CO7-1 In Vivo BNCT Effect of High Boron Content Liposomes

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INTRODUCTION: Boron neutron capture therapy (BNCT) for the treatment of cancer gained intense interest in recent years. This therapy is based on nuclear reaction of essentially nontoxic ^{10}B species and low-energy thermal neutrons (0.025 eV), that yields high linear energy transfer (LET) particles, ^{7}Li nuclei and ^{4}He (α-particles), bearing energy of approximately 2.4 MeV. These particles travel a distance equivalent to one cell diameter (approximately 5− 9 μm) to destroy cells. The key for successful BNCT highly depends on the selective and efficient boron delivery, and various boron carriers have been studied for this purpose.

Liposomes are efficient drug delivery vehicles because they can transport their contents to various tumors in a manner that is essentially independent of their contents. The accumulation of liposomes in tumor tissues caused by the enhanced permeability and retention (EPR) effect is based on the abnormal architectures of newly formed tumoral blood vessels, that loose endothelial vessel cells without tight junctions. Therefore, liposomes are considered attractive carriers for boron delivery to tumors.

In our continuous research program, we have studied boron lipid liposomes. This strategy is an attractive means to increase the overall incorporation efficiency of boron containing species, as well as to raise the gross boron content of liposomes [1]. We developed mercaptoundecahydrododecaborate (BSH)-encapsulating 10% distearoyl boron lipid (DSBL) liposomes as a boron delivery vehicle for neutron capture therapy [2]. The current approach is unique because the liposome shell itself possesses cytocidal potential in addition to its encapsulated agents. We carried out the thermal neutron irradiation of mouse colon cancer transfected mice injected with our high boron content liposomes.

EXPERIMENTS: DSPC (MC-8080) and DSPE-PEG (Sunbright DSPE-020CN) were purchased from Nippon Oil and Fats (Tokyo, Japan). Cholesterol (Chol) was purchased from Kanto Chemical (Tokyo, Japan). ^{10}B-enriched BSH and S–cyanoethyl protected ^{10}B-enriched BSH were purchased from Stella Pharma Co. (Osaka, Japan). Boron lipid (DSBL) was synthesized according to the previously described procedures with modification [3].

BSH-encapsulated DSBL-10% liposomes were injected into colon 26 tumor bearing mice (female, 6−7 weeks old, 16−20 g, 5 mice in each group) [4] via the tail vein at doses of 15 and 30 mg ^{10}B /kg (1500 and 3000 ppm of ^{10}B concentration; 200 μL of boronated liposome solution). The mice were irradiated in KUR. Mortality and survival of mice were monitored daily.

RESULTS: The survivals of mice injected with boronated liposomes are shown in Figure 1. Approximately 80% of the mice were survived 80 days after thermal neutron irradiation at doses of 30 and 50 mg ^{10}B/kg. Even at a dose of 15 mg ^{10}B/kg injection, approximately 60% of mice were survived 80 days after thermal neutron irradiation. In contrast, no survival of the mice received thermal neutron irradiation without injection of the liposomes was observed 52 days after thermal neutron irradiation.

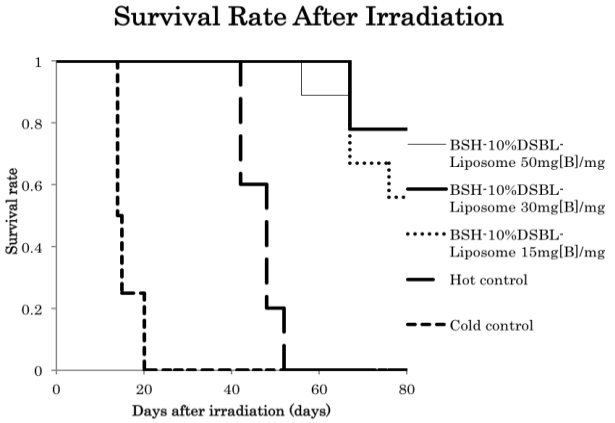

Fig. 1. The survival rate of mice (Balb/c, female, 6 weeks old, 14−20 g) bearing colon 26 solid tumor after *i.v.* injection of BSH-encapsulating 10% DSBL liposomes (15, 30, and 50 mg ^{10}B/kg) and thermal neutron irradiation for 50 min (1 MW) at a rate of (1.5−1.8) x 10^{12} neutrons/cm^2 36 h after injection.

REFERENCES:

[1] M. Ueno, *et al.*, *Bioorg. Med.Chem.* **18** (2010) 3059.
[2] H. Koganei *et al.*, *Bioconjugate Chem.* **24** (2013) 124.
[3] J.-D. Lee *et al.*, *Org. Lett.* **9** (2007) 323.
[4] H. Nakamura *et al.*, *Org. Biomol. Chem.* **10** (2012) 1374.

採択課題番号 25005 中性子捕捉療法のための新規ホウ素薬剤の開発 共同通常
（東工大・資源研）中村浩之（学習院大・理）立川将士、小金井逸人、佐藤伸一、加納大輔
（京大・原子炉）鈴木 実、近藤夏子、増永慎一郎、小野公二

CO7-2 Establishment of QA/QC for BNCT Neutron Irradiation Field (II)

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INTRODUCTION: In May 2010, the operation of Kyoto University Reactor (KUR) restarted, which had been suspended during four years for the fuel-low-enrichment. Clinical irradiation of boron neutron capture therapy (BNCT) at the Heavy Water Neutron Irradiation Facility (HWNIF) also restarted [1]. After the restart, 235 BNCT irradiations have already been carried out as of June 2014. In the while, the BNCT clinical trial using Cyclotron-based BNCT Epi-thermal Neutron Source (C-BENS) started in November 2012 [2]. Thus, this institute became a special institute in the world, in where BNCT is performed at the two-type neutron sources such as reactor-based one and accelerator-based one. It is one of the important subjects that the consistent dose-estimation is performed between the both neutron sources, and then the equivalence and homogeneity for the deposited dose during the clinical irradiation are assured. The aim of this research is the establishment of quality assurance and quality control (QA/QC) for BNCT neutron irradiation field. In 2013, one of the important tools for QA/QC, "radiation-quality-evaluation phantom", was prepared, and its efficacy was confirmed.

METHODS: In a phantom of Li-6-mixed water, the components of thermal neutron and secondary gamma ray can be largely decreased, but the fast neutron component is not decreased [3]. A phantom of 10% LiOH solution with 95%-enriched Li-6 was prepared, based on simulations. The depth distributions of neutrons and gamma ray were estimated in the epi-thermal neutron mode of KUR-HWNIF. Neutron fluxes were measured by activation method using gold for thermal neutron and indium for fast neutron. Gamma-ray absorbed dose rate was measured using thermo-luminescent dosimeter (TLD). The operation power of KUR was 1 MW.

RESULTS AND DISCUSSIONS: Figure 1 shows the depth flux distributions of thermal and fast neutrons. The curves correspond to the simulation results, and those are normalized with the measured values at the peak of thermal neutron flux distributions. The thermal neutron fluxes in the LiOH phantom could not be estimated, because the cadmium ratios were almost 1. The fast neutron distributions were almost the same for the phantoms. Figure 2 shows the depth absorbed dose distributions of gamma rays. The secondary gamma-ray distributions obtained by the simulations are also drawn. The dose rate in the LiOH phantom was decreased to almost one seventh of that in the H_2O phantom. Most of the gamma ray in the LiOH phantom can be assumed to be the primary gamma ray.

CONCLUSION: It was experimentally confirmed that the thermal neutron and secondary gamma-ray components are largely decreased, and the fast neutron component stands out, due to the LiOH phantom. The comparison and estimation of beam quality among the BNCT irradiation fields can be expected using this phantom.

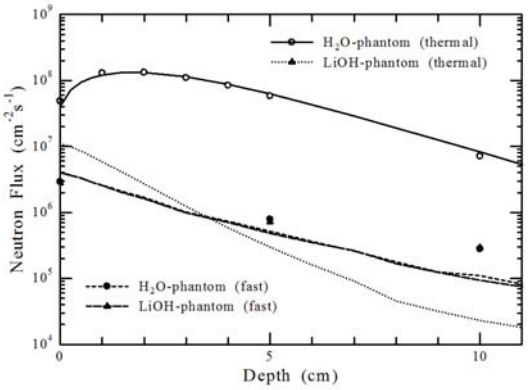

Fig. 1. Depth flux distributions of thermal and fast neutrons along the central axis in the phantoms.

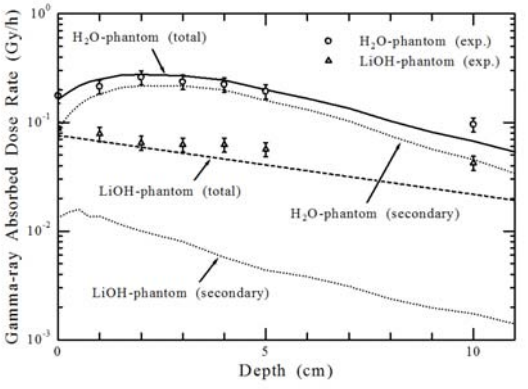

Fig. 2. Depth absorbed dose distributions of gamma rays along the central axis in the phantoms.

REFERENCES:

[1] Y. Sakurai *et al.*, Nucl. Instr. Meth. A **453** (2000) 569-596.
[2] H. Tanaka *et al.*, Nucl. Instr. Meth. B **267** (2009) 1970-1977.
[3] Y. Sakurai *et al.*, Proc. 14th Int. Congr. Neutron Capture Therapy (Comision Nacional de Energia Atomica) (2010) 254-256.

採択課題番号 25007　　ＢＮＣＴ用照射場におけるＱＡ／ＱＣの確立　　共同通常

（京大・原子炉）櫻井良憲、田中浩基、吉永尚生（京大院・工）内田良平、川村徳寛、竹田尚弘、上田治明

CO7-3 Development of an Advanced Optical Fiber Type Neutron Detector

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INTRODUCTION: The Boron Neutron Capture Therapy (BNCT) has been developed as one of the promising radiotherapies. In this radiotherapy, the neutron dose evaluation is quite important. Small size optical fiber type neutron detectors have been developed as one of the on-line small neutron flux monitors. The conventional optical fiber neutron detectors, however, show a continuous distribution without a characteristic shape, such as the full energy absorption peak corresponding to the neutron induced reactions, in a pulse height spectrum due to the non-uniform light yield and/or the poor light collection efficiency [1-3]. The sensitivity of these detectors depends on the detector signal gain, which may vary with temperature. We have developed an advanced optical fiber type neutron detector using a small piece of Eu:$LiCaAlF_6$ scintillator. Figure 1 shows the pulse height spectrum obtained from the developed detector. This detector can show an obvious neutron absorption peak and suppress the gamma-ray sensitivity because the scintillator size is controlled larger than ranges of ^{6}Li(n,t) reaction products and smaller than ranges of fast electrons induced by gamma rays. In this report, we experimentally evaluate performances of the developed neutron detector at the Heavy Water Neutron Irradiation Facility (HWNIF) of Kyoto University Research Reactor (KUR).

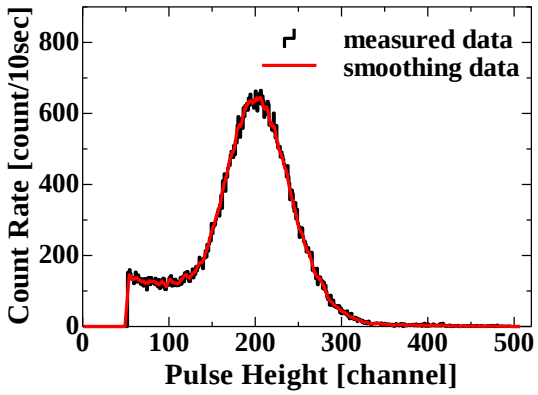

Fig. 1 Pulse height spectra obtained from the developed detector.

PERFORMANCE EVALUATION: We fabricated the optical fiber type neutron detector using a small Eu:$LiCaAlF_6$ scintillator and experimentally evaluated its performance at the HWNIF of KUR. We checked the linearity between the detector output and the neutron flux of irradiation field. The neutron flux was tuned by changing the detector position in the irradiation facility. The flux was determined with a gold activation method. Figure 2 shows the relation between the detector output and the neutron flux of the irradiation field. The detector output shows good linearity with the neutron flux of the irradiation field up to 10^9 n/cm^2/s.

