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

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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, 40 BNCT irradiations have already been carried out as of May 2011.
As this facility is a larger facility, the irradiation characteristics are influenced by the conditions of the KUR fuel. Then, we are performing the re-evaluation of the irradiation characteristics.

Methods: The irradiation characteristics were evaluated mainly for the three standard irradiation modes of epi-thermal, mix and thermal. The annual change of the epi-thermal neutron beam intensity at BNCT clinical irradiation was also estimated. The neutron flux was measured by foil activation method, and the gamma-ray dose was measured by thermo-luminescent dosimeter (TLD).

Results and Discussions: The irradiation characteristics of the main irradiation modes as of May 2011 are tabulated in Table 1. The numerical changes are within plus/minus 10%, compared with the nominal values before the fuel low-enrichment. The change within this extent hardly influences on the BNCT clinical irradiation.
Fig.1, shows the comparison for the depth distributions of thermal neutron and epi-thermal neutron fluxes along the central axis in a phantom using the clinical collimator, between before and after the fuel low-enrichment. The characteristics for the distribution in the phantom are hardly changed.
Fig.2, shows the comparison for the depth distributions of gamma-ray dose along the central axis in the phantom, between before and after the fuel low-enrichment. For the gamma-ray dose distribution, the value near the phantom surface increased almost 20%, differently from the neutron flux distribution. It is thought that this increase is not due to the effect of the fuel low-enrichment, but due to the influence of the new patient carrier and collimator, which were updated during the KUR-operation suspension.
For the epi-thermal neutron beam intensity throughout one year, its change is from 94% to 113% for the nominal value. This numerical change is within plus/minus 10%, compared with the averaged value.

Conclusion: It was finally concluded that the changes in the irradiation characteristics of this facility due to the fuel low-enrichment were not so larger for the influence on the BNCT clinical irradiation.

Table 1. New irradiation characteristics of D_2O Facility for the several irradiation modes (5MW).

Irradiation mode	Thermal	Mix	Epi-thermal
Heavy water thickness (cm)	30	0	0
Cadmium ratio	150	11	1
Thermal neutron flux ($cm^{-2}s^{-1}$)	1.8E+09	6.1E+09	1.2E+09
Epi-thermal neutron flux ($cm^{-2}s^{-1}$)	2.5E+07	1.3E+09	4.5E+07
Gamma-ray dose rate (cGy/h)	160	340	70

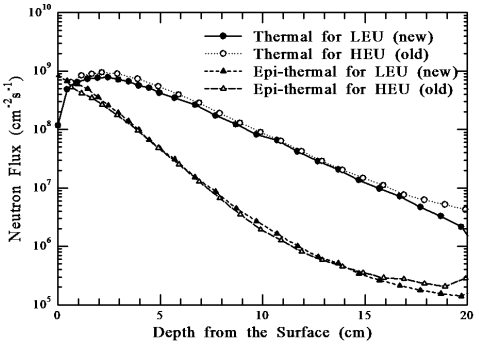

Fig. 1. Comparison for depth neutron flux distributions for the epi-thermal neutron irradiation mode.

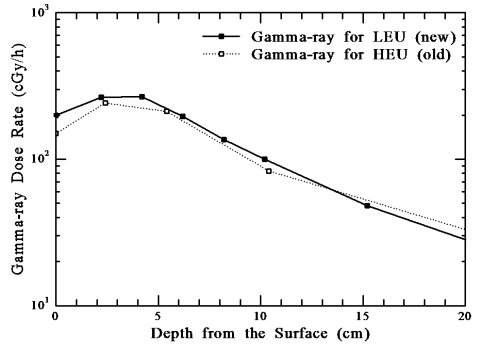

Fig. 2. Comparison for gamma-ray dose distributions for the epi-thermal neutron irradiation mode.

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採択課題番号 22004　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 Development of New Boron Carriers for Boron Neutron Capture Therapy (BNCT)

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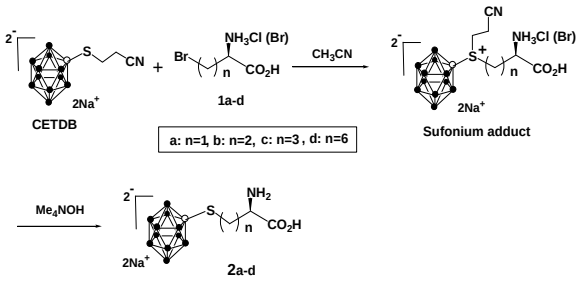
INTRODUCTION: There has been a long-standing interest of our research group on the design, synthesis and biological evaluation of anionic dodecaborate cluster containing amino acid and small molecule peptides as a boron agent for BNCT. The dodecaborate ($[B_{12}H_{11}]^{2-}$) amino acids used in the present study belong to a class of L-α-amino acid and *closo*-dodecaborane containing 12 boron atoms per molecule, linked to side chain of α-amino acid *via* boron-sulfur-carbon (B-S-C) bonds as illustrated in figures.

In this study, we report the synthesis of new dodecaborate L-α-amino acids (**2a-d**) and their biological evaluation using cultivated cancer cells focusing on their possibilities as boron agent in BNCT.

EXPERIMENTAL:
We have devised the simple and efficient synthetic method of **2a-d** as shown in Scheme 1. Thus, the mixture of *S*-cyanoethyldodeca- borate (CETDB) derived from dodecaboranethiol (BSH) and bromo amino acid (**1a-d**) [1] in acetonitrile was stirred for 24 hrs at room temperature to give the corresponding sufonium adduct as solid, which was separated by filtration under suction and used to next step without further purification. Subsequently, treatment of the sufonium adduct with tetramethylammo nium hydroxide in acetone furnished the desired amino acid **2a-d**.



Scheme 1 Synthesis of dodecaborate L-amino acid

In the present synthetic route, the absolute configuration of bromo L-amino acid (**1**) is to be introduced to the final amino acid in retention without any recemization, because all processes carried out on other than chiral carbon atom under mild conditions.

Biological uptake of **2a-d** was examined using cultivated B16, C6 and SAS cells, and boron concentration was determined by ICP analysis. Killing effects by boron neutron capture reaction against cultivated cancer cells were also evaluated by comparison with those of BPA (*p*-boronophenylalanine) used as a positive control compound.

RESULTS: As shown in figure, the killing effects and uptake amount of **2b-c** by C6 cells were higher than those of BPA. On the other hand, SAS cell was killed efficiently using **2b** and **2c** than BPA. These data suggested that dodecaborate amino acids, 2b and 2c, might be suitable for BNCT.

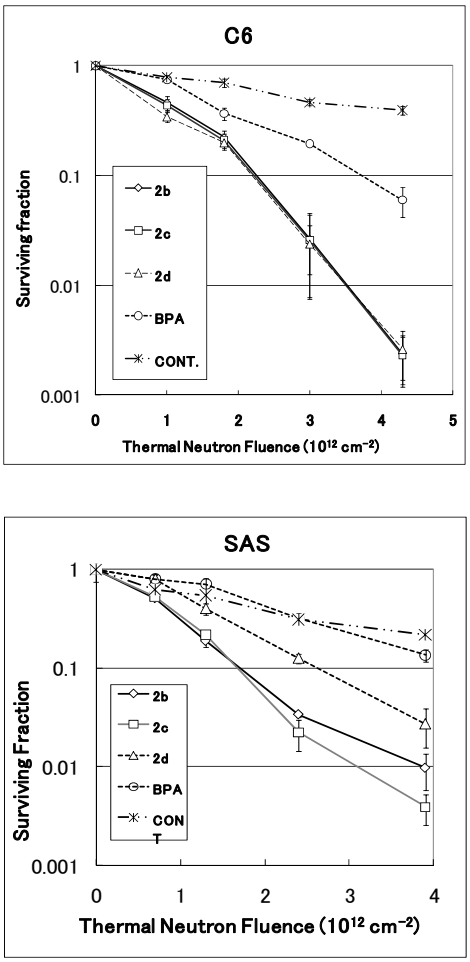


Fig. 1. Surviving fractions of C6 (above) and SAS (below) cells after thermal neutron irradiation *in vitro.*

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採択課題番号 22006　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
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CO7-3 Development of Dodecaborate Lipid Liposomes as New Boron Vehicles for Neutron Capture Therapy

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INTRODUCTION: 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 (Eq. 1).

$$^{10}B + {}^{1}n \rightarrow {}^{4}He\ (\alpha) + {}^{7}Li + 2.4\ MeV \qquad (1)$$

The resulting α-particle and Li nuclei are high linear energy transfer (LET) particles that exert the cytotoxic effect. The fact that LET particles travel a short range (approximately 10 μm) limits radiation-induced damage to cells containing boron-10 [1].

