NCT letter Vol. 7

（English version）

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Southern Tohoku BNCT Research Center

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1. <Pharmaceutical Science >

Title: Target Delivery of Cell-Penetrating Peptide-Conjugated Dodecaborate for Boron Neutron Capture Therapy (BNCT)

Authors: Ikuhiko Nakase, Miku Katayama, et al.

The source: Chem Commun (Camb), 55(93), 13955-13958 (2019).

Microsoft Word - Nakase-Katayama ChemComm Supplementary Information.docx (rsc.org)

Presented by *Tooru Andoh* (Laboratory of Frontier Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Kobe Gakuin University)

2. <Physical Engineering >

Title: A dual natural lithium formate/L-alanine EPR dosimeter for a mixed radiation field in a BNCT irradiation facility

Authors: G. Alejandro, J. Longhino, *et al.*

The source: Journal of Physics D: Applied Physics (2020) 53:19

pdf (iop.org)

Presented by *Nishiki Matsubayashi* (Graduate School of Engineering, Kyoto University)

3. <Medicine>

Title: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Authors: Christina Twyman-Saint Victor, Andrew J. Reck, *et al.*

The source: Nature 2015; 520:373-380.

https://www.nature.com/articles/nature14292.pdf

Presented by *Tsubasa Watanabe* (Program-specific Associate Professor, Institute for Integrated Radiation and Nuclear Science, Kyoto University)

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Itsuro Kato

Chief Editor of NCT letter

Department of Oral and Maxillofacial Surgery II, Graduate School of Dentistry, Osaka University

On the 7th volume of the NCT letter

Minoru Suzuki
President, Japanese Society of Neutron Capture Therapy
Professor, Particle Radiation Oncology Research Center,
Institute for Integrated Radiation and Nuclear Science, Kyoto University

Thanks to the efforts of NCT letter Editor-in-Chief Dr. Itsuro Kato and the cooperation of fellow doctors, we were able to publish this 7th volume of the NCT letter. I sincerely express my gratitude towards everyone involved.

As members already may know, accelerator-driven BNCT has been receiving a lot of attention since it began as health insurance treatment at two medical institutions in June of 2020. I hope that not only those attending this conference but also those who are not in attendance can see this. This NCT letter, which reports both a current and prospective view of BNCT medical practices and academic research, is progressively becoming a more important medium of communication for this information from this conference.

Volume 7 was also planned by Editor-in-Chief Dr. Kato and is rich with information on the current state of BNCT research institutions, the announcement of the 16th congress, paper introductions, etc. This letter will be a great lead for those who have an interest or are currently engaged in BNCT research as it is filled with information on the current affairs of fundamental BNCT research, medical practices, and a look at the future of neutron radiation locations.

With the commencement of medical treatment for head and neck cancer using accelerator-driven BNCT at medical institutions, the baton has been passed to these institutions to continue the development of boron-agents and accelerator-driven BNCT. The future results of BNCT research will be for patients to be able to receive accelerator-driven BNCT treatments in medical institutions. This "translational research", which spans from the laboratory bench to the hospital bedside, will have a larger significance than we have ever seen before. We are very much looking forward to hearing many great clinical outcomes from these medical institutions. That being said, the bidirectional exchange of research between the fundamental research and clinical practice is becoming more and more important. Specifically, this includes both fundamental research including the development of new boron agents, which will be critical for improving clinical outcomes, and the clinical practice research that feeds back into that fundamental research based on the results of human radiobiology. Up until now, in BNCT research,

from KUR being the common neutron source used in both fundamental research and clinical practice, we have already prepared the soil on which we can have this bidirectional exchange of research between the fundamental research and clinical practice. With medical institutions that use accelerator-driven BNCT facilities, integrated radiation and nuclear science that use BNCT neutron sources for research purposes, and the Aomori Prefecture Quantum Science Center, we are highly anticipating many large flowers that are the research result to bloom from this soil.

In the future, in order to continuously and steadily promote this bidirectional research, it is important to expand the range of researchers and also have many younger researchers to participate in fundamental BNCT research. I humbly ask all conference participants to introduce this NCT letter to the students and young researchers around you. Furthermore, I humbly ask all of you to contribute towards the development of the scientific field of neutron capture therapy with both clinical practice research and foundational research as the two wheels that help move us forward.

JNCT Greetings from the inaugurated President

Minoru Suzuki
President, Japanese Society of Neutron Capture Therapy
Professor, Particle Radiation Oncology Research Center,
Institute for Integrated Radiation and Nuclear Science, Kyoto University

My name is Minoru Suzuki, Professor at Kyoto University Institute for Integrated Radiation and Nuclear Science (KURNS) ・Particle Radiation Oncology Research Center. On September 8th, 2019, I was the Chairperson of the 16th Congress on Japanese Society of Neutron Capture Therapy held in Uji City, Kyoto, taking over this major role from Professor Hiroyuki Nakamura of Tokyo Institute of Technology.

From my appointment as President to the time of my writing this message in July 2020, the 17th Congress has been postponed for a year due to the unexpected pandemic COVID-19. In June of 2020, insured BNCT treatment began for head and neck cancer by accelerator-driven BNCT. A large number of participants and lively discussions based on the BNCT clinical practice were to be expected at the 17th Academic Conference which was to be held in July, therefore it is a great pity that it has been postponed. In the meantime, since there will be an interval of almost 2 years between the Academic Conference held in September 2019 to the next conference, I hope that many BNCT academic researchers will be promoted by members of the academic society and look forward to such presentations.

As representative for Japanese Society of Neutron Capture Therapy, I would like to focus in particular on the following three points: education, qualification, and international cooperation. A committee has been set up in the academic society concerning these 3 points, and I wish to promote these together with the committee professors.

In the future, I hope to rely in great part on medical institution staffs regarding human resources development related to BNCT clinical practice, including On the Job Training. As the Academic Society, including postgraduate education, we look forward to promoting activities that will lead to the development of young researchers who will lead

BNCT academic research in the future. Thanks to the efforts of former chairman Miyatake of Osaka Medical University, the BNCT certified physician system is in operation. With the start of insured BNCT medical treatment and a reliable operation of the BNCT certified physician system, I believe it is necessary to consider preparations from this point forward for certification system for medical physicists regarding BNCT in anticipation of the spread of domestic medical institutions of the accelerator-driven BNCT in the future. In regards to international cooperation, in addition to increasing the presence of Japan which succeeded in putting the accelerator-driven BNCT to practical use for the first time in the world, as an academic society, I hope we can run a project to deepen exchanges between BNCT researchers around the world.

Due to COVID-19, methods for advancing our activities have changed significantly with almost all academic conferences currently being held online. Currently, face-to-face activities are restricted, but I believe there is an aspect in which activities can be promoted even further than ever by holding remote conferences and lectures. On the other hand, for implementing accredited medical examination, given that it seems difficult to end COVID-19 pandemic in 1 to 2 years, I think it has become crucial to consider a new embodiment. For next year's academic conference, it will be necessary, consulting with the chairperson, to rethink the format.

I became president of the society during an unforeseen emergency situation. I believe all members of the society are devoting much precious time towards medical treatment and the research environment coping with COVID-19. Based on the current situation, one by one, I will review the academic society's activities, especially those of each committee, taking proper time to prepare, and steadily promote next year's activities (Jan. to Dec. 2021) with the cooperation of the academic society members.

I would like to ask all members of the universities to pay sufficient attention in preventing the spread of COVID-19, and would ask for your continued cooperation with Japanese Society of Neutron Capture Therapy.

Finishing phase II trial of accelerator-based BNCT on recurrent or locally advanced head and neck cancer and future development

Yoshihiro Takai,
Director of the Southern Tohoku BNCT Research Center
Katsumi Hirose,
Clinic Director at the Southern Tohoku BNCT Research Center

At the Southern Tohoku Research Institute for Neuroscience (general incorporated foundation), as part of the "Medical Welfare Devices and Pharmaceutical Industry Base Development Project" (The Ministry of Economy, Trade and Industry's 3rd Supplementary Budget of 2013: Great East Japan Earthquake Reconstruction Project), a policy meant to support the industrial rehabilitation of Fukushima Prefecture, we applied to the "Subsidy for Internationally Advanced Medical Device Development Projects" publicly offered by Fukushima, and were selected (June, 2012). Thereupon, we introduced the Cyclotron-Based BNCT System (C-BENS). In September of 2014, we established the Southern Tohoku BNCT Research Center and in November of 2014 we opened the facility as a non-bed clinic. Two-thirds of the gross business expenses were covered by the subsidy.

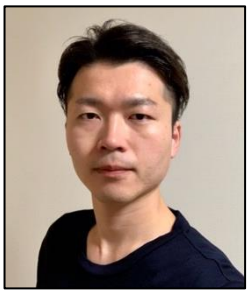
In 2016, we began a phase II trial for the recurrent malignant glioma and recurrent / locally advanced head and neck cancer.=The first case of the clinical trial for the head and neck cancer was treated on July 7th and all 21 cases were registered and treated by February 15th of 2018. 20 cases were from the Southern Tohoku Medical Clinic and 1 case was from the National Cancer Center Hospital. Treatments for all cases were carried out at the Southern Tohoku BNCT Research Center. The objective response rate (ORR) within 90 days, which was the primary endpoint for this clinical trial, was 71.4% for all cases, 75% for squamous cell carcinoma, and 69.2% for non-squamous cell carcinoma. For squamous cell carcinoma, compared to the ORR of 20% for the CDDP+5FU group in the EXTREME trial and 43% in trials using photoimmunotherapy, these results were very promising. For more details regarding the results of this trial, please read the article written by Dr. Hirose in this NCT Letter, "Winning the MERIT Award at European Society for Medical Oncology (ESMO) 2019".

