Fahad Medical City, Riyadh, Saudi Arabia. [2]Pediatric Neurosurgical Department, King Fahad Medical City, Riyadh, Saudi Arabia. [3]Radiation Oncology Department, Comprehensive Cancer Centre, King Fahad Medical City, Riyadh, Saudi Arabia. [4]Genomics Research Department, Saudi Human Genome Project, King Fahad Medical City and King Abdulaziz City for Science and Technolog, Riyadh, Saudi Arabia

The 2021WHO CNS tumor classification includes CNS tumors with internal tandem duplications in the BCL6 corepressor (BCOR) gene as a new entity of CNS embryonal tumors labelled high-grade neuroepithelial tumors with BCOR alterations (HGNET-BCOR) are characterized by genetic aberrations in the BCOR gene located at Xp11.4, leading to increased expression of BCOR mRNA and distinct DNA methylation profiles. currently no agreement on the optimal strategy to manage these rare tumors, which mostly occur in young children These tumors are usually treated as high grade glioma HGG with upfront radiation therapy with poor outcome. We report 2.5 years old boy presenting with headache and vomiting. MRI showed a well-defined left cerebellar mass, hyperintense in T2 and hypointense in T1, with restricted diffusion and no spinal CSF seeding metastases. He underwent gross surgical resection of the tumor initial pathological diagnosis was epithelioid high grade malignant neoplasm. Brain tumor methylation classifier analysis of resected tumor tissue confirmed a CNS tumor with BCOR internal tandem duplication (WHO grade 4). The patient was treated per COG ACNS0334 (3 induction cycles of vincristine, cyclophosphamide, cisplatin, etoposide, HDMTX, followed by consolidation with 3 cycles of carboplatin and thiotepa with autologous hematopoietic stem cell rescue). MRI brain before the start of chemotherapy showed a small recurrent mass within the surgical cavity. post-induction MRI detected stable-sized residual lesion in the surgical cavity; however, post-consolidation MRI showed complete resolution of the residual mass. The patient subsequently received craniospinal irradiation (36 Gy [CSI]) with a boost to the tumor bed up to 54 GY. By the time of writing this report our patient is still in complete remission. Our case showed that this aggressive brain tumor may respond well to intensive multimodalities therapy Further case studies and international prospective trials are needed to optimize the clinical management of these rare tumors.

ETMR-02. OVEREXPRESSION OF LIN28A IN NEURAL PROGENITOR CELLS IN VIVO DOES NOT LEAD TO BRAIN TUMOR FORMATION BUT RESULTS IN REDUCED SPINE DENSITY

Maximilian Middelkamp[1,2], Lisa Ruck[2], Christoph Krisp[3], Piotr Sumislawski[2], Behnam Mohammadi[2], Matthias Dottermusch[1,2], Valerie Meister[4], Lukas Küster[5], Hartmut Schlüter[3], Sabine Windhorst[5], Julia E. Neumann[1,2]; [1]Center for Molecular Neurobiology Hamburg (ZMNH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [2]Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [3]Institute of Clinical Chemistry and Laboratory Medicine, Mass Spectrometric Proteomics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [4]Institute of Neuropathology, Ludwig-Maximilians-University Munich, Munich, Germany. [5]Department of Biochemistry and Signal Transduction, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

The RNA binding protein LIN28A is a stem- and progenitor marker and one of the factors necessary to induce pluripotent stem cells. An overexpression of LIN28A has been identified in malignant brain tumors called embryonal tumors with multilayered rosettes (ETMR) but its specific role during brain development remains largely unknown. Radial glia cells of the ventricular zone (VZ) are proposed as a cell of origin for ETMR. We asked whether an overexpression of LIN28A in such cells might affect brain development or result in the formation of brain tumors. Constitutive overexpression of LIN28A in *hGFAP-cre::lsl-Lin28A* (GL) mice led to a transient increase of proliferation in the cortical VZ at embryonic stages but no postnatal brain tumor formation. Postnatally, GL mice displayed a pyramidal cell layer dispersion of the hippocampus and altered spine and dendrite morphology, including reduced dendritic spine densities in the hippocampus and cortex. GL mice displayed hyperkinetic activity and differential quantitative MS-based proteomics revealed altered time dependent molecular functions regarding mRNA processing and spine morphogenesis. Phosphoproteomic analyses indicated a downregulation of mTOR pathway modulated proteins such as Map1b being involved in microtubule dynamics within a crosstalk of Gsk3b/Rho-Rac/Map1b signaling. In conclusion, we show that Lin28A overexpression transiently increases proliferation of neural precursor cells but it is not sufficient to drive brain tumors *in vivo*. In contrast, Lin28A impacts on protein abundancy patterns related to spine morphogenesis and phosphorylation levels of proteins involved in microtubule dynamics, resulting in decreased spine densities of neurons in the hippocampus and cortex as well as in altered behavior. Our work provides new insights into the role of LIN28A for neuronal morphogenesis and development and may reveal future targets for treatment of ETMR patients.

