EMBR-03. PINEOBLASTOMA: A POOLED OUTCOME STUDY OF NORTH AMERICAN AND AUSTRALIAN THERAPEUTIC DATA

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Background: Pineoblastoma (PB) is a rare embryonal brain tumour most often diagnosed in young children. To date, no clinical trials have been conducted specific to pediatric PB. Collaborative studies performed over the past 30 years have included PB in studies accruing for other embryonal tu- mours, primarily medulloblastoma (MB), but also the entity formerly known as CNS-PNET and atypical teratoid rhabdoid tumours. Each of these studies have included only a small number of children with PB, making clinical features difficult to interpret and determinants of outcome difficult to ascertain. Patients and Methods: Published centrally reviewed series with suf- ficient event data were included to obtain MB-like outcome data from MB to assess PB. We pooled and analyzed all reported clinical features of PB and a pooled centrally reviewed, cohort analysis of cases (n=178) from the Children’s Oncology Group (COG) (n=82) groups and several published, centrally reviewed institutional series (n=96). We also found that children <3 years of age have a dramatically poorer outcome compared to older children (5-year OS 16.2% vs. 53% vs 67.3% vs. 5%), confirming new and novel approaches are needed in future clinical trials for this at-risk group. Interestingly, male gender was predictive of worse outcome possibly suggestive of gender specific subgroup risks that needs validation in fu- ture studies. Assessment of radiation therapy is not as possible as the vast majority of children under age three did not receive any form of radiation therapy. Conclusion: Given the relative scarcity of this tumor and the emerging data on subgroups of pineoblastoma, prospective, collaborative international studies will be vital to improving the long-term survival of these patients.

EMBR-04. BET INHIBITION TARGETS RADIOTHERAPY RESISTANCE IN H3K27ME3-DEFICIENT GROUP 3 MEDULLOBLASTOMA

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Medulloblastoma has been categorized into four subgroups based on gen- etic, epigenetic and transcriptional profiling. However, molecular pathways determining radiotherapy response in this tumor remain elusive. Here, we investigated the role of the EZH2-dependent histone H3K27 tri-methylation in radiotherapy response in medulloblastoma. We demonstrate that 47.2% of group 3 and 4 medulloblastoma patients have H3K27me3-deficient tumors. Loss of H3K27me3 was associated with a radiosensitive phenotype, high relapse rates and poor overall survival. We show that an epigenetic switch from H3K27me3 to H3K27ac occurs at specific genomic loci in H3K27me3-deficient medulloblastoma cells after irradiation resulting in up-regulation of EPHA2 (ephrin type-A receptor 2) stimulates an excessive activation of the pro-survival AKT signaling pathway leading to radiotherapy resistance. We show that BET inhibition targets radiation re- sistant H3K27me3-deficient medulloblastoma by decreasing H3K27me3 levels, blunting EPHA2 overexpression and mitigating the excessive AKT signaling. Additionally, BET inhibition sensitizes medulloblastoma cells to radiation by enhancing apoptotic response through suppression of Bcl-XL and up-regulation of Bim expression. Our work demonstrates a novel mech- anism of radiosensitivity and Nichnich in medulloblastoma and identifies an epigenetic marker predictive of radiotherapy response. Based on these findings we propose an epitogenetically guided treatment approach targeting radiotherapy resistance in medulloblastoma patients.

