6th Ru BNCT CONFERENCE

Book of Abstracts

of the 6th All-Russian School of Young Scientists on BNCT

November 11-13, 2024, Novosibirsk, Russia

Editor Sergey Taskaev

Invited lectures

boron compounds

New Compounds for Boron Neutron Capture Therapy of Cancer

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Compounds suitable for boron neutron capture therapy (BNCT) of cancer must have the ability to selectively accumulate in malignant tumor cells. Such selectivity can be achieved by obtaining conjugates of boron-containing compounds with molecules that are prone to selective binding to cancer cells, the so-called “tumor-seeking” molecules. The types of such compounds were previously considered [1, 2]. So far, the two molecules that have been the most studied in the world are boronophenylalanine (BPA) and borocaptate (BSH). A new ^{10}B drug, 3-borono-L-tyrosine (BTS) was created, that improves on the characteristics of the main historical BNCT drug 4-borono-L-phenylalanine (BPA) [3]. The production of carborane-containing derivatives of natural molecules intended for the targeted delivery of boron to tumor cells was realized [4].

In this lecture are presented our latest results on the synthesis of conjugates of polyhedral boron compounds with some porphyrins. For the first time, a conjugate of aminoamide chlorin e_6 with bis(dicarbollide) of iron was obtained and characterized, and its biological properties were studied on a culture of rat glioblastoma cells [5].

The use of liposomes is the high-tech methods for targeted delivery of drug compounds to cancer cells. Due to the high permeability of the blood vessel walls inside the tumor, liposomes have the property of passive targeting and are able to penetrate into the tumor. In addition, the possibility of using vector molecules in the composition the surface of liposome membrane increases the targeted properties for the tumor. Liposomal transport can also be actively used to penetrate into the tumor a wide variety of types of boron polyhedral hydrides, which by themselves are not able to penetrate through cell membranes. A series of bis(dicarbollide) cobalt and other derivatives of carboranes with cholesterol were synthesized for the purpose of their further transformation into boron-containing liposomes [6]. The new boronated cholesterols can be used for liposomal drug delivery for boron neutron capture therapy of cancer.

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boron compounds

New Derivatives of Boron Clusters with biomolecules for BNCT

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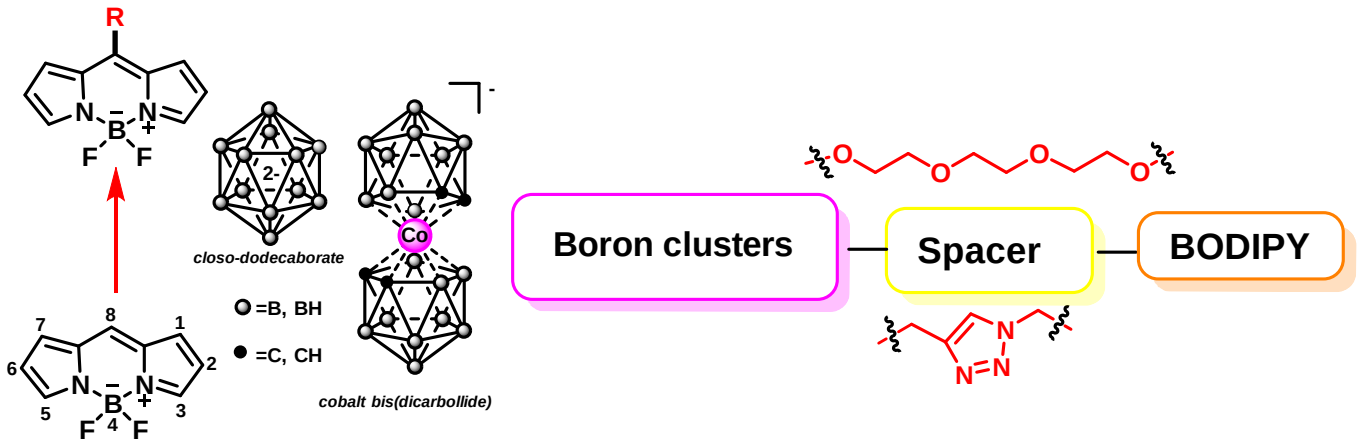
Currently, the prevalence of oncological diseases requires scientists to create new methods of treatment and diagnosis of these diseases. One of the newest ways to solve this problem is fluorescence diagnostics and boron neutron capture therapy (BNCT), which are examples of simultaneous visualization and treatment [1]. In this case, two introduced non-toxic agents (a photosensitizer or boron compounds, on the one hand, and laser radiation or a flow of slow (thermal) neutrons, on the other hand) when meeting in the target cell increase the fluorescence of the tumor and generate high-energy particles ^{4}He and ^{7}Li, which have a short range, which leads to the destruction of the tumor [2].

The report will present multicomponent boron-containing agents based on BODIPY, capable of fluorescence and tracking the accumulation of the drug in tumor cells for further treatment by boron neutron capture therapy (BNCT) of cancer.

The main approaches to solving the problem were implemented using the reaction of opening cyclic oxonium derivatives of boron clusters with various nucleophilic groups of BODIPY and the CuI-catalyzed reaction of [3+2]-dipolar cycloaddition of alkynes to azides (“click”-reaction) (Figure).



Thus, the development of methods for the synthesis of derivatives of polyhedral boron hydrides with fluorescent labels is an urgent task and its solution can serve as a basis for the creation of fundamentally new agents for BNCT.

Acknowledgments: This work was supported by the Russian Science Foundation (RSF), project 24-73-10090.

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others

The development of drugs for neutron capture therapy - from idea to implementation: physical, pharmacological, radiobiological, regulatory aspects

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Being a binary therapeutic modality, the efficacy of Neutron Capture Therapy (NCT) is highly dependent on the ability of the used for the therapy a carrier-drug to deliver required amount of neutron capture agent (boron, gadolinium, lithium etc.) to tumor [1]. Thus, availability of such carriers as approved drugs for clinical application is crucial for successful implementation and use of NCT in curing cancer. ^{10}B is not the only isotope that can be used in NCT. Other isotopes like ^{157}Gd and ^{6}Li can also be considered as neutron capture agents for NCT [2,3]. Every isotope has its advantages and disadvantages and only the properties of its pharmaceutical dosage can be a merit of its suitability for NCT.