ETMR-03. INTRA- AND EXTRA-CRANIAL BCOR-ITD TUMOURS ARE SEPARATE ENTITIES WITHIN THE BCOR-REARRANGED FAMILY

Yassine Bouchoucha[1], Arnault Tauziède-Espariat[2], Arnaud Gauthier[1], Delphine Guillemot[1], Dorian Bochaton[1], Julien Vibert[1], Matthieu Carton[1], Sarah Watson[1], Sandrine Grossetete[1], Chloé Quignot[1], Daniel Orbach[1], Nadège Corradini[3], Gudrun Schleiermacher[1], Franck Bourdeaut[1], Marie Simbozel[4], Christelle Dufour[4], Veronique Minard[4], Mehdi Brahmi[3], Franck Tirode[3], Daniel Pissaloux[3], Marie Karanian[3], Marie-Christine Machet[5], Julien Masliah-Planchon[1], Olivier Delattre[1], Liesbeth Cardoen[1], Gaelle Pierron[1], Francois Doz[1]; [1]Institut Curie, Paris, France. [2]Sainte Anne Hospital, Paris, France. [3]Centre Léon Bérard, Lyon, France. [4]Institut Gustave Roussy, Villejuif, France. [5]Université de Tours, Tours, France

BCOR-ITD tumours form an emerging family of aggressive entities with an internal tandem duplication (ITD) in the last exon of the *BCOR* gene. The family includes cerebral tumours, termed central nervous system *BCOR*-ITD (CNS *BCOR*-ITD), and sarcomatous types described in the kidney as clear cell sarcoma of the kidney (CCSK), in the endometrium as high-grade endometrial stromal sarcoma (HG-ESS), in bone, and in soft tissue as undifferentiated round cell sarcoma (URCS) or primitive myxoid mesenchymal tumour of infancy (PMMTI). Based on a series of 33 retrospective cases, including 10 CNS *BCOR*-ITD and 23 *BCOR*-ITD sarcomas, we interrogated the homogeneity of the entity regarding clinical, radiological and histopathological findings, and molecular signatures. Whole transcriptomic sequencing and DNA methylation profiling were used for unsupervised clustering. Histopathological review revealed marked differences between CNS *BCOR*-ITD and *BCOR*-ITD sarcomas. These two groups were consistently segregated by unsupervised clustering of expression (n=22) and DNA methylation (n=21) data. Proximity between the two groups may result from common somatic changes within key pathways directly related to the novel activity of the ITD itself. Conversely, comparison of gene signatures with single-cell RNAseq atlases suggests that the distinction between *BCOR*-ITD sarcomas and CNS *BCOR*-ITD may result from differences in cells of origin.

ETMR-04. EMBRYONAL TUMOR WITH MULTI-LAYERED ROSETTES (ETMR) LOCATED IN THE BRAINSTEM: A CASE REPORT ON CLINICAL DECISION-MAKING AND A MULTIMODAL, INTERDISCIPLINARY TREATMENT APPROACH INCLUDING INTERSTITIAL BRACHYTHERAPY

Stephanie T. Jünger[1,2], Daniel Rueß[1], Roland Goldbrunner[2,3], Gerrit H. Gielen[4], Torsten Peitsch[4], Pascal Johann[5,6], Pablo Landgraf[7], Thorsten Simon[7], Maximilian I. Ruge[1,3]; [1]Center for Neurosurgery, Department of Stereotactic and Functional Neurosurgery, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [2]Center for Neurosurgery, Department of General Neurosurgery, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [3]Centre for Integrated Oncology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany. [4]Department of Neuropathology, University of Bonn, Bonn, Bonn, Germany. [5]Department of Pediatric Oncology, Hematology & Immunology, Heidelberg University Hospital, Heidelberg, Germany. [6]University Children's Hospital Augsburg, Pediatric Oncology, Augsburg, Germany. [7]Department of Pediatric Hematology and Oncology, University of Cologne, Cologne, Germany

