CBL0137 preferentially suppressed cell-cycle and DNA-repair related biological processes. Moreover, it selectively disrupted transcription of MYC and NEUROD1, two critical oncogenic transcription factors of MYCamp-G3-MB, via depleting FACT complex from their promoter regions. In summary, our study demonstrates FACT-targeted CBL0137 works effectively on treating MYCamp-G3-MB, presenting another promising epigenetic-targeted therapeutic strategy against the most devastating form of MB.

EMBR-07. MYC BUT NOT MYCN GENERATES AGGRESSIVE GROUP 3 MEDULLOBLASTOMA BY ARF PATHWAY SUPPRESSION

Oliver Mainwaring[1], Holger Weishaupt[1], Sonja Hutter[1], Miao Zhao[1], Gabriela Rosén[1], Laura Breinschmid[1], Annemieke Verbaan[1], Anders Sundström[1], Karl Annusver[2], Maria Kasper[2], and Fredrik Swartling[1]; [1]Science for Life Laboratory, Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, [2]Department of Bioscience and Nutrition, Karolinska Institutet, Huddinge, Stockholm, Sweden

Medulloblastoma (MB), the most common malignant pediatric brain tumor, often harbor MYC amplifications and arise in the presence of a functional p53 suppressor protein. To elucidate the mechanism behind this inexplicable tumor development we generated an inducible, immunocompetent transgenic mouse model of MYC-driven MB. Tumors driven from the glutamate transporter promoter molecularly resembled aggressive Group 3 MB driven by an enriched photoreceptor program. They developed embryonically in a monoclonal fashion in the presence of a functional unmutated p53 gene. Compared to MYCN-expressing MB driven from the same promoter, we discovered pronounced silencing of the ARF suppressor upstream of p53. We similarly found significant methylation of the ARF promoter in MYC-amplified as compared to MYCN-amplified human MB samples. While MYCN-driven tumor malignancy was more sensitive to ARF depletion, it dramatically increased metastatic spread of MYC-driven tumors. DNMT inhibition could restore ARF levels in MYC-expressing tumors but did not show any therapeutic advantage in tumors in vivo. Computational modeling suggested the HSP90 protein to act as a more specific target and ARF could indeed be restored by the HSP90 inhibitor onalespib that promoted increased survival in our inducible animal model suggesting that HSP90 inhibition could be potentially used in patients affected by MYC-driven ARF-silenced cancer.

EMBR-08. CORRELATION OF HISTOPATHOLOGY, CHROMOSOMAL MICROARRAY, AND NANOSTRING BASED 22-GENE ASSAY FOR MEDULLOBLASTOMA SUBGROUP ASSIGNMENT ON "HEAD START" 4 CLINICAL TRIAL

Girish Dhall[1], Parth Patel[2], Megan Blue[2], Jaclyn Biegel[3], ISabel Almiraz-Suarez[4], Eugene Hwang[4], Christopher Pierson[2], Daniel Boue[2], and Jonathan Finlay[2]; [1]University of Alabama at Birmingham, Birmingham, AL, USA, [2]Nationwide Children's Hospital, Columbus, OH, USA, [3]Children's Hospital Los Angeles, Los Angeles, CA, USA, [4]Children's National Medical Center, Washington, DC, USA

"Head Start" 4 (HS 4) is a prospective randomized clinical trial that tailors treatment based on medulloblastoma molecular subgroups and response to induction chemotherapy to compare the efficacy of one versus three (tandem) cycles of myeloablative therapy. Advances in RNA and DNA profiling have identified four core molecular subgroups of medulloblastoma with prognostic significance: Sonic Hedgehog (SHH) subtype, WNT subtype, Group 3, and Group 4. In HS 4 trial, we utilize a combination of histopathology and immunohistochemistry (pathology/IHC), as well as chromosomal microarray analysis (CMA) utilizing OncoScan™ (Thermo Fisher) to classify medulloblastoma samples into either SHH, WNT, or non-WNT/non-SHH (Group 3/4) subgroups at the time of diagnosis. NanoString based 22-gene assay is performed retrospectively to test concordance. We have pathology/IHC, CMA, and NanoString data on 26 infants and young children with medulloblastoma enrolled on HS 4. Pathology/IHC was able to assign samples to SHH, WNT, and non-WNT/non-SHH subgroups in all but two cases: one case was classified as Group 3, and the second as SHH by both CMA and NanoString. CMA was indeterminate in six cases, of which, pathology/IHC was able to assign all six samples aforementioned three subgroups. NanoString was indeterminate in two cases: one case was classified as SHH by CMA and pathology/IHC, and the second case was indeterminate by CMA but was assigned as non-WNT/non-SHH on pathology/IHC. There is excellent correlation between NanoString and combination of histopathology and CMA for core medulloblastoma subgrouping on HS 4. Methylation studies are ongoing.

