

## The Solution for Cancer

Over the course of mankind's long history, cancer has proved to be its greatest enemy. Now we have a chance to overcome this foe. BNCT integrates the arts of medicine, pharmacy and physical technologies, and we need to consolidate our capabilities in all these fields.



## Cancer Therapy: A new horizon

It is my great honor and privilege to be the president-elect of the Japanese Society of Neutron Capture Therapy (JSNCT), succeeding Prof Junichi Hiratsuka and Prof Koji Ono as of September 2015.

Boron Neutron Capture Therapy (BNCT), which previously used nuclear reactors, has reached a major turning point since the world's first accelerator-driven BNCT (A-BNCT) facility was developed in Japan in 2010. The Phase I A-BNCT clinical trials for treating brain tumors are almost complete, and preparations are being made for the phase II study for head and neck cancer - similar to the phase I trials. In addition, several plans for enhancing A-BNCT are ongoing in universities and hospitals. Under these circumstances, in order to pursue a policy of combining basic research and clinical studies, and promoting industry-academia partnerships, as well as further promoting BNCT studies, I would like to announce three principal strategies as listed below, all of which will be implemented for the further development of Society:

1. Cultivating BNCT specialists and developing information-sharing protocols
2. Developing new drugs for efficient boron delivery
3. Disseminating the information obtained across the world

During the past four years, three lecture courses were held as part of the JSNCT training program for BNCT specialists. Since it is particularly important to cultivate BNCT specialists, including JSNCT-certified doctors, we will continue our work to educate people to a high level of competency in this field. We will also strive to promote information sharing among these specialists through the training programs.

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This year we inaugurated the Mishima Memorial Award for Chemistry to be presented to an outstanding researcher in clinical studies drug development. The first Award was given to Dr. Kazuo Yoshino.

One urgent issue in BNCT is the development of a new boron agent that can ensure further progress in the field. The two agents currently used were synthesized about 60 years ago.

The JSNCT is also constantly encouraging researchers to develop new drugs. We must unite basic research with clinical studies. Available resources should be devoted to the development of new drugs through industry-academia partnerships. We must also establish a standard procedure for evaluating the drugs developed, so that we can initiate translational research.

It is extremely important to disseminate the correct information across the world. We will then be able to establish an international standard for BNCT treatment. I believe this JSNCT Quarterly Newsletter will serve an essential role in this purpose.

As the president of JSNCT I will put great effort into realizing BNCT therapy for all cancer patients.

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# Topic: The accelerator-driven BNCT facility at Southern TOHOKU General Hospital

## The world's first BNCT hospital

### Introduction

The Southern TOHOKU General Hospital was established in 1981 as the Southern TOHOKU Research Institute (STR) mainly catering for neuroscience in Fukushima prefecture, a south eastern region of the Main Island, Japan. Now 34 years on we have 80 healthcare organizations and 5 general hospitals under the same headquarters. Figure 1 shows an overview of our main facilities in Koriyama city.

The mission statement of the STR is 'Japanese excellence for health and hope'. In order to achieve this mission, we intend to provide advanced new technologies and medical treatment protocols. Currently the standard cancer treatments are surgery, radiation therapy and chemotherapy.

We have a substantial range of equipment for diagnostic imaging: five instruments for Positron Emission Tomography/Computed Tomography (PET-CT), six for Magnetic Resonance Imaging (MRI) and six for CT. The STR is equipped with cutting-edge radiation treatment systems: a linear accelerator, a remote after-loading system, a Gamma Knife, a CyberKnife and a proton-beam therapy treatment system including two rotating gantry irradiation rooms and one horizontal irradiation room. The STR, in addition, provides two hyperthermia systems, two hyperbaric oxygen therapy systems and an immunotherapy system. The STR actively embraces advanced medical care by introducing diagnostic and treatment methods for all cancer types.

J Chadwick discovered the neutron in 1932. Soon after the discovery, GL Locher suggested the basic idea for using the neutron capture reaction for treating cancer in 1936. The first BNCT clinical trial for malignant tumors was performed in 1951 by WH Sweet. However, because of inadequacies in the boron agent and neutron flux, most of these trials failed.

