activation mechanisms by matched genome sequencing and DNA methyla-
profiling, respectively. Our findings will be applied to deconvolute bulk
RNA sequencing data, thus identifying therapeutically relevant signaling
networks in larger cohorts of medulloblastoma patients. Eventually, can-
diate targets will be validated on patient-derived cell models and xeno-
grafts by overexpression and inhibition studies. Together, here we aim at
identifying tumor-driving receptor/ligand interactions in medulloblastoma,
with the goal to define targets susceptible to precision oncology approaches.

MEDB-83. A NOVEL EPIDEMIOLOGIC TECHNIQUE TO INDUCE MEDULLOBLASTOMA DIFFERENTIATION

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The histone-lysine N-methyltransferase EZH2 is the catalytic component of
the PRC2 complex and is overexpressed in several medulloblastoma subtypes.
However, its role in medulloblastoma tumorigenesis has been shown to be
c context-dependent using genetic approaches. Furthermore, pharmacological ap-
proaches have been limited by the very poor blood-brain barrier (BBB) penetra-
tion of current EZH2 inhibitors in use. In recent studies, a potential gain in
expression of the ELP1 gene has been described in 14% of cases, more frequently in the SHH group. In a recent pediatric series of SHH-MB,
results were 80% overall survival and 80% disease-free survival, and one is alive with NED after PD and additional therapy. There
was no evidence of disease (NED). One patient died of consolidation-related tox-
icity, although no obvious genetic alteration in the coding sequence of
ELP1 was sequenced allows to identify 12 additional MB with bi-allelic ELP1 genetic alterations. Our results demonstrate the benefit of the ELP1 IHC as an accurate and reliable tool to screen ELP1-deficient MB. This new immunohistochemical tool will now be favorably used to screen SHH MB upfront for genetic alter-
ation in ELP1, and will subsequently help orientating these patients towards
towards genetic counseling.

MEDB-85. TRANSCRIPTIONAL COMPLEXES AS RESISTANCE DRIVERS TO BET INHIBITION

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BET-bromodomain inhibition (BETi) is a promising therapeutic strategy
target MYC-driven cancers, including Group 3 medulloblastoma, a
deadly childhood brain tumor. We have shown that BET inhibitors exhibit
cross-resistance with MYC-amplified medulloblastoma, providing a
foundation for translational clinical trials for this disease. Importantly, we have focused our efforts on elucidating the mechanisms through
which BET-resistant medulloblastoma cells can acquire resistance to BETi, suggesting that curative responses for this disease will require stringent preliminary testing. To guide the development of combina-
tion therapies, we have focused our efforts on elucidating the mechanisms
through which medulloblastoma cells acquire resistance to BETi. We found
that BET-resistant medulloblastoma cells can develop tolerance to BETi by
repressing the expression of cell-essential “rescue genes,” which include a large number of cell cycle regulators and anti-apoptosis genes. This transition to the resistant cell state is mediated through changes in chromatin structure
including the upregulation of H3K4me3 promoters. Our preliminary results suggest that BET-resistant cells maintain mRNA transcription and protein translation of important mediators of resistance. Importantly, we observe
that BET-resistant medulloblastoma cells are more dependent on specific protein complexes involved in transcriptional regulation. This project ex-
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that BET-resistant medulloblastoma cells are more dependent on specific protein complexes involved in transcriptional regulation. This project ex-
lavors the mechanisms through which these transcriptional regulators help
maintain transcription of rescue genes that drive BET resistance and evalu-
ates the potential of targeting these drivers of BETi resistance. These results will help guide the development of combination approaches to improve the efficacy of BETi for the treatment of MYC-driven medulloblastoma.

