studies provide new insights into the role of OLIG2 in radiotherapy resistance and metastasis in *MYC*-amplified MB and propose a novel therapeutic approach to treating metastatic *MYC*-amplified MB.

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

Jordan Hansford[1,2], Jie Huang[3], Andrew Dodgshun[4], Bryan Li[5,6], Eugene Hwang[7], Sarah Leary[8], Amar Gajjar[9], Katja Von Hoff[10], Raelene Endersby[11,12], Olivia Wells[13], Alison Wray[1], Rishi Kotecha[14,15], David Raleigh[16,17], Schuyler Stoller[18], Sabine Mueller[18], Steven Schild[19], Pratiti Bandopadhayay[20], Maryam Fouladi[21], Eric Bouffet[5], Annie Huang[5,6], Arzu Onar[22], and Nicholas Gottardo[14,15]; [1]Royal Children's Hospital; Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]University Melbourne, Melbourne, VIC, Australia, [3]Children's Oncology Group Department of Biostatistics, Memphis, TN, USA, [4]Christchurch Children's Haematology/Oncology Centre, Christchurch, New Zealand, [5]Division of Hematology/Oncology, Department of Pediatrics, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada, [6]Department of Laboratory Medicine and Pathobiology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [7]Children's National, Division of Oncology, Washington DC, USA, [8]Fred Hutchinson Cancer Centre, Seattle, WA, USA, [9] St. Jude Children's Research Institute, Memphis, TN, USA, [10]Department of Pediatric Oncology and Haematology, Charite University Medicine, Berlin, Germany, [11]Brain Tumour Research Program, Telethon Kids Institute, Nedlands, WA, Australia, [12]University of Western Australia, Perth, WA, Australia, [13]Royal Children's Hospital, Melbourne, VIC, Australia, [14]Telethon Kids Cancer Centre, Telethon Kids Institute, University of Western Australia, Perth, WA, Australia, [15]Department of Clinical Haematology, Oncology and Bone Marrow Transplantation, Perth Children's Hospital, Perth, WA, Australia, [16]Department of Radiation Oncology, UCSF, San Francisco, CA, USA, [17]Department of Neurologic Surgery, UCSF, San Francisco, CA, USA, [18]Department of Pediatric Oncology, UCSF, San Francisco, CA, USA, [19]Mayo Clinic, Department of Radiation Oncology, Phoenix, AZ, USA, [20]Boston Children's Hospital, Dana Farber Children's Institute, Boston, MA, USA, [21]Nationwide Children's Hospital, Department of Neuro-Oncology, Columbus, OH, USA, [22]Children's Oncology Group Department of Biostatistics, Memphis, TN, Canada

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 tumours, primarily medulloblastoma (MB), but also including the entity formerly known as CNS-PNET and atypical teratoid rhabdoid tumors. 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 sufficient treatment and outcome data from North American and Australian cases were pooled. To investigate associations between variables, Fisher's exact and Wilcoxon-Mann-Whitney tests, and Spearman correlations were used as appropriate. Kaplan-Meier plots, log-rank tests, and Cox proportional hazards models were used in survival analysis. Results: We describe a 30-year review of the 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 find young children <3 years of age have a dramatically poorer outlook compared to older children (5-year OS 16.2% +/- 5.3% vs 67.3% +/- 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 future studies. Assessment of radiation therapy is not 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

Nishanth Gabriel[1], Kumaresh Balaji[1,2], Matthew Inkman[1], Kay Jayachandran[1], Jin Zhang[1], Sonika Dahiya[1], and Michael Goldstein[1]; [1]Washington University School of Medicine, St. Louis, MO, USA, [2]Rush University School of Medicine, Chicago, IL, USA

Medulloblastoma has been categorized into four subgroups based on genetic, 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 radioresistant 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 altering the transcriptional profile. The resulting 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 resistance in H3K27me3-deficient medulloblastoma by suppressing H3K27ac 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 mechanism of radiation resistance in medulloblastoma and identifies an epigenetic marker predictive of radiotherapy response. Based on these findings we propose an epigenetically 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

Liangliang Cao and Jie Ma; Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, Shanghai, China

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 outcomes of 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 matching-comparison (piecemeal group and en bloc group formed from the first two subgroups) was conducted based on age, tumor location, lesion volume, and pathological diagnosis to investigate effect of the 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 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 compared with piecemeal concept, 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-AMPLIFIFIED GROUP 3 MEDULLOBLASTOMA BY FACT-TARGETED CURAXIN DRUG CBL0137

Jiajia Wang and Jie Ma; Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, Shanghai, China

Medulloblastoma (MB) is the most common malignant pediatric brain tumor that can be categorized into four major molecular subgroups. Group 3 MB with MYC amplifification (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 epigenetic 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 identififfied SSRP1, 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 cerebellum 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 RNA-interference approach to verify the cancer-dependency of SSRP1 in multiple MYCamp-G3-MB lines and further confiffirmed the therapeutic effifficacy 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