(subtype II) show a particularly poor outcome despite high-intensity multimodal therapy. We and others have previously shown that *MYC* amplified Group 3 MB cells are highly susceptible towards treatment with class I histone deacetylase (HDAC) inhibitors such as entinostat. However, in clinical trials HDACi as a monotherapy show only modest efficacy in solid tumours. We propose to increase the efficacy of class I HDACi by drug combinations. Methods: To identify synergistic drug combinations (entinostat + X) for the treatment of *MYC* amplified MB we performed a drug screen with a library of n=75 clinically available compounds as single agents and in combination with entinostat in n=3 *MYC* amplified vs. n=1 *MYC*-non amplified cell lines. Synergistic behaviour of the six most promising drug combinations was validated by metabolic activity assays, cell count experiments and gene expression profiling. Synergy was assessed by the Loewe additivity model using a combination of ray design and checkerboard matrix. Results: The drug screen revealed n=20/75 drugs that were particularly effective (drug sensitivity score ≥10) in combination with entinostat treatment in all three *MYC* amplified cell lines. Synergy assessment of the top n=6 drugs confirmed strong synergistic activity with entinostat for n=2 drugs (navitoclax, irinotecan). The BCL-2 family inhibitor navitoclax showed the most robust synergy with entinostat in subsequent validation experiments. Conclusion: Several drugs either clinically available or currently in clinical trials, including the BCL-2/Xl/w inhibitor navitoclax, show promising effects in a combination therapy with entinostat for the treatment of *MYC* amplified Group 3 MB.

EMBR-12. TARGETING THE RNA-BINDING PROTEIN LIN28B IN GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma (MB) is the most common pediatric malignant brain tumor and is currently divided into WNT, SHH, Group 3 and Group 4 subtypes. Even with multimodal chemotherapy, radiotherapy and surgery, many children with Group 3 MBs do not survive. We have previously demonstrated an oncogenic role for the RNA-binding protein (RBP) LIN28B in neuroblastoma. LIN28B is a key regulator of let-7 family miRNAs, which in turn inhibit LIN28A/B and other oncogenes. LIN28B has also been found to be upregulated in Wilms tumor, hepatoblastoma, germ cell tumors, leukemia among others. We hypothesize that LIN28B plays an important role in Group 3 MB and that a better understanding of LIN28B and LIN28B-driven networks will reveal novel therapeutic vulnerabilities. *LIN28B* levels are highest in Group 3 MB patients, and its overexpression is associated with significantly worse survival. Here we demonstrate that down-regulation of LIN28B using shRNA results in significant reduction in cell proliferation by CellTiter-Glo and increased apoptosis by Caspase-Glo (as well as induction of cleaved PARP on immunoblots). In contrast overexpression of LIN28B increases Group 3 cell proliferation and tumor sphere formation The LIN28 inhibitor 1632 also leads to significant reduction in G3 MB cell proliferation. In addition, we find that PDZ-binding kinase (PBK) a downstream target of LIN28B is downregulated when LIN28B is depleted. PBK knock down also leads to decreased proliferation of Group 3 MB cells. Finally RNA-seq profiling following LIN28B depletion reveals additional components of the LIN28B pathway which may be amenable to therapeutic targeting. This work will help define the role for LIN28B in Group 3 MB aggressiveness and establish LIN28B and LIN28B-driven networks as novel therapeutic targets in these patients.