Recently much attention has been focused on the liposomal boron delivery system (BDS) [2]. Development of lipophilic boron compounds embedded within the liposome bilayer is an attractive means to increase the overall incorporation efficiency of boron-containing species, as well as to raise the gross boron content of the liposome in the formation [3,4]. We focused on BSH as a hydrophilic boron cluster for boron lipids. BSH is a water-soluble divalent "*closo*-type" anion cluster that has significantly low toxicity. Because of this property, BSH has been utilized for BNCT. We were the first to synthesize *closo*-dodecaborate lipids, such as DSBL that possess the $B_{12}H_{11}S$ moiety as the hydrophilic function and have similar chirality to natural phospholipids, such as DSPC, in their lipophilic tails. In this paper, we report our BDS studies using *closo*-dodecaborate lipid liposomes[5,6].

EXPERIMENTS: Liposomes (DSBL-25%) were prepared from ^{10}B-enriched DSBL, DSPC, Chol, and DSPE-PEG (0.25: 0.75: 1: 0.11, molar ratio) and injected into colon 26 tumor bearing mice (female, 6-7 weeks old, 16-20 g) via the tail vein at a dose of 20 mg ^{10}B/kg (2000 ppm of ^{10}B concentration). The mice were anesthetized with isoflurane and placed in an acrylic mouse holder 24 h after i.v. injection. The mice were irradiated in the JRR4 for 30 min at a rate of 1.8×10^{12} neutrons/cm^2. To determine tumor volume, two perpendicular diameters of the tumor were measured with a slide caliper and calculation was carried out using the formula 0.5 ($A \times B^2$), where A and B are the longest and shortest dimensions of the tumor in millimeters, respectively. All protocols were approved by the Institutional Animal Care and Use Committee of Gakushuin University.

RESULTS: Biodistribution study of boronated liposomes in mice showed that boron concentration of 37.8 ppm was observed in tumor with a tumor/blood ratio of ~0.6 at 1 h after injection. In contrast, boron concentration of 22.7 ppm in tumor with a tumor/blood ratio of ~2 was observed 24 h after administration of DSBL-25% PEG liposomes, and boron concentration gradually decreased thereafter. High boron concentration was observed also in liver and spleen. In general drug delivery systems, the high accumulation of drug-encapsulating or -attaching nanoparticles in other tissues, such as liver and spleen, sometimes induces side effects due to the cytotoxicity of the accumulated drugs. Current boron lipid liposomes displayed significantly low toxicity and were readily eliminated from the tissues within three weeks after injection. Therefore, it is considered that the high accumulation of boron in liver and spleen observed would not have serious side effects unless thermal neutron irradiation is carried out on these tissues. In this regard, *BNCT is a double-targeting therapy that involves boron delivery to and neutron irradiation of cancers*.

The cytotoxicity of DSBL-25% PEG liposomes was examined by irradiating tumor bearing mice with thermal neutrons. As shown in Figure 1, tumor volume in mice treated with DSBL-25% PEG liposomes was significantly inhibited after thermal neutron irradiation. The tumor volumes were ~20% of those of control mice two weeks after the neutron irradiation.

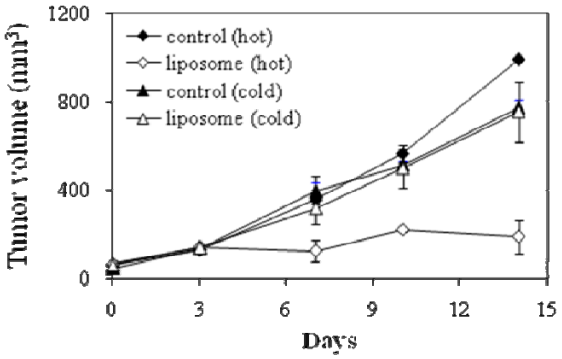

Fig. 1. Tumor volume in mice bearing colon 26 solid tumor with thermal neutron irradiation (hot) for 30 min (1.8×10^{12} neutrons/cm^2) or without irradiation (cold).

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採択課題番号 22008　　中性子捕捉治療のための新規ホウ素薬剤開発　　共同通常
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CO7-4 Hyaluronan-Conjugated Liposomes as Carrier of Sodium Borocaptate for Tumor Targeting in Boron Neutron Capture Therapy

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INTRODUCTION: Hyaluronan-conjugated PEG-liposomes (HA-Ls), is a candidate for active targeting to melanoma, many of which overexpress the hyaluronan receptors CD44 and RHAMM [1]. Sodium borocaptate (BSH) entrapped in HA-Ls is expected to deliver boron atoms from the locally released BSH directly to target cells for antitumor application in BNCT. Transdermal drug delivery system has been accepted as potential non-invasive route of drug administration, with advantages of sustained therapeutic action and better patient compliance, though, its prevalent use is restricted due to excellent impervious nature of skin. Thus, many approaches have been attempted to perturb skin barrier and enhance the transdermal delivery of drug [2]. The major approaches for enhancing transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation), vesicles, particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers. Electroporation (EP) is a physical method that enhances delivery of molecules to tissues in vivo. In this study, a unique nanoliposomal-EP-mediated approach has been developed for delivering BSH into melanocytic tumors present in skin to retard melanoma.

EXPERIMENTS: BSH-loaded bare liposomes composed of phosphatidylcholine:cholesterol at mole ratios of 2:1 were prepared by the reverse-phase evaporation method. HA-Ls or folate-conjugated PEG-liposomes (FA-Ls) were prepared using the post-insertion method to insert ligands. Briefly, HA was dissolved in water and preactivated by incubation with EDC and NHS at pH 5.5 for 2 hours at 37°C. At the end of this step, the activated HA was added to a suspension of the DSPE-PEG-NH_2 micelles, buffered by 0.1 M borate buffer at pH 8.6. Incubation with the micelles was continued for 2 hours at 37°C. The HA-coupled micelles were transferred in a simple incubation step from the micelles into the outer monolayer of pre-formed, BSH-loaded liposomes.
B16-F10 murine melanoma cells were pre-incubated with 50 ppm of liposomal BSH and BSH solution for 6 hours at 37℃ before neutron irradiation. The cells were rinsed twice in PBS and suspended in fresh medium. After irradiation the cells were plated into plastic Petri dishes 60 mm in diameter at 200 cells per dish. They were incubated for an additional 7 days to allow colony formation.

RESULTS: Intracellular targeting ability and cytotoxic effects of BSH-loaded liposomes. HA-Ls readily bound to melanoma cells, and were internalized by receptor-mediated endocytosis. As shown in Fig. 1, survival of the washed cells pre-incubated with BSH-loaded HPLs was lowest compared to survival of control cells that were pre-incubated with PEG-Ls, FA-Ls and BSH solution. But there were no statistically significant differences between HA-Ls and FA-Ls. This result suggested cytotoxicity depended on internalization of ^{10}B.
We are now ongoing to investigate the therapeutic potential of EP-mediated approach for transcutaneous BSH delivery in a three-dimensional skin reconstruction model of melanoma.

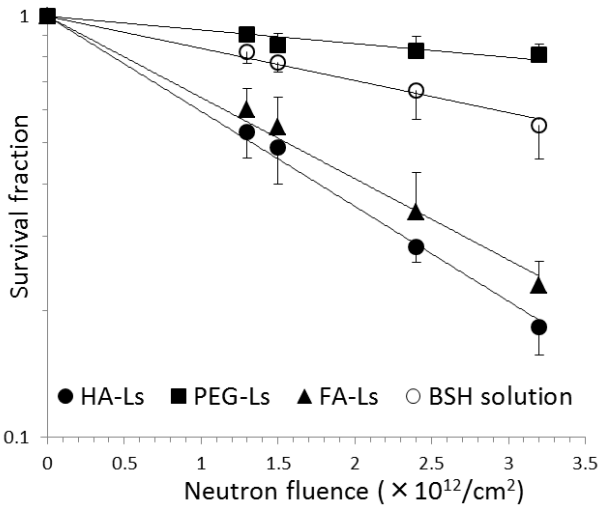

Fig. 1. Suppression of the colony formation of B16-F10 cells after in vitro BNCT. Values are means±S.D.

