studies showed that *Eed*-deleted medulloblastomas similarly showed aberrant, myocyte differentiation, but unlike CGNPs, did not undergo widespread apoptosis. *Eed*-deleted medulloblastomas progressed more rapidly than control tumors, indicating that the inappropriate, muscle-like differentiation did not slow tumor growth. *Ezh2*-deleted medulloblastomas similarly progressed more rapidly than controls. Our data show that the PRC2 complex acts to enforce neuronal lineage commitment in both development and tumorigenesis and to restrain tumor growth in SHH medulloblastoma. Myocyte differentiation in *Eed*-deleted tumors suggests that PRC2 loss of function may contribute to the medullomyoblastomas that have been observed in patients. The differences in developmental phenotype show that EZH2 and EED functions are non-identical and can be dissociated, while similar increase in tumor progression show tumor suppressive functions for both EED and EZH2.

EMBR-16. SMOOTHENED-ACTIVATING LIPIDS DRIVE RESISTANCE TO CDK4/6 INHIBITION IN HEDGEHOG-ASSOCIATED MEDULLOBLASTOMA

Vikas Daggubati[1], Jordan Hochstelter[1], Anirudh Bommireddy[1], Abrar Choudhury[1], Alexis Leigh Krup[1], Pervinder Choski[1], Pakteema Tong[2], Amy Li[2], Libin Xu[2], Jeremy Reiter[1], and David Raleigh[1]; [1]University of California, San Francisco, San Francisco, CA, USA, [2]University of Washington, Seattle, WA, USA

Background: Medulloblastoma is an aggressive pediatric brain tumor that is associated with misactivation of the Hedgehog (HH) pathway. Our lab has shown that *CDK6*, a critical activator of the cell cycle, is a direct transcriptional target of oncogenic HH signaling, and that inhibiting CDK6 blocks the growth of HH-associated medulloblastoma in mice. A clinical trial exploring the efficacy of CDK6 inhibition in medulloblastoma patients is underway, but prior attempts to target the HH pathway in medulloblastoma have been encumbered by resistance to molecular monotherapy. Thus, we sought to identify mechanisms of resistance to CDK6 inhibition in HH-associated medulloblastoma. Methods: We performed orthogonal CRISPR and CRISPR interference screens in HH-associated medulloblastoma cells treated with pharmacologic inhibitors of CDK6 *in vitro*, and RNA-sequencing of HH-associated medulloblastomas with genetic deletion of CDK6 *in vivo*. Mechanistic and functional validation of resistance pathways was performed using CRISPR interference, immunoblotting, immunofluorescence, genetics, and pharmacology. Lipid quantification was carried out by ultra-high performance liquid chromatography-tandem mass spectrometry. Results: Our results reveal that decreased ribosomal protein expression underlies resistance to CDK6 inhibition in HH-associated medulloblastoma, leading to endoplasmic reticular (ER) stress and activation of the unfolded protein response (UPR). We show that ER stress and the UPR increase the activity of enzymes producing Smoothened-activating sterol lipids that sustain oncogenic HH signaling in medulloblastoma despite CDK6 inhibition. These discoveries suggest that combination molecular therapy against CDK6 and HSD11ß2, an enzyme producing Smoothened-activating lipids, may be an effective treatment for HH-associated medulloblastoma. In support of this hypothesis, we demonstrate that concurrent genetic deletion or pharmacological inhibition of CDK6 and HSD11ß2 additively blocks the growth of multiple models of HH-associated medulloblastoma in mice. Conclusions: Smoothened-activating lipid biosynthesis underlies resistance to CDK6 inhibition in HH-associated medulloblastoma, revealing a novel combination therapy to treat the most common malignant brain tumor in children.

EMBR-17. DE-INTENSIFICATION OF RADIOTHERAPY IN RIGOROUSLY DEFINED LOW-RISK WNT-SUBGROUP MEDULLOBLASTOMA IS ASSOCIATED WITH UNACCEPTABLY HIGH RISK OF NEURAXIAL FAILURE: RESULTS FROM THE PROSPECTIVE FOR-WNT STUDY

Tejpal Gupta, Shizan Pervez, Archya Dasgupta, Abhishek Chatterjee, Rahul Krishnatry, Jayant GodaSastri, Maya Prasad, Girish Chinnaswamy, Sridhar Epari, Ayushi Sahay, Neelam Shirsat, Prakash Shetty, Aliasgar Moiyadi, Farnaz Shaikh, Nazia Bano, and Rakesh Jalali; Tata Memorial Centre, Mumbai, Maharashtra, India