On the example of boron, the "boron dose" determines more than 80% of the total delivered absorbed dose during boron mediated NCT. Consequently, absorbed dose value prescriptions for a tumor and limitations for normal tissues together define requirement for any NCT drug. Acceptable T/N ratio is determined by radiosensitivity of corresponding tumor and normal tissues while minimum concentration of dose enhancing isotope is determined by neutron beam contamination with gamma and fast neutrons. T/N ratio and minimum concentration in tumor are independent parameters and a potential drug should match both of them.

Before any substance is allowed to be administered to a human patient it should become a biocompatible pharmaceutical preparation with necessary for NCT characteristics and pass through formalized preclinical and clinical studies. Most of the substances are rejected on the stage of preclinical studies. Preclinical studies are dedicated to prove safety and efficacy of the drug for human patients, basing on the results of the studies in laboratory animals. Not every research, which was made in laboratory animals can be considered as preclinical but only that which were performed in concordance with national preclinical recommendations.

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Boron-, REE-nanotheranostics

Hybrid Inorganic-Organic Nanobiocomposites with High Response to Minimally or Non-Invasive Electromagnetic and Corpuscular Penetrating Irradiation for Multichannel 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. Nanoconstructions obtained in this way are promising for use in parallel multichannel therapy and diagnostics (theranostics). Methods for the synthesis of nanobiocomposites, their structure and diverse biomedical potential will be discussed.

dosimetry

Experimental methods of dosimetry in BNCT

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In anticipation of the introduction of BNCT into clinical practice, the development of dosimetry for BNCT is becoming an important task. Dosimetry for BNCT is complex, due to the multiplicity of the possible neutron reactions and consequently of the secondary radiation that contains photons, charged particles and recoil nuclei. Therefore, BNCT dosimetry requires suitably developed calculations and experimental methods. This lecture describes experimental methods for measuring neutron flux and dose parameters during BNCT in experiments conducted at the Budker Institute of Nuclear Physics

Acknowledgments:
This research was supported by the Russian Science Foundation (grant number 19–72-30005).

Boron imaging

Development and applications of the neutron autoradiography for microdistribution studies in BNCT: an overview

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The success of Boron Neutron Capture Therapy (BNCT) largely depends on the effective delivery of ^{10}B within tumors. Mapping ^{10}B localization at tissue and cellular levels is essential to evaluate treatment success and understand post-irradiation effects. Few techniques enable detailed boron microdistribution studies; among them, Neutron Autoradiography using Nuclear Track Detectors (NTDs) stands out for its high resolution and cost-effectiveness. This method records ion damage in NTDs, where alpha and lithium particles from the BNC reaction create latent tracks on the detector when a boron-loaded sample is exposed to neutrons. Chemical etching then reveals these tracks, allowing visualization under microscopy. In biological samples, boron distribution can be determined by co-registrating the nuclear tracks with histological images.

Polymers like polyallyldiglycol carbonate and polycarbonate are widely used as NTDs for BNCT boron imaging. Different BNCT methods allow both qualitative and quantitative analysis: overlapping tracks can indicate boron levels through grayscale, while individual track counting allows ^{10}B quantification through a calibration system and the use of reference markers for alignment. Image processing techniques, both classic and based on machine-learning methods can be applied to study boron microdistribution.

Simultaneous visualization of tissue structures and nuclear tracks enhances boron microlocalization. UV-C exposure before staining can create imprint of the biological material on the NTD. Therefore, neutron autoradiography is versatile and widely used to asses *in vitro* and *in vivo* models, and even in clinical studies, contributing valuable insights into boron compound efficacy, cell line uptake comparisons, treatment response, and dosimetric evaluations in BNCT research.

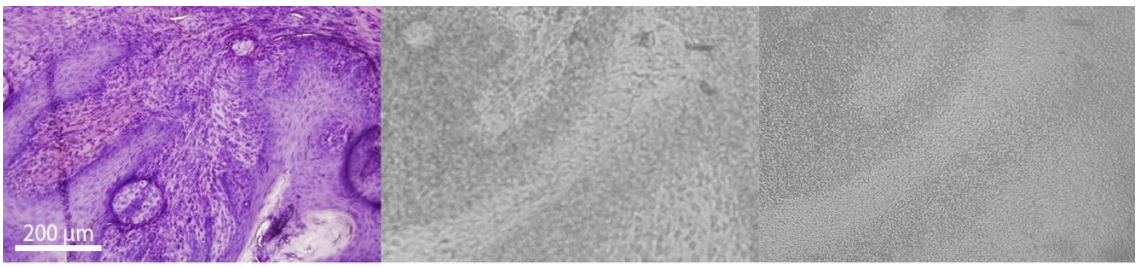

Figure 1. Left: Hamster's cheek pouch section; centre: imprint; right: nuclear tracks.

Acknowledgments:
This research was funded by Agencia Nacional de Promoción Científica y Tecnológica (Argentina). The author is thankful with all the members of the Laboratory of Nuclear Tracks and Neutron Autoradiography and with Dr. Monti Hughes and coworkers for providing tissue samples.

clinical trials

Исследование проблемы количественной оценки опухолевых поражений методом однофотонной эмиссионной компьютерной томографии

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Цель. Технологии цифровых близнецов и виртуальные испытания могут революционизировать и ускорить методы клинических испытаний. В Лаборатории моделирования в ядерной медицине НГУ, Институте математики имени С.Л.Соболева разработан программный комплекс для виртуальных испытаний в ядерной медицине с упором на его практическое применение для повышения диагностической точности метода однофотонной эмиссионной компьютерной томографии (ОФЭКТ). ОФЭКТ является распространенным клиническим методом обнаружения опухолевых поражений. Проблема получения точной количественной оценки накопления радиофармпрепарата в опухолевых очагах важна для дифференцирования злокачественных и доброкачественных поражений, стадирования заболевания и оценки эффективности проводимой терапии. Однако эта задача пока остается нерешенной. Виртуальные клинические испытания представляют собой оптимальный подход к изучению и решению этой проблемы.