With the results of the phase II trial, we applied for approval of accelerator BNCT system and boron compound (Borofaran) in October, 2019, under the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Accelerator BNCT is designated as an item covered under the SAKIGAKE Designation

System, which has a 6-month long approval screening period. As already reported, in a subcommittee of the Ministry of Health, Labor, and Welfare, manufacturing and sales were approved for the Cyclotron-Based BNCT System on February 19th, 2020, and for boron compound (Borofalan) on the 26th. They will be officially approved in the middle of March. Once approval is received, we will apply to have them covered by insurance, and are hopeful to see BNCT become acknowledged as a health insurance treatment by the middle of 2020.

BNCT is a revolutionary form of radiation therapy that selectively targets tumor cells and can treat cancer without affecting normal cells. By adding BNCT as a step for treating cancer, it can be performed as a third curative treatment for recurrent head and neck cancer patients with no more treatment options, after surgery or curative chemoradiotherapy (CRT). As stated above, BNCT has very high efficacy and does not lower tolerance towards surgeries or CRT. Thus, if we reverse the order and perform BNCT as a neoadjuvant therapy first, if a tumor still remains, it may allow for a safer and reduced surgery and perhaps CRT can be performed on a reduced-volume tumor. In this way, BNCT has the potential to become a method of treatment that causes a paradigm shift in the cancer treatment. As accelerator BNCT will start as a health insurance treatment in the middle of this year, I truly believe that this treatment can bring good news to the many patients battling against intractable cancer.

Polyvinyl alcohol as the additive enhancing the therapeutic potential of *p*-boronophenylalanine



Takahiro Nomoto,
Assistant professor
Institute of Innovative Research, Tokyo Institute of Technology

Since the Asahi Shimbun reported on this research under the heading, “Scientists find liquid glue helps destroy cancer cells in mice”, it has been introduced by many media. The use mentioned here is polyvinyl alcohol (PVA), and the method to "destroy cancer cells" is BNCT. In this study, when PVA was added to *p*-boronophenylalanine (BPA), the tumor accumulation and retention of BPA was considerably improved, and the intratumoral boron concentration was maintained at the appreciably high level even during thermal neutron irradiation, resulting in a significant improvement in therapeutic effect. [***Science Advances*** **6**, eaaz1722 (2020)]. Here, I introduce the results of animal experiments and future prospects about the complex of PVA and BPA (PVA-BPA).

First, Figs. 1A–B show the tumor accumulation and retention of PVA-BPA in subcutaneous tumor models. Fructose-BPA exhibited the apparently high tumor accumulation immediately after administration, but the amount of boron in the tumor gradually decreased. While PVA-BPA also showed a high tumor accumulation amount immediately after administration like fructose-BPA, it maintained the high value even 6 hours after administration. Although the blood retention was slightly higher than that of fructose-BPA, the tumor/blood and tumor/normal tissue boron concentration ratios were similar to those of fructose-BPA. Improvement in tumor accumulation by utilizing the enhanced permeability and retention (EPR) effect (passive targeting) using macromolecular medicine generally requires the increase of the blood retention, compromising the tumor/blood boron concentration ratio. However, PVA-BPA can offer the active targeting for LAT1 without requiring the longitudinal retention in the bloodstream, which might contribute to the high tumor/blood ratio.

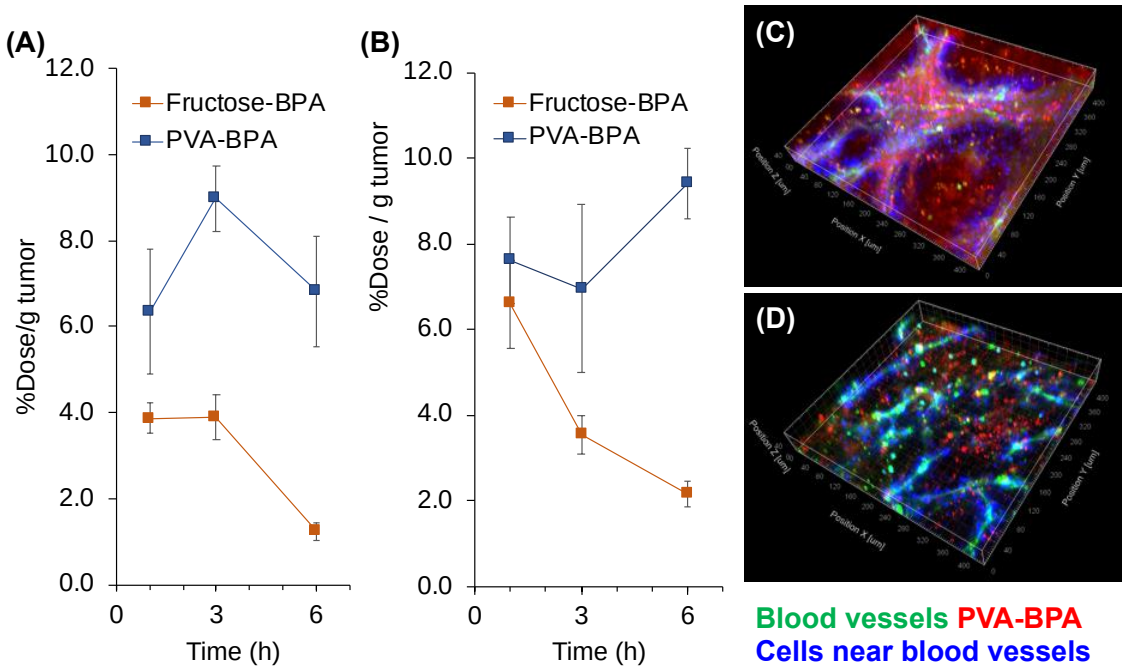


Figure 1. Tumor accumulation and intratumoral distribution. (A–B) Tumor accumulation within **(A)** subcutaneous pancreatic tumor models and **(B)** subcutaneous colon cancer models. **(C–D)** Intratumor distribution of PVA-BPA in **(C)** a subcutaneous pancreatic tumor and **(D)** a subcutaneous colon cancer.

PVA-BPA also exhibited efficient tumor permeability (Figs. 1C–D). Subcutaneous pancreatic cancer models are known to have thick stroma around blood vessels that prevent drugs from reaching tumor cells in a deep region. Although some of intravenously injected PVA-BPA was trapped in the stroma, it also penetrated deep into the tumor. Because the molecular weight of PVA was about 10,000, which is smaller in size than general macromolecular drugs, PVA-BPA might be able to penetrate the thick stroma. In the subcutaneous colorectal cancer model with less stroma, PVA-BPA was distributed throughout the tumor. Since BNCT requires the distribution of boron throughout the tumor, such distribution is important in aiming for complete cure.

In line with these results, PVA-BPA showed remarkable therapeutic effects in both subcutaneous pancreatic tumor and subcutaneous colon cancer models (Fig. 2). In particular, in the subcutaneous colon cancer model, PVA-BPA accomplished the almost complete cure, and we recently found that the similar therapeutic effect could be obtained with commercially available PVA.

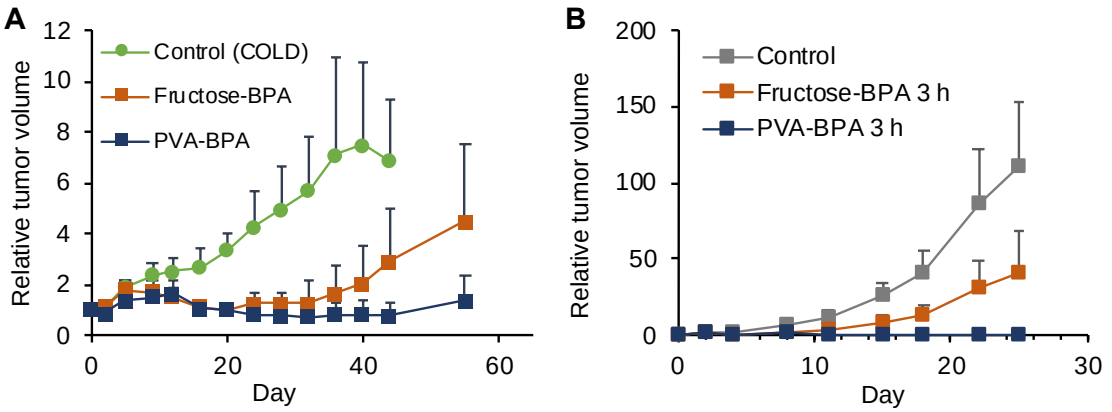


Figure 2. Antitumor activity. (A) Subcutaneous pancreatic tumor models. **(B)** Subcutaneous colon cancer models. Thermal neutrons were irradiated 3 h after intravenous injection.

PVA has been studied for a long time as a biocompatible material and is widely used in clinical situations. In addition, a previous study reported that intravenously injected PVA did not show apparent toxicity in humans at the similar dose to that used in our study, indicating the potential of PVA for the practical application in BNCT. We are planning to optimize the physical properties of PVA within a few years and carefully examine the possible side effects on normal tissues. Also, PVA-BPA has been administered by bolus injection in our animal experiments, but it should be administered by infusion for clinical applications. Since PVA-BPA is formed by the equilibrium reaction (boronate esters), we would like to investigate how the injection methods affect the pharmacokinetics.

The progress status of Tsukuba BNCT Project: iBNCT

Hiroaki Kumada
Associate Professor, Proton Medical Research Center,
Faculty of Medicine, University of Tsukuba

University of Tsukuba established an industry-government-university project team (hereinafter referred to as iBNCT project) in 2011 under the partnership with academia including High Energy Accelerator Research Organization, Japan Atomic Energy Agency, manufacturers including Toshiba Energy Systems & Solutions Corporation and local companies that deal with radiation facilities including NAT Corporation, and Ibaraki Prefecture. The team is developing the demonstration device for an accelerator based BNCT and implementing activities towards the realization of the relevant device.