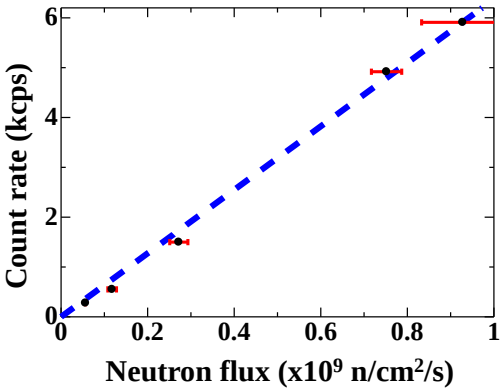

Fig. 2 Relation between the detector output and the neutron flux of the irradiation field.

We additionally checked the output stability of the neutron detector. Figure 3 shows the time trend of the neutron detector output and the KUR reactor power. The output of the detector was confirmed to be stable without sensitivity deterioration and can respond to minute fluctuations of the reactor output. The detector was confirmed to be used as a neutron flux monitor for BNCT.

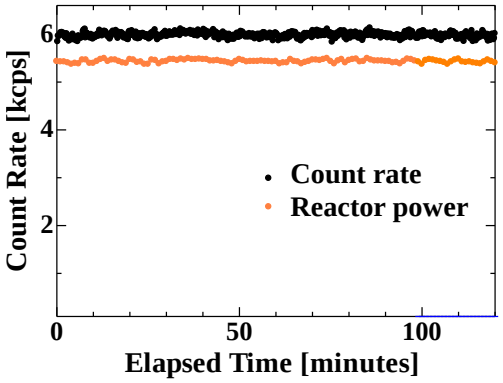

Fig. 3 Time trend of the neutron detector output and KUR reactor power.

REFERENCES:

[1] M. Ishikawa *et al.*, Appl. Rad. Isotopes, **61** (2004) 775-779.
[2] M. Ishikawa *et al.*, Nucl. Instr. Meth. A, **551** (2005) 448-457.
[3] Y. Ito *et al.*, Radiat. Prot. Dosim., **110** (2004) 619-622.

採択課題番号 25008　極少検出器を用いた中性子計測手法の高度化に関する研究　共同通常
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（京大・原子炉）櫻井良憲、田中浩基

CO7-4 Boron Neutron Capture Therapy for Lung Metastasis and Biodistribution of *p*-borono-L-phenylalanine in Lung of Human Clear Cell Sarcoma (CCS)-bearing Animal Model

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INTRODUCTION:

Clear cell sarcoma (CCS) of tendons and aponeuroses is a rare neoplasm with poor prognosis [1]. Since neither chemotherapy nor radiation therapy is effective, new therapeutic strategies, other than surgery, are needed. We have previously demonstrated the effectiveness of boron neutron capture therapy (BNCT) with the use of *p*-borono-L-phenylalanine (BPA) for tumors in the limb of the human CCS-bearing nude mouse mode [2, 3]. In the course of treatment, however, CCS often metastasizes to the lung. At prsent, such tumors are difficult to manage even surgically. We therefore evaluated the distribution of BPA in the lung of a newly created human CCS-bearing animal model for the management of lung metastasis with BNCT.

EXPERIMENTS:

All animal experiments were carried out according to the regulations of the Animal Care and Use Committee.

(1) *Tumor cell line*: Human CCS cell line, MP-CCS-SY [4] was grown in RPMI 1640 with fetal bovine serum in a 5% CO_2 humidified incubator at 37˚C.

(2) *Producing the lung metastasis in the human CCS-bearing animal model*: Cells of the CCS cell line (MP-CCS-SY) suspended in Matrigel® were transplanted into the parenchyma of the left lung of the nude mice. Eight weeks thereafter, micro-CT scans disclosed the formation of a tumor in the left lung. Histological examinations were then carried out by HE staining.

(3) *Biodistribution of ^{10}B in the lung-metastasis animal model*: BPA-Fr (24 mg ^{10}B/kg) was intravenously injected into the lung of the human CCS-bearing animal model and, at predetermined intervals, blood and lung tissue samples were collected immediately after the mice were killed. The concentration of boron in the samples was then measured by ICP-AES.

RESULTS:

Lung metastasis was successfully produced in the human CCS-bearing animal model. The formation of a solid tumor mass was formed in the left lung parenchyma was confirmed by macroscopic observation, micro-CT scans and microscopic observation. Biodistribution of ^{10}B one hour after the intravenous injection of BPA-Fr into the lung-metastasis animal model, demonstrated tumor-specific and high-level ^{10}B accumulation in the tumor mass [Fig. 1], at a concentration of 51μg ^{10}B/g of wet tumor tissue, and the ratio of tumor-to-normal tissue (lung) was 11.8. The effect of BNCT on the lung metastasis animal model is currently under analysis.

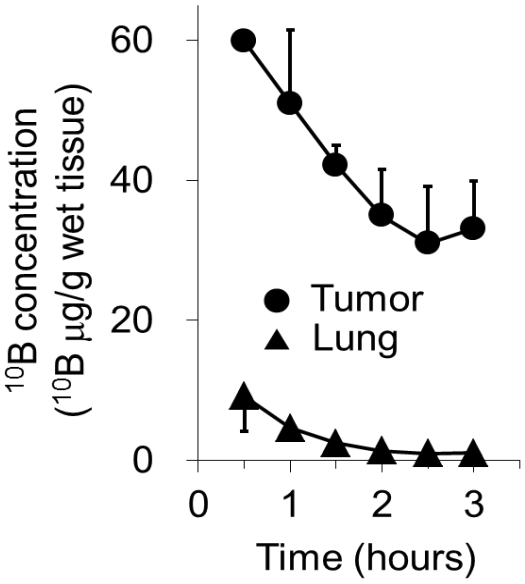

Fig.1 Biodistribution of *p*-borono-L-phenylalanine in the lung of the human clear cell sarcoma (CCS)-bearing animal model. ●: Tumor, ▲: Lung.

REFERENCES:

[1] F.M. Enzinger, Cancer, **18** (1965) 1163-1174.
[2] T. Fujimoto *et al*., Appl. Radiat. Isot. **73** (2013) 96-100.
[3] T. Andoh *et al*., Appl. Radiat. Isot. 2013 Dec 17 Epub.
[4] H. Moritake *et al*., Cancer Genet. Cytogenet., **135** (2002) 48-56.

採択課題番号 25011　　悪性末梢性神経鞘腫および明細胞肉腫に対する　　共同通常
ホウ素中性子捕捉療法の検討

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（兵庫県立がんセンター・整形外科）藤本卓也

CO7-5 BNCT for Head and Neck Cancer

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INTRODUCTION

Almost all of advanced head and neck carcinoma (AHNC) and recurrent head and neck cancer (RHNC) are well-known their resistance to radiation therapy or chemotherapy. They need to be resected widely, but it is often difficult because of their extensive growth to surrounding normal tissues. The normal tissue in RHNC, which was received postoperative radiotherapy in the past, has been severe impairment, and unsuitable to additional excision. So, alternative treatment is needed for them.
BNCT has been applied to AHNC and RHNC not to reduce QOL. In this protocol, we have applied single BNCT with BPA alone [1].
This paper reports the clinical results in patients treated by BNCT in 2013.

METHODS AND MATERIALS

Six patients were treated, consisting four men and two women; a median age of 33 years old (range 16-72 years), and follow-up periods were 1-12 months (median 6.5 months). According to the pathological type, five were squamous-cell carcinoma (SCC), and one was mucoepidermoid carcinoma of parotid gland. All cases were taken BPA-PET before BNCT to estimate the tumor/blood boron ratio (T/B ratio). T/B ratio was 2.5-3.5 (median 2.75). The irradiation time was 34-90 minutes (median 78.5 minutes).

RESULT

The local recurrence occurred in two and distant metastasis occurred in two. As follow-up period is too short for us to assess final response of target lesion. The prognosis of several cases are shown here. In a case of lingual cancer, lung metastasis occurred in a month after BNCT and local recurrence in 6 months, and die of systemic disease 8 month later. In a case of ethmoidal sinus cancer, it relapsed locally 5 months later. In a case with huge lymph node mass from cancer of unknown primary, another neck lymph node metastasis appeared after BNCT in spite of good local response, and cervical bone metastasis occurred 5 months later.
Acute adverse events like mucositis, dermatitis, edemata etc are acceptable and severe side effect have never appeared in all cases.

CONCLUSION

Although the local control in the present cases are unfavorable, longer follow-up time may be necessary to report the final results. Treatment modality for AHNC and RHNC are needed two aspects, local and systemic control. Based on this results, we need to consider new protocol combined or immunotherapy not to develop systemic disease.

Patients characteristic	
Age (median)	33 y.o. (16-72 y.o.)
Gender	
Male	4
Female	2
Pathlogical type	
SCC	
ethmoidal sinus	1
external auditory canal	1
oropharynx	1
lingual	1
unknown primary	1
(Lymph node metastasis)	
Mucoepidermoid carcinoma	
parotid gland	1
Previous treatment	
Operation	5
Chemotherapy	5
Radiation	5
Disease Presentation	
Local recurrence (SCC)	4
Cervical lymph node metastasis	1
Both	1

Result:	
Controlled	3
Local recurrence	2
Lymph node metastasis	2
Distant metastasis	2
Death	1

REFERENCES:

[1] T. Aihara, *et al.*, New Challenges in Neutron Capture Therapy (2010) 25-29.

採択課題番号 25015　中性子捕捉療法適応癌腫拡大と治療プロトコルの確立　　共同通常
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CO7-6 Study on the Generation of Gamma-rays from Lanthanide Oxide Phosphor by Neutron Irradiation and the Effect on the Living Cells

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INTRODUCTION: Neutron capture therapy (NCT) is one of available ways for intractable cancers in human body. BNCT is in practical use, in addition, gadolinium neutron capture therapy (GdNCT) is also useful because Gd ion has a toxicity against human calls by gamma-ray generation under irradiation thermal neutrons [1]. On the other hand, we were successful to control the morphology of the lanthanide oxide phosphors in our previous work [2]. Using a lanthanide phosphor including Gd synthesized by our technique, the phosphors are able to form unique shapes such as tube and hollow sphere, and the phosphor can be used as a new type drug delivery system (DDS) possessing several functions such as gamma-ray generation under irradiation of thermal neutron, drug delivery and lavel of the tumor cells in one material.

In this study, the preparation of hollow sphere lanthanide phosphor $GdBO_3:Eu^{3+}$ was performed using polymer beads as a template by hydrothermal treatment. And then the tumor cell killing effect of this material against cultured the cancer cell after irradiation of thermal neutron and icubation was investigated.

EXPERIMENTS: The phosphor sample was prepared partially following the previous work [2]. The gadolinium and europium nitrate were dissolved in water with urea and then this solution was placed into a Teflon container with polymer beads as a template in the stainless autoclave. The hydrothermal synthesis was carried out at 190 C for 3 h.

The cancer cells (KB) cultures were inoculated with 7 x 10^5 cells/dish and the cells were grown for 24h in medium. Medium including 50 and 100 ppm Gd atom was added into the cultures and then the well plates were irradiated thermal neutron for 30 and 60 min. The average neutron flux was measured by gold wire and TLD as 1.47 x 10^9 $cm^{-2}s^{-1}$. After irradiation, each well was incubated for 24, 48 and 72 h and then the absorbance at 490nm was measured by LDH assay method for evaluation of the tumor cell killing effect.

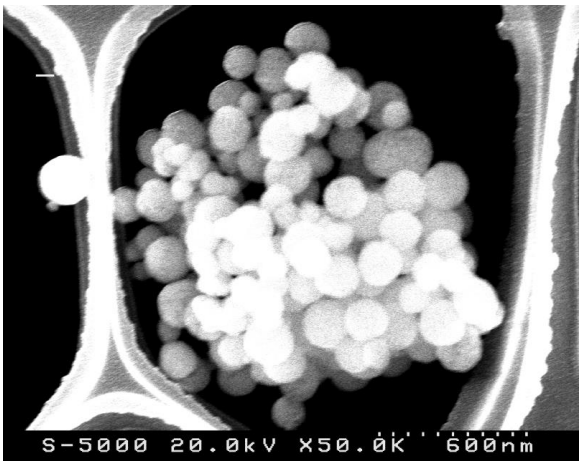

Fig. 1. FE-SEM image of $GdBO_3:Eu^{3+}$ phosphor hollow microsphere prepared by hydrothermal treatment at 190℃ for 3h.

RESULTS: X-ray diffraction studies have been coducted on the nontreated powder and on powders after hydrothermal treatment. All the X-ray diffraction peaks of the sample can be indexed as a $GdBO_3$ without impurities. As shown in Fig. 1, the lanthanide phosphor hollow microsphere without aggregation was successfully formed less than 100nm diameter. The obtained hollow sphere phosphors showed a good emission at typical three peaks of $GdBO_3:Eu^{3+}$ of 591, 610, and 624nm under excitation irradiation at 244 nm.

