CO7-1 Irradiation Characteristics of D_2O Facility in KUR with Low-enriched Uranium Fuel (II)

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Introduction: In Heavy Water Neutron Irradiation Facility (D_2O Facility) of KUR, the neutron beams with the various energy spectra are available [1]. This facility has been utilized mainly to boron neutron capture therapy (BNCT). In February 2006 just after the suspension of the KUR operation started, the total number of BNCT clinical irradiation reached to 275. In May 2010, BNCT clinical irradiation restarted concurrently with the KUR operation restarted. After the restart, 102 BNCT irradiations have already been carried out as of May 2012.
As this facility is a larger facility, it is expected that the irradiation characteristics are influenced by the conditions of the KUR fuel. Then, we performed the re-evaluation of the irradiation characteristics.

Methods: The neutron energy spectra were evaluated for the three standard irradiation modes of epi-thermal (CO-0000-F), mix (OO-0000-F) and thermal (OO-0011-F). The evaluation was performed by multi activation foil method using gold, indium, aluminum nickel, etc.. The unfolding was done using an unfolding code, MAXED [2]. The nominal spectra before the fuel low-enrichment were used as the initial guesses.

Results and Discussions: Figure 1 shows the evaluation results of the neutron energy spectra at the standard irradiation position for the three irradiation modes. The averaged data obtained from three irradiation experiments for the respective modes are drawn. The uncertainties for the three irradiations were within plus/minus 20% in the thermal neutron range, 15% for the epi-thermal neutron range and 20% for the fast neutron range.
Figure 2 shows the comparison for neutron energy spectra in CO-0000-F mode between before and after the fuel low-enrichment. It is found that the spectrum after the low-enrichment is a little softer. It is found that the neutron beam intensity after the low-enrichment is overall larger. It was confirmed that the beam intensity increased at 10 to 20% for the fast neutron range, 20 to 30% for the epi-thermal neutron range.

Conclusion: It was confirmed that the neutron energy spectra became a little softer and the neutron beam intensity increased 10 to 30% after the fuel low-enrichment. However, it was concluded that these changes in the irradiation characteristics due to the fuel low-enrichment were not so larger for the influence on the BNCT clinical irradiation, from the viewpoint of the relative values.

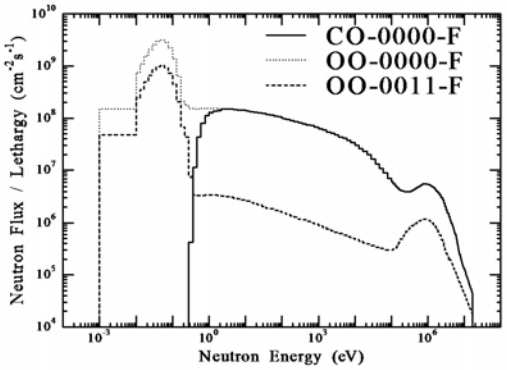

Fig. 1. Neutron energy spectra after the fuel low-enrichment for CO-0000-F, OO-0000-F and OO-0011-F modes.

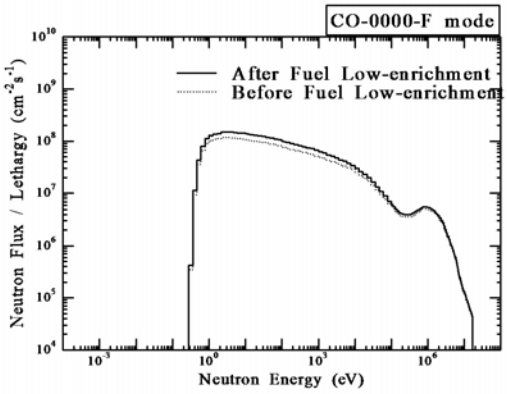

Fig. 2. Comparison for neutron energy spectra in CO-0000-F mode between before and after the fuel low-enrichment.

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採択課題番号 23006　　KUR 燃料低濃縮化後の重水中性子照射設備の特性評価　　共同通常

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CO7-2 Short-Term Outcome of BNCT for Human Clear Cell Sarcoma in Mouse Model

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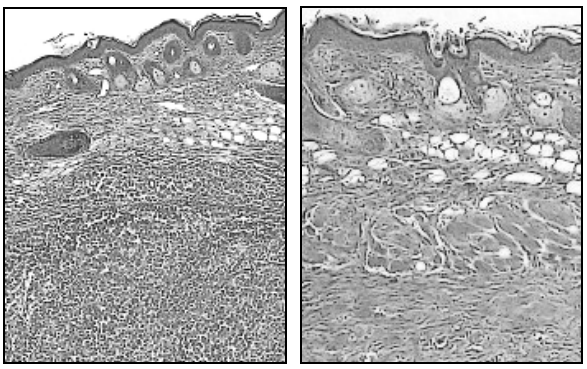
INTRODUCTION: Clear cell sarcoma (CCS) of tendons and aponeuroses is a rare and malignant tumor of poor prognosis, with a predilection for young adults [1, 2]. The standard treatment is still wide surgical resection because chemotherapy and radiotherapy are not effective. Clearly therefore, new therapeutic strategies are required. Recently, boron neutron capture therapy (BNCT) with the use of *p*-boronophenylalanine (BPA) for malignant melanoma has provided good results [3]. Since BPA is associated with the production of melanin, boron is ultimately accumulated in tumor cells. CCS also produces melanin, and with the use of a cultured human CCS cell line and through human CCS-bearing animal studies we have shown that high accumulation of ^{10}B is potentially favorable in BNCT [4, 5]. Consequently, in this study, we evaluated the efficacy of BNCT for CCS with the use of human CCS cell line-bearing nude mice and propose a new therapeutic option for the treatment of CCS.

EXPERIMENTS: (1) *Tumor cell line*: Cells of human CCS cell line MP-CCS-SY [6] were grown in RPMI 1640 and DMEM with fetal bovine serum in a 5% CO_2 humidified incubator at 37˚C.
(2) *BNCT for CCS (MP-CCS-SY)-bearing animals*: All animal experiments were carried out according to the regulations of the Animal Care and Use Committee. MP-CCS-SY cells were subcutaneously transplanted into the left femoral region of BALB/c nude mice. Four weeks thereafter, the animals were divided into four groups of 4 each. Of nonirradiated groups A and B, saline was administrated to group A and BPA-Fr (500mg BPA/kg) was administrated to group B through the femoral vein, under anesthesia, on day 0. Similarly saline (group C) and BPA-Fr (500mg BPA/kg) (group D) were administrated to irradiated groups C and D, respectively, and then the two groups were immediately placed in a chamber for thermal neutron irradiation. Thermal neutrons (1MW) were delivered from the dorsum of the mouse, in the heavy water facility at KURRI. LiF tiles were used to shield parts of the body other than the left leg. The size of the tumor was measured in groups A and B from day 0 to day 28, and in groups C and D from day 0 to day 23. Thin sections from formalin-fixed and paraffin-embedded samples of the tumor mass resected on the last day of measurement were stained with hematoxylin-eosin (HE) for histological evaluation.

RESULTS: The size of the tumor decreased time-dependently in only group D. Finally, on day 23, the tumors in 2 mice of group D had disappeared, and the tumors in the two remaining animals were excised. Although the size of the tumor increased in groups A, B and C, the growth was slightly suppressed in group C compared with that in the other two groups. There was no difference between groups A and B. Histological examination of the sections of group D revealed that the tumor mass had disappeared completely 2 tumors and had changed into granulation tissue 2 tumors — only the tumor mass was selectively destroyed with no damage to normal surrounding tissue [Fig.1]. On the other hand, saline-administrated irradiated group C [Fig.1] showed no tumor death and no normal tissue damage.



[Fig.1] Left: CCS tumor mass resected from group C (hot control) on day 23. Tumor cells are observed in the subcutaneous area. No tumor cells or skin were damaged. Magnification (80×). Right: CCS tumor mass resected from group D (BNCT) on day 28. No tumor cells are observed. The connective tissue is replaced by granulation. There is no damage to normal tissue surrounding the tumor. Magnification (80×).

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採択課題番号 23009　　明細胞肉腫に対するホウ素中性子捕捉療法の検討　　共同通常
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CO7-3 Enhanced the Effect of Boron Neutron Capture Therapy: Design of Boron-containing Nanoparticles with Highly Tumor-accumulating Character

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Introduction:

The success of BNCT is dependent on the delivery systems to accumulate a sufficient quantity of ^{10}B to tumor tissues. Herein, we designed and prepared core polymerized and boron-conjugated micelles (PM micelles) composed of poly(ethylene glycol)-*block*-poly(lactide) copolymer bearing an acetal group at PEG end and a methacryloyl group at PLA end (acetal-PEG-*b*-PLA-MA) and polymerizable boron cluster (1-(4-vinylbenzyl-*closo*-carborane): VB-carborane. This micelle enables to prolong the circulation time and deliver the boron to the tumor tissues without leakage of boron clusters in the blood stream because of the existence of covalent bonds between boron clusters and the PLA core of the micelles.