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採択課題番号 22009　新規皮膚透過性メラノーマ標的化ボロン送達システムを用いた中性子捕捉療法の開発　共同通常
（広国大・薬）笠岡　敏、中西莉沙（京大・原子炉）増永慎一郎

CO7-5 Enhanced the Effect of Boron Neutron Capture Therapy -Design of Boron-containing Nanoparticles with Highly Tumor-accumulating Character-

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INTRODUCTION: Boron neutron capture therapy (BNCT) has attracted much attention as the selective and noninvasive cancer therapy using boron-10 (^{10}B) compounds, which efficiently generate the cytotoxic α-particles and ^{7}Li nuclei within ten μm through the nuclear reaction of ^{10}B atom with low-energy thermal neutrons [1]. The success of BNCT is dependent on the delivery systems to accumulate a sufficient quantity of ^{10}B to tumor tissues. In this regard, nanoparticles such as liposome encapsulating hydrophilic ^{10}B compounds (e.g. sodium borocaptate: BSH) have been studied[2]. However, therapeutic effects of the BSH-encapsulating liposome are still controversial under *in vivo* conditions due to the leakage of encapsulated BSH from liposome in the blood stream. Herein, we prepared core-polymerized and boron-conjugated micelles (PB micelles) composed of poly (ethylene glycol)-*block*-poly(lactide) copolymer bearing an allyl group at PEG end and a methacryloyl group at PLA end (allyl-PEG-*b*-PLA-MA) and BSH. This micelle enables to conjugate with BSH through the covalent bonds by the radical addition on the allyl group and deliver the boron to the tumor tissues without leakage of boron compounds in the blood stream because of the existence of covalent bonds between BSH and the PEG brush of the micelles. In this study, the irradiation of thermal neutrons to tumor-bearing mice treated the PB micelles and non polymerized and boron-conjugated micelles (NPB micelles) were carried out in order to evaluate the therapeutic effects on BNCT.

EXPERIMENTS: The boron-conjugated micelles were prepared from ^{10}B-enriched BSH and allyl-PEG-*b*-PLA-MA by free-radical-initiated addition [3]. Moreover, the PB micelles were prepared by free radical polymerization of the methacrylic group in the micellar core [4]. The PB and NPB micelles solution injected into colon-26 tumor bearing mice (n = 5) via the tail vein at a dose of 15 mg ^{10}B/kg 24 h before irradiation. As comparison, allyl-PEG-*b*-PLA-MA micelles solution was injected 24 h before irradiation *via* the tail vein. The mice were anesthetized with pentobarbital sodium (40 mg/kg) and placed in an acrylic mouse holder. The mice were irradiated thermal neutrons for 40 min at a rate of 1.5-2.8 x 10^{12} neutrons/cm^2. The BNCT effects were evaluated in terms of the tumor size.

RESULTS: Figure 1 shows the changes of the tumor volume in mice bearing colon-26 tumor with thermal neutrons irradiation after injecting the PB micelles, NPB micelles, micelles alone (allyl-PEG-*b*-PLA-MA micelles) and normal saline (control). Note that the suppression of growth of tumor volume in mice treated the PB micelles was observed 21 days after irradiation compared to the mice treated normal saline. On the other hand, the mice treated the NPB micelles showed tumor growth similar to both the micelles alone and controls. These results indicate that the therapeutic effects enhanced by the core-polymerization of the micelles. This might be caused by the enhancement of the stability of the micelles in the blood stream. Therefore, the PB micelles represent a promising approach to the creation of novel boron carrier for cancer BNCT.

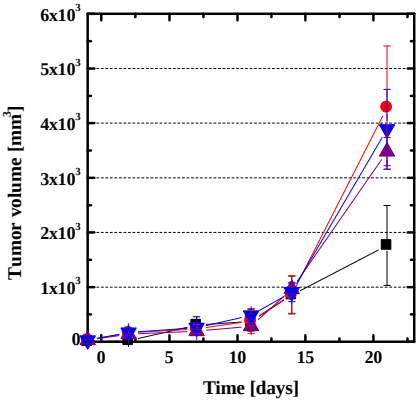

Fig. 1. Tumor growth curve of tumor-bearing mice after irradiated thermal neutrons injected the PB micelles (black squares), the NPB micelles (red circles), micelles alone (blue triangles) and controls (purple triangles). The data are expressed as means ± S.E. (n = 5).

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採択課題番号 22010 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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（京大・原子炉）鈴木 実、小野公二（東大院・工）柳衛宏宣

CO7-6 Boron Neutron Capture Therapy for Extramammary Paget's Disease

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INTRODUCTION: Extramammary Paget's disease (EMPD) of the scrotal or penile skin that was clinically and histopathologically similar to mammary Paget's disease,which was first reported by James Paget [1]. Histopathological analysis indicates that EMPD can also invade the dermis to increase the number of Paget's cells typically found within the epidermis and eccrine apparatus. Surgical procedures, such as conventional radical excision and Mohs micrographic surgery (MMS), are the only therapies to eradicate EMPD, but there are issues with recurrence and grave outcomes. In 2010 we treated two patients with extra-mammary Paget's disease (EMPD) by BNCT using BPA alone [2]. EMPD usually presents as an eczematoid, red, weeping area on the perineum. The lesions can be flat, raised, or ulcerated. Paget's disease can be mistakenly diagnosed as eczema or contact dermatitis. EMPD in the perineal region is analogous to that of the breast and is associated with invasive carcinoma in about 20% to 30% of the cases. We report the short-term clinical results of the first patient.

CASE PRESENTATION: A 75 years old man, who presented with a history of reddish and intense itching in scrotum for 5 year is being reported. After being medically treated, he was diagnosed on scrotum biopsy. Local excision of scrotum lesion was performed, and histopathology revealed Paget's disease (Fig. 1).
Because the agreement of the operation had not been obtained, boron neutron capture therapy(BNCT) was enforced. After 49 days the erythema had disappeared it had irradiated it. Moreover, the skin biopsy was performed, Paget's cell had disappeared in the epidermis(Fig.2).

CONCLUSIONS: BNCT is not only effective in EMPD but also improves patient's quality of life compared with the surgical remedy.

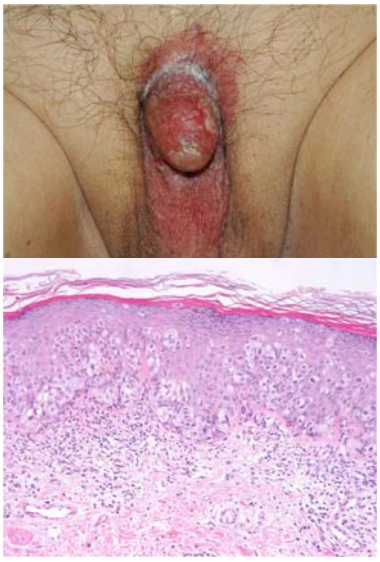

Fig. 1. Clinical and histopathological features of EMPD (a) an erythematous patch (b) Paget's cells were exclusively found in the epidermis.

Fig.2. Clinical and histopathological features of after 49 days.