These particles were dispersed onto the cultures with medium and then irradiated the thermal neutron. The cell viability was unchanged before and after the addition of the phosphor in medium and before irradiation of neutron beam. The absorbance at 490 nm of LDH assay obtained from the medium of KB cell line in the presence of 100ppm Gd after neutron irradiation for 1h and then incubated for 48 h was increased compared with the control sample.

This work was supported by JSPS Grant-in-Aid for Scientific Research (B) Grant Number 24350098.

REFERENCES:

[1] Y. Horiguchi *et al.*, Sci. Technol. Adv. Mater., **12**, (2011) 044607-044614.
[2] T. Jin *et al.*, Chem. Lett., **37(3)**, (1981) 370-371.

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採択課題番号 25016　　中性子を照射した希土類酸化物系蛍光体からの　　共同通常
ガンマ線発生と生体への影響に関する研究
（産総研）神　哲郎（京大・原子炉）田中 浩基

CO7-7 To Conquer the Clinically Relevant Radioresistant Cell Tumors Targeting Tumor Endohtelial Cells

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INTRODUCTION: Radiotherapy is one of the major therapeutic modalities for eradicating malignant tumors. However, the existence of radioresistant cells remains one of the most critical obstacles in radiotherapy. To understand the characteristics of radioresistant cells and to develop more effective radiotherapy, we have established clinically relevant radioresistant (CRR) cell lines. Because tumor tissues of CRR cells transplanted into nude mice were richer in tumor blood vessels compared with their radiosensitive parental cell lines. So, we performed boron neutron capture treatment (BNCT) targeting tumor endothelial cells using PEG-10B. Growth rate of SAS-R (CRR of SAS) tumors were not significantly different from that of non-irradiated control in 2 weeks after irradiation. Tumors of parental cells with BNCT using PEG-10B were significantly smaller than those without radiation. Moreover, the tumors treated BNC with RAD001 (Everolimus, an mTOR inhibitor) decreased tumor size in both SAS-R and SAS tumors.

EXPERIMENTS: Three days before the BNCT, $1x10^6$ cells of SAS and SAS-R were injected subcutaneously into hind legs of male Balb/c nude mice (4 weeks old). The day of the exposure experiment tumor diameter was approximately 3-4 mm. For targeted irradiation of α-particles to tumor endothelial cells, PEG-^{10}B was administered. The compound was suspended in physiological saline at a concentration of 2,500 ppm and was injected via the tail vein. Three hours after the administration, mice were exposed to neutrons at the Research Reactor Institute, Kyoto University (RRIKU). RAD001 (5 mg/kg) was administered orally daily with a vehicle by Novartis.

Tumor size was determined by caliper measurements every three days. Endothelial cells and pericytes of blood vessels in tumor tissues were immunohistochemically determined by CD31 and Type Ⅳcollagen, respectively. Functional blood vessels was visualized by tomato lectin injected from tails.

Fig.1

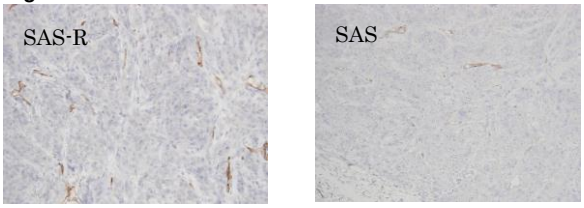

Fig.1 Tumor vessel (CD34+) of SAS-R tumor (CRR) is richer than that of parental tumor.

Fig. 2

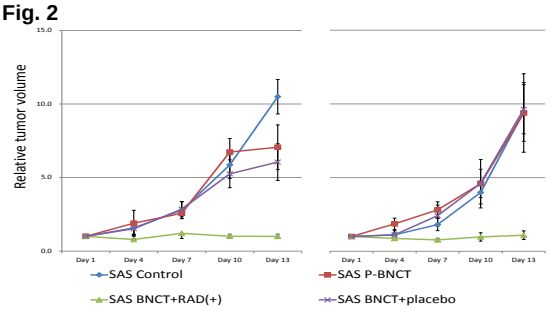

Fig.2 Tumor size of SAS was significantly decreased in Day 13.

RESULTS: We first examined the size of SAS tumors and SAS-R daily after BNCT. Within 13 days after the BNCT, the size of SAS-R tumors was not different between mice with BNCT and without. But the size of SAS tumors with BNCT significantly decreased compared to control tumors. On day 3 blood vessels were collapsed but 5 days after BNCT, blood vessels in SAS-R tumors were recovered more rapidly than SAS tumors. On the other hand, those in parental tumors remained collapsed.

DISCUSSION: In this study, we tried to target tumor endothelial cells of radioresistant SAS-R tumors, because our preliminary experiments showed that the density of blood vessels in SAS-R tumors is higher than that in SAS tumors. We selectively exposed endothelial cells to α-particles using BNCT with PEG-^{10}B. The volume was not significantly different between SAS-R tumors exposure to 8 GyEq of α-particles and those without exposure for the examination period. But SAS tumors with exposure were significantly decreased compare to tumors without exposure. Moreover, BNCT in combination with RAD001 decreased tumor size in both SAS-R and SAS tumors. Five days after BNCT, the density of CD31 positive blood vessels were destroyed in SAS tumors but were recovered in SAS-R tumors with and without BNCT.

Further studies are needed to confirm how CRR cells contributes to the protection of blood vessels from irradiation and to tumor radiotherapy.

採択課題番号 25019　　血管内皮細胞を標的とする放射線耐性腫瘍の克服にむけて　　共同通常
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CO7-8 Boron Neutron Capture Therapy with Bevacizumab May Prolong the Survival of Recurrent Malignant Glioma Patients

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INTRODUCTION: Recurrent malignant gliomas (RMGs) are very difficult to control, and no standard treatments have been established for them. We performed boron neutron capture therapy (BNCT) for these cases. BNCT enables the application of a high dose of particle radiation selectively to tumor cells. However, RMG cases generally received nearly 60 Gy X-ray irradiation prior to re-irradiation by BNCT. Even with tumor-selective particle radiation BNCT, radiation necrosis in the brain and symptomatic pseudoprogression may develop. In four of our recent consecutive RMG patients after BNCT, we applied the anti-VEGF antibody bevacizumab (BV) for these pathological entities. Here we introduce the survival benefit of this strategy for RMG cases [1,2].

Clinical Presentation:
Four patients with RMGs were treated in our institutes with BNCT. Upon the referral for BNCT, they were assessed as recursive portioning analysis (RPA) class 3 in three cases and RPA class 4 in one case (the RPA classification for RMG was advocated by Carson, et al. in 2007) [1]. The estimated median survival times for RPA class 3 and 4 are 3.8 and 10.8 months respectively after some treatment at the recurrence. We applied BNCT for these four patients and administered BV when the lesions were considered radiation necrosis or symptomatic pseudoprogression. The class 3 patients survived after the BNCT for 14, 16.5 and > 23 months, and the class 4 patient survived > 26 months, with favorable improvements in clinical symptoms.
Conclusion: BNCT with the addition of BV for radiation necrosis or symptomatic pseudoprogression improved the clinical symptoms and prolonged the survival in RMG patients.

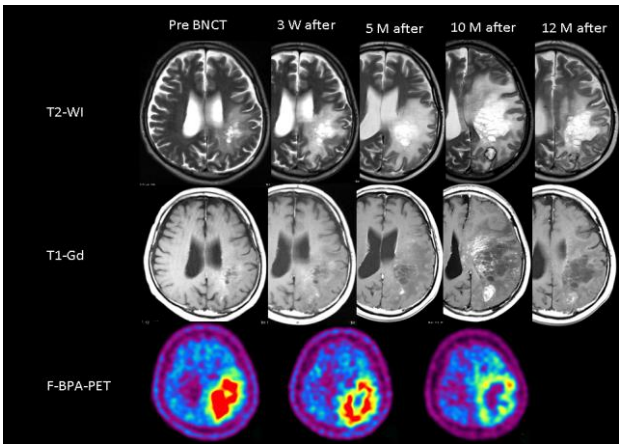

Fig. 1. Sequential change of T2-weighted MRI (upper column), Gd-enhanced T1-weighted MRI (middle column) and F-BPA-PET (lower column) of Case 1, a 44-year-old male. The timing of the MRIs is depicted above the MRIs. F-BPA-PET images were taken just before the BNCT and at 1 month and 10 months after the BNCT. These PET images show the gradual decrease of the tracer uptake as a promising effect of the BNCT. BV was started 10 months after the BNCT, and the MRI showed marked improvement by BV treatment.

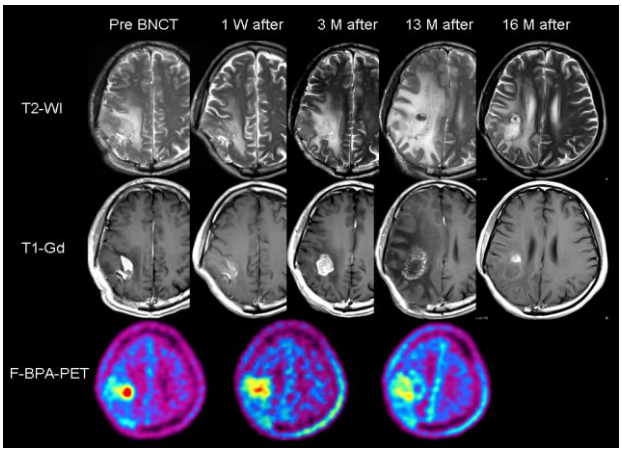

Fig. 2 Sequential change of T2-weighted MRI (upper column), Gd-enhanced T1-weighted MRI (middle column) and F-BPA-PET (lower column) of Case 2, a 41-year-old man. The timing of the MRI is depicted above the MRI. F-BPA-PET images were taken just before the BNCT, 1 month after and 12 months after the BNCT. These PET images show the gradual decrease of the tracer uptake as a promising effect of BNCT. BV was started 13 months after the BNCT, and an MRI showed a marked positive effect of the BV treatment on the perifocal edema and contrast enhancements.

REFERENCES:
[1] S. Miyatake, M. Furuse, S. Kawabata *et al.*, Neuro Oncol., **6** (2013) 650-5.
[2] S. Miyatake, S. Kawabata, R. Hiramatsu, *et al.*, Radiat. Oncol., **9** (2014).
[3] K.A Carson, S.A Grossman, J.D Fisher, *et al.*: J Clin Oncol **25** (2007) 2601-6.

採択課題番号 25026　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
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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

CO7-9 Examination of the Usefulness as the New Boron Compound of ACBC-BSH for Boron Neutron Capture Therapy

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INTRODUCTION:

Boron neutron capture therapy (BNCT) is an attractive technique for malignant brain tumor treatment. It is important to have a significant differential uptake of ^{10}B between tumor cells and normal cells to achieve potent tumor-selective antitumor efficacy. Today, clinically used dodecaboranethiol (BSH) is transferred to brain tumors only through the disrupted blood brain barrier (BBB), so it is difficult for BSH to reach regions that tumor cells invade microscopically where the BBB seems to be intact. On the other hand, boronophenylalanine (BPA), which transfers boron via L-type amino acid transporter, can deliver ^{10}B even in the infiltrating tumor cell population where the BBB is intact. However, some amounts of ^{10}B are inevitably taken into the normal cells by BPA systemic administration. A wide variety of boron delivery agents have been synthesized to solve these problems. [1] 1-amino-3-fluorocyclobutane-1-carboxylic acid (ACBC), unnatural amino acid was reported as the agent which showed intense uptake in glioblastoma [2]. Additionally, in a clinical study, [^{18}F] ACBC showed usefulness for tracer of positron emission tomography (PET) [3]. Therefore, we designed and synthesized ACBC-BSH and evaluated therapeutic effect of ACBC-BSH as boron delivery agents for BNCT in F98 glioma cell bearing rats.

MATERIALS AND METHODS:

BNCT was performed 14 days following stereotactic implantation of 10^3 F98 glioma cells. Rats were transported to the Nuclear Reactor Laboratory at Kyoto University Research Reactor Institute. Based on the results of the biodistribution study, we prepared five groups. The rats were then randomized on the basis of weight into experimental groups of 6-8 animals each as follows: Group 1, ACBC-BSH administered by Alzet pump and irradiated; Group 2, i.v. BPA and irradiated; Group 3, ACBC-BSH administered by Alzet pump + i.v. BPA and irradiated; Group 4, neutron irradiation; Group 5, untreated controls. BNCT was initiated 1 h after termination of Alzet pump infusion or i.v. administration. All irradiated rats were anesthetized with a pentobarbital sodium.
The rats were irradiated for 60 min with 1MW. The antitumor effects of BNCT on the survival rate (after irradiation) of the rat were evaluated.

