# 4th Ru BNCT CONFERENCE

## Books of Abstracts

## of the 4th All-Russian School of Young Scientists on BNCT

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**Editor Sergey Taskaev**

# Invited lectures

*Others*

**Specificity of BNCT as a cancer treatment radiotherapy modality**

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Neutron capture therapy as a modality for treating malignant tumors has a lot of specific characteristics which differ this method from any other known radiological method of cancer treatment. Though formally external irradiation with neutron beam is performed during NCT it has little in common with other beam radiotherapy methods like Fast Neutron Therapy, Proton Therapy and X-ray/Gamma Conventional Radiotherapy (RT). NCT is based on completely different physical phenomena than these modalities. In NCT absorbed dose formation in normal and tumor tissues of a patient is defined mostly by a boron carrier distribution in patient's body rather than parameters of external irradiation. From this point of view NCT acts on the patient similar to radionuclide radiotherapy but with controlled internal radiation release. NCT deals more with ensuring tolerated absorbed dose value in normal tissues rather than creating prescribed therapeutic dose in tumor. Radiobiological basis of NCT differs greatly both from RT and RNT. In NCT it is possible to deliver very high values of absorbed dose with a single neutron irradiation without unacceptable damage of normal tissues and that cause different response of tumor to the irradiation comparing to RT or RNT. Also the patient is irradiated during NCT with mixed radiation field comprised of radiation with different relative biological efficiency (RBE) and the effect of such irradiation is difficult to assess with standard formalism of "equivalent dose" which can lead to both over- and underestimation of biological effect. New radiobiological approach called "photon-isoeffective dose formalism" was suggested by Argentinian scientists [1] for assessment and prediction of tumor control probability (TCP) and normal tissue complication probability (NTCP). Clinical application of NCT for curing cancer require development and approval of completely new approaches and protocols of treatment planning and quality assurance.

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*Others*

## How to bring BNCT into a hospital

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This lecture will cover topics/issues that should be concerned and planned in order to bring BNCT into a hospital, which includes hardware, software, know-how and regulations. BNCT is a cross-disciplinary subject and it needs a multidisciplinary team and interdisciplinary talents. It is crucial to understand the complexity of a BNCT project, and any underestimation will cause costly price and some may be irreversible. Experiences from the HFR, THOR, and the Xiamen Humanity Hospital BNCT facilities have repeatedly proven the importance of multidisciplinary team work as well as project management. This lecture will provide the audience with a heads-up for what is coming on their way to bring BNCT into a hospital.

The followings are the fundamental subjects that need attention and planning:

1. Selection of your BNCT Solution
2. Environment Evaluation and Protection
3. Facility Layout and Construction
4. Treatment Planning System
5. Patient Positioning
6. On-site Boron Measurement
7. Clinical Know-how and Workflow
8. Regulatory Affairs

Bringing BNCT into a hospital not only needs the consideration of abovementioned issues, but also requires a skill set of communication and management. This lecture will focus on the first part, but the second part should not be ignored. Remember, BNCT is not a one-man job. Egocentrism and silo mentality could easily destroy your hard work. A strong but flexible mindset is necessary, and it is a good friend accompanying you to the success.

*BSA design*

**Boron Analogues of α-Amino Acid-based Anti-tumor and Anti-rheumatoid Arthritis Agents for Boron Neutron Capture Therapy**

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Following the latest development and popularization of the neutron sources, boron neutron capture therapy (BNCT) has re-attracted great efforts and interest from both academia and pharmaceutical industry. The FDA approved compounds, 4-borono-*L*-phenylalanine (BPA) and sodium borocaptate (BSH) ($Na_2B_{12}H_{11}SH$), are currently used in clinical trials. Neither BPA nor BSH has fully achieved the tumor selectivity of boron drug for BNCT treatment, preferentially, with its less accumulation in normal tissues and/or blood. Various boron agents have been explored in the last decades with limited individual successes. Nevertheless, it remained a big challenge to develop the boron drug of choice to meet all of the requirements of BNCT. This report summarizes the syntheses of the boron analogues of α-amino acid-based agents and their unique efficacy in anti-tumor and anti-rheumatoid arthritis through boron neutron capture therapy. The results suggest that the unprecedented small boron molecules are worthy of further investigation.

Acknowledgments:
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*Nuclear medicine*

## Radiology Binary Technologies

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The field of modern nuclear medicine through integration with nanomedicine is considered, which uses nanoparticles for the diagnosis and therapy of cancer, using their unique properties. The introduction of non-radioactive materials that can be activated from the outside using various external sources of nuclear particles to produce radioactivity in situ is one of the new directions of activation of nanodrugs at the site of a cancerous tumor, which can be considered as in situ production of radiopharmaceuticals.

The program of development and implementation of new diagnostic and therapy technologies based on the Proton Therapy Complex (PTC) "Prometheus" is presented. The tasks will be implemented with the close integration of the LPI, MEPhI, Center of Radiology of RF, as well as their Russian and foreign partners.

Modernization of Russian-made proton synchrotron complexes of the Prometheus system is envisaged in order to develop and implement new technologies based on them and improve existing technologies for proton and ion therapy and diagnostics. Prometheus is a unique PTC. It is a compact (outer diameter - 5 m, weight – 15 tons) synchrotron for protons with low energy consumption (up to 100 kW), which allows one to place such PTCs directly in medical centers.
Modernization of Prometheus PTC based on the developed nuclear physics technologies, their production for Russian nuclear medicine centers opens the way for solving the issue of development and introduction of new effective technologies for proton and ion diagnostics and therapy.

Acknowledgments:
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*Boron compounds*

## Laser-synthesized nanoparticles as a base for BNCT drugs

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Increasing of Boron content in using BNCT drugs allows to enhance the indicators of clonogenic and MTT assays analysis. Boron nanoparticles are promising candidate to BNCT due to their effective surface area and pure content. By now it is well known investigation of Boron and FeB nanoparticles formation and their application in [1-3]. All of these NPs are multifunctional agents for biomedical applications. We suggest to use chemically pure Boron nanoparticles for BNCT synthesized by laser ablation method. In this report it general aspects will be presented of laser ablation method to produce any kind of nanoparticles. The attention will be paid to unique properties of generated nanoparticles and their role in biology and medicine applications.

