DIPG-17. COMBINATION OF ARGinine DEPLETION AND POLYAMINE INHIBITION AS AN ANTICANCER STRATEGY FOR DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

Masahiro Shin, Hirofumi Nakamoto, Nobuhito Saito, The University of Tokyo, Tokyo, Japan

INTRODUCTION: Diffuse midline glioma (DMG) mostly affects young children. The newly-introduced disease entity DMG, H3K27M-mutant uni- or oligodendroglioma, is characterized by a high degree of malignancy and poor outcomes. A recent study showed that 51% of H3K27M-mutant GNAS inactivation resulted in reduced cell viability, consistent with their proposed function and validating knockout screen utility. Preliminary data demonstrate that GNAS is a key driver of DMG cell survival pathways and is a potential target for therapeutic exploitation. The potential of targeting GNAS cell survival pathways in DMG warrants further investigation.

METHOD: We performed a high-throughput screen using an FDA-approved drug library to identify novel therapeutic dependencies in H3K27M-mutant DIPG. Drug sensitivity screening was performed in two patient-derived DIPG cell lines using the IC50 assay with a cutoff of 10% growth inhibition.

RESULTS: Our screen identified the polyamine transport inhibitor DFMO as a potential therapeutic agent. Treatment with DFMO led to a decrease in polyamine levels, reduction in cell viability, and increased sensitivity to PARP inhibition in H3K27M-mutant DIPG cell lines. These findings suggest that targeting polyamine metabolism in DMG may have therapeutic potential.

CONCLUSION: Our study demonstrates that targeting polyamine metabolism in DMG using DFMO and PARP inhibitors may provide a novel therapeutic strategy for the treatment of this aggressive brain tumour.
DIPG-20. DETERMINATION AND MANAGEMENT OF HYDROCEPHALUS IN PATIENTS WITH DIPG, AN INSTITUTIONAL EXPERIENCE
Adriana Fonseca1, Palma Solano-Paz2, Michal Zapotocky3, Ute Bartels1, and Eric Bouf4; 1The Hospital for Sick Children, Toronto, ON, Canada, 2Hospital Universitario Virgen del Rocio, Seville, Spain, 3University Hospital Motol, Prague, Czech Republic

BACKGROUND: There is no consensus in best practices for the management of hydrocephalus in patients with Diffuse Intrinsic Pontine Glioma (DIPG). To date, the impact on survival of hydrocephalus and cerebrospinal fluid diversion was not documented in this patient population. Therefore, we describe our institutional experience. METHODS: Patients with a clinical and radiological diagnosis of DIPG were identified at the Hospital for Sick Children between 2000–2019. Images at diagnosis and at disease progression were reviewed. Treatment was guided by neurosurgical consultation. The following variables were compared: 1) treatment of hydrocephalus, and 2) survival. Outcomes were assessed using Kaplan-Meier method and Chi-square analysis. RESULTS: Eighty-nine consecutive patients with DIPG were treated at our institution. At diagnosis, 29% (n=26) of patients presented with hydrocephalus, and seven patients underwent CSF diversion. Of the remaining nineteen patients, n=6 had stable or improved hydrocephalus in follow-up scans, n=6 had persistent hydro and n=2 required CSF diversion at the time of disease progression. Seven did not undergo a follow-up scan. Out of sixty-five patients with imaging at the time of progression, fifty-five percent of patients (n=36) presented with hydrocephalus and ten of them required CSF diversion. On univariate analysis, the presence of hydrocephalus or CSF diversion at diagnosis and/or disease progression did not correlate with survival. CONCLUSION: CSF diversion for the management of hydrocephalus in patients with DIPG does not impact survival and in some cases resolves spontaneously after the initiation of radiotherapy and steroids. This observation needs to be validated in a prospective cohort.