EMBR-09. EXAMINING THE ROLE OF THE DEVELOPMENTALLY ENCODED TRANSCRIPTION FACTOR, LHX9, IN GROUP 3 MEDULLOBLASTOMA

Sarah Injac[1,2], Bryan Rivas[1,2], Amir Arabzade[3,1], Yanhau Zhao[1,2], D. William Parsons[1,2], and Stephen Mack[1,2]; [1]Texas Children's Cancer and Hematology Centers, Houston, TX, USA, [2]Baylor College of Medicine, Houston, TX, USA, [3]Graduate Program in Chemical and Biomolecular Engineering, Rice University, Houston, TX, USA

Medulloblastoma (MB) is the most common malignant brain tumor of childhood. Despite major advances in our understanding of the biology of MB, novel treatments remain urgently needed. Using a chemical-genomics driven drug repositioning strategy, we identified the cardiac glycoside family of compounds as potential treatments for Group 3 MB. We subsequently demonstrated that single-agent treatment with digoxin prolongs survival in a patient-derived xenograft model (PDOX) of Group 3 MB to a degree comparable to radiation therapy, a mainstay in the treatment of MB. Finally, we examined the mechanism of digoxin-mediated cell killing using RNA-seq. This work identified LHX9, a member of the LIM homeobox family of transcription factors, as the gene most significantly down-regulated following treatment (Huang and Injac et al, *Sci Trans Medicine*, 2018). Homologs of LHX9 play key roles in cerebellar development via spatially and temporally restricted expression and LHX9 has been proposed as a core transcription factor (TF) in the regulatory circuitry of Group 3 tumors. Loss of function of other core TFs has been shown to impact MB growth. The role of LHX9 in MB, however, has not been previously experimentally evaluated. We now report that knockdown of LHX9 in MB-derived cell lines results in marked growth inhibition. RNA-seq analysis of LHX9-depleted cells showed changes which included alterations in extracellular matrix-receptor interactions and TGFb signaling. These findings raise the possibility that loss of LHX9 plays a major role in digoxin-mediated cell killing and that LHX9 represents a key dependency required for the growth of Group 3 MB. Clinical targeting of core TFs would represent a novel approach to targeting this devastating disease.

EMBR-10. INOSITOL TREATMENT INHIBITS MEDULLOBLASTOMA THROUGH SUPPRESSION OF EPIGENETIC-DRIVEN METABOLIC ADAPTATION

Sara Badodi[1], Nicola Pomella[1], Xinyu Zhang[1], Gillian Morrison[2], Steve M. Pollard[2], Christopher D. Bennett[3,4], Steven C. Clifford[5], Andrew Peet[3,4], and Silvia Marino[1]; [1]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK, [2]Centre for Regenerative Medicine & Cancer Research UK Edinburgh Centre, The University of Edinburgh, Edinburgh, UK, [3]Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK, [4]Birmingham Children's Hospital, Birmingham, UK, [5]Newcastle University Centre for Cancer, Wolfson Childhood Cancer Research Centre, Translational and Clinical Research Institute, Newcastle upon Tyne, UK

Medulloblastoma (MB) is the most common paediatric malignant brain tumour and is classified into four distinct molecular subgroups (WNT, SHH, G3 and G4), each of them further subdivided into subtypes with different prognosis and responses to therapy. Deregulation of chromatin modifier genes plays an essential role in MB, particularly in the G4 subgroup, the least understood of all subgroups, despite being the most common and associated with poor prognosis. A $BMI1^{High}$; $CHD7^{Low}$ molecular signature identifies patients with poor survival within this subgroup. We show that $BMI1^{High}$; $CHD7^{Low}$ mediates a novel epigenetic regulation of inositol metabolism in both G4 MB cells and patients. These tumours display hyperactivation of the AKT/mTOR pathway which leads to energetic rewiring characterized by enhanced glycolytic capacity and reduced mitochondrial function. We demonstrate that inositol administration counteracts this metabolic alteration, impairs MB proliferation *in vitro* and significantly extends survival in an *in vivo* pre-clinical model. Moreover, inositol synergises with cisplatin, a chemotherapy agent currently used in MB treatment, enhancing its therapeutic effect *in vivo*. Importantly, cerebellar neural stem cells bearing the $BMI1^{High}$; $CHD7^{Low}$ signature do not show metabolic adaptation and are thus resistant to inositol treatment, highlighting a fundamental difference between normal and neoplastic metabolism in the developing cerebellum. In summary, we have identified an actionable vulnerability in a pre-clinical setting modelling a molecularly defined group of MB patients, the translational value of which can now be explored in signature-matched clinical trials in MB.

EMBR-11. SYNERGISTIC DRUG COMBINATIONS FOR THE TREATMENT OF *MYC* AMPLIFIED GROUP 3 MEDULLOBLASTOMA

Simon Zeuner[1,2], Johanna Vollmer[1,2], Heike Peterziel[1,2], Romain Sigaud[1,2], Sina Oppermann[1,2], Dina ElHarouni[3], Thomas Hielscher[4], Olaf Witt[1,2], Ina Oehme[1,2], Till Milde[1,2], and Jonas Ecker[1,2]; [1]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany, [2]Clinical Cooperation Unit Pediatric Oncology, German Cancer Research Center (DKFZ) and German Cancer Consortium (DKTK), Heidelberg, Germany, [3]Bioinformatics and Omics Data Analytics, German Cancer Research Center (DKFZ), Heidelberg, Germany, [4]Division of Biostatistics, German Cancer Research Center (DKFZ), Heidelberg, Germany

Background: Medulloblastoma (MB) is a highly aggressive brain tumour in children. Patients with Group 3 MB harbouring a *MYC*-amplification