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*Boron compounds, cell research, veterinary studies*

## Biomedical application of nanostructures of boron: elemental boron, boron carbide and boron nitride

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Recently, researchers have shown a burgeoning research interest in boron nanostructures [1,2] (elemental boron, boron carbide and boron nitride), not only regarding industrial applications but also in the field of biomedicine. Here, we provide an up-to-date summary of the recent advances in boron nanostructures-based nano-medicine.

The paper presents a systematic analysis of in vitro and in vivo studies [3]. It has been established that boron nanoparticles are not toxic in the concentration range from several tens to several hundred ppm, and also exhibit an inhibitory effect after neutron irradiation in vitro and in vivo. In a number of experiments, the suppression of the viability of cancer cells reaches 99%, but depends on the conditions of the experiment: the selected cancer cell line/tumor model, concentration and type of boron nanoparticles, neutron fluence.

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*Boron-, REE-nanotheranostics*

# Multielemental Nano-Bio-Composites With Neutron Capture, Magnetic, Photoactive and Biotarget Properties for Multi-Channel Theranostics

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A methodology is being developed for the synthesis of hybrid inorganic-organic nanobiocomposites, which are various multi-element inorganic nanoparticles (with a complex of neutron-capturing, magnetic, photoactive, and other properties) encapsulated in biotargeted polymer macromolecules [1-10]. Nanoconstructions obtained in this way are promising for use in parallel multichannel therapy and diagnostics (theranostics) [11-20]. Methods for the synthesis of nanobiocomposites, their structure and diverse biomedical potential will be discussed.

Acknowledgments:
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*Topic: Other*

## Condensed matter research at the EG-5 accelerator

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**The electrostatic accelerator (ESA) EG-5** occupies its unique niche as part of the complex of nuclear physics facilities of the FLNP. The beams of high-energy particles produced using EG-5 have high energy stability (± 15 keV per 2 MeV), which makes it possible to conduct unique studies of the elemental composition of solids, including deep profiling, conducting studies of nuclear reactions on fast neutrons, etc. and physical, chemical and biological modification of objects of inanimate and living nature, respectively.

**Condensed matter physics** At the moment, using the EG-5 accelerator, studies are being conducted on the resistance to neutron and proton radiation for $Al_2O_3$ - $ZrO_2$ - $Y_2O_3$ - ceramics, for NbTi - alloys that promising for the radiation-resistant superconducting solenoids, and for high-entropy alloys that promising for the manufacture of thermonuclear reactor shell; Also, unique studies of degradation of semiconductor heterojunctions of solar cells ($SiO_2/TiO_2$) under the action of cosmogenic radiation are going on. Another branch of the studies is connected with biological objects. In cooperation with the Kazakh Rice Research Institute named after Jakhaev on the example of rice varieties "Syr sului", "AiKerim" and "Leader" the possibility of obtaining a drought-resistant rice bred by radiation mutagenesis using neutron irradiation is investigating.

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*Cell research*

## Proton boron capture therapy as possible method for brain tumors treatment

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Proton therapy is based on the use of charged particles whose range of tissue propagation strongly depends on the energy. This results in a sharp dose increase at the end of the particle path allowing for an effective dose deposition in the tumor while sparing the normal tissue in the beam path. Clinically, this affords an opportunity to improve upon the therapeutic ratio of proton therapy for different types of cancer, including brain tumors.

Methods to increase the biological effectiveness of proton beam could be of high interest in radiation oncology. Proton boron capture therapy, a novel approach, was supposed to be related to proton-boron fusion reactions ($^{11}B + p \rightarrow 3\alpha + 8.7$ MeV), that leads to the production of high Linear Energy Transfer α-particles. In recent years, there has been some experimental evidence that, especially near the fall of the Bragg peak, the biological efficiency of protons is significantly higher for boron-11-containing prostate or breast cancer cells.

The aim of this research was to evaluate the sensitizing potential of sodium borocaptate (BSH) under proton irradiation at the Bragg peak of malignant glioma cells. In our study cells of two glioma lines were preincubated with 80 or 160 ppm boron-11, irradiated both at the middle of 200 MeV beam Spread-Out Bragg Peak (SOBP) and at the distal end of the 89.7 MeV beam SOBP. To test whether the physical nuclear reaction 11B(p,3a) results in an enhancement of the cancer cell death, cell lines were also irradiated with graded doses 2-8 Gy using γ-ray source. The radiation sensitivity was determined by assay the viability of cells, as well as their ability to form colonies.

Our results show that BSH, being non-toxic at the concentrations used, exhibit the lack of significant radiosensitizing effect of BSH. It did not depend on the time of preincubation, nor on the concentration of boron-11, or on the energy of the proton beam. At the same time, weaker similar effect was determined for gamma-irradiation that may indicate not only the physical nature of influence boron at irradiated cancer cell viability but a specific biological effect. In conclusion, the efficiency of boron-proton capture therapy raises serious doubts, although at this stage of research, it is obvious that the possibility of using this method in clinical practice is still open.

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*Neutron source*

## Overview of Accelerator-based Neutron Sources

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The boron neutron capture therapy technique is binary and requires collaboration between very different disciplines, ranging from nuclear physics to surgery, from chemistry to radiation oncology, from particle accelerator physics to radiation biology. The International Society for Neutron Capture Therapy and the International Atomic Energy Agency are making efforts to produce and disseminate reliable information. The documents published by them [1, 2] have become reference books for researchers in their scientific research. The 2nd edition of NCT book and new IAEA document coming soon [3].

The report presents an overview of the current state of development of accelerator based neutron sources for BNCT with an indication of their features.

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# Oral presentations

*Biology*

## The neutron radiation therapy in treatment of patients with progression of primary high-grade brain glioma

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**Introduction:** The objective of the present study was determining the place and the role of neutron radiation therapy in treatment of patients with relapses of highly malignant cerebral glioma.

**Materials and methods:** As the consequence of the post hoc analysis the results of treatment of 40 patients were estimated. Patient the treatment in the period since 2005 until 2020 in State Budgetary Health care Institution 'Chelyabinsk Regional Clinical Centre of Oncology and Nuclear Medicine' and in the Centre of Neutron Therapy in the city of Snezhinsk. The aver age of patients was 45 years old. The ratio of menand women was 1:1. 19 patients were diagnosed with relapse of the glioblastoma; 21 patients were diagnosed with the anaplastic astrocytoma. In 20 of the cases the neutron therapy was conducted on its own, in other 20 cases patients underwent a course of treatment of neutron-photonradiation therapy.