DIPG-21. INDUCTION OF MITOTIC ABNORMALITIES AND BMI-1 MODULATION TO TREAT DIFFUSE INTRINSIC PONTINE GLIOMA
Shiva Senthil Kamasamudram, Satyapriya Sengupta, Priya Chaudhuri, Zaida Fernandez, Deepak Kumar Mishra1, Christine Fuller1, Maryam Fouladi1,2, and Rachid Drai1

Brain Tumor Center, Division of Oncology, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, USA, 1Division of Pediatrics, Department of Biomedical Informatics, University of Cincinnati College of Medicine, Cincinnati, OH, USA, 2Department of Electrical Engineering and Computer Science, University of Cincinnati College of Engineering and Applied Science, Cincinnati, OH, USA

Diffuse intrinsic pontine glioma (DIPG) is a poor-prognosis pediatric brain tumor with a median survival of less than one year. No effective therapy is currently available, and no therapeutic advances have been made in several decades. BMI-1 is a member of the multifumetion Polycomorphic repressor complex 1 (PRC1). It has been implicated in the survival of normal and cancer cells, and in DNA damage signaling. We have previously identified BMI-1 as a potential therapeutic target in DIPG and have shown that BMI-1 is highly expressed in DIPG tumors regardless of histone 3 subtype. In the present study, we show that the modulation of BMI-1 leads to DNA damage, M phase cell cycle arrest, chromosome abnormalities and cell death. Furthermore, modulation of BMI-1 sensitizes DIPG patient-derived stem-like cells to ionizing radiation (IR). Treatment of DIPG stem-like cells with PTC596, a BMI-1 modulator, and IR, impairs the kinetics of DNA damage response (DDR). Both DDR foci formation and resolution were delayed, resulting in further reduction in cell viability compared with either treatment alone. In vivo, treatment bearing DIPG xenografts with PTC596 leads to decreased tumor volume and growth kinetics, increased in-tumor apoptosis and sustained animal survival benefit. Gene expression analysis indicates that BMI-1 expression correlates positively with DIPG stemness and BMI-1 signature. Together, these findings indicate that BMI-1 modulation is associated with mitotic abnormalities, impaired DDR and cell death, supporting the combination of BMI-1 modulation and radiation as a promising novel therapy to treat children with DIPG.

DIPG-22. DISSECTING THE ONCOGENIC ROLE OF FOXR2 IN DIFFUSE INTRINSIC PONTINE GLIOMA
Jesualdo W. Tsai1,2,3, Josephine W. K. Patel1,2,3,4, Kayleigh H. Bean2, Frank Dubois5, Prasidda Khadka3, Sophie Lu4, Elizabeth Gonzalez4, Keith Ligon4, Pratiti Bandopadhyay1, Timothy N. Phoenix2, Dana-Farber Cancer Institute, Boston, MA, USA, 1University of Cincinnati, Cincinnati, OH, USA, 2Brigham and Women’s Hospital, Neurology, Boston, MA, USA

BACKGROUND: Diffuse intrinsic pontine gliomas (DIPGs) pose particular challenges for treatment. We recently completed a genomic analysis of close to 200 DIPGs and high-grade gliomas. We identified that nearly 10% of all DIPG and high-grade gliomas have increased expression of the transcription factor FOXR2. We hypothesize that FOXR2 accelerates gliomagenesis in histone mutant DIPGs and represents a previously unexplored therapeutic target. METHODS: To determine whether FOXR2 is sufficient to mediate gliomagenesis, we applied an integrative genomics approach using both in vivo and in vitro DIPG models: mouse neural stem cell models expressing FOXR2, in vivo mouse models using in utero brainstem electroporation, patient-derived DIPG cell lines, and RNA sequencing analysis of human and mouse tumors expressing FOXR2. RESULTS: Our data shows that FOXR2 indeed is an oncogene that rapidly accelerates gliomagenesis using an in vivo brainstem in utero electroporation model of DIPG. In human tumors, increased FOXR2 expression is mutually exclusive with MYC amplification suggesting functional redundancy. In vivo, FOXR2 results in large brainstem gliomas and rapid neurologic decline of animals. Transcriptional profiling of these tumors demonstrates activation of MYC signaling pathways. In vitro, we have further identified patient-derived cell lines with increased expression of FOXR2. CONCLUSION: FOXR2 is sufficient to enhance gliomagenesis and represents a previously understudied therapeutic target for patients with the devastating disease DIPG.

