specification by altering the components of the PRC1 complex. These studies identify the mechanistic basis of BMI1 co-operation with SMARCB1 loss in ATRT and establish BMI1 inhibition as a novel therapeutic approach in ATRT.

ATRT-07. HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS STEM CELL TRANSPLANTATION FOR AN ADULT PRESENTATION OF THE ATYPICAL TERATOID-RHABDOID TUMOR (ATRT)

Maciej Mrugala[1], Aditya Raghunathan[2], and Jose Leis[1]; [1]Mayo Clinic, Phoenix, AZ, USA, [2]Mayo Clinic, Rochester, MN, USA

BACKGROUND: ATRT is a rare primary CNS tumor occurring predominantly in children with the peak age of onset at less than 3 years old. Adult presentations are exceedingly rare, associated with poor prognosis and no standard therapies exist. METHODS: Case presentation. RESULTS: 61 y old woman presented with headaches, sinus pressure, and cognitive decline. She was found to have a pineal tumor causing obstructive hydrocephalus. The patient underwent gross total resection of the tumor with pathology reported as ATRT. Her CNS staging, including CSF, was negative. She subsequently received radiotherapy to the resection bed. There was no consensus on what should be the next step in her therapy given lack of data in adults. Ultimately, we adopted a pediatric regimen and treated the patient with a combination of high-dose chemotherapy with cisplatin, cyclophosphamide, and vincristine followed by autologous stem cell transplantation (ASCT). This regimen called for up to 4 cycles of chemotherapy with ASCT and we had collected enough cells to complete 3 cycles. The patient completed 2 cycles of therapy with moderate toxicity. Her CNS imaging remained stable with no evidence of recurrence 14-months from the original diagnosis. CONCLUSIONS: ATRT continues to be an exceedingly rare diagnosis in adults. No standard therapies exist and treatment decisions are challenging given lack of data and lack of prospective clinical trials. Pediatric regimens can frequently be adopted for adults although high-dose chemotherapy with ASCT can be challenging. Our case exemplifies the feasibility of treating ATRT in an adult in the most aggressive fashion.

ATRT-08. A PHASE II STUDY OF CONTINUOUS LOW DOSE PANOBINOSTAT IN PAEDIATRIC PATIENTS WITH MALIGNANT RHABDOID TUMORS/ATYPICAL TERATOID RHABDOID TUMORS

Paul Wood[1,2], Jayesh Desai[3,4], Kelly Waldeck[3], Jason Cain[5], Nick Gottardo[6], Robyn Strong[7,8], Kathryn Kinross[7,8], Michelle Carr[7,8], Janelle Jones[7,8], Lily Wong[9], David Ziegler[10], Jordan Hansford[11,12], Michael Michael[3], and David Ashley[13]; [1]Monash Health, Melbourne, VIC, Australia, [2]Monash University, Melbourne, VIC, Australia, [3]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [4]Australia and New Zealand Sarcoma Association, Melbourne, VIC, Australia, [5]Hudson Institute of Medical Research, Melbourne, VIC, Australia, [6]Princess Margaret Hospital for Children, Perth, WA, [7]Australian and New Zealand Children's Haematology/Oncology Group, Melbourne, VIC, Australia, [8]Australasian Children's Cancer Trials, Melbourne, VIC, Australia, [9]Kids Oncology and Leukaemia Trials (KOALA), Sydney, NSW, Australia, [10]Sydney Children's Hospital, Sydney, NSW, Australia, [11]Royal Children's Hospital, Melbourne, VVIC, Australia, [12]University of Melbourne, Melbourne, VIC, Australia, [13]The Preston Robert Tisch Brain Tumor Centre, Durham, NC, USA