H Hatanaka in Japan began BNCT clinical trials for brain tumor treatments in 1968. Boron compounds and neutron flux have gradually improved since. A key requirement for BNCT is a neutron source. At first reactors were used, although installing the BNCT system is prohibited by law in most hospitals. In 2008 an accelerator-driven neutron facility was inaugurated at Kyoto University Research Reactor Institute (KURRI) by Sumitomo Heavy Industries, Ltd. The first clinical trial for brain tumor therapy was performed in 2012 using the KURRI facility.

### Southern TOHOKU BNCT Research Center

In June 2012 the STR decided to install an accelerator-driven BNCT as a novel modality for cancer patients and construction began in March 2013. The first accelerator-driven BNCT Research Center in the world was established in September 2014 (Figure 2). The BNCT facility was commissioned and completed in February 2015 and opened as a medical facility in November 2015, and the first clinical trial at the Southern TOHOKU BNCT Research Center was performed in the beginning of 2016 for a patient with a brain tumor.



Figure 1. Panoramic view of the Southern TOHOKU Research Institute (STR). (<http://www.minamitohoku.or.jp/english/>)

## The setup at Southern TOHOKU BNCT Research Center

The BNCT facility consists of a cyclotron-driven neutron source (C-BENS), a measurement system for blood boron levels and a transportation system for the patient. The C-BENS was developed with the cooperation of KURRI and Sumitomo Heavy Industries. The C-BENS was installed at the BNCT Research Center in April 2014.

The BNCT system is located on the basement floor of the Southern TOHOKU Research Center where we have a machine room for the C-BENS, a room for Inductively Coupled Plasma (ICP) analysis, two preparation rooms and two treatment rooms (Figure 3).

The C-BENS machine consists of a cyclotron, a beam transport system, a beam-shaping assembly and a collimator assembly. The wall of the cyclotron room is 2.5 m thick for radiation protection.

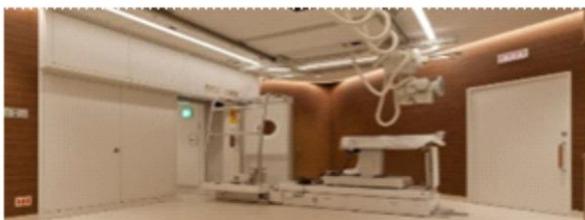
The ICP analysis room is used for measuring the concentration of boron in blood. The transport system, which transfers patients from the preparation room to the treatment room, is equipped with radiation protection.



Figure 2. Southern TOHOKU BNCT Research Center



(b) Treatment room



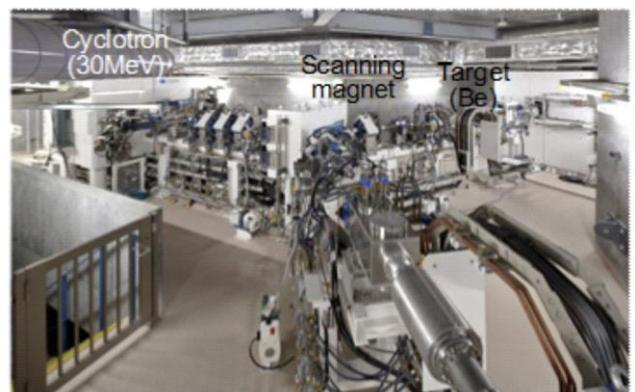
(c) Preparation room



(e) ICP analysis room



(a) Floor design



(d) Cyclotron room

Figure 3. Layout of the Southern TOHOKU BNCT Research Center

## Cyclotron: HM-30

The cyclotron HM-30 is compact in size, with a width of 3.0 m, length of 1.6 m and height of 1.7 m. It accelerates negative hydrogen ions to 30 MeV, and produces a proton beam of more than 1 mA. Note that this proton beam is extracted by a carbon foil stripper. The HM-30 can be operated for 1 hour at 1 mA in a stable manner, which suffices the requirements for its use in medical treatments.

## Beam shaping assembly (BSA)

The extracted proton beam is expanded by two scanner magnets in order to moderate the concentration of heat on the beryllium target, which is directly cooled by water to remove the heat flux of 30 kW. The neutron flux emitted is moderated by moderator equipment made from lead, iron, aluminum and calcium fluoride (Figure 4).

