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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doi:10.1017/cjn.2018.304

**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
# 12 MAY 2018

## 1105-1150 SELECTED CNO2018 ABSTRACTS

**09**

doi:10.1017/cjn.2018.305

**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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doi:10.1017/cjn.2018.306

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

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