BACKGROUND: Panobinostat treatment has been shown to terminally differentiate malignant rhabdoid tumor (MRT)/atypical teratoid rhabdoid tumors (ATRT) in pre-clinical models. This is an open label, phase II study of panobinostat in patients with newly diagnosed or relapsed MRT/ATRT. AIMS: To assess the anti-tumor activity of low dose, continuous panobinostat, its associated toxicities, the biological activity of low dose panobinostat by measuring histone acetylation status in peripheral mononuclear cells (PMNC), and markers of differentiation in fresh tumor tissue specimens. METHODS: Following cycles of induction and consolidation chemotherapy and/or radiation treatment, patients were enrolled and commenced on panobinostat as a continuous daily oral dose starting at 10mg/m^2 following a three-week wash out period between therapies. Real-time acetylation status, measuring acetylated H4 on PMNC, was performed to determine the pharmacodynamics of panobinostat. Patients were monitored for drug toxicities with the possibility of dose reductions in decrements of 2mg/m^2. RESULTS: Six patients with newly diagnosed ATRT/MRT and one patient with relapsed MRT have been enrolled to date. The average age at enrollment was 2.5 years. Currently, six patients (85.7%) remain on study with a mean treatment duration of 170 days (range 44–327 days). One patient was removed from study at day 44 due to disease progression. The main dose-limiting toxicity observed to date has been myelosuppression. Panobinostat, at a dose of 10mg/m^2, caused significant acetylation of H4 in PMNC. CONCLUSIONS: Treatment with panobinostat appears to be well tolerated in infants with MRT/ATRT, with successful real-time pharmacodynamic assessment of H4 acetylation.

ATRT-09. IDENTIFICATION OF HUB GENES IN ATYPICAL TERATOID/RHABDOID TUMORS BY MULTIPLE-MICROARRAY ANALYSIS

Wei Liu[1,2], Yi Chai[1,2], Junhua Wang[1,2], and Yuqi Zhang[1,2]; [1]School of Clinical Medicine, Tsinghua University, Beijing, China, [2]Department of Neurosurgery, Yuquan Hospital, School of Clinical Medicine, Tsinghua University, Beijing, China

BACKGROUND: Atypical teratoid/rhabdoid tumors (ATRT) are rare, highly malignant neoplasms arising in infants and young children. However, the biological basis of ATRTs remains poorly understood. In the present study, we employed integrated bioinformatics to investigate the hub genes and potential molecular mechanism in ATRT. METHODS: Three microarray datasets, GSE35943, GSE6635 and GSE86574, were downloaded from Gene Expression Omnibus (GEO) which contained a total of 79 samples including 32 normal brain tissue samples and 47 ATRT samples. The RobustRankAggreg method was employed to integrate the results of these gene expression datasets to obtain differentially expressed genes (DEGs). The GO function and KEGG pathway enrichment analysis were conducted at the Enrichr database. The hub genes were screened according to the degree using Cytoscape software. Finally, transcription factor (TF) of hub genes were obtained by the NetworkAnalyst algorithm. RESULTS: A total of 297 DEGs, consisting of 94 downregulated DEGs and 103 upregulated DEGs were identified. Functional enrichment analysis revealed that these genes were associated with cell cycle, p53 signaling pathway and DNA replication. Protein-protein interaction (PPI) network analysis revealed that CDK1, CCNA2, BUB1B, CDC20, KIF11, KIF20A, KIF2C, NCAPG, NDC80, NUSAP1, PBK, RRM2, TPX2, TOP2A and TTK were hub genes and these genes could be regulated by MYC, SOX2 and KDM5B according to the results of TF analysis. CONCLUSIONS: Our study will improve the understanding of the molecular mechanisms and provide novel therapeutic targets for ATRT.

ATRT-10. ATYPICAL TERATOID/RHABDOID TUMOR OF THE PINEAL REGION IN A PEDIATRIC PATIENT

Carlos Almeida Jr[1], Bruna Minniti Mançano[1], Marcus Matsushita[1], Stephanie Previdelli[2], Marina Lopes Lamim[2], Fabio Costa Faustino[1], Fernanda Magalhaes Souza[1], and Lucas Dias Lourenço[1]; [1]Barretos´s Children and Young Adults Cancer Hospital, Barretos, Sao Paulo, Brazil, [2]School of Health and Science Dr Paulo Prata, Barretos, Sao Paulo, Brazil

