

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.

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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