(Group 3 MB) is the deadliest with only 30% long term survival. Irradiation for Group 3 Medulloblastoma is required for long term survival of children. Methods to enhance the effect of irradiation against Group 3 MB are an active area of investigation. Immunotherapy using the anti-CD47 treatment has shown promise in treating Group 3 MB. We recently demonstrated that irradiation significantly enhanced anti-CD47-mediated phagocytosis of high-grade glioma cells *in vitro*. Furthermore, mice engrafted with human high-grade glioma that received anti-CD47 combined with irradiation showed a significant increase in the survival rate and a significant decrease in tumor growth than those that received a single treatment. We have now extended these studies to demonstrate the enhancement of anti-CD47-dependent phagocytosis of human Group 3 MB with irradiation. We also analyzed normal human neural stem cells exposed to the same treatments to assess for the potential toxicity that uniquely exists with this treatment combination.

MBRS-32. TOPOISOMERASE II B INDUCES NEURONAL, BUT NOT GLIAL, DIFFERENTIATION IN MEDULLOBLASTOMA

Hiroaki Miyahara[1], Manabu Natsumeda[2], Junichi Yoshimura[2], Yukihiko Fujii[2], Akiyoshi Kakita[3], Yasushi Iwasaki[1], and Mari Yoshida[1]; [1]Department of Neuropathology, Institute for Medical Science of Aging, Aichi Medical University, Nagakute, Aichi, Japan, [2]Departments of Neurosurgery, Brain Research Institute, University of Niigata, Niigata, Niigata, Japan, [3]Departments of Pathology, Brain Research Institute, University of Niigata, Niigata, Niigata, Japan

BACKGROUND: We previously reported that Gli3, which was a downstream molecule of Sonic Hedgehog signal, induced neuronal and/or glial differentiation in some types of medulloblastoma (desmoplastic/nodular medulloblastoma and medulloblastoma with extensive nodularity), and patients of medulloblastoma with neuronal differentiation showed favorable prognosis, but those with glial differentiation tended to show miserable prognosis (Miyahara H, Neuropathology, 2013). This time, we focused on Topoisomerase II β (Top2β), which was reported to induce neuronal differentiation and inhibit glial differentiation, and examined the expression of Top2β in medulloblastomas with neuronal and glial differentiations. METHODS: We assessed the expression of Top2β, NeuN, and GFAP using triple fluorescent immunostaining method in medulloblastoma samples with both neuronal and glial differentiations. Furthermore, the expression of Top2β, H3K4me2, and H3K27me3 were also assessed, because Top2β was positively or negatively regulated by H3K4me2 and H3K27me3, respectively. RESULTS: Many large nuclei in the nodules, in which differentiated cells were seen, was visualized by Top2β. The Top2β signals were seen in NeuN+ cells but not GFAP+ cells. H3K4me2 signals were visualized in Top2β+ large nuclei, but H3K27me3 and NeuN+ large nuclei were distributed independently. CONCLUSIONS: These results indicate that Top2β may be a molecule associated with neuronal, but not glial, differentiation of medulloblastoma cells. Drugs targeting histone modification enzymes such as EZH2 inhibitors are possible therapeutic targets as a differentiation-inducing therapy for medulloblastoma.

MBRS-33. TEMPORARY RESTORATION OF P53 ACTIVITY DURING FRACTIONATED RADIOTHERAPY IN A GROUP3 MEDULLOBLASTOMA GEMM REPRESENTS A POWERFUL TOOL FOR RADIOBIOLOGY STUDIES

Alaide Morcavallo[1], Henry Mandeville[2], Karen Barker[1], Stacey Richardson[3], Janet Lindsey[3], Nikita Lockett[1], Jessica K.R. Boult[4], Simon P. Robinson[4], Uwe Oelfke[2], Daniel Williamson[3], Steven C. Clifford[3], and Louis Chesler[1]; [1]Division of Clinical Studies, The Institute of Cancer Research, and The Royal Marsden NHS Trust, Sutton, Surrey, United Kingdom, [2]Division of Radiotherapy and Imaging, The Institute of Cancer Research, and The Royal Marsden NHS Trust, Sutton, Surrey, United Kingdom, [3]Wolfson Childhood Cancer Research Centre, Newcastle University Centre for Cancer, Newcastle upon Tyne, United Kingdom, [4]Division of Radiotherapy and Imaging, The Institute of Cancer Research, Sutton, Surrey, United Kingdom

TP53 pathway alterations are well-described events in medulloblastoma (MB) and are predictive of poor clinical outcome. Alterations are rare at diagnosis in Group3 (Gr3) and Group4, but enriched in Sonic Hedgehog and WNT subgroups. However, *TP53* mutations are observed in all subgroups at relapse. Radiation therapy, along with surgery and chemotherapy, represents the standard of care treatment for MB. Loss of p53 function correlates with increased resistance to radiation in several cancers conferring poor survival for patients. In this study, we exposed the MYCN-driven/Trp53[kiki] (with tamoxifen-inducible p53 activation) Gr3 MB GEMM to a clinically relevant fractionated radiation therapy (RT) regime, to assess the role of p53 in Gr3 radio-resistance and relapse. Mice exhibiting tumour progression (bioluminescence (BLI) signal >10^9 photons/second) were randomized to treatment groups. A small animal radiation research platform was used to deliver CT-guided cranio-spinal irradiation (CSI) and a cranial boost

(CB). Mice were followed for survival and tumour burden tracked using BLI. Bodyweight was monitored to evaluate treatment tolerability. Full dose radiation therapy (54Gy CB, 36Gy CSI, α/β=10) or dose modulation (12Gy CB, 8Gy CSI) was performed. The results showed comparable primary tumour regression in response to RT in p53 inactive and active backgrounds, followed by imminent relapse or prolonged remission respectively. No significant acute toxicity was observed. Temporary activation of p53 during RT improved tumour-free survival and decreased the incidence of relapse. In conclusion, we developed a new model which will help improve understanding of the radiobiology of high-risk MB and future preclinical trials.

