Readiness for Boron Neutron Capture Therapy*

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Abstract — A source of epithermal neutrons based on a tandem accelerator with vacuum insulation and a lithium neutron producing target was proposed and created to develop boron neutron capture therapy of malignant tumors. A laboratory was created in 2014 to be prepared for practical implementation of the therapy using the accelerator neutron source. To achieve this goal it is necessary to increase the current and the energy of the proton beam, to create a new neutron producing target, neutron beam shaping assembly and so on. The article provides a description of the created source of epithermal neutrons, presents and discusses the results of experiments and declares future plans.

Keywords — boron neutron capture therapy, epithermal neutrons, accelerator

I. Introduction

Currently, Boron Neutron Capture Therapy (BNCT) is considered as a promising technique for treatment of malignant tumors [1]. It provides selective destruction of tumor cells by prior accumulation inside them a stable boron-10 isotope and subsequent irradiation with epithermal neutrons (Fig. 1). Because of the absorption of a neutron by boron, a nuclear reaction takes place with a large release of energy in the cell, leading to its death. Clinical trials on nuclear reactors showed that BNCT could treat glioblastoma, brain metastases of melanoma and several other tumors. For the widespread introduction of this technique in practice, compact sources of epithermal neutrons based on charged particle accelerators are required.
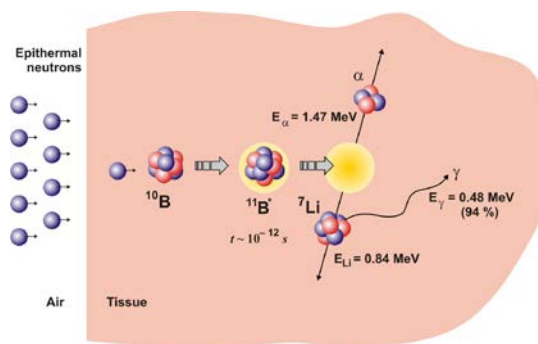

Fig. 1. Scheme of $^{10}B(n,\alpha)^7Li$ reaction.

II. Accelerator Based Epithermal Neutron Source

A. Neutron Source

It is world-recognized [1, 2] that the best reaction to form the epithermal neutron beam for BNCT is the $^7Li(p,n)^7Be$ reaction: neutron production is high, and the neutron spectrum is relatively soft. The source of epithermal neutrons based on the original tandem accelerator with vacuum insulation and the lithium neutron producing target was proposed in BINP [3]. The scheme of the proposed neutron source is shown at

Fig. 2. The facility consists of a source of negative hydrogen ions, a tandem accelerator generating a proton beam and a neutron producing target. Because of the complexity of creating such an accelerator neutron source for producing the proton beam it a new type of accelerator has been proposed, the tandem accelerator with vacuum insulation. It was also proposed to implement $^{7}Li(p,n)^{7}Be$ reaction, despite of the complexity of manufacturing the target: low melting temperature, low thermal conductivity and high chemical activity of lithium.
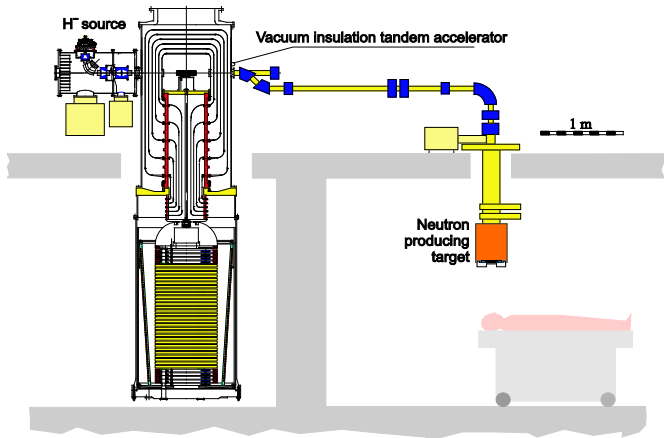

Fig. 2. Accelerator based epithermal neutron source for BNCT.