The BSA is surrounded by blocks of lithium-fluoride-loaded polyethylene and low-activation concrete to reduce radioactive effects caused by the thermal neutrons. The concrete wall is further shielded by 1 cm thick silicone rubber, which contains 20 wt% of B4C.

In order to reduce workers' exposure to additional  $\gamma$ -rays from the activated moderator, movable Pb shields with a thickness of 4 cm are installed.

The reaction between 30 MeV protons and the beryllium target emits high-energy neutrons, up to 28 MeV, in the beam direction. The BSA can reduce the neutron energy dissipated into the epithermal energy region because lead and iron work as moderators with inelastic cross-sections, and aluminum and calcium fluoride work as shaper materials. The resulting spectra of the neutron beam are in the range of several tens of keV.

The BSA is designed to obtain a sufficient intensity of epithermal neutrons and to reduce contamination by  $\gamma$ -ray and the dose from fast neutrons.

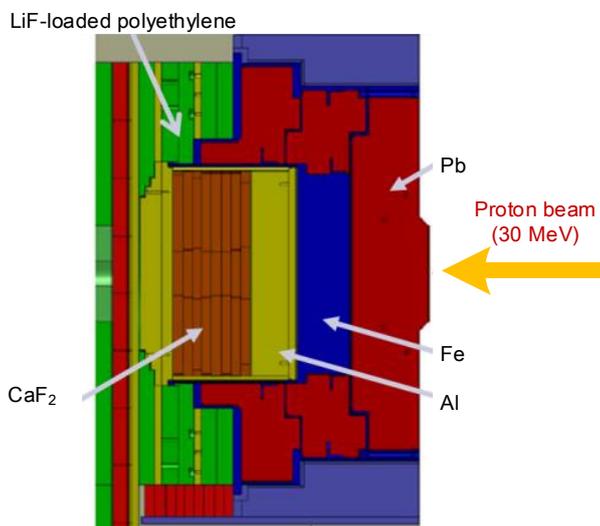


Figure 4. Schematic diagram of the beam shaping and collimator assembly

## Collimator assembly

The proton beam is injected into a target of beryllium plate for generating neutrons. The aperture diameter of the collimator for the neutron beam ranges from 100 mm to 250 mm. The collimator, which is made of polyethylene including 50 wt% of lithium fluoride, is placed in the neighborhood of the patient.

A series of tests for neutron generation started in September 2014, and were completed in February 2015. Various irradiation characteristics were evaluated such as the whole-body exposure to a patient, the reduction of exposure for workers, and the performance of the BSA. Biological characteristics were also checked using tests on cells.

In order to validate the results of Monte Carlo simulations (MCNPX), irradiation tests were performed using multi-foils for detecting high-energy neutrons ranged over a few MeV, and by using a water phantom for detecting thermal neutron distribution.

It was concluded that the simulations for reaction rates caused by high-energy neutron and thermal neutron distributions in a water phantom agreed well with the measurement results. The peak flux on the maximum collimator size (25 cm in diameter) in the water phantom was confirmed at about  $1.8 \times 10^9$  neutrons/cm<sup>2</sup>/sec at a depth of 20 mm from the surface under the 1 mA proton beam. The measured thermal distributions on the reference collimator size (12 cm in diameter) in a water phantom correspond well with the calculated results (Figure 5).

## Transportation system of patient

The transportation system for patients is newly developed to reduce the working time in the treatment room. Note that workers cannot come into the treatment room just after irradiation therapy because of the remaining radioactivity.