[Development concept and characteristics of the device]

The development concept of the demonstration device of an accelerator based BNCT: "iBNCT001" is "enhancing the intensity of the neutron beam equivalent to the nuclear reactor" and "lowering the radiation of the device". Specific target figure at the time of designing was set as "epithermal neutron flux at the beam hole location: 1.5×10^9 (n/cm^2/s) or more", "dosage around the beam aperture of 1 minute after the irradiation is 100μSv/h or less". With this target in mind, at the designing stage, we first selected the target material. We adopted beryllium, from the perspective that at that time, the treatment device made by preceding Sumitomo Heavy Industries, Ltd. was using beryllium and it already had application achievements of the same material, and because it had higher melting point than lithium, etc. Then we decided on the energy level of proton to be entered into beryllium. At this point, beryllium has the following physical characteristics. (1) It does not activate by the reaction with the proton of 13.4 MeV or less. (2) The largest energy level of neutron generated correlates with the energy of the proton that is entered. (3) The lower the proton energy is, the lower the neutron generation efficiency will be. Thus, from the perspective of "lowering the radiation", we set the proton energy as 13 MeV or less. However, because of the characteristics of (3), if we lower the proton energy

too much, we cannot have sufficient neutron intensity. Therefore, in order to make the two concepts compatible, we set the condition of proton energy being “8 MeV”. Finally, with the target of “generating neutrons of large intensity equivalent to the nuclear reactor” in mind, we set “the average current of the accelerating proton as 5 mA or more”.

With these requirements in mind, as the accelerator of iBNCT001, we adopted the linear accelerator (linac), which can accelerate the proton up to 8 MeV and can deal with the average electric current of 5 mA or more. Figure 1 shows the picture of the two accelerating tubes (RFQ and DTL) of the iBNCT001 linac.

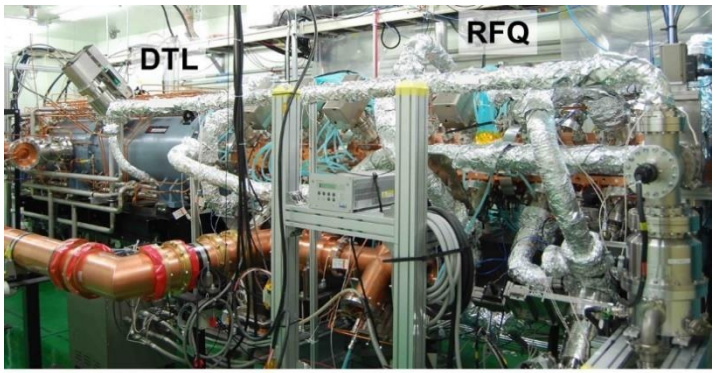
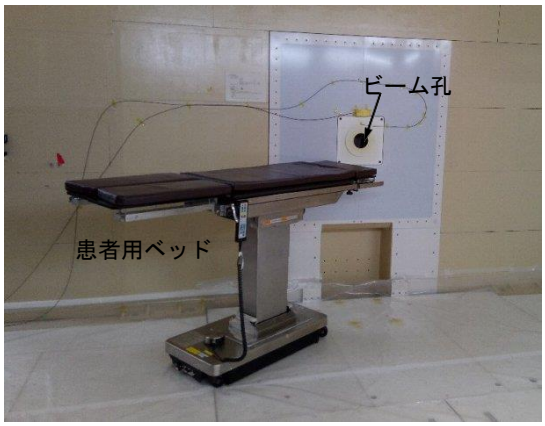


図１　iBNCT001のRFQ（右）とDTL（左）

When producing the two accelerating tubes indicated in Figure 1, the generic technology of the large intensity accelerator driven neutron source device for the large intensity research, which already had long time of operation experience: J-PARC (Tokai village), was applied. On the other hand, the requirement of proton beam current value, etc. for iBNCT001 was higher than J-PARC, so concerning the ion source, cooling system, etc., the equipment dedicated to iBNCT001 was designed, developed and combined.

iBNCT001 was installed in the facility “Ibaraki Neutron Medical Research Center” which is located at “Ibaraki Quantum Beam Research Center” (Tokai village) under the control of Ibaraki Prefecture. Figure 2 shows the exterior appearance of the Ibaraki Neutron Medical Research Center. In addition, Figure 3 shows how the irradiation room arranged in the same facility looks like. In the facility, biological test facility is established next to the irradiation room so that we can conduct nonclinical tests (cell irradiation, small animal irradiation) etc. required from clinical studies.

Figure 2 Ibaraki Neutron Medical Research Center **Figure 3** Inside the irradiation room



[Current status of the iBNCT project]

In 2016, iBNCT001 succeeded in neutron generation by the proton beam irradiation under the condition of low proton beam current. After that, it increased the current value in stages and at the time of 2019, it succeeded in generating the neutron under the condition of the proton beam of the average current: 2.8 mA. This operation condition is the one that can generate the epithermal neutron of approximately $1x10^9$ ($n/cm^2/s$) at the exit location of the beam aperture. Moreover, under the operating condition of average current: 1.4 mA, it conducted the long hour operation test multiple times and it confirmed that it can generate the neutron stably and continuously. In addition, under this operating condition, we conducted the neutron irradiation experiment against water phantom and confirmed by the measurement that the thermal neutron having intensity required for treatment in phantom can be generated. Furthermore, 5 minutes after this phantom irradiation experiment, we went into the irradiation room and measured the residual gamma-ray dose rate in the room. As a result, residual gamma-ray dose rate around the beam aperture was about 40 μSv/h. From this result, we confirmed that this device allows medical staff to come in the irradiation room and access the patient right after the irradiation or in case of emergency and confirmed that our development concept of the device “lowering the radiation” was realized. In addition, we conducted the cell irradiation test and preliminary test of irradiation experiment against mice in this facility and confirmed that the series of nonclinical test can be conducted using the iBNCT001.

From now on, the iBNCT project will promptly conduct nonclinical test for iBNCT001, and after that, based on this result, we plan to conduct clinical trial for real patients.

Progress of accelerator BNCT system in Nagoya University

Yoshiaki Kiyanagi
Designated Professor
Nagoya University Graduate School of Engineering

Nagoya University is developing an accelerator driven neutron source using an electrostatic proton accelerator. This is mainly for BNCT research, and can also be used for engineering and science applications. The accelerator is a Dynamitron accelerator manufactured by IBA. The maximum acceleration energy of the proton beam is 2.8 MeV, the maximum current is 15 mA, and the maximum power is 42 kW. Figure 1 is a photograph of the accelerator and proton beam transport line of the first beamline when set up [1]. As shown in Figure 2, three proton beamlines exist. The first beamline is used for BNCT research, the main application, deflected by 20°. The second beamline is a 70°deflection beam used in science and engineering applications. In addition, there is a straight beamline for beam commissioning.

Fig. 1 Accelerator and first beamline setup [1]

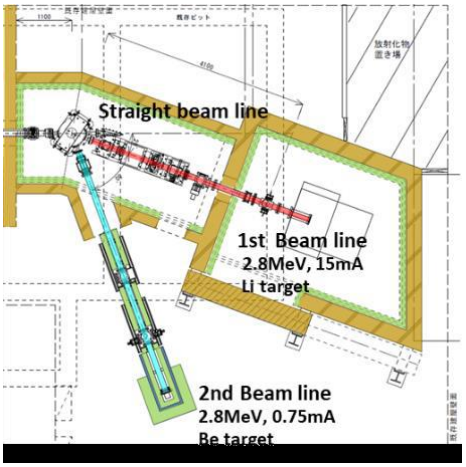


Fig. 2 Beamline layout

A neutron moderator system for BNCT, Beam Shaping Assembly (BSA), is installed at the tip of the accelerator. Figure 3 shows the BSA [2]. As a neutron generation target, Li with high production efficiency in this energy region is used. It is well known that Li produces ^{7}Be, a radioactive substance due to the neutron generation reaction by protons. To prevent Li and its products from diffusing into the accelerator vacuum lines as a result of proton sputtering, we are developing a sealed Li target with a Ti thin film on the Li surface. Due to the high accelerator power, cooling is one of the major challenges for low

melting point targets such as Li. For the copper cooling plate with rib structure water-cooling channels, a heating test was conducted using a 30 keV electron beam from an ultra-high heat load device (ACT2). As a result, it was confirmed that a high heat flux of up to 20 MW/m^2 could be removed [3], well above the heat flux required by our target. About BSA, fluoride is effective element as an epi-thermal neutron moderator [4], and after examining various fluorides, we chose MgF_2, which is suitable for proton energies less than about 10 MeV [1,4]. A nozzle was equipped at the exit of the neutron beam to allow the person being treated to sit comfortably. Figure 4 shows the energy spectrum obtained by a Monte Carlo simulation for this BSA [2]. The beam characteristics, as shown in Table 1, clear the conditions recommended in TECDOC-1223 [1].

The neutron experiment was conducted when the proton beam power was low. Since it is not easy to directly measure the intensity of epi-thermal neutron flux from BSA, a water phantom was installed and the thermal neutron flux in it was measured. The size of the water phantom was 20 cm cubic, as recommended as the standard size in the physics field in Japan. The absolute thermal neutron flux was measured by the gold foil activation method, and detailed spatial distribution was measured by a fiber detector using LiCaF [5]. Figure 5 shows the results of a thermal neutron flux distribution along the beam axis. As a result of the current 0.2 mA, it was found that 1 x 10^9 n/ cm^2 can be achieved as an epi-thermal neutron flux when converted to 15 mA. Cell irradiation is also conducted as a performance test of this device.