BACKGROUND: Atypical teratoid/rhabdoid tumor (ATRT) is a malignant neoplasm of the central nervous system and corresponds to 1.5% of all intracranial tumors. Mainly affects children under three years of age and shows aggressive behavior (most pediatric patients succumb to their disease within a year after the initial diagnosis, despite the treatment performed). Its place of occurrence in children is preferably in the posterior fossa, and it is rare to appear in other regions. There are only seven patients with ATRT reported on literature; all of them are adults. We present the case of a pediatric patient with a tumor in the pineal region diagnosed as ATRT. CASE REPORT: Three-year-old female patient admitted with occipital headache, vomiting, and seizure. Magnetic resonance imaging (MRI) showed obstructive hydrocephalus secondary to a solid-cystic lesion located at the pineal region that was 3.0 x 3.0 x 3.5 cm in size. Spine MRI did not reveal leptomeningeal spreading. We performed an occipital transtentorial approach to achieve the best safe resection possible, and a ventriculoperitoneal shunt. Histological examination revealed ATRT. The patient received adjuvant treatment with radiotherapy and chemotherapy according to the "Head Start" protocol. One year after the surgery, MRI did not identify any remaining lesion. CONCLUSION: ATRT is an aggressive and rare neoplasm whose clinical picture depends on the location of the tumor; however, it must be considered in the differential diagnosis of tumors of the pineal region in the pediatric population.

ATRT-11. PREVALENCE OF GERMLINE VARIANTS IN SMARCB1 INCLUDING SOMATIC MOSAICISM IN AT/RT AND OTHER RHABDOID TUMORS

Ryota Shirai[1,2], Tomoo Osumi[1,3], Keita Terashima[3], Chikako Kiyotani[3], Meri Uchiyama[1,3], Shinichi Tsujimoto[1,3], Masanori Yoshida[1,2], Kaoru Yoshida[1], Toru Uchiyama[4], Daisuke Tomizawa[3], Yoko Shioda[3], Masahiro Sekiguchi[5], Kenichiro Watanabe[6], Dai Keino[7], Hitomi Ueno-Yokohata[1], Kentaro Ohki[1], Junko Takita[5], Shuichi Ito[2], Takao Deguchi[3], Nobutaka Kiyokawa[1], Hideki Ogiwara[8], Tomoro Hishiki[9], Seishi Ogawa[10], Hajime Okita[11,12], Kimikazu Matsumoto[3], Takako Yoshioka[11], and Motohiro Kato[1,3]; [1]Department of Pediatric Hematology and Oncology Research, National Research Institute for Child Health and Development, Tokyo, Japan, [2]Department of Pediatrics, Yokohama City University, Yokohama, Japan, [3]Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan, [4]Department of Human Genetics, National Research Institute for Child Health and Development, Tokyo, Japan,

[5]Department of Pediatrics, University of Tokyo, Tokyo, Japan, [6]Department of Hematology and Oncology, Shizuoka Children's Hospital, Shizuoka, Japan, [7]Department of Pediatrics, St. Marianna University School of Medicine Hospital, Kawasaki, Japan, [8]Division of Neurosurgery, National Center for Child Health and Development, Tokyo, Japan, [9]Division of Surgery Oncology, Children's Cancer Center, National Center for Child Health and Development, Tokyo, Japan, [10]Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [11]Department of Pathology, National Center for Child Health and Development, Tokyo, Japan, [12]Department of Pathology, Keio University School of Medicine, Tokyo, Japan

BACKGROUND: Genetic hallmark of atypical teratoid/rhabdoid tumor (AT/RT) is loss-of-function variants or deletions in *SMARCB1* gene on 22q11.2 chromosome, which is common to extracranial malignant rhabdoid tumors (MRT). Previous studies demonstrated that approximately one-thirds of AT/RT and extracranial MRT patients harbored germline *SMARCB1* variants as the rhabdoid tumor predisposing syndrome. We studied herein intensive analysis of the *SMARCB1* gene in AT/RT and extracranial MRT patients focusing on prevalence of germline genetic variants. PROCEDURE: In total, 16 patients were included. Both tumor-derived DNA and germline DNA were obtained from all patients. First, screening for *SMARCB1* alterations in the tumor specimens was done by direct sequencing, ddPCR and SNP array analysis. Then, analysis of germline DNA samples focusing on the genomic abnormalities detected in the paired tumors in each case was performed. RESULTS: In eight of 16 cases (50%), genomic alterations observed in the tumor-derived DNA were also detected in the germline DNA. It is worth noting that three patients had germline mosaicism. Two of three patients had mosaic deletion, including *SMARCB1* region, and the average copy number of the deleted region in the *SMARCB1* gene in the germline was 1.60 and 1.76. For another patient, the fraction of *SMARCB1* variants in normal cells was as low as 1.7%. CONCLUSIONS: Approximately half the MRT cases in this study had *SMARCB1* germline alterations. Considering the presence of low-frequency mosaicisms which conventional methods might overlook, inherited germline variants in predisposition genes are more important than previously assumed for the pathogenesis of pediatric cancers.

