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7TH YOUNG RESEARCHERS' BORON NEUTRON CAPTURE THERAPY MEETING

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Book of Abstracts

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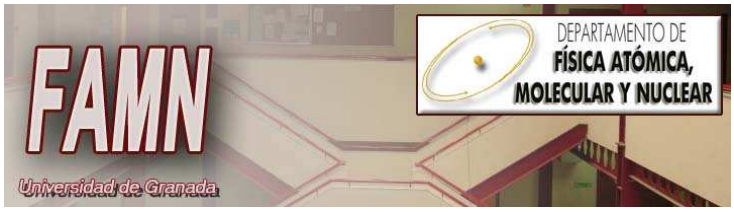

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7TH YOUNG RESEARCHERS IN BORON NEUTRON CAPTURE THERAPY MEETING

HOTEL SARAY, SALA ALHAMAR

Granada, 22nd to 26th September, 2013

Sunday 22nd

19:30	WELCOME RECEPTION	Hotel Saray

Monday 23rd

9:00	I. Porras	Opening
9:10	L. Kankaanranta	BNCT in the treatment of Head and Neck Cancer
9:50	A. Kreiner	Present status of Accelerator-Based BNCT
10:30	*Coffee Break*	
	Neutron Sources 1	***Chair: J. Praena***
11:00	H. Kumada	Current status of the development of the linac based BNCT facility of University of Tsukuba
11:30	L. Evangelista	The MUNES project: State of the art of the INFN BNCT initiative
11:55	S. Domanski	Epithermal neutron source at Maria reactor
12:20	A. Kuznetsov	VITA neutron source for BNCT- Status & prospects
12:45	*Lunch*	
14:00	C. Viñas	The uniqueness of boron clusters for drugs in pharmacology and BNCT
	Boron compounds	***Chair: H. Nakamura***
14:40	R. Núñez	Design and synthesis of boron-rich large molecules for BNCT
15:10	C.-Y. Hsieh	Design and Synthesis of Boron Containing Nanoparticles as BNCT Carrier Agent
15:35	A. Ilinova	Design and biological investigations of the boron cluster conjugates with 5-ethynyl-2'-deoxyuridine as potential BNCT drugs
16:00	M. Bartok	Formation of pores in bilayers with dodecahalogen dodecaborates
16:25	*Coffee Break*	
17:00	***Poster presentations***	***Chair: M.-H. Hsu and G. Vivaldo***
17:30	Poster viewing	

Tuesday 24th

8:00	A. Matsumura	Past, present & future of i- BNCT project
	Clinical Applications and biological studies	***Chair: D. Ngoga***
8:40	N. Protti	Dose calculation in Sprague-Dawley rats affected by limb osteosarcoma for BNCT in vivo tests at the TRIGA reactor in Pavia
9:10	T. Aihara	Boron-neutron capture therapy for newly diagnosed head and neck cancer in initial treatment.
9:40	T. Andoh	Boron neutron capture therapy (BNCT) as a new therapeutic approach for treatment of clear cell sarcoma (CCS): Basic study on a lung metastasis model of CCS for BNCT
10:05	A. Molinari (A. Portu)	Tumor blood vessel normalization prior to Sequential Boron Neutron Capture Therapy (Seq-BNCT) achieves 100% tumor response in an experimental model of oral cancer
10:30	*Coffee Break*	
11:00	D. Nigg	Physical Dosimetry and Spectral Characterization of Neutron Sources for Neutron Capture Therapy - A Brief History and Overview
	Neutron Sources 2	***Chair: H. Kumada***
11:40	Y.-H. Liu	Mixed Field Dosimetry at the THOR BNCT Facility
12:05	Y. Kasesaz	Conceptual Design of an epithermal neutron beam in thermal column of Tehran Research Reactor
12:30	M. Mitev	Sensitivity study of F/M materials for IRT-Sofia NCT beam
12:55	*Lunch*	
14:00	S. Green	Developing the accelerator neutron source for BNCT in Birmingham: dosimetry and radiobiology studies
	Dosimetry and T.P.	***Chair: Y.-H. Liu***
14:40	H. Koivunoro	BNCT treatment planning options for head and neck cancer patients
15:10	K. Yamanashi	Verification of the new BNCT treatment planning system in Tsukuba
15:35	T. Schmitz	The Response of Formate ESR Dosimeters in Thermal Neutron Fields
16:00	M.-C. Hsiao	In-phantom gamma-ray dose mapping in the THOR BNCT epithermal neutron beam
16:25	*Coffee Break*	
17:00	G. Santa Cruz	Microdosimetry: principles and applications
17:30	Poster viewing	
20:00		RECEPTION AT THE ALHAMBRA AND NIGHT VISIT TO THE PALACE

Wednesday 25th

8:30	D. Gabel	How do we find the ideal compound for BNCT?
	Chemistry and pharmacology	***Chair: R. Núñez***
9:10	H. Nakamura	Development of high boron content molecules and their liposome encapsulation for neutron capture therapy
9:40	S. Lin-Chiang Huang	Targeted Drug Delivery System Design & Development for Boron Neutron Capture Therapy
10:05	L. Ciani	Rational design of gold nanoparticles functionalized with carboranes for application in BNCT
10:30	N. Dewi	In vivo Study of Gadolinium-based Compounds as Neutron Capture Therapy Agent
10:55	*Coffee Break*	
	B detection and imaging 1	***Chair: N. Protti***
11:30	Y. Sakurai	A study of boron-dose estimation using boron concentration in plasma
12:00	M. Manabe	Study on measuring device arrangement method of Array-type CdTe Detector for BNCT-SPECT
12:30	A. Portu	Autoradiography in nuclear track detectors: simultaneous observation of cells and nuclear tracks from BNC reaction
12:55	*Lunch*	
14:00	K. Ono	BNCT research in KURRI and start of clinical BNCT trial by small cyclotron neutron generator in KURRI
	Neutron beams	***Chair: S. Bortolussi***
14:40	K. Tanaka	Monte Carlo investigation on measuring spatial distribution of neutrons and gamma rays using multi imaging plate system
15:05	W.-L. Chen	The error index of Monte-Carlo-based detector combination optimization for neutron spectrum deconvolution
15:30	A. Makarov	Neutron spectrum measurement on the tandem accelerator for BNCT using a new time-of-flight method
15:55	Z.-C. Lee	Neutron beam shielding patch for absorbing overdose of neutron radiation
16:20	*Coffee Break*	
	B detection and imaging 2	***Chair: Y. Sakurai***
16:50	H. Tanaka	Study on the evaluation of 10B concentration using proton-induced prompt gamma ray analysis for BNCT
17:20	I. Postuma	An improved neutron autoradiography set-up, applied to 10B concentration measurements for biological samples
20:00		CONFERENCE DINNER

Thursday 26th

8:10	D. Ngoga	The lessons learnt from the Birmingham pharmacokinetic study of BPA-mannitol in patients with high grade glioma to optimise uptake parameters for clinical trials of BNCT
	Applications and biological studies 2	***Chair: G. Santa Cruz***
8:50	A. Monti Hughes	Radioprotective agents to reduce BNCT-induced mucositis in premalignant tissue: Preliminary study in an oral precancer model
9:15	H.-H. Lin	BNCT as alternative radiotherapy ---an application on radioresistance GBM
9:40	C. Rovelli	In situ lung BNCT in a rat model: preliminary histological results on treatments toxicity and efficacy
10:05	N. Kondo	Detection of gamma H2AX foci in mouse brain tissue after neutron capture therapy
10:30	*Coffee Break*	
11:00	T. Kobayashi	Future of Accelerator Based BNCT Neutron Irradiation System using Liquid Lithium Target - The Usage of Neutrons by 7Li(p,n)7Be Near Threshold Reactions -
	Simulations for new applications	***Chair: H. Tanaka***
11:40	M. Ziegner	Monte Carlo dose assessment in cell cultures after enrichment with Gadolinium and irradiation in the neutron field of the TRIGA Mainz
12:05	K. Alikaniotis	Radiotherapy dose enhancement using BNCT in conventional LINACs high-energy treatment: simulation and experiment
12:30	M. Sabaté-Gilarte	Measurement of the 33S(n,α) cross section at n_TOF: applications to BNCT
12:55	*Lunch*	
14:00	***Round table***	***A look ahead to the future of BNCT***
15:00		IAEA TEC-DOC DISCUSSIONS

Posters

P1	M.E. Capoulat	Measurement of the double-differential neutron yield of the 9Be(d,n)10B reaction in the low bombarding energy regime.
P2	V.A. de Castro	Monitoring and evaluation of the irradiation beam of BNCT research facility at IPEN
P3	L. Gagetti	Neutron Production Target for Accelerator - Based Boron Neutron Capture Therapy
P4	M.S. Herrera	New computational method to evaluate the 7Li(p,n)7Be reaction near threshold for accelerator-based BNCT and other applications
P5	M. Sabariego	Rapid evaluation of the gamma dose due to Hydrogen radiative capture in BNCT simulations.
C1	J. Cabrera	Boron enrichment of porphyrin dendrimers with potential application in BNCT
C2	C. Bi	Determination of the isolated quantitation of BSH and BPA by liquid chromatography-electrospray ionization-mass spectrometry (LC/MS)
C3	A. Ogarkov	New efficient methods for the synthesis of cluster anion [B12H12]2– derivatives with the exopolyhedral B-OH reaction site for the subsequent modification in developing BNCT preparations
C4	K. Saito	Simultaneous determination of trace amount of boron-10 chemical species and their concentration in blood by 10B-NMR
C5	C. Schütz	Histomorphological analysis and quantitative determination of p boronophenylalanine in thin tissue sections by LA-ICP-MS for BNCT
C6	M. Shirakawa	Boron Neutron Capture Therapy (BNCT) for liposomal Drug Delivery System by passive targeting.
C7	Y. Yamaguchi	Method development for boron isotope analysis in whole blood by HR-ICP-MS
B1	S. Masunaga	The dependency of compound biological effectiveness factors on the type and concentration of administered neutron capture agents in BNCT
B2	E. Pozzi	Design and characterization of a novel neutron shield for BNCT in an experimental model of oral cancer in the hamster cheek pouch at RA-3
	S. Naserbakht	Design and Simulation of a Target for a Neutron Source Based on the 9Be (p,n) 9B Reaction for BNCT
	W. Zhang	Preliminary Experiment Based on the 10MeV High Intensity Cyclotron(CYCIAE-10) as Neutron Source for BNCT
	L. Zaidi	Monte Carlo simulation of depth–dose distribution in brain model for boron neutron capture therapy

INVITED SPEAKERS

- Lenna Kankaanranta, HUCH, Finland
- Akira Matsumura, Tsukuba University, Japan
- Koji Ono, KURRI, Japan
- David Nigg, INL, USA
- Andrés Kreiner, CNEA, Argentina
- Detlef Gabel, Jacobs University Bremen, Germany
- Tooru Kobayashi, KURRI, Japan
- Stuart Green, QE Hospital, Birmingham, UK
- Gustavo Santa Cruz, CNEA, Argentina
- Clara Viñas, ICMAB-CSIC, Barcelona, Spain

Talks

Present status of Accelerator-Based BNCT

A.J.Kreiner [1-3], J. Bergueiro[1], M. Baldo[1], D. Cartelli[1-3], W. Castell[1], J. Gómez[1], J. Padulo[1], J. C. Suarez Sandín[1], M. Igarzábal[1], J. Erhardt[1],
D. O. Mercuri[1], D. M. Minsky[1-3], A. A. Valda[1,2], J. M. Kesque[1], M. E. Capoulat[1-3], M. S. Herrera[1-3], S. González[1-3], H. Somacal[1,2], M. E. Debray[1,2], M.F. del Grosso[1,2], L. Gaggetti[1-3], M. Suárez Anzorena[1],
N. Canepa[1], N. Real[1], M. Gun[4], H.Tacca [4] , L. Rogulich[1,2].

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Accelerator-Based BNCT (AB-BNCT) is establishing itself worldwide as the future modality to start the phase of in-hospital facilities. There are projects in Israel, Italy, Japan, Russia, UK and Argentina to develop AB-BNCT around different types of accelerators. They will be mentioned and compared. In particular, the present status and recent progress of the Argentine project [1] will be presented. The topics will cover: accelerator prototypes under development and construction, transport of intense beams, beam diagnostics, high power targets, the ^{9}Be(d,n) reaction as a possible neutron source, treatment planning assessment of clinical cases, etc. A complete 200 kV accelerator prototype has been built and results will be shown. A 600 kV prototype is under construction. An ion source test stand has been built and commissioned for intense proton beam production and characterization. Beam diagnostics has been performed through the observation of induced fluorescence in the residual gas. Selfconsistent space charge beam transport simulations have been performed and compared with experimental results. In addition to the traditional ^{7}Li(p,n)^{7}Be reaction, ^{9}Be(d,n)^{10}B using a thin Be target has been thoroughly studied as a candidate for a possible neutron source for deep seated tumors, showing a satisfactory performance [2]. Results on Be-based neutron production targets will be briefly mentioned [3]. Realistic clinical treatment planning cases for ^{7}Li(p,n)^{7}Be–based AB-BNCT have also been studied showing very good results [4].

[1] A J Kreiner, W Castell, H Di Paolo, M Baldo, J Bergueiro, A A Burlon, D Cartelli, V Thatar Vento, J M Kesque, J Erhardt, J C Ilardo, A A Valda, M E Debray, H R Somacal, J C Suarez Sandin, M Igarzabal, H Huck, L Estrada, M Repetto, M Obligado, J Padulo, D M Minsky, M Herrera, S J Gonzalez and M E Capoulat, ”Development of a Tandem-Electrostatic-Quadrupole facility for Accelerator-Based Boron Neutron Capture Therapy”, Appl. Radiat. Isotopes 69, (12)1672–1675 (2011) and references therein.
[2] E Capoulat, D M Minsky and A J Kreiner, “Computational assessment of deep-seated tumor treatment capability of the 9Be(d,n)10B reaction for Accelerator-Based Boron Neutron Capture Therapy (AB-BNCT)”, Physica Medica, EJMP-D-13-00018R2 (2013).
[3] M Suarez Anzorena, L Gagetti, M F del Grosso and A J Kreiner, “Caracterizacion de depositos de Be sobre sustratos de Mo, W y Cu para implementar un blanco de producción de neutrones para AB-BNCT”, 13 Congreso Internacional de Ciencia y Tecnología de Metalurgia y Materiales, en prensa (2013).
[4] M Herrera, S Gonzalez, D M Minsky, A J Kreiner, “Evaluation of performance of an accelerator-based BNCT facility for the treatment of different tumor targets”, Physica Medica (Europ. Journal Medical Physics), 272, DOI information: 10.1016/j.ejmp.2013.01.006.

Current status of the development of the linac based BNCT facility of University of Tsukuba

Hiroaki Kumada[1], Akira Matsumura[1], Hideyuki Sakurai[1], Takeji Sakae[1], Masakazu Yoshioka[2], Hitoshi Kobayashi[2], Yoshiaki Kiyanagi[3], Fujio Hiraga[3], Hiroshi Nakashima[4] , Takemi Nakamura[4],

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To establish accelerator based boron neutron capture therapy (BNCT), development of an RFQ and DTL type linac based BNCT facility is being performed by a project team headed by University of Tsukuba launched [1]. The project has chosen beryllium as neutron target material. And proton energy was set to 8MeV and average current of proton has been set to 10mA. At present we are designing neutron generator device which can generate suitable epithermal neutrons. And we are also developing several medical devices such treatment planning system, and patient setting device and PG-SPECT in addition to the accelerator based neutron source.

The neutron generator consists of beryllium target system, moderator, collimator and radiation shield. To design the neutron generator, Monte-Carlo transport analysis using PHITS [2] is being performed. Materials and shapes of each device were determined by the PHITS estimation while changing the parameters of material, dimensions and shape of each element. Furthermore analysis using DCHAIN-SP [3] is being performed to estimate amount of activity of the device.

Depth of Bragg peak of 8MeV proton energy is less than 1mm. Thus thickness of the beryllium is set as 0.5mm. For moderator design, iron is located behind of beryllium target system as fast neutron filter. And PHITS estimation proved that MgF_2 can decelerate fast neutrons to epithermal neutrons effectively than other materials such as $CalF_2$ and FLUENTAL^{TM}. Thus we have chosen MgF_2 as moderator material. Finally we found a proper model of the neutron generator which can emit high-intensity epithermal neutrons (>2.0 n/cm^2/s) with 80kW proton.

We fix the design in the near future and then production of the neutron generator based on the design is begun in 2013. And in the schedule, epithermal neutrons with full power accelerator operation will be emitted in 2014.

[1] H. Kumada, et al., Abstract of 15th ICNCT, 109, (2012)
[2] H. Iwase, et al., J. Nucl. Sci. Technol., 39, 1142-1151, (2002)
[3] T.Kai et al., JAERI-Data/Code 2001-016 (2001)

The MUNES project

State of the art of the INFN BNCT initiative

Sabina Chiriotti Alvarez [1,2,3]

[1]*Laboratori Nazionali di Legnaro, Legnaro INFN-LNL, Legnaro, Italy.*

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In the framework of MUNES (MUltidisciplinary NEutron Source) project [1], INFN is building an accelerator-driven neutron source devoted to BNCT applications and to radioactive waste characterization. Neutrons are generated by 9Be(p,n)9B nuclear reaction in a high power (150 kW) beryllium target. A neutron source rate higher than 1014 n/s can be obtained with a 30 mA, 5 MeV primary proton beam. The project aims to construct: i) a high-power radiofrequency quadrupole accelerator (RFQ); ii) a beryllium proton-neutron converter equipped with a beam shape assembly (BSA) for treating superficial tumours and iii) a microdosimetric setup for monitoring the therapeutic field quality (TFQ).
The talk will give an overview of the state of the art of the MUNES project. The three MUNES aims will be presented. Firstly, details about the RFQ high power tests will be shown which have been successfully passed recently. The second part of the presentation will deal about the high-power beryllium target power and neutron-damage tests. However, recent proton-damage studies have pointed out significant swelling effects. Therefore, further investigations are on-going for minimizing the swelling effects and preventing blistering. Finally, the microdosimetric setup for TFQ characterization which has been recently used at the BNCT irradiation facility of LENA nuclear reactor in Pavia will be presented. Results from the experimental measurements are promising, despite of the difficulty to precisely determine the 10B concentration in the counter wall.

[1] URL: http://www.lnl.infn.it/~munes/

Ephitermal neutron source at Maria reactor

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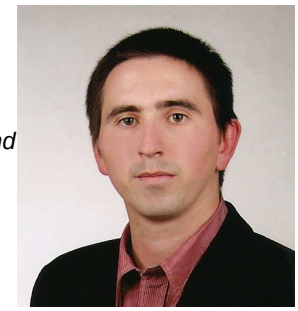

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BNCT research program started in Poland in 2001, in former Institute of Atomic Energy in Świerk (now the Institute is included to National Centre for Nuclear Research). The underwater neutron line for BNCT was mounted along the H2 horizontal beam tube of the research reactor MARIA in Świerk. At that time the line consisted of two pneumatic caissons coupled with a pneumatic system for emptying/refilling. The neutron spectrum of the beam contained mostly thermal neutrons, so a fission converter was designed at the mouth of the channel, but never constructed. After six years in the reactor pool, one of the caissons was broken. It was decided to remove both caissons and to replace them by one pipe coupled with the same pneumatic system as before. A new concept of an underwater, in pool fission converter has been elaborated and the line was constructed in 2010.