OBJECTIVE: Embryonal tumors with multi-layered rosettes (ETMR) (CNS WHO grade 4) comprise a rare and malignant tumor type affecting predominantly infants below 3 years of age. The treatment consists of maximal safe surgical resection, irradiation, and intensive medulloblastoma type chemotherapy. Despite aggressive treatment, the prognosis of these patients remains poor, especially for brainstem tumors. We present the case of a male infant diagnosed with a brainstem ETMR, successfully treated with an interdisciplinary multimodal approach, including stereotactic interstitial brachytherapy. RESULTS: A 19 month old boy first presented with hemiparesis, intermittent bradycardia and reduced consciousness. Initial imaging showed a brainstem lesion with characteristic features of a diffuse intrinsic pontine glioma (DIPG). We performed stereotactic biopsy to confirm the diagnosis and initiated temozolomide treatment. While the pathology result was still pending, the boy's clinical condition deteriorated to a soporic state with stretch synergisms. By emergency open surgery, partial resection was achieved. Eventually, the patient recovered rapidly. After the diagnosis of ETMR was established, medulloblastoma type chemotherapy (systemic carboplatin/etoposide; intrathecal methotrexate) was administered. After two cycles, the patient showed only residual right-sided hemiparesis. However, imaging demonstrated only a minimal reduction of the tumor size. Therefore, stereotactic interstitial brachytherapy using 125iodine seeds and subsequent high-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) was performed and overall tolerated well. After two months of brachytherapy and two

additional cycles of chemotherapy, the MRI showed ≥ 50% reduction in tumor volume and no neurological deficit can be clinically detected. CONCLUSION: This case indicates that stereotactic interstitial brachytherapy during intensive systemic chemotherapy is feasible. It may provide a suitable treatment for malignant infant brain tumors. Furthermore, it shows that paediatric patients are capable of recovery even after devastating neurological symptoms. Lastly, it emphasizes the importance of multidisciplinary and multimodal treatment for rare diseases.

ETMR-05. SINGLE-CELL TRANSCRIPTOMICS OF ETMR REVEALS DEVELOPMENTAL CELLULAR PROGRAMS AND TUMOR-PERICYTE COMMUNICATIONS IN THE MICROENVIRONMENT

Flavia W. de Faria[1], Carolin Walter[1,2], Marta Interlandi[1,2], Viktoria Melcher[1], Nicole Riedel[1], Monika Graf[1], Natalia Moreno[1], Melanie Schoof[3,4], Dörthe Holdhof[3,4], Christian Thomas[5], Michael C Frühwald[6], Bruno Maerkl[7], Ben Ho[8], Sarah Sandmann[2], Julian Varghese[2], Martin Ebinger[9,10], Martin Schuhmann[11], Aysegül Canak[9], Annie Huang[12,13], Ulrich Schüller[3,4], Thomas K. Albert[1], Kornelius Kerl[1]; [1]Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, NRW, Germany. [2]Institute of Medical Informatics, Westphalian Wilhelms-University Münster, Münster, NRW, Germany. [3]Institute of Neuropathology, University Medical Center Hamburg-Eppendorf, Hamburg, HH, Germany. [4]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, HH, Germany. [5]Institute of Neuropathology, University Hospital Münster, Münster, NRW, Germany. [6]Swabian Children's Cancer Center, Paediatric and Adolescent Medicine, University Medical Center Augsburg, Ausburg, Bavaria, Germany. [7]General Pathology and Molecular Diagnostics, Medical Faculty, University of Augsburg, Ausburg, Bavaria, Germany. [8]Department of Cell Biology, Hospital for Sick Children, Toronto, Ontario, Canada. [9]Department Pediatric Hematology/Oncology, Children's University Hospital, Eberhard Karls University of Tuebingen, Tübingen, BW, Germany. [10]German Cancer Consortium (DKTK) partner site Tübingen, Tübingen, BW, Germany. [11]Division of Pediatric Neurosurgery, Department of Neurosurgery, University Hospital of Tuebingen, Eberhard Karls University of Tuebingen, Tübingen, BW, Germany. [12]Division of Haematology Oncology, Department of Paediatrics, Hospital for Sick Children, Toronto, Ontario, Canada. [13]The Arthur and Sonia Labatt Brain Tumour Research Centre, Hospital for Sick Children, Toronto, Ontario, Canada

