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Development of an Accelerator-Based Epithermal Neutron Source for Boron Neutron Capture Therapy

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Abstract—The paper presents a review of the current state of development of accelerator-based epithermal neutron sources for boron neutron capture therapy (BNCT), a promising method for the treatment of malignant tumors. Special attention is paid to an epithermal neutron source based on a new type of accelerator of charged particles: a tandem accelerator with vacuum insulation and a lithium neutron-producing target.

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INTRODUCTION

According to the World Health Organization, cancer incidence is steadily increasing and leads to significant mortality. The development of drugs and methods for the treatment of malignant tumors is an important and still unsolved scientific problem. A promising approach to the treatment of a number of malignant tumors, primarily intractable brain tumors, is boron neutron capture therapy (BNCT), which is extremely attractive due to its selective effect directly on the cells of malignant tumors [1, 2].

BNCT is a form of binary radiotherapy that uses the uniquely high ability of a nonradioactive boron-10 nucleus to absorb a thermal neutron. The cross section of this absorption reaction is 3837 b. Neutron absorption by the ^{10}B nucleus leads to the instantaneous ^{10}B(n,α)^{7}Li nuclear reaction with an energy release of 2.79 MeV. In 6.1% of cases, the energy is distributed only between the lithium nuclei and α-particle and, in 93.9% of cases, the lithium nucleus escapes in an excited state and emits a γ quantum with an energy of 0.48 MeV (Fig. 1). The nuclear reaction products, the lithium nucleus with an energy of 0.84 MeV and α-particle with an energy of 1.47 MeV, are characterized by a high stopping power (with the mean values of 162 and 196 keV μm^{-1}, respectively) and a small range of these particles in water or in body tissue: 5.2 and 7.5 μm, which are comparable with the characteristic size of mammalian cells. The stopping power for a gamma quantum is significantly lower: 0.3 keV μm^{-1}. Therefore, the release of the main part of the energy in the ^{10}B(n,α)^{7}Li reaction, namely 84%, is limited to the size of a single cell. Thus, selective accumulation of boron-10 inside tumor cells and subsequent neutron irradiation should lead to the destruction of the tumor cells with relatively minor damage to the surrounding normal cells.

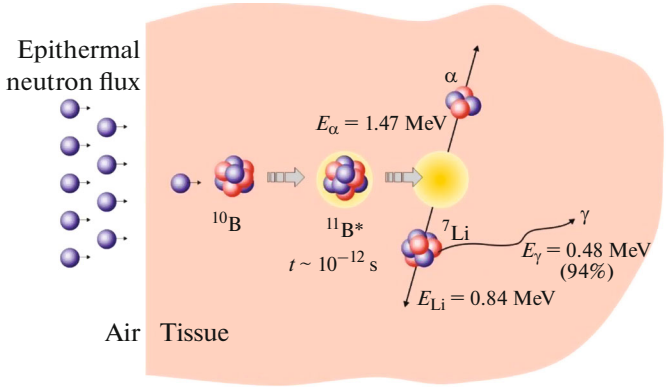

Fig. 1. Schematic representation of the BNCT principle.

According to the introductory article of Professor Sauerwein in the recently published book on neutron capture therapy [1], there have been four periods of development of the BNCT method: (i) early clinical trials conducted in the US from 1951 to 1961; (ii) pioneering work by Professor Hatanaki with coworkers, conducted in Japan since 1968 to the end of the 1980s; (iii) clinical trials of deep intracerebral tumors with application of epithermal neutron beams from nuclear reactors; and iv) the use of accelerators of charged particles to produce epithermal neutron beams.

The main requirement to a therapeutic neutron beam is often formulated as follows: an epithermal neutron flux density should be higher than 10^9 cm^{-2} s^{-1} in order that the duration of therapy be less than an hour. Epithermal neutrons are understood as neutrons with energies from 0.5 eV to 10 keV. Over the past decade, significant progress has been achieved in the development of the accelerator conception of BNCT, in particular, in the optimization of Beam Shaping Assembly, and a better understanding of what is required has been obtained. It became clear that the term "epithermal neutrons" needs clarification. The range of neutron energy is too wide to be optimal for BNCT. Neutrons that are ideal for BNCT should have energies of 1 to 30 keV [1].