Методы: Разработан программный комплекс «Платформа для виртуальных испытаний ОФЭКТ/КТ», который включает три базовых модуля. Модуль «Виртуальный пациент» создает цифровую модель пациента. Модуль «Виртуальный томограф» имитирует сбор необработанных данных с использованием метода Монте-Карло. Модуль «Алгоритмы реконструкции изображений» включает библиотеку современных алгоритмов реконструкции. Виртуальные клинические испытания проводились в ядерной онкологии, кардиологии и неврологии в сотрудничестве с клиническими врачами.

Результаты: Результаты компьютерного моделирования показали близкое соответствие с результатами клинических испытаний. В частности, виртуальные испытания с использованием стандартного клинического протокола привели к тем же ошибкам на изображениях, которые наблюдались в клинической практике. Моделирование ОФЭКТ показало, что количественная оценка очагов поражений искажается краевыми артефактами.

Заключение: Метод виртуальных клинических испытаний с использованием цифровых близнецов пациентов и технологий визуализации имеет огромный потенциал для поддержки реальных клинических исследований. Программный комплекс «Платформа для виртуальных испытаний ОФЭКТ/КТ» — это новая технология, которая позволяет использовать виртуальные клинические испытания для изучения и решения фундаментальных проблем, связанных с недостатками и ограничениями количественной оценки ОФЭКТ изображений опухолевых очагов.

cell research

Application of LC-MS/MS-based metabolomic screening in the study of biological response to X-ray and Terahertz radiation

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Metabolites are low-molecular-weight products of biochemical reactions that play a key role in the energy dynamics of living systems and signaling. Metabolomics is a technique for quantitative assessment of small molecules in biological systems. A metabolomic profile reflects the biochemical activity of an organism and is widely used in the study of pathologies, pharmaceutical development and diagnostics.

We have previously developed an approach to metabolomic screening of polar and hydrophobic metabolites using a monolithic organic polymer-based column enables separating metabolites in two chromatographic modes, hydrophilic and reversed-phase chromatography. This approach makes it possible to achieve coverage of a large number of metabolites with different physicochemical properties comparable or superior with methods utilizing commercially available columns with sorbents of various types [1]. Using the approach, metabolomic screening of dried blood spots samples of mice exposed with X-ray was performed, and metabolites that could be considered as potential markers of irradiation exposure and organ tissue damage were detected. Analysis of marker metabolites revealed metabolic pathways altered by radiation exposure.

In another study, we investigated the effects of 2.3 THz radiation [2] on SK-MEL-28 cells using metabolomic and gene network analysis. Forty metabolites, mainly related to purine and pyrimidine pathways, were significantly altered after irradiation, along with lipids like ceramides and phosphatidylcholines. Gene network analysis identified key regulatory enzymes involved in the biosynthesis and degradation of these metabolites. Mitochondrial membrane components, including the respiratory chain complex and ATP synthase complex, responded to THz radiation. We hypothesize that THz radiation causes reversible disruption of the lipid raft structure, which affects the transport of mitochondrial molecules, preserving protein integrity, and potentially explains the high cell survival rate. Our results provide insights into the biological effects of THz radiation and the role of membrane components in cellular responses.

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Other

Spectral Boron Analysis in BNCT

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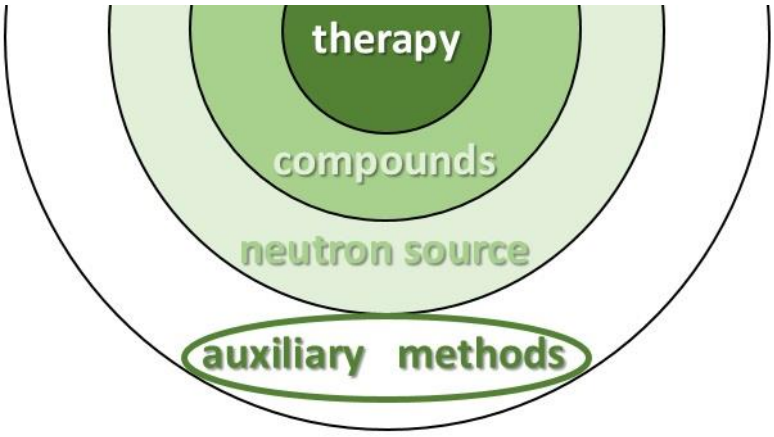
Neutron Capture Therapy (NCT) is a binary therapeutic modality, the efficacy depends on a large number of factors. The overall success of the treatment depends on the carrier compound (a drug containing boron) and the density and quality of the neutron flux. Professionalism and effective communication of physicists, chemists, biologists and physicians will be an important step in this direction. It should be noted that most of the "invisible" work is performed using auxiliary physicochemical methods, including elemental analysis methods such as spectral methods. Reliable results of spectral methods for determining boron are the basis for understanding the process of accumulation, distribution and elimination of boron-containing preparations.

The report presents and discusses the methods for boron quantification determination, such as atomic absorption spectrometry **AAS**; atomic emission spectrometry **AES**; mass spectrometry **MS**. The listed methods have high analytical characteristics, which allow determining boron in a wide range of concentrations. The advantages and limitations of each method, metrological characteristics and other features will be compared. Various methods of preliminary sample preparation will be considered separately, including acid dissolution, lyophilization, combustion in an air atmosphere, etc.