**Results:** The overall survival median for all patients with the relapses of highly malignant cerebral gliomas after the conducted treatment is rated at 50 months, the indices of 1-year overall survival are 94,1%; the 2-years overall survival indices are 77,8%; the 3-years one is 66,7% accordingly. The survival median after the relapse is 27 months. The main predictive factors that have influenced the treatment results are the age of patients, the histopathology report, and the period before the relapse. The method-specific survival was credibly higher among the patients who had undergone the combined treatment of the neutron-photon radiation therapy: 48 months versus 20 months where the neutron therapy was conducted on its own ($p=0,052$).

**Conclusion:** The refore, it is possible to increase the life span of the patients with the relapses of highly malignant gliomas through adding the neutron component into the radiation treatment regimen.

**Key words:** neutron radiation therapy, cerebral tumor relapses, re irradiation.

*Boron compounds*

## The results of the work of the Ural Center for Neutron Therapy 1999-2018

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**Introduction:** To analyze the results of photon-neutron radiation theraphy (PNRT) in patients with malignant tumors of the head and neck area, in the Chelyabinsk District Clinical Oncology Center from 1999 to 2018.

**Materials and Methods:** Over 20 years of work of the Ural Center for Neutron Therapy, more than 1217 people with tumors of the brain, head and neck, metastatic lesions of the lymph nodes of the neck without a primary focus have been treated. The main group included 320 patients with malignant neoplasms in the head and neck, 140 patients with brain tumors, metastases in the lymph nodes of the neck without a primary focus - 174 patients who underwent PNRT in the period 1999 to 2018. The control group consisted of 1220 patients who received a course of photon therapy in Chelyabinsk region clinical oncological dispensary – Ural clinical base of Federal State Establishment Russian Scientific Center of Roentgenoradiology (RSCRR) of Ministry of Health and Social Development of Russian Federation in 1981-92. An independent course of radiation therapy (RT) was held in main group. In the main group, the RT course was supplemented with PNRT, according to the original, developed method. Median observation of patients 54 months.
**Results:** Immediate results were assessed clinically after 1 month, after PNRT. In the main group, the median complete-84.52% in the control-46.7%, respectively. When assessing long-term results: with tumors of the larynx in the main group, relapse-free survival (FR) was 65%, which is 30% higher than in the control group - 35% Overall survival (OS) was 76% and 66%, respectively ($p<0.005$) . With tumors of the parotid salivary glands, FR in the main and control groups was 40% and 14%, respectively ($p>0.05$).

With tumors of the pharynx, the three-year FR after a course of PNRT is higher by 18+3% ($p=0.002$) than after photon therapy. OS was 46% and 20%, respectively. In oral and tongue malignancies, PNRT increases FR by 11+5% and OS by 17% compared to photon therapy ($p<0.005$). FR in MN of the nasopharynx and paranasal sinuses, the conduction of PTRT is 62% in the control group 60% ($p>0.05$). With metastatic lesions of the lymph nodes of the neck without a primary tumor, the use of PNRT increases the 1-year OS by 10%, 2-year OS by 21%, 3-year OS by 23% respectively.

With a tumor size of T1 in the main group, OS -81%, T2-62%, T3-70%; in the control, respectively, 89%, 48%, 51%. BV in the main group was at T1-68%, T2-78%, T3-65%, in the control, respectively, 52%, 56%, 35%. The dynamics of changes in OS and FR presented below:

| Localization | Tumor depth (cm) | Average depth (cm) | FR increase | RH increase |
|---|---|---|---|---|
| Larynx | 3,7-5,5 | 4,1 | +25% | +8% |
| Nasopharynx | 6,0-7,5 | 6,5 | +2% | +0% |
| Parotid salivary gland | 1-5,5 | 3,7 | +26% | - |
| Oral cavity | 1,5-6,5 | 4,5 | +20% | +8% |
| Oropharynx | 2,5-7,4 | 4,2 | +26% | +4% |
| Metastasis to the lymph nodes of the neck without a primary focus | 1,5 – 3,5 | 2,7 | - | + 15 % |
| brain primary tumors | | | | |
| Relapse of brain tumors | | | | |

**Conclusions:** PNRT in the program of a radical course of RT increases the median of complete resorption of head and neck tumors to 84.52% in the main group, in the control group, respectively - 46.7%. PNRT leads to an increase in the FR and OS with an increase in the size of the primary tumor. The most significant difference in treatment outcomes in terms of OS and FR was in patients with T3 primary tumor size. The increase in OS and FR was in groups of patients with tumors of the larynx, parotid salivary gland, oropharynx, where the average depth of the tumor was up to 3.7-4.5 cm. 5-3.7 cm (median 2.7 cm), OS in the main group was 15% higher than in the control group.

*Boron compounds*

## Novel Glucose-BSH BNCT Targeting high CA19-9 Pancreatic Cancer

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Pancreatic cancer has a poor prognosis with a 5-year survival rate of less than 10%. CA19-9, a tumor marker for pancreatic cancer, has been used for diagnosis and treatment for many years. High CA19-9 pancreatic cancer has been reported to be of high-potential malignancy and poor prognosis. This time, we propose a new BNCT targeting high CA19-9 pancreatic cancer.

Gene analysis of pancreatic cancer patients in the public database showed low expression of LAT1 (L-type amino acid transporter 1), which was the target of BPA, and high expression of glucose transporter (GLUT) in the high CA19-9 pancreatic cancer group. In this time, we synthesized a novel boron drug, Glucose-BSH, and evaluated its efficacy *in vitro* and *in vivo* experiments using several types of human pancreatic cancer cell lines. Neutron irradiation was performed at Kyoto University Research Reactor (KUR).

As a result of comparing the expression of GLUT and LAT by Western blotting using several human pancreatic cancer cell lines with high and low CA19-9, LAT1 was weakly expressed in high CA19-9 pancreatic cancer, and GLUT1, 3 was strongly expressed. When the intracellular boron concentration was measured with BPA, BSH, and Glucose-BSH, high uptake of Glucose-BSH and low uptake of BPA were confirmed in high CA19-9 pancreatic cancer. Pharmacokinetics using a cancer-bearing model evaluated the high tumor accumulation of Glucose-BSH. Finally, Glucose-BSH BNCT succeeded to perform the therapeutic effect to pancreatic cancer model at KUR.

This was a new first step leading to Precision Medicine BNCT for pancreatic cancer.