ATRT-13. DIFFERENT CELLS OF ORIGIN PAVE THE WAY FOR MOLECULAR HETEROGENEITY IN RHABDOID TUMORS

Monika Graf[1], Marta Interlandi[2,1], Natalia Moreno[1], Dörthe Holdhof[3], Viktoria Melcher[1], Dennis Kastrati[1], Gerd Meyer zu Hörste[4], Martin Dugas[2], Michael C. Frühwald[5], Thomas K. Albert[1], Ulrich Schüller[3,6], and Kornelius Kerl[1]; [1]Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany, [2]Institute of Medical Informatics, University of Münster, Münster, Germany, [3]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [4]Department of Neurology with Institute of Translational Neurology, University Hospital Münster, Münster, Germany, [5]Swabian Children's Cancer Center, University Children's Hospital Augsburg, Augsburg, Germany, [6]Research Institute Children's Cancer Center, 20251 Hamburg, Hamburg, Germany

Rhabdoid tumors (RT) are rare but highly aggressive pediatric neoplasms. These tumors carry homozygous loss-of-function alterations of *SMARCB1* in almost all cases with an otherwise low mutational load. RT arise at different intracranial (ATRT) as well as extracranial (MRT) anatomical sites. Three main molecular subgroups (ATRT-SHH, ATRT-TYR, ATRT-MYC) have been characterized for ATRT which are epigenetically and clinically diverse, while MRT show remarkable similarities with ATRT-MYC distinct from ATRT-SHH and ATRT-TYR. Even though there are hypotheses about various cells of origin among RT subgroups, precursor cells of RT have not yet been identified. Previous studies on the temporal control of *SMARCB1* knockout in genetically engineered mouse models have unveiled a tight vulnerable time frame during embryogenesis with regard to the susceptibility of precursor cells to result in RT. In this study, we employed single-cell RNA sequencing to describe the intra- and intertumoral heterogeneity of murine ATRT-SHH and -MYC as well as extracranial MYC tumor cells. We defined subgroup-specific tumor markers for all RT classes but also observed a notable overlap of gene expression patterns in all MYC subgroups. By comparing these single-cell transcriptomes with available single-cell maps of early embryogenesis, we gained first insights into the cellular origin of RT. Finally, unsupervised clustering of published human RT methylation data and healthy control tissues confirmed the existence of different cells of origin for intracranial SHH tumors and MYC tumors independent of their anatomical localizations.

ATRT-14. MACROPHAGE-TUMOR CELL INTERACTION PROMOTES ATRT PROGRESSION AND CHEMORESISTANCE

Viktoria Melcher[1], Monika Graf[1], Marta Interlandi[1,2], Natalia Moreno[1], Flavia W. de Faria[1], Su Na Kim[1], Dennis Kastrati[1], Sonja Korbanka[1], Amelie Alfert[1], Joachim Gerß[3], Gerd Meyer zu Hörste[4], Wolfgang Hartmann[5], Michael C. Frühwald[6,7], Martin Dugas[2], Ulrich Schüller[8,9], Martin Hasselblatt[10], Thomas K. Albert[1], and Kornelius Kerl[1]; [1]Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany, [2]Institute of Medical Informatics, University of Münster, Münster, Germany, [3]Institute of Biostatistics and Clinical Research, University of Münster, Münster, Germany, [4]Department of Neurology with Institute of Translational Neurology, Münster, Germany, [5]Gerhard-Domagk-Institute of Pathology, University of Münster, Münster, Germany, [6]Swabian Children's Cancer Center, University Children's Hospital Augsburg, Augsburg, Germany, [7]EU-RHAB Registry Center, Augsburg, Germany, [8]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [9]Research Institute Children's Cancer Center, Hamburg, Germany, [10]Institute of Neuropathology, University Hospital Münster, Münster, Germany

