Abstracts

**ET-04**

**ENHANCING DRUG DELIVERY WITH MRI-GUIDED FOCUSED ULTRASOUND FOR DIFFUSE INTRINSIC PONTINE GLIOMA MODEL**

Joji Ishida,1,2 Saia Alli,1 Andrew Bondoc,2 Naohide Fujita,2 Hynynen Kullervo,2,3 Rutka James,1,2 1Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

Diffuse intrinsic pontine glioma (DIPG) is surgically unresectable and one of the most devastating tumours in children. To date, there have been no effective chemotherapeutics against DIPG, despite a myriad of clinical trials. The intact blood-brain barrier (BBB) is partly responsible for the limited clinical response to chemotherapy. MRI-guided focused ultrasound (MRgFUS) is a promising non-invasive tissue ablation method for treating CNS tumours. Moreover, MRgFUS allows for temporary and repeatable BBB disruption. Our first objective was to determine the feasibility and safety of temporary BBB disruption within the brainstem using MRgFUS following intravenous administration of microbubbles in vivo. Our second objective was to select effective chemotherapeutics against DIPG cell lines, and to examine their therapeutic effects with MRgFUS in a murine model of DIPG which exhibits an intact BBB. Non-invasive opening of the BBB was determined in the brainstem of normal rodents using physiological monitoring and histological analysis. Doxorubicin was selected from a drug screen consisting of conventional chemotherapeutics tested against DIPG cell lines. We established an in vivo model of DIPG17 orthotopic xenografts which demonstrated diffusely infiltrative tumour growth. By LC-MSMS analysis, MRgFUS led to a 4-fold increase in doxorubicin concentrations within the brainstem tumours as compared to controls. Moreover, the volumetric tumour growth rate was significantly suppressed in MRgFUS-treated animals, which also exhibited decreased Ki-67 expression. We demonstrated the feasibility and safety of MRgFUS in the rodent brainstem and have shown that MRgFUS increases doxorubicin uptake in the brainstem of a rodent model of DIPG. This preclinical data provides critical support for clinical trials investigating MRgFUS-mediated BBB opening, which may greatly improve chemotherapeutic efficacy against DIPG in children.

**ET-05**

**ALECTINIB AND CERTINIB, THE SECOND-GENERATION ALK INHIBITORS, EFFECTIVELY INDUCE GLOBLASTOMA CELL DEATH**

Daisuke Kawashita,1,2 Masamichi Takahashi,1 Shun Yamamura,1,3 Tatsuya Kobayashi,4,5 Eita Uchida1,4 Yasuo Iwadate,1 Kosichi Ichimura1, Arata Tomiyama,1,2,3 1Division of Brain Tumor Translational Research, National Cancer Center Research Institute

Anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that only expresses in the developmental stage of the central and peripheral nervous system. A variety of ALK gene alterations, such as oncogenic fusion, activating point mutation, or wild type gene amplification, have been recently discovered as the powerful oncogene in various tumors. These ALK mutations are expected as potential therapeutic targets. Some ALK inhibitors have already been approved and used for the clinical treatment of non-small cell lung cancers harboring oncogenic ALK fusion.

Previously, we reported classical ALK inhibitors triggered cell death in human glioblastoma (GBM) cells, which did not express ALK, via suppression of transcription factor STAT3 activation but not in normal tissue-derived cells. In this study, we investigated the anti-tumor effect of newly-developed ALK inhibitors in GBM cells. As a result, second-generation ALK inhibitors, alecimib and ceritinib, induced cell death in various human GBM cell lines with lower concentrations than other ALK inhibitors. Also, alecimib and ceritinib suppressed STAT3 family activity in these GBM cell lines. We consider alecimib and ceritinib might be a novel therapeutic agent against GBMs. Further investigation about the specific anti-tumor mechanism of these second-generation ALK inhibitors in GBM cells is currently ongoing.

**ET-06**

**SUPPRESSION OF GLOBLASTOMA THROUGH NOVEL DRUG BASED ON “GENE SWITCH TECHNOLOGY”**

Etsuru Yamamoto,1,4 Yoshikazu Arakawa,4 Yashiro Yonehara1, Masamitsu Mikami,1,2 Yasuzumi Matsui,1,2 Hiroshi Sugiyama,4 Susumu Miyamoto,1 Souichi Adachi,1,2 Yasuhiko Kamikubo,4 1Department of Neurosurgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Glioblastoma (GBM) is one of the most common and aggressive malignancies primarily affecting adults. Despite intensive multimodal therapies, the prognosis of GBM is dismal and a novel therapy is needed. Here, we focused on RUNX, a transcription factor discovered in childhood acute myeloid leukemia, and in this study, similar results were found for glioblastoma in vitro. Specific inhibition of RUNX1 led to a marked inhibition of cell growth through cell cycle arrest and apoptosis. By using apoptosis array, we isolated several candidate genes which are regulated by RUNX1. And some types of glioblastoma cell lines treated with Cbb-M’ showed increased expression of p21 and decreased survivin. From in silico analysis, we predicted that there was a significantly higher in GBM and it was possibly involved in maintaining the malignancy of GBM. Mechanistically survivin was found to be directly transcriptionally regulated by RUNX1 through Chb assay and reporter assay. In addition, survivin Kd’ cells upregulated p21 expression and accelerated apoptosis. Taken together, we hypothesized that the RUNX1-survivin-p21 pathway can potentially be exploited in the management of this malignancy. Cbb-M’ mediated regulation of RUNX1 can be a novel therapeutic strategy against GBM.

**COMPUTATIONAL OMICS (CO)**

**CO-01**

**PREDICTION OF PATHOLOGICAL AND RADIOLOGICAL NATURE OF GLIOMA BY MASS SPECTROMETRY COMBINED WITH MACHINE LEARNING**

Tomoyuki Kawakatsu,1 Mitsuto Hanahara,1 Keiko Suzuki,2 Kentaro Yoshimura,1 Sen Takada,3 Hiroyuki Kondo4 1Department of Neurosurgery, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi

BACKGROUND: We have previously developed a medical diagnostic pipeline that employs mass spectrometry and machine learning. It does not annotate molecular markers that are specific to cancer but uses entire mass spectra for predicting the properties of glioma. OBJECT: To validate the power of our diagnostic method in predicting the pathological and radiological properties of glioma with a simple sample preparation procedure. METHODS: Ten patients with glioma and 4 non-glioma patients who went through surgical resection were enrolled in our hospital. A total of 1020 mass spectra were acquired from 88 specimens. In order to examine the prediction power of the diagnostic pipeline that we have developed, we performed ten-fold cross-validation for pathological and radiological findings and calculated agreement rates with the conventional methods such as pathological diagnosis (WHO grading, MIB-1 labeling index (LI), mutations in the isocitrate dehydrogenase (IDH)-1 gene and positive 5-AIA fluorescence) and radiological information (gadolinium (Gd)-enhanced area, high-intensity area on fluid-attenuated inversion recovery (FLAIR) imaging). RESULTS: Prediction accuracy for WHO malignant grade was 91.37%. Those for MIB-1 LI more than 10% and IDH-1 mutation-positive were 82.84% and 87.75%, respectively. Our method achieved an accurate prediction of 95.00% for the 5-AIA-positive lesion. The present method displayed an accuracy of 82.36% in predicting the area of FLAIR hyperintensity and 81.27% for the Gd enhanced area. CONCLUSION: Our methodology achieved a higher rate of prediction of glioma in terms of pathology and radiology. Research is ongoing to develop a validation cohort to verify the biological profiles of glioma specimens.