Acknowledgments:
The Russian Science Foundation (grant number 19–72-30005) supported this report.

others

Study of sensitization mechanisms of cancerous cells to nanoparticle-enhanced radiotherapy

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Both X-ray therapy (XRT) and proton therapy (PT) are commonly applied to suppress cancerous tumors; however, it often inflicts collateral damage to nearby healthy tissue. Therefore, radiosensitization with nanoparticles (NP) has been extensively studied to increase the therapeutic ratio. It is assumed that embedding nanoparticles (NP) consisting of elements with significant nuclear and electromagnetic cross-sections can enhance energy deposition in tissue. This report summarizes findings on roles of nuclear and atomic mechanisms in sensitization of cancerous cells to nanoparticle-enhanced radiotherapy using simulations with GEANT4. In particular, we assessed an enhancement of nuclear reactions due to the presence of Bi, Au, ^{11}B, and ^{10}B in soft human tissue in proton therapy. Thus, proton beam induces a noticeable amount of nuclear reactions in tissue, nevertheless the enhancement of nuclear reaction products due to radiosensitizing NP is found to be negligible [1]. In XRT, huge photoelectric cross-sections are assumed to be the main mechanism of a dose enhancement and, hence, radiosensitization. Gold nanopartilces (GNP) are considered as the most promising radiosensitizer of this kind due to high atomic number and biocompatibility. Therefore, we investigate the physics picture of GNP-enhanced RT emerging in electromagnetic process, using an MC simulation with GEANT4_DNA equipped with the most recent physics models, taking into account a wide range of physics processes relevant for realistic PT and XRT [2]. Namely, we measured dose enhancement factors in the vicinity of GNP, with diameters ranging from 10 nm to 80 nm. The dose enhancement in the vicinity of GNP reaches high values for XRT, while it is very modest for PT. The macroscopic dose enhancement factors for realistic therapeutic GNP concentrations are rather low for all RT scenarios; therefore, other physico-chemical and biological mechanisms should be additionally invoked for an explanation of the radiosensitization effect observed in many experiments. That is highly probable that the increase of NP charges under irradiation results in the radiation-induced GNP cytotoxicity. This conjecture is consistent with similar effect observed in experimental data on irradiated Ti02 NPs [3].

Acknowledgments: This work was supported by the Ministry of Science and Higher Education of Russia within the Agreement no. 075-15-2021-1347.

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neutron source

Evolution of Accelerator based Neutron Source VITA

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Budker Institute of Nuclear Physics has proposed, developed and is operating accelerator based neutron source VITA, which includes an electrostatic tandem accelerator of charged particles of an original design (a tandem accelerator with vacuum insulation), a lithium neutron-generating target and a number of neutron beam shaping assemblies. The facility ensures the production of the continuous beam of protons or deuterons with the energy of up to 2.3 MeV, with the current of up to 10 mA, the generation of a powerful neutron flux and the formation of a beam of neutrons of various energy ranges, from cold to fast. The facility is actively used for the development of boron neutron capture therapy of malignant tumors (BNCT), radiation testing of promising materials, measuring the cross-section of nuclear reactions and a number of other applications.

The second version of the accelerator based neutron source VITA-II is distinguished by the presence of pre-acceleration to increase the proton energy, the use of a volumetric source of negative hydrogen ions instead of a surface plasma source to increase the proton beam current, and a decrease in the height of the installation due to the modernization of the high-voltage power supply and its connection to the accelerator. The accelerator based neutron source VITA-IIα was delivered to the BNCT clinic in Xiamen (China) for the treatment of patients with the BNCT method. The second accelerator neutron source VITA-IIβ was manufactured to equip Blokhin National Medical Research Center of Oncology in Moscow with the purpose of conducting clinical trials of the BNCT technique in the Russian Federation starting in 2025.

Based on the experience gained, the third version of the accelerator based neutron source VITA-III is being developed. Burnazyan Federal Medical Biophysical Center in Moscow will be equipped with the accelerator based neutron source VITA-IIIα.

The research team is also developing the accelerator based neutron source VITAmin, which is compact due to the placement of the Cockcroft-Walton generator in the upper part of the feedthrough insulator.

The lecture presents and discusses the design of neutron sources, their features, parameters and applicability.

Acknowledgments:
This research was supported by the Russian Science Foundation (grant number 19–72-30005).

Oral presentations

neutron source

Evolution of the ion beam diagnostics on the accelerator based neutron source VITA

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Diagnostics of the ion beam parameters is an important part of the accelerator based neutron source work cycle. Such parameters are ion beam energy, current, profile, size, phsase portrait etc from an ion beam source to the lithium neutrongenerating target. These diagnostics system should cover wide range of ion beam energy, current and power density – beam energy from 0.1 to 2.3 MeV, beam current from 0.1 nA to 10 mA, power density from 1 mW/cm^2 to 20 kW/cm^2. These wide ranges of parameters are required to conduct investigations from performing BNCT to measuring cross-sections of different nuclear reactions.

This paper describes the ion beam parameters at the accelerator based neutron source VITA, lists the researches that are performed at VITA, and summarizes the evolution of the diagnostic tools used at VITA over the last decade from exotic ones, which were improvisations during investigations to permanent diagnostics that work routinely.

Acknowledgments:
This research was funded by Russian Science Foundation, grant number 19-72-30005

Boron compounds

Boron quantification in biological samples after boron nanoparticles administration in mice by the TJP OES method

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For successful boron neutron capture therapy (BNCT), it is necessary to use suitable boron drugs. Preparations for BNCT must meet the basic requirements: selectively accumulate in the tumor, provide concentrations of the isotope ^{10}B in the tumor of at least 20-35 μg/g and have low toxicity for the body [1].

Promising potential drugs include boron nanoparticles (BNP). They probably selectively accumulate in tumor cells and provide the necessary content of the isotope ^{10}B in one cell. We have previously found that BNP do not completely dissolve in inorganic acids [2]. Therefore, it is advisable to use an analysis method that does not require preliminary samples dissolution. Such methods include atomic emission spectrometry with a double-jet arc plazmatron (TJP OES).

The aim of this work was to develop a method for determining boron in animal tissues and organs after the introduction of BNPs using the TJP OES method. To achieve this goal, the sample preparation conditions were optimized. The optimal temperature for burning biological samples was selected – 400 °C. The degree of dilution of samples for TJP OES analysis was determined and the analytical boron line was selected. The boron limits of detection in various biological samples were estimated, which is in the range from 0.005 μg/g to 0.2 μg/g. The accuracy of the developed method was confirmed by spike experiments. The developed method was used to analyze biological samples after an in vivo experiment with BNPs. Boron content was determined in the following samples – tumor, brain, spleen, liver, kidneys, skin. Thus, the proposed TJP OES method will allow us to study the applicability of BNPs as drugs for BNCT.

Acknowledgments:
This work was supported by the Russian Science Foundation, project no. 24-23-00105, https://rscf.ru/en/project/24-23-00105/.