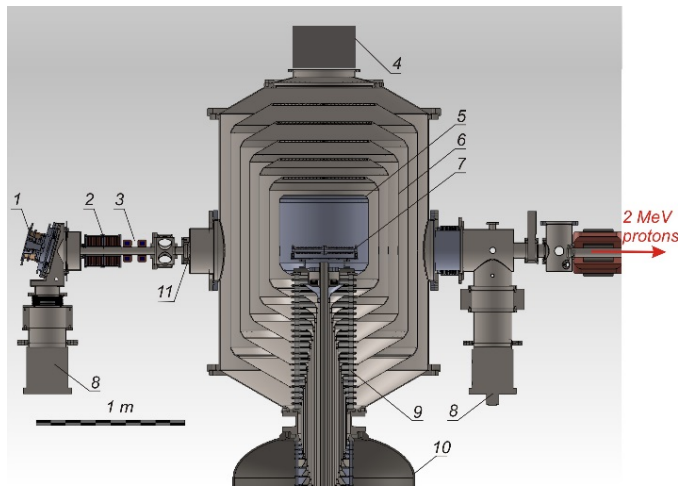*B. Tandem accelerator with vacuum insulation*

Fig. 3. Tandem accelerator with vacuum insulation: 1 – source of negative hydrogen ions, 2 – magnetic lenses, 3 – correctors, 4 – cryogenic pump, 5 – high voltage electrode, 6 – intermediate electrodes, 7 – gas stripping cell, 8 – turbomolecular pump, 9 – insulator, 10 – high-voltage power supply, 11 – inlet diaphragm.

Fig. 3 shows the accelerator. Coming from the source *1* negative hydrogen ion beam with 23 keV energy is rotated in a magnetic field at an angle of 15 degrees, focused by a pair of magnetic lenses *2*, injected into the accelerator and accelerated up to 1 MeV. In the gas (argon) stripping cell *7*, which is installed inside the high-voltage electrode *5*, negative hydrogen ions are converted into protons. Then protons by the same 1 MV potential are accelerated to 2 MeV energy. The

potential for the high-voltage *5* and five intermediate electrodes *6* of the accelerator is supplied by a high-voltage source *10* (most of the source is not shown) through the insulator *9*, wherein the resistive divider is set. Evacuation of gas is performed by turbomolecular pumps *8* mounted at the ion source and at the exit of the accelerator, and a cryogenic pump *4* via jalousies in the electrodes. A photograph of the tandem accelerator with vacuum insulation is shown in Fig. 4.
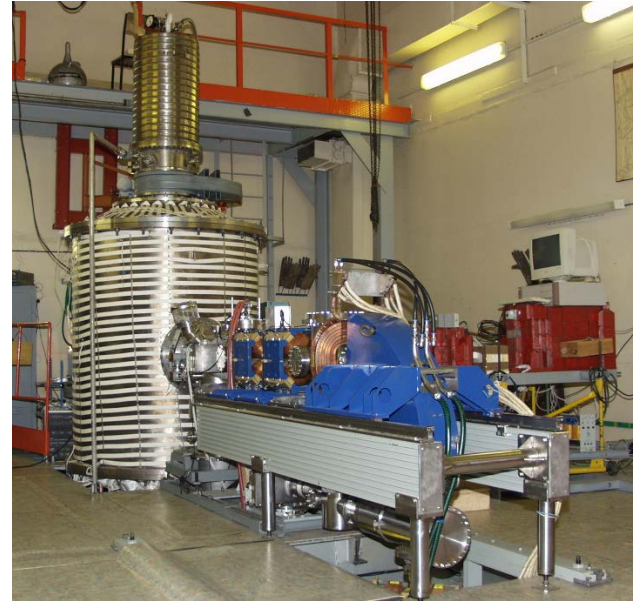

Fig. 4. Photo of the tandem accelerator with vacuum insulation.