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採択課題番号 22011　　中性子捕捉療法適応癌腫の治療プロトコールの確立　　共同通常
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小西 圭、牧野英一、石原武明、神谷伸彦、（京大・原子炉）小野公二、鈴木 実、櫻井良憲、丸橋 晃

CO7-7 Tumour Growth Suppression by Gadorinium Neutron Capture Therapy with -arterial Administration of Gadoteridol-Entrapped Water-in-Oil-in-Water Emulsion as Novel Gadrinium Carrier in VX-2 Rabbit Hepatic Cancer Model

H. Yanagie[1,2], S. Higashi[3], I. Ikushima[4], R.Mizumachi[5], Y. Murata[5], Y. Morishita[6], A. Shinohara[7], K. Yokoyama[8], M. Fijiwara[9], N. Iyomoto[1], D. Novriana[1], Y. Sakurai[2], K. Mouri[2], H. Sugiyama[2], R. Nishimura[10], M. Yanagawa[10], T. Iizuka[10], Y. Sakurai[11], M. Suzuki[11], K. Ono[11], J. Nakajima[12], M. Ono[12], M. Eriguchi[1,13] and H. Takahashi[1,2]

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INTRODUCTION: Tumour cell destruction(Gd) in gadorinium neutron-capture therapy (GdNCT) is due to the nuclear reaction between Gd and thermal neutrons [1]. It is necessary for effective neutron capture therapy to accumulate Gd atoms in the tumour cells without affecting adjacent healthy cells. According to the Higashi's clinical results, Water-in-oil-in-water(WOW) emulsion has been used as the carrier of anti-cancer agents on intra-arterial injections in clinical [2]. We prepare Gadoteridol entrapped WOW emulsion for selective intrarterial infusion for rabbit hepatic cancer model applicating to GdNCT, and evaluate the emulsion as selective Gd delivery carrier to cancer tissues [3].

EXPERIMENTS: With these double emulsifying technique, Gadoteridol solution (1396.5 mg/5ml) was filtrated of controlled pore glass membrane emulsifying into 5 ml of IPSO (Lipiodol) containing surfactant, and then Gadoteridol entraqpped WOW emulsion was prepared [2]. Gd-WOW emulsion had been administrated with intra-arterial injections via proper hepatic artery on VX-2 rabbit hepatic tumour models (Gadoteridol 93mg/kg). We performed GdNCT on day 2 after intra-arterial injection of Gd-WOW emulsion at KUR

RESULTS: We can detect the superior accumulation of Gd atoms in the VX-2 tumour by intra-arterial injection of Gadoteridol entrapped WOW emulsion until 72 hrs after injection by ICP-MAS. We also recognised the tumor growth suppression with thermal neutron irradiation(5 x 10E12 cm^{-2}) after intraarterial injection of Gadoteridol entrapped WOW emulsion(Fig 1, 2).

Therefore, we will be able to apply Gadoteridol en trapped WOW emulsion to GdNCT for hepatocellular carcinoma. Gd entrapped WOW emulsion will be applied to novel intra-arterial boron delivery carrier on GdNCT to cancer.

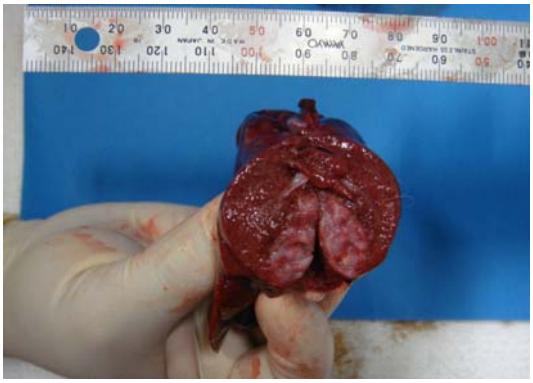

Fig. 1. Gd NCT group : The tumour growth suppression was seen. Tumour invasion to the surface of liver nor disseminations into the peritomeum are not seen.

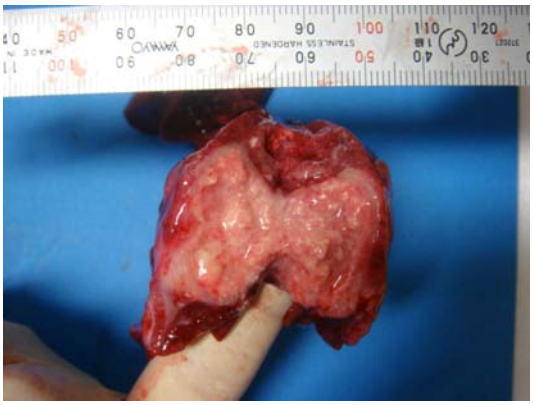

Fig. 2. Non-treated group : The VX-2 tumours are grown up with several nodules in left lobe and right lobe of liver. The over-growth of tumnour was occuered and central necrosis was seen. Disseminations into the peritomeum and abdominal cavity are seen.

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採択課題番号 22012　　中性子捕捉療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

（東大院・工）柳衛宏宣、伊豫本直子、Novriana Dewi（東大病院）櫻井由里子、毛利きくえ
（東大院・農）柳川将志、飯塚智也（宏仁会　海老原記念病院）東　秀史、瀬口浩司、太田嘉一
（大阪市大・工）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 Serious Radiation Necrosis after BNCT on Grade III Glioma of von Recklinghausen's Disease – Case Report

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***Case presentation*:** Grade-III glioma of 57y female was treated by BPA-based BNCT. The patient incidentally diagnosed as grade II glioma (diffuse Astrocytoma grade II、MIB-1 Index < 1%) in the left frontal lobe on 2008 with the progress of multiple dermal tumors, von Recklinghausen's disease. The tumor has been treated by TMZ successfully, but the patient showed recurrence of the tumor 21 months after the diagnosis, and its biosamples revealed malignant-change toward grade III glioma. Then, the patients was treated by BPA-based BNCT using the current protocol, BPA T/N ratio=2.59, tumor dose < 31.0-61.2 Gy-Eq, surrounding normal parenchyma dose < 12.5Gy-Eq.

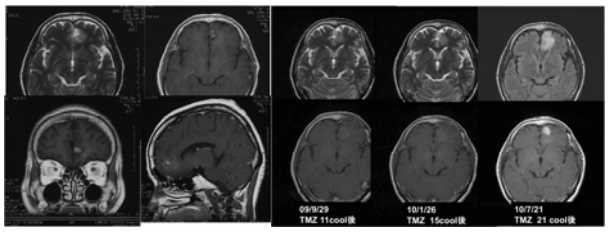

Fig. 1. MRI at the onset of grade II glioma (left), and serial progression with TMZ (right).

Figure 1 shows a MRI view at the onset (*left*) and the progression of the tumor (*right*) before BNCT.

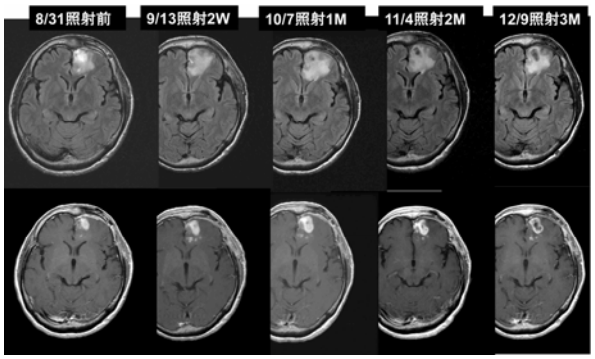

Fig. 2. Serial MRI after BNCT.

The tumor showed central necrosis on 3 months after BNCT as shown in Figure 2. However, swiftly, the patient showed abnormal behavior, gate disturbance 4.5 months after BNCT with serious necrosis (Fig. 3).

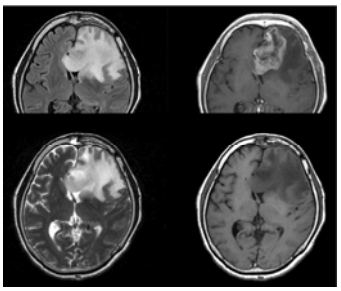

Fig.3. Radiation necrosis, 4.5 months after BNCT.

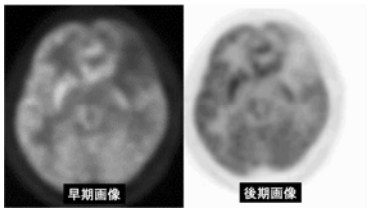

Fig. 4. FDG-PET, almost negative study.

Malignant glioma cells were pathologically observed, although FDG-PET study showed necrosis (Fig. 4). However, fortunately, the mass effect of radiation necrosis was treated successfully, and the Karnofsky performance status of the patient drastically improved up to 60-70%. Now the patient has been controlled the chemotherapy of the combination of ACNU – carboplatin – vincristine - IFNbeta chemotherapy.

***Summary*:** Although there is lack of adequate knowledge about radiation necrosis and /or vascular biology on von Recklinghausen's disease, BNCT might be a treatment option for recurrent malignant glioma.