EMBR-13. NOVEL SYNERGISTIC APPROACHES FOR TARGETED THERAPY OF MYC-DRIVEN MEDULLOBLASTOMA USING CRISPR/CAS9 GENE EDITING

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Introduction: Resistance to chemotherapy is a common cause of treatment failure in cancer patients and a major problem facing current cancer research. Targeted modulation of oncogenic signaling pathways may be used to systematically characterize drug resistance mechanisms across tumor entities and may help to identify new therapeutic strategies. Since the transcription factor MYC is aberrantly activated in many cancers including pediatric malignant brain tumors, like medulloblastoma (MB), our study focused on MYC-related drug resistance. Methods and Results: We performed high-throughput drug screening using our in-house semi-automated platform and identified the HDAC inhibitor Entinostat as a drug that shows promising effects in MYC-driven MB. Investigating genome-wide dCas9-based transcriptional activation screening, potential drug response modulators, mainly TGFB1/Erk/MKNK1 signaling including *neural EGFL like 2* (*NELL2*), were discovered. For further validation, we stably overexpressed *NELL2* in MYC-driven MB cells and treated overexpressing cells and the corresponding control cells with Entinostat. Using PI staining, cell cycle status was tracked. Entinostat treatment led to modest induction of cell death in MYC-driven MB control cells but only slightly increased cell death rate in MYC-driven MB cells with *NELL2*-overexpression. Conclusion: We report that the combination of genetic and pharmacological approaches is a powerful approach to study drug resistance. Our data suggest that activation of the TGFB1/Erk/MKNK1 signaling pathway desensitizes MYC-driven MB cells to Entinostat. Synergistic targeting of TGFB1/Erk/MKNK1 signaling and MYC could therefore provide a novel therapeutic option in this aggressive MB subtype.

EMBR-14. INFLUENCE OF MRI FEATURES ON THE SURVIVAL AND IMPACT ON INDIVIDUAL MOLECULAR SUBGROUPS: RESULT FROM 171 PATIENTS WITH MEDULLOBLASTOMA

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Background: To investigate the influence of different MRI features on survival in patients with medulloblastoma. Methods: A total of 171 patients were included in the study, including 131 pediatric and 40 adults (> 18 years). A set of 16 pre-defined semantic MRI features was analyzed using T1W (pre and post-contrast), T2W, and diffusion-weighted imaging (additional sequences as available). Patients with a definitive event (recurrence) or a minimum follow up of 12 months (in case of no recurrence) were included in the current analysis. All patients were treated and followed up according to standard institutional practice. Log-rank test was used for univariate analysis (UVA) and Cox regression for multivariate analysis (MVA). Results: The molecular subgroups were as follows: WNT-27 children, 7 adults; SHH-31 children, 29 adults; group 3–32 children, 3 adults; and group 4–41 children, 1 adult. The median follow up was 45 months (range 1 to 137 months). For all the patients, on UVA the recurrence-free survival (RFS) was significantly ($p<0.05$) influenced by location-vertical, brainstem involvement, contrast uptake area, contrast heterogeneity, necrosis, and calcification. Similar factors (T2W homogeneity instead of area of contrast) impacted overall survival (OS). On MVA, location-vertical, brainstem involvement, and calcification were significant features for both RFS and OS. Tumor location-vertical was the only feature influencing RFS and OS within the SHH subgroup. For group 3 tumors, contrast uptake area (RFS and OS) and calcification (RFS alone) had a significant influence (MVA). Within group 4, contrast pattern (RFS) and T2W homogeneity (RFS and OS) were significant factors on UVA, none on MVA. Conclusion: Several MRI features can be linked with survival in patients with medulloblastoma, with a specific impact on individual molecular subgroups. Considering the entire population, non-central location on the vertical aspect, tumors away from brainstem, calcification are risk factors associated with inferior outcomes.

EMBR-15. PRC2 COMPLEX ENFORCES NEURONAL LINEAGE AND SUPPRESSES TUMOR GROWTH IN SHH MEDULLOBLASTOMA

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Hyperactivation of Sonic Hedgehog (SHH) signaling pathway drives tumor progression in the largest medulloblastoma subgroup. During cerebellar development, promoters of SHH target genes show inhibitory trimethylation of histone H3 at lysine 27 (H3K27me3), mediated by the Polycomb Repressive Complex 2 (PRC2). Here, we explored the regulation of cerebellar growth and medulloblastoma tumorigenesis by PRC2 complex components EED and EZH2. For developmental studies, we conditionally deleted *Eed* or *Ezh2* in the *Atoh1* lineage that gives rise to the cerebellar granule neuron progenitors (CGNP) that are cells of origin for SHH medulloblastomas. For tumor studies, we bred the conditional *Eed*- or *Ezh2*-deleted mouse lines with mice genetically engineered to develop SHH medulloblastoma. Our developmental studies showed that *Eed* was absolutely required for cerebellar growth. *Eed*-deleted CGNPs underwent aberrant, myocyte-like differentiation and spontaneous apoptosis, resulting in cerebellar hypoplasia. In contrast, *Ezh2* deletion produced no developmental phenotype, despite blocking all H3K27me3 in CGNPs. Our tumor