We continue commissioning to increase the beam current, since stable operation is at present possible at 3

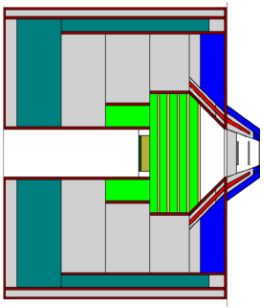


Fig. 3 BSA structure [2]

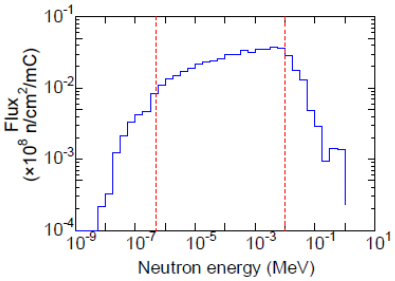


Fig. 4 Energy spectrum [2]

Table 1 Beam characteristics [1]

	Evaluate Value	Reference Value	Unit
Epi-Thermal Neutron Intensity	1.06	≧1.0	×10^9 n/cm^2/sec
Fast Neutron Rate	1.94	≦2.0	×10^{-13} Gy・cm^2
Gamma Ray Rate	1.87	≦2.0	×10^{-13} Gy・cm^2
Thermal Neutron Rate	0.048	<0.05	—

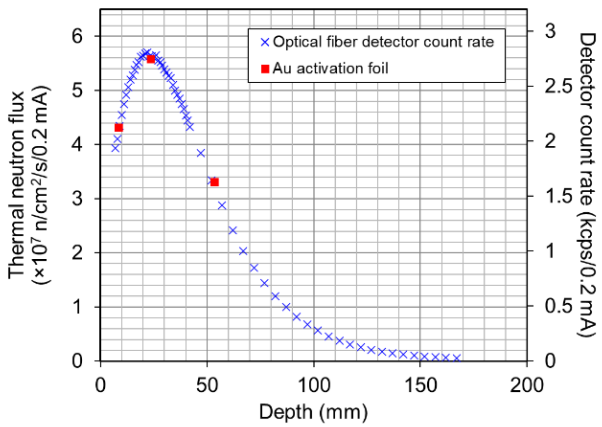


Fig. 5 Beam axial thermal flux distribution

mA. In the future, we plan to further increase the current and develop a target usable at high current situation.

[1] A. Uritani, et al., JPS Conf. Proc., 011002 (2018). doi:10.7566/JPSCP.22.011002
[2] K. Sato, et al., JPS Conf. Proc., 011003 (2018). doi:10.7566/JPSCP.22.011003
[3] S. Yoshihashi et al., submitted to Journal of Instrumentation.
[4] Y. Kiyanagi, Ther Radiol Oncol, 4 (2018). doi: 10.21037/tro.2018.10.05
[5] A. Ishikawa, et al, Radiat. Meas. 133, 106270 (2020). doi: 10.1016/j.radmeas.2020.106270

Status of the Institute for Integrated Radiation and Nuclear Science, Kyoto University

Minoru Suzuki
Professor, Particle Radiation Oncology Research Center,
Institute for Integrated Radiation and Nuclear Science, Kyoto University

The Kyoto University Research Reactor (hereinafter referred to as KUR) of the Institute for Integrated Radiation and Nuclear Science, Kyoto University (hereinafter referred to as KURNS) has conducted more than 580 cases of BNCT treatment, which is the largest number in the world. Since June 1, 2020, the health insurance treatment of pharyngeal cancer using accelerator based BNCT at medical institutions started. In response to this, KURNS, which is not a medical institution, stopped accepting BNCT medical practice. From FY2021, concerning the joint use research public invitation of KURNS, invitation for BNCT clinical research (medical irradiation) topics will not be included.

The start of KUR activation in the FY2020 is postponed to October because we needed to deal with COVID19 pandemic. Operation from Tuesday to Thursday is as usual but since we do not accept medical irradiation, on Thursdays we accept full irradiation experiments at 5 MW. The operation of irradiation experiments at 1 MW on Tuesdays and Wednesdays is the same as last fiscal year.

Although we continue to be cautious enough to prevent the spread of COVID19, KURNS will cooperate as much as possible to promote the joint use research so that the progress of the basic research using the KUR will not slow down. Operation pattern from FY2021 onward is not yet decided as of now, but we would like to work even harder to make progress in the basic research related to BNCT.

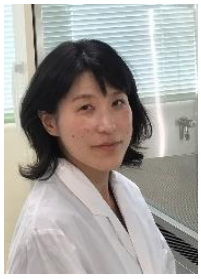
We are currently preparing for the application of the accelerator based BNCT irradiation system used in the clinical trial installed at KURNS to the BNCT basic research. From now on, we will keep you updated about our progress of preparation on the Particle

Radiation Oncology Research Center website.

KUR is currently the only source of neutron in academia that can be used for BNCT basic research by the researchers at home and abroad. For the BNCT related research, neutron irradiation is indispensable as Proof of Concept. In recent years, the number of application by the researchers of the joint use research topics that use the KUR of KURNS exceeded 90 cases. We are contriving ways to arrange the irradiation system and improving the jig so that each research topic can have necessary number and time of irradiation allocated for conducting the research. We look forward to receiving participation of joint use research from many researchers so that the report of the research results from the KUR at KURNS concerning the BNCT basic research will continue to be state of the art in the world.

Every year around September and October on the KURNS website, the invitation for the joint use in the next fiscal year is announced. We would like to ask anyone who is thinking of participating in the BNCT basic research for the first time, if you have anything unclear or have any request, please contact us anytime from the contact form that you can find on the KURNS website: https://bnct.rri.kyoto-u.ac.jp/access.

Report on the 16th Congress on Japanese Society of Neutron Capture Therapy



Natsuko Kondo
Executive Committee Chairperson
Assistant Professor of Particle Radiation Oncology Research Center, Institute for Integrated Radiation and Nuclear Science, Kyoto University

The 16th Congress on Japanese Society of Neutron Capture Therapy was held at Uji Obaku Plaza in Kyoto University in Uji city in Kyoto prefecture on September 7th (Sat) and 8th (Sun) in 2019. (The chairperson of the congress was Minoru Suzuki, Professor of Particle Radiation Oncology Research Center, Institute for Integrated Radiation and Nuclear Science, Kyoto University.) The 7th BNCT Workshop (hosted by the Human Resource Development Committee of the Japanese Society of Neutron Capture Therapy and supported by this congress) was held on September 8th (Sat), the second day of the congress. Amid the lingering summer heat and concerns for the impact on transportation due to Typhoon Faxai (Typhoon No.15) approaching the area on the second day of the congress (8th), we managed to successfully hold and finish the meeting. At the congress, 235 participants (108 regular members, 92 non-members, and 35 students) joined to present the latest research results and had lively discussions in the fields of physics, clinical medicine, pharmacy and chemistry, and biology. We would like to take this opportunity to thank the participants very much for their active participation.

Welcome from Chairperson Prof. Suzuki

Using the experiences in many basic and clinical studies at reactor-based Boron Neutron Capture Therapy (BNCT) research facilities, BNCT is transferring to be performed at accelerator-based BCNT facilities attached to medical institutions. Several countries are developing and installing the BCNT accelerators in or near hospitals, following Japan. Therefore, we set the theme of this congress "Thinking about the Diversity in Neutron Capture Radiation (NCR) Research" in the hope that the Institute for Integrated Radiation and Nuclear Science, which has two neutron sources: nuclear reactor and accelerator, will continue to disseminate academic research information on BNCT from Japan to the world. In the congress, there were extensive discussions about research of radiobiology, neutron capture therapy using NCR, new drug development, and medical physics that supports all

of the other research. The number of the presentations was 76 in total: 2 educational lectures, 4 symposium lectures, 47 general presentations, and 23 poster sessions.

Poster Display Session

The Educational Lecture 1 with the theme of "Challenges for application of cancer immunotherapy to radiation therapy and development of personalized cancer immunotherapy" was delivered by Toshihiro Suzuki, from General Medical Education and Research Center, Teikyo University. The Educational Lecture 2 with the theme of "Basic research on heavy ion beam induced damage to biomolecules in water using liquid secondary ion mass spectrometry" was delivered by Hidetsugu Tsuchida, Associate Professor of Quantum Science and Engineering Center, Graduate School of Engineering, Kyoto University. At the symposium, four speakers presented "Status Report of the International Society for Neutron Capture Therapy (ISNCT)": (1) the current status and challenges of ISNCT, (2) activity of the working group (WG) of BNCT in medical physics, (3) operating principles of ISNCT-Medicine WG, and (4) the future direction of the Chemistry Technical Committee in ISNCT.

The speakers explained about ISNCT as an organization strengthened to continuously conduct planned and strategic operations, the current challenges and progress reports in each field of physics, medicine, and chemistry, and its future direction. Researchers gained comprehensive understanding of the current challenges of BNCT that ISNCT is working on.

“Kagami biraki” at Congress dinner

The Congress dinner was successfully held with more than 135 attendees at Restaurant Kihada and Hybrid Space in Obaku Plaza. We had a Japanese traditional ceremony "Kagami biraki" (opening a sake cask by breaking its lid with wooden mallets, performed at celebratory events). The sake in the cask was Daiginjo KOTO, the product of Sasaki Shuzo in Fushimi, Kyoto, and the attendees enjoyed tasting it.

Finally, I would like to express my appreciation to Prof. Hiroyuki Nakamura, the President of the Japanese Society of Neutron Capture Therapy, Prof. Masayori Ishikawa,

Members of congress management commmittee

the chairperson of the previous Congress, and the members of the Society for their fruitful advice and cooperation, and to Junko Ikeda at the congress secretariat, Kiyoshi Yamauchi from Secand Co., Ltd., the management committee office, and the staffs of Institute for Integrated Radiation and Nuclear Science, Kyoto University for the management and practical business for this congress. Let me also express sincere appreciation toward 14 companies which supported the management of this congress in the form of advertisements, setting up of booths, and sponsorship. For further details of this congress, please refer to the "Information on Nuclear Technology in Medicine" Vol. 20 issued by the Association for Nuclear Technology in Medicine.

Guide for the 19th International Congress on Neutron Capture Therapy at Granada, Spain

Ignacio Porras
Congress Chair of ICNCT-19, President of ISNCT
Professor, Ph.D., Granada University

Dear Colleagues,

We hope that you and your families are well during this difficult time.
We are all together in this crisis.

Many countries have been critically affected by COVID-19. We all have to deal with uncertainties in almost every aspect of our lives and it is clear that we will need time to recover. For this reason, and taking into account the high importance of ICNCT for our community, we have decided, with the approval of the Board of Councilors of the ISNCT, to postpone the ICNCT 19, originally scheduled for September 2020.