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treatment planning

Validation of neutron and γ-ray dose calculations using three neutron beam shaping assemblies and a scintillation detector

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For therapy planning and evaluation of the results of boron neutron capture therapy, the VITA dosimetric planning system (VITA DPS) is being developed at BINP. To ensure the effectiveness and safety of therapy, the VITA DPS includes determining the direction and power of neutron and γ-radiation, as well as analyzing the ratio of dose component distributions (boron, nitrogen, fast neutrons and photon) in the patient's body to ensure the possibility of optimal distribution of these doses, taking into account the limit values for different types of tissue. The result of the VITA DPS is an irradiation plan containing information on the spatial distribution of dose components in the patient's body. The article presents the results of the VITA SDP validation in experiments with the measurement of the boron dose and γ-radiation dose in a water phantom by the developed sensors for three beam formation systems: a target unit with a lithium target, a target unit with a lithium target with a moderator made of organic glass, a target unit with a lithium target placed inside the beam formation system developed by us earlier with a moderator made of MgF2 and a bismuth γ-radiation filter. The results of the studies demonstrate good agreement between the measured and calculated depth distribution of the boron dose and γ-radiation dose for all the cases considered. The deviation of the calculated and experimental data for the boron dose and γ-radiation dose for all experiments does not exceed 5%, comparable with the statistical error.

Acknowledgments:
This research was funded by a grant from the Russian Science Foundation (project No. 19-72-30005).

neutron source

Transportation and storage of the lithium neutron-generating target

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The principal parts of the accelerator based neutron source VITA are the ion source for producing the primary H^- beam, the tandem accelerator with vacuum insulation for obtaining the accelerated proton beam, the lithium neutron-generating target for neutron generation and the beam shaping assembly for obtaining an epithermal neutron beam. Neutrons are produced as a result of the threshold reaction $Li^7(p,n)Be^7$ which occurs when protons with the energy more than 1.882 MeV hit the lithium neutron-generating target. The lithium neutron-generating target consists of a thick copper disk with cooling channels and a thin lithium layer thermally sputtered on it.

As lithium on the target rapidly interacts with air and it leads to the decrease in the efficiency of the neutron generation, the lithium target has to be made and used under high vacuum conditions. However, it is possible to store the lithium target in an inert gas (argon) atmosphere. Both vacuum and argon atmosphere options were considered to prevent damage to the lithium target during transport to clinics where VITA is installed.

After neutron generation, the lithium target becomes radioactive due to Be^7, a product of the neutron generating reaction with the half-life of 53 days. According to the sanitary standards and precautions when working with a source of ionizing radiation, especially in clinics, it has to be sealed. For the safe removal of the activated lithium target after neutron generation the method of sealing of the activated layer on the target was proposed.

The report discusses in detail methods of transportation the lithium neutron-generating target to the clinic and its storage after use.

Acknowledgments:
This research was funded by Russian Science Foundation, grant No. 19-72-30005.

boron compounds.

Synthesis and Immobilization of Gd-DTPA Carborane-Containing Compounds on Iron Oxide Nanoparticles for Neutron Capture Therapy.

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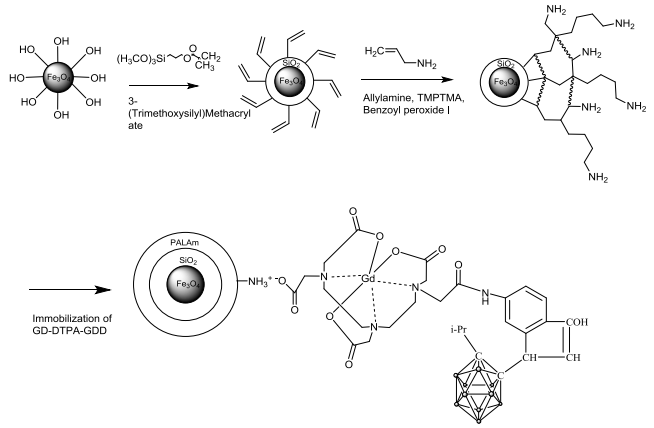
The increasing incidence of cancer demands the development of more effective treatments, such as neutron capture therapy (NCT). This study presents the synthesis of magnetic iron oxide nanoparticles incorporating carborane and gadolinium to enhance NCT's efficacy and add diagnostic potential.

Nanoparticles were modified via silane polycondensation and allylamine polymerization to introduce functional groups on their surface. A boron-containing carborane complex with Gd-DTPA was immobilized on the modified nanoparticles. Characterization was performed using FTIR, X-ray diffraction (XRD), dynamic light scattering (DLS), and transmission electron microscopy (TEM). Biocompatibility and cellular uptake were evaluated using the T98G glioblastoma cell line.



The nanoparticles successfully immobilized boron (3.56 ppm/mg) and gadolinium (0.26 ppm/mg). Gadolinium release peaked at 61.74% within 4 hours. Cytotoxicity assays confirmed low toxicity, and boron accumulation reached 5.724×10^{10} atoms per cell, sufficient for NCT. Nanoparticles showed good dispersibility with a hydrodynamic diameter of 173 nm and a core size of 25 nm.

Acknowledgments:
This research was funded by the Ministry of Energy of the Republic of Kazakhstan (BR20081011) and partly supported by a Grant-in-Aid for Scientific Research (C) JSPS KAKENHI [23K06738] from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

Boron compounds

Synthesis and investigation of carboranyl-containing α-hydrindones as potential agents for BNCT

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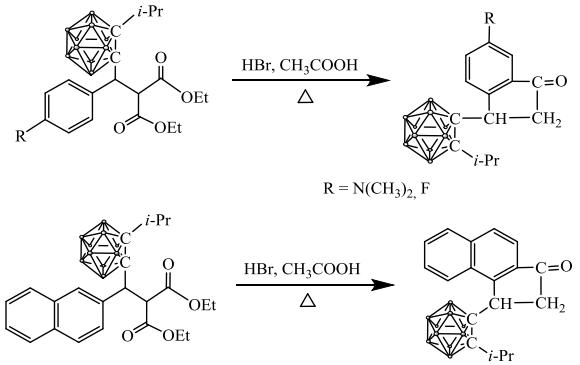
Boron Neutron Capture Therapy (BNCT) is an innovative cancer treatment strategy that relies on the selective destruction of malignant cells through the neutron irradiation of boron isotopes ^{10}B. The high-energy nuclear reaction between ^{10}B and thermal neutrons produces alpha particles and lithium nuclei, which cause localized damage to cancerous tissues while minimizing harm to surrounding healthy cells. This study explores the synthesis of carboranyl-containing derivatives of α-hydrindone and their reaction with primary/secondary amines also with metals and their hydroxides as potential drugs for BNCT.