BACKGROUND: Embryonal tumors with multilayered rosettes (ETMR) are pediatric brain tumors bearing a grim prognosis, despite intensive multimodal therapeutic approaches. Insights into cellular heterogeneity and cellular communication of tumor cells with cells of the tumor microenvironment (TME), by applying single-cell (sc) techniques, potentially identify mechanisms of therapy resistance and target-directed treatment approaches. MATERIAL AND METHODS: To explore ETMR cell diversity, we used single-cell RNA sequencing (scRNA-seq) in human (n=2) and murine ETMR (transgenic mode; n=4) samples, spatial transcriptomics, 2D and 3D cultures (including co-cultures with TME cells), multiplex immunohistochemistry and drug screens. RESULTS: ETMR microenvironment is composed of tumor and non-tumor cell types. The ETMR malignant compartment harbour cells representing distinct transcriptional metaprograms, (NSC-like, NProg-like and Neuroblast-like), mirroring embryonic neurogenic cell states and fuelled by neurogenic pathways (WNT, SHH, Hippo). The ETMR TME is composed of oligodendrocyte and neuronal progenitor cells, neuroblasts, microglia, and pericytes. Tumor-specific ligand-receptor interaction analysis showed enrichment of intercellular communication between NProg-like ETMR cells and pericytes (PC). Functional network analyses reveal ETMR-PC interactions related to stem-cell signalling and extracellular matrix (ECM) organization, involving factors of the WNT, BMP, and CxCl12 networks. Results from ETMR-PC co-culture and spatial transcriptomics pointed to a pivotal role of pericytes in keeping ETMR in a germinal neurogenic state, enriched in stem-cell signalling. Drug screening considering cellular heterogeneity and cellular communication suggested novel therapeutic approaches. CONCLUSION: ETMR demonstrated diversity in the microenvironment, with enrichment of cell-cell communications with pericytes, supporting stem-cell signalling and interfering in the organization of the tumor extracellular matrix. Targeting ETMR-PC interactions might bring new opportunities for target-directed therapy.

ETMR-06. MOLECULAR AND CLINICAL CHARACTERISTICS OF CNS TUMORS WITH *BCOR(L1)* FUSION/INTERNAL TANDEM DUPLICATION

Johannes Gojo[1,2], Felix Schmitt-Hoffner[2,3], Monika Mauermann[2,3], Katja von Hoff[4], Martin Sill[2,3], Andrey Korshunov[5,6], Damian Stichel[5,6], David Capper[7], Arnault Tauziede-Espariat[8], Pascale Varlet[8], Kenneth Aldape[9], Zied Abdullaev[9], Andrew Donson[10], Jens Pahnke[11], Ulrich Schüller[12], Ivy Tran[13], Kristyn Galbraith[13], Matija Snuderl[13], Sanda Alexandrescu[14], Sebastian Brandner[15], Maria Łastowska[16], Evelina Miele[17], Jasper v. Lugt[18], Lisethe Meijer[18], Jens Bunt[18], Christof Kramm[19], Jordan R. Hansford[20], Lenka Krskova[21], Michal Zapotocky[22], Sumihito Nobusawa[23], David Solomon[24], Christine Haberler[25], Barbara Jones[2,3], Dominik Sturm[2,3], Felix Sahm[2,5], Natalie Jäger[2,3], Stefan M. Pfister[2,3], Marcel Kool[2,18]; [1]Department of Pediatrics and Adolescent Medicine, Comprehensive Cancer Center and Comprehensive Center for Pediatrics, Medical University of Vienna, Vienna, Austria. [2]Hopp-Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany. [3]Division of Pediatric Neurooncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany. [4]Department of Pediatric Oncology and Hematology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany. [5]Department of Neuropathology, Heidelberg University Hospital, Heidelberg, Germany. [6]Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), Heidelberg, Germany. [7]Department of Neuropathology, Charité Universitätsmedizin, Berlin, Germany. [8]Department of Neuropathology, GHU Paris Psychiatry and Neurosciences, Sainte-Anne Hospital, Paris, France. [9]Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. [10]Morgan Adams Foundation Pediatric Brain Tumor Research Program, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA. [11]Department of Pathology, Section of Neuropathology, Translational Neurodegeneration Research and Neuropathology Lab, University of Oslo and Oslo University Hospital, Oslo, Norway. [12]Department of Pediatric Hematology and Oncology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. [13]Department of Pathology, New York University School of Medicine, New York, New York, NY, USA. [14]Department of Pathology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA. [15]Department of Neurodegeneration, Institute of Neurology, University College London, London, United Kingdom. [16]Department of Pathomorphology, The Children's Memorial Health Institute, Warsaw, Poland. [17]Department of Oncology, Hematology, Cell Therapy, Gene Therapy and Haemopoietic Transplant, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy. [18]Princess Máxima Center for Paediatric Oncology, Utrecht, Netherlands. [19]Division of Pediatric Hematology and Oncology, University Medical Center Goettingen, Göttingen, Germany. [20]Department of Oncology and Haematology, Perth Children's Hospital, Perth, WA, Australia. [21]Department of Pathology and Molecular Medicine, Second Faculty of Medicine, Charles University, Prague, Czech Republic. [22]Prague Brain Tumor Research Group, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic. [23]Department of Human Pathology, Gunma University Graduate School of Medicine, Maebashi, Japan. [24]Department of Pathology, University of California, San Francisco, [513] Parnassus Ave, Health Sciences West[451], San Francisco, CA, USA. [25]Institute of Neurology, Department of Neurology, Medical University of Vienna, Vienna, Austria