MEDB-86. A RE-INDUCTION REGIMEN FOR CHILDREN WITH RECURRENT MEDULLOBLASTOMA

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Medulloblastoma is the most common malignant brain tumor of child-
hood. Despite multi-modal therapies, ~30% of patients experience disease recurrence, which portends a poor prognosis. At initial recurrence, inten-
sive chemotherapy may be effective prior to various consolidation therapies including high dose chemotherapy with autologous stem cell rescue or
radiation. We report outcomes for nine children treated at two institutions
with the following regimens: cyclophosphamide 1500mg/m2/dose days 1,2;
irinotecan 125mg/m2/dose days 1,8; temozolomide 150mg/m2/dose days 1-5, and oral etoposide 30mg/m2/dose days 1-7. Patients received 2-4 cycles based upon disease response and physician preference. The mean time from
initial diagnosis to first recurrence was 19 months. After receiving two cycles of therapy, two patients had complete response (CR) and proceeded to consolidation. Of the remaining seven patients, five had partial response (PR) and two had stable disease (SD). Overall response rate was 78% improve BETi for the treatment of MYC-driven medulloblastoma.

MEDB-84. THE FRENCH EXPERIENCE OF ELP1-RELATED MEDULLOBLASTOMAS

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Medulloblastoma (MB), the most frequent embryonic tumor of the cere-
bellum, is the most common CNS tumor in children. It is defined by four molecular subgroups (SHH group, group 3 and 4). Although the vast majority of MB arise sporadically, predisposing genetic diseases have been described in rare WNT MB and more frequently in the SHH group. In a recent pediatric series of SHH-MB, germline alterations of the ELP1 gene have been described in 14% of cases, making this gene the most frequent genetic predisposition in MB. We have
investigated the potential interest of ELP1 immunostaining on a large cohort of 132 MB. A complete loss of ELP1 staining was observed in 12 SHH MB (among 37 total SHH MB: 21%). The loss of ELP1 immunostaining was well-coordinated with the presence of a bi-allelic alteration. Even in the genetic setting for one case for which the MB had a loss of ELP1 protein expression dem-
strated by immunohistochemistry (IHC) and confirmed by whole proteome analysis, although no obvious genetic alteration in the coding sequence of
ELP1 was found. Molecular analysis of a large cohort of 266 MB from French centers for which somatic ELP1 was sequenced allowed to identify 12 additional MB with bi-allelic ELP1 genetic alterations. Our results demonstrate the benefit of the ELP1 IHC as an accurate and reliable tool to screen ELP1-deficient MB. This new immunohistochemical tool will now be favorably used to screen SHH MB upfront for genetic alter-
ation in ELP1, and will subsequently help orientating these patients towards
towards genetic counseling.
plication. Five patients had febrile neutropenia and two developed sepsis. One patient required dose reduction for prolonged thrombocytopenia. Peripheral blood stem cell collection was achieved in all patients for whom it was attempted. This re-induction regimen is generally well-tolerated and effective in inducing responses for children with recurrent medulloblastoma.

MEDB-87. TRANSCRIPTOME-DRIVEN DRUG REPURPOSING IN GROUP 3 MEDULLOBLASTOMA

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Across the molecular spectrum of medulloblastoma (MB), group 3 (G3) tumors represent the most aggressive with 5-year overall survival of the lowest of all MB subgroups. G3 MB tumors are characterized by frequent metastases at diagnosis, unique methylation profiles, MYC amplification, and i17q, but these unique molecular features have yet to be exploited for therapeutic purposes despite their promise. As such, we sought to address this gap in survivorship by identifying FDA-approved compounds with the potential to inhibit cellular processes critical to G3 MB tumor proliferation and metastasis, aiming to exploit the unique molecular pathogenesis of G3 tumors. Guided by analysis of RNA-sequencing data from locally obtained, patient-derived MB samples against the LINCS chemical perturbagen database, we identified nortriptyline (NT), a tricyclic antidepressant, as a candidate MB therapeutic due to: 1) its ability to revert the epigenetic signature of G3 MB tumors (i17q) and (2) its ability to cross the blood-brain barrier. We first identified the IC50 of NT in D425 and HDMB03 cells as 28µM and 200µM, respectively. Then, we observed that NT increased apoptosis of HDMB03 cells 3-fold by flow cytometry and confirmed our observations with Western blotting of the apoptotic markers. Additionally, NT treatment resulted in abrogation of colony formation, impairment of wound healing, and inhibition of cell migration and invasion in vitro in HDMB03 cells. In all, transcriptome-driven drug repurposing holds great promise, as identifying novel therapeutic agents with a known safety profile can deliver effective treatments into the hands of both patients and physicians in an expedited manner when compared to traditional means.