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*BSA design*

**Human serum albumin as a universal platform for constructing theranostics in the framework of boron neutron capture therapy**

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Despite the fact that boron neutron capture therapy already has a number of boron-containing molecules used to treat patients, problems such as insufficient specificity of therapeutic agents, tumor recurrence and necrosis due to high radiation dose still occur during treatment. Thus, it remains actual to create more selective, well accumulating, and biocompatible boron-containing constructs that have a minimum of side effects when used as drugs.

Various albumin conjugates have shown their high biocompatibility and efficacy as therapeutic agents over the years. Moreover, some of them were approved by the FDA and are currently clinically used. Structural features of albumin make possible to create multifunctional covalently bound therapeutic constructs, carrying drug residues and various signaling molecules. However, the chemistry of targeted introduction of boron into serum albumin is currently very limited. In addition, some modifications of albumin may adversely affect the ability of the final conjugate to pass into the tumor.

The aim of our work is construction of the albumin based theranostics containing boron atoms. The constructs we have created include a homocysteine fragment as a tool for maintaining the number of thiol groups in the protein sites where the modification will not impair the ability of albumin to penetrate into the tumor. These groups are useful for attaching other building blocks through a thiol-click interaction. We used dyes such as Cy5, Cy7, and BODIPY as fluorescent labels. The boron-containing molecules used in this work are the undecahydro-closo-dodecarborate residue and the photostable derivative of 4,4-difluoro-4-boron-3a,4a-diaza-s-indacene. In addition, the developed constructs contain fluorine atoms, which can be used for in vivo imaging using 19F MRI. The successful preparation of boron-containing structures was confirmed by MALDI-TOF-MS, inductively coupled plasma atomic emission spectroscopy, electron and fluorescence spectroscopy. *In vitro* cytotoxicity some of the conjugates have been increased while irradiation with epithermal neutrons and was about cytotoxicity of borophenylalanine. *In vivo* cytotoxicity some of the obtained constructs was also studied in mice of the SCID line free from specific pathogens. The results show that the drugs belong to the fourth class of toxicity in accordance with the GHS classification.

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*Neutron source*

## Investigation of the possibility of using the R7-M accelerator for the purposes of BNCT

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One of the methods of cancer treatment is boron neutron capture therapy (BNCT). Research nuclear reactors and accelerators of various types are used as a source of the necessary epithelial neutron flux for BNCT [1]. Currently, accelerators are used for BNCT treatment.

In this paper, it is proposed to carry out calculations on the cyclic accelerator R7-M of Tomsk Polytechnic University to justify the use of the BNCT method. It is planned to take the fourth channel of the accelerator as a basis, where the interaction of a deuteron flux with an energy of 13.6 MeV and a current of 45 μA with a beryllium target – $Be^9(d,n)B^{10}$ (figure 1) is carried out.

The initial characteristics of the neutron flux at the outlet of the channel are $5.3 \cdot 10^9$ neut/cm$^2 \cdot$s [2] and an energy of 4÷11.8 MeV. It is planned to carry out calculations in PHITS and MCU software complexes to determine and place the most suitable moderator (Fluental, $AlF_3$, $D_2O$, $CaF_3$) in the accelerator collimator channel to obtain the necessary characteristics of the neutron flux for BNCT [3].

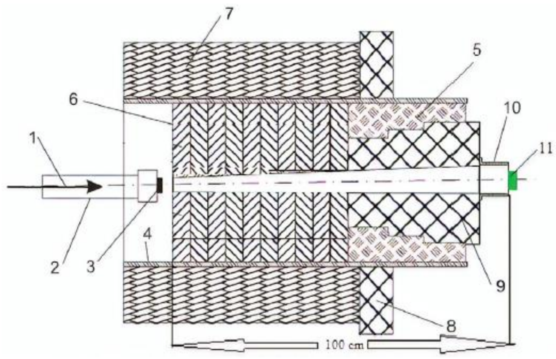


Figure1 – The detailed structure of the collimator:
1 – deuteron beam; 2 – ion beam channel; 3 – Be-target; 4 – iron pipe; 5 – polyethylene collimator; 6 – iron disks; 7 – concrete wall; 8 – radiation protection of polyethylene; 9 – removable polyethylene collimator; 10 – cone; 11 – detection foils

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*Boron compounds*

## A new multimodal construct for BNCT

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The effectiveness of BNCT largely depends on the ability of boron-containing agents for accumulation in tumor tissues. To date, there are no BNCT agents being capable to accumulate in the tumor at the concentration required for therapy (20-50 μg/g of $^{10}B$ per weight of tumor). The agents currently used in clinical practice (sodium borocaptate and boron phenylalanine) do not satisfy all the criteria required for BNCT. Therefore, there is a need to develop new boron-containing compounds that have more favorable biodistribution and uptake for clinical use.

Previously, a specific agent was proposed at the Laboratory of Organic Chemistry of IChBFM SB RAS to modify certain HSA lysine residue [1]. Such modification does not lead to a reduction in the circulation time of albumin in blood, at the same time HSA retains the ability to accumulate in tumor tissues. HSA modified this way is a promising protein for targeted delivery of agents in tumor cells. Moreover, the effectiveness of the use of HSA for the delivery of cytostatics to tumor tissues has been proven before [2]. It was planned to use the valuable properties of HSA as a drug delivery agent for the purposes of BNCT.

The aim of this work is to develop multifunctional BNCT construct comprising not only boron-containing fragment but also a cytostatic and functional group for attachment to HSA. Such design could be useful for mixed therapy and allows the combination of two cancer treatments: chemotherapy and neutron capture approach. For this purpose, a new BNCT construct has been developed and synthesized. The new construct contains closo-dodecaborate as a source of boron, the cytostatic gemcitabine, and a functional group for covalent attachment to HSA. The structure of the new derivative was confirmed by a wide variety of physicochemical methods.

This research was funded by the Russian Science Foundation grant No. 19-74-20123.

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*Boron compounds, boron imaging*

## Synthesis of complex compounds of gold for cancer diagnosis

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Recently, many attempts have been made to apply harmless compounds based on various metals in the diagnosis and therapy of cancer. In particular, the interest of researchers is focused on the synthesis, surface modification, and application of gold nanoparticles [1]. However, gold nanoparticles are hardly excreted from the body, which causes some concern when they are used in cancer diagnostics and therapy. For example, it was found [2] that AuNPs, even at a low (non-lethal) dose, rapidly accumulate inside cells without causing cell death, but at the same time leading to increased stress on the endoplasmic reticulum. The safest use of gold is in the form of complex compounds.