Central nervous system (CNS) tumor with *BCOR* internal tandem duplication (*BCOR*-ITD) have recently been introduced in the 5th edition of the WHO classification of CNS tumors, however, their molecular makeup and clinical characteristics remain widely enigmatic. This is further complicated by the recent discovery of tumors characterized by gene fusions involving *BCOR* or its homologue *BCORL1*. We identified a cohort of 206 *BCOR* altered CNS tumors via DNA methylation profiling and conducted *in-depth* molecular and clinical characterization in an international effort. By performing t-SNE clustering analysis we found that *BCOR*-fusion tumors form a distinct cluster (n=61), adjacent to *BCOR*-ITD cases (n=145). The identified fusion partners of *BCOR(L1)* included *EP300* (n=20), *CREBBP* (n=5), and *NUTM2HP* (n=1). Notably, three cases within the *BCOR*-ITD cluster harbored a c-terminal intragenic deletion within *BCOR*. With respect to clinical characteristics gender ratio was balanced in *BCOR*-fusion cases (m/f, 1.1), whereas predominance of male patients was observed in the *BCOR*-ITD group (m/f, 1.5). Moreover, age at diagnosis of *BCOR*-fusion patients was higher as compared to *BCOR*-ITD cases (15 vs 4.5 years). Interestingly, *BCOR*-fusion tumors were exclusively found in the supratentorial region being originally diagnosed as ependymomas or gliomas whereas *BCOR*-ITD emerged across the entire CNS with diverse original diagnoses. 8% of *BCOR*-ITD and none of *BCOR*-fusion cases were disseminated at diagnosis. In line with this observation, 40% of first relapses within the *BCOR*-ITD group were metastatic which was less frequent in *BCOR*-fusion tumors. Survival estimates demonstrated no differences, generally showing short median PFS (*BCOR*-fusion, 2 years, n=15; *BCOR*-ITD, 1.8 years, n=55) and intermediate OS rates (*BCOR*-fusion, 6.8 years, n=18; *BCOR*-ITD 6.3 years, n=60). Further molecular and clinical characterization is ongoing potentially revealing first therapeutic leads for these highly aggressive CNS tumor types.

ETMR-07. DNA METHYLATION PROFILING OF A SERIES OF RARE CNS EMBRYONAL TUMORS IN CHILDREN: DIAGNOSTIC AND CLINICAL IMPACT

Vito Andrea Dell'Anna, Stefano Gabriele Vallero, Franca Fagioli, Paola Peretta, Paola Cassoni, Luca Bertero; Città della Salute e della Scienza and University of Turin, Turin, Italy

BACKGROUND: CNS embryonal tumors are a clinically and biologically heterogeneous group of tumors, more frequently arising in very young chil-