The 19th International Congress on Neutron Capture Therapy (ICNCT 19) will be held in Granada, Spain from 5th to 10th September, 2021*.

This postponement is a fully-equivalent replacement for the planned event originally scheduled. It will appear in the website quite soon.

Registration fees for the conference will be unchanged for the new congress date. **Registration will remain open until 15th August 2021**.**

Deadline for abstract submission will be open until 30th April, 2021*.**

Specific information for participants who already made arrangements for September 2020 is as follows:

Abstracts:

If you have already submitted abstract(s) for ICNCT you will be contacted soon by the ICNCT 19 secretariat, who will offer the following three opportunities:

● You may keep the abstract as originally submitted;
● You may modify the abstract;
● You may withdraw the abstract.

Registration:

If you have already registered for the Congress you will be contacted soon by the ICNCT 19 secretariat, who will offer the following two opportunities:
● You may keep your registration in place (and in that case no action is required from your side);
● You may withdraw your registration, with a full refund of the registration fee.

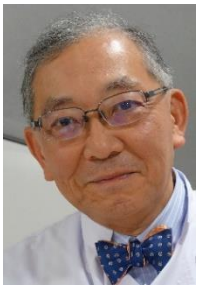
Our aim is to hold a conference that will help to maintain and strengthen the bonds and collaborations in the BNCT community.
Therefore, we are already looking forward to welcoming you in Granada in September, 2021!

Yours sincerely,

Javier Praena, ICNCT 19 Congress Chair.
Ignacio Porras, President of ISNCT

*,**,***：each underlined date is update one.

Guide for the 17th Congress on Japanese Society of Neutron Capture Therapy



Jun Itami
Head of the Department of Radiation Oncology at the National Cancer Center Hospital

This year, thanks to all of my fellow scholars, I have been given the opportunity to hold the 17th Congress on Japanese Society of Neutron Capture Therapy in Atami over the two-day span of July 11th-12th. I am truly honored as a clinician specializing in radiation oncology. This would not have been possible were it not for the efforts of the doctors who laid the groundwork of boron-neutron capture therapy (BNCT) through nuclear reactors and the doctors who exerted themselves to realize BNCT through particle accelerators. The maintenance of theoretical systems like these and the development of BNCT facilities capable of being established within hospitals are what have enabled even doctors ordinarily performing radiation oncology practices to participate in BNCT. BNCT is truly following the path from something unique to something progressively more common.

While it seems like ages ago now, when I was just a rookie doctor going into the medical office, I met a prestigious, aging old man. He was the former teacher of my former teacher, Dr. Hirotake Kakehi, Professor Emeritus. He was a doctor with extensive knowledge such that he could identify meningitis from an abnormal accumulation in the cranium by image reading through a bone scintigraphy. However, he wasn't just your average good-natured old man. He created a new era of nuclear medicine. All of the nuclear medicine techniques and equipment at the beginning of my career as a doctor were developed upon the foundation laid by Dr. Kakehi.

In the beginning, there was a liver scintigram drawn onto paper represented by an accumulation of dots from a dot printer. Then that became film, which later became digitized images. The development of tracers thereafter were built upon the physical science foundations set by doctors like Dr. Kakehi and my former teacher Dr. Noboru Arimizu, who did not even have computers to aid them. The particle accelerator BNCT that we see today has reached a stage in development that has extensively grown, stemming out of these foundations. We have come to understand that we can attain a sufficient quantity of neutrons using particle accelerators in BNCT. In the future, we must aim towards improving the efficiency of neutron generation out of neutron sources, the

miniaturization of devices, and mobilization of gantries. Furthermore, we must develop new boron agents using those neutron sources. It is also vital that we examine CBE for each organ.

Karl Marx once said ”Daher stellt sich die Menschheit immer nur Aufgaben, die sie lösen kann”, meaning "Mankind inevitably sets itself only such tasks as it is able to solve." Were it not for the ability to output a sufficient quantity of neutrons using particle accelerators, we would not have been able to set these tasks for ourselves. These tasks that have come before us are ones that we can solve.

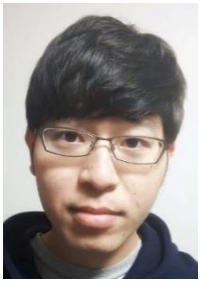
The topic these days has been photoimmunotherapy. In photoimmunotherapy, it is clear that it is necessary to irradiate antibodies that have bound with tumors using light and that the heterogeneity within this photoirradiation is connected to recurrence. The same problem is thought within BNCT, but compared to photoimmunotherapy, in BNCT, it is believed that the problem is more easily solvable using permeable neutrons.

10 years in the future, the things on which we now gingerly spend time might become simple routine tasks. 20 years in the future, BNCT might become the initial treatment towards large numbers of primary tumors. Apologies for all of the citations, but in the words of Hegel, “die Eule der Minerva beginnt erst mit der einbrechenden Dämmerung ihren Flug” (“the owl of Minerva spreads its wings only with the falling of the dusk”). The Owl of Minerva that is BNCT may not take flight given its current stage. The challenge we face over the next 10 to 20 years is to bring this Owl of Minerva into fruition. I hope that this conference in Atami will leave an impact on the future of BNCT.

I am truly excited to welcome everyone in the Department of Radiation Oncology at the National Cancer Center Hospital and everyone here in the beautiful city of Atami. Let's all have a great and worthwhile time.

At the board meeting in April, 2020 held via Zoom, it was decided to postpone the 17th Congress on Japanese Society of Neutron Capture Therapy (Chairperson: Dr. Jun Itami) until July 2021.

The Best Presentation Award of the 16th Congress on Japanese Society of Neutron Capture Therapy



Study on QA by phantom using 3D printing technology in BNCT

[1]Akinori Sasaki, [2]Takushi Takata, [3]Shinji Kawabata
[4]Shin-ichi Miyatake, [2]Yoshinori Sakurai
[2]Minoru Suzuki, [2]Hiroki Tanaka

1) Graduate school of Engineering, Kyoto University,
2) Institute for Integrated Radiation and Nuclear Science, Kyoto University
3)Osaka Medical College

Introduction:

In order to improve the quality of treatment in BNCT, it is desirable to evaluate the thermal neutron flux of each patient and to verify the dose before irradiation. In this study, patient-specific water phantoms were created using 3D printing technology to enable patient QA, and dose verification was performed. We report on the verification of the dose distribution based on the irradiation test before the treatment according to the treatment plan.

Materials and methods:

A case of angiosarcoma was selected in this study. Surface data around the affected area was created from CT data for treatment planning using the 3D surface rendering function of OsiriX. This surface data was processed using 3D data processing software Meshmixer and Autodesk Fusion 360, and a phantom of the affected area was created using a 3D printer AGILISTA-3110 manufactured by Keyence. The structure of the phantom was designed to allow water to be sealed inside the phantom.

The thermal neutron flux on the surface of the phantom was measured using the gold activation foil method. Gold foil and gold wire with cadmium cover were placed on the phantom surface and irradiated with an epithermal neutron beam from the KUR heavy water neutron irradiation facility. To increase the thermal neutron flux on the skin surface, a bolus was installed on the phantom surface. After the irradiation, the thermal neutron flux distribution on the phantom surface was derived by measuring the amount of gold activation, and the thermal neutron flux at the position of the gold foil was calculated by

SERA and compared with the measured results.

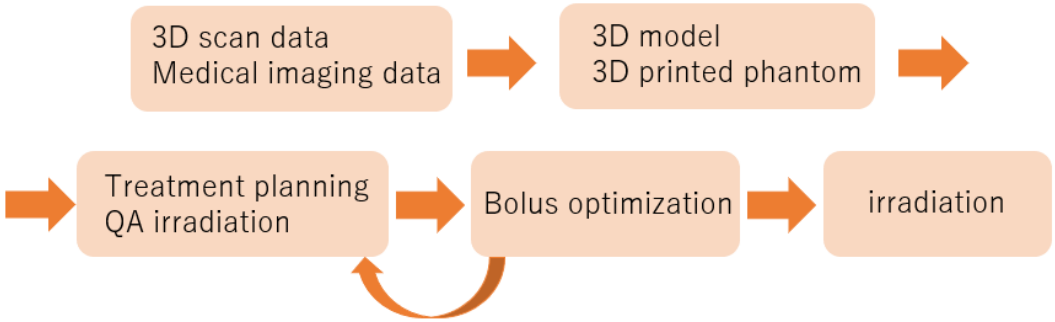
Results:

As a result of the irradiation test, the thermal neutron flux distribution on the phantom surface was obtained. By comparing the results of this phantom irradiation test with the treatment plan, it was possible to evaluate the dose distribution on the surface of the affected skin. In addition, by performing the irradiation test of the phantom of the affected area created from the CT data of the treatment plan, it was possible to confirm the dose distribution in the area with a complicated shape by actual measurement, and to verify the treatment planning. Furthermore, the effect of the bolus was confirmed.

Conclusions:

In this study, a phantom of the affected area was created from the CT data for treatment planning, and an irradiation test simulating the actual treatment was performed for a case of angiosarcoma in KUR. The results of the irradiation tests and the treatment plan by SERA were compared and verified. It was confirmed that the proposed method in this study can contribute to the improvement of the quality of treatment through patient-specific QA.

In the future, this method will be verified and refined. In addition, by using 3D printing technology, it will be possible to create a bolus that can adhere to the complex skin surface and form a uniform thermal neutron flux distribution. We will also develop such a bolus.



Finally, I would like to express my sincere gratitude to Dr. Minoru Suzuki, the conference director, Dr. Hiroyuki Nakamura, the secretariat of the 16th Neutron Capture Therapy Conference, and the judges for selecting this presentation as the Best Presentation Award. I would also like to express my sincere gratitude to Dr. Itsuro Kato for giving me the opportunity to write in NCT Letter.