Atypical teratoid/rhabdoid tumors (ATRT) are pediatric brain neoplasms that are known for their heterogeneity concerning pathophysiology and outcome. The three genetically rather uniform but epigenetically distinct molecular subgroups of ATRT alone do not sufficiently explain the clinical heterogeneity. Therefore, we examined the tumor microenvironment (TME) in the context of tumor diversity. By using multiplex-immunofluorescent staining and single-cell RNA sequencing (scRNA-seq) we unveiled the pan-macrophage marker CD68 as a subgroup-independent negative prognostic marker for survival of ATRT patients. ScRNA-seq analysis of murine ATRT-SHH, ATRT-MYC and extracranial RT (eRT) provide a delineation of the TME, which is predominantly infiltrated by myeloid cells: more specifically a microglia-enriched niche in ATRT-SHH and a bone marrow-derived macrophage infiltration in ATRT-MYC and eRT. Exploring the cell-cell communication of tumor cells with tumor-associated immune cells, we found that Cd68+ tumor-associated macrophages (TAMs) are central to intercellular communication with tumor cells. Moreover, we uncovered distinct tumor phenotypes in murine ATRT-MYC that share genetic traits with TAMs. These intermediary cells considerably increase the intratumoral heterogeneity of ATRT-MYC tumors. *In vitro* co-culture experiments recapitulated the capability of ATRT-MYC cells to interchange cell material with macrophages extensively, in contrast to ATRT-SHH cells. We found that microglia are less involved in the exchange of information with ATRT cells and that direct contact is a prerequisite for incorporation. A relapse xenograft model implied that intermediary cells are involved in the acquisition of chemotherapy resistance. We show evidence that TAM-tumor cell interaction is one mechanism of chemotherapy resistance and relapse in ATRT.

ATRT-15. LY6D – A CANDIDATE FOR NANOPARTICLE-BASED TARGETED THERAPIES OF ATRT

Lea Hagemeier[1], Marthe Sönksen[1], Natalia Moreno[1], Romy Ettlinger[2], Hana Bunzen[2], and Kornelius Kerl[1]; [1]Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany, [2]Institute of Physics, University Augsburg, Augsburg, Germany

Atypical Teratoid Rhabdoid Tumors (ATRT) are aggressive brain malignancies of the infant. Despite intensive multimodal therapy, the overall prognosis remains poor, making investigations on targeted therapies crucial. Arsenic trioxide (ATO) is known to inhibit cell growth of ATRT *in vitro* and *in vivo* but its efficacy in solid tumors is limited by its adverse effects. We aimed to characterize whether a nanoparticle-based drug delivery could overcome these limitations. Therefore metal-organic frameworks containing ATO (MOF-ATO) were constructed. To improve drug specificity further, we searched for unique proteins on the surface of ATRT, in order to create antibody-drug-conjugates out of MOF-ATO and an ATRT-specific ligand. ATRT are marked by a biallelic loss of *SMARCB1*, which results in an activation of the repressive histone methyltransferase EZH2. After chemical inhibition of EZH2 with GSK126, a mass spectrometric based screening for differentially expressed surface proteins was performed. Treatment with ATO, as well as MOF-ATO and GSK126 each reduces the cell viability of ATRT cell lines. It results in a cell cycle arrest and an induction in apoptosis, being analysed *via* MTT test and flow cytometry. GSK126 treatment causes a significant upregulation of several cell surface proteins, upon them the Lymphocyte antigen 6 family member D (LY6D). Being rarely expressed on other human cells, this protein is an interesting candidate. An antibody-drug-conjugate consisting of MOF-ATO and LY6D-ligands could be a promising approach for future targeted therapies of ATRT.