***Summary of clinical time course*:**

2008/10/9	Open biopsy: diffuse Astrocytoma G-II、MIB-1 Index < 1%
2010/1/26	Nearly CR with TMZ 21 cool
2010/7/21	MRI revealed recurrence without neurological deficit.
2010/8/10	Tumor extirpation :diffuse astro- cytoma G-III、MIB-1 Index > 80%
2010/9/9	BNCT（maximum tumor dose < 61.2Gy-Eq, minimum deepest dose > 31Gy-Eq, FBPA-PET T/N ratio = 2.59）
2011/1/26	Serious radiation necrosis with IICP
2011/1/31	FDG-PETstudy revealed radiation necrosis
Currently	KPS = 60-70%

採択課題番号 22014　悪性脳腫瘍のための熱外中性子捕捉療法の臨床的的研究　共同通常
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CO7-9 Boron Neutron Capture Therapy for Malignant Brain Tumors Using Epithermal Neutron

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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 malignant 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).

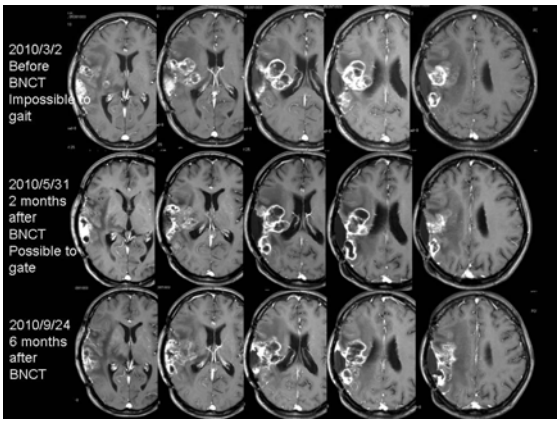

Fig. 1. Clinical course of recurrent GBM treated by BNCT.

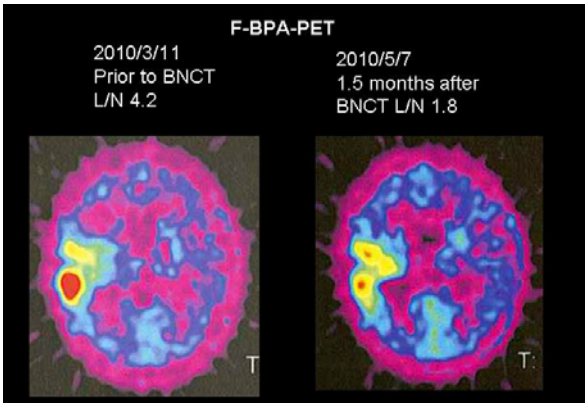

Fig. 2. F-BPA-PET of pre and post-BNCT .

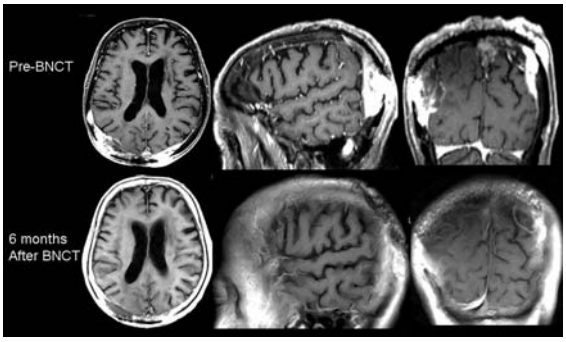

Fig. 3. Clinical course of malignant meningioma treated by BNCT.

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採択課題番号 22017 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臨床的研究 共同通常

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（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

CO7-10 Development Reserch on Boron Neutron Capture Therapy for Malignant Brain Tumors (Improvement of a Further Therapeutic Efficacy)

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K. Takahashi, T. Kuroiwa, H. Michiue[1], A. Mori[1]
H. Matsui[1], K. Tomizawa[2] and K. Ono[3]

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INTRODUCTION: Boron neutron capture therapy (BNCT) is based on the nuclear capture and fission reactions that occur when non-radioactive ^{10}B is irradiated with low energy thermal neutrons to produce alpha-particles ($^{10}B[n, alpha]^{7}Li$). Carboranylporphyrins or chlorins are a class of substituted porphyrins containing multiple carborane clusters [1,2]. One of these compounds, designated tetrakis (*p*-carboranylthio -tetrafluorophenyl) chlorin (TPFC) [3], has been evaluated in our study. The goals were two-fold. First, to determine their biodistribution following intracerebral (i.c.) administration by convection enhanced delivery (CED) to F98 glioma bearing rats. Second, to determine the efficacy of TPFC as boron delivery agents for BNCT in F98 glioma bearing rats.

EXPERIMENTS: Tumor boron concentrations immediately after i.c. delivery were high and they remained so at 24 h. The corresponding normal brain concentrations were low and the blood and liver concentrations were undetectable. Based on these data, therapy studies were initiated at the Kyoto University Research Reactor Institute (KURRI) with TPFC 24 h after CED.

RESULTS: Median survival times (MST) ± standard deviations of animals that had received TPFC and TPFC with i.v. BPA, followed by BNCT, were of 31 (95%CI; 28 – 42) and 42 (37 – 43) days, compared to 42 (10 - NA) and 25 (23 – 28) days, respectively, for i.v. BPA, untreated control. However, since the tumor boron concentrations of the carboranylporphyrins were much higher than intravenous (i.v.) boronophenylalanine (BPA), we had expected that the MSTs would have been greater (Fig. 1).

Our data provide a cautionary note that high ‘‘tumor’’ boron concentrations do not necessarily mean that the boron delivery agent is localized within tumor cells [4]. The challenge will be synthesize and evaluate non-toxic carboranylporphyrins with improved water solubility, which attain high *in vivo* tumor cell uptake following either systemic injection or direct i.c. administration [2]. Based on our study, it can be concluded that these compounds are a class of boron delivery agents that warrant further investigation.

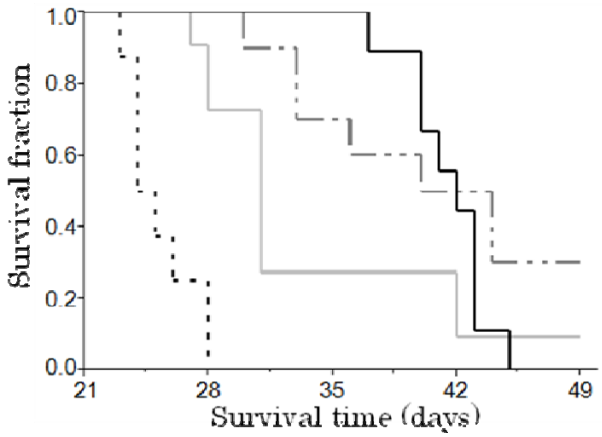

Fig. 1. Kaplan–Meier survival plots for F98 glioma bearing rats following CED of TPFC followed by BNCT. Survival times in days after implantation have been plotted for untreated animals (ditted), TPFC (gray), i.v. BPA (dashed) or i.v. BPA + TPFC (black).

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採択課題番号 22032　　悪性脳腫瘍に対する硼素中性子捕捉療法の開発研究　　共同通常
（さらなる治療効果の改善を目指して）

（大医大・脳外）宮武伸一、黒岩敏彦、川端信司、高橋賢吉、平松　亮、矢木亮吉
（岡山大・生理）松井秀樹、道上宏之、森亜希子（熊本大）富澤一仁、（京大炉）小野公二

CO7-11 Tumor Accumulation and Neutron Capture Efficacy of ε-Poly-Lysine Based Polyamines Conjugate with Boron Clusters

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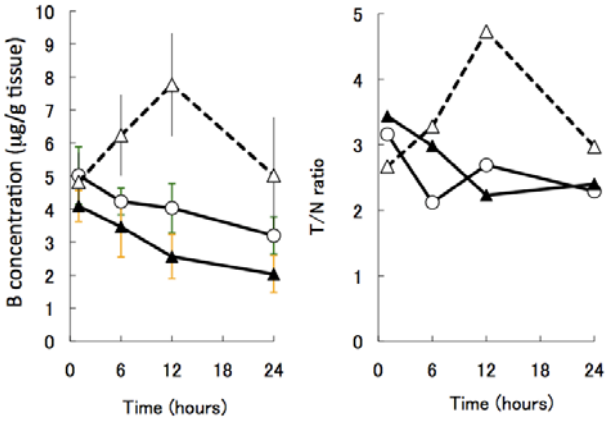
Graduate School of Engineering, Osaka City University, [1]Graduate School of Engineering, The University of Tokyo, [2] Graduate School of Life and Environmental Sciences, Osaka Prefecture University, [3]Research Reactor Institute, Kyoto University

INTRODUCTION: Boron Neutron Capture Therapy (BNCT) is one of the potent cancer radiotherapy using nuclear reaction between ^{10}B atoms and the neutron. Whether BNCT will succeed or not depends on tumor selective delivery of ^{10}B compounds. ε-Poly-L-lysine (ε-PLL, Mw ca. 4000) is a naturally occurring polyamaine. Because of high safety ε-PLL is applied practically as a food additive due to its strong antimicrobial activity. In this study, we focus on a development of a novel delivery system for BNCT by using biodegradable ε-PLL containing ^{10}B-contining clusters. This ^{10}B polymer will be expected to accumulate at tumor tissue based on Enhanced Permeability and Retention (EPR) effect.

