Abstracts

ET-04 ENHANCING DRUG DELIVERY WITH MRI-GUIDED FOCUSED ULTRASOUND FOR DIFFUSE INTRINSIC PONTINE GLIOMA MODEL
Joji Ishida1,2, Sairi Alli1, Andrew Bondoc2, Naohide Fujita2, Hynynnell Kullervos1, Rutka James1,2, 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 SU-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 CERTITINIB, THE SECOND-GENERATION ALK INHIBITORS, EFFECTIVELY INDUCE GLOBLASTOMA CELL DEATH
Daisuke Kawakazi1,2, Masamichi Takahashi1, Shun Yamamura1,2, Tatsuya Kobayashi1,2, Eita Uchida1,3, Yasuo Iwadate1,2, Koichi Ichimura1,2, Arata Tomiyama1,2, 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, alectinib and ceritinib, induced cell death in various human GBM cell lines with lower concentrations than other ALK inhibitors. Also, alectinib and ceritinib suppressed STAT3 family activity in these GBM cell lines. We consider alectinib and ceritinib might be a novel therapeutic agent against GBM. 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”
Etsutaro Yamamoto1,2, Yoshihiro Aoyama1,3, Kenjiro Mineharu1,2, Etsuko Yamamoto1,2, Masamitsu Mikami1,3, Yasuzumi Matsui1,2, Hiroshi Sugiyama1,2, Susumu Miyamoto1,2, Souichi Adachi1,2, Yasuhiro Kamikubo1,2, 1Department of Neurosurgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Glioblastoma (GBM) is the most common and aggressive malignancy 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 involved in the malignant transformation of GBM, and developed a novel Chlorambucil-conjugated PI-polyamides (Chb-M’), which “switches off” RUNX family. Chb-M’ specifically recognizes the consensus RUNX-binding sequences (TGTTG) and alcalxylates it to inhibit the transcription of the downstream gene of RUNX family. Chb-M’ has been shown to induce apoptosis and suppress proliferation in a variety of cancers including leukemia, and in this study, similar results were found for glioblastoma cells in vitro. Specific inhibition of RUNX1 led to a marked inhibition of tumor growth through cell cycle arrest and apoptosis. By using apoptosis array, we isolated several candidate genes which regulated by RUNX1. And some types of glioblastoma cell lines treated with Chb-M’ showed elevated expression of p21 and decreased survival. From in silico analysis we selected a panel of candidate genes. In order to examine the mechanism of transcriptional repression by Chb-M’, we performed ten-fold cross-validation for pathological and radiological findings of glioma. Prediction accuracy for WHO malignant grade was 88.18%, for MIB-1 LI more than 10% was 86.83%, for IDH-1 mutation-positive were 85.78%, for FLAIRE intensity area on fluid-attenuated inversion recovery (FLAIR) imaging, 84.21% with 3.5-fold increase of sensitivity. Non-invasive opening of the BBB was achieved by magnetic resonance imaging (MRI). In an orthotopic xenograft 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-07 OF GLIOMA BY MASS SPECTROMETRY COMBINED WITH MACHINE LEARNING
Tomoyuki Kawakazi1,2, Keisuke Fujita1,2, Takayuki Kikuchi1,2, 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 3-ALA 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 a higher accuracy of 95.00% for the 3-ALA-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.

Computational Omics (CO)

CO-01 PREDICTION OF PATHOLOGICAL AND RADIOLOGICAL NATURE OF GLIOMA BY MASS SPECTROMETRY COMBINED WITH MACHINE LEARNING
Tomoyuki Kawakazi1,2, Mitsuto Hanahara1,2, Keisuke Fujita1,2, Kentaro Yoshimura1,2, Sen Takeda1,2, Hiroaki Kinouchi1,2, 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 3-ALA 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 a higher accuracy of 95.00% for the 3-ALA-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.