According to the new concept, the uranium converter is located in the reactor pool, near the front of the H2 channel. Tubular design of the internal channel makes the construction resistant to mechanical load. The converter consists of 99 densely packed fuel elements EK-10 with enrichment of 10%, placed in the triangle lattice with the distance of 12 mm. All fuel elements were carefully re-attested with special attention to leak tightness. There is a possibility to remove the converter and to replace it with an aluminium dummy. It is also possible to mount the converter after turn by 180° around the vertical axis, in order to equalize thermal and neutron loads. A measuring probe with two thermocouples measures the temperature increase in the converter. The line was equipped with moderator-filter system made with lithium fluoride; nickel, titanium, bismuth and B_4C.

At present, the line is technically ready for use, however, there was no possibility to get financing for the BNCT scientific program, so the converter never was irradiated in the reactor, in order to avoid production of nuclear waste.

Monte-Carlo calculations showed that the total neutron flux density at the entrance to the converter is of about 10^{13}n $cm^{-2}s^{-1}$ and flux density of epithermal neutrons at the entrance to the filter/moderator of the beam is of about $2 \cdot 10^{9}$ n $cm^{-2}s^{-1}$.

Conducting of the biological research at the accelerator-based epithermal neutron source

V. Aleynik[1], Z. Annayev[4], N. Gubanova[3], V. Kanygin[4], D. Kasatov[2], A. Kichigin[4], A. Kiskayev[4], A. Kuznetsov[1], A. Makarov[1], R. Morozov[2], S. Sinitskiy[1], S. Taskaev[1], **I. Shchudlo[1]**

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Ivan SHCHudlo (cshudlo.i.m@gmail.com)

At BINP (Novosibirsk, Russia) it is constructed and put into operation a neutron source based on a tandem accelerator with vacuum insulation and the generation of neutrons using ^{7}Li(*p,n*)^{7}Be reaction [1]. The parameters of the generated neutron flux allow us to carry out *in vitro* and *in vivo* experiments for BNCT.
Spatial distributions of the dose rate of the generated neutrons and associated gamma-rays and their energy spectra are measured. This paper presents the results of these studies and discussion.
In vitro studies on radiation effect on cells were conducted. The cells were exposed to fast and slow neutrons separately. Some of cells have been previously enriched with boron using BPA. The obtained results demonstrate the possibility of using our accelerator for BNCT development.

[1] V. Aleinik, A. Burdakov, V. Davydenko, A. Ivanov, V. Kanygin, A. Kuznetsov, A. Makarov, I. Sorokin and S. Taskaev. *BINP accelerator based epithermal neutron source*. Proceedings of 14-th International Congress on Neutron Capture Therapy. October 25-29, 2010, Buenos Aires, Argentina, p.441-444.

VITA neutron source for BNCT – Status and Prospects

V. Aleynik[1], N. Gubanova[3], D. Kasatov[2], **A. Kuznetsov[1]**, A. Makarov[1], R. Morozov[2], S. Sinitskiy[1], S. Taskaev[1], I. Shchudlo[1]

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Aleksandr Kuznetsov (A.S.Kuznetsov@inp.nsk.su)

At BINP (Novosibirsk, Russia) the epithermal neutron source based on the Vacuum Insulated Tandem Accelerator (VITA) is constructed and put into operation. The generation of neutrons is carried out using ^{7}Li(*p*,*n*)^{7}Be reaction [1]. The parameters of the generated neutron flux allow us to carry out *in vitro* and *in vivo* experiments for BNCT.
During last years we tested and confirmed all ideas initially proposed for the facility. Steady state current transported through the accelerator system can rich 2.5 mA. Proton energy reached 2 MeV. Investigations of the neutron spectrum and spatial distribution dose rate as well as preliminary *in vitro* biological experiments were carried out.
The neutron beam shaping assembly is designed. That assembly makes possible to provide a higher neutron dose to the patient: 0.3 Sv/min per 1 mA at 2.5 MeV beam energy [2]. It is already possible to get a minimal required neutron flux using this beam shaping assembly with the obtained proton beam.
To the present moment all the reasons that limit the accelerator current are investigated and several approaches to increase the current are proposed. The first approach is to avoid the influence of the stripping gas to the accelerator electrodes. The second approach is to use a new negative hydrogen ion source. New source is now under construction and it will allow us to obtain 10 mA of proton current which is acceptable for BNCT in clinic.

[1] V. Aleynik, A. Burdakov, V. Davydenko, A. Ivanov, V. Kanygin, A. Kuznetsov, A. Makarov, I. Sorokin, and S. Taskaev. BINP accelerator based epithermal neutron source. Applied Radiation and Isotopes, 69 (2011) 1635-1638.
[2] E. Kashaeva, G. Malyshkin, S. Samarina, S. Taskaev. Regimes of therapeutic beam shaping from an accelerator neutron source. Abstracts of the 15th International Congress on Neutron Capture Therapy, 10-14 September 2012, Tsukuba, Japan, p. 138-139.

The uniqueness of boron clusters for drugs in pharmacology and BNCT

A. Cioran[1], F. Teixidor[1], A. Vaca[1], A. Pepiol[1], M. Lupu[1], R. Sillanpää[2], M. Brust[3], and **Clara Viñas**[†,1]

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[2] *Department of Chemistry, University of Jyväskylä, Finland.*

[3] *Department of Chemistry, University of Liverpool, U.K.*

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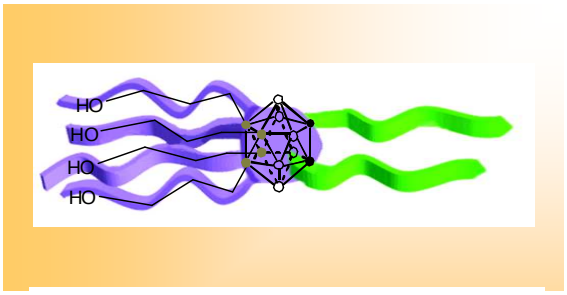
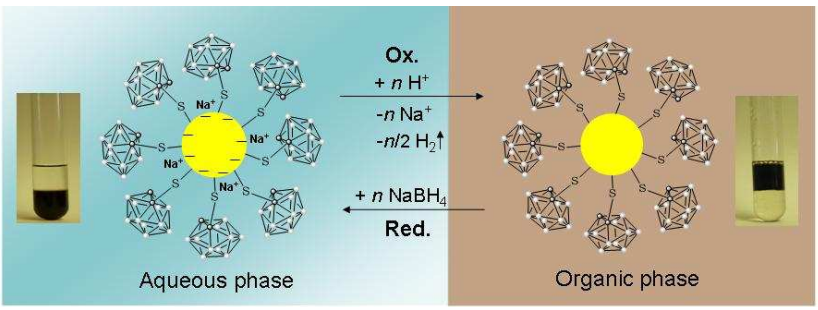
The aim of this presentation is to show the ability of boron clusters in producing new molecules, large molecule and dendrons for their desired application in pharmacology, medicine, neutron sensing and BNCT. For these purposes new methods of functionalizing the boron clusters are needed [1]. These shall facilitate the synthesis of molecules and macromolecules with high boron content [2], of relevance in medicine for BNCT and neutron sensing, or the grafting of the boron clusters on surfaces of different nature.

1) Carboranes are molecules with unique structural features due to their rigid geometry and rich derivative chemistry, which make them of great interest as building blocks for macromolecular or supramolecular entities. o-Carborane derivatives with precisely defined patterns of substitution have been prepared from 8,9,10,12-I_4-1,2-*closo*-$C_2B_{10}H_8$ [3] by replacing the iodine atoms, bonded to four adjacent boron vertices in the cluster, with allyl, and subsequently 3-hydroxypropyl groups [2]. The resulting structures, comprising four pendant arms in a compact region and two reactive vertices located on opposite sides of a central o-carborane core can be envisaged as versatile precursors for dendritic growth. The formation of high content and highly dense boron compounds shall be relevant in facets as diverse as Boron Neutron Capture Therapy, Drug Delivery or neutron sensing.



2) A new type of MPC, which is hydrophobic and completely insoluble in water when uncharged, but, when offered electrons by a suitable reducing agent, transfers readily to an aqueous phase where it behaves as a Henglein-type electron pool is here described. In addition, exchangeable cations can be stored in the ligand shell. When discharged, the particles precipitate in water and re-dissolve readily in less polar solvents. These unprecedented properties are due to the use of mercaptocarborane clusters as capping agents, which like other thiol ligands, effectively stabilize the gold core, but owing to their spherical shape necessarily leave gaps that allow



direct access of reactants and solvent molecules to the gold surface. The design of water-soluble boron rich macromolecules or particles is of significance for Boron Neutron Capture Therapy (BNCT) and for drug delivery. The design of water-soluble boron rich macromolecules or particles is of significance for medicine and for drug delivery. The excellent water-solubility of these materials is highly unusual, representing a rare case of a carborane-based macromolecular unit with potentially high bioavailability for application in BNCT.[4]

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Design and Synthesis of Boron Containing Nanoparticles as BNCT Carrier Agent

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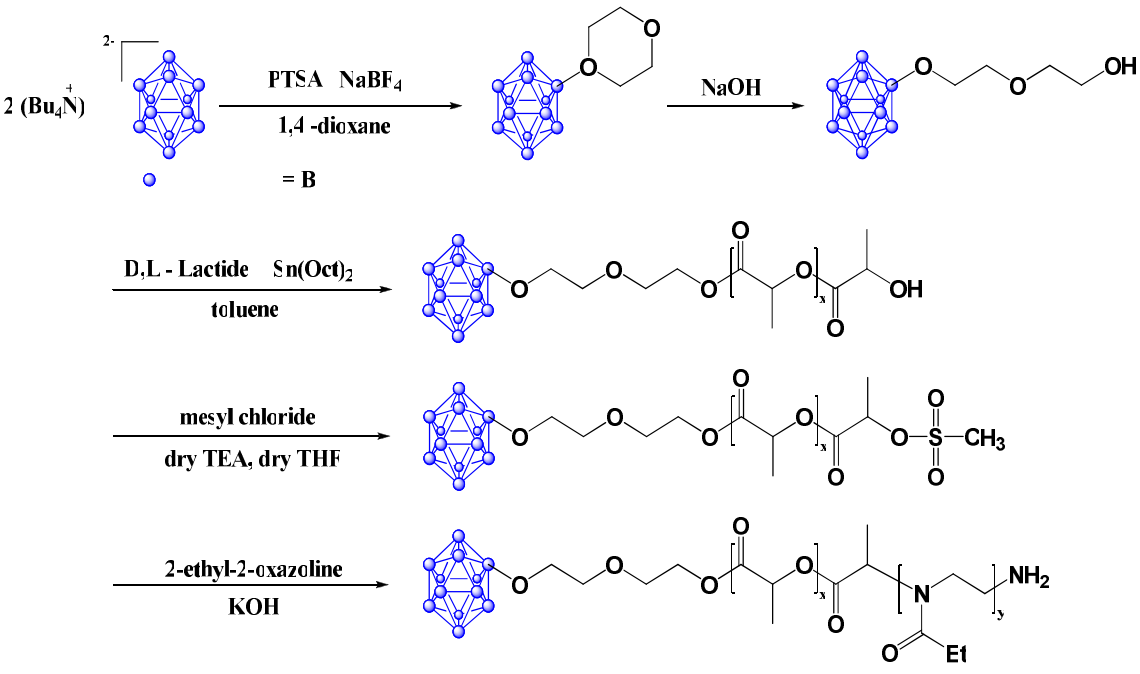
The boron neutron capture therapy (BNCT) had been developed over 50 years. But currently still only two compounds are used on the clinical trial. One is sodium mercaptoundecahydro-closo-dodecaborate (Na2B12H11SH, also knowm as BSH). The other is an amino acid : (L)-4-dihydroxy-borylphenylalanine(also known as L-BPA).
Nanoparticles are not a new issue but still a very useful concept on drug delivery system. Block copolymer had been develop for many years, the hydrophobic segment and hydrophilic segment will help the copolymer formed a core-shell micelles. The hydrophobic core of micelles can be loaded drugs inside while the hydrophilic shell contributes the stability and solubility in aqueous solution. And we can change different equivalent of the reagent to make different size of copolymer.

Now we plan to develop the boron containing block copolymers for BNCT which incorporated boron rich compound, dodecahydro-closo-dodecaborate anion [B12H12]2-
into the biodegradable polymer, poly(L-lactide)-block-poly(2-ethyl-2-ozazoline). The copolymer (PLA-PEOz) will self-assemble into micelles which able to diffuse and accumulate into tumor cells through enhanced permeability and retention (EPR) effect.



Design and biological investigations of the boron cluster conjugates with 5-ethynyl-2'-deoxyuridine as potential BNCT drugs.

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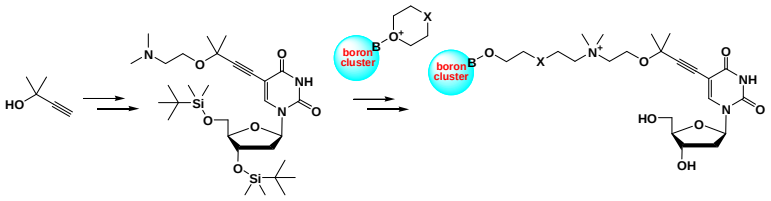
Boron containing nucleosides are considered to be potential boron carriers for the boron neutron capture therapy (BNCT) of tumors [1, 2]. Various 5-alkynyl modified 2'-deoxyuridines have incessant interest because substitution at position 5 of the pyrimidine nucleobase often does not attenuate susceptibility to nucleoside metabolizing enzymes and does not impart any significant conformational changes in oligonucleotides incorporating the modified unit [3, 4]. Potential incorporation of the boronated nucleoside into replicating DNA of tumor cells is important for the delivery of the boron into the tumor cell nuclei directly and increases of BNCT efficacy. Therefore, 5-ethynyl-2'-deoxyuridine fragment as potential boron carrier seems to be very prospective. Surprisingly, only one compound of such kind, bearing *o*-carborane cluster (5-(4-(o-carboran-1-yl)-l-butynyl)-2'-deoxyuridine) was designed till now to our best knowledge [5].



In this contribution we would like to present synthesis of novel derivatives of 5-ethynyl-2'-deoxyuridine with *closo*-dodecaborate and cobalt-*bis*-dicarbollide. At the first step of our investigation new 5-ethynyl-2'-deoxyuridine modification was effectively synthesized. Then, desired conjugates were prepared by its reactions with a range of cyclic oxonium adducts of *closo*-dodecaborate and cobalt-*bis*-dicarbollide boron clusters. Cytotoxicity of these new conjugates in several cell lines was examined. *Closo*-dodecaborate conjugates showed low cytotoxicity in all examined cell lines, and thus these compounds are prospective for the further studies as potential agents for boron neutron capture therapy (BNCT) of tumors.

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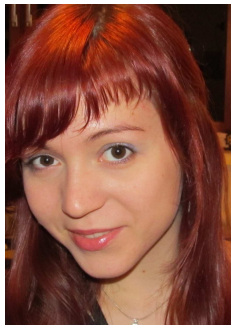
Formation of pores in bilayers with dodecahalogen dodecaborates



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Dodecahalogen dodecaborate molecules, with an icosaedrical structure and two negative charges, were synthesized by an eletrophile substitution reaction from dodecahydro-dodecaborates[1]. Their interaction with lipid membranes was studied. The zeta potential measurements show a strong interaction of the cluster molecules to the liposomal surface. This interaction can induce complete leakage of an encapsulated fluorophore at a very low concentration (5 μM), which makes these molecules great candidates for drug release. Interestingly when DPPC liposomes are heated in the presence of $Na_2B_{12}I_{12}$ above the phase transition temperature of the lipid, major structural changes of the liposomes occur. Also in black lipid membranes, electrophysiological measurements show strong interaction of the $Na_2B_{12}I_{12}$ cluster. These interactions lead to transient holes in the lipid bilayers, resulting in the flow of ions across the membrane. The holes are open for very short time, mostly below the time resolution of the instrument used for the measurements. The average pore size in DPhPC bilayers is 10 Å, and the holes are open just under potential, when the voltage is removed the pores are closed, but the original state is not restored, because when voltage is applied again, much stronger interaction of the cluster on the bilayer is seen, even at very low voltages.
These results can have bearing on the use of boron cluster compounds for BNCT.

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Synthesis of monosubstituted functional derivatives of *ortho*-carborane for boron neutron capture therapy

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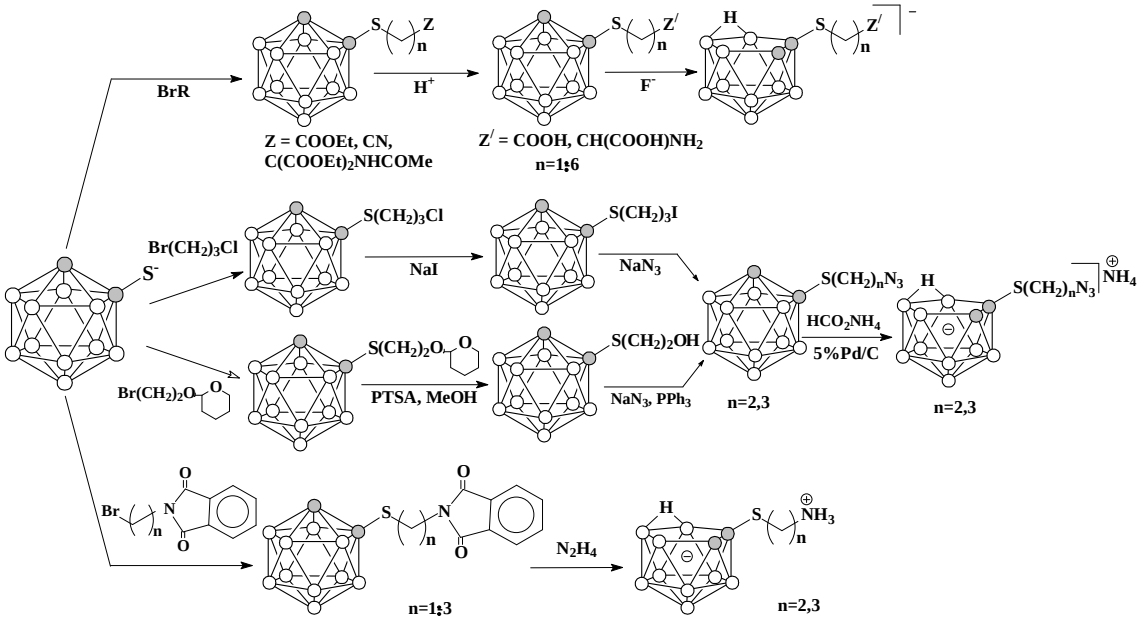
The 1-mercapto-*ortho*-carborane [1] is a good precursor for synthesis of monosubstituted functional derivatives of 1,2-dicarba-*closo*-dodecaborane. In this contribution we report about the synthesis of acids, amines, aminoacids and azides on the base of 1-mercapto-*ortho*-carborane in *closo*- and water-soluble *nido*-forms.



