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

complicated in part by widespread inter- and intratumoural heterogeneity. To characterize this heterogeneity, we performed regional subsampling of primary glioblastomas and derived organoids from these tissue samples. We then performed single-cell RNA-sequencing (scRNA-seq) on these primary regional subsamples and 1-3 matched organoids per sample. We have profiled samples from six tumour sets to date and have obtained sequencing data for 21,234 primary tissue cells and 14,742 organoid cells. While the most apparent differences in gene expression appear to be between individual tumours, we were also able to identify similar cellular subpopulations across tissue samples and across organoids. Importantly, organoids derived from the same tissue sample appeared to be composed of similar cellular subpopulations and were highly comparable to each other, indicating that replicate organoids faithfully represent the original tumour tissue. Overall, our scRNA-seq approach will help evaluate the utility of tumour-derived organoids as model systems for GBM and will aid in identifying cellular subpopulations defined by gene expression patterns, both in primary GBM regional subsamples and their associated organoids. These analyses will allow for the characterization of clonal or subclonal populations that are likely to respond to different therapeutic approaches and may also uncover novel therapeutic targets previously unrevealed through bulk analyses.

Clinical/Translational

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Metabolic profiling of gliomas reveals distinct subgroups of tumors independent of IDH mutation status

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Background: Gliomas are the most common and fatal adult brain tumor with distinct genomic subgroups defined by isocitrate dehydrogenase (IDH) mutation status. Mutations in IDH result in overproduction of the oncometabolite 2-hydroxyglutarate (2HG). The landscape of metabolic changes that define gliomas has not previously been explored. Methods: We performed liquid chromotography-mass spectrometry (LC-MS) to examine over 700 metabolites on 90 fresh-frozen glioma samples (30 IDH-wildtype, 30 IDH-mutant 1p/19q codeleted, 30 IDH-mutant 1p/19q non-codeleted) from our institutional biobank. R and S enantiomers of 2HG were quantified using high pressure liquid chromatography tandem mass spectrometry coupled with a CHIROBIOTIC R column. Genome wide DNA methylation was performed on all tumors using Illumina 850k EPIC array. Unsupervised consensus clustering of differentially expressed metabolites and methylated post-processed probes was performed. Copy number variations were determined based on intensity values of the methylation array. Survival of unsupervised cluster groups was determined using the Kaplan-Meier Estimate. Results: Unsupervised clustering of 689 metabolites revealed 2 distinct subgroups of gliomas associated with recurrence-free survival (RFS, P = 0.021). IDH mutant tumours were found in both cluster groups where as IDH-wildtype tumors were found only in Group 2. Group 2 IDH-mutant tumors had unfavourable PFS, higher R/S-2HG levels, and higher proportion of copy number alterations (4q, 9p, 13q, 17q) compared to group 1 IDH-mutant tumors (P=0.048, P=0.0194, P<0.0001 respectively) compared to group 1 IDH-mutant tumors. (P= p=0.048). Conclusions: Metabolic profiling of gliomas reveals 2 distinct subtypes of IDH-mutant independent of 1p/19q codeletion status with differing survival patterns and large scale chromosomal alterations that may be driven by varying levels of R/S-2HG.

1535 - 1620
SESSION EIGHT ~ GLIOMA

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Identifying and prognosticating malignant brain tumors non-invasively using unique metabolomic signatures derived from patient serum and urine samples

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BACKGROUND: Metabolomics technology has the potential to revolutionize how we screen, diagnose, and treat cancer, as well as improve upon existing cancer molecular tests that may not sufficiently capture the complexity of most malignancies. In this study, we explore the clinical potential of metabolomics analysis in the diagnosis and risk-stratification of brain tumors. METHODS: To test the hypothesis that brain tumor type and survival could be predicted with metabolomics, we analyzed the pre-operative serum and urine samples of patients with glioblastoma (GBM), oligoastrocytoma (OA2), meningioma (M1) and compared them to healthy controls. (HC). Sera from immune-deficient NOD-SCID mice xenografted with human GBM brain tumor initiating cells were also studied. RESULTS: Metabolomics analysis of patient samples was able to accurately differentiate GBM, OA2, M1 and HC (p = 2.3 x 10-26). Subsequently, a prediction model developed and validated internally was able to diagnose GBM with a sensitivity of 86.7% and specificity of 93.8%, and distinguish whether a GBM patient possess O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (p = 7.4 x 10-10). Within the MGMT methylated group, the model was able to predict longevity (p = 3.25 x 10-4). The model was also able to predict survival irrespective of MGMT methylation status (p = 2.9 x 10-6). CONCLUSIONS: In this study, we demonstrate that metabolomic analysis of patient biofluids can identify brain tumors, distinguish brain tumor subtypes, and independently predict MGMT status as well as longevity among GBM patients. Metabolomics analysis may facilitate non-invasive diagnosis of aggressive brain tumours.

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Integration of multiple platforms to discover idh-mutant glioma subtypes

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Purpose: Diffuse gliomas can be divided on the basis of presence or absence of mutation in IDH genes. IDH-mutant diffuse gliomas represent a wide range of clinical outcome, which is not accounted for by current clinical and pathologic parameters. We aim to