1. NEUTRON-PRODUCING REACTIONS

Nuclear reactors were used as a source of neutrons in the clinical trials of BNCT. In the reactors, thermal neutron-induced fission of ^{235}U nuclei takes place. The energy spectrum of the emitted neutrons is described well by the distribution $F(E) = 0.77\sqrt{E}\exp(-0.775E)$ [1]. The spectrum extends to 10 MeV and has an average energy of about 2 MeV. To conduct BNCT, neutrons are moderated using a Beam Shaping Assembly including a moderator, a reflector, an absorber, and filters.

To produce neutrons by using charged particle beams, nuclear reactions involving nuclei with weakly bound neutrons are commonly used. From an energy point of view, there are reactions of two types. Exothermic reactions do not require minimal kinetic energy of particles. A typical example is the d-d reaction, which results in the formation of tritium and a neutron. The energy release in this reaction is 3.265 MeV. This means that the resulting neutron has an energy of 2.451 MeV, if we neglect the energy of the deuteron, and more, if it is not neglected. It can be seen that the neutron energy is even greater than the average neutron energy of nuclear fission. Another type of reaction is called endothermic and requires a minimum threshold energy of the particles. Near the threshold, the neutron energy is low; therefore, using these neutrons for BNCT is very efficient.

The main neutron-producing reactions and graphs of their cross sections are presented in [3]. The main parameters of these reactions are given in Table 1 [4, 5].

In [4], it was noted that most attention was focused on the following four reactions: ^{7}Li(p,n)^{7}Be, ^{9}Be(p,n)^{9}B, ^{9}Be(d,n)^{10}B, ^{13}C(d,n)^{14}N, of which ^{7}Li(p,n)^{7}Be was recognized as the best due to the maximum yield and minimum neutron energy. However, the construction of a lithium target seemed problematic due to the low melting point, low thermal conductivity, high chemical activity of lithium, and the accumulation of the radioactive isotope ^{7}Be. Ten years later, Professor Kreiner, in the review of accelerator-based neutron sources in [1], emphasizes that it is worth considering only three reactions that provide the production of neutrons with energies lower than that obtained in nuclear reactors. These are the threshold reactions ^{7}Li(p,n)^{7}Be, ^{9}Be(p,n)^{9}B, and ^{12}C(d,n)^{13}N. The latter is not actually considered due to the low neutron yield.

In any case, the energy of produced neutrons is higher than that required for therapy and, therefore, the neutrons have to be moderated in reactions of elastic and inelastic scattering by the moderator nuclei. This process has a probabilistic nature. The motion of a neutron is similar to the motion of a Brownian particle. Therefore, the smaller the initial neutron energy, the narrower the neutron energy spectrum, as required for BNCT.

2. ACCELERATOR-BASED EPITHERMAL NEUTRON SOURCES IN THE WORLD

Over the past 30 years, many projects of accelerator-based neutron sources have been proposed, but only a few of them are close to successful completion.

The most advanced project is the project of the Japanese company Sumitomo Heavy Industries, Ltd., which built and commissioned a neutron source based on a 30-MeV 1-mA cyclotron and a beryllium target for the Kyoto University Research Reactor Institute. Since 2012, on this source, clinical trials of the methodology have been conducted, the results of which are not yet disclosed because these tests were necessary for obtaining a license. Currently, at the expense of the Reconstruction Fund after the Great East Japan Earthquake, they are building a similar source for the clinic in South Tohoku in Fukushima Prefecture.

Currently, the University of Tsukuba together with Mitsubishi Heavy Industry Co. and the KEK and JAERI scientific organizations have produced an 8-MeV 5-mA linac with a beryllium target. To date, a proton beam with a current of 2 mA has been obtained.

The project being developed by the Cancer Intelligence Care Systems for the National Cancer Center in Tokyo is potentially attractive. The AccSys Technology, Inc. (California, United States), a subsidiary of Hitachi, manufactured a 2.5-MeV linac with a current of 20 mA. To generate neutrons, it is proposed to use a