The Best Presentation Award of the 16th annual Congress on Japanese Society of Neutron Capture Therapy

Evaluation of BNCT therapeutic efficacy by a novel boron compound (BAMP)

Makoto Shirakawa [1,2], Kei Nakai [2], Takumi Omoto [1], Maki Shigeto [1], Fumiyo Yoshida [2], Ryota Takeuchi [3], Minoru Suzuki [4], Hitoshi Hori [3,5], Akira Matsumura [2]

[1] Department of Pharmaceutical Sciences, Fukuyama University
[2] Department of Neurosurgery, Faculty of Medicine, University of Tsukuba
[3] Morita Pharmaceutical Ind., Ltd.
[4] Institute for Integrated Radiation and Nuclear Science, Kyoto University
[5] Niigata University of Pharmacy and Applied Life Sciences

To perform BNCT most effectively, it is desirable that the boron drug is selective and accumulates in a large amount in the tumor. It is a well-known fact that the required boron concentration is more than 25 ppm per tumor tissue, and in addition, the formulation must have low toxicity, water solubility, and low distribution in normal tissues.

As methods to accumulate boron, there remains an ever-increasing interest and challenge to use ligands such as antibodies, proteins, and peptides. These methods are used to increase biological selectivity of boron compounds. However, the necessity of significant biological selectivity is unsolved for boron drugs, because BNCT can achieve physical selectivity depending on the site and extent of neutron irradiation.

Therefore, when developing a novel boron compound, the authors chose the idea of safety, solubility in water and the possibility of high dose administration, rather than the idea of increasing its biological selectivity.

The novel compound (named BAMP) is designed, with polyethylene glycol (PEG) and BSH whose safety has already been established in clinical studies. Since no organic solvents are used for the synthesis, and both compounds are highly water-soluble, BAMP is expected to high safety and water solubility.

In addition, we confirmed the pharmacokinetics and anti-tumor effect of BAMP. From the results, we found that BAMP remained in the tumor for a long time, and significantly

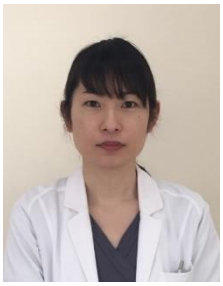
inhibited tumor growth by neutron irradiation at the research reactor of the Institute for Integrated Radiation and Nuclear Science, Kyoto University.

As the next step, we are optimizing the dosage, administration time, and also the length of PEG chain.

Finally, I would like to acknowledge Prof. Minoru Suzuki and Dr. Itsuro Kato for giving me the opportunity to introduce this study. I would also like to thank Prof. Yoshinori Sakurai, Dr. Hiroki Tanaka, and Dr. Takushi Takata for their kind support about neutron irradiation.

The Best Presentation Award of the 16th Congress on Japanese Society of Neutron Capture Therapy

Changes in the immune profile of tumor cells after BNCT



Mariko Sato, Katsumi Hirose, Yoshihiro Takai

Department of Radiation Oncology, Southern Tohoku BNCT Research Center

Several anticancer drugs and radiation therapy have been shown to produce immunogenic cell death (ICD), a cancer cell death that induces an antitumor immune response. In ICD, calreticulin and high mobility group box-1 (HMGB1), called damage-associated molecular patterns (DAMPs), act as mediators of antitumor immunity. It has been reported that radiation therapy induces the expression of calreticulin and the release of HMGB1. We hypothesized that BNCT may induce the activation of anti-tumor immunity in a shorter time and more potently than conventional radiotherapy, and evaluated the changes in calreticulin expression and HMGB1 secretion by BNCT. Furthermore, there are several reports of favorable treatment outcomes (1) and abscopal effects (2, 3) in radiotherapy combined with immune checkpoint inhibitors. We investigated the effect of BNCT on programmed death-ligand 1 (PD-L1) expression.

Human tongue cancer SAS cells and human glioblastoma A172 cells were used in this study. Cells were collected into a suspension and incubated with/without ^{10}B-borono-phenylalanine (BPA). Thereafter, the cell suspensions were irradiated with neutrons. Irradiation was performed using the accelerator neutron generator system (20 MeV cyclotron with Be target, Pb+D2O moderator) in Aomori prefecture Quantum Science Center, and the proton charge was 60 mC. Irradiated cells were evenly seeded in 6 well plates. The medium and cells were collected separately at 24, 48, 72 and 96 hours after neutron irradiation (NR). HMGB1 concentration of the medium was measured by ELISA. The expression of calreticulin and PD-L1 were measured by flowcytometry using PE-conjugated anti-calreticulin antibodies and FITC-conjugated anti-human CD274 antibodies.

BNCT significantly increased the concentration of HMGB1 and continued to increase in SAS cells. The expression of calreticulin was increased by BNCT in SAS and A172 cells. The mean fluorescence intensity (MFI) increased approximately 2-fold in SAS cells and 1.5-fold in A172 cells compared to the control. PD-L1 positive cells markedly increased by BNCT in both cells and continued to increase.

We revealed that BNCT dramatically promotes HMGB1 secretion and calreticulin expression. Moreover, since PD-L1 expression was promoted by BNCT, it was suggested that an environment where the combined use of BNCT and PD-L1 inhibitors can be effective for tumor control effect of BNCT may be induced.

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Travel Grants Award of the 10th Young Researchers BNCT Meeting

A study on development of remote-changeable Bonner sphere spectrometer for characterization in BNCT irradiation field

Shiraishi Sadaaki[1)], Takushi Takata[2)], Hiroki Tanaka [2)] and Yoshinori Sakurai[2)]

1) Graduate School of Engineering, Kyoto University,
2) Institute for Integrated Radiation and Nuclear Science, Kyoto University

Introduction:

At the Kyoto University Reactor (KUR), the multi-foil activation method is used to evaluate the energy spectrum of the neutron irradiation field for BNCT. However, there are few types of activation foils that can be used to evaluate the epi-thermal neutron region, especially the keV region. Then, a Bonner sphere spectrometer is also used. There are some problems with a general Bonner sphere spectrometer such as (1) It is necessary to enter the irradiation chamber to replace the moderator. (2) Responses are obtained for each moderator thickness, but not all response data are effectively utilized in the final spectral evaluation. (3) In the epi-thermal neutron region, the energy resolution is poor due to the flat response function regardless of the thickness of the moderator. In order to solve these problems, a new-type Bonner sphere spectrometer by the name of "Remote-changeable Bonner sphere spectrometer" has been developing. An optimization study was performed for this new-type spectrometer mainly by simulation.

Methods:

The Bonner sphere was optimized assuming the following configurations and conditions with reference to the previous studies.

- A five-layer concentric spherical acrylic shell is used as a container for the Bonner spheres.
- Pure water and 0.15-weight-percent boric acid water for boron-10 (45 g/L solubility at 20 degree Centigrade) are used as liquid moderators.
- The moderator injection part is 10 mm or 20 mm with the same thickness in each layer.

- Each acrylic wall is 1 mm, 2 mm, 3 mm, 4 mm or 5 mm, and all walls have the same thickness.
- A LiCaF scintillation detector is used for online measurement.

The simulation was performed for thirty-three different injection patterns for the moderators in each of 10 types of multi-layer concentric spheres with different acrylic wall thickness (5 types) and moderator injection layer thickness (2 types) using Monte Carlo calculation code "PHITS". Widely different response functions were selected using the obtained response function matrix, and the combinations for the moderator injection patterns was optimized.

Results:

From the optimization study, it was resulted that the thickness of the acrylic wall was 3 mm, the thickness of the moderator injection layer was 10 mm, and five combinations for the injection patterns were sufficient. Figure 1 shows an example of the optimized combinations for the moderator injection patterns.

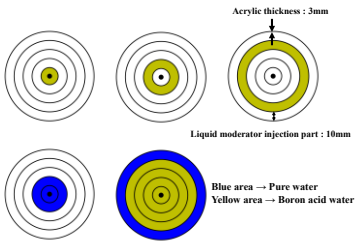


Fig. 1 An optimized combinations.

Future plan:

Based on the optimization, a prototype spectrometer is to be built with experiments planned of the BNCT irradiation field at KUR to confirm its effectiveness.

Impressions of attending the conference:

This is the second time I have attended the Young Researcher's BNCT Meeting, following the previous one held in Uji, Kyoto, and the second time since the International Congress on Neutron Capture Therapy held in Taiwan in 2018. This is the second time I have participated in an international conference, so I could calmly give a presentation and listen to presentations by foreign researchers. In addition, at the social gathering, I could have direct discussions with foreign researchers. I would like to continue to actively participate in international conferences.

Lastly, I would like to thank Prof. Takushi Takada, Prof. Hiroki Tanaka and Prof. Yoshinori Sakurai for their instruction. I also would like to thank Dr. Hanna Koivunoro (Meeting Chair) for selecting my presentation to Travel Grants Award, and Prof. Itsuro Kato for giving me the opportunity to write this article.

Travel Grants Award of the 10th Young Researchers BNCT Meeting

Evaluation of a treatment planning system used for BNCT at the Kansai BNCT medical center

Naonori Ko

1) Kansai BNCT Medical Center, Osaka Medical College
2) Institute for Integrated Radiation and Nuclear Science, Particle Radiation Oncology Research Center, Kyoto University

The 10th Young Researchers' BNCT meeting was held in Finland, Helsinki from 2019/9/26 ~ 2019/9/29. This was my first attendance at an international conference after graduating from university. As many of you are aware, it is difficult to obtain research funds early in your career to attend international conferences. I was fortunate enough to receive a travel grant to attend this conference.

The title of my presentation was evaluation of a treatment planning system used for BNCT at the Kansai BNCT Medical Center. At the Kansai BNCT Medical Center, a phase II clinical trial of grade 2 and 3 meningioma has begun, and the center is aiming to provide BNCT medical care in the year 2020. The center is fitted with a cyclotron-based epithermal neutron source (C-BENS), providing high flux of epithermal neutrons to treat tumors located several centimeters below the surface of the skin. The treatment planning system used during the clinical trial was the Simulation Environment for Radiotherapy Applications (SERA). Evaluation of a TPS is crucial to understand the limitations of the system to allow a better understanding on the treatment outcome. This study aims to evaluate SERA TPS by comparing the results against measured data.