In this paper the complex compound of gold is studied and the technique of synthesis, control, automated calculation of the number of particles and their size is presented. Complex studies of the structure of the obtained compositions by methods of 1H-NMR and electrography were carried out. The dependence of the particle size of complex compounds on the pH value in the solution by the DLS method has been determined, a method for counting the number of particles on nanoscale images of electron microscope with the use of machine learning methods for dry compositions has been developed.

This study can serve to further develop the synthesis of complex compounds of gold in the creation of preparations for teranostics.

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*Boron compounds, boron nitride nanoparticles, boron carbide nanoparticles, elemental boron nanoparticles*

## Boron nanostructures in boron neutron capture therapy: synthesis, properties

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Boron nanostructures have many applications in various fields, including medical applications. Nanoparticles of nitride, carbide and elemental boron are among the most widely studied boron compounds in medicinal chemistry. The paper will present in detail modern aspects in the synthesis and physicochemical properties of boron nanostructures for their use in in vitro/in vivo experiments for boron neutron capture therapy [1, 2].

For the successful application of boron nanostructures in boron neutron capture therapy, it is important to understand which precursors were used for synthesis, since the composition of the final form of a nanopreparation directly affects the main criterion for their effectiveness - bioavailability. It is important to correctly select a material for the synthesis of nanoparticles, which, along with efficiency, should demonstrate biocompatibility and the absence of toxicity, as well as a method for implementing the synthesis of nanoparticles. Evaluation of the shape, morphology, size, and composition of the surface is an integral part of the characteristics of boron nanostructures, since they are important for further stages of modification by biologically active molecules [3].

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# Posters

*Boron-, REE-nanotheranostics*

## Multielemental (B, Gd) NanoBioComposites For Multi-Channel Theranostics

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A methodology is being developed for the synthesis of hybrid inorganic-organic nano-bio-composites, which are various multi-element inorganic nanoparticles (with a complex of neutron-capturing, magnetic, photoactive, and other properties) encapsulated in biotargeted polymer macromolecules [1-20].

In particular, the nanobiocomposite was synthesized with a complex of magnetic and potentially neutron-capturing properties, which is gadolinium borate nanoparticles encapsulated in Siberian larch arabinogalactan macromolecules, that can pass through the blood-brain barrier.

Acknowledgments:
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*Boron compounds*

## Synthesis and investigation of carborane containing hydrindons as potential agents for BNCT

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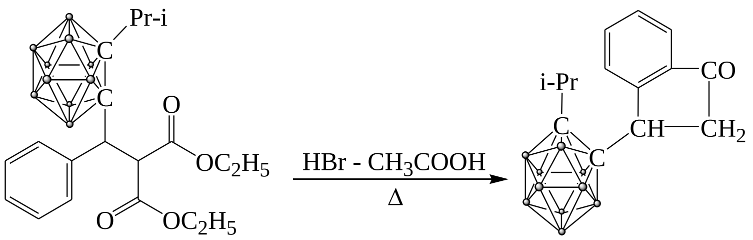
Requirements for potential drugs which could be used in BNCT are low-toxicity, high chemical and biological stability, high selectivity to the tumor cells, a maximum amount of boron in the molecule relative to other elements, solubility in water. Among the variety of potentially suitable boron compounds for the BNCT and actively investigated in many research centers, a special place belongs to carboranes.

In this research, carborane derivatives hydrindones were synthesized. The reactions of C-metal derivatives of isopropyl-o-carborane with benzylidenemalonic ether and their derivatives were studied. 3- (isopropyl-o-carboranyl) -hydrindone was obtained by cyclization with borohydric acid.



(1) (2)

The reactions of 3-(isopropyl-o-carboranyl)-hydrindones with various amines (butylamine, methylamine, morpholine, cyclohesylamine), alkali metals and their hydroxides were studied. It was found that amines with higher basicity selectively interact with hydrindone derivatives at the carbonyl group, forming Schiff bases. Whereas the weaker amine (morpholine) forms a salt at a reagent ratio of 1:1, predominantly interacts with the acidic proton of the C-H group of 3-(isopropyl-o-carboranyl) -hydrindone. The cytotoxic properties of the water soluble potassium salt of hydrindone were studied. Studies of the cytotoxicity of the obtained compounds were carried out using the example of human hepatocarcinoma cells (HepG2) and human fibroblasts. LD50 is around 1 mg/ml for HepG2 and 0.5 mg/ml for human fibroblasts.

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*BSA design*

## New concept of a neutron beam shaping assembly for boron neutron capture therapy

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The Vacuum Insulated Tandem accelerator have been developed in Budker Institute of Nuclear Physics. Neutrons are generated in $^7Li(p,n)^7Be$ reaction. Neutron beam shaping assembly is used for therapeutic beam forming. It consists of the moderator, reflector and filter. Magnesium fluoride is considered optimal material for neutron slowing down because of noticeable cross section of inelastic neutron scattering. Previously, we showed that it is optimal to use proton beam at energy 2.3 MeV for neutron generation.

As a result of a critical analysis of our earlier decisions on the methods used to form a therapeutic neutron beam and decisions of other research groups, as well as successful experiments on the irradiation of laboratory pets and cell cultures carried out at our experimental facility, we noticed that with the recent trend towards a decrease in proton energy the process of inelastic scattering in $MgF_2$ is no longer decisive in neutron moderation, and it was decided to consider materials based on plexiglass as a moderator material.

In this work we considered Poly-Biz as moderator material and get the neutron beam the same quality as with $MgF_2$ moderator and proton energy 2.3 MeV but at lower proton energy and current that can cause treatment time reducing and allows more reliable neutron generation.

The report provides a critical analysis of the methods used to form a therapeutic neutron beam and proposes a new concept of a neutron beam shaping assembly, supported by the results of numerical simulation.

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*Dosimetry*

## Characterization of the neutron flux for boron neutron capture therapy

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With the increase in the number of cancer patients around the world, the challenges in obtaining effective treatment that can cure them increase. Radiation therapy is the most common type of treatment. For this purpose, a compact accelerator-based neutron source has been developed at the Budker Institute of Nuclear Physics in Novosibirsk, Russia [1]. Two neutron beam shaping assembly are used, one with magnesium fluoride moderator [2] and one with plexiglass moderator. In this study, the distribution of boron dose and gamma-ray dose within a water phantom is measured using a detector with an optical fibre readout [3], which includes three different sensors (the first based on a plastic scintillator enriched with boron, the second based on a simple plastic scintillator, and the third having no scintillator at all). The experimental results are presented and features of these beam shaping assemblies are discussed.