The accelerator is characterized by fast acceleration of charged particles (25 kV/cm), large distance between ion beam and insulator (on which electrodes are mounted), large stored energy in the accelerating vacuum gaps and strong input electrostatic lens. The high-voltage strength of centimeter vacuum gaps with large stored energy was investigated [4]. The way of consistent training of accelerating gaps was proposed and realized and the required voltage of 1 MV was obtained [5]. The behavior of dark currents was studied and then they were reduced to an acceptable level by long staying under voltage [6]. An auto-emission current was detected, the cause of its occurrence was established, and changes in the design of the accelerator to prevent it were made [6]. It was proved that the application of a magnetic focusing lens allows realizing a input of a beam of negative hydrogen ions into the accelerator without loss [7]. A method of calibrating a gas stripping target was proposed and implemented. It is based on the measurement of the gas flow when the proton current is equal to the negative hydrogen ion current at the output of the accelerator [8]. These investigations allowed us to significantly increase the proton beam current. In the initial experiments the characteristic value of the current was 100 – 200 μA [9, 10], but now we obtain 1.6 mA in a long steady mode [11].

C. Neutron Producing Target

Lithium neutron producing target was proposed, developed and studied experimentally [12] (Fig. 5). System of thermal

evaporating of thin lithium layer on the target substrate was developed. Method for determining the thickness of lithium by measuring the electrical conductivity of distilled water with lithium tablets was proposed and implemented [13]. It is proved that the density of the deposited lithium is equal to the crystal density. By mass spectrometry of secondary ions it is found that the purity of the lithium layer and its resistance to the residual gas are sufficient for the efficient generation of neutrons [14]. It is proved that the turbulent water flow in the cooling channels of the target maintains the lithium layer in the solid state at a heating power density under the proton beam up to 300 W/cm^2 [15]. Neutrons generated by the reaction $^7Li(p,n)^7Be$ are inevitably accompanied by the accumulation of radioactive isotope ^7Be with a half lifetime of 53.3 days. To deactivate the target it was proposed, optimized and put into operation a protective subsurface container for temporary storage of activated targets made as a long steel tube immersed in the ground and covered with lead [16].
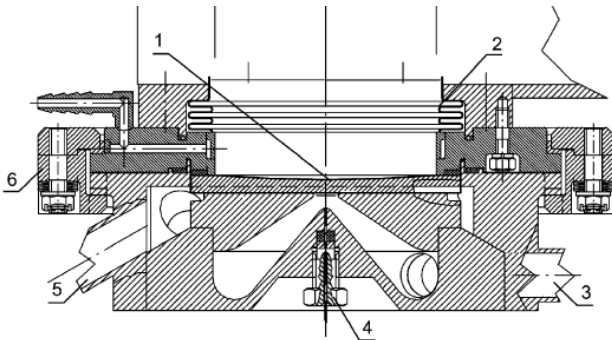

Fig. 5. Neutron producing target: 1 – backing with lithium layer, 2 –silphon, 3 – water input, 4 – thermocouple, 5 – water output, 6 – bayonet.

Proton beam with a typical size of 10 mm is delivered to the lithium neutron producing target by a pair of quadrupole magnetic lenses, bending magnet, another pair of quadrupole lenses and a scanner. The scanner provides uniform illumination by the beam across the target surface 100 mm in diameter. Total neutron yield is $1.1 \cdot 10^{11}$ s^{-1} at 1 mA 2 MeV proton beam [17]. Neutron energy spectrum was measured by time-of-flight technique [18].

D. In vitro Investigations

It was experimentally shown that the effect of neutrons on human U87 glioblastoma cells leads to their death, probably due to apoptotic process [19]. The response of the cell line U87 to the cytotoxic effect is gradually developed and is completely fulfilled on the 14-th day after the action. The optimal method to assess the irradiation cytotoxicity for the cell line U87 is the clonogenity test. Neutron flux irradiation of the cell line U87 previously incubated with boron-10 enriched boronophenylalanine (BPA) decreases the clonogenic properties of the cell line by ~90% in comparison with the untreated cells incubated under the standard conditions.

