The 6th Japan Russia Neurosurgical Symposium

Program & Abstracts

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suggesting that TERT can be directly targeted to suppress tumor cell proliferation. We have previously identified eribulin mesylate, which is an FDA-approved drug used to treat breast cancer and liposarcoma, as a specific inhibitor of RdRP activity of TERT and investigated the antitumor efficacy of eribulin using multiple human GBM cell lines in preclinical mouse brain tumor models. All GBM cell lines tested in vitro that harbored TERT promoter mutations were highly sensitive to eribulin with IC50 below 1nM. Intraperitoneal administration of eribulin (0.5 mg/kg), which was equivalent to the dose used in human (1.4 mg/m^2), significantly prolonged the survival of multiple mouse brain tumor models established with U87MG or LN229 (p <0.001 or 0.01, respectively). We also found that high concentration of eribulin was detected in the brain tumour tissues as early as 15 minutes after intravenous injection of eribulin and it remained even 24 hours later. Further, RdRP activity in tumor tissue was supressed with eribulin administration in dose-dependent manner. Based on these results, we have recently started the mutli-center, open-labelled, investigator-initiated registration-directed phase II clinical trial using eribulin mesylate in the patients with recurrent GBM in Japan (UMIN000030359). This is the first phase II clinical trial that eribulin mesylate is evaluated in the patients with glioblastoma and the relationship of eribulin and TERT promoter mutations are investigated. Trial designs and current status will be presented at the meeting.

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Japan-Russia collaborative research on accelerator-based boron neutron capture therapy for malignant glioma.

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In 2015, collaborative research of the Department of Neurosurgery, University of Tsukuba, Novosibirsk and Irkutsk State Medical Universities, and Budker Institute of Nuclear Physics (BINP) on accelerator-based boron neutron capture therapy (BNCT) for malignant glioma was initiated. Proton accelerator with lithium target at BINP was used as a neutron source. Two years of consecutive preclinical cell and animal experiments proved the efficacy of the neutron source, which was also used to test newly developed boron compounds and a unique method of in-sample absorbed dose evaluation, never applied before.
In preclinical experiments, human and animal cells (U251MG, T98G, CHO-K1, and V79) were incubated in the medium with boronophenylalanine (BPA) or boric acid at different boron-10

concentrations (10, 20, 40 ppm). Immunodeficient SCID mice were inoculated with human U87 glioma cells. The animals were injected with BPA or sodium borocaptate (BSH) at different concentrations and irradiated under anesthesia. Before irradiation, the samples were placed in a plexiglass phantom, and the animals were placed in a container made of 25 mm lithium-polyethylene plates. The samples and animals were irradiated with epithermal neutrons during 2 to 3 hours with 2.0 MeV proton energy, 1-3 mA proton current, and a maximum fluence of 2.16 x 1012 neutrons/cm^2. After irradiation, all cells were counted, diluted, and seeded into round dishes for CF-assay. Animal survival revealed that the efficacy of BNCT depends on boron accumulation and irradiation dose, and that the machine is capable of producing a sufficient number of neutrons for BNCT, which results in decreased colony formation in tumor cells and control over tumor growth in laboratory animals. The current study is ongoing and more detailed report will be presented at the symposium.

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Development of novel spray-type fluorescent probes for brain tumors

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Purpose:
In glioma surgery, dissecting unclear tumor margin may result in postoperative neurological deficits, which can effectively be avoided when tumor margin is clearly visualized with intraoperative fluorescent probe. At present, 5-amino levulinic acid (5-ALA) is widely used in the resection of malignant glioma, but there are some limitations such as false positivity, false negativity, and inability of re-administration. We aim to develop a safe fluorescent probe which can be repeatedly administered in spray during surgery, complementing 5-ALA.

Methods:
Four groups of homogenized samples were prepared from frozen tissues of 10 non-tumors, 5 glioblastomas, 5 oligodendrogliomas, and 5 astrocytomas. Probe screening was performed using the fluorescent probe library comprising of HMRG (green) and 2MeSiR 600 (red) host fluorescent nuclei combined with various combinations of dipeptides. A total of 720 types of fluorescent probes were applied to homogenized lysates. The fluorescence intensity after application was measured over time, and the top probes with high focal change and high difference between non-tumor and tumor were selected as valid probes. The selected probes were validated by the experiment using fresh specimens.

Results
The top seven probes were selected based upon the experiment using homogenized lysates. Furthermore, similar results were obtained in experiments with fresh specimens using the selected probes. Detailed results will be presented.