Thus, a series of compounds, including 2,3-(*p*-fluorophenyl)-4-(isopropyl-*o*-carboranyl)hydrindone, 2,3-(naphthalene)-4-(isopropyl-*o*-carboranyl)hydrindone, 2,3-(*p*-dimethylaminophenyl)-4-(isopropyl-*o*-carboranyl)hydrindone and its corresponding salts and amine derivatives were synthesized. At the initial stage of preclinical experiments, the potassium salt of 2,3-(*p*-dimethylaminophenyl)-4-(isopropyl-*o*-carboranyl) hydrindone demonstrated good solubility and stable concentration in phosphate buffer solution. The compound showed low toxicity compared to three types of human and animal cells: T98G (human glioblastoma), CT26 (murine colorectal carcinoma), and F98 (undifferentiated malignant rat glioma). The toxicity was evaluated at a range of concentrations that significantly exceeded therapeutic ones 20-100 μg/ml.



Scheme of synthesis of carboranyl-containing α-hydrindone

The research suggests that carboranyl-containing α-hydrindone derivatives could be potential candidates for BNCT, while further investigation is required.

Acknowledgments:
This research was funded by the Ministry of Energy of the Republic of Kazakhstan (BR20081011).

boron compounds

Synthesis and Immobilization of Carborane-Containing Compounds on Iron Oxide Nanoparticles for Neutron Capture Therapy

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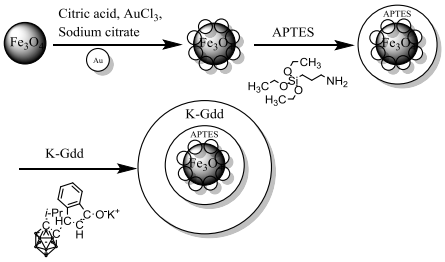
As cancer incidence rises, effective treatments like neutron capture therapy (NCT) are increasingly needed. This study proposes synthesizing magnetic iron oxide nanoparticles with carborane to enhance NCT. These nanoparticles allow precise delivery of boron agents to cancer cells, improving treatment efficacy while minimizing harm to healthy tissues, ultimately aiming to enhance therapeutic outcomes.

Nanoparticles were modified by gold and creating core shield on surface, followed by this article[1]. Next Fe_3O_4@Au were modified by APTES. A boron-containing carborane compound were immobilized by protonation of silane group through hydrochloric acid of solution. Characterization was conducted using FTIR, DLS and zeta potential measurement (ELS), UV-vis spectroscopy.



FTIR analysis revealed a characteristic peak at 2600 cm^{-1}, indicating the presence of the carborane core within the tested samples. Amination of Fe_3O_4 using APTES resulted in a zeta potential change to +20 mV in an acidic environment. Upon immobilization of carboranes, the zeta potential stabilized at -20 mV due to the coverage of amino groups with a shell, which reduces interaction with the surrounding environment. UV spectroscopy results demonstrated that the maximum release of carborane occurs within 48 hours; however, most of the carborane remains bound to the nanoparticles, as confirmed by FTIR spectroscopy.

Acknowledgments:
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cell research

Structure of the kidney after administration of high doses of lithium carbonate to mice with skin melanoma

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Lithium represents a promising agent for neutron capture therapy (NCT) of cancer, as it has a large thermal neutron absorption cross-section and provides 100% localization of energy release inside the cell, compared to boron, which is traditionally used in NCT. It is assumed that the introduction of high doses of lithium will promote the accumulation of lithium in tumor cells at concentrations required for successful NCT; however, it is currently unknown whether such doses will be toxic to the body, given that kidney damage is one of the most common side effects of lithium therapy. The aim of this study was to evaluate kidney structure when administering high doses of lithium carbonate (LC) to mice with implanted B16 skin melanoma. The B16 skin melanoma cell line and C57BL/6 mice were used in the experiment. The animals were divided into 11 groups (n=5): a control group; 5 groups receiving LC at a dose of 300 mg/kg, and 5 groups receiving LC at a dose of 400 mg/kg. Animals were sacrificed at 15 minutes, 30 minutes, 90 minutes, 180 minutes, and 7 days after LC administration. Autopsy material (kidneys) was prepared using standard techniques for electron microscopy; morphometric analysis of electronograms was performed using the ImageJ program.

No significant differences were found between the control and experimental groups among the studied parameters (thickness of the glomerular basement membrane and the basement membrane of proximal tubular epithelial cells, width and number of podocyte foot processes, number of fenestrae in the endothelial cells of the glomerular capillaries, and width of the slit diaphragm). Swelling of the epithelial cells in the proximal tubules and a decrease in endosomes were observed at early stages of the experiment (15-180 minutes), indicating dystrophic changes with subsequent regeneration while maintaining areas of cytoplasmic swelling in epithelial cells after 7 days. The results obtained indicate the potential for using LC in doses necessary for a successful neutron capture reaction.

