

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);  $\geq 34$  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);  $\geq 60$  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.

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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

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#### 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.

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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

previously identified a role for the CD271/p75 neurotrophin receptor (p75NTR) in regulating stem/progenitor cells in the SHH MB subgroup. Here, we demonstrate the utility of CD271 as a novel diagnostic and prognostic marker for SHH MB using immunohistochemical analysis as well as transcriptome data across 763 primary tumors. Characterization of CD271+ and CD271- cells by RNA sequencing revealed that these two subpopulations are molecularly distinct, co-existing cellular subsets both in vitro and in vivo. MAPK/ERK signaling is upregulated in the CD271+ population and inhibiting this pathway reduced CD271 levels, stem/progenitor cell proliferation and cell survival as well as cell migration in vitro. Importantly, the MEK inhibitor selumetinib extends survival and reduces CD271 levels in vivo. Our study demonstrates the clinical utility of CD271 as both a diagnostic and prognostic tool for SHH MB tumors and reveals a novel role for MEK inhibitors in targeting CD271+ SHH MB cells.

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### **Intracranial growing teratoma syndrome (IGTS): An international retrospective study**

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**BACKGROUND:** IGTS is a rare phenomenon of paradoxical germ cell tumor (GCT) growth during or following treatment despite normalization of tumor markers. We sought to evaluate the frequency, clinical characteristics and outcome of IGTS in patients in 21 North-American and Australian institutions. **METHODS:** Patients with IGTS diagnosed from 2000-2017 were retrospectively evaluated. **RESULTS:** Out of 739 GCT diagnoses, IGTS was identified in 33 patients (4.5%). IGTS occurred in 9/191 (4.7%) mixed-malignant GCTs, 4/22 (18.2%) immature teratomas (ITs), 3/472 (0.6%) germinomas/germinomas with mature teratoma, and in 17 secreting non-biopsied tumours. Median age at GCT diagnosis was 10.9 years (range 1.8-19.4). Male gender (84%) and pineal location (88%) predominated. Of 27 patients with elevated markers, median serum AFP and Beta-HCG were 70 ng/mL (range 9.2-932) and 44 IU/L (range 4.2-493), respectively. IGTS occurred at a median time of 2 months (range 0.5-32) from diagnosis, during chemotherapy in 85%, radiation in 3%, and after treatment completion in 12%. Surgical resection was attempted in all, leading to gross total resection in 76%. Most patients (79%) resumed GCT chemotherapy/radiation after surgery. At a median follow-up of 5.3 years (range 0.3-12), all but 2 patients are alive (1 succumbed to progressive disease, 1 to malignant transformation of GCT). **CONCLUSION:** IGTS occurred in less than 5% of patients with GCT and most commonly after initiation of chemotherapy. IGTS was more common in patients with IT-only on biopsy than with mixed-malignant GCT. Surgical resection is a principal treatment modality. Survival outcomes for patients who developed IGTS are favourable.

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### **Genes preserving stem cell state in Group 3 MB BTICs contribute to therapy evasion and relapse**

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Medulloblastoma (MB) is the most common malignant pediatric brain tumor. Current clinical trials for recurrent MB patients based on genomic profiles of primary, treatment-naïve tumors, provide limited clinical benefit since recurrent metastatic MBs are highly genetically divergent from their primary tumors. By adapting the existing Children's Oncology Group treatment protocol for children with newly diagnosed high-risk MB for treatment of mice intracranially engrafted with human MB cells, we have characterized the rare treatment-refractory cell population in Group 3 MBs. MB cell populations recovered separately from brains and spines during the course of tumor development and therapy were comprehensively profiled for gene expression analysis, stem cell and molecular features to generate a global, comparative profile of MB cells through therapy to relapse. One of the most intriguing observations from our gene expression data was consistent over-expression of proteins belonging to Inhibitor of DNA-binding/differentiation (ID) family and a longevity associated protein bactericidal/permeability-increasing fold-containing-family-B-member-4 (BPIFB4) in our refractory population. The persistent upregulation of genes preserving undifferentiated state and cellular longevity further strengthens the hypothesis of stem-cell like cells driving tumor relapse in MB. Targeting BPIFB4 using both knockdown (KD) and knockout (KO) strategies have resulted in decreased proliferation and self-renewal of both primary and recurrent MB cells, further highlighting its potential as a novel therapeutic target in MB. Our differential genomic and gene expression profiles of the "treatment-responsive" tumors against those that fail therapy have successfully contributed to discovery and characterization of novel therapeutic targets for the most aggressive subgroup of MB.

1450-1545

### **Young Investigator Awards & Presentations**

#### **Basic/Translational**

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### **Exploring cellular subpopulations in glioblastoma and matched organoids using single-cell RNA-seq**

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Glioblastomas (GBMs) account for nearly half of all primary malignant brain tumours, and current therapies are often only marginally effective. Our understanding of the underlying biology of these tumours and the development of new therapies have been