EMBR-05. THE TENTATIVE APPLICATION OF EN BLOC CONCEPT IN THE PEDIATRIC BRAIN TUMOR: EXPERIENCE FROM A LARGE PEDIATRIC CENTER IN CHINA

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Background: The less allowable blood loss and tolerance of intraoperative blood loss of children lead to the high rate of massive blood transfusion in the treatment of brain tumor. The surgical concepts of en bloc resection may contribute to the improvement of brain tumor resection. Objective: To investigate the effects of en bloc concept on short- and long-term outcomes in pediatric brain tumors and factors associated with the application of en bloc concept. Methods: According to the surgical concept involved, the patients were divided into three subgroups-complete en bloc concept, partial en bloc concept and piecemeal concept. The machine comparison (preoperative age, gender, en bloc and en bloc group formed from the first two subgroups) was conducted based on age, tumor location, lesion volume, and pathological diagnosis to investigate the effects of en bloc concept on the short-term outcomes. Then the patient data after January 2018, when the en bloc concept was routinely integrated into brain tumor surgery in our medical center, were reviewed and analyzed to find out the predictors associated with the application of en bloc concept. Results: In the en bloc group, the perioperative outcomes including hospital stay (p=0.001), PICU stay (p=0.003), total blood loss (p=0.015), transfusion rate (p=0.005) and complication rate (p=0.039), were all significantly improved. The multinomial logistic regression analysis showed that tumor volume and imaging features, like bottom vessel, encasing nerve or pass-by vessel, finger-like attachment, ratio of “limited lysis” showed that tumor volume and imaging features, like bottom vessel, encasing nerve or pass-by vessel, finger-like attachment, ratio of “limited line” and ratio of “clear line” remained independent factors for the application of en bloc concept in our medical center. Conclusion: This study supports the application of complete or partial en bloc concept in the pediatric brain tumor surgery referring to the preoperative imaging features, and consequently, en bloc concept can improve the short outcomes without significant increases in neurological complication. Large series and Additional supportive evidence are still warranted.

EMBR-06. EFFECTIVE INHIBITION OF MYC-AMPLIFIED GROUP 3 MEDULLOBLASTOMA BY FACT-TARGETED CURAXIN DRUG CBL0137

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Medulloblastoma (MB) is the most common malignant pediatric brain tumor that can be categorized into four major molecular subgroups. Group 3 MB with MYC amplification (MYCamp-G3-MB) has been shown to be highly aggressive and exhibited worst prognosis, indicating the need for novel effective therapy most urgently. A few epitogenic targeted therapeutic strategies have recently been proven to effectively treat preclinical models of MYCamp- G3-MB, including BET inhibition, HDAC inhibition and SETD8 inhibition, unveiling a promising direction for further investigation. In this study, we carried out systemic bioinformatic analyses of public-available MB datasets as well as functional genomic screening datasets of primary MYCamp-G3-MB lines to search for other potential therapeutic targets within epigenetic modulators. We identified SRRP1, a subunit of histone-chaperone FACT complex, to be the top drug target candidate as it is highly cancer-dependent in whole-genome CRISPR-Cas9 screening across multiple MYCamp-G3-MB lines; significantly upregulated in MYCamp-G3-MB compared to normal cere- bellum and most of the rest MB subtypes; its higher expression is correlated with worse prognosis; and it has a blood-brain-barrier penetrable targeted drug that has entered early phase human clinical trials already. Then we utilized DNA-interference approach to verify the cancer-dependency of SRRP1 in multiple MYCamp-G3-MB lines and further confirmed the therapeutic efficacy of FACT-targeted curaxin drug CBL0137 on treating preclinical models of MYCamp-G3-MB in vitro and in vivo, including an orthotopic intracranial xenograft model. Mechanistically, transcriptome analyses showed
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CBLO137 preferentially suppressed cell-cycle and DNA-repair related biological processes. Moreover, it selectively disrupted transcription of MYC and NEUROD1, two critical oncogenic transcription factors of MYC-driven G3-MB, via depletion of FACT complex from their promoter regions. In summary, our study demonstrates FACT-targeted CBLO137 works effectively on treating MYC-Medulloblastoma, presenting another promising epigenetic-targeted therapeutic strategy against the most devastating form of MB.

