identify clinically and biologically relevant subgroups within IDH-mutant gliomas to gain a deeper insight into finer sub-classification. Methods: We used 412 IDH-mutant glioma samples that were profiled by The Cancer Genome Atlas (TCGA) Research Network, utilising methylation/mRNA datasets to identify subtypes with unique molecular signatures. We applied a Similarity Network Fusion (SNF) on individual platforms and their integrations. Results: SNF approach split glioma into four groups. The integrated RNA/methylation subtype produced a highly prognostic groups that predict survival (p-value=0.003) compared to mRNA and methylation alone. We observed a high degree of correlation between integrative subtypes and somatic mutations. Groups 1&4 had higher TERT promoter mutations (35% and 16%, respectively) compared to groups 2&3. Groups 1&4 showed increased TERT expression (34% and 14% respectively), and high percentage of TP53 and ATRX mutations. Multivariate analysis after adjusting for confounding factors including grade and age showed prognostic factors associated with survival (HR=3.2, p-value=0.001) in group 4 versus others. Conclusions: The results indicate that clinically relevant alterations exist within IDH-mutant gliomas that could stratify patients for treatment. Interestingly, group 4 showed high expression of HOX genes (18/18) (p-value=0.01) and higher methylation of Hox genes (21) (p-value=0.01) compared to others. Higher expression of specific Hox genes were associated with worse survival.

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Dianhydrogalactitol (VAL-083) reduces glioblastoma tumor progression in vivo, upon bevacizumab-induced hypoxia

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Standard-of-care for glioblastoma (GBM) includes surgery, radiation and temozolomide. Nearly all tumors recur and 5-year survival is less than 3%. Unmethylated promoter status O6-methylguanine-DNA-methyltransferase (MGMT) is a validated biomarker for temozolomide-resistance. Second-line treatment with bevacizumab has not only failed to improve survival, but has also been shown to induce intratumor hypoxia and increased chemoresistance. VAL-083 is a bi-functional DNA-targeting agent that readily crosses the blood-brain barrier. VAL-083 targets N7-guanine, causing DNA double-strand breaks and cancer cell-death in GBM cancer stem cells (CSCs) and non-CSCs, independent of MGMT. To investigate the in vivo anti-tumor effect of VAL-083+bevacizumab, we used an orthotopic GBM T16 PDX model. All mice carried MGMT-unmethylated, temozolomide-resistant recurrent GBM tumors detected by MRI 35 days post-implantation. Tumor progression was measured by MRI on days 49 and 56, and was calculated for the entire study (day 35 vs. 56) and for the last 7 days (day 49 vs. 56). Mice were grouped into control, bevacizumab, VAL-083, and VAL-083+bevacizmab. VAL-083 treatment started 3 days after bevacizumab treatment to ensure induction of hypoxia. Results: Tumors were significantly smaller in VAL-083-treated mice both compared to control (-83%, $p<0.001$) and compared to bevacizumab-treated (-75%, $p<0.001$) mice. Additionally, analysis of tumor growth in-time showed significantly reduced tumor progression for VAL-083+bevacizumab compared to VAL-083 alone ($p<0.01$). Conclusions: These results show strong in vivo anti-tumor efficacy of VAL-083 against MGMT-unmethylated, recurrent GBM. This effect was further augmented in combination with bevacizumab, providing rationale of clinical investigation of VAL-083+bevacizumab in GBM.

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Unraveling molecular drivers of brain cancers at the clinical setting

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Brain tumor behavior is driven by aberrations in the genome and epigenome. Many of these changes, such as IDH mutations in diffuse low-grade glioma (DLGG), are common amongst the same class of tumour and can be incorporated into the diagnostic criteria. However, any given tumor may have other, less common genomic aberrations that are essential for its biological behavior and may inform on underlying aberrant cellular pathways, and potential therapeutic agents. Precision oncology is a genomics-based approach which profiles these alterations to better manage cancer patients and has established itself within the practice of oncology and is slowly making its way into neuro-oncology. The BC Cancer‟s Personalized OncoGenomics (POG) program has profiled 16 adult tumours originating from the central nervous system using whole genome and transcriptome analysis (WGTA), for the first time, within a meaningful clinical timeframe/setting. As expected, primary genomic drivers were consistent with their respective diagnoses, though secondary drivers were found to be unique to each tumour. Although these analyses did not result in altered clinical management for these patients, primarily due to availability of drug or clinical trials, they highlight the heterogeneity of secondary drivers in cancers and provide clinicians with meaningful biological information. Lastly, the data generated by POG has highlighted the frequency and complexity of novel driver fusions which are predicted to behave similarly to canonical driver events in their respective tumours. The information available to clinicians through POG has provided paramount knowledge into the biology of each unique tumour.