Experimental Methods:

The PM micelle was prepared from acetal-PEG-*b*-PLA-MA (PEG; M_n=5,600, PLA; M_n=5,100) micelle encapsulating VB-carborane and radical initiator (azobisisobutyronitrile: AIBN) by solvent evaporation method. The polymerization of the core was carried out by thermo-induced radical copolymerization at 60 °C for 24 h. For comparison, NPM micelles encapsulating VB-carborane were prepared by the same procedure as that for PM micelles, without the addition of AIBN and heating. Neutron irradiation was carried out at Kyoto University Reactor of Kyoto University Research Reactor Institute. ^{10}B-enriched PM and NPM micelles were prepared from ^{10}B-enriched VB-carborane and acetal-PEG-*b*-PLA-MA by same procedure above. ^{10}B-enriched PM and NPM micelles solution injected into colon-26 tumor bearing mice (n = 5) via the tail vein at a dose of 15.6 mg ^{10}B/kg 24 h before irradiation. As comparison, ^{10}B-enriched BSH solution was injected 1 h before irradiation *via* the tail vein at a dose of 30.0 mg ^{10}B/kg. The mice were anesthetized with pentobarbital sodium (40 mg/kg) and placed in an acrylic mouse holder. The mice were irradiated thermal neutrons for 37 min at a rate of 1.6-1.8 x 10^{12} neutrons/cm^2. Figure 1 shows the neutron irradiation to tumor bearing mice at Kyoto University Research Reactor. The BNCT effects were evaluated in terms of the tumor size.

Results and discussion:

The average diameter of the PM micelles (67.3 nm, μ_2/Γ^2 = 0.113) was almost similar to that of the NPM micelles (60.2 nm, μ_2/Γ^2 = 0.119), suggesting that the core polymerization process does not influence to the average diameter and size distribution of the micelles. The loading content of boron atoms in the NPM and PM micelles was determined to be 8.5 wt% (loading efficiency: 23.5 %) and 7.7 wt% (loading efficiency: 21.5 %), respectively. Note that the significant suppression of growth of tumor volume in mice treated the ^{10}B-enriched PM micelles was observed from 12 days compared to the mice treated normal saline ($p < 0.01$). On the other hand, the mice treated the ^{10}B-enriched NPM micelles and free BSH showed tumor growth similar to the control. These results indicate that the concentration of ^{10}B atoms in tumor tissues of the mice treated the ^{10}B-enriched NPM micelles or free BSH was insufficient for BNCT.[1]

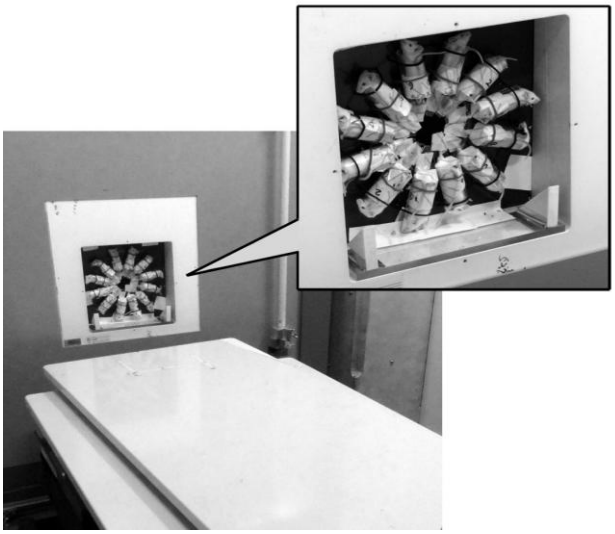

Fig. 1. Neutron irradiation to tumor bearing mice at Kyoto University Research Reactor

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採択課題番号 23015　高い腫瘍選択性を有するボロン含有ナノ粒子の創製と中性子捕捉療法への展開　共同通常

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CO7-4 **Development of Novel Boron Compounds for BNCT**

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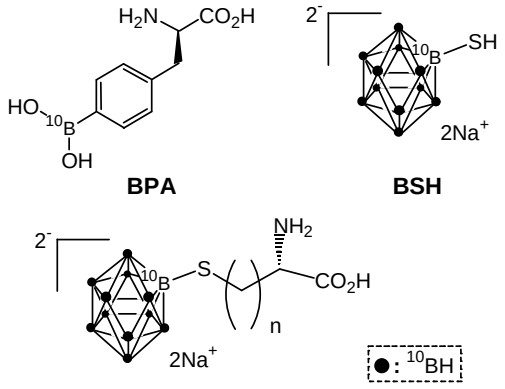
INTRODUCTION: Although many kinds of boron compounds such as amino acid, nucleic acid and liposome have been reported as boron boron carrier for boron neutron capture therapy (BNCT) [1], only two compounds, *p*-borono-L-phenylalanine (BPA) and mercapto-*closo*-undecahydrododecaborate (BSH) of them, are clinically used in cure of cancer with BNCT.
To develop practical materials utilizing ^{10}B carrier, we had already designed and synthesized new boron containing amino acids [2] such as C4-BSH-AA (n=2) (**1a**), C5-BSH-AA (n=3) (**1b**), C8-BSH-AA (n=6) (**1c**), which include the undecahydro-*closo*-dodecaboranylthio ($[^{10}B_{12}H_{11}S]^{2-}$) unit by boron-sulfur-carbon bond connection in the side chain of α-amino acid (Fig. 1). Here, we report the tumor cell killing effects of BSH-amino acids **1a-c**.
Material and Method: Cultures were inoculated with 1.0 x 10^6 cells/dish, and cells were grown for 24 h in DMEM. The medium was replaced with the each medium containing each boron amino acid (final concentration was 2.0 mM in each case). The cells were cultured



1a - c (**1**a: n = 2, **1b**: n = 3, **1c**: n = 6)

Fig. 1. Boron compounds

for 24 h, and the medium was removed by aspiration. The cells were washed with PBS, harvested by trypsinization, and then cell numbers were counted. After centrifugation, the tripsin was removed by aspiration, and to the residual cells was added DMEM. The suspension of the cell in DMEM (5.0 x 10^3 cells/mL, 1mL) was irradiated with thermal neutron for 0 - 90 min in column-shape tube. The thermal neutron fluence was determined by averaging two gold foils symmetrically attached to the surface of the column-shape tube along the direction of incidence of thermal neutrons. After thermal neutron exposure, 600 cells were placed in three Corning 60 mm tissue culture dishes containing 3 mL DMEM to examine colony formation. Seven days later, the colonies were fixed with ethanol and stained with 0.1% crystal violet for quantitative visualization by the naked eye.
To confirm the usefulness of BSH-amino acids **1a-c** for BNCT, we examined the tumor cell killing effects of BPA and the compounds **1a-c** against three kinds of tumor cell such as C6 (rat glioma), B16 (mouse melanoma), and SAS (human oral squamous cell carcinoma).

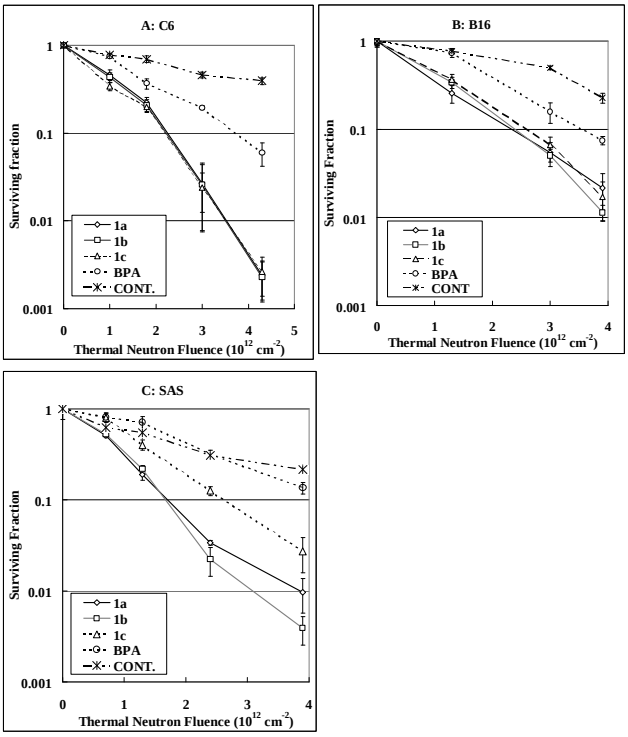


Fig. 2. Tumor cell killing effects of boron amino acids. A: against C6 cell. B: against B16 cell. C: against SAS cell.

RESULTS: As shown in Fig. 2, **1a-c** showed higher killing effects than that of BPA in the case of each tumor cells. These results suggest that BSH-amino acids **1a-c** are useful for ^{10}B carrier on BNCT.

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採択課題番号 23017　ホウ素中性子捕捉療法の新規ホウ素薬剤の開発研究　共同通常
（阪府大院・生命環境）切畑　光統、椋本　麻里、上田　さおり、上田　晋平、村上　広和　（京大・原子炉）小野　公二、増永　慎一郎、鈴木　実　（阪府大・地域連携）服部　能英

CO7-5 Fluorescence-labeled *closo*-dodecaborate Lipid: Synthesis and its Liposome Formation for *in vivo* Imaging Targeting to Tumor on BNCT

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INTRODUCTION: Recently much attention has been focused on the liposomal drug delivery system (DDS) using drugs-embedded nano carriers including liposomes, micelles, proteinaceous or polymer-conjugated macromolecules, and lipid particles.[1] This nano carrier-based DDS is based on the enhanced permiability and retention (EPR) effect discovered by Maeda and Matsumura. Abnormal architectures and impaired functional regulation of newly formed tumoral blood vessels lead to abnormal molecular and fluid transport dynamics especially for macromolecular species. Thus nano particles extravasate through these tumoral blood vassels and accumulate in tumor.