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Past, present & future of i- BNCT project

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Boron Neutron Capture Therapy (BNCT) has been based on the thermal or epithermal neutron from the research reactors. The neutron beam from the research reactors were optimized for the BNCT with high neutron flux. This lead the clinical trial to various cancers such as malignant brain tumour, skin melanoma and recently application to the head & neck cancer has been spread extensively.

Our clinical trial for glioblastoma resulted in favourable outcome with a median survival period of 25 months compared to 12 months in conventional therapy (before Temozolomide era). (1, 2). Selective high dose irradiation to the glioblastoma provide relative good outcome if the radiation necrosis could be avoided. For this purpose BNCT and/or proton therapy are ideal treatment modalities (3)

With the recent advancement in accelerator technology, an interest of the neutron source for BNCT has been increased and several practical projects for in-hospital accelerator based BNCT has been started. Recently, the team of University of Tsukuba, High Energy Accelerator Research Organization, Hokkaido University, Japan Atomic Energy Agency (JAEA) and private companies has created a project for LINAC based BNCT treatment system. The accelerator technology was based on the previous R&D from the J-PARC LINAC accelerator and it was modified for the special use for BNCT. The accelerator consists of RFQ and DTL with beam energy of 8MeV and max. Electrical current at 10mA.

If the in-hospital BNCT treatment facility could realized many type of cancers which has been treated by conventional radiation methods could be introduced to BNCT (i.e., breast cancer, thyroid cancer, lung cancer, liver cancer, chest wall cancer. etc.).

We will present the possibility of accelerator BNCT in our hospital and discuss about the future prospects of in-hospital BNCT.

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Dose calculation in Sprague-Dawley rats affected by limb osteosarcoma for BNCT *in vivo* tests at the TRIGA reactor in Pavia

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Osteosarcoma is the most common non-hematologic primary cancer that affects bones. The patients are typically very young, the first incident peak being between 10 and 20 years. The conventional treatment is multiagent chemotherapy combined with extensive surgical resection, which can require the amputation of the entire limb. Nevertheless, the infiltrative growth of the tumour leads to a high incidence of local and distant recurrences that reduce the percentage of cured patients to less than 60%. Because of these poor outcomes, the identification of a new treatment option is very timely. A research project on the BNCT for osteosarcoma is ongoing at the University of Pavia.

To perform the experiments, a suitable animal model has been developed, using immunosuppressed Sprague-Dawley rats inoculated with $1 \cdot 10^7$ UMR-106 cells through the femoral condyle. Tumour cells are then loaded by innovative ^{10}B carriers, based on liposomes and nanoparticles developed at the University of Florence and of Eastern Piedmont. The *in vivo* experiments are performed at the thermal neutron facility of the TRIGA research nuclear reactor in Pavia. The original thermal column has been modified to house an irradiation chamber characterized by a non collimated neutron field with a low contamination of epithermal and fast neutrons as well as of photons. To spare the healthy organs of the animal, the irradiation set-up has been designed and optimized using the simulation code MCNP5. In particular, a suitable neutron shield made of 95% ^6Li enriched carbonate is used.
The talk will show the results of the treatment planning, in particular the optimization of the neutron shield and the dose estimations in the tumour and in the radiosensitive organs obtained by the Monte Carlo calculations.

Boron-neutron capture therapy for newly diagnosed head and neck cancer in initial treatment.

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

MATERIALS and METHODS: seven patients were treated with BNCT at KUR and JRR-4 from Aplei 2006 to March 2013. The histologic type of carcinoma, primary region, and TNM staging in each patient were as follows: Patient 1: acinic cell carcinoma; palotid gland; T4N0M0, Patient 2: adenoid cystic carcinoma; lacrimal sac; T4N0M0, Patient 3: ACC; maxillary sinus; T4N0M0, Patient 4: epitheliomyoepithelial carcinoma; nasal cavity; T3N0M0, Patient 5: squamous cell carcinoma; Neck; TxN2aM0, Patient 6: leiomyosarcoma; Neck; T4N0M0, Patients 7: salivary duct carcinoma; Pterygoid fossa; T4N1M0. Acceptable criteria is followings: (1) With newly diagnosed head and neck T3/T4 tumors that surgical treatment is not indicated, (2) The depth of tumor, less than 6cm, and without distant metastases, (3) PS□ 2, (4)T/N ratio □2.5 using 18F-BPA□PET, (5)Consent to perform BNCT, (6)With the approval of our Medical Ethics Committee. The procedures for BNCT using BPA were as follows: 1) Intravenous administration of BPA-fructose complex (500mg/Kg.BW) for 2.5 to 3 hour and blood sampling at the time of just finished BPA-drip and just before irradiation. The 10B concentration in the blood was measured by prompt γ-ray spectrometry. 2) Epithermal neutron irradiation at the KUR/JRR4 with a reactor power of 5MW/3.5MW. The irradiation field was large enough to cover the target area for the neutron beam (10 cm×10 cm). 3) Neutron flux measurement using gold wire 15 min. after the start of irradiation. 4) Optimization of the neutron dose based on the measured blood 10B concentration and neutron flux. The tumor dose and normal tissue dose calculated ranged from 20.0 to 30.0Gy-Eq and from Less than 15Gy-Eq, respectively. The median duration of observation is 29.9 months after BNCT.

RESULTS: Five patients demonstrated regional CR, One patient were PR, another patient were NC. The effective rate [(CR + PR)/total cases] was 83%. PR patient and NC patients were operated on after radiation. This reaction was disappeared within 3-5 weeks. Four patients are living. All patients had no acute severe complications such as skin ulcers, xerostomia, and palsy of the cervical spinal cord. There were evidence of visual disturbance

and cataract 3 years after BNCT in the ipsilateral side of eye being included in radiation field in patients 2.

CONCLUSION: Our results validate the efficacy of BNCT in the treatment of patients with AHNC. Although this is a report of only 7 patients, and additional long-term follow-up should be required to assess this treatment. We have estimated T/N boron ratio using 18F-BPA-PET in every cases. The T/N ratios measured are the values of BPA alone. If T/N ratio was more than 2.5, according to our adaptation, it is thought that therapy effect is good. We believe that head and neck tumors are suitable for BNCT and that such excellent results will have a great impact on patients in the near future.

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Boron neutron capture therapy (BNCT) as a new therapeutic approach for treatment of clear cell sarcoma (CCS): Basic study on a lung metastasis model of CCS for BNCT

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Clear cell sarcoma (CCS) is a rare malignant tumor with a poor prognosis. Metastasis occurs in more than 50% of such patients. The standard treatment for CCS is wide surgical resection, and neither chemotherapy nor common radiotherapy is effective. Our previous study demonstrated that in vitro cultured CCS cells have the ability to highly take up p-borono-L-phenylalanine (L-BPA) [1] and remarkable accumulation of 10B in tumor occurred after L-BPA-Fructose complex (BPA-Fr) was intravenously administered to subcutaneously CCS-bearing mice in vivo [2]. As a result, disappearance of the tumor could be achieved after BNCT was carried out for the mice [3]. In the present study, we established a lung metastasis model of CCS and evaluated biodistribution of 10B after intravenous administration of BPA-Fr (24 mg 10B/kg) for BNCT trial.

L-BPA (Stellra Pharma Corp., Osaka, Japan) was used as BPA-Fr (4000 µg 10B/mL). MP-CCS-SY, a CCS cell line of human origin, was suspended in 10 µg Matrigel®. The cell suspension (1× 106 cells/mouse) was injected into a parenchyma of left lung in 7 weeks old female nude mice [4]. After 8 weeks, tumor in the mouse was observed by a CT scan using R-mCT2 (Rigaku Corp., Tokyo, Japan) in Kitasuma Animal Hospital (Hyogo, Japan). BPA-Fr (24 mg 10B/kg) was intravenously administered to the CCS-bearing mice. At a predetermined time after administration, the mice were sacrificed and blood and tissue samples were collected immediately. The boron concentration in the samples was determined by ICP-AES.

The lung metastasis model of CCS was obtained successfully; the tumor mass was found to be localized in surface of left lung parenchyma of the mice by macroscopic observation and a

CT scan. HE staining data revealed that the tumor tissue was composed of nests monotonous polygonal cells with clear cytoplasm. The lung metastasis model and the subcutaneously CCS-bearing model previously developed [2] shared many similarities in the biodistribution profile of 10B after intravenous administration of BPA-Fr to each model animal. One hour after the BPA-Fr administration, 10B concentration in tumor tissue in the lung metastasis model reached 51 μg 10B/g wet tumor tissue. Tumor-to-blood and tumor-to-normal tissue (left lung) ratios were 5.3 and 11.8, respectively, at the same time point. A preclinical BNCT trial using a lung metastasis model of CCS will be a next issue to clarify whether BNCT using BPA-Fr can be a promising therapeutic option for the CCS.

Acknowledgments
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Tumor blood vessel normalization prior to Sequential Boron Neutron Capture Therapy (Seq-BNCT) achieves 100% tumor response in an experimental model of oral cancer

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Purpose: We previously proved the therapeutic efficacy of Sequential Boron Neutron Capture Therapy (Seq-BNCT), i.e. BPA-BNCT followed by GB-10-BNCT 2 days later, in the hamster cheek pouch oral cancer model. Additionally, we proved that tumor blood vessel normalization improves boron targeting in BPA-BNCT in the same model. The aim of the present study was to evaluate the therapeutic efficacy and potential boron microdistribution changes of Seq-BNCT preceded by tumor blood vessel normalization for experimental oral cancer in the hamster cheek pouch model.
Methods and Materials: Gross boron content and boron microdistribution were assessed by ICP-MS and neutron autoradiography respectively. Therapy studies were performed in 2 groups, i.e. Th+Seq-BNCT: Tumor bearing animals treated with two doses of thalidomide on 2 consecutive days for tumor blood vessel normalization, followed by Seq-BNCT at RA-3 Nuclear Reactor in the window of normalization; Th+Seq-BO: Tumor bearing animals treated with thalidomide followed by Sequential Beam only irradiations, matched for neutron fluence with BNCT irradiations.
Results: At 28 days post-treatment Th+Seq-BNCT induced overall tumor response of 100 ± 0%, with 87 ± 4 % complete tumor response. No cases of severe mucositis in dose-limiting precancerous tissue were observed. Th+Seq-BO induced a significantly lower overall tumor response of 6 ± 4 %, with no complete tumor response and no mucositis.
Conclusions: Tumor blood vessel normalization followed by Seq-BNCT achieved, for the first time, response in all the treated tumors, with only slight-moderate mucositis in precancerous tissue. This protocol offers a therapeutic advantage compared to Seq-BNCT alone and would contribute to the optimization of BNCT for head and neck cancer. Boron microdistribution analysis revealed that increased homogeneity in tumor boron targeting is associated to an improvement in tumor control.

Mixed Field Dosimetry at the THOR BNCT Facility

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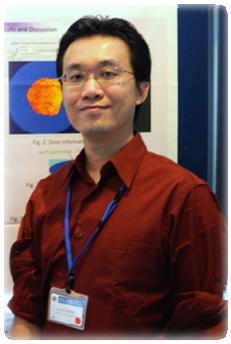

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The administration of boron neutron capture therapy involves neutron beams, which contain two very different neutral radiation particles, neutrons and gamma rays. The two radiation components make the BNCT dosimetry affiliated to mixed field dosimetry, which concerns the separation of different radiation components in a mixed radiation field.

This presentation aims to have the audience a general ideal of BNCT dosimetry. Many tools and methods have been proposed for the mixed field dosimetry for BNCT; for the sake of illustration, the dosimetry means used at the Tsing Hua Open-pool Reactor (THOR) will be introduced and summarized, including the methods/determinations of, 1) real-time monitoring, 2) thermal and epithermal neutron fluxes, 3) neutron energy spectrum, 3) neutron angular and spatial distributions; 4) neutron and gamma-ray dose rates; 5) 2-dimentional distribution of gamma-ray dose.

The detection system hardware and software involves the following tools/methodologies: 1) fission chambers; 2) multiple neutron activation detectors; 3) paired ionization chambers; 4) imaging plate system; 5) Gafchromic EBT2 film system; 6) Monte Carlo determined detector response functions; 7) indirect neutron radiography; 8) SAND-EX unfolding computer code. With the aid of abovementioned tools/methods, we are able to successfully establish thorough information with regards to the beam neutron and gamma-ray characteristics. In addition, some more advanced studies concerning the BNCT dosimetry will be presented.

Conceptual Design of an epithermal neutron beam in thermal column of Tehran Research Reactor

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Tehran Research Reactor (TRR) is a 5 MW MTR, pool type research reactor. It has seven beam tubes with different sizes and geometries, a thermal column which is filled with removable graphite blocks, and a medical room which is provided behind the east wall of the open pool (Fig.1). In order to using TRR for BNCT, energy spectrum and spatial distribution of neutrons measured and calculated in all irradiation facilities. It was found that long length beam tubes cannot provide appropriate neutron flux for BNCT. On the other hand, using the medical room is difficult in practice and needs some basic changes in the reactor pool wall. It was found that thermal column is the best choice if all graphite blocks can be removed from it. Considering this situation a Beam Shaping Assembly (BSA) has been designed and optimized based on IAEA recommended BNCT neutron beam parameters [1] using MCNP4C code [2]. The suggested BSA configuration in cylindrical geometry consists of 30 cm Al as a moderator, 35 cm Pb as a reflector and gamma shield, and two 2mm Cd sheets as thermal neutron filters. The results show that epithermal neutron flux at the exit of the BSA can be 1.15 × 109 n/cm2.s. In-phantom dose analysis indicates that the designed neutron beam can be used for treatment of deep-seated brain tumors in acceptable time.

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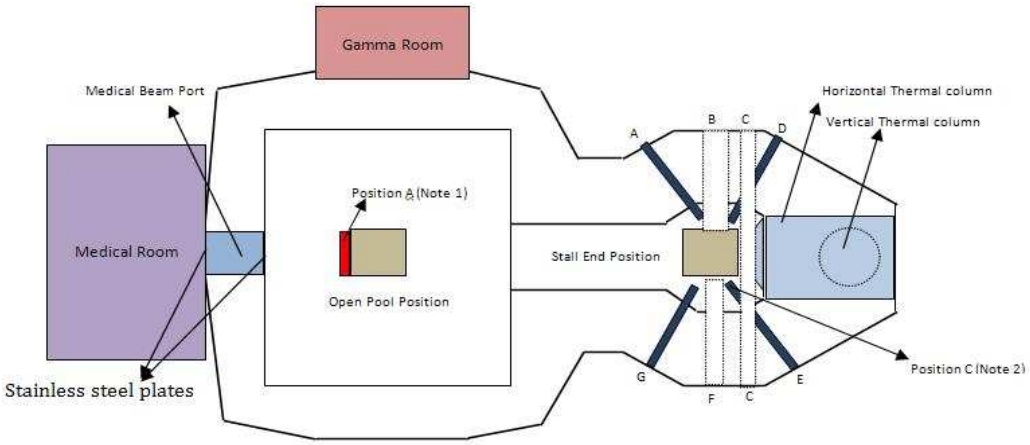

Fig.1 Schematic view of TRR pools and its irradiation facilities, A, D, G, E: 6” diameter beam tube, C: 6” diameter through tube, B: 12”×12” beam tube, F: 8” diameter beam tube
Note 1: When the reactor core set in the open pool position, open pool experiment is done in position A.
Note 2: E beam tube experiment is performed in this position when the reactor core set in stall end position.

Sensitivity study of F/M materials for IRT-Sofia NCT beam

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The Research Reactor IRT-Sofia of the Institute for Nuclear Research and Nuclear Energy of Bulgarian Academy of Sciences is in a process of fuel conversion and refurbishment. Building of a channel for Boron Neutron Capture Therapy (NCT) is ongoing. The optimization study of IRT-Sofia BNCT beam tube based on MIT/FCB (Massachusetts Institute for Technologies/Fission Converter Based) facility experience [1] was presented on 14th ICNCT at Buenos Aires by Belousov et al. It was shown [2] that the IRT's BNCT channel will provide an epithermal beam with properties close to the best values in the world. Further investigations showed [3] that the PTFE in the filter/moderator (F/M) will degrade significantly highly radiation resistant material as a suitable substitution for the PTFE. Two options - Al_2O_3 and Graphite - were investigated. The in-air and in-phantom results showed [4], that both the Graphite and the Al_2O_3 can be successfully used as a filter/moderator material at IRT-Sofia.

Further sensitivity study on finding the proper correlation of Al_2O_3 and Graphite with the Aluminum slab in IRT-Sofia NCT tube F/M is in progress. The in-air parameters of the epithermal neutron beam for NCT were determined. Having in mind the great calculational effort in this type of studies, an advanced methodology was applied for the Monte Carlo calculations. The methodology is based on Discrete Ordinates calculation of the adjoint function of the transport equation. It allows to automatically create optimal weight windows for MCNP and significantly speeds up the investigation process.

Three models of different configurations for the Al_2O_3 and Aluminum have been investigated. The results for the flux showed that all beams meet the required values [5] for the epithermal flux intensity (Fig.1). The results for the fast neutrons and the gamma contamination of the beam are also close to the recommended values.

Two models with different correlation of Graphite and Aluminum have been investigated. The results for the epithermal flux intensity (Fig.2) show that both of them are a viable option for NCT. The results for the fast neutrons and the gamma contamination show that only the beam line with extended Graphite slab (2) as a F/M material of the IRT-Sofia NCT beam tube meets the requirements for fast neutron/gamma contamination.

The results for the greater part of the investigated models show that there are viable options for replacement of the PTFE in the F/M area of IRT-Sofia NCT beam tube with materials of higher radiation resistance. The decision on the optimal configuration should be made based on the in-phantom beam parameters.