Acknowledgments:
This research was funded by the grant from the Russian Science Foundation (project No. 19-72-30005).

boron compounds

Elemental Boron Nanoparticles obtained by the method of pulsed laser ablation in liquids as sensitizers of BNCT

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The great issue of boron neutron capture therapy (BNCT) is related to the lack of effective and safe boron delivery systems. An ideal boron containing compound should provide selective uptake of ^{10}B by tumor tissues at concentration 20 μg of ^{10}B per 1 g of tumor tissue or more, high boron concentration ratios between tumor: normal tissue and tumor: blood, the retention of ^{10}B in the tumor for several hours, and rapid clearance from organs and blood [1]. High expectations are now related to the employment of nanotechnology approaches [2]. We have investigated several types of elemental boron nanoparticles fabricated using the methods of pulsed laser ablation in liquids. Amorphous BNPs of 10-30 nm size were synthesized by the ablation of a pure boron micropowder by nanosecond laser radiation, followed by the laser fragmentation of the formed solution [3]. For the formation of partially crystalline BNPs with a mean size of 50 nm, a technique of ultrashort femtosecond laser ablation from a bulk boron target was used [4]. Both BNPs were coated with polyethylene glycol to improve their biocompatibility and colloidal stability. The BNPs did not show any cytotoxicity effects in ^{10}B concentrations necessary for successful BNCT. The U87 and SW-620 cells were previously incubated with BNPs and then were irradiated at the accelerator-based neutron source VITA with a thermal neutrons for 30 min. Colony forming capacity of cells from BNCT groups dropped down significantly, whereas the effect of irradiation by neutron beam without boron was negligible. In vivo biodistribution studies of boron after intratumoral administration of BNPs in SCID mice with heterotopic U87 xenograft recorded excellent retention of boron in tumor.

Acknowledgments:
This research was funded by a grant from the Russian Science Foundation № 24-62-00018, https://rscf.ru/en/project/24-62-00018/.

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other

Application of α-spectrometry at the accelerator based neutron source VITA

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The tandem electrostatic charged particle accelerator of the unique design, named the Vacuum Insulated Tandem Accelerator (VITA), was proposed, created, and now is in operation at Budker Institute of Nuclear Physics. The accelerator generate stable direct current proton or deuteron beams with the energy up to 2.3 MeV and the current up to 10 mA. It is equipped with γ-, α-, and neutron spectrometers and dosimeters. The accelerator is used for the development of boron neutron capture therapy of malignant tumors, radiation testing of promising materials, and more recently for measuring cross-sections of nuclear reactions.

α-spectrometry at the accelerator based neutron source VITA has been successfully applied in testing various materials under a proton beam, providing knowledge of the composition of the sample under investigation and providing control of the sample surface atomization during irradiation. The method has been successfully applied to determine the thickness of a number of thin films. More recently, α-spectrometry has been successfully applied to the measurement of a number of cross sections of nuclear reactions of proton and deuteron with lithium and boron. This paper will present an overview of the practical application of the α-spectrometer at the VITA facility for various purposes.

Acknowledgments:
This work was supported by the Russian Science Foundation (grant number 19-72-30005).

BSA design

Beam Shaping Assembly for Boron Neutron Capture Therapy

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The accelerator-based neutron source VITA has been proposed and developed at Budker Institute of Nuclear Physics (Novosibirsk, Russia) for boron neutron capture therapy, which includes a vacuum-insulated tandem accelerator for proton beam production, a lithium target for neutron generation through the $^{7}Li(p,n)^{7}Be$ reaction and a number of beam shaping assemblies (BSA) for therapeutic beam generation.

The report provides a description of beam shaping assemblies that were designed and manufactured: Beam shaping assembly with MgF_2 moderator to generate epithermal neutrons for treatment of deep seated tumors and beam shaping assembly with hydrogenous moderator with impurities of Bi atoms for thermal neutrons beam generation for BNCT researching on cells cultures and laboratory pets. Beam parameters of both BSA meet IAEA requirements and supported by the results of measuring using developed neutron and γ-ray detectors with cast polystyrene scintillators, one of which was enriched in boron.

Acknowledgments:
The study was carried out with the support of the Ministry of Science and Higher Education of the Russian Federation

Neutron source, other

Experimental study of the interaction of the proton and deuteron with the atomic nuclei of lithium and boron for therapy application

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The interaction of deuteron and proton beams with light nuclei is characterized by a wide variety of reactions of interest for both medical and fundamental applications. The reaction ^{7}Li(d,n)α is characterized by a high neutron yield and high neutron energy (13.125 MeV), which is relevant for conducting therapy of fast neutrons [1].

For the reaction ^{11}B(p,α)αα, reliable knowledge of the cross section is relevant for proton therapy of cancer [2]. Despite the long-standing interest in these processes, the experimental data on cross-sections vary greatly among different authors, and for a number of reactions, cross-section values are not available in the databases. At the Institute of Nuclear Physics of the Siberian Branch of the Russian Academy of Sciences, at the VITA accelerator neutron source, the cross-sections of the following reactions were measured experimentally in the energy range of 0.3-2.3 MeV: ^{6}Li(d,α)α, ^{6}Li(d,p)^{7}Li, ^{6}Li(d,p)^{7}Li*, ^{7}Li(d,α)^{5}He, ^{7}Li(d,nα)α, ^{10}B(d,α_0)^{8}Be, ^{10}B(d,α_1)^{8}Be*, ^{10}B(d,p_2)^{9}Be*, ^{11}B(d,α_0)^{9}Be, ^{11}B(d,α_2)^{9}Be*, ^{11}B(p,α)αα, ^{11}B(p,α_0)^{8}Be, ^{11}B(p,α_1)^{8}Be*.

Acknowledgments:
This research was funded the Russian Science Foundation grant No.19-72-30005, https://rscf.ru/project/19-72-30005/

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Boron compounds

Using DC Arc Atomic Emission Spectrometry to Determine Boron in Cells after Boron Nanoparticle Administration

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Synthesis of boron-containing drugs with the required properties will be one of the key points for the successful application boron neutron capture therapy (BNCT) for cancer. One of the directions in the synthesis of new drugs is nanomaterials based on elemental boron, boron nitride or carbide, etc.

To assess the applicability of elemental boron nanoparticles (BNPs) [1] to BNCT, the first step is to study the toxicity and accumulation in *in vitro* experiments. Thus, boron quantification in cells is necessary. BNPs are poorly soluble in inorganic acids due to their physicochemical properties. No more than 35 % of boron was determined by inductively coupled plasma atomic emission spectrometry after dissolving a BNPs dispersion in HNO_3, mixtures of HNO_3 and HCl; HNO_3 and H_2O^2; HNO_3, $HClO_4$ and HF.