The cytotoxic effect of boron neutron capture therapy BNCT is due to the nuclear reaction of two essentially nontoxic species, boron-10 and thermal neutrons. It has been considered that the nano carrier-based DDS is an attractive approach for efficient boron delivery system (BDS) to tumor on BNCT. We were the first to synthesize boron cluster lipid. Although the first generation boron cluster lipid showed acute toxicity against tumor bearing mice,[2] the second generation boron cluster liposomes, such as DSBL that possess the $B_{12}H_{11}S$ moiety as the hydrophilic function, did not display the acute toxicity up to 30 mg boron per kg body in mice.[3] In BDS, it is very important to know detailed boron biodistribution in tissues because the distrubution of tumor cells are often heterogeneous and liposomes may spread in a certain distance from tumoral blood vessels. In this paper, we report developemnt of fluorescent-labeled *closo*-dodecaborane lipid (FL-SBL) and its liposome formation.

EXPERIMENTS: PEGylated DSPC-liposomes were prepared from DSPC, CH, and DSPE-PEG-OMe (1:1:0.11, molar ratio) by the reverse-phase evaporation (REV) method. Briefly, a mixture of DSPC, CH, and DSPE-PEG-OMe were dissolved in 10 ml of chloroform/diisopropylether mixture (1:1, v/v) in a round-bottom flask. To the lipid solution was added 5 mL of water, forming an emulsion. The emulsion was sonicated for 1 min, and then the organic solvent was removed under reduced pressure in a rotary evaporator at 37 °C, generating a suspension of liposomes. The liposomes obtained were subjected to extrusion using an extruder device. Purification was accomplished by ultracentrifuging at 200,000 g for 20 min. FL-SBL was dissolved in normal saline solution and the FL-SBL solution were mixed with DSPC liposome solution. The mixture was maintained at 25°C for 5 min and free FL-SBL was removed by ultracentrifugation at 200,000 g. The obtained FL-SBL-labeled liposomes were resuspended in PBS. Liposome size and Zeta potential were measured with an electrophoretic light scattering spectrophotometer (Nano-ZS, Sysmex, Japan). The compositions of FL-SBL and DSPC in liposomes were calculated from data obtained by the simultaneous measurement of boron and phosphorus concentrations by inductively coupled plasma atomic emission spectroscopy (ICP-AES, HORIBA, Japan). The fluorescence intensity of each sample was measured at a range of emission-wave length from 475 to 650 nm using an excitation wavelength of 460 nm.

RESULTS: The results are summarized in Table 1. The PEGylated DSPC liposomes displayed 97.22 nm in diameter with -29.3 mV of Zeta potential. With increase of volumes of the additive FL-SBL solution, the boron concentration in liposomes increased. The boron/phosphorus concentration ratio increased roughly in proportion from 1.9 to 7.1% w/w without affecting their particle size. However, addition of the FL-SBL solution increased the zeta potential of each liposome from -29.3 to -20.0 mV.

Table 1. Boron and phosphorus concentrations, particle size, and zeta potential of the FL-SBL-labeled liposomes

Volume of FL-SBL (μL)	Boron conc. (ppm)	Phosphorus conc. (ppm)	B/P ratio (%)	Particle size (nm)	Zeta potential (mV)
0	-	1876.2	0	97.2±0.15	−4.10±0.35
10	41.3	2153.4	1.9	97.6±0.47	−23.2±2.35
20	73.8	2169.2	3.4	97.4±0.20	−23.3±3.04
30	112.6	2066.1	5.4	96.2±1.38	−21.1±1.70
40	146.7	2054.5	7.1	97.8±1.15	−20.0±3.52

Preliminary *in vivo* imaging study of the boron liposomes using colon 26 tumor-bearing mice showed that the boron liposomes are delivered to the tumor tissue but not distributed to hypoxic tissue which is located far from blood supply in tumor.[4]

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採択課題番号 23018　　中性子捕捉治療用新規ホウ素薬剤の開発　　共同通常

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（京大・原子炉）鈴木　実、増永　慎一郎、小野　公二

CO7-6 Basic Investigation of BNCT with Novel Boron Compound for Malignant Pleural Mesothelioma Cells

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INTRODUCTION: Malignant pleural mesothelioma (MPM) is an aggressive and refractory cancer of the pleural linings of the lungs and chest wall caused by asbestos exposure. The therapy of MPM is required the multidisciplinary techniques: surgery, chemotherapy , and radiotherapy. However, surgical therapy, especially extrapleural pneumonectomy is limited to the locally advanced MPM. The chemotherapeutic regimens have resulted in an improved tumor response, but they have not been breakthrough tools yet. Radiotherapy is limited utility because the extensiveness of the tumor requires large fields and it is impossible to administer tumoricidal dose without injuring the adjacent lung and mediastinal organs [1, 2].

Boron neutron capture therapy (BNCT) could be a breakthrough strategy to treat MPM, because it is suitable for the treatment of diffuse and invasive tumor. However, the success of BNCT depends upon the selective delivery of ^{10}B-atoms to tumor cells to complement the attenuation of thermal neutron. BNCT is done against the tumors that occupied near the body surface area efficiently. Concerning BNCT for deep site tumor (MPM), novel compound that possesses high affinity to tumor cells than conventional boron compounds are craved for BNCT for deep site tumors [3]. We developed novel boron compound that bound with MPM cells preferentially, and BNCT with this novel compound showed significant efficiency compared with other boron compound including conventional boron compound. We examined *in vitro* experiments: boron neutron capture reaction with this boron compound at KUR.

EXPERIMENTS: The murine malignant pleural mesothelioma cells were seeded into 35 mm dish, and novel boron compound(HA-BND-S) or BSH was administered into cells for 24 hrs or 1 hr. The concentration of boron compounds was 0.003 ppm per cell. After discarding boron compounds and washing with PBS, each group of cells was set into Eppendorf tubes, and neutron irradiation was performed at JRR4 for 23 min at a rate of 1.8 x 10^{12} neutrons/cm^2. After neutron irradiation, the cells were washed with PBS, and seeded into 96 well plates at the concentration of 2,000 cells/200 μL/well. The cytotoxicity of BNCT with born compounds for MPM cells was measured with Cell Cycling-8 kit using tetrazolium assay.

RESULTS: As shown in Fig. 1, HA-BNS-S had the highest cytotoxicity compared with the other boron compounds including no discard of BSH group, despite discarding before neutron irradiation.

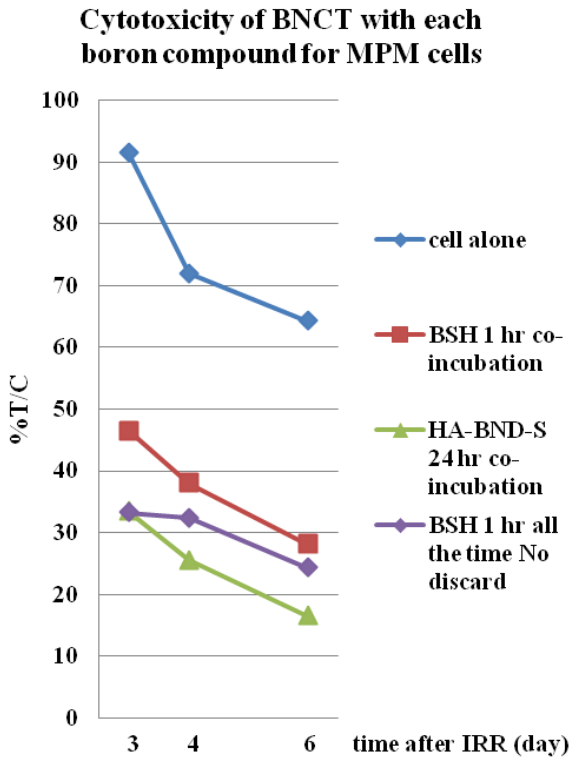

Fig. 1. Cytotoxicity of BNCT with each boron compound for MPM cells. Neutron irradiation was done at a rate of 1.8 x 10^{12} neutrons/cm^2 at JRR-4.

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採択課題番号 23025　　深部腫瘍性病変に対するホウ素中性子捕捉療法の治療効果改善のための新規ホウソ製材の開発　　共同通常

（阪大・医）李　千萬、寒川延子、笹井雅夫（京大・原子炉）鈴木　実、増永慎一郎、櫻井良憲

CO7-7 Pilot Application of Gadrinium-Platinum Nanomicelles to Gd- Neutron Capture Therapy

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SUMMARY : Considering the benefits that Gd-NCT offers, especially its possibility of improving patient's quality of life by reducing irradiation time, and also the prospective combination of chemotherapy and radiotherapy to increase treatment effectivity. Our purpose in this research is to evaluate the feasibility of gadolinium-platinum nanomicelles as Gd-NCT agent by performing in vivo experiment using Colon-26 bearing mice.

INTRODUCTION: The use of gadolinium as neutron capture therapy (NCT) agent has been getting attention because of its highest neutron cross section (255 000 barns) and the fact that secondary particle produced after capturing neutron have total kinetic energy about 3 times of that produced by ^{10}B. On our previous experiment we have shown that gadolinium-entrapped liposome is a potential agent for Gd-NCT. In this current study, our objective is to evaluate the possibility of using gadolinium-platinum nanomicelles developed by Kaida et. al.[1)] as Gd-NCT agent considering that there is a promising combined effect between gadolinium as NCT agent and platinum-based drugs as chemotherapy agent. It is expected that we could enhance tumor-cell killing effect and reduce negative side effect of the treatment, which eventually give the possibility to improve patient's quality of life.