III. BNCT Laboratory at BINP

A BNCT Laboratory consisting of experts in physics, chemistry, biology, medicine was created in September 2014 at BINP. The aim of the laboratory is to be ready for BNCT to the end of 2016. To achieve the goal it is necessary to increase the proton beam current from 1.6 to 3 mA, energy – from 2 to 2.3 MeV, to develop and manufacture a new thin neutron producing target and a neutron Beam Shaping Assembly (BSA), to provide necessary diagnostic equipment, to prepare it for patient irradiation, and so on.

Currently, six PhD students are working in the Laboratory, including one from the University of Sciences and Technology Houari Boumediène (Algiers, Algeria), and also several students. One of the Russian PhD students has a practice at the Fukuoka clinic (Japan). In November 2015 we plan to conduct experiments at our facility together with the staff and PhD students of the Hospital of Tsukuba University (Japan).

IV. Current Results and Future Prospects

The main problem of achieving the objective of the Laboratory is double increase of the proton beam current. To clarify the reasons of breakdowns preventing an increase in current the process of acceleration of the ion beam in the accelerator has been studied. It was found that the acceleration of the ion beam is accompanied by additional flux of charged particles in the accelerating channel. It was found [19] that the appearance of charged particles is due to ionization of stripping gas and residual gas by the injected beam and due to penetration of positive argon ions of the stripping cell into the accelerating channel. The electrons caused by ionization of the gas are accelerated mainly to 1-MeV and absorbed by the elements of high-voltage electrode or stripping cell leading to a significant bremsstrahlung. Penetration of positive argon ions from the stripping cell into the accelerating channel is accompanied by their further acceleration to 1 MeV, which can lead to a significant secondary emission of electrons due to absorption of accelerated argon ions in the wall of the vacuum chamber. To suppress the flux of accompanying particles it was proposed to implement two modernizations. Firstly, we should improve vacuum conditions particularly in the beginning of the acceleration of the ion beam. For this purpose we have made a new input node, wherein a vacuum resistance formed as a cooled aperture was set and a cryopump On-Board 10 (CTI-Cryogenics, USA) with a pumping speed 2500 l/s for argon and 5000 l/s for hydrogen was mounted. Secondly, the wall of the vacuum chamber bombarded by positive argon ions and ultraviolet radiation from the stripping cell should be covered with a grid under 300 V potential to lock the secondary electron emission.

For the possibility of further increase of the proton beam current a new source of negative hydrogen ions with a current up to 15 mA was designed and manufactured. Currently, we are finishing the production of the new transporting channel of the low energy beam, which provides beam pre-acceleration up to 150 kV to facilitate its entry into the accelerator.

In order to increase the energy of the proton beam the high-voltage strength of the accelerator at 1.25 MV was studied. It was found that the increase in stored energy does not lead to loss of electric strength. Reducing of residual pressure, dark current and dose of X-rays shows that the process of training goes well and it takes time to reach a mode without breakdowns. Change of the outer surface geometry of

the isolator insulating rings from smooth to ribbed was proposed to provide double increase in the electric strength.

