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BACKGROUND: Atypical teratoid rhabdoid tumors (ATRTs) are among the most malignant brain tumors in early childhood and remain incurable. Myc-ATRT is driven by the Myc oncogene, which directly controls the intracellular protein synthesis rate. Proteasome inhibitor bortezomib (BTZ) was approved by the Food and Drug Administration as a primary treatment for multiple myeloma. This study aimed to determine whether the upregulation of protein synthesis and proteasome degradation in Myc-ATRTs increases tumor cell sensitivity to BTZ. METHODS: We performed differential gene expression and gene set enrichment analysis on matched primary and recurrent patient-derived xenograft (PDX) samples from an infant with ATRT. The expressions of proteasome-encoding genes were compared among this paired model as well as between the 24 human ATRT samples and normal brain tissues. The antitumor effect of BTZ was evaluated in three human Myc-ATRT cell lines (PDX-derived tumor cell line Re1-P6, B1-T2, and CHLA-266) and in the orthotopic xenograft models of Re1-P6 cell. RESULTS: Concomitant upregulation of the Myc pathway, protein synthesis, and proteasome degradation were identified in recurrent ATRTs. In ATRTs, the proteasome-encoding genes were highly expressed compared with in normal brain tissues, correlated with the malignancy of tumor cells, and were essential for tumor cell survival. BTZ inhibited proliferation and induced apoptosis through the accumulation of p53 in vitro and in vivo drug tests. Furthermore, BTZ inhibited tumor growth and prolonged survival in Myc-ATRT orthotopic xenograft mice. CONCLUSIONS: Our findings suggest that BTZ may be a promising targeted therapy for Myc-ATRTs.

ATRT-02. MEK/ERK SIGNALLING DEPENDENCY IN ATYPICAL TERATOID RHABDOID TUMOURS
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Atypical teratoid rhabdoid tumours (ATRTs) are high-grade malignant paediatric brain tumours with a less than one-year survival rate after diagnosis. Current treatment for ATRT, which includes high-intensity radiotherapy and chemotherapy, results in long-term side effects on ATRT patients. Hence, there is an urgent need to discover targeted therapies that could be used to treat patients with ATRT. As part of the Hudson Monash Paediatric Precision Medicine Program, we have collected 23 ATRT cell lines which we used to perform high-throughput small molecule and genetic (CRISPR) screening to identify new therapies and therapeutic targets. In parallel, we characterised the ATRT cell lines based on transcriptional (RNA-seq) and epigenetic (methylated) signatures. An integrative multi-omic approach was then used to uncover discrete vulnerabilities in specific subsets of ATRT patients. Strikingly, these include a number of druggable dependencies, such as MEK, CDK, HDAC, and Topoisomerase, that offer a promise of rapid clinical translation. In our study, we focus on MEK dependency in a subtype of ATRT lines to further define the underlying mechanisms and biomarkers. While future studies validating the MEK/ERK signalling dependency in a wider cohort of patient models and in vivo models are required, these data provide a framework for applying an integrative multi-omic approach in paediatric cancer precision medicine.

ATRT-03. IDENTIFICATION OF MICRORNA-BASED PROGNOSTIC BIOMARKERS AND CANCER THERAPEUTIC AGENTS FOR ATYPICAL TERATOID/RHABDOID TUMOR
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BACKGROUND: MicroRNA (miRNA) has been found to be involved in development of many malignant pediatric brain tumors, including atypical teratoid/rhabdoid tumor (AT/RT) that is highly aggressive and carries a dismal prognosis. The current study investigated the potential value of miRNAs and pivotal genes associated with AT/RT using bioinformatics analysis, aiming to identify new prognostic biomarkers and candidate drugs for AT/RT patients. METHODS: Differentially expressed miRNAs (DEMs) and genes (DEGs) between AT/RT and normal control samples were obtained from GEO database. The target genes of DEMs were predicted via TargetScanHuman version 7.2 and miRDB, and then intersected with DEGs. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes analyses of overlapping genes were conducted, followed by construction of protein-protein interaction network. Hub genes were determined by Cytoscape
Choroid plexus carcinoma (CPC) and Atypical teratoid/rhabdoid tumor (ATR/T) are two rare, malignant brain cancers most commonly arising in children less than 3 years of age. These tumors often have genetic alterations in the tumor suppressor gene SMARCB1/INI1. Rhabdoid predisposition syndrome (RTPS) categorizes patients with germline mutations in SMARCB1/SMARCA4, leading to a risk of developing rhabdoid tumors. Both CPC and ATR/T have been demonstrated in patients with these rhabdoid predisposition syndromes. In general, these tumors tend to have a poor prognosis. However, with the presence of a SMARCB1 mutation, patients may have improved overall survival. We present two interesting cases of siblings with maternally inherited SMARCB1 mutations; one a 21-month-old male who presented with an ATR/T and another a 10-month-old female who presented with a CPC. The ATR/T was treated as per the Cure Foundation’s AT/RT registry, with systemic chemotherapy and stem cell rescue as well as cranial radiation. The CPC was treated as per the CPT-SCOP 2009 with etoposide, cyclophosphamide and vincristine. Unlike other patients with aggressive tumors, both of these patients are alive without evidence of disease recurrence 8 and 7 months post therapy, respectively. Additional genomic testing on both tumors is currently pending in order to potentially identify other alterations that may impact survival. These cases further illustrate the similar profile of two very different tumors with improved overall survival that may be secondary to mutations in SMARCB1 in RTPS.