EXPERIMENTS: In this experiment, we prepared colon26-bearing mice for in vivo experiment and performed thermal neutron irradiation at Kyoto University Research Reactor Institute with a collimated neutron beam. Two hundred microliter of Gd-Pt nanomicelles was injected into each mouse and qualitative analysis was performed by using MRI facility in Kashiwa campus, The University of Tokyo, while quantitative analysis was performed by using ICP-MS at Juntendo University. Thermal neutron irradiation was performed with 1 x 10E12 n/cm^2 thermal neutron fluence and then antitumor effect was evaluated on the basis of the change in tumour growth and survival rate of the mice.

RESULTS: Gd-Pt nanomicelles-injected mice revealed about three times higher tumor growth suppression compared to non-treated group as shown in Fig.1. Some results of tumor growth suppression revealed that toxicity is existed after neutron irradiation in treated groups with Gd-Pt nanomicelles. There is possibility of platinum photoactivation caused by reaction between secondary particles produced after Gd-NCR such as gamma rays and x-ray with energy above K-edge energy of platinum. Moreover, as the nanomicelles compound bind gadolinium and platinum together very close, the possibility of secondary reaction to occur is higher since the effective solid angle is very large. The effectivity of Gd-Pt nanomicelles as Gd-NCT agent is quite promising and further investigation is necessary to determine optimum combination between Gd-Pt concentration and neutron fluence applied for the treatment.

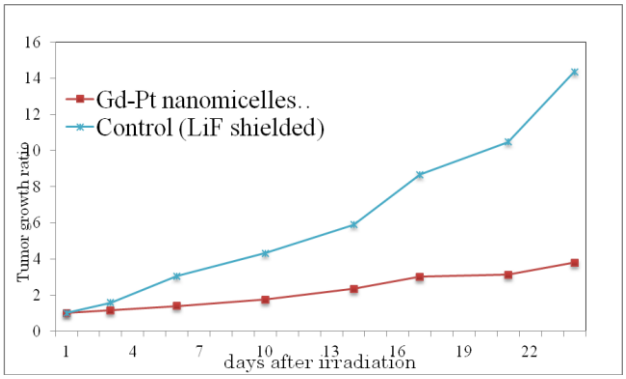

Fig. 1. Comparison of tumor growth suppression between Gd-Pt nanomicelles-injected group and non-treated (control) group

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採択課題番号 23034　　中性子捕捉療法法の一般外科領域癌への展開に向けた基礎的・臨床的研究　　共同通常

（東大・原子力国際専攻）柳衛宏宣、伊豫本直子、Novriana Dewi（東大・獣医）柳川将志、飯塚智也（東大・心臓外科）櫻井由里子、毛利きくえ（宏仁会メディカルシティ東部病院）東　秀史、瀬口浩司、太田嘉一（大阪市大・バイオ）長崎　健、馬野正幸、瓜生田貴聡（京大・原子炉）小野公二、増永慎一郎、鈴木　実、櫻井良憲

CO7-8 Boron Neutron Capture Therapy for Advanced Head and Neck Carcinoma

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INTRODUCTION: Advanced head and neck carcinoma (AHNC) and recurrent head and neck cancer (RHNC) are often radio-/chemo-resistant and show extensive growth, requiring a wide resection including surrounding normal tissues. To avoid severe impairment of head and neck structures, it is necessary to explore new treatment for AHNC. Mishima first proposed employing boron neutron capture therapy (BNCT) for malignant melanomas utilizing the specific melanin synthesis activity of melanoma cells[1)]. Kato et al.[2)] began BNCT using both BSH (Na2B12H11SH) and BPA (para-boronophenylalanine) for recurrent parotid gland carcinoma for the first time and reported excellent preliminary results. On the basis of the encouraging results of their pioneering clinical trial, our many years' experience with melanoma BNCT and the trend toward emphasizing the quality of life after treatment, we also started treating our patients with BNCT using BPA alone[3)4)]. In this report, we summarize our clinical results of AHNC and RHNC cases treated by BNCT using BPA alone in 2011.

MATERIALS and METHODS: Between April 2011 and September 2011, Two patients with AHNC (One maxillary salivary duct carcinoma, one left jugular leiomyosarcoma), 5 patients with RHNC (3 recurrent SCC, one parotid gland adenoidcystic carcinoma, one cervical amelanotic melanoma), and one patient with skin melanoma received BNCT using BPA alone in the condition that a tumor/normal tissue boron concentration ratio (T/N ratio) exceeded 2.5 based on ^{18}F-BPA PET studies. Acceptable criteria is followings: (1) With head and neck T3/T4 tumors that surgical treatment is not indicated, (2) The depth of tumor, less than 6cm, and without distant metastases, (3) PS≦ 2, (4)T/N ratio ≧2.5 using ^{18}F-BPA・PET, (5)Consent to perform BNCT, (6)With the approval of our Medical Ethics Committee. The procedures for BNCT using BPA were as follows: 1) Intravenous administration of BPA-fructose complex (500mg/Kg.BW) for 2.5 to 3 hour and blood sampling at the time of just finished BPA-drip and just before irradiation. The ^{10}B concentration in the blood was measured by prompt γ-ray spectrometry. 2) Epithermal neutron irradiation at the KUR with a reactor power of 5 MW. The irradiation field was large enough to cover the target area for the neutron beam (10 cm×10 cm). 3) Neutron flux measurement using gold wire 15 min. after the start of irradiation. 4) Optimization of the neutron dose based on the measured blood 10B concentration and neutron flux. The tumor dose and normal tissue dose calculated ranged from 20.0 to 30.0Gy-Eq and from Less than 15Gy-Eq, respectively. The median duration of observation is 6.5 months after BNCT (4-10 months).

RESULTS: Six patients demonstrated regional partial remission (PR), and two patients were no change (NC). One patient out of NC cases was operated on after irradiation. Six patients are living with disease. Two patients were death of carcinoma. All patients had no acute and/or chronic severe complications such as skin ulcers, xerostomia, and palsy of the cervical spinal cord.

CONCLUSION: Our results validate the efficacy of BNCT in the treatment of patients with AHNC and RHNC. Although this is a clinical report of only eight patients, additional long-term follow-up should be required to assess this treatment. We have estimated T/N boron ratio using ^{18}F-BPA-PET in every cases. The T/N ratios measured are the values of BPA alone. If T/N ratio was more than 2.5, according to our adaptation, it is thought that therapy effect is good. We believe that head and neck tumors are suitable for BNCT and that such excellent results will have a great impact on patients in the near future.

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採択課題番号 23035 中性子捕捉療法適応癌腫の治療プロトコルの確率 共同通常
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（京大・原子炉）小野公二、丸橋 晃

CO7-9 **Carboranyl Glucose and Ribose Derivatives for BNCT**

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Glucose and/or ribose attached carborane and their isomers has been investigated for boronated agents of BNCT［1］.

Although carborane attached 5-thio-d-glucose and carborane attached 5-thio-d-glucopyranose were highly toxic, toxicity could be decreased in 78% by a replacement form of carborane attached 5-thio-D-glucose with ribose, carboranyl ribose (fig.1).

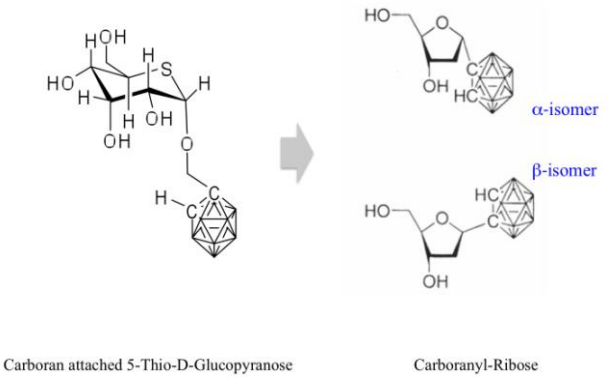

Fig. 1. Carboranyl ribose.

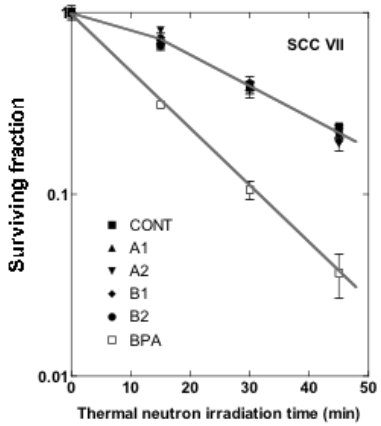

Fig.2. Survival fraction for glucose conjugated carborane.

However IC_{50} was still high, 5.77 x 10^{-2} mM. And, furthermore, uptake of them into SCCVII tumor cells was very low and No any in-vitro BNCT effect were observed even even after oreincubation of B-loading in maximum tolerable B concentration. (Fig. 2)

Recently, toxicity could be decreased to 1/100 by modifying carboranyl-thio-D-glucose and cesium salt form of carboranyl ribose. The uptake of them into SCCVII tumor cell was observed. In-vitro BNCT and bio distribution study has been under investigation at KUR (#2457).

Temporally Summary

1. A glucose conjugated carborane; carborane attached 5-Thio-D-Glucopyranose, was extremely toxic.
2. A form of ribose conjugated carborane reduced its toxicity in 78%, but still highly toxic.
3. The mechanism of toxicity is unknown, but it might be caused by a carborane-related chemical toxicity.
4. In-vitro BNCT has been under investigation in a new protocol using newly synthesized novel models of glucose and/or ribose conjugated carborane.