Table 1. Basic parameters of neutron-producing reactions

Reaction	Threshold energy, MeV	Particle energy, MeV	Yield, n/mA s	Neutron energy, keV	
				max	min
$^{7}Li(p,n)^{7}Be$	1.880	1.880	0	30	30
		1.890	6.3×10^{9}	67	0.2
		2.500	9.3×10^{11}	787	60
		2.800	1.4×10^{12}	1100	395
$^{9}Be(p,n)^{9}B$	2.057	2.057	0	20	20
		2.500	3.9×10^{10}	573	193
		4.000	1×10^{12}	2120	
$^{9}Be(d,n)^{10}B$	0	0	0	3962	3962
		1.500	3.3×10^{11}	4279	3874
$^{13}C(d,n)^{14}N$	0	0	0	4974	4974
		1.500	1.9×10^{11}	6772	5616
$^{12}C(d,n)^{13}N$	0.327	0.327	0	4	4
		1.500	6×10^{10}	1188	707
$d(d,n)^{3}He$	0	0	0	2451	2451
		0.120	3×10^{8}	2898	2123
		0.200	1.1×10^{9}	3054	2047
$t(d,n)^{4}He$	0	0	0	14050	14050
		0.150	4.5×10^{10}	14961	13305

target with a thin lithium layer on a palladium substrate. To date, a proton beam with a current of 11 mA has been obtained.

All three Japanese BNCT centers are planning to begin melanoma treatment in the near future.

Neutron Therapeutics (United States) (formerly GT Advanced Technology, and even earlier, Twin Greeks Technologies) has begun construction of a 2.6-MeV 30-mA Hyperion™: a direct-action electrostatic accelerator for the clinic of the University of Helsinki (Finland). To produce neutrons, a rotating lithium target will be used.

The fifth successful project is the project of the Budker Institute of Nuclear Physics, Siberian Branch of the Russian Academy of sciences (SB RAS), which will be discussed in more detail in the next section. Presently, a similar facility is being constructed for a clinic in China: a tandem accelerator with vacuum insulation and a lithium target.

3. ACCELERATOR-BASED EPITHERMAL NEUTRON SOURCE AT THE BUDKER INSTITUTE OF NUCLEAR PHYSICS, SB RAS

In 1998, a project for an accelerator-based neutron source for BNCT using three new ideas was proposed [6]. The first idea was to create a new type of accelerator to obtain a high-current proton beam: a tandem accelerator with vacuum insulation of electrodes. The second idea concerned the choice of the neutron-producing reaction: since the $^{7}Li(p,n)^{7}Be$ reaction is the best for producing epithermal neutrons, it should be used despite the low melting point, low thermal conductivity, and high chemical activity of lithium. The third idea was to try using the near-threshold neutron production mode for the therapy. In this mode, due to kinematic collimation, the produced neutrons escape mainly forward and have relatively low energy of about 40 keV.

The first two ideas were implemented with full success: a proton beam with an energy of up to 2.3 MeV and a current of up to 7 mA was obtained in a compact accelerator. The third idea was slightly transformed: it turned out that the optimal proton energy is not a near-threshold energy but an energy of about 2.3 MeV [7].

Figure 2 shows a photograph and schematic diagram of a vacuum-insulated tandem accelerator. The beam of negative hydrogen ions with an energy of 21–23 keV, generated by source *1*, is rotated by an angle of 15° by the magnetic field of the source, focused by magnetic lenses *2* at the entrance to accelerator *3*, and accelerated in it to an energy of 1 MeV. In gas stripping target *7*, installed inside high-voltage electrode *6*, the negative hydrogen ions are converted into protons, which are then accelerated by the same potential of 1 MeV to an energy of 2 MeV and transported to the neutron-producing target. The potential of high-voltage electrode *6* and five intermediate electrodes *5* is supplied from high-voltage power supply *9* (a sectionalized rectifier, most of which is not shown) through