ATRT-06. SMARCB1 LOSS DRIVEN NON-CANONICAL PRC1 ACTIVITY REGULATES DIFFERENTIATION IN ATYPICAL TERATOID RHABDOID TUMORS (ATIR) Ina Alimova1,2, Etienne Damis1, Marla Weetall1, Angela M Pierce1,2, Dong Wang1, Natalie Serkova1, Ilango Balakrishnan1, Krishna Madhavan1,2, Cole Michaels1,2, and Nicholas K Foreman1,2, John Baird1, Sujatha Venkataraman1,2, and Rajeev Vihakara1.1,2 Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 2Department of Biomedical Sciences, Skaggs School of Pharmacy, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 3Department of Radiology, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 4Department of Pharmaceutical Sciences, Skaggs School of Pharmacy, University of Colorado Anschutz Medical Campus, Aurora, CO, USA, 5Department of Pediatrics, Department of Neurosciences, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Loss of SMARCB1 is the hallmark genetic event that characterizes ATR/T. SMARCB1 is a member of the SWI/SNF chromatin remodeling complex that is responsible for determining cellular pluripotency and lineage commitment. To identify co-operating epigenetic factors, we performed an unbiased shRNA screen targeting 408 epigenetic/chromatin molecules in patient-derived ATR/T cell lines and identified BMI1, a component of the Polycomb Repressor Complex 1 (PRC1), as essential for ATR/T cell viability. Genetic and Chemical inhibition of BMI1 induced clonogenic potential and induced apoptosis. Reciprocal inhibition of both BMI1 and SMARCB1 resulted in significantly prolonged survival compared to stage M0 and stage Mx. BMI1 dysfunction increased the efficacy of chemotherapeutic agents including cytarabine, methotrexate, and prednisolone than among the patients who got only methotrexate or none at all: 40%, 5%, and 0% respectively. The survival was higher among the patients who got intraventricular methotrexate, cytarabine, prednisolone than among the patients who got only methotrexate or none at all: 40%, 5%, and 0% respectively. CONCLUSIONS: Survival was significantly better in patients more than 12month, without metastases, with total removal tumor, chemotheradiotherapy by ATR/T-2006 protocol with i/v, i/t Methotrexate/ cytarabine/Prednisolone.

ATRT-05. RESULTS OF MULTICENTER TRIAL CONCERNING THE TREATMENT OF CHILDREN WITH ATYPICAL TERATOMA/ RHABDOID TUMORS (ATIR) OF THE CENTRAL NERVOUS SYSTEM Olya Zhelezhkou1, Lyudmila Olikho2, Yuri Kushel3, Armen Melikyan4, Marina Ryazanov5, Alexey Kiseyakov6, Evgeny Shaltl7, Irina Borodina8, Svetlana Gorbatykh8, Vladimir Popov9, Marina Mushinaya10, Olga Polushkina11, Eugenia Inyushkina12, Natalya Yudina12, Lyudmila Prvalova13, Lyudmila Minkina13, Artem Zhichkov14, Dina Sakun15, Nadezhda Dunina16, Vladimir Mitrofanov16, Sergey Kovalenko17, Ekaterina Grishina18, Eduard Chulkov19, Nadezhda Pishcheva19, Asim Gvorkyen20, Evgeny Nesheynyk21, Elena Slobina21, Natalya Popova22, Dmitriy Pogorelov23, Alexander Matysyn24, Alexander Shapochnik24, Valentina Timofeeva24, Andrey Korchunov24, and Nikolay Vorobiev24.

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