EXPERIMENTS: ε-PLL is kindly supplied by Chisso Corporation (Tokyo, Japan). The novel ^{10}B polymer (BPP) consists of PEG-cross-linked ε-PLL (23EG-PLL and 9EG-PLL: 23 and 9 ethyleneoxy units per linker, respectively) and ^{10}B enriched sodium mercaptododecaborate (BSH) [1]. Some nanoparticle containing BPP were prepared through the assembly of BPP and 23EG-PLL and/or 9EG-PLL at any weight ratio. Mouse colorectal carcinoma cell line (colon 26) was used *in vitro* and *in vivo* experiments. BALB/c mice were transplanted with 6 x 10^5 colon 26 cells into the thigh. After 10 days of transplantation, tail-vein injections of boron compounds were carried out for the evaluation of tumor accumulation and BNCT effect.

RESULTS: The size and zeta potential of BPP were determined as 5.2 nm with a negative charge (-14 mV). Therefore, polyion-complexation between BPP and 23EG-PLL and/or 9EG-PLL was attempted to prepare bigger size particles suitable for EPR effect. BPP/23EG-PLL (2/1, w/w), and BPP/23EG-PLL/9EG-PLL (8/4/1, w/w/w) showed average size with 24 and 91 nm and -2.6 and -3.5 mV zeta potential, respectively. The 5-fold higher uptake of boron by colon 26 cells was observed by treatment of BPP/23EG-PLL/9EG-PLL compared with BSH *in vitro*. *In vivo* tumor-accumulation studies were performed with BPP, BPP/23EG-PLL, and



BPP/23EG-PLL/9EG-PLL (Fig.1). BPP/23EG-PLL/9EG-PLL affords the highest tumor boron concentration and T/N ratio because of the largest particle. BPP/23EG-PLL/ 9EG-PLL can be delivered to tumor tissue based on EPR effect. When bearing tumor was irradiated with 2 x 10^{12} neutrons/cm^2, highest antitumor activity was observed with BPP/23EG-PLL/9EG-PLL (Fig. 2). BPP/22EG-PLL/9EG-PLL will be expected to act as a promising ^{10}B carrier for BNCT.

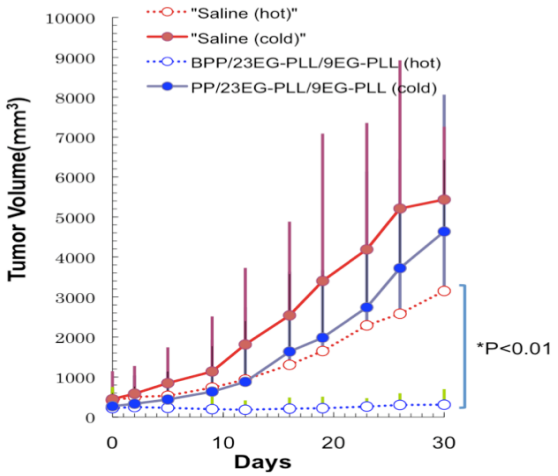


Fig. 2. Relative changes of tumor volumes of mice treated with (hot) and without (cold) neutron irradiation using BPP polyioncomplex ; volumes were estimated as V = 1/2 x length (mm) x [width (mm)]^2 .

REFERENCES:

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採択課題番号 22033　　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

（阪市大院・工）長﨑　健、馬野正幸、瓜生田貴聡（東大院・工）柳衛宏宣
（阪府大院・生命環境科）切畑光統（京大・原子炉）劉　勇、小野公二、増永慎一郎、櫻井良憲

CO7-12 The Study of the BNCT Effect Using the Boron Carriers on Oral Squamous Cell Carcinoma Cell

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INTRODUCTION

The extent to which the intracellular boron concentration can be raised is an important aspect of boron neutron capture therapy (BNCT) and is the focus of research using liposomes in our laboratory [1, 2].

Here, we used treated oral squamous cell carcinoma cell line SAS with boron with modified liposome carriers to deliver sodium borocaptate (BSH), followed by irradiating the cells with neutrons. We then used a colony formation assay to investigate tumor destruction.

MATERIALS AND METHODS

Tumor cells were cultured in serum- free- medium and divided into culture medium containing bare-BSH, PEG-liposomal BSH, or TF-PEG-liposomal BSH with a boron concentration of 50 PPM, or no boron. The cells in each group were cultured in their respective culture medium for 6 h, after which the culture medium was removed. The cells were then suspended to a concentration of 1×10^5 cells/ml in culture medium containing 50 PPM boron or no boron, and transferred to Teflon tubes for irradiation. The samples were irradiated with neutrons for predetermined intervals. After irradiation, the cells were cultured at 200 cells/dish for 7 days and assayed.

RESULTS AND DISCUSSION

Irradiating a sample of 50 PPM boron with neutrons for 20 min theoretically amounts to a gamma ray dose of 15 Gy. The results of irradiating SAS with gamma rays are shown in Fig. 1. The results of irradiating boron-treated SAS with neutrons in culture medium containing boron compound are shown in Fig. 2. The tumor destruction effect was higher for modified BSH than for bare-BSH, and was higher for the use of gamma rays. The results of irradiating boron-treated SAS with neutrons in the absence of boron compound are shown in Fig. 3. While the same result as in Fig. 2 was obtained with TF-PEG-liposomal BSH, no neutron irradiation effect was found for other boron compounds. This finding is explained by the expunging of boron compound but not the TF-PEG-liposome from the tumor cells by the time of neutron irradiation [1].

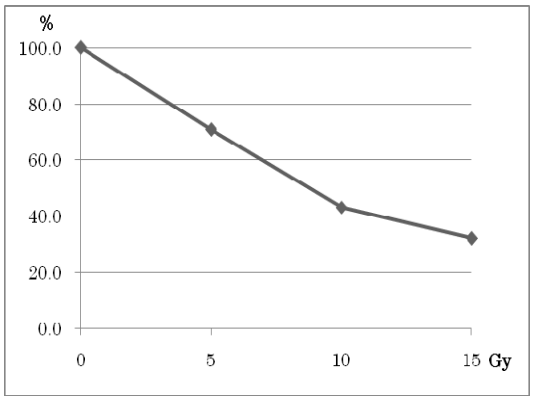

Fig. 1. Gamma ray

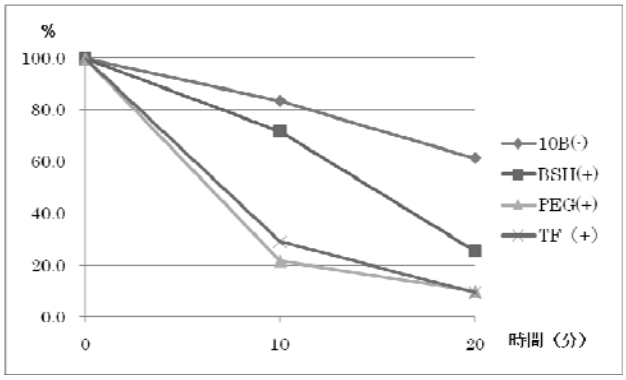

Fig. 2. No boron at neutron irradiation

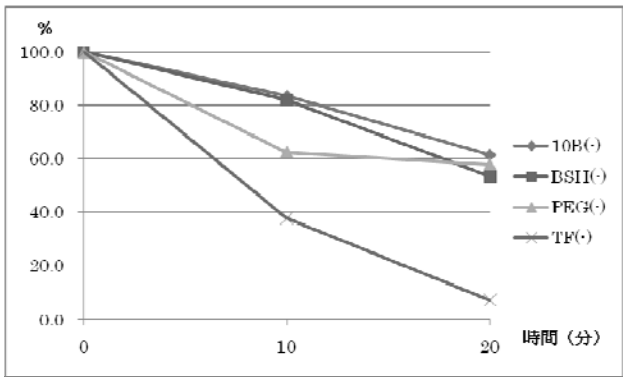

Fig. 3. Include boron at neutron irradiation

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採択課題番号 22038　　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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木村吉宏、島原武司、武井祐子

CO7-13 Boron Neutron Capture Therapy for Malignant Pleural Mesothelioma

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1. INTRODUCTION: In 2005, 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 clinical outcome provoked us to start a prospective clinical trial of BNCT for MPM.