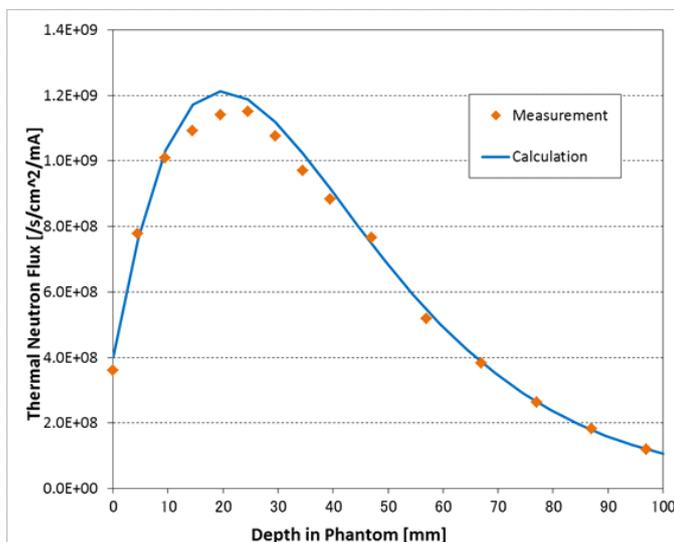


Figure 5. Thermal neutron distribution in a water phantom on the center axis. The collimator size is 12 cm in diameter, which is our reference collimator size.



## Technology Solution

### Measuring system of boron concentration in blood by ICP

In the ICP analysis laboratory room we provide two ICP Emission Spectrometers for measuring the boron concentration in the blood. It is extremely important to measure the boron concentration, because it is used to determine the irradiation time.

### Medical team for BNCT treatment

Clinical BNCT treatment requires a team of physicians, including internal medicine, surgery, radiation therapy, radiology diagnostics, radiation oncology, and pathology, with other healthcare professionals on standby. The team members meet to discuss the best therapy for the patient, select and combine treatments, and finally determine a personalized therapy program for each patient. We firmly believe that this system provides the right medical treatment for the patient.

### Further scope of BNCT

In the near future the BNCT will benefit from combining with other treatments such as surgery, radiotherapy, chemotherapy and target therapy including immunotherapy (see Figure 6). This procedure will be standardized for patients with primary tumors.

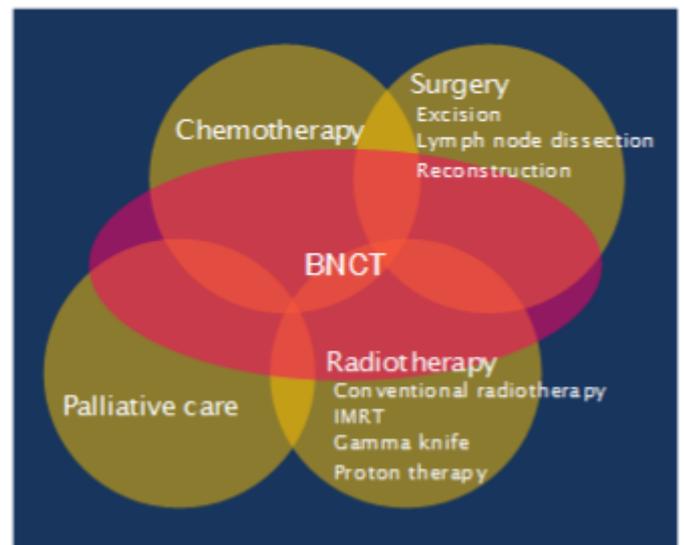


Figure 6. Combined modality therapy

# Report of the 12th Congress

The 12th Congress of JSNCT was held at Kobe Gakuin University during September 4 and 5.



The proceedings

Prof. Hideki Ichikawa of Kobe Gakuin University organized the 12th Congress of JSNCT during September 4 and 5, 2015. The Congress was held at the beautiful campus of the University in Kobe Port Island.

The cover pages of the proceedings are blue and green, which are a symbol of Seto Inland Sea surrounding the Port Island and the well-kept lawn at the University campus.

The thematic words of the Congress were “The upcoming Boron Neutron Capture Therapy”, and Prof Ichikawa introduced three main subjects: 1) development of accelerator-driven neutron generators, 2) clinical application of BNCT and 3) development of drugs for boron delivery.

The total number of participants was 250. More than ten members from Taiwan - mainly from National Tsing Hua University and Taipei Veterans General Hospital - joined and presented their works.



Prof Hideki Ichikawa inaugurating the opening address



The former President Prof Jun-ichi Hiratsuka and Dr Kazuo Yoshino, the winner of Mishima Memorial Award for Chemistry.

Educational lecture given by Prof Koji Ono



At the gala dinner party

During the Congress there was one educational lecture, two plenary lectures, three work-shop presentations, two luncheon seminars, thirty oral presentations, and twenty-three poster presentations, that is, all together sixty-two lectures and presentations.