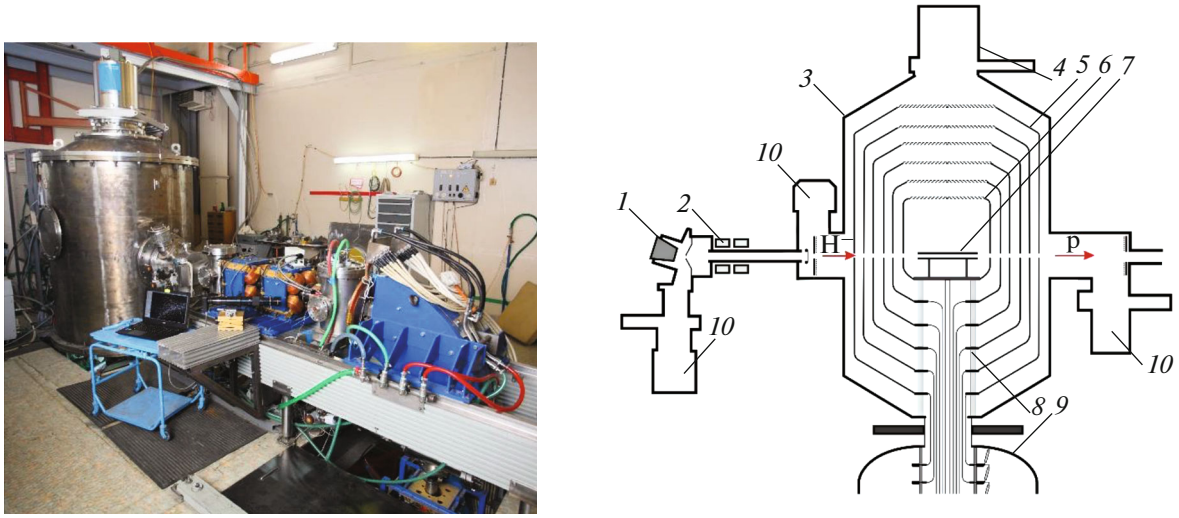

Fig. 2. Vacuum-insulated tandem accelerator: (left) photo, (right) schematic design: (*1*) H^- source, (*2*) magnetic lenses, (*3*) accelerator, (*4*) cryogenic pump, (*5*) intermediate electrodes, (*6*) high-voltage electrode, (*7*) gas stripping target, (*8*) bushing insulator, (*9*) high-voltage power supply, and (*10*) turbo-molecular pumps. The arrows show the direction of propagation of negative hydrogen ions (H^-) and protons (p).

the feedthrough insulator *8* with a resistive divider. The gas is pumped out by turbo-molecular pumps *10*, installed near the ion source at the accelerator entrance and exit, and cryogenic pump *4* through the electrode shutters.

The proton beam exiting from the accelerator is directed downward by a bending magnet and is spanned by a scanner over a neutron-producing target with a diameter of 10 cm. To produce neutrons, a stationary target, difficult for implementation but providing the optimal quality of the therapeutic neutron beam, is used. In its manufacture, the following factors were taken into account: (1) The neutron-producing lithium layer must be thin, such that protons be decelerated in it to the neutron production threshold. This will significantly reduce the accompanying 0.478 MeV γ-quantum flux and reduce the temperature at the lithium surface. (2) The lithium layer must be pure lithium for the maximum neutron yield. The neutron yield from lithium hydride, oxide, and fluoride is lower than that from pure lithium by the factor of 1.43, 2, and 3.3, respectively. (3) The lithium layer must be in the solid state to prevent the spread in the facility of lithium vapor and the resulting radioactive isotope beryllium-7. (4) The substrate on which the lithium layer is deposited should be thin. This will allow placement of the optimal moderator as close as possible to the source of neutron production and to form the best therapeutic neutron beam. (5) The substrate should be intensely cooled in order to maintain the lithium layer in a solid state upon its heating by a powerful proton beam. (6) The substrate should be resistant to radiation damage. (7) The substrate should be easy to manufacture. (8) The substrate must be easily removable for its disposal after activation.

In [3], a detailed description of the accelerator and the target, as well as the results of scientific research conducted by that time, are presented. Below, we present the results of the studies conducted over the past four years.

One of the main results is that the proton beam current has been significantly increased from 1.6 to 7 mA. This was mainly achieved due to the suppression of secondary charged particles in accelerating gaps by upgrading the accelerator [8]. An important aspect in increasing the current and improving the stability of the accelerator has been the discovered impact of the spatial charge and spherical aberration of magnetic lenses on the phase portrait of the ion beam injected into the accelerator [9].

For the development of the neutron-producing target, two important studies were carried out.

First, at the accelerator, irradiation of samples made of lithium, graphite, magnesium fluoride, barium fluoride, aluminum, silicon, titanium, vanadium, stainless steel, copper, molybdenum, and tantalum with a proton beam was carried out. The dose rate and the X- and γ-ray spectra, the neutron radiation dose rate for the absorption of protons with an energy of 2 MeV in materials, and the residual activity emission spectrum were measured [10]. It was found that the absorption of protons with an energy of 2 MeV in molybdenum or tantalum is accompanied by a minimum level of X- and γ-ray dose rates and does not lead to the production of fast neutrons and to residual activity. Consequently, to reduce unwanted accompanying γ radiation, the substrate of the neutron target with a thin lithium layer should be made of molybdenum or tantalum.