RESULTS:

The estimated physical radiation doses delivered to tumor, brain and blood were calculated according to boron concentrations. The highest physical radiation doses delivered to the tumor were 3.7Gy for ACBC-BSH by Alzet pump infusion. The corresponding normal brain doses were 1.1Gy. The survival data following BNCT showed that the MSTs were 37.0±5.2 d and 37.4±2.6 d, respectively, for rats that received ACBC-BSH administered by Alzet pump and i.v. BPA. Further studies were carried out using ACBC-BSH administered by Alzet pump, in combination with i.v. BPA. The corresponding MST were 44.3±8.0 d. We accepted meaningful duration of survival time of the rats group using the combination of ACBC-BSH administered by Alzet pump and i.v. BPA, compared a group using i.v. BPA alone ($p<0.0382$).

CONCLUSION:

Survival times of group1-3 were meaningful prolonged compared with untreated group. The therapeutic effect of both ACBC-BSH administered by Alze pump and iv BPA was approximately same. We did not compete for the therapeutic effect by using ACBC-BSH together BPA and accepted longest meaningful duration of survival time. This study suggested that ACBC-BSH was the drug to add therapeutic effect to.

REFERENCES:

[1] MW Renner *et al*, Anti-cancer Agents in Med. Chem., **6** (2006) 145-57.
[2] BF Kimler *et al*, J. Neuro-Oncol., **20** (1994) 103-9.
[3] TM Shoup *et al*, Official Publication, Soc. Nucl. Med. **40** (1999) 331-8.

採択課題番号 25030　　新規硼素化合物の有用性と腫瘍幹細胞の克服　　共同通常

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（岡山大）道上宏之
（京大原子炉）増永慎一郎、小野公二

CO7-10 Development of Novel Boron Compounds for BNCT

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INTRODUCTION: Boron neutron capture therapy (BNCT) is an attractive technique for cancer treatment. In the development of useful boron carriers for BNCT [1], unusual boron amino acids represented by L-*p*-boronophenylalanine (BPA) have long being recognized as tumor seeking compounds due to structural analogy to usual L-amino acid, because L-amino acid transport system is enhanced compared with normal tissues to sustain the proliferation of tumor cells. On the other hand, dodecaborate ($[B_{12}H_{12}]^{2-}$), the mother nucleus of mercapto-*closo*-dodecaborate (BSH) and ammonio-*closo*-dodecaborate (BNH_3), is a versatile and available boron cluster bearing high boron occupancy.
We have already reported the syntheses of various types of *closo*-dodecaborate ($[B_{12}H_{11}]^{2-}$) unit containing amino acids by the coupling reaction of *closo*-dodecaborate derivatives with halogenated L-α-amino acid derivatives, such as BSH amino acids **1** [2] and **2** [3], and also reported their biological evaluation as boron carrier for BNCT (Fig. 1). To develop practical materials utilizing ^{10}B carrier, we have newly synthesized ammonio-*closo*-dodecaborate-containing L-BPA derivatives (BPA-BNH_2 **3**), by our reported method [4]. Here, we report the cell killing effects of **3** against cultivated cancer cells.

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 1.0 mM in each case). The cells were cultured 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.

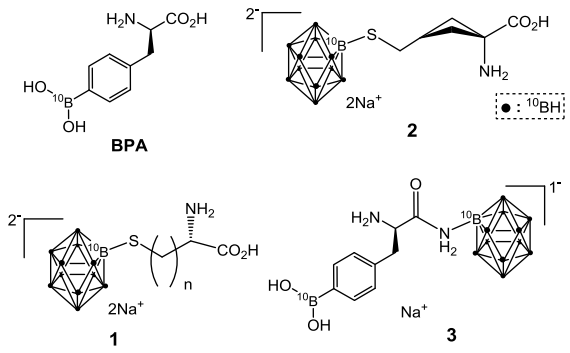

Fig. 1. Boron Compounds.

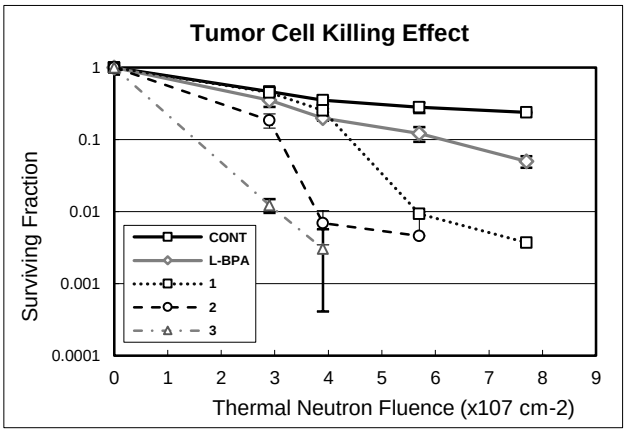

Fig. 2. Tumor cell killing effects of boron amino acids against C6 Cell.

RESULTS: To confirm the usefulness of BPA-BNH_2 for BNCT, we examined the tumor cell killing effects of **3** toward C6 (rat glioma) cell. As shown in Fig. 2, BPA-BNH_2 showed higher killing effects than that of BPA and BSH containing compounds. These results suggest that BPA-BNH_2 is useful for ^{10}B carrier on BNCT for glioma.

REFERENCES:

[1] A.H. Soloway *et al. Chem. Rev.*, **98** (1998) 1515-1562.
[2] Y. Hattori *et al. J. Med. Chem.*, **55** (2012) 6980-6984.
[3] Y. Hattori *et al. Peptide Science 2012*, 2013, 86-88.
[4] Y. Hattori *et al. Peptide Science 2013*, 2014, 177-180.

採択課題番号 25036　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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CO7-11

Radiobiological Responce of Conbination Effect, with Boron and Gadolinium Neutron Capture

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INTRODUCTION: Boron Neutron Capture Therapy (BNCT) has been meets with new situation of changing neutron source, reactor to accelerator system. On the other hand, the boron delivery drug that could clinical application is not developed more than 40 years. ^{157}Gadolinium has a large cross-section (255,000 $10^{-24}cm^2$) and Gadolinium based Neutron capture therapy (Gd-NCT) was discussed [1], but Gd-NCT produces gamma ray which have an average energy of 2.2 MeV with a range of several centimeters, and it is not used clinically because gamma ray contradicts a concept of the cell selectivity. Clinical BNCT trial for malignant brain tumor to use additional external gamma ray irradiation is performed and gives a promising result [1]. Therefore we focused on an advantage of the boron combination of the Gd compound that is clinically used. The development of gadopentetate dimeglumine, $[Gd(DTPA)(H_2O)]^{2-}$ prevented from the toxicity of Gd^{3+}.

EXPERIMENTS: Mouse colon cancer CT 26 cells, Chinese hamster fibroblast V79 cells, rat glioma C6 cells, and U251 human glioma cell lines were used. Boron agent was Bolonophenylalanine (BPA)-fructose solution and Gadolinium agent was gadopentetate dimeglumine (Gd-DTPA). Cells were prepared as a cell suspension, for the neutron targeting compounds, ^{10}B (BPA) at 0, 10, 20, and 40 ppm, and natural Gd (Gd-DPTA) at 0, 0.5, 5, 10 and 50 ppm, were combined. The neutron irradiation was performed with thermal neutrons at KUR for 90 min just after adding the Boron and Gadolinium agents. Thermal neutron fluence was measured by gold activation, and gamma dose was measured by TLD. The survival fraction was measured by colony forming assay.

RESULTS: Thermal neutron fluence was 3.9-4.1 $\times 10^{12}$ and TLD showed 1.0 to 1.7 Gy. As shown in Fig. 1, low dose of Gadolinium revealed additional cell killing effect with concentration-dependent manner. Because natural Gadolinium is containing about 15% of ^{157} Gd, 5 ppm Gadolinium meant 0.75 ppm of ^{157}Gd, 50ppm Gadolinium meant 7.5 ppm of ^{157}Gd. High concentration of Gadolin-ium had a shielding effect to thermal neutron [3]. Low dose Gadolinium and Boron combined radiobiological effect will be therefore warrants further investigation for clinical translation. .

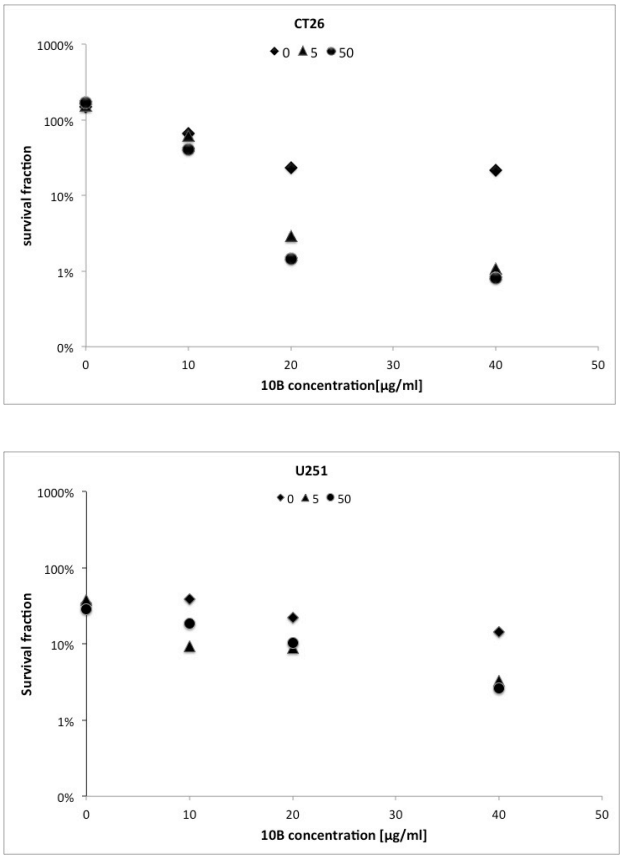

Fig. 1. (Upper) CT26 cell lines and (Lower) U251 cell lines survival fractions combined with Boron and Gadolinium. ◆ without Gadolinium ▲ containing 5 ppm of natural Gadolinium, ● containing 50 ppm of Gadolinium. Horizontal axis showing boron concentrations.

REFERENCES:

[1] A. Matsumura *et al.*, Neurol. Med. Chir. (Tokyo), **37**(1997) 327-31.
[2] T.Yamamoto *et al.*, Radiother. Oncol., **91** (2009) 80-4.
[3] A. Matsumura *et al.*, J Exp Clin Cancer Res., 24(2005) 93-8.

採択課題番号 25041　新規化合物および中性子捕捉反応による細胞生存試験および腫瘍・血管内皮増殖抑制効果　　共同通常

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CO7-12 Cancer Therapy of C6 Glial Tumor Model by BNCT and PDT Sensitized by a Boron-10 Rich Porphyrin Derivative (Compound-^{10}B)

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INTRODUCTION: The distribution of BNCT as one of clinical cancer treatments will be spread by the progress of the sensitizers and the compact instruments in future. We had developed a sensitizer with lich of F(16) and ^{10}B(44) elements in one molecules by collaboration research of Russian groups [1]. The molecule has both effects of photosensitizing and the other capture effects of neutron, which is easy water-soluble (<10 mM) and the photosensitizing effect is very high even at the low (μM) concentration. We had been studied photodynamic therapy (PDT) of cancer for 30 years using many porphyrin derivatives. There did not report yet about the combination study with PDT using one sensitizer.

EXPERIMENTS:

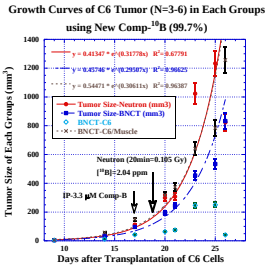
(1) Conditions for Administration: C6 rat glial tumor cells were transplanted under the skin of femora in the both sides of BALB-c-nu/nu strain nude mouse.

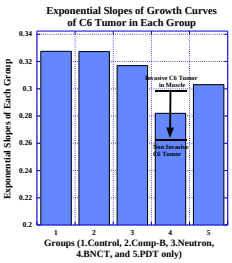
(2) Irradiation Dose: The neutron beam dose was 0.245Gy (0.105 Gy x 2.04 ppm = 0.214 Gy) for 20 min. The laser dose at 665 nm was 115.2 J/cm^2 for 10 min. The photodynamic irradiation was done at 36 hr after IP-injection of 3.3 μM Compound-B.