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採択課題番号 23036　悪性脳腫瘍のための熱外中性子捕捉療法の基礎的研究　共同通常
（藍野大学）高垣政雄（東邦大学・医）東丸貴信（京大炉）増永慎一郎

CO7-10 **BNCT Case Report of Malignant Brain Tumor 2011**

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Case Report: Grade-III glioma 56y female was treated via BPA-based BNCT on Oct. 6, 2011.
The patient initially diagnosed as Grade III glioma for her temporally dysarthria and numbness of her upper extremity and face. Those symptoms disappeared for 10 minutes. However the patient had the same symptoms on the next morning and consulted a doctor.
The patients showed no any neurological deficit except dysarthria and NIHSS=1.
The magnetic resonance imaging showed a irregular round shaped tumor in less than 3cm diameter in the superficial convexity of the right frontal lobe (Fig. 1).

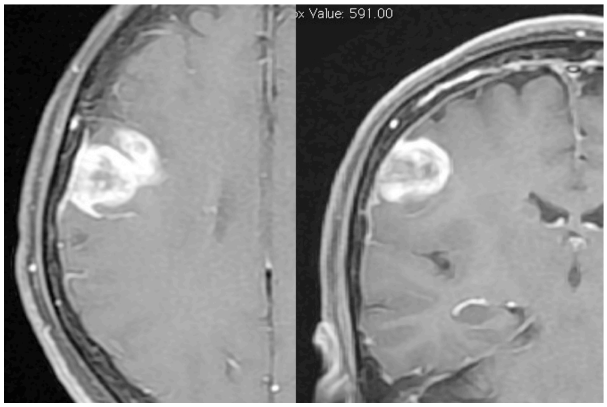

Fig.1. Magnetic resonance image of the patient's tumor before BNCT. The tumor located superficially in the parietal convexity with peripheral low density rim.

The open biopsy proved Grade-III glioma initially but the definite diagnosis was changed to be Grade-IV glioma via precise inspection of the biopsy specimen.
1 month after the onset, the patient gradually showed aggravation of the numbness and then the patient was treated by BNCT under the maximum tolerance normal brain dose, T/N=2.5, av. 20ppm ^{10}B.

2 days after BNCT, the patient showed conscious dist. (GCS:E2-3, V4, M6, somnolence) and left hemiparesis (MMT UE 1/5, LE 2/5) for the rapid enlargement of the tumor cystic cavity and peripheral edema shifting the mid-line structures after BNCT. The patient emergently received cyst drainage via Ommaya reservoir and condition drastically improved.
The patient received TMZ, 120mg/day 12 days after BNCT, and also received a booster radiation 10Gy (Cyber Knife) on the deepest lesion which dose was less than 30Gy. Then the cytological findings of the repeatedly removed fluid of the cystic cavity improved Class IV to Class II.
The current KPS was stable 70 at home. The cystic cavity was still enhanced in stable configuration 7 Mo after BNCT (Fig. 2).

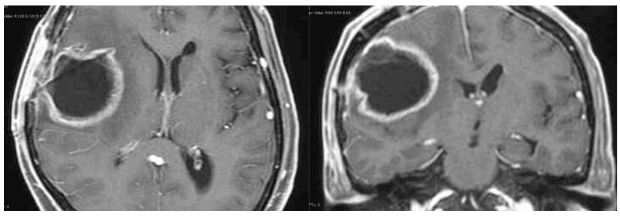

Fig. 2. Magnetic resonance Gd-DTPA enhanced image 7Mo after BNCT. Tumor remained with ring-like enhancement lesion, although the cyto-hystological serial findings the cystic fluid changed into benign.

The spatial radiation measurement of the post BNCT head of this patient: Post BNCT spatial γ-ray was serially measured by Aloka NaI(Tl) scintillation survey meter. The background γ-ray dose in the word was 0.07-0.08 μSv/h. The figures shows the treatment and/or nursing close to the patient's head should be managed within minimum duration for 2 days after BNCT.

Day after BNCT	Time	Head surface	1m from the head	Urine	Gaurze
1	21:00	3.7-3.8	0.15-0.17		
2	08:15	2.6-2.8	0.1-0.12	0.23-0.25	0.07-0.08
2	17:30	2.2-2.3	0.1-0.12		
3	08:45	1.0-1.2	0.09-0.1		

Table 3 Serial measurement of the special γ-ray radiation dose of the post BNCT head.

採択課題番号 23037　悪性脳腫瘍のための熱外中性子捕捉療法の臨床的研究　共同通常
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（京大・原子炉）小野公二

CO7-11 Hyaluronan-Conjugated Liposomes as Carrier for Oral Squamous Cell Carcinoma in Boron Neutron Capture Therapy

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Introduction

In Boron neutron capture therapy (BNCT), selective and highly concentrated boron accumulation in tumor cells is important. A study was carried out in our division using various liposomes ［1,2］.

Hyaluronan is a ligand of CD44 and RHAMM, which is excessively expressed in tumor cells, and Hyaluronan-conjugated PEG Liposome (HA PEG Liposome) is an active targeting candidate for tumor cells.

In this study, BSH transport using HA PEG Liposomes was investigated for oral squamous cancer cells, and the effect of neutron irradiation was investigated by colony formation assay.

Material and Methods

・Experiment on boron transport to tumor cells over time.

For oral squamous cancer cells, SAS was used. SAS was cultured in a serum-free media, and divided into groups using Bare-BSH, PEG Liposomal BSH, and HAPEG Liposomal BSH. The media was prepared so that each group would contain a boron concentration of 30 ppm, and each group was exposed to boron for 3 hours, 6 hours, 12 hours and 24 hours. After the specified time, the media was removed, and cells were collected to count. Then, nitric acid was added and ICP-AES was used to measure boron concentration.

・Experiment on neutron irradiation effect.

SAS was cultured in a serum-free medium, and divided into groups using Bare-BSH, PEG Liposomal BSH and HA PEG Liposomal BSH, which were then adjusted to a boron concentration of 30 ppm. After exposure to boron for 6 hours, cells were collected. Media which did not contain boron was used to dilute the cells to 1×10^5 cells/mL, and set as samples of neutron irradiation. The neutrons were irradiated for the pre-determined times. After the neutrons were irradiated, cells were adjusted to 200 cells/petri dish and cultured for 7 days, and then an assay was carried out.

Results

・Boron transport to tumor cells over time

In the HA PEG Liposome group, boron concentration in the cells increased over time. Moreover, increase in cell concentration was hardly observed in the Bare-BSH and PEG Liposome groups. When the PEG Liposome and HA PEG Liposome groups were compared, a significant difference was observed at 3 hours (Fig. 1).

・Neutron irradiation effect

In the experimental results of the colony formation assay (Fig.2), the lowest number of surviving tumor cells was observed in the HA PEG Liposome group.

These experiment results suggest that for SAS, liposomes combined with HA significantly transported more boron into the cell, in comparison with Bare BSH. In the future, we plan to investigate the effect of HA PEG Liposomes on other oral squamous cell cancers and the possibility of their use.

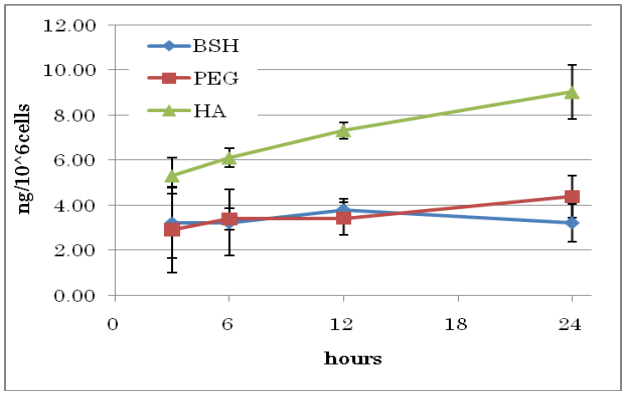

Fig.1 Boron Uptake

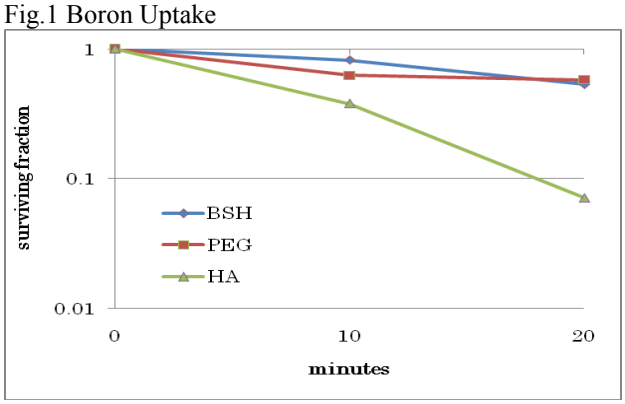

Fig.2 Surviving Fraction

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採択課題番号 23042　　口腔癌に対する硼素中性子補足療法の基礎的研究　　共同通常

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CO7-12 Boron Neutron Capture Therapy for Malignant Pleuritis

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Research Reactor Institute, Kyoto University

INTRODUCTION: In2005, we have treated a patient with left malignant plural mesothelioma (MPM) with BNCT [1]. This attempt of BNCT for MPM was the first case in the world. Relief of clinical symptom was experienced at a few days after BNCT and regression of the tumor was observed on the computed tomography (CT) at six months after BNCT. Although the patient died of local tumor progression 10 months after BNCT, the survival time was far over the expectation (less than 3 months) of the attending physician. Based on this clinical experience we are doing mul-ti-institutional clinical trials of BNCT for MPM. It is prohibited to show a result of the trial in the midway. But another type of malignant disease of the pleura, a malignant pleuritis of lung cancer, was treated according to the similar protocol this year. Here we report this clinical case.