Background: Medulloblastoma is a heterogenous disease comprising four molecular subgroups (WNT, SHH, Group 3, and Group 4) with varying outcomes. Excellent long-term survival (>90%) has prompted de-intensification of therapy in WNT-subgroup medulloblastoma globally. FOR-WNT is one such prospective study (CTRI/2017/12/010767) testing the hypothesis that focal conformal radiotherapy (RT) (54Gy/30 fractions/6-weeks) with avoidance of upfront craniospinal irradiation (CSI) followed by standard adjuvant chemotherapy significantly reduces RT-related late toxicity without unduly compromising survival in low-risk WNT-subgroup medulloblastoma (residual tumor <1.5cm^2 with no evidence of metastases in children aged between 3–16 years). Methods: Patients with low-risk WNT-subgroup medulloblastoma were enrolled after written informed consent/assent. To ensure patient safety, stopping rules were devised according to group-sequential method. Results: Between July 2017 till Feb 2019, seven children of WNT-pathway medulloblastoma were treated with focal conformal RT followed by 6-cycles of adjuvant chemotherapy (cisplatin, cyclophosphamide, and vincristine). One child succumbed to acute renal failure during chemotherapy, while the other 6 patients completed all 6-cycles as planned. Three children were detected with neuraxial failure (supratentorial brain and/or spine) without synchronous local recurrence in the treated tumor-bed on surveillance neuro-imaging between 1.5–2 years from index diagnosis following which the study was terminated prematurely. All 3 children with relapse were treated with salvage CSI (35Gy/21 fractions) with (conformal avoidance of previously treated tumor-bed) plus boost irradiation (10.8-18Gy/6–10 fractions) of metastatic deposits resulting in complete/near complete response and are alive with controlled disease. The other 3 children have not shown any evidence of relapse for over 2-years from index diagnosis and remain on active clinico-radiological surveillance. Conclusion: In rigorously defined low-risk WNT-subgroup medulloblastoma, avoidance of upfront CSI is associated with unacceptably high risk of neuraxial failure. A successor study (FOR-WNT 2) incorporating low-dose CSI (18Gy/10 fractions) with similar tumor-bed dose and adjuvant systemic chemotherapy is currently underway.

EMBR-18. LASER INTERSTITIAL THERMAL THERAPY FOR RECURRENT MEDULLOBLASTOMA

Jordan Xu[1,2], Jodi Pathare[1], Clay Hoerig[1], Aaron Goldberg[1], Chenue Abongwa[1], Ashley Plant[1], and Joffre Olaya[1,2]; [1]Children's Hospital of Orange County, Orange, CA, USA, [2]University of California, Irvine Medical Center, Orange, CA, USA

Background: Medulloblastoma is one of the most common malignant childhood brain tumors and is managed by maximal surgical resection followed by cranio-spinal irradiation and adjuvant chemotherapy. The estimates for survival have not significantly improved over the last two decades, and survivors have an increased risk of poor quality of life. Disease relapse occurs in around 30% of children and survival is less than 20%. Laser interstitial thermal therapy (LITT) is a minimally invasive approach that has been increasingly used to treat brain lesions, particularly for high-risk surgeries. While LITT has been described in a variety of primary brain tumors, including glioblastoma multiforme and metastatic brain tumors, there have been few reports of LITT for recurrent medulloblastoma. Case Description: We describe a case of an 11-year-old female with recurrent medulloblastoma first treated at age 5. She initially underwent gross total resection complicated by severe posterior fossa syndrome followed by chemotherapy and radiation (per ACNS0332). She was unfortunately found to have a new enhancing lesion on surveillance imaging 6 years later, and a biopsy confirmed recurrent tumor. Due to morbidity from initial surgery, the family did not wish to pursue further open resection but agreed to proceed with laser ablation as an alternative. She continues on Avastin/irinotecan/TMZ. Surveillance MRI nearly a year later shows a significant reduction in tumor size and enhancement. Conclusion: Recurrent medulloblastoma is a highly aggressive tumor that conveys a poor prognosis. LITT offers a less invasive procedure that may serve as an adjunct in treating recurrent tumor or as palliation. Longer term follow-up and additional cases will help understand the efficacy of LITT in recurrent medulloblastoma.

EMBR-19. SHH-DRIVEN MEDULLOBLASTOMA WITH CONCURRENT UNILATERAL RENAL AGENESIS

Ashley Aaroe[1], Sanila Sarkar[2], Farha Sherani[3], Mary McAleer[4], Greg Fuller[5,6] and Wafik Zaky[2]; [1]Department of Neuro-Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2]Department of Pediatrics, Division of Pediatrics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [3]Cancer & Blood Disorders Center, Driscoll Children's Hospital, Corpus Christi, TX, USA, [4]Department of Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [5]Department of Anatomic Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA, [6]Department of Neuroradiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Case Presentation: A 3-year-old female with insignificant past medical history presented with 6 weeks of headaches, emesis, and lethargy. MR imaging identified a heterogeneously enhancing right cerebellar hemispheric mass and obstructive hydrocephalus. Gross total resection was performed without complications; pathology revealed classical WHO grade 4 medulloblastoma (MB). MR imaging of the spine and cerebrospinal fluid testing were negative for disseminated disease. Treatment for standard risk medulloblastoma was initiated, comprising proton craniospinal irradiation with posterior fossa boost and concurrent vincristine, followed by adjuvant chemotherapy with vincristine, lomustine, cisplatin, and cyclophosphamide as standard of care. Next generation sequencing of the tumor tissue performed using a high-