The SERA simulation showed a good agreement with measured values (difference of less than 2%), with the exception near the buildup region (i.e. up to 2 cm depth) and at depths greater than 5 cm. From a clinical perspective, the surface dose (i.e. dose delivered to the skin region) is extremely important and an accurate determination is desirable. Given the calculation voxel size used in SERA is a 10 mm cube, the uncertainty in the flux and dose simulation around the buildup region is high. A more robust Monte Carlo system, such as Particle and Heavy Ion Transport code System (PHITS), will be used to evaluate the thermal neutron flux and dose distribution at these regions.

The author would like to thank Hanna Koivunoro and the organising committee members of the 10th YBNCT for kindly supporting my travel.

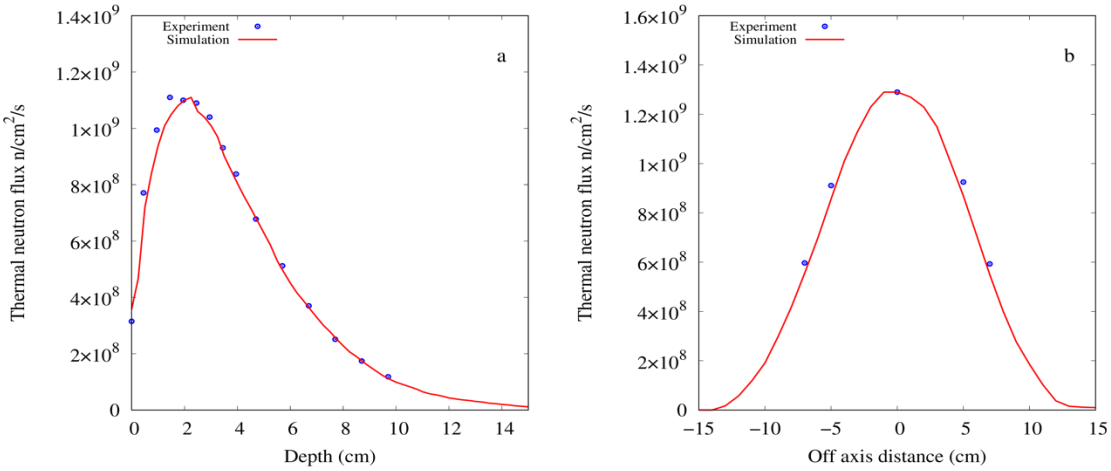


Figure 1a) Thermal neutron flux along the central axis for the 10 cm diameter collimator. b) Off-axis thermal neutron flux at a depth of 2.5 cm for a 12 cm diameter collimator.

Figure 2 (Top) South Harbour, Helsinki. (Bottom left) Author and graduate engineering students at Kyoto University, (Bottom right) Entrance hall of the conference venue.

Travel Grants Award of the 10th Young Researchers BNCT Meeting

Development of Gamma-ray Dosimeter Using Radio-Photoluminescence Glass Dosimeter and Gamma-ray Filter in A Neutron/Gamma-ray Mixed Field for BNCT

Tokiya Inoue

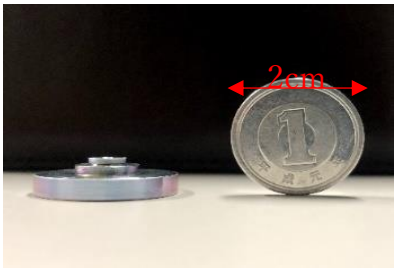
Division of Sustainable Energy and Environmental Engineering, Graduate School of Engineering, Osaka University

1. Introduction

Boron neutron capture therapy (BNCT) is a radiation therapy that requires an accurate understanding of the patient's dose. However, since the irradiation field is a mixed field of neutrons and gamma-rays, it is difficult to accurately measure the patient's dose. Therefore, we have proposed a method to measure the gamma-ray exposure dose in the mixed field using RadioPhoto-Luminescence Glass Dosimeters (RPLGD) that is generally used as a personal dosimeter. In this study, two dosimeters are used and covered with different shielding filters appropriately designed so that the difference in their gamma ray responses becomes equal to the air kerma coefficient. We named this method the "shielding filter method". Currently, we are studying a method of controlling the response of one RPLGD by giving a distribution to the thickness of the shielding filter. By setting the response of one RPLGD to be equal to the air kerma coefficient, it can measure dose in a wide-energy gamma-ray field. This time, we describe the result of irradiation experiments with one RPLGD with a shielding filter made by iron.

2. Materials and methods

The response $\boldsymbol{f}_A$[μGy/h/(cm^{-2}·sec^{-1})] of the RPLGD covered with a shielding filter can be expressed as $\boldsymbol{f}_A = \boldsymbol{R} \cdot \boldsymbol{t}$ using the response function matrix $\boldsymbol{R}$[μGy/h/(cm^{-2}·sec^{-1})] of the RPLGD with the filter material and the filter thickness ratio $\boldsymbol{t}$. The filter shape was designed by solving $\boldsymbol{\alpha} = \boldsymbol{R} \cdot \boldsymbol{t}$ for $\boldsymbol{t}$ using Baysian estimation method so that this response $\boldsymbol{f}_A$ is equal to the air kerma coefficient $\boldsymbol{\alpha}$ [μGy/h/(cm^{-2} · sec^{-1})]. $\boldsymbol{R}$ is



calculated absorbed dose of RPLGD when covered with a shielding material of each thickness using the particle and heavy ion general-purpose Monte Carlo code PHITS (Particle and Heavy Ion Transport code System) [1]. This time, we adopted iron as the shielding material. As shown in Fig. 1, the design results were 0 mm: 20%, 2 mm: 20%, 4 mm: 25%, 10 mm: 35% with respect to the reading area (6 mm in height) of RPLGD (GD-301). Irradiation experiments with this filter were conducted with standard radiation sources (^{133}Ba, ^{137}Cs, ^{60}Co) and in a nuclear fuel storage room (~2 tons of natural uranium) in OKTAVIAN facility of Osaka University, Japan.

Figure 1 Photo of the designed filter.

3. Result

Figures 2 and 3 show the results of irradiation experiments with standard radiation sources and in front of the nuclear fuel storage room, respectively. From Fig. 2, it can be seen that in the case of ^{137}Cs and ^{60}Co, the agreement of experiment and calculation is acceptable, however, in the case of ^{133}Ba, the measured dose is slightly smaller than the calculated value. In addition, the irradiation result in front of the nuclear fuel storage shows that the experimental value is slightly larger.

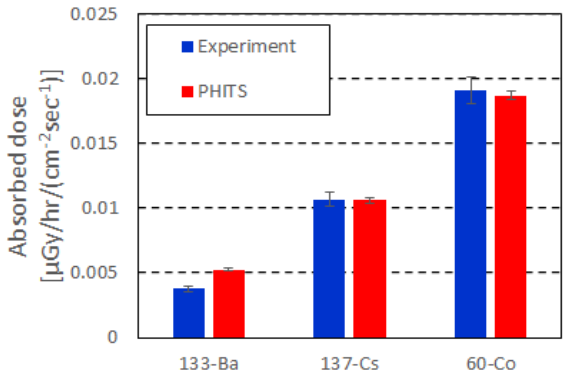


Fig.2 Experimental result. (Standard γ-ray sources)

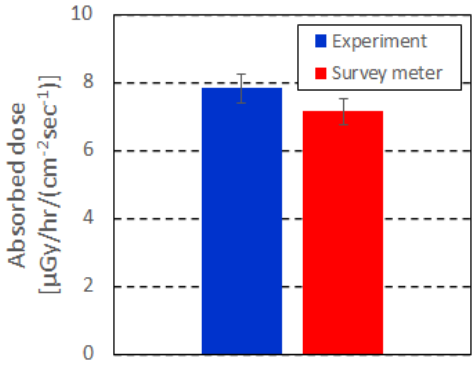


Fig. 3 Experimental result. (Nuclear fuel storage room)

4. Discussion and conclusion

For the discrepancy observed in the result of ^{133}Ba we expect that it is due to a difference between the actual response in the low energy region of RPLGD (read with FGD-1000) and the estimation by PHITS (calculated absorbed dose). It is generally said that the actual response in the low energy region shows lower than Monte Carlo simulation, which seems to be consistent with the experimental result.

As for the reason why the measured dose shows slightly larger in front of the nuclear fuel storage room, we expect it is that the filter is designed under the condition that the gamma-rays are incident in parallel from the side. In other words, for accurate dosimetry we should consider strictly photons entering the RPLGD from various directions when irradiated with a volumetric source such as the case in front of the nuclear fuel storage room.

5. Future work

The R matrix will be modified by making clear the response difference between PHITS response and the actual one. In addition, we think that the effect of random photon incidence can be reduced by making the filter thinner. And for that, we plan to design a new filter that employs multiple materials to reduce the thickness.

Acknowledgement

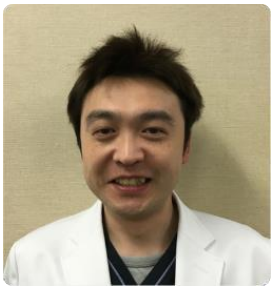
Finally, I would like to express my sincere gratitude to Dr. Isao Murata for his cooperation in making the presentation at this conference and Dr. Itsuro Kato for giving me the opportunity to write a paper in this NCT Letter.

【Reference】

[1] Y. Iwamoto et al., “Benchmark study of the recent version of the PHITS code”, *J. Nucl. Sci. Technol*., **54**[5], pp. 617-635(2017).

Receiving ESMO 2019 Merit Award of ESMO

Updated results of a phase II study evaluating accelerator-based boron neutron capture therapy (AB-BNCT) with borofalan(^{10}B) (SPM-011) in recurrent squamous cell carcinoma (R-SCC-HN) and recurrent and locally advanced non-SCC (R/LA-nSCC-HN) of the head and neck



Katsumi Hirose
Southern TOHOKU BNCT Research Center

I have attended European Society for Medical Oncology (ESMO) Congress held in Barcelona from Sep. 27th to Oct. 1st in 2019 and have presented the results of the phase II study of accelerator-based boron neutron capture therapy (BNCT) for recurrent and locally advanced head and neck cancer.