Fig. 3. Neutron-producing target: (left) the target used in 2008–2018 and (right) the new target.

Secondly, using a CCD camera and an Infinity K2 remote microscope, for the first time, the blistering of copper and tantalum samples irradiated with a 2 MeV proton beam was observed in situ [11]. Using a thermal resistor, a pyrometer, and an infrared camera, the sample temperature during irradiation was measured. The surface of the irradiated samples was examined with an X-ray diffractometer and laser and electron microscopes.

It has been established that the threshold for the formation of blisters on a copper surface depends on the purity of copper, which is higher in purer copper. The maximum threshold value is 3×10^{19} cm^{-2}, and the minimum is 7 times smaller. After the appearance of blisters on the copper surface, further irradiation does not lead to surface modification, which may be associated with the formation of holes and cracks when the blisters emerge. Consequently, it is not at all obvious that, after the emergence of blisters on the surface of the copper substrate of the target, it cannot be further used for neutron production, since the accumulated hydrogen can escape through the holes and cracks formed during the emergence of blisters and the reduction in thermal conductivity due to blisters will not be critical for melting lithium.

It was determined that the samples made by four different technologies for applying tantalum to copper—explosion welding, diffusion welding, soldering, and plasma arc deposition of tantalum and copper powders—are mechanically resistant to stationary and pulsed heat loads up to 1 kW/cm^2. Tantalum is much more resistant to the blister formation than copper. The blister formation threshold at a temperature of 160–200°C exceeds 6.7×10^{20} cm^{-2}. With proton fluence of 3.6×10^{20} cm^{-2}, a modification of the tantalum surface in the form of a relief (grid) is observed with a cell size on the order of 1 μm. It has been established that, during the irradiation of tantalum, an increase in the sample surface temperature takes place, which may be associated with a decrease in thermal conductivity due to the appearance of cavities inside tantalum and the incorporation of hydrogen into the tantalum crystal structure.

As a result of these studies, in March 2018, after 10 years of use, the target, which is described in [12], was replaced with a new one, made in the form of a set of thin tantalum tubes [13]. Photographs of the targets are shown in Fig. 3.

To produce a therapeutic neutron beam for BNCT on accelerator-based neutron sources, a Beam Shaping Assembly consisting of a moderator, a reflector, an absorber, and filters is used. We were the first to propose the use of a composite moderator: magnesium fluoride near a neutron producing target and aluminum fluoride near the exit and a composite reflector: graphite in the front hemisphere and lead in the back hemisphere, and to produce neutrons as a result of the ^{7}Li(p,n)^{7}Be reaction at a proton beam energy of 2.3 MeV. By the numerical simulation of the neutron and γ-radiation transport, it was shown that the solutions proposed make it possible to form a therapeutic neutron beam best satisfying the requirements of BNCT [7, 14].

To confirm the required quality of the neutron beam at the facility, together with the team of the University of Tsukuba, irradiation of cell cultures incubated in a medium with boron was carried out. The results were quite expected [15]: the higher the boron concentration, the lower cell survival; the higher the dose, the lower the survival rate of the cells (Fig. 4).

An even more illustrative result was obtained in experiments on the irradiation of mice with a grafted tumor, carried out jointly with the Institute of Cytology and Genetics of the SB RAS. In the experiment, three groups of SCID mice with orthotopic transplantation of U87MG human glioblastoma cells were used. The first group of animals, 4 hours after the injection of boronophenylalanine, was anesthetized and placed in a heat-stable container under a neutron beam for 60 minutes. The second group of animals was injected with borfenilalanin but not irradiated. As intact control, animals in which the tumor was not subjected to

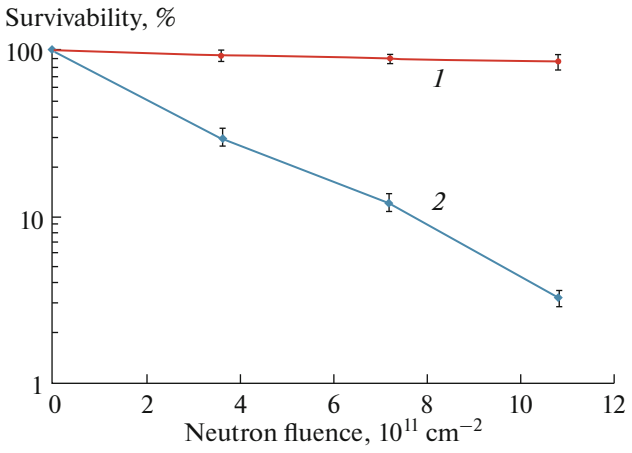

Fig. 4. Survival of U251MG cells (*1*) without boron and (*2*) with a boron concentration of 40 ppm as a function of the neutron fluence.