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*Others*

## Lithium as a promising therapeutic agent for Neutron Capture Therapy

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One of the promising methods of tumor elimination is boron neutron capture therapy (BNCT), based on the selective destruction of tumor cells by accumulating a stable $^{10}B$ isotope in them and subsequent irradiation with epithermal neutrons. The main problem of this technology is the insufficient selectivity of $^{10}B$ accumulation in cancer cells. An alternative approach to NCT can be to use lithium isotopes ($^{6}Li$) instead of boron isotopes.

The prospects for the use of lithium, on the one hand, are due to the physiological characteristics of the absorption of lithium ions by the cell, on the other hand, the energy yield in the $^{6}Li(n,\alpha)^{3}H$ nuclear reaction is higher than in the $^{10}B(n,\alpha)^{7}Li$ reaction, and at the same time, which is extremely important for therapy, there is no emission of gamma rays that adversely affect healthy organs. It should also be noted that drugs for cancer therapy with $^{6}Li$ can be created based on the technologies existing in Russia.

The aim of this study was to determine the concentration of lithium in the tumor, surrounding tissues, and organs remote from tumor growth in experimental animals with B16 skin melanoma. The ICP method was used to determine the concentration of lithium in tumor samples and distant organs with the introduction of lithium carbonate at doses of 300 and 400 mg/kg. The tumor-to-blood ratio (T/B) was shown to peak at 30 min post-administration and was 2.12 ± 0.67 for the 300 mg/kg dose and 1.79 ± 0.52 for the 400 mg/kg dose. Skin-to-blood ratios (S/B) were obtained. Values varied throughout the procedure and were 0.6 to 1.9 for the 300 mg/kg dose and 1.0 to 1.9 for the 400 mg/kg dose. PAS staining of kidney sections and transmission electron microscopy were used to assess the potential acute nephrotoxicity of lithium. It was found that single doses do not cause acute kidney injury and can be used for further experiments using the lithium isotope ($^{6}Li$) to evaluate the effectiveness of irradiation.

The paper presents the results of the study, demonstrating the possibility of implementing lithium neutron capture therapy.

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*Neutron source*

## Instrumentation for the generation of neutrons for the diagnostics of advanced materials

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The use of neutron radiation provides important data on the composition and structure of prospective materials. Neutron flux is generated at nuclear reactors or at accelerator based neutron sources. Accelerator-based neutron source at the Budker INP generates neutrons with different energies: cold neutrons for neutronography, thermal neutrons for activation spectrum measurements, epithermal neutrons for studies in boron neutron capture therapy and fast neutrons for radiation testing of advanced materials, such as optical fibers of the CMS laser calibration calorimeter during operation of the Large Hadron Collider in high-energy regime and samples of carbides for the ITER.

When generating neutrons the proton beam parameters – energy, current and profile are measured and monitored and the neutron dose rate is controlled. To determine the energy of the proton beam a continuous calibration is carried out using neutron generation threshold reactions - $^{9}Be(p,n)^{9}B$ with threshold energy of 2.057 MeV and $^{7}Li(p,n)^{7}Be$ with threshold energy of 1.882 MeV and analysis of back-scattered proton spectrum detected by a semiconductor silicon detector. The proton beam current is measured using a non-contact current transformer NPCT (Bergoz), enterable Faraday cups and a lithium neutron generating target used as a Faraday cup, electrically isolated from the ground potential. Optical diagnostic techniques, a wire scanner and an emittance meter are used to measure the position, profile and phase portrait of the beam. To measure the dose rate of neutron radiation a neutron detector with lithium glass, a neutron detector with an injection moulded polystyrene scintillator enriched with boron and a neutron dosimeter UDMN-100 are used. The use of all of the above measurement and diagnostic methods contributes to the long-term and stable generation of neutron flux.

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This research was funded by a grant from Novosibirsk State University “Instrumentation for the generation of neutrons for the diagnostics of advanced materials” within the framework of the project X-ray, synchrotron, neutron methods of interdisciplinary research.

*Neutron source*

## Fast neutron beam for radiation testing of advanced materials

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At the Budker Institute of Nuclear Physics the neutron source was invented and constructed initially for the development of the boron neutron capture therapy. The source consists of an electrostatic tandem accelerator with vacuum insulation and a solid lithium target. Neutron generation occurs when the beam of protons or deuterons hits the lithium target, which is an efficiently cooled copper substrate with a thin (~ 100 μm) lithium layer. Thus, at a deuteron energy of 2 MeV and a current of 1 mA, a fast neutron flux of $1.35 \times 10^{12}$ $s^{-1}$ is generated in the reaction $^{7}$Li(*d*,*n*).

During the prolonged experiments with the fast neutron beam special radiation protection is provided in order to prevent devices and staff from the radiation. The radiation level is controlled in the irradiation room, inside and outside the bunker, where the facility is located, and in the control room. The parameters of the fast neutron beam are measured with the set of diagnostics: sets of activation foils SWX-1551 and SWX-1552 (Shieldwerx, USA), detection device for continuous measurement of the dose rate of neutron radiation UDMN (Doza, Russia), a neutron detector with a GS20 lithium-containing scintillator (The Saint-Gobain Crystals, USA), a universal neutron spectrometer-dosimeter of the SDMF type based on a scintillation detector made of a single crystal of stilbene ($C_{14}H_{12}$), compact neutron detector with lithium polystyrene scintillator enriched with boron.

The fast neutron beam is used to test promising materials to justify their performance under conditions of high neutron fluxes. Thus, samples of boron and steel carbide developed for the ITER (International Thermonuclear Reactor) have been tested, it is planned to conduct radiation tests of optical cables, diodes and charging pumps designed to operate the electromagnetic detector of the compact muon solenoid (CMS) at the Large Hadron Collider in high luminosity mode (HL-LHC).

The use of various diagnostics will make it possible to determine the parameters of the generated neutrons with high accuracy. When testing promising materials, the developed set of diagnostics will make it possible to control the parameters of the neutron flux in real time.

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*Neutron source*

# Software control for the water phantom in the neutron flux measurements experiment for BNCT

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A compact accelerator-based neutron source has been developed at the Budker Institute of Nuclear Physics in Novosibirsk, Russia [1]. The lithium target installed in the BSH is used to generate neutrons. A water phantom is used to measure the neutron flux. The water phantom is a volume, with a movable carriage, which is driven by two stepper motors. Neutron flux is measured with a fast neutron sensor [2] with Boron-10 mounted on a movable carriage. Software was developed that allows automatic measurements of the neutron flux in the entire volume of the phantom. This paper describes the software of the phantom and the processing of the measured data.