It was the first time for me to attend an ESMO, and I was impressed by the scale and quality of the lectures. It incorporated a lot of useful tips on established standard treatments that would help clinical oncologists with tomorrow's practice, and that was different from ASCO (American Society of Clinical Oncology), which lays great emphasis on advanced and important clinical trials that can change the future standards of the therapies. There were many people who stopped at my poster presentation, and asked me questions or gave their opinions frankly such as "What is boron neutron capture therapy?" "What is that?" or "I didn't know there was such a treatment." Those comments made me realize that BCNT was still not well known and left me feeling deflated. Even so, when I had discussions with those participants, they formed positive expectations for this treatment with the desired outcomes, and many said that they hoped that the application of the treatment would be extended to treat various types of cancers. Although I was unable to take part in the Young Researchers BNCT Meeting held in Finland during the same period, the experience in ESMO reminded me of the importance of disseminating information at these international conferences of clinical oncology.

The presentation was titled "Updated results of a phase II study evaluating accelerator-based boron neutron capture therapy (AB-BNCT) with borofalan (^{10}B) (SPM-011) in recurrent squamous cell carcinoma (R-SCC-HN) and recurrent and locally advanced non-SCC (R/LA-nSCC-HN) of the head and neck." I showed the updated results of the phase

II study I presented at ASCO this year. Eight patients with local and locoregionally recurrent squamous cell carcinoma of head and neck and thirteen patients with locally advanced non-squamous cell carcinoma of head and neck were continuously administered with 500 mg/kg borofalan (^{10}B) (generic name of ^{10}B-BPA). After two hours, neutron was irradiated until the maximum dose of the oral mucosa, nasopharyngeal, oropharyngeal, and hypopharyngeal mucosa and laryngeal mucosa reached 12 Gy-Eq. The primary endpoint was the objective response rate of 90 days, and the antitumor efficacy and safety were evaluated as the secondary endpoint. The objective response rate for all the patients were 71.4%, and CR/PR (complete response/partial response) of patients with squamous cell carcinoma (R-SCC-HN) and patients with non-squamous cell carcinoma (R/LA-nSCC-HN) were 50.0%/25.0% and 7.7%/61.5% respectively. With a median follow up of 21.3 months (range, 9.2–30.6), 1-year progression-free survival (PFS) by investigator review were 70.6%. For adverse event, nausea, dysgeusia, acute parotitis were observed frequently.

I have received Merit Award from ESMO for this poster display session. This achievement is not at all the result of myself or of a facility, but the result of the efforts made by the researchers of this society who have led the world's BNCT research. As an extension of their assiduous work, I would be very happy if our clinical ingenuity helped bring about this successful outcome.

Introduction of the articles

1. <Pharmaceutical Science >

Tooru Andoh
Assistant Professor
Laboratory of Frontier Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Kobe Gakuin University

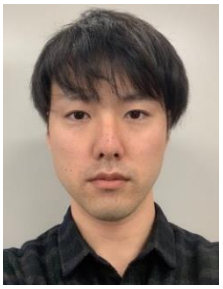
Title: Intracellular Target Delivery of Cell-Penetrating Peptide-Conjugated Dodecaborate for Boron Neutron Capture Therapy (BNCT)

Authors: Ikuhiko Nakase, Miku Katayama, Yoshihide Hattori, Miki Ishimura, Shunsuke Inaura, Daisuke Fujiwara, Tomoka Takatani-Nakase, Ikuo Fujii, Shiroh Futaki, Mitsunori Kirihata

The source: Chem Commun (Camb) 2019; 55(93), 13955-13958.
Microsoft Word - Nakase-Katayama ChemComm Supplementary Information.docx (rsc.org)

2. <Physical Engineering >

Nishiki Matsubayashi
Graduate school of Engineering, Kyoto University



Title: A dual natural lithium formate/L-alanine EPR dosimeter for a mixed radiation field in a BNCT irradiation facility

Authors: G. Alejandro, J. Longhino, N. R. Alvarez, E.Pawlak, A. Butera

The source: Journal of Physics D: Applied Physics 2020; 53:19
A dual natural lithium formate/L-alanine EPR dosimeter for a mixed radiation field in a boron neutron capture therapy irradiation facility - IOPscience

3. <Medicine>

Tsubasa Watanabe
Program-specific Associate Professor
Institute for Integrated Radiation and Nuclear Science, Kyoto University

Title: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer

Authors: Christina Twyman-Saint Victor, Andrew J. Reck, Amit Maity, Ramesh Rengan, Kristen E. Pauken, Erietta Stelekati, Joseph L. Benci, Bihui Xu, Hannah Dada, Pamela M. Odorizzi, Ramin S. Herati, Kathleen D. Mansfield, Dana Patsch, Ravi K. Amaravadi, Lynn M. Schuchter, Hemant Ishwaran, Rosemarie Mick, Daniel A. . Pryma, Xiaowei Xu, Michael D. Feldman, Tara C. Gangadhar, Stephen M. Hahn, E. John Wherry, Robert H. Vonderheide, Andy J. Minn.

The source: Nature 2015; 520:373-380.
https://www.nature.com/articles/nature14292.pdf

<Review of the paper>

In recent years, X-ray irradiation to tumors has been shown to evoke a variety of tumor immunostimulatory effects, which is thought to be a new aspect of the anti-tumor effects of radiotherapy. The primary purpose of this paper was to investigate the effect of radiation and immune checkpoint inhibitors (ICBs) such as an anti-PD1 antibody (P1) and anti-CTLA4 antibody (C4). Mechanistic analysis has revealed that irradiation has an immunostimulatory effect that does not overlap with other immunotherapies. First, the combined effect of RT+P1+C4 was demonstrated in an abscopal mouse model (tumors were implanted on both sides, and only one side was irradiated) (Figure 1, d), (https://www.nature.com/articles/nature14292/figures/1), and this was due to an increase in functional CD8+ T cells. (Figure 1, d) (https://www.nature.com/articles/nature14292/figures/1), indicating that the increase in functional CD8+ T cells was a contributing factor why RT + ICBs combination had better effects on tumor control. Next, they examined the clonality of T cells infiltrating tumor tissue in the C4 alone group compared to the RT+C4 combination group and found that the clonal frequency of T cells increased and the diversity of T cell receptors increased with irradiation (Figure 3, c, d)

(https://www.nature.com/articles/nature14292/figures/3). Surprisingly, irradiation increased significantly the repertoire of T-cell receptors and thus their reactivity. They showed that RT has non-redundant synergistic effects on anti-tumor immune reactions (Extended Data Figure 6, e) (https://www.nature.com/articles/nature14292/figures/10).

<Comments>

This is an exciting paper focusing on the immunostimulatory effects of radiation with detailed analyses.

In clinical practice, the tumor cure rate of X-ray irradiation and immunotherapy combination is still not satisfactory. In the future, it will be necessary to develop a treatment strategy that combines not only radiation and C4/P1/anti-PD-L1 antibody but also other immunomodulators. In recent years, we conducted a mouse study using an indoleamine 2,3-deoxygenase inhibitor, one of the immunomodulators, as combination therapy of RT + P1 + α, and obtained a positive effect and analyzed the mechanism (Watanabe et al. Clinical Cancer Res 2020).

In reading this paper, along with BNCT standpoint of view, the following point should be noted. The combination of C4+P1 has a high incidence of adverse events, and the regimen including the combination of C4+P1 should not be recommended for all patients routinely, and this is also the case with BNCT. Regarding BNCT, we need to know whether BNCT + immunotherapies is better than BNCT alone first, and the mechanisms underneath it.

Editor's Postscript **On the Publication of NCT letter Vol. 7**

Chief Editor of NCT letter
Itsuro Kato
The 2nd Department of Maxillofacial Surgery, Graduate School of Dentistry, Osaka University

I would like to take this opportunity to wish every success to all of the members of the Japanese Society of Neutron Capture Therapy (JSNCT). We could publish the NCT letter No. 7 supported by the all of contributors. I worked with Prof. Mitsuko Masutani (Nagasaki University) and Prof. Teruyoshi Kageji (Tokushima Prefectural Kaifu Hospital). Prof. Minoru Suzuki, a new president of this Society also gave us suggestions.

Prof. Suzuki wrote "JNCT Greetings from the inaugurated President" with enthusiastic thought at the beginning of NCT letter No. 7. BNCT System NeuCure® by Sumitomo Heavy Industry for an unresectable, locally advanced, and recurrent carcinoma of the head and neck region under the national health insurance system on 1st June in 2020.

The related articles have been written by Prof. Takai and Prof. Hirose in the Special article, and that of the Awardees of BNCT related Conferences or Meetings, respectively. Prof. Nomoto of Tokyo Institute of Technology, wrote on the hot topic about "liquid glue", PVA-BPA which is additively enhancing the therapeutic potential of BPA. His animal model experiments demonstrated its usefulness and possibility in BNCT.

About the progress of each BNCT facility was reported by Prof. Kumada (Tsukuba University), Prof. Kiyanagi (Nagoya University) and Prof. Suzuki (Kyoto University).
I asked Associate Prof. Watanabe (Kyoto University) to introduce articles which demonstrate the relationship between radiation therapy and host immunity, from various viewpoints. I will recommend the young members to read "*Introduction of the articles*"

I expect and wish every success to all of the members of JSNCT and I will try to send all activity of JSNCT members to foreign countries as much as possible at real time, through linking HPs of ISNCT and TCNCT to that of JSNCT.

I would like to take up the media news, the transfer of the members, a new plan, an article about BNCT including the contribution to this letter desired widely. I would like to think about with you a new role of our committee in New Era of "with corona virus"
I'm very happy if you could frankly give me your opinion. Thank you for your cooperation.