2. METHOD and PATIENT

2-1.Treatment protocol

The whole ipsilateral lung should be regarded as clinical target volume(CTV). Since the maximum diameter of collimator available in BNCT was 25cm, the whole lung was irradiated with posterior-upper and posterior-lower beams in the first BNCT and with anterior-upper and anterior-lower beams in the second BNCT. The two BNCTs were performed at 5-week interval. BPA(500 mg/kg)was administered intravenously at the speed of200 mg/h in two hours just before irradiation and 100 mg/h during irradiation.

The Simulation Environment for Radiotherapy Applications (SERA) system, a currently available BNCT treatment planning system, was used for the calculation of neutron fluence in each beam to deliver 5.0 Gy-eq to normal lung tissues in the ipsilateral lung.

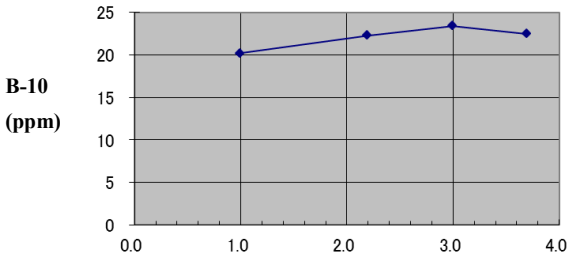
2-2.Case report: A55-year-old man with right malignant pleuritis from lung cancer was referred to our center for further treatment with BNCT. He had received the surgery, chemotherapy of primary lung cancer (adenocarcinoma) in 2003, and thereafter radiotherapy was applied to the solitary metastasis in the lung in 2009. Limited pleural lesion and brain metastasis appeared in early 2010 and 2011, respectively. They were treated by stereotactic radiotherapies. Brain lesion was controlled well by radiotherapy, but pleural lesion was gradually spreading to whole pleura.

The patient received ^{18}F-BPA PET, and ^{18}F radioactivity ratio between tumor and blood is > 2.0 (Tmax=5443Bq/ml vs. Bmean=2719Bq/ml, Bmin.=2432Bq/ml). Based on this examination data, we concluded BNCT is applicable.

First BNCT was performed on Dec.22 in 2011. Two anterior neutron beams irradiated the upper and lower portions of the ipsilateral lung. In second BNCT, the dorsal portion of the ipsilateral lung was irradiated with two posterior neutron beams on Jan.26 in2012.

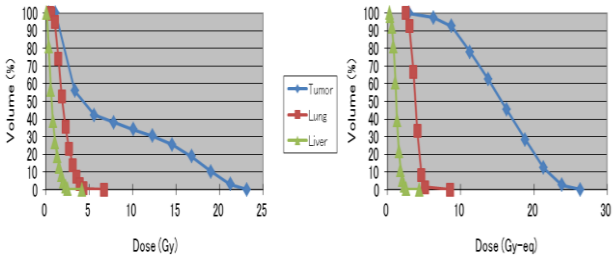
Figures 1 show a B-10 level in the blood before and during BNCT. The B-10 level was very stable at 22.5-24 ppm during neutron irradiation.

Fig.1



Dose volume histograms of the tumor, normal lung and liver were presented in figure 2 and 3. They show the first and second BNCT, respectively. Large dose difference between the tumor and normal organs, which is not achievable by X-ray therapy, was successfully obtained.

Fig. 2 **Fig.3**



The tumors in the pleura decreased in size and the condition of the patient is quite well. He has no respiration difficulty, ex. short breath, cough and sputum. There is no change in the normal lung by medical image examination at present.

This new clinical experience in this year demonstrated that if high enough accumulation ratio of BPA is expected by ^{18}F-BPA PET general malignant pleuritis is also a good indication of BNCT.

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CO7-13 Intracellular Distribution of BSH-Appended Polyamine at Tumor Tissue of Colon 26 Carcinoma-Bearing Mice

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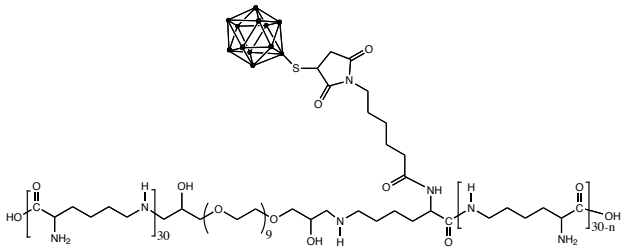
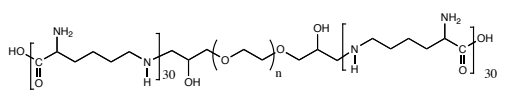
INTRODUCTION: Recently, we reported the evaluation of a polyion complex nanoparticle composed of mercaptoundecahydrododecaborane-appended high molecular weight polyamine (BPP, Fig. 1) as a novel BNCT drug [1]. Since this polymeric ^{10}B carrier has anionic zeta-potential, polyion complexes with cationic polymer (nEG-PLL, Fig.1) afford nanoparticles suitable for safe and effective delivery into tumor tissues due to Enhanced Permeability and Retention (EPR) effect. The neutron irradiation experiment by using polyion complex containing BPP showed suppressive effect for the tumor growth in colon 26 carcinoma-bearing mice. Although the boron concentration at tumor tissue was less than 10 ppm, the sufficient BNCT effect was observed. Here, we report the intracellular distribution of fluorescently labeled BPP and BSH residues introduced into the polymeric carrier using an immunostaining with anti-BSH antibody.

EXPERIMENTS: For visualization of BPP, an amino group of BPP was covalently modified with 5-(and-6)-carboxy-X-rhodamine succinimidyl ester (Molecular Probes). Colon 26 cells (8 x 10^5 cells) were transplanted into a left thigh of mice (4 weeks old BALB/c, male). After 10 days of transplantation, the rhodamine-labeled BPP complex solution was injected *via* tail vein at a dose of 4.0 mg ^{10}B/kg (400 ppm of ^{10}B concentration; 200 μL). Twelve hours after injection, the mice were euthanized. After the tumors were removed and fixed in 4% formaldehyde, the tissues were freezed in liquid nitrogen. Ten μm section were cut and treated with slow fade Gold antifade reagent with DAPI (Molecular Probes). Immunohistochemical characterization of BSH was carried out with pre-fluorescently labeled anti-BSH antibody by using Zenon mouse IgG Alexa Fluor 488-labeling kit (Molecular Probes).



BSH-PEG-PLL (BPP)



nEG-PLL (n=9, 23)

Fig. 1. BSH-appended polyamine and based polyamines.

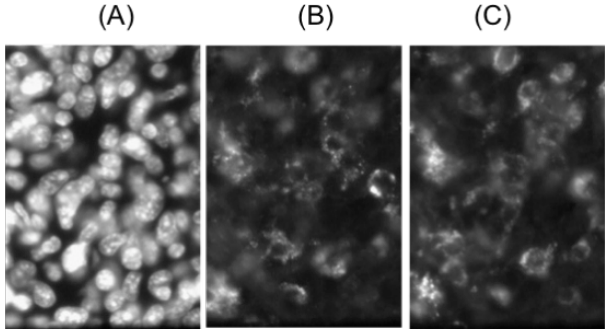


Fig. 2. *In vivo* cellular uptake of BSH-modified polyamine by transplanted colon carcinoma. DAPI stained nucleus (A), Rhodamine-labeled polyamine (B), and immunostained BSH (C) were observed with confocal fluorescent microscopy.

RESULTS AND DISCUSSION: BNCT using the BPP complex was previously carried out with colon 26-bearing mice at left thigh. Tumor growth in mice treated with the BPP complex was obviously suppressed after neutron irradiation. Under same conditions, injected BPP-modified polyamine was fluorescently observed in tumor cells. The colocalization of polyamine and BSH residue indicates that BSH modification is stable during *in vivo* experiment. Interestingly, perinuclear localization was confirmed. It was reported that among proteins traveling between the cytoplasm and the nucleus, small proteins (up to 9 nm in diameter) can freely diffuse through nuclear pore complex (NPC) [2]. As average particle size of BPP complex was estimated to be 91 nm, BPP complex could not pass NPC. Therefore, they remain at perinuclear regions. Morrison *et al*. reported that nuclear localization of boron drug increased tumor-killing effect by BNCT [3]. The intracellular distribution in which BSH is close to genome DNA might contribute higher BNCT efficacy by BPP complex.

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採択課題番号 23056　ホウ素クラスター修飾ポリアミンの腫瘍集積性および中性子捕捉反応効率評価　　共同通常

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CO7-14 Boron Neutron Capture Therapy for Malignant Brain Tumors Using Epithermal Neutron

S. Miyatake, S. Kawabata, R. Hiranatsu, Y. Hirota T. Kuroiwa, Y. Sakurai[1], H. Tanaka[1], A. Maruhashi [1], M. Suzuki[1], N. Kondo, S.. Masunaga[1], Y. Kinashi[1] and K. Ono[1].

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INTRODUCTION: Between March 2010 and Februarry 2011, we applied BNCT using epithermal neutron for
1) newly diagnosed GBM (8 cases),
2) recurrent malignant gliomas (7 cases)
3) malignant meninigiomas (MM)(4 cases).
These BNCT were appied in KUR (15 cases) and JRR4 (4 cases).

Methods

BNCT using epithermal beam were applied in 3 different categories of maliganant brain tumors as menitioned above.
1) Newly diagnosed GBM patients were treated as Phase II Study of Boron Neutron Capture Therapy Followed By Radiotherapy and Concurrent and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma Multiforme (TRIBRAIN0902).
2) All recurrent malignant gliomas treated by BNCT were TMZ-refractory cases.
3) All malignant meningiomas were recuurent cases after different radiation modalities.