Prof Emeritus Koji Ono of Kyoto University, the founder of JSNCT, presented an educational lecture under the title of "Perspectives of BNCT research from CBE (Compound Biological Effectiveness) analysis, and Prof Minoru Suzuki presented "Accelerator-based BNCT and clinical application."

Dr Kazuo Yoshino of Shinshu University was commended for the Mishima Memorial Award for Chemistry on the second day of the Congress, and as awardee presented the results of his research.

The following lectures presented also drew attention:

- Prof Mitsunori Kiriata of Osaka Prefectural University: "Development of low molecular weight boron agent and the perspectives of the agent"
- Dr Chikako Shikata of the Regulatory Science Foundation: "Process for development and approval of medical drugs in Japan"
- Prof Hiroyuki Nakamura of Tokyo Institute of Technology: "What are the obstacles for development of new boron drug".



Delegates from Taiwan at the dinner party



Scoring at the gala dinner party



Poster session



Report for visiting IAEA given by Prof Hideki Matsui and discussions

Prof Hideki Matsui of Okayama University, as the representative of JSNCT, presented a report to the visiting IAEA (International Atomic Energy Agency). He met and exchanged information with the IAEA experts who are in charge of BNCT, that is, Dr. Meera Venkatesh, Director of the Division of Physics and Chemical Sciences, and the Department of Nuclear Sciences and Applications (NA), and Dr. Ahmed Meghzifene, Head of Dosimetry and the Medical Radiation Physics Section. Note that IAEA is the organization responsible for all radiation therapies.

Prof Matsui said that at IAEA he showed the detailed status of research and development of BNCT in Japan both for the accelerator-based neutron facilities and for boron agents, which attracted great attention from IAEA experts. Both organizations - JSNCT and IAEA - agreed to continue to exchange. Dr. Meghzifene requested that Prof Matsui join an international conference on BNCT to be held in 2017.

After the first day of presentations a gala dinner party was held, and participants fully enjoyed the famous million-dollar night view of the Kobe port.



## Professional Development

We now stand on the brink of a new stage in the clinical application of BNCT. It is important we cultivate our capabilities with no discrimination based on gender, since the BNCT requires all the abilities of a diverse set of professionals.

## Events & News

### • Phase I clinical trial using the accelerator-based neutron source (ABNS) was completed for recurrent malignant gliomas (GBM)

BNCT clinical studies using the reactor-based neutron source were mostly completed by 2012. Another possibility is to use the accelerator-based neutron source (ABNS). ABNS is in the process of development for applying BNCT under hospital settings. Sumitomo Heavy Industries has produced a small size of ABNS facility in collaboration with Stella Pharma. A cyclotron (C-BENS) is used for generating the proton beam. A Japanese group has just successfully finished the case registration of the phase I clinical trial by using the C-BENS system for recurrent malignant gliomas (GBM). They now plan to start the phase II clinical trial by using the same system under the same clinical entity. (Reported by Prof Shinichi Miyatake, Osaka Medical College)

### • The next congress of JSNCT for the year of 2016 will be held in Tokyo

Prof Hironobu Yanagie, Meiji Pharmaceutical University, will organize the 13th Congress of JSNCT in 2016. It will be held on August 6th and 7th, 2016 at the Ito Hall of Ito International Research Center at Hongo Campus, the University of Tokyo. In association with the Congress the 4th lecture meeting for the BNCT technologies will be held in the evening of August 5th at the same venue.

### • Nagoya University introduced an accelerator-driven neutron facility

A compact neutron facility that provides a low-energy high-current DC accelerator (IBA Dynamitron; 2.8MeV, 15mA proton beam) was introduced in September 2015 at Nagoya University for use in the application of BNCT. The target is made from Li, which uses the  ${}^7\text{Li}(p,n){}^7\text{Be}$  reaction. The output neutron flux will be moderated by a compact beam-shaping assembly (BSA). The low-energy protons incident on the lithium target may be suitable for the accelerator-driven BNCT. However, the lithium target involves several difficulties (i.e., low melting point, high chemical activity and  ${}^7\text{Be}$  production). A new sealed Li target will be developed for pursuing easy and safe maintenance work. (Reported by Prof Kuzuki Tsuchida, Nagoya University)



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