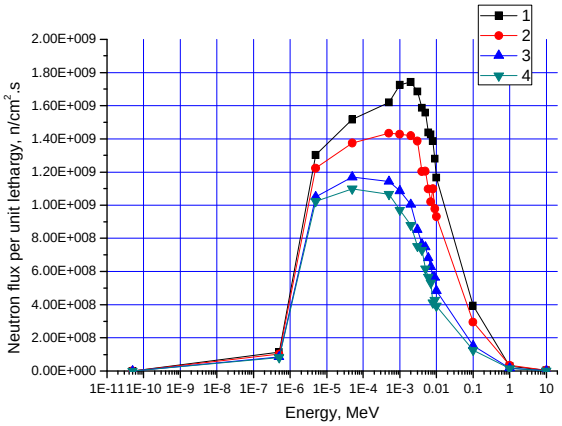

Fig.1. Neutron spectra at the beam exit for the base model (1) and F/M built of 0,81 m ^{27}Al and 0,13 m Al_2O_3 (2); 0,83 m ^{27}Al Al_2O_3 (3); 0,83 m ^{27}Al and 0,17 m Al_2O_3 (4)

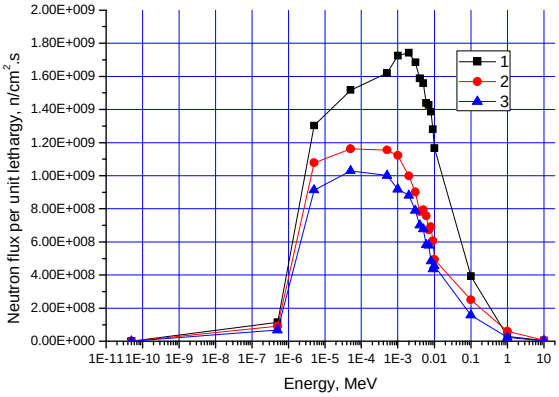

Fig. 2. Neutron spectra at the beam exit for the base model (1) and F/M built of 0,81 m ^{27}Al and and 0,16 m 0,13 m ^{12}C (2); 0,96 m ^{27}Al and 0,12 m ^{12}C (3)

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Developing the accelerator neutron source for BNCT in Birmingham: dosimetry and radiobiology studies

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Over the last 15 years the Birmingham team has been developing an accelerator source for clinical BNCT studies, exploiting the capabilities and characteristics of a 3 MV Dynamitron accelerator (IBA Industrial / Radiation Dynamics). The developed epithermal neutron source uses the ^{7}Li(p, n)^{7}Be reaction with a vertical proton beam at 2.8 MeV incident onto a horizontal solid thick Li target. The target is 38mm diameter and 0.7mm thick Li heat-bonded to a copper backing plate which is cooled by a central submerged jet system using heavy water [1]. At a coolant flow rate of 30 litres/minute the target is designed be irradiated with a uniform 2 mA proton beam without melting.

The Li target is embedded in a Pb shield and FLUENTAL™ moderator and graphite reflector with an outer shield of Li-polythene. The epithermal neutron beam is extracted orthogonally to the incident proton beam[2], such that the maximum neutron energy in the direction of the patient is 700 keV (maximum generated is 1.1 MeV). The lack of significant fast (MeV energy) neutrons means that some parameters for ionisation chamber dosimetry need to be carefully considered. In particular the value of k_t in the analysis of ionization chamber responses has been reduced to 0.85 [3]

The present accelerator ion source is a modified version of the original duoplasmatron source which is capable of reliably producing a protons up to 1mA current, with the maximum target current achieved to-date of 1.6mA. At 1mA this delivers a total neutron source strength of 1.37 x 10^{12} s^{-1}, a useful epithermal fluence of approximately 2 x 10^{8} $ncm^{-2}s^{-1}$. Typical treatment times to deliver 12.6 Gy weighted dose to healthy brain (using BPA typical values of 15 μg/g and CBE=1.3) of approx.150 minutes for a single field treatment and 230 minutes for a 2-field treatment at proton currents of 1.5mA.

The low dose rate has radiobiological consequences which could have important implications for clinical treatments. This has stimulated a programme of research to begin to evaluate this effect and the preliminary results will be discussed in this presentation [4]. This has built upon a long programme of radiobiological work to understand the interaction between the high LET (alpha and neutron) and low LET (photon) dose components delivered simultaneously as they are in BNCT treatments[5]. The data gathered to-date has revealed a significant interaction between these two components which appears to enhance the effect (or reduce the repair) of the low LET dose component [6].

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BNCT treatment planning options for head and neck cancer patients

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In Finland, clinical BNCT trials have been carried out applying BPA as a ^{10}B carrier and epithermal neutrons from the Finnish Research Reactor 1 (FiR 1) in malignant cancer patients since 1999. So far 249 patients have been treated with BNCT in 308 treatment sessions. Treatment planning has been performed with the SERA treatment planning system. In most cases the treatment has been given with two irradiation fields, but in some cases single-field or three-fields has provided optimal treatment plan. In this paper, treatment plans with one, two or three fields for three different head and neck cancer patients are introduced. The realized boron concentrations in blood during the neutron irradiation, calculated radiation doses to planning target volume (PTV) and healthy tissues, and irradiation parameters (such as field sizes and source-to-skin distances) are presented.

In every case, intravenous BPA-F infusion of 400 mg/kg was given in two hours. In case of patient with 1 field treatment plan, applied field size was 11 cm in diameter, the PTV size was 138 cm^3 and the boron concentration during the treatment was 19 ppm (part per million). In the cases of two and three field plans, the PTV sizes were 382 cm^3 and 602 cm^3 respectively. In the two-field treatment, the both irradiation field sizes were 14 cm in diameter and the blood boron concentrations 22 and 19 ppm for the first and the second irradiation field, respectively. In the three-field treatment, each field size was 11 cm in diameter and the blood boron concentrations 20, 17 and 15 ppm for the first, second and the third irradiation field. The minimum and average PTV doses for the single-field, two-field and three-field treatments were 15 and 29 Gy (W), 12 and 24 Gy (W) and 18 and 31 Gy (W) respectively.

Number of fields applied in our BNCT treatments depends on the PTV size and tumor location. Single field, two-field and three-field treatment plans can provide PTV doses of similar level. Blood boron concentration during the neutron irradiation has been highly dependent on the individual patient.

Principles and practical guidelines in selecting the optimum irradiation field settings for head and neck tumor patients will be discussed.

Verification of the new BNCT treatment planning system in Tsukuba

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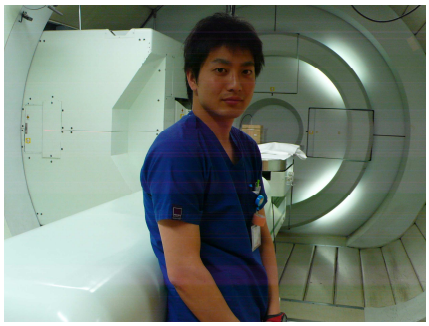

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We are developing a new-generation treatment planning system for BNCT. The development code name of the system is Tsukuba-Plan. Tsukuba-plan has applied a new Monte-Carlo code which was based on PHITS (Particle and Heavy Ion Transport code System)[1)]. PHITS can calculate the particle transport for not only neutron, but also photon and charged particles including protons and carbons. In addition, Tsukuba-Plan is getting creative in various efforts to calculate more comfortable. The representative examples that adopted JENDL (Japanese Nuclear Data Library) as nuclear data and definition of voxel model are included. We aim that Tsukuba-Plan will be applied to other radiotherapies such as proton therapy and photon therapy in the near future. By the past research for verification of PHITS was good agreement with MCNP (Monte Carlo N-Particle Transport Code)[2)]. The aim of this study is to verify the applicability of JENDL and new voxel modeling method.

We defined voxel model of cube shape phantom that formed various materials (soft tissue, bone, tumor and air), we determined neutron and photon fluxes and several absorbed doses in the phantom. Using the new PHITS based Monte-Carlo code. In the verification BNCT beam was assumed the epithermal neutron beam of JRR-4 (Japan Research Reactor -4) applied to actual BNCT. And then calculation results with JENDL were compared with the results with ENDF (Evaluated Nuclear Data File). The calculation results with JENDL were in good agreement with the ENDF calculations. Thus the comparison results demonstrated that JENDL can be applied to the treatment planning system

We are going to report other verification results in the meeting.

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The Response of Formate ESR Dosimeters in Thermal Neutron Fields

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ESR dosimetry is based on the measurement of radiation induced radicals. Besides alanine formate salts are well-known ESR dosimeters [1]. Towards thermal neutrons their response is expected to depend strongly on the corresponding anion. In contrast to the organic elements of the formate the anion can have high cross sections for the production of secondary, dose-depositing particles.
Different formate detectors have been irradiated in different experimental conditions in the mixed field of the research reactor TRIGA Mainz, Germany. The field consists of photons and predominately thermal neutrons. Read-out of the dosimeters has been performed with Electron Spin Resonance Spectrometry using photon calibration. Absorbed doses and dose components have been calculated using the Monte Carlo Codes FLUKA. In conjunction to this, considerations towards the Relative Effectiveness (RE) have been made using the Hansen & Olsen model. The RE takes account for the nonlinear dose response towards particle species and energy.
The measured dose response of the dosimeters in different experiments will be shown and compared to model predictions. RE values and calculated dose compositions will be discussed with the measured data. Finally a comparison to previous alanine results will be made. A combination of measurements with different detectors can lead to the experimental identification of dose components.

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In-phantom gamma-ray dose mapping in the THOR BNCT epithermal neutron beam

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A new approach combined two kinds of passive plane detectors to measure the in-phantom gamma-ray dose distribution in an epithermal neutron beam is presented in this work. This work aims to separate dose components of the Gafchromic EBT2 film irradiated by the THOR BNCT beam. Indirect neutron radiography (INR), a technique for determining the 2D neutron capture reaction rate, was applied to know the 2D neutron dose to the film. The measured result of the EBT2 film was in terms of the gamma-ray equivalent dose. A general detector response model has been developed to separate dose components of the film [1]. The neutron dose to the film was dominated by the ^{6}Li capture reaction in the thermal neutron energy range, so that INR and the absolute capture reaction rate measurement were carried out to obtain the 2D neutron dose of the film. The subtracted dose by the EBT2 film and INR using image plate (IP) can be regarded as the gamma-ray dose to the active layer. The in-phantom gamma-ray dose was converted by collision kerma ratio of the PMMA material to the active layer. In addition, in-phantom gamma-ray doses measured by paired ionization chambers were done at the central spots for verification.

The average difference between the measured results of this method and the paired ionization chambers was within 5%. The influence of room scattering can also be seen on the obtained dose maps. This work showed that the coalescence of the EBT2 film and INR using IP is able to measure the in-phantom 2D gamma-ray dose distribution in the neutron and gamma-ray mixed field.

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How do we find the ideal compound for BNCT?

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Compound development for BNCT ist quite slow, and not many new compounds have been considered for clinical use. This is in stark contrast to the constantly expressed demand by researchers in biology, physics, and medicine, who have challenged the chemists with finding more suitable compounds. The field finds itself in a frustrating situation.

The demands for new compounds in BNCT will be reviewed and explained on the basis of radiobiology and physiology. Present and past efforts from the own work, but also the work of other groups, will be reviewed, in order to identify the points where the development might have proceeded in such a way that the results were suboptimal.

Some of the reasons for the difficulty of developing suitable compounds might be found in the peculiar types of interaction of boron-containing molecules with biological surfaces. These properties, which we are just beginning to understand, will be highlighted on examples from BNCT and from other application of boron compounds.

Development of high boron content molecules and their liposome encapsulation for neutron capture therapy

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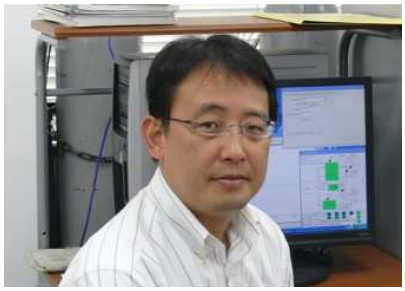

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Boron neutron capture therapy (BNCT) functions as a double targeting therapy for cancer. Its therapeutic effect is realized by neutron beam irradiation and a boron delivery system (BDS). So far, two boron compounds have been utilized for BNCT.
Mercaptoundecahydrododecaborate (BSH) is an anionic boron cluster that is used for the treatment of malignant brain tumors and L-p-boronophenylalanine (L-BPA) is a tyrosine mimic that is used to treat skin cancers. In the past decade, BNCT was utilized for various cancers, including head and neck cancers, malignant meningeal tumors, and hepatocellular carcinoma. However, there is still an urgent need to develop new ^{10}B carriers that deliver a sufficient concentration of ^{10}B atoms to a tumor to realize effective BNCT for a wide variety of cancer treatments.

Liposomes are efficient drug delivery vehicles because they can transport their contents to various tumors in a manner that is essentially independent of their contents. The accumulation of liposomes in tumor tissues caused by the enhanced permeability and retention (EPR) effect is based on the abnormal architectures of newly formed tumoral blood vessels that lose endothelial vessel cells without tight junctions [1]. Although various boron compounds encapsulated liposomes have been developed, the concentration of boron used in the preparation of liposomes was limited due to osmotic reasons [2]. Therefore, high total liposome dose has been required to obtain efficient BNCT of cancers. In order to decrease the total liposome dose, the development of liposomes with higher boron content and higher B/P ratio is necessary for practical use in BDSs. We recently succeeded in preparation of high boron content liposomes by incorporating boron into both the interior aqueous core and the membrane of liposomes. BSH-encapsulating 10% DSBL liposomes have high boron content (B/P ratio: 2.6) that enables us to prepare liposome solution with 5000 ppm boron concentration. Indeed, this strategy yielded significant antitumor effect on tumor-bearing mice after neutron irradiation, as well as a reduction of the total liposome dose, revealing that the current boronated liposome is one of the most promising candidates for practical use in BDSs for BNCT [3].

In the current study, we developed the high boron content molecules for preparation of highly boron concentrated liposomes using our recently developed click chemistry of dodecaborates [4]. The high boron content molecules are expected to accumulate into liposomes at higher concentrations under the similar osmotic pressure. Liposomes encapsulated with the synthesized boron compound which contains 48 boron atoms in a molecule have highest boron content with B/P ratio of up to 5.1. The detailed synthetic procedures of these high boron content molecules and their liposome encapsulation will be presented.

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Targeted Drug Delivery System Design & Development for Boron Neutron Capture Therapy

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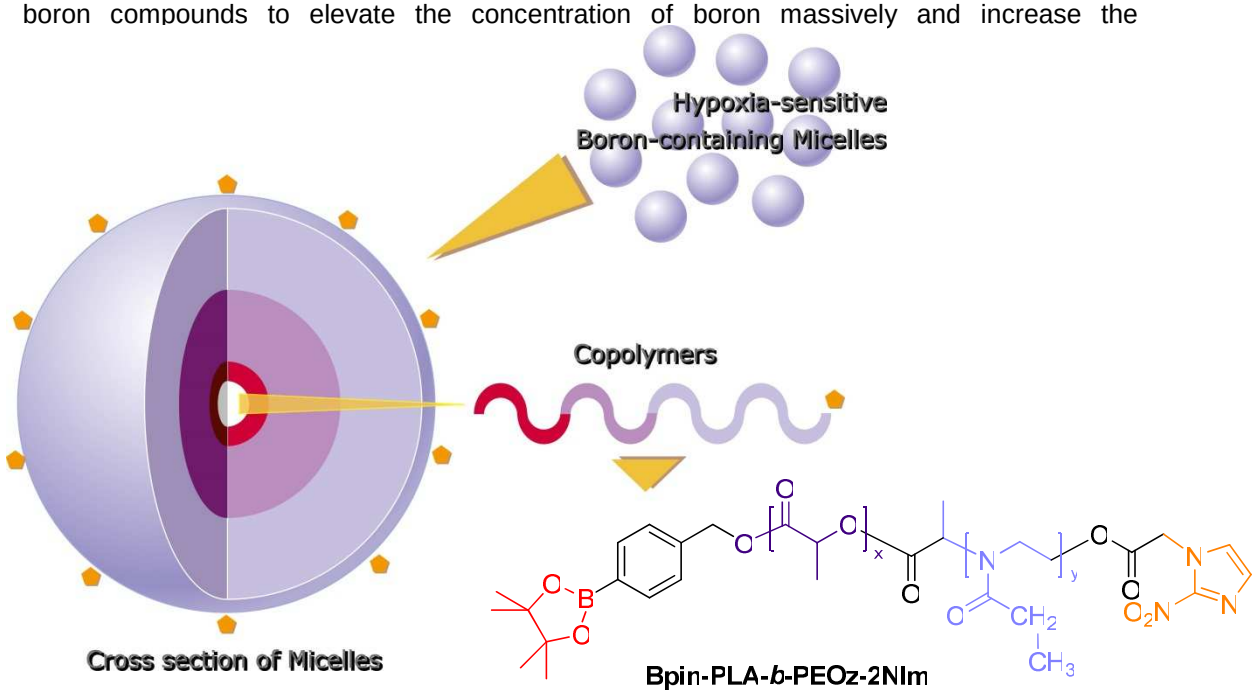
Boron neutron capture therapy (BNCT), a potential treatment for brain cancer, head and neck cancer, and melanoma, is based on the nuclear fission reaction that boron-10 (^{10}B)is irradiated with low-energy thermal neutrons to yield high linear energy transfer (LET) α particles (^{4}He) and recoiling lithium-7 (^{7}Li) nuclei[1]. BNCT is a binary therapy with selective delivery of non-radioactive ^{10}B to cancer cells and thermal neutron beam. When ^{10}B and thermal neutron irradiation are kept distinct, each has only a minor effect on cancer cells; albeit uniting both elements at a tumor releases intense radiation destroy malignant cells. Because the path lengths of the particles are only in the single cell range, approximately 9-10 μm, tumor containing ^{10}B compounds are selectively destroyed by BNCT therapy. The selective tumor targeted boron delivery system is very crucial for effective treatment.

The rising nanomedicines which improve drug bioavailability could be the best solution to the site-specific drug delivery. With the assistance of advanced nanotechnology and numerous tumor markers studies, a new type nano drug carrier with hypoxic cell sensitizer modified surface to trace the tumor was designed and synthesized in this research. The poly(D,L-lactide)-*b*-poly(2-ethyl-2-oxazoline) (PLA-*b*-PEOz) diblock copolymer was selected for the main structure of micelles. This diblock copolymer consists of biodegradable poly(L-lactide) (PLA) block and water-soluble polyelectrolyte poly(2-ethyl-2-oxazoline) (PEOz) block. PEOz and PLA are both FDA approved biomaterials. This copolymer was synthesized by ring-opening polymerization using a pinacol boronate ester-containing (Bpin) initiator, which provides access to boron-terminated copolymers. The assembly of tumor targeted moiety was designed by the conjugation of nitroimidazole (hypoxic cells sensitizer) to the end of the copolymer. Also, the synthesized micelle also has the capacity for encapsulating additional boron compounds to elevate the concentration of boron massively and increase the



Rational design of gold nanoparticles functionalized with carboranes for application in Boron Neutron Capture Therapy

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One of the open questions of BNCT is the possibility to know the biodistribution and the concentration of ^{10}B immediately before the irradiation procedure. These information are essential to set the treatment planning, i.e. the neutron irradiation configuration and time, to better evaluate the dosimetry and the outcome of each patient. In clinical practice radiotherapists infer the parameters needed for these calculations from the boron concentration measured in the blood stream. However, it is known that the real biodistribution and accumulation ability of tumor tissues are case-specific and should be treated accordingly. This is the same concern that underlines theranostic, a discipline combining imaging and therapeutic functions into one platform.[1]

Nanomaterials engineered with multiple functions have great potentiality to solve the problem of locating drugs and performing treatment with a single agent. Among possible materials to be used for theranostics, gold nanoparticles (GNPs) have reached a "gold standard" position. In fact, they have been used for imaging, diagnosing and treating diseases. GNPs show peculiar physico-chemical properties such as surface plasmon resonance in the visible or near infrared region (the so called therapeutic window) and can be easily functionalized through bonding with thiol, amine or carboxylic groups. The absorbance in nanoscale gold particles is much stronger than in the bulk material and can be easily tuned by changing size and morphology.[2]

So far, metallic nanoparticles have been scarcely used as vectors for boronated compounds in BNCT.[3-6] This is probably due to the intrinsic difficulty of combining high boron uptake, water solubility and biocompatibility in the resulting formulation.