Acknowledgments:
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*Neutron source*

## Cold neutron producing in the accelerator-based neutron source VITA

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The use of neutron radiation provides important data on the composition and structure of prospective materials. Neutron flux is produced at nuclear reactors or at accelerator based neutron sources. Accelerator-based neutron source VITA at the Budker Institute of Nuclear Physics produce neutrons with different energies: thermal neutrons for activation spectrum measurements, epithermal neutrons for studies in boron neutron capture therapy (BNCT) and fast neutrons for radiation testing of advanced materials, such as optical fibers of the CMS laser calibration calorimeter during operation of the Large Hadron Collider in high-energy regime and samples of carbides for the ITER. The production of cold neutrons at the compact accelerator provides new opportunities for neutron diffractometry and BNCT researches.

In this work, a scheme for the production of cold neutrons obtained by moderation of the neutrons generated in the threshold reaction $^{7}Li(p,n)^{7}Be$ is proposed. The moderator is heavy water ($D_2O$) and ordinary water cooled to liquid nitrogen temperature. A series of experiments were carried out to test several moderator designs, including a multilevel moderating system and a cold neutron detection system consist of GS-20 lithium containing scintillator (The Saint-Gobain Crystals, USA) and polysterene-based plastic scintillators, enriched with boron (IHEP, Protvino). Neutrons with energies less than $10^{-3}$ eV have been produced and the dependence of their number on the thickness and temperature of the moderator material has been obtained.

The report presents the results of the study, demonstrating the possibility of cold neutron generation on the Vacuum Insulated Tandem Accelerator.

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*Dosimetry*

## The new design and validation of an epithermal neutron flux detector using $^{71}Ga(n,\gamma)^{72}Ga$ reaction for BNCT

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To measure the neutron flux density in the epithermal energy range, an activation neutron detector with a moderator using the $^{71}Ga(n,\gamma)^{72}Ga$ reaction is proposed and optimized by Monte-Carlo simulations [1]. Activation material for the detector is pure gallium wafer, which is sensitive to epithermal neutrons [2].

The report describes the design of the detector and the results of measurements of the neutron flux, carried out at the accelerator based neutron source VITA [3]. Since the upper limit of the sensitivity of the proposed detector is slightly higher than the upper limit of the epithermal energy range, it is proposed and implemented to reduce the sensitivity in this region due to the additional placement of a titanium plate. It is found from the performance validation on results that the detector works well and it can determine the epithermal neutron flux of the BNCT neutron beam in a high accuracy.

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*Dosimetry*

## Investigation of promising materials by activation analysis

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The efficiency and possibility of using promising materials in the latest developments directly depend on their composition and the presence of impurities in them. This makes it a task to determine the elemental composition of materials. The activation method is often used to determine the elements that comprise the sample. It is based on irradiating the material with a neutron flux, which produces radioactive isotopes in the substance, the activity of which is measured by a spectrometer, and the resulting spectrum is used to determine the composition of the tested material. This method is used widely because of its simplicity and precise result. The measurement process is independent from the irradiation process, and the test sample can easily be moved to the detector. The spectrum obtained is homogeneous and in addition to the elemental composition the percentage of the element in the sample can be measured when the detector is absolutely calibrated.

An original accelerator source of neutrons was proposed and developed at the Budker Institute of Nuclear Physics. At present, the neutron source is actively used for scientific research in the field of boron neutron capture therapy and in other applications. A beam of protons with an energy of up to 2.3 MeV is produced in a vacuum insulated tandem accelerator, directed to a lithium target, and as a result of the threshold reaction $^{7}$Li(p,n)$^{7}$Be, a neutron flux is generated. The dynamics of impurity accumulation in the lithium layer of the target during long-term neutron generation was studied by the method of energy analysis of backscattered protons. The paper draws conclusions about the quality of lithium deposition and the measurement results of thin layers of oxygen and carbon that appear on the surface of the target over time.

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*Neutron source*

**Implementation of automation system and visualization of experimental data in real time at the BNCT facility BINP**

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A source of epithermal neutrons based on an electrostatic tandem accelerator of the Vacuum Insulation Tandem Accelerator type and a lithium neutron target was proposed and developed at the BINP for boron neutron capture therapy. It is a promising method for treating tumors (such as Glioblastoma and melanoma) and for other applications.

This article proposes and implements an automation and data acquisition system with the possibility of flexible and customizable data processing, which allows operators and physicists to receive and analyze information during the experiment without the need for data post-processing.

The use of the developed system accelerates the process of obtaining informative data during experimental studies and automates the analysis process. The process of distributed logging of the results of the experiment is also proposed and implemented. As a result of the implementation of the proposed tools, the productivity of the analysis of experimental data and the detailing of the experimental log has increased.

The developed and implemented online data processing system has shown its effectiveness and has become an integral part of the control system, data collection and storage of the epithermal neutron source.

*Other*

## New features of the Rutherford Backscattering Spectroscopy Method in nanotechnologies with the use of powders

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Rutherford Backscattering Spectrometry (RBS) is an ion scattering technique used for compositional thin film that are less than 1μm thick analysis. During an RBS analysis, high-energy $He^{2+}$ ions with energies in the region from several hundred kiloelectron-volts to 2 - 3 MeV are directed onto the sample and the energy distribution and yield of the backscattered $He^{2+}$ ions at a given angle is measured. Since the backscattering cross-section for each element is known it is possible to obtain a quantitative compositional depth profile from the RBS spectrum obtained.

The capabilities of this method can be significantly expanded. In particular, the method can be used in powder nanotechnology to study elemental composition in microscopically small objects.

The application of methods based on Rutherford Backscattering Spectrometry is extremely interesting for adsorption energy devices, in particular, these methods can be used with maximum efficiency for various chemoelectronic converters.

The preparation of planar-distributed chemoelectronic converters and the study of the elemental composition of adsorbates using the Rutherford Backscattering Spectrometry technique was the purpose for the investigation.

The tasks of this study include: to develop and optimize technology for producing a functional layer of planar chemoelectronic converters in the form of rounded drops that are containing monodisperse nanosized (7.5 μm) particles of a solid solution of the $ZrO_2$ system - 3 mol% $Y_2O_3$ (YSZ) in the PVA polymer matrix, to study theoretical characteristics of the obtained chemoelectronic converters[1], to study elemental composition of the obtained chemoelectronic converters using Rutherford Backscattering Spectrometry.