Interaction of protons with lithium in addition to generation of neutrons leads also to a significant output of γ-rays with energy 0.478 MeV. To reduce this unwanted accompanying flux of γ-rays the thickness of neutron producing lithium layer should be such that it slowed down protons to threshold energy of neutron generation – 1.882 MeV. Further absorption of protons should be in a substance where the reactions (p,γ), (p,p/γ), (p,nγ) and (p,αγ) do not cause significant output of γ-rays. Proton beam irradiation of samples made from lithium, graphite, magnesium fluoride, barium fluoride, aluminum, silicon, titanium, vanadium, stainless steel, copper, molybdenum and tantalum was conducted. Dose and spectrum of X-ray and γ-radiation, dose rate of neutron radiation and the emission spectrum of the residual activity were measured [21]. Neutron generation from lithium, vanadium, stainless steel and titanium were registered. Lithium, graphite and titanium were activated. It was determined that the absorption of protons with energy of 2 MeV in molybdenum and tantalum is accompanied by minimal dose of X-ray and γ-radiation and does not lead to generation of fast neutrons and residual activity. Taking into account previous studies of blistering [22] we recommend to make tantalum substrate of lithium neutron producing target for BNCT, ensuring minimum flow of unwanted radiation and maximum resistance to radiation damage.

Taking into account these studies a new neutron producing target was made. It consists of 21 tantalum tubes 5 mm in diameter with 0.25 mm wall thickness arranged in two parallel rows. All tubes are soldered to the copper body with a cavity for water supply. A thin layer of lithium is deposited on the surface of the tubes. This target is characterized by minimum volume of construction materials near the neutron generation area that will allow close Beam Shaping Assembly mounting and forming a therapeutic neutron beam of the best possible quality.

Fig. 6. Beam Shaping Assembly.

Optimization of Beam Shaping Assembly is done and a project for its production is made (Fig. 6). For the first time a composite moderator is applied: magnesium fluoride near the target, aluminum fluoride near the output, which is adapted to the slowing down process of neutrons. For the first a composite reflector is applied: graphite in the forward hemisphere and lead without antimony in the back. This design allows graphite to slow down the neutrons emitted forward. Since the energy of these neutrons is higher than the energy of neutrons emitted backward, such a reflector will give narrower neutron spectrum, which is desirable for BNCT.

It was determined that at energy of 2.3 MeV proton beam it is possible to generate a neutron beam with better quality than at energies of 2.5 – 2.8 MeV traditionally considered. In the BSA consisting of magnesium fluoride moderator with 21 cm height, 20 cm diameter and a reflector with 80 cm diameter, increasing of proton energy from 2.3 MeV to 2.5 MeV increases the neutron flux density by 1.75 times and as a consequence leads to almost the same increase in absorbed dose in the tumor: from 1.95 to 3.46 GyE/min at 10 mA proton beam current. However, due to the appearance of noticeable component of fast neutrons at 250 keV – 1 MeV region the absorbed dose in healthy cells on the skin increases by 2.56 times, that is why the therapeutic ratio decreases from 5.4 to 3.7. In order to reduce the impact of the fast neutrons it is necessary to increase the height of the moderator. Increasing height from 21 to 26 cm reduces the influence of fast neutrons to such a degree that the same therapeutic ratio 5 is reached, but the dose decreases to 2.17 GyE/min. Thus, in terms of getting the best quality of therapeutic neutron beam we should use the proton beam with energy of 2.3 MeV. Using a proton beam with higher energy can be justified only for treatment of tumors at of more than 7 cm a depth. In this case, we should generate hard neutrons for their deeper penetration and reducing of the dose on the skin should be achieved by directing the neutron beam from different angles using an orthogonal neutron beam shaping assembly with the possibility of rotation [23].