In this paper we propose a bottom up approach to design a new boron carrier built by ortho-carborane functionalized with a thiol group to stabilize the interaction with Au surface and to carry a large quantity of boron atoms per molecules. A further challenge of this work was to enhance the water solubility of carboranes functionalized GNPs, to be safety used in biological test.

For this purpose we choose a appropriately tailored diblock copolymer PEO-b-PCL, that are known to enhance biological fluid compatibility and low protein interaction. GNPs functionalization was followed through spectroscopic (UV-Vis and FTIR) and microscopy (TEM) techniques. These composites showed a very good biocompatibility and also an interesting boron accumulation into osteosarcoma cells, which is encouraging evidenced to pursue applications in vivo.

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In vivo Study of Gadolinium-based Compounds as Neutron Capture Therapy Agent

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The most commonly used neutron capture therapy (NCT) agent is ^{10}B isotope, which undergoes the reaction ^{10}B(n,α)^{7}Li with products of high linear energy transfer particles, alpha particles and lithium ions, where the combined path length is approximately one cell diameter i.e. about 12 microns. This theoretically limits the radiation effect to those tumour cells that have taken up a sufficient amount of ^{10}B. On the contrary, this short flight range of alpha particles and lithium ions is actually making an inherent problem that it is necessary to deposit boron intracellularly to destroy the cell [1]. Recently, the use of gadolinium as NCT agent has been getting more attention because of its highest neutron cross section (255 000 barns), which is around 65 times larger compared to boron thermal neutron cross section. Gadolinium neutron capture reaction (Gd-NCR) also produces secondary particles with total kinetic energy about 3 times of that produced by boron in BNCT. In contrast to boron-neutron capture, gadolinium-neutron capture results in release of gamma rays followed by a series of low-energy conversion and Auger electrons which makes it a favorable characteristic because the location of the element is not critical with regard to target cell due to their longer flight ranges.

Considering the benefits that Gd-NCT offers; it is expected that we could reduce irradiation time in the treatment and eventually improve patient's quality of life. It is necessary to accumulate the Gd atoms to cancer lesions for effective NCT without affecting the neighbouring normal tissues, so we apply ^{10}B/^{157}Gd delivery systems in NCT fields [2,3]. In this study, we evaluated gadoteridol-entrapped liposome as neutron capture therapy agent by *in vivo* experiment on colon-26 tumour-bearing mice. The tumour growth in gadoteridol-entrapped liposome injected group was significantly suppressed compared to the control group. No significant weight loss observed has proved the low systemic toxicity of this compound [4]. The results of experimental data as well as pathological and morphological analysis will be discussed.

Prospective combination of chemotherapy and radiotherapy to increase treatment effectivity had also given the motivation to investigate the feasibility of utilizing Gd-DTPA-(1-2,diaminocyclohexane)platinum(II) nanomicelles, which were developed by Kataoka et al., [5] for simultaneous MRI diagnosis and treatment of solid tumours as NCT agent by performing the same experimental method with the previous gadoteridol-entrapped liposome compound. Preliminary results of data analysis will be shown and discuss for further investigation to optimize this compound as Gd-NCT agent.

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A study of boron-dose estimation using boron concentration in plasma

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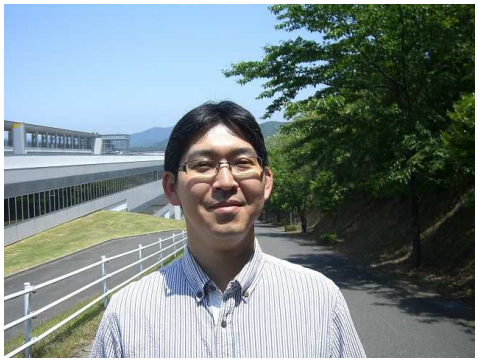

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In boron neutron capture therapy (BNCT) at Heavy Water Neutron Irradiation Facility of Kyoto University Reactor (KUR-HWNIF) [1], boron dose is estimated based on the next equation: boron dose = $C_{BPA} \times R_{T/B} \times CBE_{BPA} \times D_{BPA} + C_{BSH} \times CBE_{BSH} \times D_{BSH}$. Here C: boron concentration (ppm), $R_{T/B}$: ratio of tumor to blood (T/B ratio) for BPA, CBE: compound biological effectiveness, D: physical dose per 1ppm of boron-10 (Gy/ppm). For BPA, it is actively uptaken into tumorous cell by amino acid transporter. The degree of uptake for tumorous cell is expressed using T/B ratio based on whole blood, and T/B ratio is decided using the result by F-BPA-PET. In some tumorous cells, BPA uptake is smaller than T/B ratio, or almost zero. Here, the boron dose for tumor due to BPA is assumed to be as follows: the maximum estimated value is in proportion to T/B ratio and CBE=3.8. For the minimum estimated value, boron dose is similar to that for BSH, as BPA exists just surround the cell. CBE is assumed to be 2.5, the same for BSH. The boron concentration for whole blood is used in maximum estimation. In minimum estimation, the boron concentration for plasma is used. Based on these assumptions, tumor dose was re-estimated for the recent BNCT clinical studies.

From the measured data, the ratio of plasma to blood (P/B ratio) for BPA is almost 1.4 for head and neck tumors, and 1.3 for brain tumors. It is confirmed that the ratio of minimum estimated value to maximum estimated value (Min./Max. ratio) changes according to T/B ratio. Especially, as T/B ratio is larger, Min./Max. ratio is smaller. Then, the target dose should be decided in consideration of the minimum estimated dose, for the larger T/B ratio. P/B ratio for BSH is 1.3 to 1.5 for brain tumors, and the dispersion is larger than that for BPA. It is thought that the estimation based on boron concentration not in whole blood but in plasma is necessary, also for BSH.

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Study on measuring device arrangement method of Array-type CdTe Detector for BNCT-SPECT

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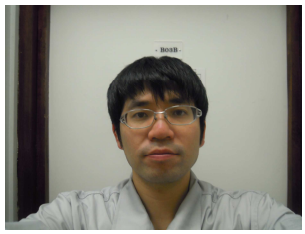

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There are some very serious unsolved problems, which need to be addressed, in boron neutron capture therapy (BNCT). One of them is that the treatment effect cannot be known during BNCT in real time. We thus have been developing a so-called BNCT-SPECT which can obtain a three-dimensional image of the BNCT treatment effect (radiation exposure dose) by measuring 478keV gamma-rays emitted from the exited state of ^{7}Li nucleus created by ^{10}B(n,α) reaction. A CdTe detector was selected as an elemental measuring device for BNCT-SPECT, because it has high detector efficiency and excellent energy resolution. Except for CdTe detector,possibilities were reported with scintillator and germanium semiconductor detector.

However, their practical use is not yet realized, because BNCT-SPECT requires the following strict conditions, i.e.,(1) 478 keV gamma-rays should be detected with small devices, which can realize a good spatial resolution, i.e., several mm, (2) measurement of 478keV gamma-rays should be carried out in a high statistical accuracy. (We aimed at the net count of over 1000 per hour at the photo-peak.), and (3)the signal to noise (S/N) ratio should be more than unity under an intense neutron background field.

The size of CdTe element, which satisfies the above basic requirments, could be determined by our previous researches. Also, the expected performance was confirmed through test measurements with actually produced CdTe crystals.[1] It was found that both gamma-rays of 478keV and 511keV could be measured separately in an experiment, though it had been pointed out to be difficult before.

In the present study, we then investgeted the feasibility of the BNCT-SPECT system. Practically, by assumming that a currently obtainable largest CdTe element, which we can obtain commercially at present, was manufactured by cutting a presently-achieved largest CdTe wafer, we investigated a detector assembly (how to make a combination of CdTe detector, collimator and shield) to confirm whether the whole detector system could work appropriately.

Calculations were carried out by considering an actual BNCT spot and by modelling the CdTe elements, using the general purpose Monte Carlo code, MCNP5.

As a result, the count rate of the detector was sufficiently large, being more than the target value of over 1000 counts/hour. However, the S/N ratio did not meet the target value (S/N >1).[2]

However, we found that from the results of calculations for a practical arrangement of many CdTe elements set in the real system, instead of one element, there were many valuable events occurring, that is, several radiations produced via Compton scattering from one incident gamma-ray were detected in several CdTe detectors at the same time. By simulating Compton scattering events precisely with MCNP5, it was shown that the coincidence or anti-coincidence would possibly increase the S/N ratio.

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Autoradiography in nuclear track detectors: simultaneous observation of cells and nuclear tracks from BNC reaction

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The distribution and concentration of ^{10}B atoms in tissue samples coming from BNCT protocols can be determined through the quantification and analysis of the tracks forming its autoradiography image on a nuclear track detector [1]. The location of boron atoms in the cell structure could be known more precisely by the simultaneous observation of the nuclear tracks and the sample image on the detector [2]. We present here a methodology to produce an "imprint" of cells cultivated on a polycarbonate detector by exposure of the detector to UV C radiation. Cells of a human metastatic line of melanoma (MELJ) were seeded on polycarbonate foils (Lexan^{TM}). They were incubated with BPA (10 ppm), washed and fixed and then exposed to different thermal neutron fluences. They were irradiated with a UV C lamp (254 nm) for different times, stained and explored with a light microscope. An appropriate monolayer cells distribution could be obtained and UV exposure does not affect cell visualization. The foils were processed with a KOH solution for different times. The images of both cells and nuclear tracks were found to be optimal for a neutron fluence of 10^{13} n.cm^{-2}, UV exposure during 6 h and an etching time of 4 min (Fig. 1). The etch pits are only present inside the cells, indicating a preferential boron uptake. These findings pave the way for an extensive comparison between cell lines and the evaluation of different boron compounds through their distribution in vitro. Tissue slices were also analyzed with this technique and the preliminary results will be presented.

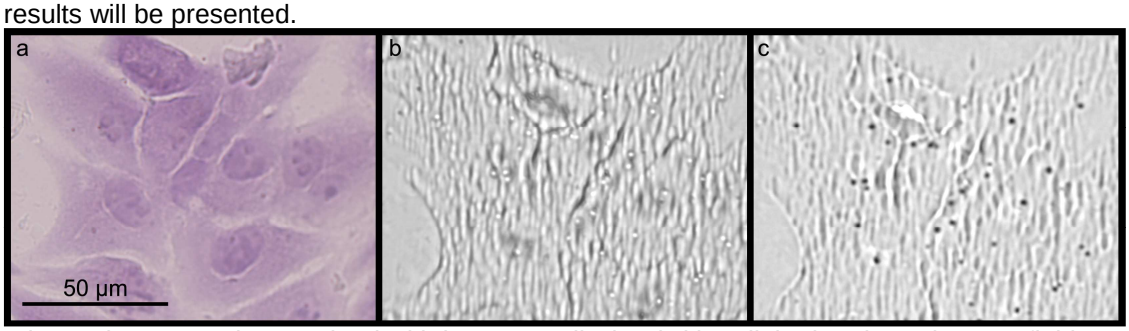

Fig. 1. a) MEL J culture stained with haematoxylin (40x). b) Cellular imprints. c) Same field as (b), focusing on nuclear tracks.

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BNCT Researches in KURRI (Kyoto University Research Reactor Institute) and Start of Clinical BNCT Trial by Small Cyclotron Neutron Generator

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Introduction

KURRI started clinical BNCT research in 1974, 6 years later the first clinical trial in Japan, by Prof. H. Hatanaka. He gave an intra-operative BNCT to the patient of malignant glioma with BSH. But, clinical outcome was not good probably due to an inadequate patient selection and rack of basic researches including related technologies. No simulation of neutron or dose distribution in the brain and also no method to immediately measure ^{10}B concentrations were available. KURRI stopped clinical research after this treatment for 15 years. We restarted the research in 1989 firstly to treat malignant melanoma by using BPA. After then, clinical BNCT research to malignant brain tumor was also started again. At present, KURRI group has accumulated over 500 cases of BNCT, and new accelerator neutron irradiation system for clinical BNCT has been developed and started clinical trial from last October. In this paper, we report the present status of BNCT in KURRI and new accelerator.

Experiences of Basic Research and Clinical Trial by KUR

The BNCT effect is different between BSH and BPA in culture cells. The effects was evaluated by micronucleus assay and compared each other. BPA accumulates in the cell. Therefore, the effect is about 1.5 time larger than BSH. When their effects on solid tumors are compared, that of BPA-BNCT is larger than BSH-BNCT on the whole cell tumor population. However, BPA has a disadvantage which the effect to the quiescent tumor cells is small. This is easily expected from the mechanism of accumulation of BPA.

Another important factor is the relation of the range of particles and target cell size. Hepatocyte is a good example. In general, cancer cell has large nucleus and N/C ratio. Therefore, even if the BSH locates outside the cell, particles can hit nucleus and break double strands of DAN to induce cell death. On the other hand, hepatocyte is a large cell with small N/C ratio, and particles from BSH may not be able to hit the nucleus. In experiment of BNCT to the liver, actual RBE to hepatocyte becomes smaller than 1.0 as expected. Based on actual RBE of boron-neutron reaction to hepatocyte, we made an idea to treat liver cancer with multiple lesions. For that, we did confirm the usefulness of BNCT to such tumors through animal experiments. We made a model of liver cancer by injecting tumor cells to the rat liver. Seven to ten days later, we infused the mixture of BSH and embolization substance via the hepatic artery. Thereafter, boron concentrations in each tissue were measured with time. The boron concentration in a tumor was maintained at an enough high level 6 hours later. On the other hand, that in a normal liver tissue decreased quickly. After 6 hours, big ratios of the concentration was achieved between a tumor and a normal liver. They were over 15.

Pre-estimation of ^{10}B concentration in tumor and normal tissue is useful to do successful BNCT. BPA is a good compound from this view point. It can be labeled with F-18, a positron emitter, and make an image of its accumulation and examine the ratio of ^{18}F-BPA radioactivity.

BNCT dose is composed of neutron-hydrogen dose, neutron-nitrogen dose, neutron-boron dose and gamma ray dose. According to the dose distribution map and DVH analysis, BNCT can deliver 7 to 10 time large dose to the tumor compared with normal brain because of selective accumulation of BPA in the tumor. This large difference of dose makes possible to deliver large single dose irradiation to the tumor. Rapid shrinkage of the tumor are frequently observed.

Recurrent glioblastoma is an important candidate of BNCT. The case is still small in number, however, survival time after BNCT is superior to that after general treatment. Moreover, median survival time after BNCT is equal or a little longer than those after special treatment, SRS or SRT in spite of much larger tumor volume in BNCT group than those in special treatment groups. The major cause of death after BNCT to malignant glioma is a dissemination of tumor cells to spinal cord et al. The decrease in survival after 2 year is mainly caused by tumor cell dissemination. This is a reflection of an improvement of local tumor control.

Recurrent H & N neck cancer was treated by BNCT first in the world at the end of 2001. First BNCT performed with 50% of the prescription dose. Second BNCT was applied one month later, checking that an effect was achieved without no acute serious adverse effects. The tumor was regressed completely without inducing critical damage to the skin in spite of retreatment by radiation of BNCT. A huge tumor of malignant melanoma also completely disappeared by BNCT without inducing unacceptable skin damage.

We did BNCT to 26 recurrent head and neck cancer patients. They are the patients who had an alternative of treatment other than BNCT. We can estimate the prognosis of them from the beginning part of survival curve that these patients would die in one year if they did not receive BNCT. About one fourth of the patients survived for five years or longer.

Malignant pleural mesothelioma is known well that exposures to asbestos induce this tumor and it became a big social problem in Japan in recent years. ^{18}F-BPA accumulated well in the tumor in PET. The ratio of the radioactivity of tumor to normal lungs was 7.68. Then, we did BNCT to the patient. In CT at the time of BNCT, a part of tumor spreading irregularly along with the pleura invaded subcutaneous tissue through inter-costal space, and it formed a nodule. For this, the patient suffered very severe pain and morphine was given daily. Respiratory physician expected his life expectancy to be two to three months. After BNCT, the pain disappeared within several days and the patient needed no morphine. The patient lived for ten months. CT examination at six months after BNCT revealed the tumor regression.

New Accelerator Neutron Irradiation System for Clinical BNCT and Start of Clinical Trial

I and Dr. Maruhashi, he is a professor of medical physics in KURRI, started the project of accelerator neutron BNCT development in 2004 based on the results achieved by reactor neutrons. The accelerator was placed in my institute at the end of 2008 by the collaboration research with Sumitomo Heavy Industries. In this system, 1mA proton beam is accelerated to 30MeV with the cyclotron, and neutrons are generated with Be target. As performance of an accelerator, the maximum acceleration current is 2mA.

The energy spectrum of cyclotron neutrons is higher than the KUR neutron. The neutron fluence rate of cyclotron, 1.2×10^9 n/cm^{2}sec is about 1.8 times the KUR. The dose distribution within the brain is improved because of high energy neutron utilization. The investigation of the biological and physical characteristics of the neutron beam was completed. Average of neutron RBE is 2.4. When the prescribed dose of the skin is 11Gy-Eq, the maximum dose to a normal brain is 12 Gy-Eq or less and, on the other hand, a tumor dose exceeds 20 Gy-Eq at 8cm depth. Therefore, if neutron beam is delivered from both sides, the dose of over 40 Gy-Eq can be easily given to the tumor cells scattered all over the brain.

In last October, We started phase I clinical trial for recurrent malignant glioma to test the safety of BPA and cyclotron neutron generator. In present protocol of clinical trial, we are employing a single neutron field irradiation. However, according to the tumor location, it is expected that dose distribution will be improved by two field irradiation. In both neutron source BNCT, two field irradiation significantly improved DVH to the tumors. Increase of minimum dose is larger than that of maximum dose. This tendency is more prominent in cyclotron neutron beam. From this simulation, it is apparent that two field irradiation is superior to single field. However, it needs longer time for treatment, and neutron fluence rate of present neutron generator is not enough to apply two field irradiation in one session.

Research Subjects for the Near Future BNCT

Development of new boron compound will be a most important research subject. If we can use a B-compound with high T/N ratios over 20. Multiple liver tumors disseminated through whole liver will be treated by BNCT safely. Compounds also have to distribute homogeneously through tumor tissue including *tumor stem cells* at the concentration of over 100 ppm ^{10}B. For that an intensive research work to apply DDS is necessary. Simple and rapid method to make an image of ^{10}B distribution in tissues to facilitate drug development. For powerful neutron generator, target system tough enough to heat and blistering by H accumulation is indispensable. We already started the project for new powerful machine.