(3) Growth Curves Analysis and The Exponential Slopes of the Growth Curves: The tumor size were measured before and after the irradiations of Neutron and Laser for 30 days according the approximated volume formula (= **a** x **b** x **c** x **π / 6**) [Fig. 1]. The exponential slopes of these growth curves of C6 tumor in each group were compared, especially, between the cases of tumor tissues which in the invasive (N=3 tumors) or not (N=3 tumors) into muscle tissue [Figs. 1 and 2].

RESULTS: The Compound-^{10}B was used for BNCT and PDT at even low concentration of 3.3 μM-Compound-B (2.04 ppm in tumor tissue).

It was gotten the results of BNCT of compound-B as showing in Figs. 1 and 2. The anti-cancer effects of the BNCT of C6 tumors presented in the changing exponential slopes between each groups as shown in Figs. 1 and 2 which the slope of BNCT-compound-^{10}B was decreased 14% against the control. Especially, the growing slope in the case of non-invasive tumor was blocked 19% for the growing, which is shown clearly by lower curve in Fig. 1 comparing with in the case of the invasive into the muscle tissue in Fig. 2. It was found that the invasive tumor tissue into the muscle one was resistant for the compound-^{10}B-BNCT.





[Fig. 1]:Growth Curves of C6 Tumor (N=3–6) in Each Groups using New Compound-^{10}B.
Red color-1: Neutron only without Compound-^{10}B.
Blue color-2: BNCT (with Compound-^{10}B)
Water color:-3 BNCT (non-invasive tumors (N=3))
Black color-4: BNCT (invasive tumors (N=3) into muscle).
[Fig. 2] Exponential Slopes of Growth Curves of C6 Tumor in Each Groups (1:Control; 2:Compound-B only; 3:Neutron only; 4:BNCT; 5:PDT only)

CONCLUSION: A new compound-^{10}B was synthesized using boron-10 cages (carborane) to use as a capture of neutron and as a photosensitizer of LD laser. It was recognized of these sensitizing effects as an anti-tumor one using the experimental tumor model. Especially, it was shown to observed a resistance in the case of the invasive tumors into the muscle tissue.

Compound-^{10}B will be useful sensitizer for neutron, ionizing X-rays and laser lights (658 nm) in clinical cancer photo-diagnosis and treatments of cancer in future.

REFERENCES:

[1] D. Kaluzhny *et al.*, PLoS One, **6**(11**)** (2011) e27.

採択課題番号 25043　　BNCT と光線力学治療の併用療法に両用の増感剤を使用した癌培養細胞共同実験　　共同通常

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CO7-13 Evaluation of Biocompatible Polylysine Bearing BSH as a Polymeric Agent for Boron Neutron Capture Therapy

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INTRODUCTION: Boron Neutron Capture Therapy (BNCT) is a highly selective treatment that can target the tumor tissues without causing excessive radiation damage to the normal tissues. The success of BNCT depends on the delivery that ^{10}B compounds accumulate effectively and deeply inside the tumor cells. Clinically, boronophenylalanine (BPA) and borocaptate sodium (BSH) are currently used for BNCT although these agents have some disadvantages on accumulation or selectivity toward tumor tissue. We previously reported the development of a novel polymeric delivery system for BNCT by using biodegradable ε-PLL conjugated with ^{10}B-containing clusters (BSH) [1]. The polyion complex of this anionic BSH-containing polymer with cationic polyamine worked as safe and effective boron carrier into tumor tissues based on Enhanced Permeability and Retention (EPR) effect. However, the stability of polyion complex in blood stream seemed to be improved. Herein, biocompatible ε-PLL bearing BSH whose size is suitable for EPR effect without additional treatment such as polyion complexation.

EXPERIMENTS: The improved ^{10}B polymer (BPP) consisting of PEG-cross-linked ε-PLL and ^{10}B enriched sodium mercaptododecaborate (BSH) was synthesized as shown in scheme 1. The detail optimization on synthetic conditions such as molar ratio of cross-linkers such as diglycidyl ether and maleimido carboxylic acid succinimidyl afford desired BSH-bearing high molecular-weight ε-PLL with the suitable hydrodynamic size (100 nm) and zeta-potential (-13 mV). 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 (10 mg B/kg) were carried out with 200 μl of BPP or BPP complexes (1000 ppm B) for the evaluation of biodistribution and tumor accumulation. Boron concentration was measured by ICP-AES (Vista-MPX, Seiko instruments Inc.). Neutron irradiation (4 x 10^{12} fluences/cm^2) was carried out at Kyoto University Reactoer (5 kW, 18 min).

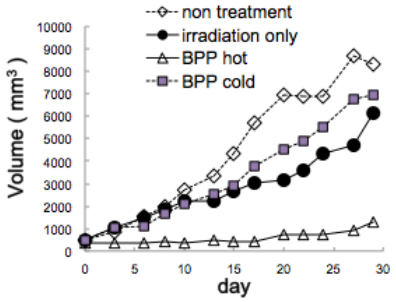
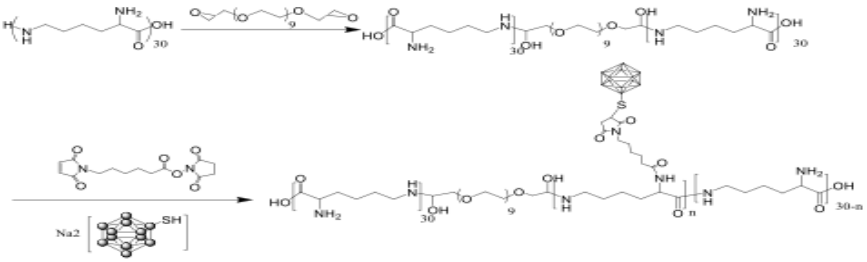


Fig. 1. Inhibition effect of CKA complex on metastasis to lung after BNCT.

RESULTS AND DISCUSSION: While the boron concentration in tissues other than liver decreased along with the disappearance of boron in the blood due to renal clearance, the boron concentration in tumor gradually decreased after injection. Although the boron concentration in tumor is still lower than that in kidney, it reached to about 7 ppm B. Maximum T/N ratio was observed at 12 h after injection. Significant tumor suppression effect was observed with BPP and neutron irradiation (Fig. 1).

REFERENCES:

[1] M. Umano *et al.*, *Appl. Radiat. Isot.*, **69** (2011) 1765.



Scheme

採択課題番号 25051　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、櫻本昌士、河崎　陸、飯塚俊輔（阪府大・21 研究機構）切畑光統
（京大・原子炉）小野公二、増永慎一郎、櫻井良憲

CO7-14 Characteristics of Radiation-Resistant Real-Time Neutron Monitor for Accelerator-Based BNCT

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INTRODUCTION: Recently, projects of an accelerator-based Boron Neutron Capture Therapy (BNCT) have been carried out in several areas in Japan, which aims at the advanced medical care. At the Ibaraki Prefecture, a BNCT project has been carried out by a collaboration of University of Tsukuba, KEK, JAEA, Hokkaido University and Ibaraki Prefecture. In this project, we have developed a prototype scintillator-based detector as a candidate to the real-time monitor. The detector is a Scintillator with Optical Fiber (SOF), which has scintillator on the tip of plastic optical fiber. The SOF detector has two sensing fibers, i.e., one has plastic scintillator with LiF powders on the tip and the other has only plastic scintillator. Thus one can obtain neutron signals by subtracting signals without LiF powders from those with LiF powder. However, in the irradiation test performed at Japan Research Reactor No.4 (JRR-4) of JAEA, degradation of output from the SOF detector was observed after irradiation of thermal neutron fluence of $1x10^{15}$ n/cm^2[1]. It can be considered that the degradation should originate from the radiation weakness of plastic fiber itself. Thus, we have fabricated a new detector consisting of quartz optical fibers that have excellent radiation-resistant characteristics. The aim of this experiment is to estimate and validate the performances of our scintillation detector developed as a candidate to the real-time monitor for the accelerator-based BNCT.

EXPERIMENTS: The developed SOF detectors were irradiated at Heavy Water Neutron Irradiation Facility (HWNIF) of KUR. In this experiment, the pulse height spectrum and the linearity performance with the SOF detector were measured. On the other hand, to evaluate the degradation characteristics, the irradiation samples which were made from the optical fiber and the scintillator using the developed SOF detector were irradiated at Slant of KUR. The degradation ratios were evaluated from the counting ratios with X-ray irradiation before and after the slant experiment.

RESULTS: Figure 1 shows the pulse height spectrum by the plastic scintillator with and without the ^{6}LiF neutron converter of the SOF detectors consisting of quartz optical fiber and plastic optical fiber. As shown in Fig. 1, the signals from neutron are obviously observed over 500 channels. Fig.2 shows the degradation ratios by the quartz fiber, plastic fiber and plastic scintillator. As shown in Fig. 2, the change of the degradation ratio with the quartz fibers is small. But, the degradation ratio is large in the early irradiation. Fig. 3 shows the result of the linearity performance test with the SOF detector consisting of quartz optical fiber. As shown in Fig. 3, a good linearity was observed. From these results, we confirmed that this SOF detector consisting of quartz optical fibers is useful as the real-time monitor for the accelerator-based BNCT.

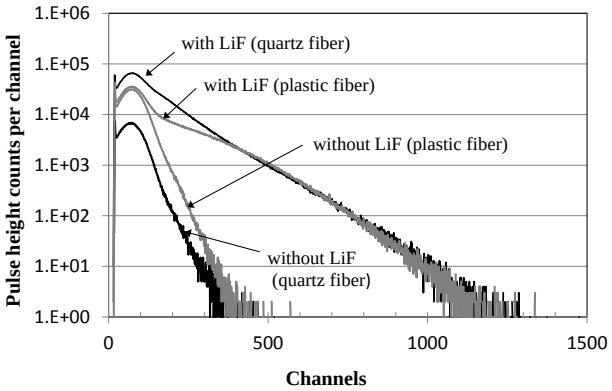

Fig. 1 Pulse height spectrum of SOF detector

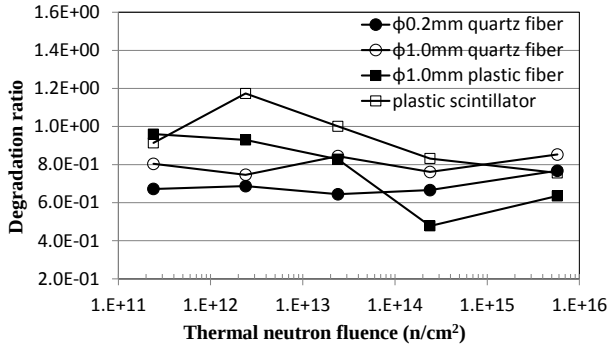

Fig.2 Degradation ratios of the quartz fiber, plastic fiber and plastic scintillator

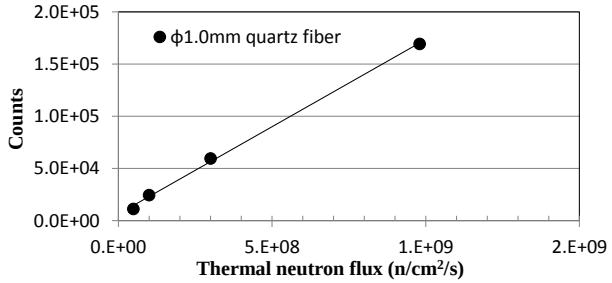

Fig.3 Result of the linearity performance test with the SOF detector consisting of quartz optical fiber

REFERENCES:

[1] M. Komeda *et al.*, Appl. Radiat. Isot., **67** (2009) S254-S257.

採択課題番号 25057　加速器 BNCT 中性子照射場測定用中性子検出器の特性測定および劣化・損傷に関する実験的検討　共同通常

（原子力機構・研究炉加速器管理部）中村剛実、坂佐井馨、中島宏、柴田徳思
（京大・原子炉）高宮幸一

CO7-15 Application of B_4C Nanoparticles for Boron Neutron Capture Therapy

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INTRODUCTION:

We investigated the possibility of intra-tumoral administration of B_4C as a drug delivery system (DDS) in boron neutron capture therapy (BNCT). B_4C nanoparticles injected directly into the tumor are expected to reside in the tumor for longer period compared to other boron compounds such as boronophenylalanine (BPA) and borocaptate sodium (BSH). Retention of B_4C at 24 or 72 h after intra-tumoral administration of B_4C may make it possible to carry out two or three-fractionated BNCT in a week.

EXPERIMENTS:

In this preliminary experiment, four BALB/C nude mice were used. Since the tumor cells inoculated in the hind legs did not grow to the size available for intratumoral injection, B_4C nanoparticles were injected in the muscles of both hind limbs.

B-10 rich B_4C nanoparticles ($^{10}B_4C$) were prepared for intra-muscular injection at a dose of 1,000 μg B_4C /50 μl saline. For intra-muscular injection, 34-gauge needles were used.