RESULTS and Discussion

1)TRIBRAIN 0902 is now in progress, Thereafter results will be opened a cupple of years later..
2) For recurrent malignant gliomas, 2 cases were dead by CSF dissemination and 5 cases are still alive. A representative case of maliognnant gliomas is depicted in Fig. 1 and 2.. Radiation necrosis should be a serious problem in the recurrent cases treated by BNCT. We applied bevacizumab for the treatement of symptomatic radiation necrosis. {1,2}
3) We depicted the representative case of MM in Fig.3. Original tumors are controlled well, but unfortunatedly a new lesion was noticed in the right frontal base (out of radiation field).

Fig. 1.

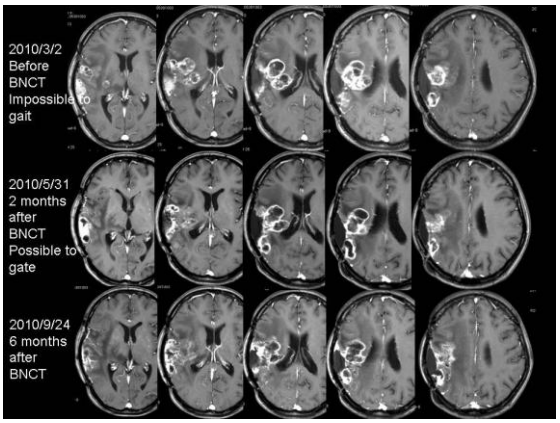


Fig. 2

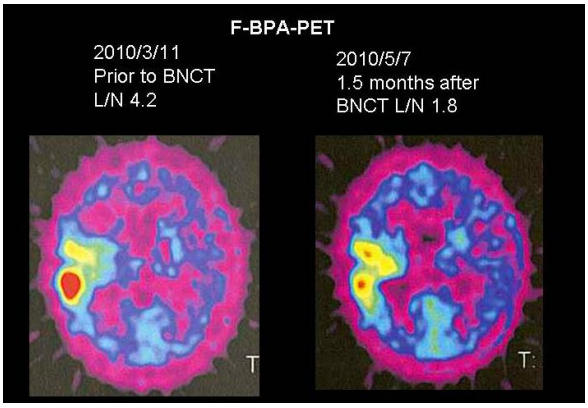
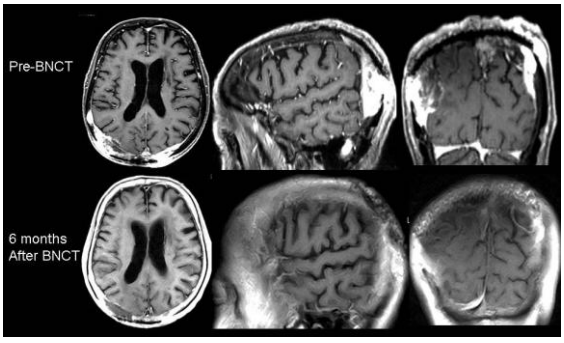


Fig. 3



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採択課題番号 23060 熱外中性子を用いた悪性脳腫瘍に対する非開頭中性子捕捉療法の 共同通常臨床的研究

（大医大・脳外）宮武伸一、黒岩敏彦、川端信司、平松亮（京大原子炉）小野公二、増永慎一郎、鈴木 実、近藤夏子、田中浩基、櫻井良憲, 丸橋 晃

CO7-15 High LET-radiation Can Overcome Radioresistance of Glioma Stem-Like Cells Which are Radioresistant to Low LET-radiation

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PURPOSE:
Ionizing radiation is applied as the standard treatment for glioblastoma multiforme (GBM). However, radiotherapy remains only palliative because of existence of glioma stem cells (GSC), which are regarded as highly radio-resistant to low linear energy transfer (LET) photons[1, 2]. On the other hand, we have applied boron neutron capture therapy (BNCT) for GBM. This is a unique tumor-selective particle radiotherapy using neutron irradiation, especially thermal neutron irradiation. Boron-10 (^{10}B) releases alpha (^{4}He) and ^{7}Li particles by ^{10}B(n,α)^{7}Li reaction. The key players of anti-tumor effects in BNCT are these high linear energy transfer (LET) particles. With BNCT, good results have been achieved for patients with GBM and recurrent malignant glioma[3, 4]. Here we analyzed whether high LET particles can overcome the radio-resistance of GSC or not.

MATERIALS AND METHODS:
Glioma stem-like cells (GSLCs) were induced from GBM cell lines A172 and U251 MG in stem cell-culture medium[3]. The phenotype of these GSLCs and wild type cell lines were confirmed by western blot analysis using stem cell markers. These cells were irradiated with ^{60}Co gamma rays or neutron beams. Radio-sensitivity was assessed in terms of clonogenicity using colony forming assay[4] and the number of DNA double strand breaks (DSBs) using histone gamma-H2AX foci detection assay[5, 6].

RESULTS:
In stem cell-cultured medium, GSLCs could form neurosphere-like cell and expressed neural stem cell markers more frequently. GSLCs were radio-resistant to gamma-rays in comparison with parental cultured cell lines, but neutron beams could overcome the resistance. Twenty-four hours after irradiation with gamma-rays, the number of gamma-H2AX foci in GSLCs was significantly less than that of parental cells, while there was no apparent difference in the number of these foci between GSLCs and parental cultured cell lines following neutron beam irradiation.

CONCLUSION:
Neutron beams can induce elastic scattering and nitrogen neutron capture reaction, and produce proton particle (H^{+}). This particle is high LET radiation and it could overcome radioresistance of GSLCs with unrepairable DSBs. Therefore, High LET radiation therapy has a promising potential to overcome X-ray resistance of glioblastoma in clinical setting.

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採択課題番号 23061　　新規硼素化合物の有用性と腫瘍幹細胞の克服　　共同通常
（大阪医大）宮武伸一、弘田祐己、川端信司、平松亮、米田隆
（岡山大）松井秀樹、道上宏之、森亜希子、秋田直樹
（熊本大）富澤一仁
（京大原子炉）小野公二

CO7-16

The Tumor Control Effect by the Sonoporation in BNCT

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INTRODUCTION: The sonoporation which is the ultrasonic irradiation of a low output is one of the methods of introducing a medicine and a gene into a cell. Use of the microbubble which is an ultrasonic contrast agent will raise introductory efficiency.[1,2] We have reported that the boron concentration in tumor cells is increase by useing sonoporation. We experimented by carrying out nude-mouse use for the purpose of curative effect verification of BNCT in human oral squamous cell carcinoma (SAS).

EXPERIMENTS: We transplanted SAS of the thigh subcutaneous part of the nude mouse (bulb/c 4week), and the major axis used what became not less than 5 mm. We carried out intraperitoneal injection of the BPA, and injected 0.1 ml of microbubble into the tumor 2 hours afterward. We performed ultrasonic irradiation immediately and irradiated with neutron ray at KUR.

RESULTS: Into the group which carried out neutron irradiation, the tumor control effect was seen as compared with control. In the group which carried out neutron irradiation after injected BPA and performed sonoporation、the individual for which a tumor disappears existed (Fig. 1).The average survival period of the group extended.

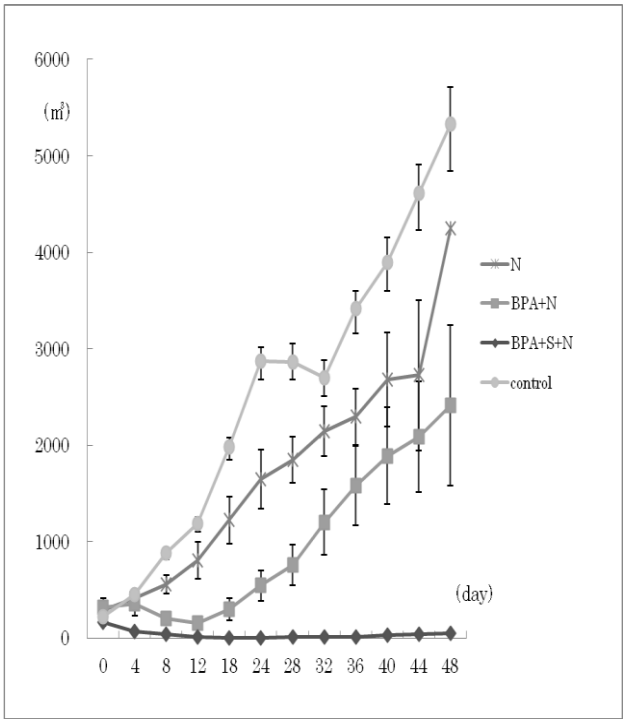

Fig.1. Change of tumor volume by BNCT (S: sonoporation with microbubble, N:neutron irradiated).

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採択課題番号23063　　口腔悪性腫瘍におけるホウ素中性子捕捉療法に関する基礎研究　共同通常

（京大・原子炉）　小野公二、丸橋晃、鈴木実、増永慎一郎、櫻井良憲、田中浩基（阪大院・歯）加藤逸郎、由良義明、山本直典、（武蔵野大・薬）岡本正人（泉佐野病院・口外）藤田祐生　　共同通常

CO7-17 Clinical Studies on BNCT for 4 Cases of Head and Neck Cancer

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INTRODUCTION: We have first reported that six patients with head and neck malignancies (HNM) had been treated with BNCT [1]. We summarized 4 patients with HNM who had treated with BNCT at KUR in last year in Table 1. Moreover we also report here long term (more than 5-year) clinical outcomes of our 26 patients with recurrent HNM treated with BNCT [2].