Monte Carlo investigation on measuring spatial distribution of neutrons and gamma rays using multi imaging plate system.

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Handy detection system for the distributions of neutrons and gamma rays is one of the potential and essential options, in accomplishing the quality assurance and quality control for neutron capture therapy. The system is desired to measure the neutron components dependently on its energy, e.g., thermal, epithermal, and fast, separately. The configuration of the converter to enhance and separate three neutron components and gamma ray component was previously investigated for usage with a radiation detector"imaging plate"[1]. However, the fast neutron component was found to have the energy deposition in the imaging plate about two orders lower than that of the gamma ray component and expected to be difficult to measure. This paper describes an attempt to enhance the fast neutron contribution by shielding gamma rays.

The investigation was performed with the code PHITS. The calculation geometry consisted of the imaging plate and the converter. The imaging plate assumed to be utilized is "BAS-TR" by Fuji Film Corporation, Japan. The sensitive region of BAS-TR is not covered with packing material, accordingly the secondary charged particles from the converter such as electron, proton, alpha particle, ^{7}Li ion reach the sensitive part and make signals. PHITS was operated in the event generator mode so that the transport of the secondary charged particles are simulated. The energy deposition at the sensitive region of BAS-TR was computed as a representative of the imaging plate signal. The converters considered are the epoxy resin doped with ^{10}B in varied concentrations for thermal and epithermal neutrons, epoxy resin for fast neutron, and graphite for gamma rays. The converters and imaging plates were included in a Bismuth box as a gamma ray shield. The required dimension and ^{10}B concentration was investigated.

As a result, a potential configuration found was a 6 cm thick Bismuth, which had 1 mm thick epoxy resin plates with 10 wt% 10B for thermal neutron, 50 wt% 10B for epithermal neutron, without 10B for fast neutron, and 1 mm thick graphite for gamma rays. The contributions of the individual components to the energy deposition in the imaging plate are 62%, 76%, 23%, and 55%. The fast neutron contribution was drastically improved by including Bismuth, i.e., from 2 % to 23 %, and expected to be detected successfully. However, the configuration found depresses the original gamma ray field, hence gamma ray component should be evaluated with additional measurement without Bismuth.

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The error index of Monte-Carlo-based detector combination optimization for neutron spectrum deconvolution

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In order to improve the accuracy over the fast neutron energy region of the unfolded THOR BNCT spectrum, we previously designed 4 different series of detector complexes to obtain a large number of varied detector response functions (RFs). A total of 98 RFs were created. To find a satisfactory detector combination with a reasonable number of detectors, thorough and time-consuming tests & comparisons are required. Hence, we developed an automatic optimization program base on the SAND-EX and Monte Carlo method. It randomly picks up detectors from the 98 RFs to form a combination, and then run a spectrum unfolding; afterward the program estimate the corresponding error index of the unfolded spectrum by comparison with a given standard solution (spectrum). Through a great number of iterations (i.e. 10^7 times), the program tells a semi-optimal detector combination. Note that, for illustration, to find out the best combination of 15 different detectors from 98 RFs, it needs more than 7.2×10^{141} iterations, which is nearly impossible to be done.

In this study, we recorded all detailed information of every unfolding result, and the relationship between error index and detector combinations were analysed. The result showed several remarkable peaks on error index histogram; these peaks were generated by specific detector combinations. Thus, according to the information of error index distribution, we can eliminate useless RFs and make preference to specific detectors, which will consequently enhance the automatic optimization program.

Neutron spectrum measurement on the tandem accelerator for BNCT using a new time-of-flight method

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At BINP (Novosibirsk, Russia) it is constructed the prototype of the future accelerator-based neutron source to carry out boron neutron capture therapy at hospital. The tandem accelerator uses the reaction ^{7}Li(*p,n*)^{7}Be and generates neutrons since 2008 [1]. Up to date a lot of work has been done to upgrade the accelerator [2]. Thanks to this work the accelerator is currently able to operate daily and stable during several hours with 1-1.5 mA proton beam current, 2 MeV of proton energy and neutron flux respectively ~ 2 10^{11}/s. The first *in vitro* experiments are already conducted and to continue the experiments we must know exactly the spectrum of generated neutrons. But so far we had only the Monte Carlo calculations of the spectrum and rough data from experiments with bubble detectors. Finally the reached parameters of the accelerator allowed us to carry out the neutron spectrum measurements using a new time-of-flight method, the idea of which was described by us in detail previously in [3]. Briefly the essence of the method is the following: the proton beam at the output of the accelerator has the energy of 1.88 MeV (below the neutron production threshold) and neutrons are not generated. But during 200 ns the energy of protons increases from 1.88 up to 1.92 MeV by supplying the square pulse of 40 kV on the lithium target, which is electrically isolated from facility body. During these 200 ns neutrons are generated. The spectrum is obtained by measuring the time of flight by a remote neutron detector. The proposed technical solution is implemented for the first time and has no analogues.

The present work contains the discussion of problems related to the new method, provides the detailed description of experiments and technical solutions and contains the experimental spectrum and its comparison with calculation. The measured neutron spectrum of the existing lithium target is in good agreement with the theoretical one. With the new TOF method it is planned also to measure the spectrum of the new lithium target.

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Neutron beam shielding patch for absorbing overdose of neutron radiation

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Radiotherapy plays a very important role in cancer treatment. From Cobalt-60 generated Gama-rays; to nowadays accelerators based X-rays, the radiotherapies make stable and reliable contributions for cancer treatment. However, not every types of cancer could be treated by traditional radiotherapy due to the physical condition of radiation and radio resistance of cancer cells (such as, melanoma, malignant and malignant brain tumors sarcoma, etc.), conventional radiotherapy only has little impact and cannot treat efficiency. Therefore, in the current radiotherapy development, Boron Neutron Capture Therapy (BNCT) was investigated to solve these problems. BNCT adapts the nuclear fission reaction of boron-10 with thermo neutron beam, and release two particles: α particles, and lithium-7; the effective ranges of these particles have only 9 μm and 5 μm, less than the diameter of the single tumor cell range (about 10-20μM), so the destruction is limited to the boron containing tumor cells. Compared to the traditional radiotherapies cause homogenous effect to radiated area, BNCT provides more specific treatment to the tumor sites. During the development of radiotherapy, the radiation overdose has been a very serious and fatal incident to not only the patient but the personnel. Accidental radiation exposures will lead to acute radiation syndromes (ARS), radiation injury, and death. Prevention in advance is necessary for avoiding unnecessary casualties and loss; a very good example, blocking or absorbing radiation is the direct way to prevent overexposure. This is the motivation of this research, to develop a new material to absorb the excess neutron beam, which is the radiation source of BNCT. The material could be made as the form of patch, and attached to the surface of normal skin around irradiation area to absorb neutrons beam, thereby protect the normal tissue from excessive neutron beam. In this research, boron nitride (BN) was dispersed in silicon, and the mixture was made to a square-shaped patch for neutron protection. Boron nitride has advantage of good thermal conductivity, which can help to dissipate the heat, to keep patient cool and comfortable during the treatment of BNCT.

Study on the evaluation of ^{10}B concentration using proton-induced prompt gamma ray analysis for BNCT

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1. Introduction

At Kyoto University Research Reactor Institute, as of May 2013, over 450 clinical studies of BNCT have been performed using a research reactor. On the other hand, cyclotron-based epithermal neutron source was installed at KURRI on December 2010 and clinical trial started on October 2012. In terms of the dosimetry of BNCT, the information not only neutron fluence but the ^{10}B concentration in whole blood is needed for determination of the prescribed dose. Prompt Gamma ray Analysis (PGA) using thermal neutron is usually used for the evaluation of ^{10}B concentration for reactor-based BNCT. However, accelerator-based BNCT cannot establish the thermal neutron guide tube for PGA because of the lack of neutron intensity at the neutron production target. Thus, it is desire to develop the alternative method of PGA using thermal neutron guide tube. We propose the method of the evaluation of ^{10}B concentration using proton-induced PGA instead of PGA using thermal neutrons. In this presentation, we will show the detail description of our proposed method and the verification test using tandem accelerator of Kyoto University.

2. Experiments and results

Prompt gamma ray with the energy of 429 keV induced by protons with over 1 MeV is emitted from the reaction of ^{10}B(p,□□)7Be. However, the existing of ^{23}Na in whole blood makes difficult for evaluation of ^{10}B concentration because of the reaction of ^{23}Na(p,p1□)^{23}Na with the emission of the prompt gamma rays of 440 keV. Furthermore, the yields of ^{10}B(p,□□)7Be and ^{23}Na(p, p1□)^{23}Na are 3.5x10^{6}, 3.4x10^{6} (N□/□C sr), respectively for the injection of protons with the energy of 2.4MeV. In this research, we select the prompt gamma ray with the energy of 718 keV from the reaction of ^{10}B(p,p1□)^{10}B in order to prevent the competition of ^{23}Na(p, p1□)^{23}Na reaction.

In order to confirm the principle of the derivation of ^{10}B concentration by proton-induced PGA, the experiment was performed using the tandem accelerator of Kyoto University. The sample with ^{10}B concentration of 2000 ppm was prepared for easy detection. Diluted solution of boric acid was evaporated on backing material as an irradiation sample. Backing material is conductor in order to monitor the proton currents. Prompt gamma rays were detected by the high purity germanium semi-conductor detector. It was found that the ratio of counts at the peak of 429 and 718 keV was corresponded to the ratio of each yield of prompt gamma rays. According to this experimental method, it was also found that the uniformity of sample on backing material was important to estimate precisely ^{10}B concentration.

An improved neutron autoradiography set-up, applied to ^{10}B concentration measurements for biological samples

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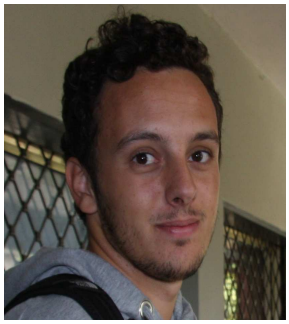

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The development of a new ^{10}B delivery system, with higher selectivity for the tumor with respect to clinically used sodium borocaptate (BSH) and boronophenylalanine (BPA), underlies future improvements in clinical outcomes of Boron Neutron Capture Therapy. A ^{10}B concentration measuring technique for biological samples is needed in order to evaluate the performance of the new boronated formulations. At the Triga Mark II nuclear facility in Pavia, two techniques have been set-up: Alpha Spectrometry (AS) [1] and Quantitative Neutron Capture Radiography (QNCR) [2]. The latter has been recently improved, to ensure a higher accuracy and an optimized efficiency when a high number of samples is analyzed.

In the first QNCR set-up, described by M.A Gadan et al. [2] a suitable calibration curve and a sufficient resolution were achieved; however, there were still margin for improvements. Firstly it was necessary to reduce the timing of the overall procedure, caused by an etching time longer than 2 hours. Secondly, in order to reduce the background, only the tracks due to ^{7}Li and α ions had to be visualized. The second condition would simplify the data acquisition, avoiding the implementation of the morphological track selection algorithm that was previously necessary to reject the tracks due to protons; this possibility would lead to an improvement of the resolution of the concentration measurement. These goals were reached employing PEW ($KOH + C_2H_5OH + H_2O$) as a chemically etching solution at 70 ºC. This set-up decreased the etching time from 2 hours to 10 minutes. Moreover only tracks from ^{7}Li and α ions are detected, decreasing by consequence the relative error of the calibration from 7% at 1σ of C.L to 5% at 1σ of C.L. .

This improved neutron autoradiography method was then applied to ^{10}B concentration measurements in tissues from small animals and cell cultures treated with new carriers, in the frame of the BNCT feasibility study for osteosarcoma [3]. The experiments were conduced testing three categories of carriers: gold nano-particles, liposomes and polymeric nano-particles and BPA as a reference. In particular, ^{10}B loaded liposomes and BPA were administered to Sprague-Dawley rats bearing osteosarcoma. After treatment, healthy bone and muscle and the tumor mass were explanted and prepared for QNCR and AS. The results concerning boron biodistribution obtained in these tissues will be presented and discussed. Boron biodistribution obtained in vivo will be used in the following part of the experiment, consisting in in vivo irradiation of rats with osteosarcoma to test BNCT efficacy in tumor remission and BNCT toxicity for healthy tissues.

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Radioprotective agents to reduce BNCT-induced mucositis in premalignant tissue: Preliminary study in an oral precancer model

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We previously evidenced the therapeutic efficacy of BNCT to treat oral cancer in an experimental model in the hamster cheek pouch (1, 2, 3, 4). We also demonstrated a significant inhibitory effect of BNCT on the development of tumors in a novel model of premalignant tissue in the hamster cheek pouch (5). Despite therapeutic success, BNCT-induced mucositis in premalignant tissue was dose limiting and favored tumor development (e.g. 5). In a clinical scenario, oral mucositis limits the dose delivered to head and neck tumors (6). The present preliminary study aims to evaluate the effect of the administration of radioprotective agents, seeking to reduce BNCT-induced mucositis to acceptable levels in premalignant tissue.

The DMBA-cancerized pouch of 3 groups of hamsters was exposed to BPA-BNCT at 5 Gy total absorbed dose at RA-3 Nuclear Reactor: G1) treated with histamine (n=4, 1 mg/kg, sc administration); G2) treated with JNJ7777120 (n=4, 10 mg/kg, sc administration); G3) no radioprotective treatment (n=8). Histamine and JNJ7777120 were previously proved to exert a radioprotective effect in other experimental models (7).

Sixty seven percent of the animals treated with BNCT only exhibited unacceptably severe mucositis with significant loss of premalignant pouch tissue. On the other hand, all animals (100%) treated with BNCT but treated with histamine or JNJ7777120 exhibited reversible moderate mucositis in premalignant tissue. This preliminary study would suggest the potential use of histamine and JNJ7777120 to prevent severe and unacceptable mucositis associated with BPA-BNCT at 5 Gy total dose.

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In situ lung BNCT at Pavia University: preliminary histological results on treatment toxicity and efficacy

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The goal of the WIDEST (WIDE Spread Tumour BNCT) project is to evaluate the efficacy of BNCT against the lung tumours invading the whole organ.
The project carried out at the University of Pavia thanks to a collaboration between the Department of Biology and Biotecnology L. Spallanzani, the Laboratory of Experimental Surgery and the Physics Department, is now evaluating the efficacy of the treatment through *in vivo* tests on a model of lung metastases induced in BDIX rats starting from DHD tumour cells of colon-adenocarcinoma. The colon-adenocarcinoma (1-1.5 x 10^6 DHD) cells were inoculated through the inferior vena cava. After 3-4 weeks BPA-f was intraperitoneally administered (300mg/kg b.w.) and then 4 hours later the rats were irradiated with thermal neutrons.
Until now, several irradiations have been performed, both to evaluate the toxicity of BNCT for the radiosensitive organs of the thorax (first of all, the lung itself) and to collect evidences of the efficacy of the treatment against the lung metastases.
The rats were sacrificed with anesthetic lethal dose at different times to observe early and late effects of the irradiation; The most important and radiosensitive organs were explanted, fixed in 10% formalin, included in paraplast, and finally sectioned using a microtome. The sections were deposited on glass slides and stained with hematoxylin and eosin.
The analysis of the tissues has been recently started, beginning from the lungs of some irradiated healthy animals, testing different protocols of irradiations. To date, the healthy lungs have shown no sign of radiation damage and no fibrosis has been evidenced at the histological analysis. These preliminary results will be shown and discussed, while further studies are being carried out also for other tissues and for lungs affected by metastases.

Detection of gamma H2AX foci in mouse brain tissue after neutron capture therapy

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Boron neutron capture therapy (BNCT) is a particle radiation therapy in combination of thermal neutron irradiation and boron compound that specifically accumulates in the tumor. ^{10}B captures neutrons and produces an alpha (^{4}He) particle and a recoiled lithium nucleus (^{7}Li). These particles have the characteristics of high linear energy transfer (LET) radiation and therefore have marked biological effects. High LET radiation cause severe DNA damage, DNA DSBs. As the high LET radiation induces complex DNA double strand breaks (DSBs) [1], large proportions of DSBs are considered to remain unrepaired in comparison with exposure to sparsely ionizing radiation. [1]
It is also known that DSBs induced by high LET radiation are larger than those induced by low LET radiation [2]. As tumour tissue takes up more Boron compared to normal tissue, larger DSBs might remain in tumour tissue after BNCT.
In this study, we investigate gamma H2AX foci as markers of DSBs in mouse brain tissue after neutron irradiation by immunohistochemistry. In preliminary tests, we successfully detected gamma H2AX foci in normal mouse brain tissue 30 min or 24h after neutron irradiation.
Next, we use brain tumour mouse model and investigate localization of gamma H2AX foci after BNCT.
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Future of Accelerator Based BNCT Neutron Irradiation System using Liquid Lithium Target
-- The Usage of Neutrons by ^{7}Li(p,n)^{7}Be Near Threshold Reactions --

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The neutron irradiation system (NIS) for boron-neutron capture therapy (BNCT) can supply low-energy neutron irradiation field less than several tens of keVs. The NIS for BNCT (BNCT-NIS) has two kinds which are the Reactor based one and the Accelerator based one. All nuclear reactors have similar characteristics because of the ^{235}U fission reaction during the critical state. They are capable of generating superior neutron intensity and temporal stability. Acc-based BNCT-NIS has been examined using of the ^{7}Li(p,n)^{7}Be, ^{9}Be(p,n)^{9}B, ^{9}Be(p,xn)X reactions. The characteristics of the produced neutrons, such as energy spectra and its angular dependence, varies for each reaction. Moreover, Acc-based BNCT-NIS needs to satisfy not only the necessary conditions for BNCT irradiation, but also the stability required of a neutron source. Technical issues related to accelerator neutron sources include the method for removal of 30-80 kW of heat and the radiation damage at the neutron producing target. In addition, high reliability and socially acceptable economical efficiency, which are brought about by the safety, stability, security of the system, are required for Acc-based BNCT-NIS. From these viewpoints, the design standards for the Acc-based BNCT-NIS development, in contrast with the Reactor BNCT-NIS, for its clinical implementation were suggested. The secondary cancer induced by BNCT in normal tissues in the affected and unaffected areas should be considered in the design standards for the Acc-based BNCT-NIS. It was established that the accelerator BNCT-NIS using neutrons from ^{7}Li(p,n)^{7}Be near threshold reaction is a good combination with the liquid lithium target which is possible to achieve and use a stable liquid lithium film flow for the neutron producing target. It was also found that ^{7}Li(p,n)^{7}Be near threshold reaction using a liquid lithium target is the most suitable neutron source for an Acc-based BNCT-NIS in a hospital-setting at a downtown. The combination of a long-life neutron producing target such as a liquid lithium target and a stable proton accelerator such as RFQ is a promising candidate for this system.