EMBR-07. MYC BUT NOT MYCN GENERATES AGGRESSIVE GROUP 3 MEDULLOBLASTOMA BY ARF PATHWAY SUPPRESSION Oliver Mannweiler1, Holger Weisshaupt2, Sonja Hutter4, Maoo Zhao2, Gabriela Rösten3, Laura Bremschmid4, Annemieke Verbeet1, Anders Sundström1, Karl Annesuver5, Maria Kasper2, and Frederik Swartling1. 1Science for Life Laboratory, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden; 2Department of Bioscience and Nutrition, Karolinska Institutet, Huddinge, Stockholm, Sweden

Medulloblastoma (MB), the most common malignant pediatric brain tumor, often harbor MYC amplifications at 8q24. In the presence of a functional p53 suppressor protein, to elucidate the mechanism behind this inexplicable tumor development we generated an inducible, immunocompetent transgenic mouse model of MYC-driven MB. Tumors driven from the glutamate transporter promoter molecularly resembled aggressive medulloblastoma subgroups. In one case was classified as Group 3, and the second as SHH by both CMA and histopathology/IHC, and the second case was indeterminate by CMA but was as classified as Group 3 by degree comparable to radiation therapy, a mainstay in the treatment of MB. Finally, we examined the mechanism of digoxin-mediated cell killing using RNA-seq. This work identified LHX9, a member of the LIM homeobox family of transcription factors, as the gene most significantly down-regulated following treatment (Huang and Injac et al, Sci Trans Medicine, 2018). Homologs of LHX9 play key roles in cerebellar development via spatially and temporally restricted expression and LH9X may be proposed as a therapeutic strategy against the most devastating form of MB. Clinical targeting of core TFs would represent a novel approach to targeting this devastating disease.

EMBR-08. CORRELATION OF HISTOPATHOLOGY, CHROMOSOMAL MICROARRAY, AND NANOSTRING BASED 22-GENE ASSAY FOR MEDULLOBLASTOMA SUBGROUP ASSIGNMENT ON “HEAD START” 4 CLINICAL TRIAL Girish Dhobale1, Patricia O'Regan Blue1, Jiri Krome2, Isabel Almizra-Suarez1, Eugene Hwang1, Christopher Peterson2, Daniel Boue1, and Jonathan Finlay1. 1University of Alabama at Birmingham, Birmingham, AL, USA, 2Nationwide Children's Hospital, Columbus, OH, USA. 1Children's National Medical Center, Washington, DC, USA

“Head Start” 4 (HS 4) is a prospective randomized clinical trial that tailors treatment based on medulloblastoma molecular subgroups and response to induction chemotherapy to compare the efficacy of one versus three (tandem) cycles of myeloablative therapy. Advances in RNA and DNA profiling have identified four core molecular subgroups of medulloblastoma with prognostic significance: Sonic Hedgehog (SHH) subtype, WNT subtype, Group 3, and Group 4. In HS 4 trial, we utilize a combination of histopathology and immunohistochemistry (pathology/IHC), as well as chromosomal microarray analysis (CMA) utilizing OncoScan2.3 (Thermo Fisher) to classify medulloblastoma samples into either SHH, WNT, or non-WNT/non-SHH (Group 3/4) subgroups at the time of diagnosis. NanoString based 22-gene assay is performed retrospectively to test concordance. We have pathology/IHC, CMA, and NanoString data on 26 infants and young children with medulloblastoma at our institution. It was feasible to assign samples to SHH, WNT, and non-WNT/non-SHH subgroups in all but two cases: one case was classified as Group 3, and the second as SHH by both CMA and NanoString. CMA was indeterminate in six cases, of which, pathology/IHC was able to assign any samples aforementioned three subgroups. NanoString was indeterminate in two cases: one case was classified as SHH by CMA and pathology/IHC, and the second case was indeterminate by CMA but was assigned as non-WNT/non-SHH on pathology/IHC. There is excellent correlation between NanoString and combination of histopathology and CMA for core medulloblastoma subgrouping on HS 4. Methylation studies are ongoing.