To measure the parameters of the ion beam the accelerator is equipped with Faraday cups, current proximity sensors and oscillating wire scanner probe OWS-30 (TRIUMF-licenced, D-Pace, Inc., Canada). For measuring the neutron flux and γ-radiation the facility is equipped with NaI and BGO γ-spectrometers, BDT and BD100R bubble detectors (Bubble Tech. Ind., Canada), neutron detector with cerium activated lithium silicate glass scintillator GS20 (The Saint-Gobain Crystals, USA), set of activation foils SWX-1552 (Shieldwerx[TM], USA), ionization chambers, a gamma detector LB6500-3H-10 (Berthold Tech., Germany), the dosimeter-radiometer DKS-96 (Doza, Russia). To measure the concentration of boron in the investigated or irradiated samples the laboratory is equipped with Atomic Emission Spectrometry with inductively coupled plasma parallel action with the axial and radial viewing ICPE-9820 (Shimadzu, Japan). As agents for targeted delivery of boron to the tumor we use boron-10 enriched sodium borocaptate $Na_2{}^{10}B_{12}H_{11}SH$ (BSH) and boronophenylalanine $C_9H_{12}{}^{10}BNO_4$ (BPA), purchased from Katchem Ltd., Czech Republic.
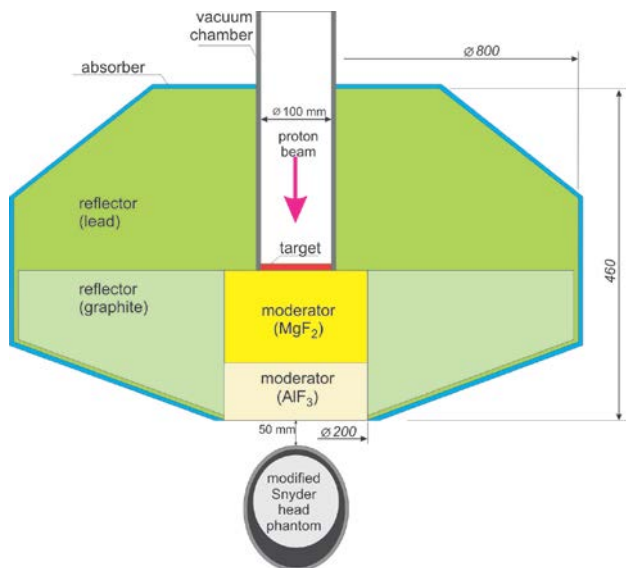
A new concept of the tandem accelerator with vacuum insulation is proposed [24]. The high voltage sectioned rectifier is located inside the accelerator insulator with high voltage and intermediate electrodes mounted on it, significantly reducing the height of the facility. Design of such a facility with an orthogonal neutron Beam Shaping Assembly [23] is presented at the Fig. 7.
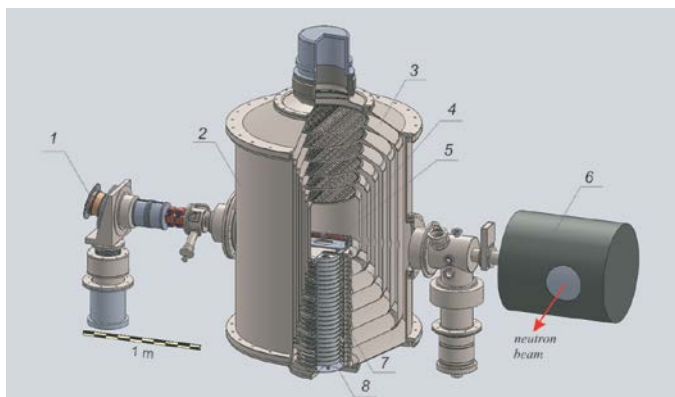

Fig. 7. New design of accelerator based epithermal neutron source: 1 – negative gydrogen ion source, 2 – tandem accelerator with vacuum insulation, 3 – intermmediate electrods, 4 – high voltage electrod, 6 – orthogonal neutron Beam Shaping Assembly, 7 – feedthrough insulator, 8 – high voltage sectioned rectifier

V. CONCLUSION

At Budker Institute of Nuclear Physics an accelerator based epithermal neutron source for BNCT is created and the Laboratory for preparation for the therapy is formed. It is necessary to increase the proton beam current from 1.6 to 3 mA, energy – from 2 to 2.3 MeV, to manufacture the new neutron producing target, to manufacture neutron beam shaping assembly, to work out the procedure for the treatment to be ready for BNCT. The next step will be to conduct BNCT at the facility.

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