10B-concentrations were measured at 0.5 and 18 h after B_4C-nanoparticle injection with prompt gamma-ray analysis (PGA). In PGA, the hind limbs were set to receive neutron beam. The body of the mouse was covered by a box made by LiF which prevent the gamma-ray emission from the body.

RESULTS:

B_4C nanoparticles were successfully injected into the muscles in both hind limbs using a 34-gauge needle. Results on 10-B concentrations in the hind limbs were shown in Table 1.

Table 1. 10-B Connentration in the hind legs after intra-tumoral injection of $10B_4C$ nanoparticles

Injection site	Elasped time after injection	
	0.5 h	18 h
1-Rt. Hind leg	35.3 ppm	136.9 ppm
1-Lt. Hind leg	25.3 ppm	97.6 ppm
2-Rt. Hind leg	10.9 ppm	17.6 ppm
2-Lt. Hind leg	21.2 ppm	17.5 ppm
3-Rt. Hind leg	29.9 ppm	33.5 ppm
3-Lt. Hind leg	418.4 ppm	542.8 ppm
4-Rt. Hind leg	534.1 ppm	431.9 ppm
4-Lt. Hind leg	366.5 ppm	451.5 ppm

The results shown in Table 1 indicated retention of the nanoparticles at 18 h after the injection.

Although the same amount of B_4C nanoparticles were injected into the muscles, the values for 10-B concentrations widely ranged from 10.9 to 534.1 ppm at 0.5 h after injection. These results might be attributed to injection of unequal amounts of B_4C due to coagulation of the nanoparticles in the syringe.

In some hind limbs, 10-B concentrations at 18 h were greater than those at 0.5 h. Inaccurate setting of the hind limbs at 0.5 and 18 h in PGA were responsible for these inconsistent results since 10-B concentrations depended on neutron- irradiated volumes in the hind limbs.

DISCUSSION:

The result in this preliminary experiment suggests the long-period retention of B_4C nanoparticles by intra-tumoral injection of the nanoparticles.

There are many issues to be investigated toward clinical application of B_4C nanoparticles in BNCT. The most important issue is toxicity and pharmacokinetics of the nanoparticle after intra-tumoral injection. Toxicity of nanomaterial such as carbon-nanotube has been reported. Another important issue is the microdistribution of the nanoparticles in the tumor following intra-tumoral injection. In BNCT, inhomogeneous distribution of 10-B atoms causes low-dose irradiated area in the tumor, which leads to local recurrence.

A head and neck cancer may be a good candidate for B_4C-BNCT, since intratumoral injection is easily performed compared to deeply-situated cancers. We have planned to carry out fractionated *in vivo* BNCT experiments using intratumoral injection of $^{10}B_4C$ nanoparticles.

採択課題番号 25078　炭化ホウ素粒子を利用した硼素中性子捕捉療法の可能性　プロジェクト
（北海道大学・工）越崎直人　（産総研）石川善恵（京大原子炉実験所）鈴木 実

CO7-16 Investigation of Intracellular Boron Distribution by High Position Resolution Alpha Autoradiography

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K. Takamiya, A. Maruhashi and K. Ono

Research Reactor Institute, Kyoto University

INTRODUCTION: It is important to develop new boron compounds for Boron Neutron Capture Therapy (BNCT). The accumulation ratio of the tumor to the normal tissue of the boron compound which can be used now is about 8 at the maximum. For an expansion of BNCT adaptation, a boron compound with tens times accumulation ratio is desired. However, the biological effectiveness of a boron compound cannot be determined only by an accumulation ratio. Because the boron concentration measured by ICP or prompt gamma ray analysis is the average value of the group of cells with different uptake of boron compound. If cells with same boron concentration are irradiated by same neutron fluence, the biological response changes greatly with the kind of boron compounds. In order to confirm the effect of boron compound, tumor-bearing mouse administrated with boron compound and irradiated with neutrons should be bred for a long time. Then, the prediction of the characteristic of boron compound is performed by comparing with the boron micro-distribution in a cell. Alpha autoradiography is used as a method of measuring boron micro-distribution in a cell [1,2]. In this research, the high position resolution and simple measurement technique of intracellular boron distribution have been developed.

EXPERIMENTS: At alpha autoradiography, to obtain image of etched pits, corresponding to reaction position of $^{10}B(n,\alpha)^{7}Li$, CR-39 track detector is treated with chemical etching process. During the chemical etching process, tissue sample mounted on CR-39 is vanished. In order to merge the fluorescence cell image and etched pits image, the crossed scratch marker is used as reference position. The shape of etched pits includes the information of the emitted angle of charged particles of $^{10}B(n,\alpha)^{7}Li$ reaction. If the shape of etched pits are true circle, it is shown that charged particles perpendicularly enter into CR-39 with no the deviation between the etched pits position and reaction point. On the other hand, charged particles enter into CR-39 with the given angle and the deviation between etched pits positon and reaction point, the shape of etched pits become ellipsoidal. In order to obtain high position resolution image of etched pits, the events of true circle were chosen. The brief description about this method is shown in the reference [3]. Demonstration test for the mouse brain that was administrated with BPA of 500 mg/kg was performed. After one hour injection of BPA, frozen section of brain with the thickness of 10 μm was set on CR-39. CR-39 was irradiated with thermal neutron using thermal column at KUR. Total neutron fluence was $10^{12}(cm^{-2})$. After the irradiation, brain tissue sample was stained by propidium iodide solution to obtain cell nuclear image using fluorescence microscope. CR-39 was etched by the 7N NaOH solution on 70ºC. Etched pits image was observed by the conventional microscope.

RESULTS: Figure1 shows the etched pits image merged by cell image strained by propidium iodide. Etched pits was selected by using the information of circularity of etched pits. It was founded that etched pits were located near the cell nucleus. This method can simply and rapidly observe the boron micro distribution in cell with high position resolution using conventional microscope and CR-39.

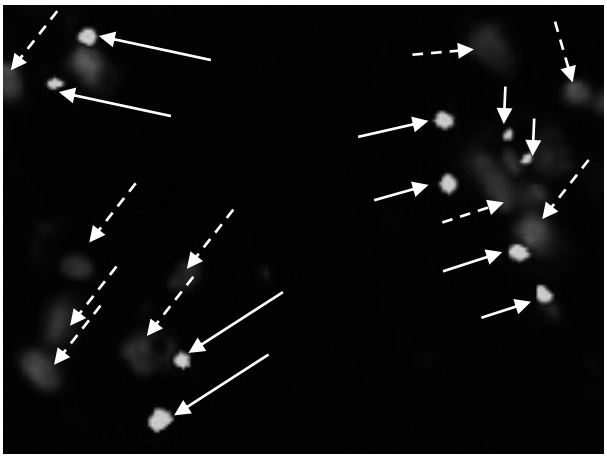

Fig.1. ^{10}B micro-distribution of cell of mouse brain. Dot line arrow shows etched pits with the perpendicular incident. Solid line arrow shows the cell nucleus image strained by propidium iodide solution.

REFERENCES:

[1] S. Altieri, S. Bortolussi, P. Bruschi, *et. al.,* Nucl. Technol. Appl., Radiat. Isot., **66** (2008), 1850– 1855.
[2] K.Ogura, A. Yamazaki, H. Yanagie, *et.al.,* Radiat. Meas., **34** (2001) 555–558.
[3] H. Tanaka, Y. Sakurai, *et. al.,* J. Radiat. Res., **55** (2) (2014) 373-380.

採択課題番号 25080　　高分解能α-ARG によるホウ素化合物のミクロ分布の探索と　一般通常
放射線組織生物学の新規開拓 通常　（京大・原子炉）田中浩基、櫻井良憲、鈴木実、増永慎一郎、高宮幸一、丸橋晃、小野公二

CO7-17 Design and Preparation of Boron Cluster-containing Nanoparticles for High Performance Nanoparticle Assisted Boron Neutron Capture Therapeutics

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[2]*Master's School of Medical Sciences, Graduate School of Comprehensive Human Sciences, University of Tsukuba*
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INTRODUCTION

The success of boron neutron capture therapeutics (BNCT) is dependent on the boron delivery system to achieve high specific tumor accumulation, keeping low toxicity. However, the current low molecular weight boron compounds for clinical trial of BNCT are excluded rapidly from the blood circulation, which causes non-specific dispersing in whole body. In order to obtain therapeutic effect, high dose is required by using this kind compound, that increase the risk of suffering side effect such as renal toxicity. Recently, it is confirmed that highly dispersed nanoparticles with several tens of nanometers in diameter tend to accumulate in tumor environment due to the leaky neovascularization and immature lymphatic systems, which is called enhanced permeability and retention (EPR) effect. In this work, we designed and prepared a novel boron cluster-containing nanoparticle that performed high tumor specific accumulation tendency, enhanced tumor therapeutic effect and suppressed side effect.

EXPERIMENTS

Preparation of boron-containing redox nanoparticle

4-Amino-2,2,6,6-tetramethylpiperidine-N-oxyl (4-amino-TEMPO) was introduced to the hydrophobic polystyrene segment of poly(ethylene glycol)-b-poly(methylstyrene) (PEG-b-PMS) to prepare PEG-b-polycation (PEG-b-PMNT) via an amine linkage. ^{10}B enriched sodium mercapto- dodecaborate (BSH) was introduced to the polystyrene segment of PEG-b-PMS separately to prepare PEG-b-polyanion (PEG-b-PMBSH) via a thiol linkage. BNP was prepared by mixing PEG-b-PMBSH and protonated PEG-b-PMNT phosphate buffer saline (PBS) solutions.

Preparation of tumor bearing mice (BLAB/c, male, 6-week-old)

Tumors were prepared in mice legs by hypodermic injection of colon-26 cells (1,000,000 cells per mouse). This procedure was carried out a week before the neutron irradiation.

Neutron irradiation

The administration of the BNP were carried out via tail vein 3 d before the neutron irradiation (dose of ^{10}B was 5 or 15 mg/kg). BPA was used as positive control by giving dose of ^{10}B at 40 mg/kg 2.5 h before the irradiation. The mice were then irradiated thermal neutrons for 40 min at a rate of 1.8×10^{12} neutrons/cm^2). After the neutron irradiation, the tumor sizes of mice were measured for 31 d. Whole blood of each group was collected 3 d after irradiation.

RESULTS

Evaluation of obtained boron-containing redox nanoparticle

The size of the BNP was evaluated by DLS. The result showed that the average size of BNP was ca. 35 nm and the dispersion property of the particles is quite stable enough that no aggregation nor disassembly was observed after incubation with the exist of mice plasma for 2 days under 37 C.

Neutron Irradiation:

The tumor grew up to 7 cm^3 after 31 d in PBS treated groups (with/without irradiation, n = 3). On the other hand, the growth was effectively suppressed in the mice treated with BNP with the irradiation of thermal neutron (average size was 3.6 and 4.8 cm^3, while the dose of ^{10}B was 15 and 5 mg/kg, n = 3). The suppression of tumor growth was also observed in the mice treated by BPA irradiation of thermal neutron (n = 3). Dose of ^{10}B was 40 mg/kg, (average size was 5.3 cm^3). By using much lower dose, 5 mg/kg (5 ppm boron in tumor tissue), we got similar or even better therapeutic effect compared with BPA. Furthermore, we observed that high white blood cell (WBC) level in BPA treated group, while the WBC in BNP treated group (15 mg/kg) almost similar as the one in the non-tumor healthy mice. This result inspired us to believe that BNP not only enhanced the therapeutic effect, but also suppressed the side effect during BNCT. The molecular biology mechanism of this phenomenon is under going currently.

採択課題番 25085　　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

（筑波大・数理）長崎幸夫、高 振宇、堀口諭吉（筑波大・人間）松村 明、中井 啓、山本陽平
（京大・原子炉）鈴木 実、小野公二 （東大院・工）柳衛宏宣（京大・RIセ）木村寛之

CO7-18 Precise Determination of Boron Location in Tissue via E-Tracks

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In this report our basic research for e-track are presented instead of paucity of annual progressive results for BNCT agents. For bio-distribution study of boron atom in tissue section, α-track using solid state track detector (SSTD) have been investigated. We present one of how to determine micro-distribution of boron in ultra thin section using electron microscopic α–track (e-track).

Experiment 1: Ultra thin SSTD was prepared using formval membrane method using cellulose nitrate solution. After α ray bombardment by RaD+E isotope, the SSTD was etched in 1N NaOH solution at RT. Various shapes of etched tracks were observed via electron microscope (Fig.1).