EMBR-09. EXAMINING THE ROLE OF THE DEVELOPMENTALLY ENCODED TRANSCRIPTION FACTOR, LHX9, IN GROUP 3 MEDULLOBLASTOMA Sarah Injac1,2, Bryan Rivas1,2, Amir Arbabzadeh1,3, Yanhau Zhao1,4, D. William Parsons1,2, and Stephen Mack1,2. 1Texas Children’s Cancer and Hematology Centers, Houston, TX, USA; 2Baylor College of Medicine, Houston, TX, USA, 3Graduate Program in Chemical and Biomolecular Engineering, Rice University, Houston, TX, USA

Medulloblastoma (MB) is the most common malignant brain tumor of childhood. Despite major advances in our understanding of the biology of MB, novel treatments remain urgently needed. Using a chemical-genomics driven drug repurposing strategy, we identified the cardiac glycoside family of glycosides as potential therapeutic agents for Group 3 MB. We now report that knockdown of LHX9 in MB-derived cell lines results in marked growth inhibition. RNA-seq analysis of LHX9-depleted cells showed changes which included alterations in extracellular matrix-receptor interactions and TGFβ signaling. These findings raise the possibility that LHX9 is a cis-regulated mediator of cell killing and that LHX9 represents a key dependency required for the growth of Group 3 MB. Clinical targeting of core TFs would represent a novel approach to targeting this devastating disease.

EMBR-10. INOSITOL TREATMENT INHIBITS MEDULLOBLASTOMA THROUGH SUPPRESSION OF EPIGENETIC-METABOLIC DRIVING METABOLIC ADAPTATION Tovinca Biegel1, Nicola Pommela2, Xinyu Zhang1, Gillian Morrison2, Steve M. Pollard2, Christopher D. Bennett3, Steven C. Clifford1, Andrew Pett4, and Silvia Marino1. 1Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK, 2Centre for Regenerative Medicine & Cancer Research UK Edinburgh Centre, The University of Edinburgh, Edinburgh, UK, 3Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK, 4Birmingham Children’s Hospital, Birmingham, UK, 5Newcastle University Centre for Cancer, Wolfson Childhood Cancer Research Centre, Translational and Clinical Research Institute, Newcastle upon Tyne, UK

Medulloblastoma (MB) is the most common paediatric malignant brain tumour and is classified into four distinct molecular subgroups (WNT, SHH, G3 and G4), each of them further subdivided into subtypes with different prognoses and responses to therapy. Deregression of chromatin modifier genes plays an essential role in MB, particularly in G4 subgroup, that offers many targets for therapy. The diseased group 4 MB samples are mainly being treated as Group 3 MB, however, has not been previously experimentally evaluated. We now report that knockdown of LHX9 in MB-derived cell lines results in marked growth inhibition. RNA-seq analysis of LHX9-depleted cells showed changes which included alterations in extracellular matrix-receptor interactions and TGFβ signaling. These findings raise the possibility that LHX9 is a cis-regulated mediator of cell killing and that LHX9 represents a key dependency required for the growth of Group 3 MB. Clinical targeting of core TFs would represent a novel approach to targeting this devastating disease.

EMBR-11. SYNERGISTIC DRUG COMBINATIONS FOR THE TREATMENT OF MYC AMPLIFIED GROUP 3 MEDULLOBLASTOMA Simon Zeuner1,2, Johanna Vollmer1,2, Heike Peterziel1,2, Romain Siguid1,2, Sina Oppermann1,2, Dina ELHarouni1, Thomas Hielscher1, Olaf Wint1,2, Ina Ochlem1,2, Till Mikes1,2, and Jonas Eckert1,2. 1Hope Children’s Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, 2Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany, 3Bioinformatics and Omics Data Analytics, German Cancer Research Center (DKFZ), Heidelberg, Germany, 4Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: Medulloblastoma (MB) is a highly aggressive brain tumour in children. Patients with Group 3 MB harbouring a 3MYC-amplification