MBRS-37. RECURRENT ACTIVATING MUTATIONS OF AKT GENES IN WNT-ACTIVATED MEDULLOBLASTOMAS

Julien Masliah-Planchon[1], Emmanuelle Lechapt-Zalcman[2], Jean-Baptiste Aillaud[1], Olivier Ayrault[3], Célio Pouponnot[4], Francois Doz[5], Olivier Delattre[5], and Franck Bourdeaut[5,6]; [1]Unité de Génétique Somatique, Institut Curie, Paris, France, [2]Neuropathology, Centre Hospitalier Sainte-Anne, Paris, France, [3]PSL Research University, CNRS UMR, INSERM, Orsay, France, [4]INSERM U1021, Orsay, France, [5]SIREDO Center, Institut Curie, Paris, France, [6]RTOP Unit, Institut Curie, Paris, France

Medulloblastoma (MB) can be classified into four distinct molecular subgroups (WNT group, SHH group, group 3, and group 4). Medulloblastoma of the WNT subgroup (WNT-MB) are commonly associated with favorable prognosis. Prospective molecular analysis based on a combination of CGH-array, targeted NGS and Nanostring-based subgrouping on 272 MB was conducted. Our custom targeted NGS panel of 75 genes includes genes recurrently affected in MB together with actionable genes with therapeutic purpose including some involved in the PIK3/AKT signaling pathway. Among the 272 MB analyzed, 26 cases (9.6%) belonged to the WNT subgroup based on *CTNNB1* mutations, monosomy of chromosome 6 and Nanostring-based molecular subgrouping. Our targeted NGS revealed three hotspot activating mutations in *AKT3* in WNT-MB and only one cases in another MB subgroup (in a group 4 MB; among the 33 cases of confirmed group 4 MB in our cohort). We subsequently performed Sanger sequencing of the hotspot Glu17 codon of *AKT1*, *AKT2*, and *AKT3* in 42 additional WNT-MB. This analysis revealed six additional activating mutations of AKT genes (four *AKT3* and two *AKT1* hotspots mutations) in WNT-MB. Altogether, we report 9/68 (13.2%) cases of WNT-MB with AKT genes mutations (two mutations in *AKT1* and seven mutations in *AKT3*). Our molecular analysis revealed AKT hotspot mutations that presumably activate the PIK3/AKT signaling pathway in WNT-MB. Even though WNT-MB is the subgroup of MB with the most favorable prognosis, this result emphasizes a possibility of targeted therapy that need to be further explored *in vitro* and *in vivo*.

MBRS-38. MOLECULAR CLASSIFICATION AND CLINICAL CHARACTERISTICS OF 236 MEDULLOBLASTOMAS IN JAPAN

Yonehiro Kanemura[1,2], Tomoko Shofuda[1,2], Ema Yoshioka[1,2], Daisuke Kanematsu[1,2], Koichi Ichimura[3,2], Atsushi Sasaki[4,2], Takeshi Inoue[5,2], Junko Hirato[6,2], Yoshinori Kodama[7,2], Masayuki Mano[8,2], Soichiro Shibui[9,2], Hajime Arai[10,2], Hiroaki Sakamoto[11,2], Isao Date[12,2], and Ryo Nishikawa[13,2]; [1]Department of Biomedical Research and Innovation, Institute for Clinical Research, National Hospital Organization Osaka National Hospital, Osaka, Japan, [2]Japanese Pediatric Molecular Neuro-oncology Group, Tokyo, Japan, [3]Division of Brain Tumor Translational Research, National Cancer Center Research Institute, Tokyo, Japan, [4]Department of Pathology Saitama Medical University, Moroyama, Jersey, [5]Department of Pathology, Osaka City General Hospital, Osaka, Japan, [6]Department of Pathology, Public Tomioka General Hospital, Tomioka, Japan, [7]Division of Pathology Network, Kobe University Graduate School of Medicine, Kobe, Japan, [8]Department of Central Laboratory and Surgical Pathology, National Hospital Organization Osaka National Hospital, Osaka, Japan, [9]Department of Neurosurgery, Teikyo University Hospital, Mizonokuchi, Kanagawa, Japan, [10]Department of Neurosurgery, Juntendo University, Tokyo, Japan, [11]Department of Pediatric Neurosurgery, Osaka City General Hospital, Osaka, Japan, [12]Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [13]Department of Neuro-Oncology/Neurosurgery, International Medical Center, Saitama Medical University, Hidaka, Japan

Recent intensive genomic and molecular biological analyses have made a consensus that medulloblastomas (MBs) are at least classified into four core subgroups, and the new 2016 WHO brain tumor *classification* has introduced the *classification* of MBs genetically defined in addition to classical histopathological diagnosis. To establish a nationwide network of a molecular diagnosis system for pediatric brain tumors, the JPMNG co-organized by the Japan Society for Neuro-Oncology and the Japanese Society for Pediatric Neurosurgery have started the clinical researches in