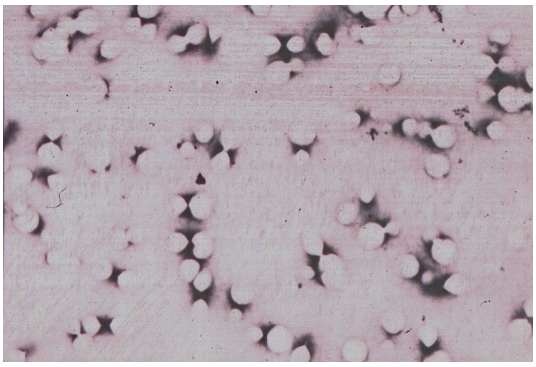

Fig. 1 Electron microscopic views of shell shaped e-tracks.

E-tracks strongly geometrically related to the incident angle and direction of α rays (Fig.2).

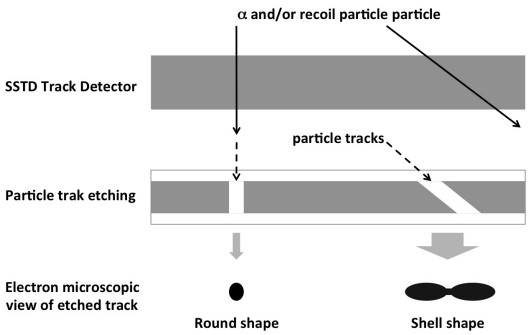

Fig. 2 Relation ship between particle incidence of e-tracks.

Experiment 2: Ultra thin resin containing 1000ppm ^{10}B was mounted on the SSTD and was bombarded with thermal neutron to produce α and/or recoil 7Li particles in the resin. The free surface of the SSTD has been etched and e-tracks are shown in Figure 3.

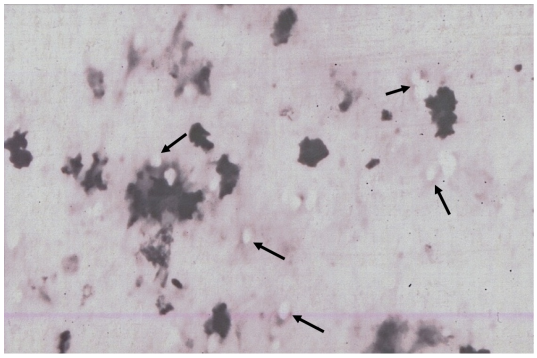

Fig. 3 Electron microscopic views of semi-shell form e-tracks (*arrow head*).

Geometric relationship between the shape of e-track and the boron location in tissue is shown in Figure 4.

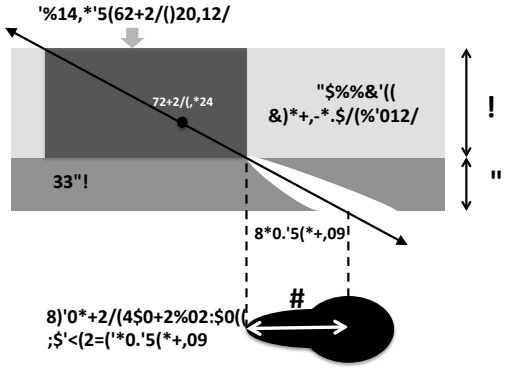

Fig. 4 Relation ship between boron location and e-track. (D: thickness of ultra thin section of tissue, ca 100nm, T: thickness of SSTD, L: tangential length of the tracks.)

In conclusion, in our experimental condition using ultra thin SSTD in the thickness of ca.100nm, the possible location of boron atom in tissue can be determined with an accuracy of ca.100nm.

CO7-19 A Case Report: Current Status of GBM 33Mo after BNCT

M. Takagaki , T. Tachizawa [1], H. Tanaka[2], Y. Sakurai[2], M. Suzuki[2], A. Maruhashi[2], N. Kondo[2], SI. Masunaga[2], and K. Ono[2]

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Case Report: Grade-IV glioma 56y female was treated via BPA-based BNCT on Oct. 6, 2011.
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).

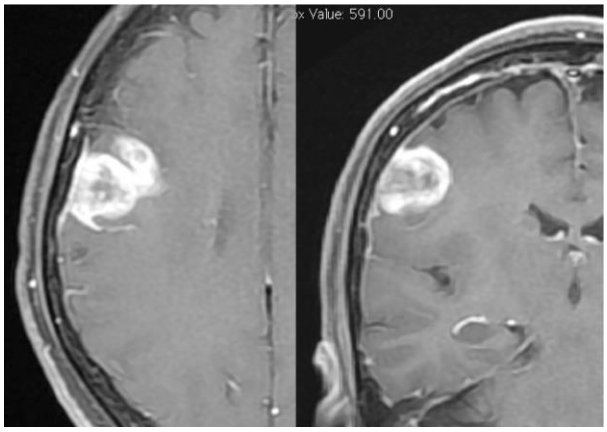

Fig.1 Magnetic resonance image of the patient before BNCT.

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 (Cyber Knife) on the deepest lesion with less than 30Gy. The cytological findings of the repeatedly removed fluid of the cystic cavity improved Class IV to Class II. The KPS was stable 70 at home. The cystic cavity was still enhanced in stable configuration 7 Mo after BNCT (Fig. 2).

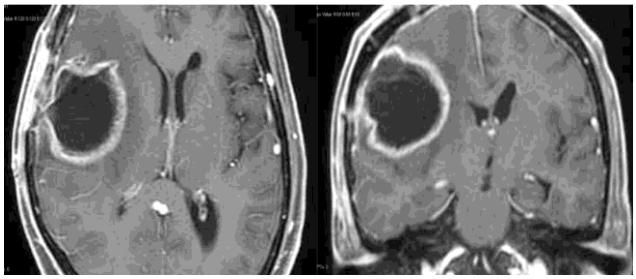

Fig. 2 Magnetic resonance image 7Mo after BNCT.

1y after BNCT, local control of the tumor has been still poor even after Tomo-Therapy+. Tumor extirpation and TMZ-Therapy has been done repeatedly.
Patient's consciousness is clear but performance status has been getting worth, KPS=30.
A completely non-invasive and immediate BNCT followed by non-surgical MRI assessment of the tumor malignancy should be planned. Perhaps no any surgery followed by immediate BNCT might be one of the best treatment option for malignant gliomas.

採択課題番号 25087 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
（藍野学院）高垣政雄（関東労災病院）立澤孝幸（シミズ病院）大山憲治
（京大・原子炉）小野公二

CO7-20 Clinical Study on Boron Neutron Capture Therapy (BNCT)

M. Suzuki, S. Masunaga, K. Ono, N. Kondo,
M.Narabayashi, T. Kinashi, Y. Sakurai, H. Tanaka,
A. Maruhashi and M. Ishikawa[1]

Research Reactor Institute, Kyoto University
[1]Hokkaido University, Graduate School of Medicine,
Research Center for Cooperative Projects

Patient characteristics

In this study, twenty boron neutron capture therapy (BNCT) were carried out for sixteen patients. Three patients with malignant pleural mesothelioma (MPM) and one with recurrent head and neck cancer received BNCT twice.

Table 1 shows patient characteristics.

Table 1. Patient characteristics

	n
Total	17
Gender	
Male	11
Female	6
Age	
11-20	2
21-30	0
31-40	3
41-50	0
51-60	5
61-70	4
71-80	3
Tumor sites	
Head and neck	10
Mesothelioma	4
Lung	1
Liver	1
Brain	1

We will follow up the medical status or images of the patients.

採択課題番号 25089　　中性子捕捉療法の臨床的研究　　共同通常
（京大・原子炉）鈴木　実、増永慎一郎、小野公二、近藤夏子、木梨友子、櫻井良憲、田中浩基、丸橋　晃
（北大・医）　石川正純

CO7-21 Application of Gd-DTPA-Incorporated Calcium Phosphate Nanoparticles as Neutron Capture Therapy Agent

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INTRODUCTION: The use of gadolinium as neutron capture therapy (NCT) agent has been getting attention because of its high thermal neutron cross section (255 000 barns). Compared to short range secondary particles produced after neutron capture by ^{10}B isotope, which is currently used for clinical trial of NCT, gadolinium neutron capture reaction (Gd-NCR) results in release of gamma rays, which makes it a favorable charac-teristic because the location of the element is not critical with regard to target cell due to their longer flight ranges. Another advantage of Gd-NCT is that several gadolinium-based com-pounds are already approved in clinical as MRI contrast agent.

In our previous study, we investigated the use of gadoteridol-entrapped liposome as NCT agent and the results had shown significant tumor growth suppression after neutron irradiation[1]. This has given the motivation to evaluate PEGylated calcium phosphate nanoparticles incorporating Gd-DTPA (Gd-DTPA/CaP) developed by P. Mi et al., which has been proven to retain high stability in physiological[2] [3].

EXPERIMENTS: We performed *in vivo* evaluation of Gd-DTPA/CaP for further investigation of this compound as a feasible Gd-NCT agent. We prepared tumour-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-DTPA/CaP was injected into each mouse and thermal neutron irradiation was performed with 2 x 10^{12} 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 (Fig. 1).

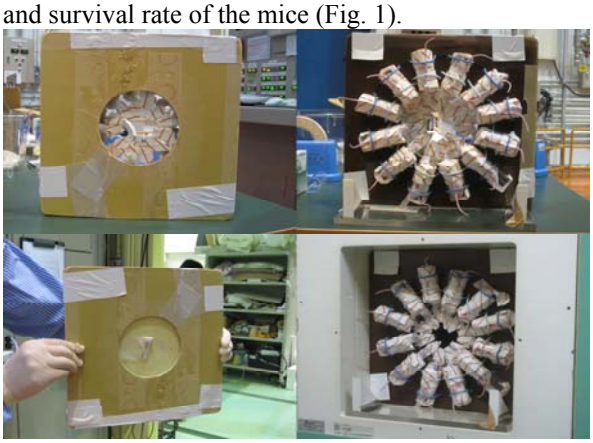

Fig. 1 Set up position for thermal neutron irradiation to tumour-bearing mice.

RESULTS: Gd-DTPA/CaP-injected mice revealed about two times higher tumor growth suppression compared to non-treated group as shown in Fig.2. There was no acute toxicity in the treated mice. The effectivity of Gd-DTPA/CaP as Gd-NCT agent is quite promising, and further investigation is necessary to determine optimum combination between Gd-DTPA/CaP and neutron fluence applied for the treatment.

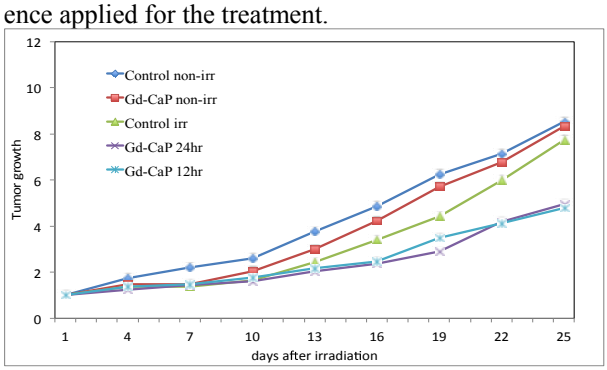

Fig. 2 Comparison of tumor growth suppression between Gd-DTPA/CaP-injected group and non-treated (control) groups.

REFERENCES:

[1] N. Dewi, *et al.*, Biomed Pharmacother, **67** (2013) 451-7.
[2] P. Mi, *et al.,* J Control Release, **174** (2014) 63-71.
[3] Haracio C, *et al.,* Science Translational Medicine, (2011)

採択課題番号 25099　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研究　共同通常

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CO7-22 Neutron Dose Estimation & Evaluation on Neutron Capture Therapy for Hepatocellular Carcinoma Using Intra-Arterial Administration of Boron-Entrapped Water-in-Oil-in-Water Emulsion

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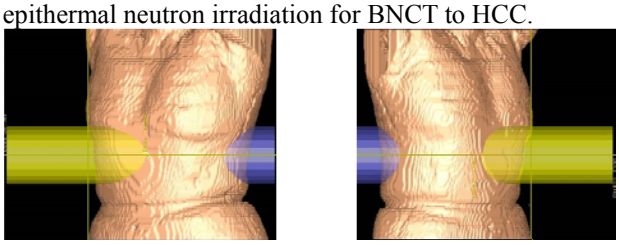
INTRODUCTION: Hepatocellular carcinoma (HCC) is one of the most difficult to cure with operation, chemotherapy, or other combinational therapies. Water-in-oil-in-water (WOW) emulsion has been used as the carrier of anti-cancer agents on intra-arterial injections (IA) in clinical. We prepared ^{10}BSH entrapped WOW emulsion by double emulcifying technique using iodized poppy-seed oil (IPSO), ^{10}BSH and surfactant, for selective IA to HCC, and performed simulations of the irradiation in order to calculate the dose delivered to the patients for boron neutron-capture therapy (BNCT). WOW emulsion had been administrated with IA via proper hepatic artery on VX-2 rabbit hepatic tumour models. We simulated the irradiation of epithermal neutron and calculate the dose delivered to the tissues with JAERI Computational Dosimetry System (JCDS) using the CT scans of a HCC patient.

