.57). In addition, 10 surgical PIMO cases were dissociated, immune labeled using PIMO antibody, followed by DNA isolation and methylation profiling. Our analysis of differentially top 4000 differentially methylated probes suggests that PIMO-positive (hypoxic) cells are differentially methylated compared to the PIMO-negative cells and these changes are associated with genes involved in hypoxic cellular response. We will validate these findings in additional glioblastoma cases and assess the mechanism of these epigenetic alterations in vitro in glioma stem cell culture conditions and upon exposure of the cells hypoxic conditions.

# 1355-1450
# SESSION SEVEN ~ PEDIATRICS

**13**

doi:10.1017/cjn.2018.293

**The genetic landscape of pediatric low-grade gliomas: Incidence, prognosis and response to therapy - a SickKids pLGG Task Force update**

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Molecular characterization of pediatric low-grade glioma (pLGG) over the last decade has identified recurrent alterations, most commonly involving BRAF, and less frequently other pathways including MYB and MYBL1. Many of these molecular markers have been exploited clinically to aid in diagnosis and treatment decisions. However, their frequency and prognostic significance remain unknown. Further, a significant portion of cases do not have any of these alterations and what underlies these cases remains unknown. To address this we compiled a cohort of 562 patients diagnosed at SickKids from 1990-2017. We identified molecular alterations in 454 cases (81% of the cohort). The most frequent events were those involving BRAF; either as fusions (most commonly with KIAA1549 (30%)) or V600E mutations (17%) and NF-1 (22%). Less frequently, we identified recurrent FGFR1 fusions and mutations (3%), MYB/MYBL alterations (2%), H3F3AK27M (2%) or IDH1R132H (0.5%) mutations, as well as other novel rare events. Survival analysis revealed significantly better progression-free survival (PFS) and overall survival (OS) of KIAA1549-BRAF fused patients compared to BRAFV600E with 10-year OS 97.7% (95%, CI 95.5-100) and 83.9% (95%, CI 72.5-95.6), respectively. In addition to survival, molecular alterations predicted differences in response to conventional therapeutics; BRAF fused patients showed a 46% response-rate, versus only 14% in V600E patients. pLGGs harboring H3F3AK27M progressed early with median PFS of 11 months. In patients with MYB/MYBL1, FGFR1/FGFR2 alterations, we observed only one death (FGFR1N546K case). The work here represents the largest cohort of pLGGs with molecular profiling and their impact on the clinical behaviour of the disease.

**15**

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**CD271/p75NTR is a novel diagnostic marker, prognostic indicator and therapeutic target for SHH medulloblastoma**

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The extensive heterogeneity both between and within the medulloblastoma (MB) subgroups underscores a critical need for variant-specific biomarkers and therapeutic strategies. We