PURPOSES: The purpose of this study was to estimate safety and effectiveness of BNCT for patients with advanced/ recurrent HNM for which there were no other treatment options.

RESULTS: All cases are advanced such as 15 out of 26 patients (58%) had developed regional lymph node metastases. Distant metastases were developed in 6 cases during treatment. (1)^{10}B concentration of tumor/normal tissue ratios (T/N ratio) of FBPA-PET studies were SCC: 1.8-5.7, sarcoma: 2.5-4.0, parotid tumor: 2.5-3.7. (1) Regression rates were CR: 12cases (46%), PR: 10cases (39%), PD: 3cases (12%), NE (not evaluated):1case. Response rate was 85%. (2) Mean Survival time was 33.6 months. 2-year overall survival rate (OS) and 6-year OS were 37.0% and 31.7%, respectively. (3)BNCT improved QOL, PS and survival periods. (4)Survival periods after BNCT were 1-84 months. (5) Adverse events were brain necrosis, osteomyelitis and transient mucositis and alopecia and so on [2]. After 5-year interval for renewal of low enriched uranium-KUR BNCT was restarted in 2010. We had treated 4 times of BNCT for 4 patients last year.

Case 1: A 60 year-old female with op. upper gingival carcinoma (rT0N3M0, SCC) had got maxillectomy in 2009. About half and a year after the operation, as she had developed lt-cervical metastatic lymph nodes, she had go the neck dissection. FBPA-PET study revealed ^{10}B concentration of T/B ratio was 2.6. Then she has been treated with BPA (500mg/kg) mediated BNCT at KUR in December 2011 and she has been disease free survival for so far 6-month.

Case 3: A 63-year old woman had been to the department of oral and maxillofacial surgery of a municipal hospital with chief complaint of swelling and pain at the left temporal mandible joint (TMJ) since July 2011 and she was diagnosed as temporal mandibular disorder (TMD) type I. She was prescribed indomethacin cream and Ternelin, but the swelling of L-TMJ become worse. She had referred to our hospital. MR image revealed that the swelling was caused by mass lesion which was T2-high signal and with calcification. She was diagnosed as benign tumor at TMJ and the lesion was incised at the municipal hospital in November. Histopathological diagnosis was “Osteogenic sarcoma, chondroblasitc type ”

We consulted diagnosis and treatment method in this case with Prof. Yoshikawa at the department of orthopedics, medicine, Osaka University. and he suggested us that in this case, heavy particle therapy including BNCT was indication but multi drug chemotherapy was contraindication for her age. FBPA-PET study resulted that T/N ratio=2.3、T/B ratio=2.2. She treated BNCT in January 26, 2012. Then she has been disease free survival for so far 5-month.

CONCLUSIONS: BNCT was effective in 22 out of 26 patients and safe in all case. BNCT represents a new and promising treatment even for far-advanced patients with a huge HNM.

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Table 1. Treatment Summary of 4 Cases (May , 2012)

Case No.	Pt's Initial (Age)	Clinical Diag. (Histopathol. Diag.)	10B-conc. Blood(ppm)	T/B ratio	T-max of thermal neutron (D)		Total-RBE-Dose Eq (Gy-Eq)			Irradiation time(min.)	% Reduction (Period) Prognosis (Survival)
					Fluence (E+11n/cm^{-2})	History of RT: (Gy)	T-Peak Gy-Eq	T-deepest Gy-E	Skin/Mucosa		
1	W・Y (60)	Op.OKK, Lt-LN meta(SCC)	20.0	2.6	18.0	63.3	28.3(2.2 ㎝)	25.0(4cm)	4.9/12.0	87	CR(5M)・Alive(5M)
2	F・M(79)	bds-mandible Ca.(ACC)	28.0	2.2	23.0	—	42.0(2.4 ㎝)	21.0(6cm)	6.2/13.0	61	(4M)・Alive
3	Y・Y (63)	L-TMJ Tumor (Osteosarcoma)	32.0	2.2	25.0	—	52.0(2.4 ㎝)	28.0(4cm)	/15.0	60	CR(4M) Alive((4M)
4	O・Y(34)	0p.OKT (ACC)	22.7	2.9	15.0		29.0	23.0	4/14	44	CR(3M) Alive((3M)

採択課題番号 23064　頭頸部悪性腫瘍におけるホウ素中性子捕捉療法の臨床的研究　共同通常（阪大２口外）加藤逸郎、岩井聡一、墨哲郎、中澤光博、由良義明（阪大工）村田勲（慶大先端医研）岡本正人（りんくう医療セ）大前政利（済生会千里）道澤雅裕（東大阪総合）千足浩久（市立池田）大西徹郎（田中クリニック）田中善（京大炉）田中浩基、鈴木 実、櫻井良憲、増永慎一郎、丸橋晃、小野公二

CO7-18 Basic Cell Survival Analysis of New Boron and Gadolinium Compounds for Neutron Capture Therapy

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INTRODUCTION: In Neutron Capture Therapy (NCT) , the therapeutic effect of the boron compound is based on alpha particles produced by the B(n, α) reaction. On the other hand, that of gadolinium compound is gamma rays derived from the Gd (n, γ) reaction. There is no clinical trial using Gd-NCT because the long pathway of gamma ray may cause the radiation damage of normal surrounding tissue and the uptake and washout of Gd-DTPA within the tumor tissue is only several minutes. In a previous study, we analyzed Gd-containing porphyrin[1], and combined boron and gadolinium are warranted to prove the efficacy. we select and analyzed the neutron capture effect for the cancer cell line with the boronated liposome and Gadolinium containing nanoparticles to investigate this possibility.

EXPERIMENTS: Colony assay with CT26 (undifferentiated colon carcinoma cell line) and C6 (rat glioma cell line) were performed.
For the gadolinium targeting compounds, Gd contaioning nanoparticle was used in this study. Gd containing nano particle was diluted to reach a final gadolinium concentration of 0, 20 and 40 ppm.
The boronated liposomes were prepared by the lipids (table 1). The lipid mixture prepared using the constant ratio was dissolved in organic solvent. It was prepared by the conventional lipid-film method. The resulting liposomes were extruded through polycarbonate membrane using an extruder, yielding the modified liposome.

	DSPC	Cho	PEG-B-Lip	DSPE-PEG
PBL5%	**47.5**	**47.5**	**5**	
PBL10%	**45**	**45**	**10**	
PEG	**47.5**	**47.5**		**5**

Table1 composition of liposomes.
DSPC: α-phosphatidylcholine distearoyl Cho: cholesterol PEG: polyethylene glycol DSPE: α-distearoylphosphatidylethanolamine

Thermal neutron irradiation was performed at Kyoto University Research Reactor (Osaka, Japan). The irradiation times were 0, 15, 30 and 45 minutes.

RESULTS: As shown in Fig. 1, Gd nano-particle and Boronated liposomes have some enhancement effects. further investigation of *in vivo* and *in vitro* experiments are expected.

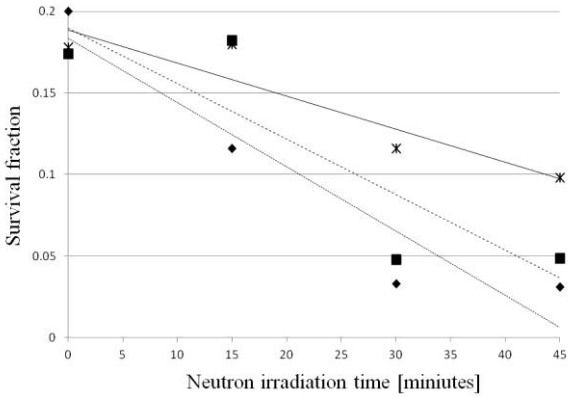

Fig.1 The results of colony formation assay (Gd nano particle). The survival fraction was plotted as a function of neutron irradiation time. ◆40ppm Gd/MEM, ■ 20ppmGd/MEM, ＊neutron only.

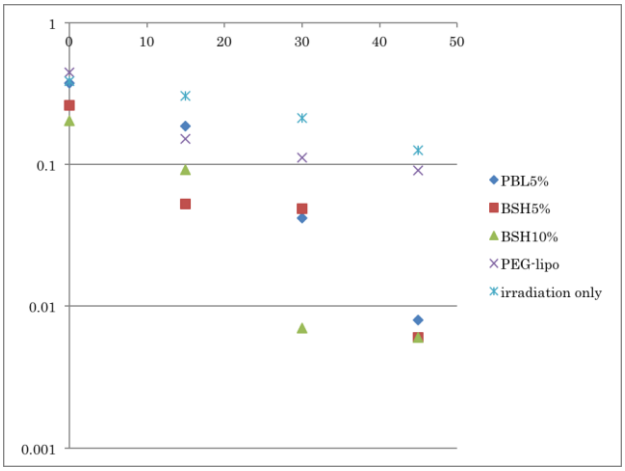

Fig.2 The result of colony formation assay (boronated liposome and BSH). PBL modified 5% liposome group (◆) showed same cytocidal effect the BSH 5% group (■) and lower cytocidal effect than the BSH 10% group (▲).

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採択課題番号23078 新規化合物および細胞内濃度変調による中性子捕捉反応による細胞生存試験 共同通常

（筑波大学・人総）中井啓、山本哲哉、吉田文代、白川真、山本陽平、上前洋二、佐藤英介（京大・原子炉）田中浩基、櫻井良憲、増永慎一郎