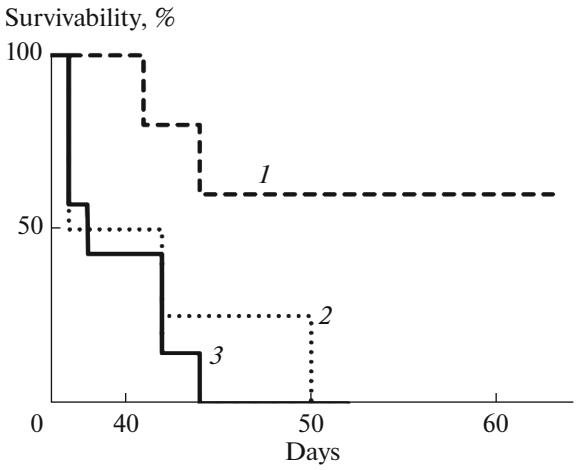

Fig. 5. Kaplan–Meier graph: (*1*) group of irradiated mice, (*2*) group of mice with injected boronophenylalanine but not irradiated, and (*3*) intact control.

any effect were used. All animals underwent intracranial transplantation of U87MG cells on the same day, 32 days before irradiation. To do this, a skin incision 3–4 mm in length was made on the head in the caudal-cranial direction near bregma and 5 μL of a suspension containing 0.5 million U87MG cells was injected through a hole in the skull. On the day of irradiation, on a BioSpec 117/16 USR ultra-high-resolution tomograph (Bruker, Germany), tumor volumes were measured for all animals; the experimental groups were collected so that the mean values did not differ significantly; the mean tumor volumes were 25 ± 7 μL. The results of the experiment are presented in Fig. 5. As we can see, all mice that were not exposed to radiation died quite soon. Of the five mice exposed to radiation, three recovered. For them, on the fourth day after irradiation, the tumor volume decreased and, on the seventh day, the tumor was not detected. These mice were euthanized on day 92 after tumor transplantation without signs of disease. The two mice that were irradiated but did not recover had the largest tumor volumes in the group. The recovery of mice with glioblastoma can be considered a very successful experiment because, due to the smallness of the size of a mouse, it all had to be irradiated, while, in humans, the region of irradiation can be localized. As it was found out with the use of an atomic emission spectrometer, boron accumulates not only in a tumor but also in other organs of the mouse (Table 2), and these organs receive a significant dose.

Currently, on the facility, a study to produce a proton beam with a current of 10 mA, an energy of 2.3 MeV is being conducted, and a neutron Beam Shaping Assembly is being installed. Soon it is planned to form a therapeutic neutron beam suitable for the treatment of patients.

CONCLUSIONS

A promising method of treating many malignant tumors, especially incurable brain tumors, is boron neutron capture therapy, which is extremely attractive because of the selective effect directly on the tumor cells. It is expected that accelerator-based epithermal neutron sources will be created soon for the widespread implementation of this technique into clinical practice. One of such sources can be an original accelerator-based neutron source constructed at the Budker Institute of Nuclear Physics of the SB RAS, to which special attention was attracted in this work. The new type of accelerator is a vacuum-insulated electrostatic tandem accelerator, characterized by a high acceleration rate of charged particles. In the accelerator, a stationary proton beam with an energy of 2.3 MeV and a current of 7 mA, sufficient for therapy, was obtained. A neutron-generating target, optimal for forming an epithermal neutrons flux that meets the requirements of boron neutron capture therapy, has been developed and experimentally studied. To confirm the required quality of the neutron beam, the

Table 2. Boron concentration (μg/g body weight)

Time after injection, h	In glioma	In brain	In blood	In liver	In kidney	In skin
1	24	5	30	14	86	34
2.5	20	6	14	5	28	17
5	12	3	4	2	8	5

effect of neutron radiation on cell cultures and laboratory animals was studied. In the near future, it is planned to form a therapeutic neutron beam suitable for the treatment of patients.

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