BNCT can contribute to the improvement of the field of radiotherapy by enabling the complementary relationship between different radiotherapy modalities because of its capability for selective treatment of only tumor cells. BNCT, together with other radiation therapy modality, has the potential for providing patient-tailored cancer therapy by combining surgery, chemotherapy, etc. as necessary. When Acc-based BNCT-NIS approaches its practical implementation, the following important matters should be emphasized. The conditions and requirements related to BNCT should be carefully evaluated as much as possible. Scientists should find not only a solution of the faults and/or the risks, but also should inspect these characteristics scientifically with positive thinking. A new design standard for an Acc-based BNCT-NIS derived from the viewpoints of secondary cancer induced by BNCT will be reported.

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Monte Carlo dose assessment in cell cultures after enrichment with Gadolinium and irradiation in the neutron field of the TRIGA Mainz

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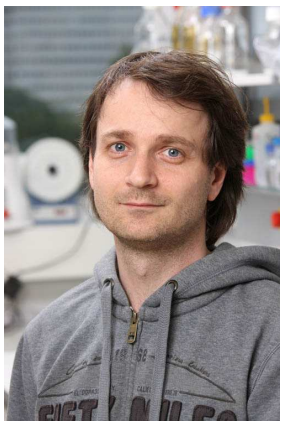

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Neutron capture therapy (NCT) makes advantage of the secondary particles produced in a neutron capture reaction in order to selectively destroy tumour cells. For this purpose the patient is injected with a tumour localizing tracer that carries isotopes with a high probability of neutron absorption, such as ^{10}B and ^{157}Gd. Gadolinium has not only the advantage of the higher absorption cross section (254000 barn vs. 3840 barn for ^{10}B), but it is also established as a contrast agent in MRI (magnetic resonance imaging). The (n,γ) reaction of ^{157}Gd yields a high amount of inner conversion electrons and Auger electrons of low energy and short range in human tissue. Therefore a very local dose deposition is possible in the case of GdNCT (gadolinium neutron capture therapy). When it comes to dosimetry and the determination of the relative biological effectiveness of the irradiation one has to rely on Monte Carlo methods and experiments on biological samples. MCNP5 code is employed which is a well-established code to simulate the transport of neutrons, electrons and photons. A detailed model of the composite neutron/gamma field of the TRIGA Mainz was validated and benchmarked using various phantoms and dosimeters (TLD's, alanine dosimeters, gold activation foils) and then simplified to allow for a closer look on in vitro experiments regarding the survival rates of cell cultures. For this purpose the Monte Carlo model was extended by means of cell culture plates representing medium with different ^{157}Gd concentrations that are irradiated within the thermal column of the TRIGA Mainz.
The results show that the dose deposition by the secondary electrons yielded in the ^{157}Gd reaction prevails over all other dose components. This way the relation between ^{157}Gd concentration and cell survival can be used to deduct factors describing the relative biological effectiveness.

Radiotherapy dose enhancement using BNCT in conventional LINACs high-energy treatment: simulation and experiment

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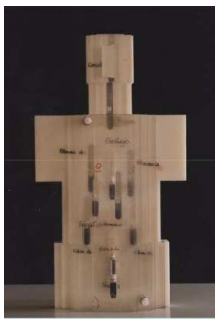
Conventional high energy ($15MV-25MV$) linear accelerators (LINACs) for radiotherapy produce fast secondary neutrons due to (γ,n) reaction. Neutron production results from the interaction of electrons and photons with various nuclides present in LINACs gantry. The production is governed by the Giant Dipole Resonance (GDR) [1], and neutrons are generated when the energy of the incident photon γ exceeds the GDR reaction threshold ($6MeV-20MeV$) with a mean energy around 1MeV [2]. Moreover, due to the moderating effect of human body, a not avoidable thermal neutron fluence is localized in the tumour area. A 18 MV Elekta Precise Accelerator has been employed for this study. An anthropomorphic tissue-equivalent phantom, Jimmy, (Fig.1), especially designed and manufactured by the INFN Turin section, in collaboration with the Ispra JRC (Join Research Centre), has been used; the distribution of fast and thermal neutron component inside phantom at various positions has been evaluated, both by experimental measurements and MC simulation [3]. Measurements have been carried out by superheated bubble detectors (BTI, Ontario, Canada) [4]: BD-PND dosimeters for fast neutrons ($100KeV<En<10MeV$) and BDT dosimeters for thermal neutrons ($En<0,4eV$). The experimental results confirm the simulation prevision (Fig.2) [5]: consistent thermal neutron fluence of $1,55E07\ n_{th}cm^{-2}\ per\ Gy$ is present in the treatment zone. In this work the possibility of employing this thermal neutron background to enhance the radiotherapy efficacy is analysed. As a matter of fact by previously administering ^{10}B-Phenyl-Alanyne (^{10}BPA) to the patient, the thermal neutron peak could be exploited for BNCT, delivering an additional dose of $10\%-15\%$ photon dose, concentrated in the tumour cells, i.e. acting as a localized radiosentizer. This can be very interesting, considering the actual trend in dose escalation in radiotherapy [6]: in fact the improvement in photon beam collimation techniques, resulting in a better treatment zone localization, allows the use of higher MU number, sometimes released in few sessions.



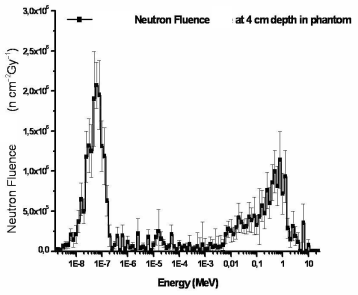


Figure 1: Jimmy Anthropomorphic phantom

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Measurement of the ^{33}S(n,α) cross section at n_TOF: applications to BNCT

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In addition to B-10, other isotopes have been studied as target for neutron capture therapy, being the main requirement a high value of the (n,α) cross-section in the thermal energy range. However, the most recent reactors as well as the proposed accelerator-based neutron sources produce epithermal neutron beams which are considered the most suitable ones for BNCT. Combining these ideas, ^{33}S, a stable isotope of sulfur having a large (n,α) cross-section in the epithermal energy range, has been studied as a cooperating target for BNCT [1-2].

Only one dedicated measurement of the ^{33}S(n,α) cross section as a function of the energy can be found in the literature [3]. Such measurement provided data from 10 keV to 1 MeV, thus the cross-section is unknown for neutron energies below 10 keV that is the most important one for BNCT since neutrons are moderated by the tissue. Also, there is only measurement of the (n,tot) cross-section [4]. Both experiments showed that the lowest-lying and strongest resonance of ^{33}S(n,α) cross section occurs at neutron energy of 13.5 keV. Nevertheless, the set of resonance parameters that determine such resonance, as well as the second one at 24 keV, show important discrepancies (more than a factor two) between the mentioned measurements [3,4]. Also a value of the integral cross-section can be found in the literature. All the previous measurements were performed with the motivation to clarify the origin of the S-36 in the Universe which is still today an open question. Moreover, the most popular evaluated databases such as ENDF or JENDL do not show any resonances in the cross-section.

Therefore the measurement of the ^{33}S(n,α) reaction cross section was proposed to the ISOLDE and Neutron Time-of-Flight Experiments Committee of CERN in 2012 [5]. The experiment was performed at n_TOF (CERN) at the end of 2012. The major challenges are to provide data for the first time below 10 keV, and to set the resonance parameters of the most important resonances. In this work we will present a brief overview of the experiment as well as preliminary results of the data analysis in the neutron energy range from thermal to 100 keV. These results will be taken into account to calculate the kerma-fluence factor corresponding to ^{33}S in addiction to ^{10}B and those of a standard four-component ICRU tissue. Furthermore, MCNPX simulations of the deposited dose including our experimental data will be presented. The comparison between different evaluated data and experimental data will be also shown.

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Posters

Measurement of the double-differential neutron yield of the $^{9}Be(d,n)^{10}B$ reaction in the low bombarding energy regime.

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In the last few years, the potential use of the $^{9}Be(d,n)^{10}B$ reaction as an epithermal source of neutrons for BNCT has been thoroughly investigated by our group [1-3]. The computational assessment of the deep-seated tumor treatment capability showed that acceptable treatments are feasible using thin beryllium targets and a low-energy and high-current deuteron beam. In particular, MCNP simulations showed that acceptable dose performances can be obtained by means of ~5-to-8 µm thick beryllium targets bombarded with a 30 mA deuteron beam from 1.35 to 1.45 MeV. These neutron source models were built from cross-sections and total yield data available in the literature and nuclear data bases. However, in the bombarding energy regime we are interested in, the lack of complete and accurate experimental data makes it necessary to validate the above mentioned neutron source models.

In this context, a set of measurements of the double-differential neutron yields produced by 1.2 and 1.35 MeV deuterons through the $^{9}Be(d,n)^{10}B$ reaction were carried out at the Laboratori Nazionale di Legnaro (LNL). The experiment consisted in the measurement of the neutron energy spectra at different emission angles (0°, 30°, 60°, 90° and 120°) using a plastic-silicon-based recoil-proton spectrometer developed by Agosteo et al [4]. The detection system consists in a 1 mm polyethylene converter coupled to a monolithic silicon telescope, a device constituted by a ΔE and an E stage-detector. Neutron energy distributions are derived by unfolding the distribution of the energy deposited in the thick E stage by recoil-protons, which is obtained from the measurement of the ΔE-ETOT scatter plots (i.e. the distributions of the energy imparted by recoil-protons in the ΔE stage versus the total energy deposited in the telescope, ETOT). The unfolding algorithm is based on a CT image reconstruction algorithm developed by Shepp and Vardi [5] and on an analytical model of the detector response matrix developed by Agosteo and Pola [6].

These results together with the data available in the literature reinforce the possibility of using the $^{9}Be(d,n)$ reaction on a thin target as an advantageous option for accelerator-based BNCT.

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Monitoring and evaluation of the irradiation beam of BNCT research facility at IPEN

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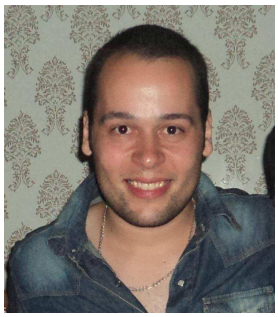

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In Brazil there is a facility for BNCT studies coupled to the IEA-R1 Research Reactor in the Nuclear and Energy Research Institute at São Paulo (IPEN). The facility is located along of the beam hole 3 which has 261.5 cm of length and 12.8 cm of diameter. The radiation from the reactor core goes into the BH #3 and passes through a filter and moderator set, which has the function of adjusting the radiation beam (neutron and gamma intensity and spectra) and reaches the sample irradiation position. Filter and moderator set is not fixed and may be changed as needed for each experiment to be performed. The aim of this study is to monitor and evaluate the beam irradiation facility for BNCT studies in order to evaluate the needs for improvements in the irradiation conditions. Therefore, neutron beam intensity and energy spectrum have been evaluated through neutron activation foils experiments while gamma contamination has been evaluated with TLDs.

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Neutron Production Target for Accelerator - Based Boron Neutron Capture Therapy

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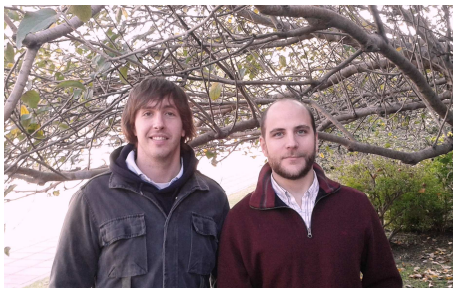

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This work is part of a project for developing Accelerator–Based Boron Neutron Capture Therapy (AB- BNCT) for which the generation of neutrons through nuclear reactions like ^{9}Be(d,n) is necessary [1]. In this paper first results of the design and development of such neutron production targets are shown.

For this purpose, the neutron production target has to be able to withstand the mechanical and thermal stresses produced by intense beams of deuterons (of 1.4 MeV with a total current of about 30mA). In particular, the target should dissipate an energy density of up to 1 kW/cm^2 and must preserve its physical and mechanical properties for a sufficient length of time under irradiation conditions and hydrogen damage.

To maximize the adhesion of Be deposits on different substrates surface treatments were made, like blasting and metal deposits [2], to favor the affinity between Beryllium and the substrate, obtaining significant improvements in adhesion.

Subsequently, Be deposits on different substrates were characterized by means of different techniques including Electron Microscopy (SEM), roughness, thickness, etc. Subsequently thermal stress tests were made to simulate operation regimes.

To satisfy the power dissipation requirements for the neutron production target, microchannel system simulations in a turbulent flow circulation regime using the physical model proposed in [3] are presented. The results obtained were compared with those in several publications [3,4,5] and discrepancies lower than 10% were found in all cases.

A prototype for model validation is designed here for which simulations of fluid and structural mechanics were carried out and is discussed in this paper. These simulations allow the determination of geometric parameters of the prototype complying with the requirements of a microchannel system.

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New computational method to evaluate the ^{7}Li(p,n)^{7}Be reaction near threshold for accelerator-based BNCT and other applications

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Many potential applications of neutron sources have recently motivated the increase in research and development for accelerator based devices. The endothermal ^{7}Li(p,n)^{7}Be reaction near threshold is of particular interest in Boron Neutron Capture Therapy because low-energy neutrons, suitable for clinical applications (from a few eV to 10 keV), are easily produced. The neutron production near threshold is particularly efficient since it minimizes the necessary proton energy and hence accelerator voltage, the generation of direct and indirect radiation and the volume of the associated beam shaping assembly. This reaction is also useful in a series of different problems, such as the study of quasistellar neutron spectra.

Within this context, our work contributes with a new description of the ^{7}Li(p,n)^{7}Be reaction near threshold using center-of-mass and relative coordinates, yielding a mathematical representation which allows a simpler access to all relevant quantities in the reaction and gives new insight into the numerical evaluation problem. The method, implemented as a C-code, was validated both with numerical and experimental data finding a good agreement. This tool is also used here to analyze scattered published measurements such as (p,n) cross sections, differential and total neutron yields for thick targets. Using these data we derive a consistent set of parameters to evaluate neutron production near threshold.

Rapid evaluation of the gamma dose due to Hydrogen radiative capture in BNCT simulations.

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Monte Carlo (MC) simulation of neutron transport becomes an essential tool in research and dosimetry calculations for boron neutron capture therapy (BNCT) of cancer because of the complex interactions of neutrons in tissue. The radiation delivered in BNCT consists of a mixed field of secondary particles with high and low linear energy transfer (LET) values -therefore a different relative biological effectiveness (RBE)-. The absorbed dose is usually separated in four main components: thermal neutron, fast neutron, photon -primarily 2.224 MeV gammas from $^{1}H(n,\gamma)^{2}H$ radiative capture reaction-, and ^{10}B dose -from the reaction $^{10}B(n,alpha)^{7}Li$-. Two reasons make the photon dose evaluation to become essential, specially for healthy tissue. First, due to the nature of photon interaction with matter -mean free path for 2MeV gamma is 20.4 cm in soft tissue[1]-, it is likely that part of the photon dose will be delivered outside the target volume, affecting normal tissue. Second, the photons are produced by the capture of thermal neutrons which are spread in the medium. In particular, the latter reason causes a loss of statistic for the MC evaluation of dose delivered. Therefore, it is required to simulate a higher number of primary neutrons in order to achieve enough accuracy in photon dose estimation, which implies an increasing computation time. Reference MC calculations of BNCT based on the use of kerma/fluence factors approximate this dose component by the photon kerma [2], using tabulated factors, with a loss of accuracy with respect to the other dose components.

The aim of this work is the fast and accurate evaluation of the photon dose by the use of a statistical method developed for point-like sources [3]. First, the number of photons generated via radiative capture in a particular cell is obtained using the Monte Carlo code MCNP5 [4]. Then, this photon map is used as a multiple point source input for the statistical model and its dose is calculated in a rapid and precise way. Finally, the results are compared with full simulations of photon dose in BNCT.

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Boron enrichment of porphyrin dendrimers with potential application in BNCT

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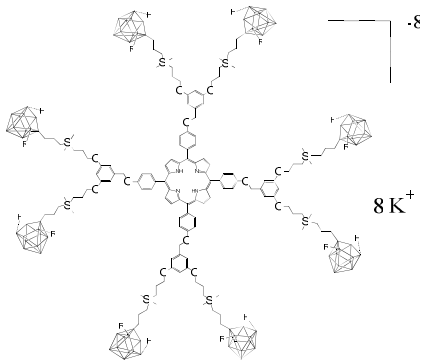
Our group has developed different types of dendrons and dendrimers that incorporate boron-based clusters in order to obtain high boron-content molecules for further applications in biomedicine,[1] most specifically in Boron Neutron Capture Therapy (BNCT). According to this, due to the biocompatibility of carbonyl porphyrin,[2,3] we have considered interesting the possibility to synthesize new boron rich dendrimers in which the *meso*-porphyrins are the core molecules.

For this purpose, different generations of starting aryl-ether dendrimers with porphyrin as core have been used as platforms. These dendrimers have the suitable terminal functional groups, to make them react with boron cluster derivatives. For all compounds, the reactions conditions have been optimized to obtain a total functionalization of the porphyrin dendrimers with a high yield. The high-boron content dendrimers have been characterized by usual techniques, such as FTIR and ^{1}H, ^{13}C and ^{11}B NMR spectroscopies, and elemental analyses. Furthermore, chemical and biological properties are being evaluated, since they are a relevant point to carry out cell culture tests.



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Determination of the isolated quantitation of BSH and BPA by liquid chromatography-electrospray ionization-mass spectrometry (LC/MS)

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Abstract:
BNCT (boron neutron capture therapy), which the ^{10}B of concentration in blood samples are measured to estimate radiation dose delivered to tumor and normal tissue, has been investigated widely for clinical treatments of different types of cancer since decades. In general, *p*-boronophenylalanine (BPA) and borocaptate sodium (BSH) enriched with ^{10}B are employed as the drug-targeted binary radiotherapy. Although ^{10}B concentration in blood samples from the boron compounds could be measured by prompt gamma-ray spectrometer or inductively coupled plasma (ICP) method, it is difficult to ascertain ^{10}B origin.
We are developing a separation method for the determination of the isolated quantitation of BSH and BPA. Because of the highly hydrophilic nature of BSH, it is difficult to extract BSH on hydrophobic reversed-phase HPLC (high-performance liquid chromatography) column. Herein, ion-pairing HPLC coupled with electrospray ionization-mass spectrometry (ESI-MS) are studied for the separation and the quantitative determination of BSH and BPA. According to different chemical property between BSH and BPA, an ion-pairing reagent (DHAA: di-hexylammonium acetate) as the mobile phase on HPLC are employed to form an extractable ion-pairing complex with aqueous BSH on a reversed-phased column to improve the isolation. The mobile phase is methanol loaded with 5mM DHAA flowing at 0.2mL/min., and the chromatography is performed by a Shim-pack FC-ODS column. It is confirmed that BSH and BPA are extracted at the different retention time with ion chromatogram. The pseudo-molecular ion $[(^{10}B_{12}H_{11}SH)^{2-}\square 3DHA^{+}]^{+}$ at m/z 722.9 in the ESI positive-ionization mode and $[^{10}B_{12}H_{11}SH]^{2-}$ at m/z 82.2 in the ESI negative-ionization mode are observed with mass spectrum. Furthermore, ^{10}B concentration isolated from BSH and BPA, and the isotopic ratio $^{10}B/^{11}B$ is measured by a high resolution inductively coupled plasma mass spectrometry (HR-ICP-MS).