We are preparing for a new protocol to start multi-institutional clinical trials of BNCT for MPM. We presented a case report on BNCT for MPM using this new protocol.

2. METHOD and PATIENT

2-1. Treatment protocol

In BNCT for MPM, the whole ipsilateral lung should be regarded as clinical target volume (CTV). Since the maximum diameter of collimator available in BNCT was 25 cm, 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 3-week interval. BPA (500 mg/kg) was administered intravenously at the speed of 200 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: A 68-year-old man with right MPM was referred to our center for further treatment with BNCT. He had received the standard chemotherapy for MPM. Although partial regression of the tumor was achieved by the chemotherapy, he refused to receive the chemotherapy due to renal toxicity and general fatigue. The chief complaint was chest and back pain due to tumor progression.

First BNCT was performed on Oct. 21 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 onNon.11 in 2011.

Figures 1 and 2 show the dose distributions and dose volume histograms (DVH) for the normal lung and tumor, respectively.

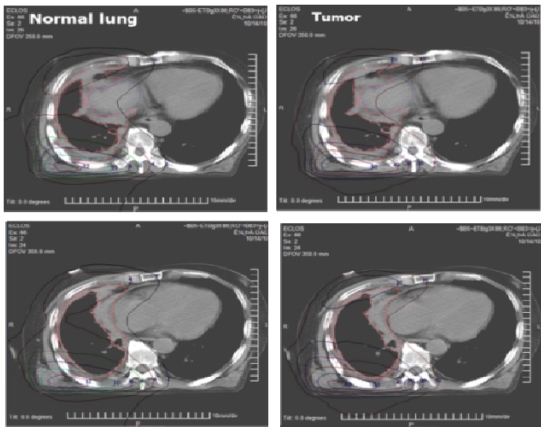

Fig.1. Left two slices and right two slices show dose distribution in the normal lung and tumor, respectively.

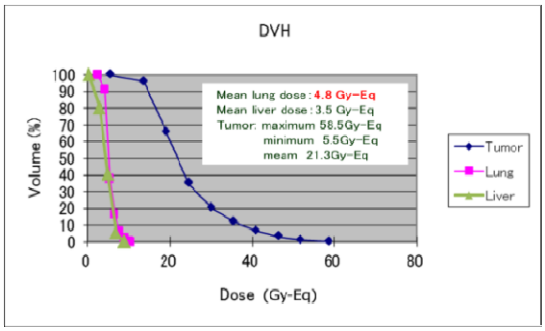

Fig. 2. This figure shows DVH for tumor, normal lung and liver.

As shown in Fig. 2, mean lung dose for ipsilateral lung was 4.8 Gy-Eq, which is satisfactory result.

No acute adverse effect was experienced. In a few months after BNCT, decrease in the value of tumor marker was observed and relief of back pain was obtained. Although regrowth of the tumor was observed on the CT at five months after BNCT, no radiation pneumonitis appeared in the normal lung. Although further observation is needed, no serious adverse effect has been experienced. Normal lung response by BNCT will be analyzed in the multi-institutional clinical trials for BNCT. In addition, the result will be available in BNCT for multiple lung metastases/

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採択課題番号 22048 中性子捕捉療法の臨床的研究 共同通常
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CO7-14 Influence of the Sonoporation to the Boron Neutron Capture Therapy in Oral Squamous Cell Carcinoma

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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]. In order to heighten the curative effect of BNCT in human oral squamous cell carcinoma (SAS), we performed sonoporation to the cultured cell for the purpose of the improvement of taking in of boron.

EXPERIMENTS: We measured boron concentration, after cultivating SAS and cultivating for a definite period of time by the DMEM with 10% FBS which adjusted BPA and BSH to 50 ppm in the confluent state. we irradiated with the ultrasonic wave (1MHz, 0.5W/cm^2,duty cycle 20%,10s)SAS cultivated on the same conditions for 2 hours under microbubble existence.SAS was irradiated with a thermal neutron beam. The irradiation time was 40 min. We evaluated cellular proliferative potential by MTTassay.

RESULTS: As shown in Fig.1 and Fig.2 the rise of intracellular boron concentration was not seen in an ultrasonic irradiation independent. When ultrasonic irradiation was performed under microbubble existence, boron concentration increased 2 times in BPA and increased 2.9 times in BSH.As shown in Fig.3 Cellular proliferative potential fell intentionally, when the group which used sonoporation and BNCT together was compared with the control group.

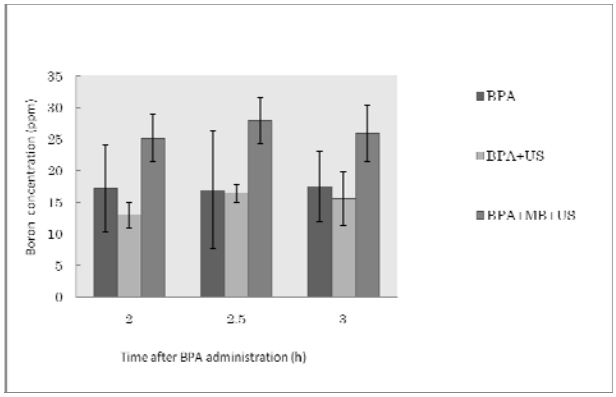

Fig.1. Boron concentration after sonoporation under BPA existence (MB: micro bublle, US: ultra sound).

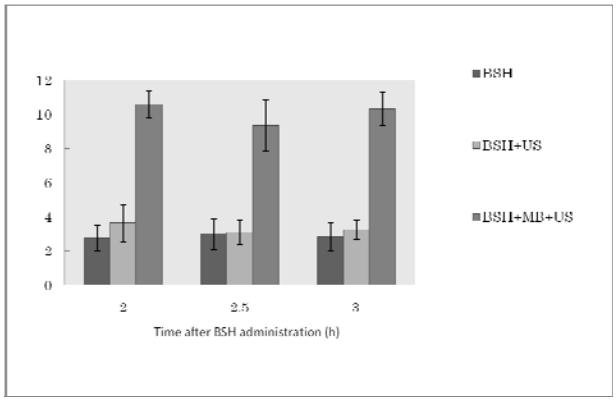

Fig.2. Boron concentration after sonoporation under BSH existence (MB: micro bublle, US: ultra sound).

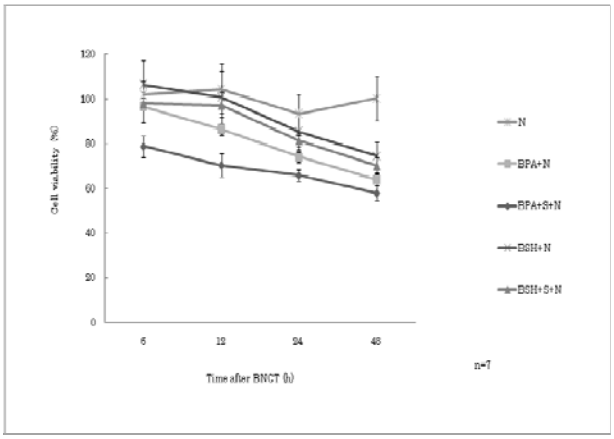

Fig.3. Change of the cellular proliferative potential by BNCT (S: sonoporation with microbubble, N:neutron irradiated).