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Microglia and macrophages display heterogeneous phenotypes in IDH-mutant and -wildtype glioblastomas

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Background: CNS innate immune cells, microglia and macrophages (MMs), are the largest component of the inflammatory infiltrate in glioblastoma (GBM). They initially participate in tumor surveillance, but are subverted by GBM. Immunotherapies have proven incredibly successful in cancers

such as melanoma, but not against GBM in part because GBM-associated MMs are not well understood. We hypothesized the content and inflammatory phenotype of MMs in GBM is variable between patients. We suspect MMs in IDH-wildtype and –mutant GBMs display divergent inflammatory phenotypes that helps explain the latter's better prognosis. Understanding GBM-associated MM heterogeneity will allow for better immunotherapy development and selection. Methods: MMs were isolated from untreated human IDH-wildtype and -mutant GBMs using flow cytometry and cultured for collection of conditioned media and analysis of secretory products. Automated segmentation with a high-content analysis system was used to quantitate MM content and inflammatory phenotype in frozen sections. New bioinformatics techniques allowed the comparison of MM profiles in publicly available single-cell RNA-sequencing databases with IDH-wildtype and -mutant GBMs. Results: Surprisingly marked variation in MM content exists between GBMs ranging from ~0-70%. A mixture of pro- and anti-inflammatory MMs are found in each GBM. Interestingly, IDH-mutant GBM-associated MMs were more activated than MMs in IDH-wildtype GBMs. Conclusions: Taken together, the highly variable MM content and phenotype of GBMs suggests the success of immunotherapies hinges on taking a precision medicine approach. MM-rich GBMs would benefit more from therapies that target them. MM activation in IDH-mutant GBMs may contribute to better patient prognoses.

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Peroxiredoxin1 is a therapeutic target in group-3 medulloblastoma

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Group-3 medulloblastoma (MBL) is highly resistant to radiation (IR) and chemotherapy and has the worst prognosis. Hence, there is an urgent need to elucidate targets that sensitize these tumors to chemotherapy and IR. Employing standard assays for viability and sensitization to IR, we identified PRDX1 as a therapeutic target in Group-3 MBL. Specifically, targeting PRDX1 by RNAi or inhibition by Adenanthin led to specific killing and sensitization to IR of Group-3 MBL cells. We rescued sensitization of Daoy and UW228 cells by hypermorphic expression of PRDX1. PRDX1 knockdown caused oxidative DNA damage and induced apoptosis. We correlated PRDX1 expression to patient outcomes in a validated MBL tumor-microarray. Whole genome sequencing identified pathways/genes that were dysregulated with PRDX1 inhibition or silencing. Our in vivo studies in mice employing flank/orthotopic tumors from patient derived xenografts/Group-3 MBL cells confirmed in vitro observations. Animals with tumors in which PRDX1 was targeted by RNAi or Adenanthin (using mini osmotic pumps) showed decreased tumor burden and increased survival when compared to controls. Since, Adenanthin does not cross the blood brain barrier (BBB) we used HAV6 peptide to transiently disrupt the BBB and deliver Adenanthin to the tumor. Immunohistochemistry confirmed that targeting PRDX1 resulted in increased oxidative DNA damage, apoptosis and decreased proliferation. In summary, we have validated PRDX1 as a therapeutic target in group-3 MBL, identified Adenanthin as a potent chemical inhibitor of PRDX1 and confirmed the role of HAV peptide (in the transient modulation of BBB permeability) in an orthotopic model of group-3 MBL.

ORAL PRESENTATIONS
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Could DLX2 regulation of neural progenitor cell fate contribute to differentiation of diffuse intrinsic pontine glioma (DIPG)?

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Introduction: Diffuse intrinsic pontine glioma (DIPG) is refractory to therapy. The identification of histone H3.1/H3.3 K27M mutations in most DIPG has provided new insights. The DLX homeobox genes are expressed in the developing forebrain. The Dlx1/Dlx2 double knockout (DKO) mouse loses tangential GABAergic interneuron migration to the neocortex. We have identified genes that encode glutamic acid decarboxylase (GAD) enzymes as direct targets of DLX1/DLX2. In DIPG patients with H3.3 K27M mutations there is decreased Dlx2 and increased expression of the myelin transcription factor, Myt1. Methods and Results: We used bioinformatics approaches and chromatin immunoprecipitation (ChIP) assays to identify Olig2, Nkx2.2 and Myt1 promoter sequences as candidate DLX2 targets in vivo. DNA binding specificity was confirmed. The functional consequences of Dlx2 co-expression with reporter constructs of ChIP-isolated promoter fragments of Olig2 and Nkx2.2 demonstrated repression of gene targets in vitro. qPCR showed increased Olig2 and Nkx2.2 expression in the DKO forebrain. Stable transfection of a murine DIPG cell line with Dlx2 resulted in increased Gad1 and Gad2 and decreased Olig2 and Nkx2.2 expression. Of significance, we demonstrated decreased expression of H3.3 K27M and restoration of H3.3 K27 tri-methylation (me3). Conclusions: DLX transcription factors promote GABAergic interneuron and concomitant inhibition of oligodendroglial differentiation in neural progenitors by repression of a suite of genes including Olig2 and Nkx2.2. Restoration of H3 K27me3 expression in DIPG provides a promising lead towards exploration of differentiation as a therapeutic strategy for DIPG.

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Malignant primary brain and other central nervous system tumours diagnosed in the Canadian population from 2009 to 2013

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