According to the rabbit model, the boron concentrations (ppm) at day 3 after IA in tumour, normal liver tissue, and blood is 61.7, 4.3, 0.1, respectively. Normal liver biologically weighted dose is restricted to 4.9 Gy-Eq (CBE; liver tumour: 2.5, normal liver: 0.94); the maximum, minimum and mean tumour weighted dose are 43.1, 7.3, and 21.8 Gy-Eq, respectively, in 40 minutes irradiation[1]. In this study, we evaluated the two direction effects of epithermal neutron irradiation in the situation with IA of ^{10}BSH entrapped WOW emulsion.

EXPERIMENTS: The irradiation simulation was performed with CT scans of a patient existing a 7 cm tumor in the left lobe of liver using JCDS. We performed the simulation with two directional epithermal neutron irradiation, and each beam regulated as 4.9 Gy-Eq for normal liver tissue in the same situation using ^{10}BSH WOW emulsion. We evaluated the contents for Neutron Dosimetry; neutron fluence of hepatic tumour, and neighbour normal tissue.

To decrease side effects to neighbor normal organs, the biologically weighted dose to normal liver was limited to 4.9 Gy-Eq, the biologically weighted dose to left lung was limited to 2.3 Gy-Eq, the biologically weighted dose to right lung was limited to 2.9 Gy-Eq, and the max skin biologically weighted dose was limited to 3.2 Gy-Eq, according to the experience of BNCT for HCC by Suzuki et al.[2].

RESULTS: We evaluated the two direction effects of epithermal neutron irradiation for BNCT to HCC.



Frontal view
1: Beam irradate from right 60° angle
2 : Beam irradate from left 40° angle
Neutron Beam
Φ12cm Collimation, Epithermal neutron mode Boron concentration with WOW emulsion
Tumour : 61.7ppm (CBE : 2.5), Normal Liver : 4.3ppm (CBE : 0.94), Blood : 0.1ppm

In the two dimensional epithermal neutron dosimetry (4.0×10^{12} n/cm^2), mean tumour RBE dose and minimum tumour RBE dose are 23.5 and 9.9 Gy-Eq, respectively in 51.4 min and 56.2 min irradiation. The result means that two dimensional irradiation could increase the average irradiational dose. The mean and minimum tumour RBE dose are in left lung, right lung, liver, are 0.7 / 0.2, 0.9 / 0.2, 2.1 / 0.5, respectively. The maximum skin dose was 3.8 Gy-Eq.

We hope to perform the evaluations of several epithermal neutron irradiation planning for the clinical trials of BNCT for HCC patient.

REFERENCES:

[1] H. Yanagie, *et al.*, Appl. Radiat. Isot., **9** (2011) 1854-7.
[2] M. Suzuki, *et al.*, Jpn. J. Clin. Oncol., **37** (2007) 376-81.

採択課題番号 25100　中性子捕捉療法の一般外科領域癌への展開に向けた臨床的研究　　共同通常

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CO7-23 Application of B_4C particle to Boron Neutron Capture Therapy

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INTRODUCTION: B_4C nano particles are produced by liquid phase laser irradiation method [1]. The diameter of the particle is 200 nm. Sonoporation is a low ultrasound which makes small transient holes in the cell membrane and introduces external materials such as drug and gene into the cell [2]. In this study, we investigated whether sonoporation could be used to introduce B_4C particles into the oral squamous cell carcinoma (SCC) cells.

EXPERIMENTS: SAS cells derived from oral SCC were used. Cells were exposed to thermal neutron at Kyoto University Reactor (KUR). In other words, we measured the boron concentration by the neutron-induced prompt gamma-ray analysis [3]. An ultrasound machine, Sonitron 2000V, and a microbubble, SV-25, were used [4].

RESULTS: After sonoporation in the presence of microbubbles, small holes (1-2 μm) were observed on the cell surface by a scanning electron microscope. The cell boron concentration in the groups with B_4C was higher than that in the group with neutron alone. B_4C in combination with sonoporation (ultrasound in the presence of microbubble) had most highest boron concentration (Tab. 1). The tumor of mouse boron concentration in the groups with B_4C was higher than that in the group with neutron alone. B_4C in combination with sonoporation (ultrasound in the presence of microbubble) in tumor had most highest boron concentration (Tab. 2).

CONCLUSION: B_4C particle can be used as a boron compound for BNCT.

Table. 1 Boron concentration in SAS cells and physical dose.

Group	Boron concentration (ppm)	Physical dose (Gy)
N	0	0.97
B_4C+N	1.42±0.39	1.28±1.05
B_4C+US+N	2.05±0.56	1.41±1.09
B_4C+MB+US+N	4.45±0.76	1.93±1.13

Table. 2 Boron concentration in tumors and physical dose.

Group	Boron concentration (ppm)	Physical dose (Gy)
N	0	2.05
B_4C+N	18.57±2.66	13.06±3.63
B_4C+MB+US+N	31.48±6.76	20.71±6.06

REFERENCES:

[1] Y. Ishikawa *et al.* Journal of Nanoscience Nanotechnology **8** (2010) 5467-70.
[2] J M. Escoffre *et al.* Current Gene Therapy **13** (2013) 2-14.
[3] Y. Fujita *et al.* Radiation Oncology **4** (2009) 63.
[4] M. Shintani *et al.* Virology Journal **8** (2011) 446.

採択課題番号 25101　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的研究　共同通常（阪大・歯）岩上隆紀、多田晋也、加藤逸郎、由良義明（済生会千里病院）山本直典（東大阪総合病院）藤田祐生(京大・原子炉)田中浩基、櫻井良憲、増永慎一郎、鈴木 実、丸橋 晃、小野公二

CO7-24 Microdosimetry of Neutron Field with Low-Enriched Uranium at Kyoto University Reactor

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INTRODUCTION: Kyoto University Reactor was shut down in 2006. After that, the fuel has been changed from high-enriched uranium of 93% to low-enriched uranium of 20%. The reactor has been restarted from 2010. The neutron energy spectrum has not hopefully unchanged by this change. However, there are lacking of measurements. Our group had accumulated data of microdosimetric studies at BNCT beam therapeutic beam before the changes of the fuel enrichment [1,2]. In this study, microdosimetric measurements are carried out to estimate BNCT neutron beam for the low-enriched fuel operation and compared with previous spectra.

EXPERIMENTS: Microdosimetric single event spectrum for the BNCT clinical irradiation filed (epithermal neutron mode: CO0000 and mixed neutron mode: OO0000) [3] has been measured with carbon walled proportional counter (CWPC) with a condition of a 1 μm site size. In order to take wide lineal energy range, signals from TEPC were divided into two types of amplifier-gain (high-gain and low-gain). Pulse heights were analyzed by two USB-MCAs (Kromek Co LTD, Kspec). Pulse height distribution of two types of gain have been connected and microdosimetric single event spectrum have been obtained.

RESULTS: The microdosimetric single event spectrum of *yd*(*y*) for epithermal neutron mode: CO0000 and mixed neutron mode: OO0000 are shown in Fig. 1. The broad structure below 20 keV/μm of the both modes are due to the (n,γ) reaction by thermal neutrons. These gamma-rays are identified by the CWPC. However the electric nose revel could not be reduced in this measurement. Therefore the relatively higher cut off for lineal energy was used. We have to improve noise level in future measurement.

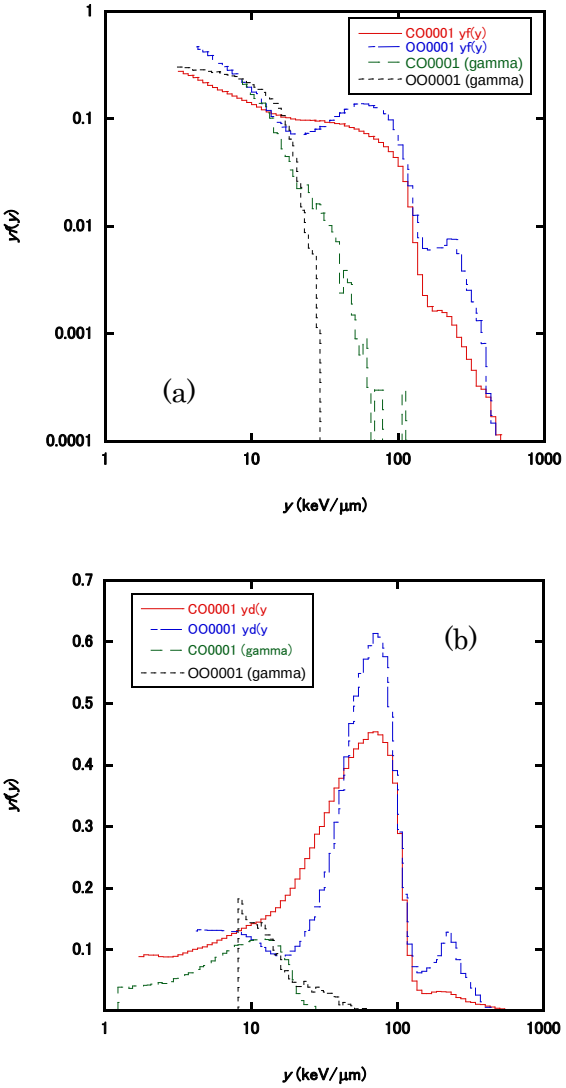

Fig. 1 (a) *yf*(*y*) and (b) *yd*(*y*) for CO0001 and OO0001 mode. Gamma shows results of CWPC.

REFERENCES:

[1] Y. Onizuka, S. Endo, M. Ishikawa, M. Hoshi, M. Takada, T. Kobayashi, Y. Sakurai, H. Utsumi, S. Uehara, N. Hayabuchi, N. Maeda, T. Takatsuji, and K. Fujikawa, "Microdosimetry of epithermal neutron field at the Kyoto University Reactor," Radiat. Prot. Dosim. 99, 383–385 , 2002.

[2] S. Endo, Y. Onizuka, M. Ishikawa, M. Takada, Y. Sakurai, T. Kobayashi, K. Tanaka, M. Hoshi, K. Shizuma, Microdosimetry of neutron field for boron neutron capture therapy at Kyoto University Reactor, Radiat. Prot. Dos. 110, 641-644, 2004.

[3] Sakurai, Y., Kobayashi, T., Ono, K. and Kanda, K. The Irradiation Characteristics of the Upgraded Heavy Water Facility of the Kyoto University Reactor. In: Advances in Neutron Capture Therapy, Vol. I, Medical Physics, Eds B. Larsson, J. Crawford, and R. Weinreich, (Amsterdam: Elsevier) pp. 316–320 (1997).

採択課題番号 25106　低濃縮燃料移行後の BNCT 医療照射場のマイクロドシメトリ　　共同通常
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CO7-25 Boron Neutron Capture Therapy for Recurrent Head and Neck Cancer

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INTRODUCTION: 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 RHNC. 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 cancer 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 began treating our patients with BNCT using BPA alone [3,4]. In this report, we summarize our clinical results of RHNC cases treated by BNCT using BPA alone in 2014 at the University of Tsukuba.

MATERIALS and METHODS: Between April 2014 and May 2014, Four patients with RHNC (Two squamous cell carcinomas, one Adenoid cystic carcinoma, and one Rhabdomyosarcoma) received BNCT using BPA alone as salvage treatment, 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 recurrent cancer 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 (12 cm×12 cm). 3) Neutron flux measurement using gold wire 10 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 1 months after BNCT (0.3-2 months).

RESULTS: One patient demonstrated regional complete response (CR). We were not able to evaluate other cases, and this is because it had a too short observation period after the treatment. All patients had no acute 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 RHNC. Although this is a report of only 4 patients, and 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.

REFERENCES:

[1] Y. Mishima *et al.*, Pigment Cell Res., **1** (1973) 215-221.
[2] I. Kato *et al.*, Appl. Radiat. Isot., **61** (2004) 1069-1073.
[3] T. Aihara *et al*., Appl. Radiat. Isot., impress. 2014
[4] T. Aihara *et al*., Int. J. Clin. Oncol., 2013 Jun 25

採択課題番号 25109　　難治癌に対する中性子捕捉療法の治療プロトコルの確立　　共同通常

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