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*Other*

## Investigation of bulk porous structures by Rutherford backscattering (RBS)

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The Rutherford backscattering method was used to study ceramic samples of the composition $Al_2O_3$ (fig. 1).

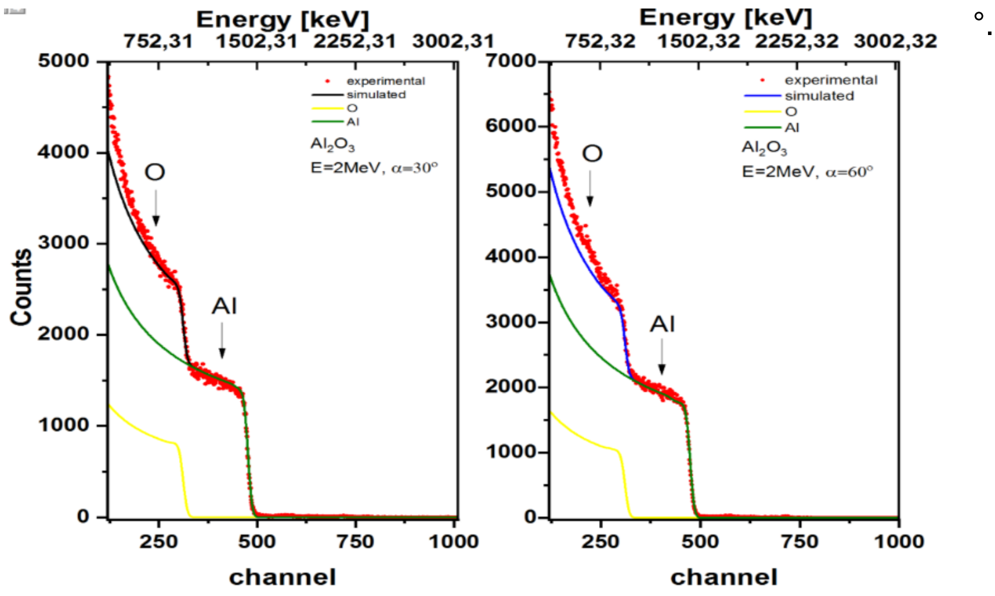


*Figure 1 Experimental and simulated RBS spectra of $Al_2O_3$ compact*

The experiment was carried out using $^4He$ ions with an energy of 2 MeV. The ion scattering angle in the entire experiment was θ = 170°, the angle of incidence of the ion beam on the sample was α = 60° and 30.

Figure 1 shows the RBS spectra of $Al_2O_3$ ceramics. The spectrum shows two gentle steps, which indicates the formation of a uniform oxide layer over the entire depth of the compact. The sample was measured at two tilt angles of the target to determine the elemental composition of atoms in the surface layer. Based on the RBS spectra, the concentrations of elements were calculated and the depth distribution profiles of elements were obtained. The SIMNRA standard international program [1] was used to calculate the concentration of elements and obtain profiles of the distribution of elements over depth. The data are presented in table 1.

Thus, it has been shown that the RBS technique is applicable with a certain error to nanopowder compacts.

*Table 1. Atomic concentration of elements in $Al_2O_3$*

| **Target inclination angle** | **No. Layer** | **Thickness, , $10^{15}$ at./cm$^2$** | ***Concentration of elements in the layer, atomic %*** | |
|---|---|---|---|---|
| | | | **Al** | **O** |
| 60° | 1 | 1000 | 40.0 | 60.0 |
| | 2 | 12000 | 41.0 | 59.0 |
| 30° | 1 | 1000 | 40.0 | 60.0 |
| | 2 | 12000 | 41.0 | 59.0 |

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*Other*

**Device for determining the elemental composition by means of inelastic scattering of fast neutrons by matter at the EG-5 accelerator (Dubna)**

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A new nuclear physics facility that allows determining the elemental composition of materials is developing at the FLNP JINR (Dubna, Russia) at the moment (Fig. 1). The method is based on the inelastic interaction of fast neutrons with matter. An analysis of the Y-quanta spectra from inelastic scattering of fast neutrons makes it possible to carry out a quantitative analysis of almost all elements of the periodic table, excluding unstable elements and noble gases, using the available tabular values of the Y-quantum spectra. energies and intensities of gamma transitions (schemes of emission of levels and their population directly in the course of the reaction). The first experimental results have been obtained.

The setup presented in [1] was used as a prototype. The authors of [1] succeeded in increasing the selectivity of the measurement of Y-quanta fluxes in the extracted and filtered beam of fast neutrons of the reactor due to a special measurement geometry. Registration of Y-quanta was carried out by germanium-lithium detectors with working volumes of 30-40 cm3 (resolution 2-4 keV for Y-quanta with an energy of 1.2 MeV). The Y-radiation spectra for most elements were measured in the energy range from 0.12 to 3.4 MeV. Similar parameters are expected to be achieved at the installation, which is being developed by the authors of the work.

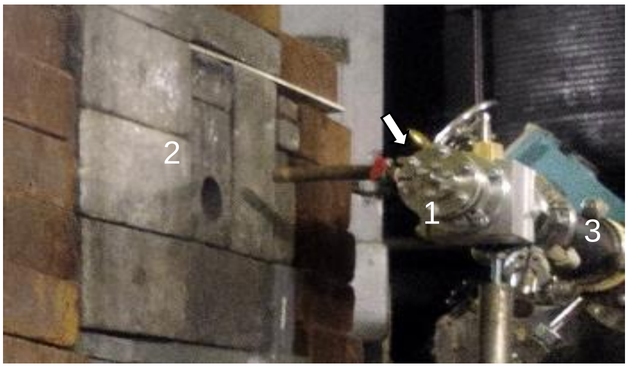


Fig.1 Appearance of the installation without an object, where 1. neutron-producing gas target;
2. detector protection unit;
3. ion guide..

Acknowledgments:
The study was funded by the Plenipotentiary Representative of the Government of the Poland Republic in JINR within the framework of the Poland – JINR Cooperation Projects PPPB/120-25/1128/2022, PPPB/120-26/1128/2022 and within the framework of the JINR-Romania cooperation program in 2022 (topic 03-4-1128-2017/2022 and 04-4-1143-2021/2025), JINR-Serbia cooperation program in 2022 Order No. 178, point 7.

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