MEDB-88. BA60C/SMARCD3-MEDIATED NOVEL NEURODEVELOPMENTAL EPIGENOMIC PROGRAM PROMOTES METASTATIC DISEASE IN MEDULLOBLASTOMA

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Normal brain development relies on precise genetic and epigenetic spatiotemporal regulation of gene expression. How dysregulation of neurodevelopment relates to medulloblastoma, the most common pediatric brain tumor, remains elusive. Here, we uncovered a novel neurodevelopmental epigenomic program that regulates Purkinje cell migration in developing cerebellum is hijacked to induce tumor metastatic dissemination in medulloblastoma. Integrating publicly available datasets with our in-house data, unsupervised analyses revealed that BA60C/SMARCD3, a subunit of SWI/SNF chromatin remodeling complex, promotes tumor cell migration in vitro and metastasis in vivo. Based on analyzing the single-cell RNAseq data of cerebellum developmental trajectory in mice and humans, aligning with the medulloblastoma patients’ datasets, we found that BA60C/SMARCD3 regulated DAB1-mediated Reelin signaling is involved in Purkinje cell positioning during cerebellum development and medulloblastoma metastasis by orchestrating the co-regulatory elements (CREs) at the DAB1 gene locus. Analysis of spatiotemporal gene expression and chromatin architecture in the human and mouse cerebellum demonstrated that transcription activity of the BA60C/SMARCD3-DAB1 circuit is altered at key maturation state of cerebellum. Further, we found BA60C/SMARCD3 upregulated in metastatic medulloblastoma. We further identified that a core set of transcription factors, enhancer of zeste homolog 2 (EZH2) and nuclear factor I X (NFIx), bind-direcionaly control BA60C/SMARCD3 transcriptional regulation by coordinating with the CREs at the BA60C/SMARCD3 gene locus to form a chromatin hub during developing cerebellar development and medulloblastoma metastatic dissemination. Highly expressed BA60C/SMARCD3 activates the Reelin/DAB1 signaling pathway downstream Src kinase, which was validated in the pair-wised primary and metastatic medulloblastoma mouse models revealed that inhibiting Src activity reduces tumor cell migration and metastatic dissemination at a lower and safe dose. Together, these data deepen our understanding of how the developmental program influences disease progression and provide an opportunity for the development of therapeutics for this devastating brain cancer in children.

MEDB-89. ELUCIDATION OF THE ONCOGENIC ROLE OF NUCLEAR FACTOR I/B (NFIB) IN GROUP 3 MEDULLOBLASTOMA

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Amongst the 4 subgroups of medulloblastoma (MB), tumors falling into group 3 are the most aggressive and associated with increased incidence of aberrations on chromosome 17p, c-Myc amplification, metastases at diagnosis, and rapid tumour relapse. Thus, patients with group 3 tumors suffer the worst prognosis with a 5-year survival rate of <50%. We have prior identified a novel miRNA, miR-212, silenced on i17p and its deregulated oncoprotein target, Nuclear Factor I/B (NFIB). Here, we sought to identify the role of NFIB in group 3 MB pathophysiology. NFIB is a transcription factor that regulates chromosomal gene accessibility and expression in various cancers. Transcriptional interrogation of group 3 tumors revealed deregulated expression of NFIB. Kaplan-Meier survival analysis confirmed poorer survival in NFIB high-expressing patients. Using inducible silencing of NFIB in a classic group 3 MB cell line, HDMB03, we observed downregulation of key stemness markers and evidence of cell cycle arrest. miR-212, increased expression of key stemness genes and attenuation of NFIB knockdown, further confirmed the onco-suppressive effects of NFIB. In conclusion, we provide proof-of-concept for exploiting group 3 MB tumor vulnerabilities to c-Myc as a potential therapeutic target for medulloblastoma.