DIPG-23. SINGLE CASE REPORT OF LOW DOSE RADIOTHERAPY AND CHEMOTHERAPY IN THE TREATMENT OF DIPG
Chen Kan Tseng1, and I-Jun Chou2; 1Proton and Radiation Therapy Center, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan, 2Department of Pediatrics, Chang Gung Children’s Hospital, Taoyuan, Taiwan

A 3-year-old girl, was noted to have progressive gait disease since Nov. 2017 and brought to hospital for checkup. Brain MRI on Jan. 2018 showed diffuse infiltrative pontine lesion, favoring intrapontine glioma. She was treated with low-dose radiotherapy and chemotherapy. MRI follow-up images of the pontine lesion revealed no progression during the 2 years. At the end of the total dose of 25.5Gy in 17 fractions, the patient’s general condition returned to normal, and no signs of recurrence were noted on further follow-up MRI. With this case report, we aimed to report the use of low-dose radiotherapy and chemotherapy in the treatment of DIPG.

DIPG-24. KETOGENIC DIET IN DIFFUSE INTRINSIC PONTINE GLIOMA IN CHILDREN: A RETROSPECTIVE STUDY INVESTIGATING THE FEASIBILITY
Alexandre Pérez1,2, Janak Nathan1, Moatasem El-Ayady1,2, Christian Körfi3, Marc Ansari1,2, and André van Bueren1,2; 1Department of Pediatrics, Obstetrics and Gynecology, Division of Pediatric Hematology and Oncology, University Hospital of Geneva, Geneva, Switzerland, 2Department of Pediatrics, Obstetrics and Gynecology, CANSEARCH Research Laboratory, Faculty of Medicine, University of Geneva, Geneva, Switzerland, 3Department of Neurology, Shubhshash Hospital, Mumbai, India

Five cases of DIPG were reviewed between January 2017 to December 2020. Three patients presented with initial neurologic deficit of the fork head domain transcription factor FOXR2. One patient presented with hydrocephalus. The ketogenic diet was initiated at the completion of radiotherapy, with total dose of 25.5Gy in 17 fractions as our usual practice. The ketogenic diet was well tolerated. The symptoms improved partially after the treatment, with residual weakness over left extremity. We are still treating the patient with adjuvant therapy.

DIPG-25. GENETIC DIET IN DIFFUSE INTRINSIC PONTINE GLIOMA IN CHILDREN: A RETROSPECTIVE STUDY INVESTIGATING THE FEASIBILITY
Alexandre Pérez1,2, Janak Nathan1, Moatasem El-Ayady1,2, Christian Körfi3, Marc Ansari1,2, and André van Bueren1,2; 1Department of Pediatrics, Obstetrics and Gynecology, Division of Pediatric Hematology and Oncology, University Hospital of Geneva, Geneva, Switzerland, 2Department of Pediatrics, Obstetrics and Gynecology, CANSEARCH Research Laboratory, Faculty of Medicine, University of Geneva, Geneva, Switzerland, 3Department of Neurology, Shubhshash Hospital, Mumbai, India

Background: Diffuse Intrinsic Pontine Glioma (DIPG) is one of the most devastating diseases amongst children with cancer, thus novel strategies are urgently needed. We aimed to retrospectively evaluate the feasibility of the carbohydrate restricted ketogenic diet (KD) in DIPG patients. METHODS: Searches identified factors of MEDLINE and Embase identified factors of publications meeting the inclusion criteria (diagnosis of DIPG and exposition to a KD ≥ 3 months). One additional case was identified by contact with experts. The minimal feasibility criteria were defined as the ability to use the KD for ≥ 3 months. Individual patient data were extracted from the publications or obtained from investigators. RESULTS: Five cases (male, n=3; median age 4.4 years; range, 2.5–17 years) met the inclusion criteria (one