Key Words: BSH, BPA, separation method, LC/MS

New efficient methods for the synthesis of cluster anion $[B_{12}H_{12}]^{2-}$ derivatives with the exopolyhedral B-OH reaction site for the subsequent modification in developing BNCT preparations

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The first stage of the development of BNCT preparations based on polyhedral $[B_{12}H_{12}]^{2-}$ boron anion consists in the introduction of primary substituent (reaction site) in the *closo*-dodecaborate system, which subsequently can be modified. In the present study, efficient methods for the synthesis of *closo*-dodecaborate anion derivatives in using hydroxyl group as the primary substituent are suggested.

An original method for the synthesis of water-soluble 1,2-$[B_{12}H_{10}(OH)_2]^{2-}$ cluster boron anion derivative via the alkaline hydrolysis of product of the reaction between the bis(tetrabutylammonium) dodecahydro-*closo*-dodecaborate (2–) and benzene-1,2-dicarboxylic acid melt at temperatures of 190-195 ℃ in a dry ar gon atmosphere. In the reaction under consideration, the benzene-1,2-dicarboxylic acid is both reagent and solvent. The synthesis was performed using the tetrabutylammonium salt, which is sufficiently soluble in the benzene-1,2-dicarboxylic acid. The nucleophilic attack of benzene-1,2-dicarboxylic acid molecule to boron skeleton was found to be realized almost simultaneously on two sites with the formation of only a dihydroxy derivative. The attack of substrate with more than one benzene-1,2-dicarboxylic acid molecule is limited by the temperature of melting (accompanied by decomposition) of benzene-1,2-dicarboxylic acid oneself.

The single-stage method of introduction of hydroxyl group into monosubstituted $[B_{12}H_{11}X]^{2-}$ (X = SCN, I, $OC(O)CH_3$) cluster boron anion derivatives was developed. It was found that the reaction between monosubstituted $[B_{12}H_{11}X]^{2-}$ derivatives and acetic acid in the presence of oxygen and atmospheric moisture leads to the single-stage formation of $[B_{12}H_{10}X(OH)]^{2-}$ hydroxy derivatives without the formation of acetoxy derivatives. The experimental data allow us to suggest the mechanism of the process.

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Simultaneous determination of trace amount of boron-10 chemical species and their concentration in blood by ^{10}B-NMR

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Introduction: In the development of boron neutron capture therapy (BNCT), determinations of ^{10}B chemical species and their concentrations in blood, tumor and normal tissues are important to reveal the pharmacokinetics of injected boron compounds. However, general determination methods such as ICP-AES, PG-SPECT can measure the total ^{10}B concentration in blood, tumor and normal tissue but cannot determine ^{10}B chemical species severally. ^{10}B-NMR can determine the total boron concentration as well as that of ^{10}B chemical species. We have succeeded to determine trace amount of ^{10}B-BPA and ^{10}B-BPA-complex and their concentrations in blood derivative (BD) simultaneously using ^{10}B-NMR [1]. However, BD does not contain blood plasma which constitutes approximate 55% of whole blood (WB). Blood plasma contains lipids, saccharide and plasma proteins. These substances might affect quantitative ^{10}B-NMR analysis. Hence, we have investigated ^{10}B-NMR analysis in whole blood.

Results and discussion: Three ^{10}B-BPA WB solutions (10, 15 and 20 ppm^{10}B) were prepared from 50 ppm^{10}B ^{10}B-BPA in saline with whole blood (male, 63 years old), and measured by ^{10}B-NMR spectrometer under following conditions; JEOL ECA500, NMR-Freq: 53.735 MHz; Receiver gain: 60; Relaxation delay: 30 ms; 100000 scans; $BF_3{\cdot}OEt_2$ ref. (= 0 ppm), temperatures: 25, 37 and 50℃. Same concentra tions samples of ^{10}B-BPA in BD and saline were used as the control. Obtained spectra were corrected by the mathematical technique. The areas of each peak were calculated by the Delta NMR analysis software (JEOL, Kyoto). Two peaks at 30 ppm and 7~9 ppm which were assigned to boronic acid of BPA and boronic acid-complex (BPA-complex) respectively were observed for both BD and WB samples. However, WB samples showed temperature dependent broaden peaks (half widths of 30 ppm peak in 10 ppm^{10}B samples at 50 ℃: 810 Hz for WB sample; 356 Hz fo r saline sample). Relative concentration ratio of boronic acid and boronic acid complex in WB samples also depended on the temperature. These results suggest that BPA interacts with blood plasma components.

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Histomorphological analysis and quantitative determination of *p*-boronophenylalanine in thin tissue sections by LA-ICP-MS for BNCT

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The radiation dose applied in BNCT is proportional to the boron concentration in cells and tissues. Therefore, in clinical application and preclinical research, reliable boron determination in blood samples, tissues, and cells is mandatory. Locally selective boron analysis in tissues is of particular interest, if the efficacy of a boron compound is tested, e.g., to assess enrichment in specific cells or tissues or pharmacokinetic distribution. In BNCT the most frequently used methods (ICP-MS, ICP-OES, PGAA) are incapable to provide boron analysis with respect to the distribution in tissue. Other qualitative, semi-quantitative and quantitative techniques with higher resolution haven been tested and applied (EELS, HRQAR, SIMS, among others), but require time consuming and complicated sample preparation, as well as long time periods for the measurement. In recent years, ICP-MS analysis in combination with laser ablation (LA-ICP-MS) has emerged as a very reliable technique for surface analysis of different materials. However, for quantification of various elements in tissue by LA-ICP-MS there are often no standard reference materials (SRM) available.

Therefore, a new quantitative imaging method for ^{10}B in tumorous tissue using LA-ICP-MS was developed. For external calibration SRMs produced originally for analysis of cryosections with Quantitative Neutron Capture Radiography (QNCR) from a solution of p-boronophenylalanine-fructose (BPA-f) in heparinised whole blood samples are used. This mixture was frozen in a block of carboxymethylcellulose to enable sectioning with a microtome.

Our findings qualitatively and quantitatively agree with results from QNCR analysis of the same samples. We will demonstrate the usefulness of these matrix-matched calibration standards as reference material for boron analysis in thin tissue sections by LA-ICP-MS.

Boron Neutron Capture Therapy (BNCT) for liposomal Drug Delivery System by passive targeting.

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The long blood circulation of poly ethylene glycol (PEG) are well known. The liposome modified PEG is accumulated at tumor by passive targeting. The reason is escape of reticulo endothelial system (RES). By the liposomal surface modified PEG, the macrophage cannot recognize foreign substance and phagocytose. In addition, it is controlled uptake by MPS (Mononuclear Phagocyte System: which belongs to RES such as liver, the spleen) . As a result, the liposome modified with PEG circulated for a long time in blood and accumulates to a tumor tissue having high blood vessel permeability passively (EPR effect).[1]

However, in a recent study, the membrane detachment half--life of PEG lipid is up to 70 hours and engagement of the serum protein is could not completely inhibited.[2]

So, we were obtained for further improvement of blood circulation and developed novel lipid which have longer blood circulation than PEG lipid. The identification of the novel lipid (PBL) performed ^{1}H-NMR, ^{10}B-NMR, TOF-MS, and purity assay of PBL performed HPLC.

We prepared liposome using PBL, distearoylphosphocholine(DSPC) and cholesterol (CH). PBL 5% (PBL:DSPC:CH=47.5:47.5:5) were incorporated a liposomal surface 73.8% and PBL10% (PBL:DSPC:CH=45:45:10) were 63.7%.

The liposome modified with PBL were measured particle size and zeta-potential. As for results, particle size was about 100nm and zeta-potential was anion.

With this boron liposome, chemical characteristics will be discussed.

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Method development for boron isotope analysis in whole blood by HR-ICP-MS

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Precise and accurate measurements of concentration and isotope ratios of boron in whole blood are important to determine the irradiation time in boron neutron capture therapy (BNCT), since accurate estimation is required of the blood boron level before irradiation [1]. In this study, High-resolution inductively coupled plasma mass spectrometry (HR-ICP-MS) was used to measure boron concentration and isotope ratios. Measurement of boron abundance by Quadrupole ICP-MS (Q-ICP-MS) are typically hindered by $^{40}Ar^{4+}$ interference at mass m/z 10 [2]. However, the two peaks ($^{40}Ar^{4+}$ and ^{10}B) were well separated using HR-ICP-MS, therefore it provides better sensitivity and precision than Q-ICP-MS. In measuring isotope ratios by mass spectrometer, measured values will deviate from true values due to mass bias effect. Therefore, mass bias correction is important for highly accurate isotope ratios determination [3]. A correction factor was calculated as the mean of the measured isotope ratios of the standard of known isotopic composition (using NIST-SRM 951a Boric Acids Isotopic standard), compared to the measured isotope ratios. Calculating the mass bias factor, □) time (every 1 hour × 5) fluctuation □) inter-day (5 days) fluctuation were not observed (with a precision of □) 0.3% □) 0.8% RSD for n=3). Evaluating the validation of the isotopic ratio measurements using mass bias correction by analyzing NIST-SRM 1643e, good agreement was obtained between measured value and natural abundance of boron isotope ratio with a relative error of 0.35%. Elements in blood may pose undesireble effects on boron determinations, thus we tried to separate boron from blood matrix by a solid-phase extraction column (using Nobias Chelate-PA1). High recovery rate was obtained when we added Azomethine H which combined well with boron to the column.

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The dependency of compound biological effectiveness factors on the type and concentration of administered neutron capture agents in BNCT

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Purposes: To examine the effect of the concentration of neutron capture agents on the values of compound biological effectiveness (CBE) [1] in boron neutron capture therapy *in vivo*, referring to the response of intratumor quiescent (Q) cells.

Methods: After the subcutaneous administration of a ^{10}B-carrier, boronophenylalanine-^{10}B (BPA) or sodium mercaptododecaborate-^{10}B (BSH), at 3 separate concentrations, the ^{10}B concentrations in the tumors were measured by □-ray spectrometry. SCC VII tumor-bearing C3H/He mice received 5-bromo-2'-deoxyuridine (BrdU) continuously to label all intratumor proliferating (P) cells, then treated with BPA or BSH. Immediately after reactor neutron beam irradiation, during which intratumor ^{10}B concentrations were kept at levels similar to each other, cells from some tumors were isolated and incubated with a cytokinesis blocker. The responses of the Q and total (= P + Q) tumor cells were assessed based on the frequencies of micronucleation using immunofluorescence staining for BrdU.

Results: The values of calculated CBE were higher in Q cells and in the use of BPA than total cells and BSH, respectively. In addition, the higher the administered concentrations were, the smaller the values of CBE became, with a more marked tendency in the use of BPA than BSH. The CBE values for neutron capture agents that deliver to solid tumors more dependently on intratumor heterogeneity become more changeable.

Conclusion: Tumor heterogeneity is now thought to be one of the major difficulties in the treatment of solid tumors [2,3,4]. Although a lot of research on tumor heterogeneity are now going on, there are not yet any apparent indices for evaluating the degree of intratumor microenvironmental heterogeneity. The CBE factor for each tissue and tumor, which greatly depends on the degree of the possibility for distributing ^{10}B from a ^{10}B-carrier, is a promising candidate for the index for estimating tumor heterogeneity. In the future, we would like to analyze the CBE factor not only as s significant parameter in BNCT, but also as a significant index for assessing intratumor heterogeneity.

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Design and characterization of a novel neutron shield for BNCT in an experimental model of oral cancer in the hamster cheek pouch at RA-3

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Our research group at the Radiation Pathology Division of the Department of Radiobiology (National Atomic Energy Commission) has previously demonstrated the therapeutic efficacy of different BNCT protocols to treat oral cancer in an experimental hamster cheek pouch model. In particular, to perform studies in this experimental model at the thermal facility constructed at RA-3, we designed and constructed a shielding device for thermal neutrons, to be able to expose the cheek pouch while minimizing the dose to the rest of the body [1]. This device allowed for the irradiation of one animal at a time. Given the usage rate of the device, the aim of the present study was to design and construct an optimized version of the existing shielding device that would allow for the simultaneous irradiation of 2 animals at the thermal facility of RA-3.

Taking into account the characteristics of the neutron source and preliminary biological assays, we designed the shielding device for the body of the animal, i.e. a rectangular shaped box with double acrylic walls. The space between the walls contains a continuous filling of $^{6}Li_2CO_3$ (95% enriched in ^{6}Li), approximately 6 mm thick. Two small windows interrupt the shield at one end of the box through which the right pouch of each hamster is everted out onto an external acrylic shelf for exposure to the neutron flux. The characterization of the shielding device showed that the neutron flux was equivalent at both irradiation positions confirming that we were able to design and construct a new shielding device that allows for the irradiation of 2 animals at the same time at the thermal facility of RA-3. This new version of the shielding device will reduce the number of interventions of the reactor operators, reducing occupational exposure to radiation and will make the procedure more efficient for researchers.

In addition, we addressed the generation of tritium as a product of the capture reaction in lithium. It was considered as a potential gaseous effluent discharge and the maximum amount that would be generated during normal operation was calculated. The presence of tritium in a sample of irradiated powder was qualitatively confirmed. The amount of tritium generated was within the allowed range even if the total amount produced were discharged as an effluent. Regarding the tritium retained within the shielding box, the maximum energy of the beta particles emitted in tritium decay is only 19 keV. Thus, they are absorbed within the walls of the shielding box and would not affect the operators or the experimental animals.

Additionally, after irradiation, the exposure rate in contact with the shielding device was higher than expected. Based on the activation analysis of the irradiated powder, it was possible to infer the presence of a pure positive beta emitter whose semi-decay period corresponds to ^{18}F. The presence of this nuclide could be due to the secondary reaction $^{16}O(t,n)^{18}F$, described for similar conditions (Siri, personal communication) [2],and would explain the activation of $^{6}Li_2CO_3$ employed in the shielding device. We are currently analyzing the possibility of varying the composition of the material by chemically transforming Li_2CO_3 to a compound such as LiF. This strategy would avoid intimate contact between oxygen and the tritium generated, and generation of ^{18}F. Furthermore, LiF would pose an advantage in terms of shielding properties due to its higher density (Kobayashi, personal communication).

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Design and Simulation of a Target for a Neutron Source Based on the ^{9}Be (p,n) ^{9}B Reaction for BNCT

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The neutron source for Boron Neutron Capture Therapy is in the transition stage from nuclear reactor to accelerator based neutron source. Generation of epithermal neutron can be achieved by ^{9}Be (p, n) ^{9}B reaction using accelerated proton beam. Development of small-scale and safe neutron source is within reach. A sufficient neutron yield for BNCT is obtained by using an accelerator-based neutron source. In order to get high flux of epithermal neutrons, a combination of 30MeV proton beam and a beryllium target was selected.

The main challenge is to design the target as holding device equipped with proper cooling material. In this effort, a V-type target with opening angle of 30^{o} degree, which depends on the situation, to grasp whole proton beam was designed. Using mA current heats up the target quite fast, therefore efficient cooling device is needed. We choose gallium cooling material for heat removal from the surface of the target.

To optimize setup and maximize neutron flux the Monte Carlo code MCNPX2.3 simulated the system. Thickness of the target is 0.55cm that is slightly shorter than the range of 30MeV protons in beryllium. The results of our simulation by MCNPX code showed that the system created neutron flux $10^{14}(n/cm^{2}.s)$ at 1mA proton beam, with an energy spectrum extending in 1keV-28MeV.

Preliminary Experiment Based on the 10MeV High Intensity Cyclotron(CYCIAE-10) as Neutron Source for BNCT

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Abstract: In order to test the feasibility of the 10MeV high intensity cyclotron (CYCIAE-10), developed in China Institute of Atomic Energy, as a neutron source for BNCT, preliminary experiments were performed. A beryllium target with the dimension of Φ100×6mm was assembled at the exit of the cyclotron and bombarded by a 10MeV proton beam, neutrons were generated by the nuclear reaction. Behind the target, a tank full of water serving as a neutron beam shaping assembly was placed. The relation between the thermal neutron flux density in the tank and the proton beam intensity was measured by two ionization chambers, and the neutron flux distribution along the axis of the target and the absolute neutron flux density in the tank were measured by Au foil activation method.

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Monte Carlo simulation of depth–dose distribution in brain model for boron neutron capture therapy

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BNCT is a technique that was designed to selectively target high LET heavy charged particle radiation to tumors at the cellular level [1]. In-phantom measurement of physical dose distribution is very important for Boron Neutron Capture Therapy (BNCT) planning validation.
Absorbed dose delivered to the normal tissue and tumor during BNCT result from possible reactions from three types of directing ionizing radiations with different LET characteristics such as $^{14}N(n,p)^{14}C$, $^{10}B(n,\alpha)^{7}Li$, $^{1}H(n,\square)^{2}H$, $^{1}H(n,n)^{1}H$ and all of (n,□) reactions due to neutron activation of elements.
Determination of total absorbed dose required complex calculations because the neutron and gamma rays in the normal tissue and tumor cells have an energy distribution. All of the calculations were carried out using the Monte Carlo MCNPcode [2].
The epithermal neutron beam from an accelerator [3] was the primary neutron source for the calculation and the computational head phantom model is SNYDER, which consists of the skin, the skull, the head volume and the tumor, and elemental compositions were taken from ICRU Report 46 (1992).
The simulated neutron flux distributions along the central axis of the ellipsoidal head phantom are calculated. It was found that epithermal and fast neutron fluxes decrease sharply with increasing penetration length, while maximum thermal neutron flux occurs at adepth of 3 cm. The obtained results are similar to the literature [4].

The advantage depth, one of the important dosimetric properties used to evaluate the ability of neutron beam to treat deep-seated tumors, was also calculated. It was recognized that the tumor positioned at the maximum depth of 7 cm from head skin could be treated by using an epithermal neutron flux beam from the accelerator.

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A few ending words…

There is only one day for the beginning of the 7th Young Researchers' BNCT meeting and I am finishing the compilation of all the abstracts submitted.

There is great work here. This is the main thing that is running in my head. It seems simple to fill these pages with brief abstracts but one realizes how much work is behind this book: theoretical calculations, simulations, engineering work, biomedical experiments, synthesis of compounds, clinical trials…

Thank you very much for all the submissions. Some of the contributors to this book have not being able to come to the meeting, but at least I wished to include their abstracts. This will allow them to communicate their work to the BNCT community.

Thanks to all members of the International Committee who have reviewed the papers submitted.

I cannot refrain myself from saying that I am proud to be writing these ending words in, what is at least for me, a great piece of science.

Thanks to all.

Granada, September 21st, 2013.

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