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採択課題番号 22049　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（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

CO7-15 Clinical Studies on BNCT for 2 Cases of Recurrent 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 summarize 2 patients with HNM who had treated with BNCT at KUR in last year in Table 1. We also report clinical outcome of our BNCT for recurrent HNM [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: Most of 26cases were recurrent and far advanced HNM such as 15 out of 26cases (58%) developed regional lymph node metastases and 6 out of 26 cases (23%) developed distant metastases.

So far for 6years, we have treated with 42 times of BNCT for 26 patients with a recurrent HNM since 2001. Results are as follows. ^{10}B concentration of tumor/normal tissue ratios (T/N ratio) of PET studies were SCC: 1.8-5.7, sarcoma: 2.5-4.0, parotid tumor: 2.5-3.7. Regression rates were CR:12cases (46%), PR:10cases(39%), PD:3cases(12%), NE:1case. Response rate was 85%. 9 patients were survive (35%) and 7 patients (27%) were disease free survival. BNCT improved QOL, PS and survival periods. Survival periods after BNCT were 1-84 months (mean: 23.3 months). 6-year survival rate was 24% by Kaplan-Meier analysis. Adverse events were brain necrosis, osteomyelitis, transient mucositis and alopecia. After 5-year interval for renewal of low enriched uranium-KUR BNCT was restarted in 2010. We had treated 3 times of BNCT for 2 patients with SCC.

Case 1: A 34 year-old man with a tongue carcinoma (T4N1M0, SCC) had got glossectomy in 2007. About half a year after the operation, when he had developed lt-cervical metastatic lymph node, he had been recommended to get the neck dissection. But he had refused to get the operation and get chemotherapy and immunotherapy instead of that. The size of the cervical lymph node metastasis was growing day by day and finally to be 6 cm. FBPA-PET study revealed ^{10}B concentration of T/B ratio was 3.1. Then the patient was treated with BPA (500mg/kg) mediated BNCT twice at KUR in September and November 2010. But he developed lung metastasis and cervical skin metastasis 2 month after 2nd BNCT.

Case 2: In February 2006, a 56-year old man who had suffered from 1st cancer of the left maxillary sinus (SCC, $T_4N_0M_0$). He had been treated with chemotherapy (TS-1:120mg/day for 2weeks per os 2 Kur and between the first and second Kur CDGP80mg/m^2 was administered intravenously and followed by operation of maxillectomy and disease free survival so far. 3 years later, he had suffered from 2nd primary cancer of the right maxillary cancer (SCC, $T_2N_0M_0$). He insistently refused operation and had been treated with super-selective intraarterial chemoradiotherapy (44Gy, CDDP 30mg/m^2+STS, 6 Kur) in July, 2009. After 7 months the tumor was recurrent and he was treated with TPF chemotherapy and again treated with super-selective intra-arterial chemotherapy (TXT: 10mg/m^2, CDDP: 30 mg/m^2+STS, 6Kur) in May-July, 2010 and again recurrent in September. He had treated with BPA mediated BNCT at KUR in October. Then he has been disease free survival so far 5-month.

CONCLUSIONS: BNCT represents a new and promising treatment even for far-advanced patients with a huge HNM.

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Table 1. Treatment Sumary of 2 Cases (May, 2011)

Case No.	Pt's Initial (Age)	Histopathol. Diag.	10B-conc. Normal Tissue, Blood	T/B ratio of ^{18}F-BPA	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:	T-Peak Gy-Eq	T-deepest Gy-E	Skin/Mucosa		
1-1st	K・T (34)	S.C.C. OpZK, LN	22.7	3.1	20.0	–	29.6	15.9	5.7/14	90	(8M)・Alive(8M)
1-2nd			21.7			–	30.9	15.3	6.2/14	70	
2	Y・S (60)	S.C.C.(R-OKK)	26.0	2.7	23.2	44	38.0	27.0	5.2/14	70	CR(7M) Alive((5M)

採択課題番号 22050　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
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（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
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CO7-16 Clinical Study of Boron Neutron Capture Therapy for Oral Cancer

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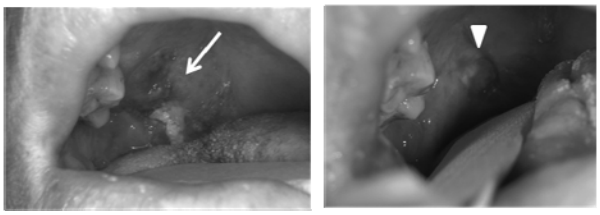
INTRODUCTION: No effective radical treatment methods for recurrent and/or far advanced oral malignancy have been presented. Nearly all affected patients have previously undergone surgery, chemotherapy, and/or radiotherapy treatments, thus palliative treatment strategies including pain relief tend to be chosen. In such cases, we often perform boron neutron capture therapy (BNCT) for quality of life (QOL) improvements and to control the tumor [1, 2]. Herein, we report 2 cases of recurrent oral squamous cell carcinoma that responded well to BNCT.

CASE REPORT: Case 1: A 67-year-old female was referred to our clinic because of mass formation in the soft palate. An incisional biopsy was performed and histopathological results led to a diagnosis of squamous cell carcinoma. The patient refused surgery and underwent systemic chemotherapy followed by radiotherapy (total dose, 65.0 Gy). The tumor responded well to these non-surgical treatments, though local re-growth was noted (Fig. 1a). An ^{18}F-BPA-PET examination was done to assess the accumulation of BPA in the tumor mass, which showed a tumor/normal tissue boron concentration ratio (T/N ratio) of 3.9. BNCT was performed using BPA (total dose, 500 mg/kg body weight) (Table 1) and the tumor mass responded well, with marked down-sizing (Fig. 1b). There were no severe systemic adverse effects noted after therapy, except for grade III stomatitis and pharyngeal edema, which appeared 1 day after BNCT and were well controlled by steroid administration. One month after BNCT, the tumor mass was locally obliterated except for superficial ulceration and there was no skin rupture in the irradiation field. Although additional systemic chemotherapy was performed, tumor re-growth was noted 3 months after BNCT. Ten months after BNCT, the patient died because of uncontrollable local re-growth.
Case 2: A 74-year-old male suffered from a recurrent squamous cell carcinoma in the left side of the tongue, which had been treated by a combination of surgery, chemotherapy, and radiotherapy (total dose, 52.0Gy). Local recurrence was noted and BNCT was planned to control the ulcerated tumor mass. ^{18}F-BPA-PET scanning was performed and the T/N ratio was 2.8. BNCT was performed (total dose of BPA, 500 mg/kg body weight) (Table 1). Following therapy, there were no severe systemic adverse effects seen, while grade III stomatitis was noted. One month after BNCT, the tumor was found to have responded well and was markedly decreased in size. Two months after BNCT, a portion of the left mandibular alveolus became exposed, which was diagnosed as radiation osteomyelitis. Professional oral care and pain control with narcotics were performed.



(a) (b)

Fig.1. Before and after BNCT (Case 1)

Prior to BNCT, an ulcerated mass lesion was seen in the right soft palate (arrow). One month after BNCT, the tumor was apparently decreased in size, with only a superficial ulcer in the area where the tumor was previously located (arrowhead).

Table 1. BNCT Parameters

Case No	Skin surface (Gy-Eq)	Mucosa (Gy-Eq)	Tumor peak (Gy-Eq)	Tumor minimum (Gy-Eq)
1	4.1	14.8	40.0	19.0
2	4.9	14.6	20.0	14.6

COMMENTS: A locally recurrent oral tumor after conventional treatment that was extremely difficult to cure was seen in each of the present cases. For such patients, we consider that BNCT is one of the best treatment modalities, as it has a potential to obliterate the tumor mass, at least tentatively, as seen in the present cases. In addition, this therapy can improve QOL for patients who suffer from a bulky mass in the oral cavity, which interferes with eating and causes severe pain. On the other hand, the adverse effects of BNCT were not severe, though it is important to pay attention to stomatitis and edema of the mucosa, which we saw in the present case 1, as the pharynx was included in the irradiation field. In addition, osteomyelitis was seen in case 2. Thus, it is also important to note patients who have previously undergone irradiation of the jaw bone before performing BNCT.

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採択課題番号 22051　　口腔癌に対する硼素中性子捕捉療法の臨床的研究　　共同通常
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