A method for boron quantification in cells using direct current arc atomic emission spectrometry (DCA AES) is proposed. The DCA AES method does not require prior sample dissolution. Sample preparation consists of drying cells with administered BNPs on graphite powder with the addition of a spectral additive (4% wt. NaCl). Boron limit of quantification (LOQs) in cells is 22×10^{-6} ng for the 249.667 nm line and 7×10^{-6} ng for the 249.772 nm line. LOQs in solution is 0.5 μg/g and 0.18 μg/g respectively. The method accuracy has been confirmed by spike experiments, recovery rate is 98-107%.

The proposed DCA AES method was applied to determine the boron content in human glioblastoma U87 MG cells 24 hour after the administration of BNPs stabilized in hydroxyethyl cellulose.

Acknowledgments:
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Posters

others

Study of the ^{11}B+p reaction at 0.15-2.15 MeV energy

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There are controversial results on whether boron can increase the efficiency of proton therapy of cancer or not [1]. To resolve the discrepancy, scientists need to have credible and accurate knowledge about the reaction ^{11}B+p. Oliphant and Rutherford [2] in 1933 and Gilbert and Dee [3] in 1936 were pioneers studying the reaction of proton-boron fusion. However, accumulated by many scientists for more than 90 years of research data differ significantly.

Having analyzed the reaction theoretically, we concluded that the reaction can be thought as the three particles decay with an intricate angular distribution. We measured the differential cross-section in the energy range from 0.15 to 2.15 MeV at two angles of detecting 135° and 168° with the respect to the beam momentum at Vacuum-Insulated Tandem Accelerator at Budker Institute of Nuclear Physics. The accelerator allows generating proton beams with the energy and current accuracy of 0.1 % and 0.4 % respectfully [4], the boron targets composition and thickness were defined both directly and indirectly - all this allowed minimizing the experimental error.

As well as understanding of the reaction angular distribution needs further research, and calculations of the total cross-section require knowledge about the angular distribution, in this work we represent only differential cross-section of ^{11}B+p reaction at two angles of detection.

In future we plan to conduct experiments detecting the reaction products at a few more angles to study the angular distribution of the reaction. Then obtained total cross-section of the reaction will help to answer the question of boron usage in proton therapy of cancer.

Acknowledgments:
This research was funded by Russian Science Foundation, grant No. 19-72-30005.

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dosimetry

Development of a liquid Fricke dosimeter for boron neutron capture therapy

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Along with neutron sources and boron delivery agents, dosimetric control is necessary in BNCT. Currently, there are no clinically applicable dosimetry methods that would take into account all doses in BNCT: boron dose (dose from the α-particle and ^{7}Li nucleus), nitrogen dose (from thermal neutrons captured by nitrogen), hydrogen dose (arising from the reaction of ^{1}H absorption of a thermal neutron), background gamma dose (accompanying the neutron flux) and dose from fast neutrons (dose contributions of epithermal and fast neutrons from elastic scattering, mainly due to interaction with hydrogen atoms) [1]. Such dosimetry methods as activation foils, prompt gamma spectroscopy, water phantom and calculations on the NMC-based software package [2] are used on VITA setup for the treatment of domestic animals with spontaneous tumors.

It is proposed to use a chemical dosimeter, namely a ferrosulfate system or a Fricke dosimeter, to measure the total dose. When such a dosimeter is irradiated, Fe^{2+} is converted into Fe^{3+}. By measuring the concentration of Fe^{3+}, the dose can be determined.

The aim of the work is to develop a ferrosulfate dosimetry system for BNCT.

As a result, a method for chemically measuring the dose for BNCT was proposed, "conventional" and "neutron-sensitive" dosimeters with a complexing agent were developed, these dosimeters were calibrated in the range from 0 to 8 Gy, and a test irradiation was performed on the VITA neutron source, samples were analyzed on a spectrophotometer and spectra were obtained for further determination of the dose associated with neutrons. As an intermediate result, the total equivalent dose was calculated, which was 35 Gy.

Acknowledgments:
This research was funded by the Russian Science Foundation (grant number 19-72-30005).

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boron imaging

Prompt gamma spectrometry method for measuring therapeutic dose during boron neutron capture therapy

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For the implementation of boron neutron capture therapy (BNCT) in clinical practice, the issue of therapy planning and control of doses received by the patient during injection is still very important and unresolved. In cancer treatment with BNCT, it is necessary to control the dose to both tumor-affected tissues and healthy tissues. The dose received by tissues during BNCT is multicomponent, however, in case of effective accumulation of boron-10 in the tumor, the main contribution to the total dose is the dose from the interaction of boron with epithermal neutrons. The contribution of this dose is the only one among others has a selective character. Thus, it is of priority to control the boron dose during therapy.

The method of prompt gamma spectrometry could be an excellent solution to the issue of boron dose measurement, it would allow real-time monitoring of the dose received by patients during therapy. The method is based on the registration of the instant gamma quanta with the energy of 478 keV, born as a result of the reaction $^{10}B(n,\alpha)^{7}Li$.

As a result of this study, an implementation plan of the prompt gamma spectrometry method at the accelerator based neutron source VITA was proposed. The possibility of using a semiconductor detector made of high-purity germanium to measure boron dose in BNCT was demonstrated. A comprehensive calibration of the detector is carried out, the signals obtained from boron-containing samples are investigated, and the attenuation of the 478 keV line during passage through water is studied. The obtained spectra with a clearly distinguishable 478 keV line with predicted Doppler broadening are discussed. The first results on the application of the prompt gamma spectrometry method during the treatment of pets with spontaneous tumors by BNCT are demonstrated. The dynamics of boron removal from the animal organism as well as the spatial distribution of boron in the tumor area of the animal is presented.

Acknowledgments:
The research was financially supported by the Russian Science Foundation, grant No. 19 72 30005, https://rscf.ru/project/19-72-30005.

Boron compounds

Влияние высоких доз облучения in vitro на жизнеспособность клеток глиобластомы U87 при БНЗТ

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С каждым годом все больше диагностируется онкологических заболеваний. Для терапии таких сложных случаев, как глиобластома, меланома и др. предлагается бор-нейтронозахватная терапия (БНЗТ), так как этот метод характеризуется высоким избирательным облучением опухоли и практически не затрагивает здоровые ткани. В качестве препаратов адресной доставки бора в опухоль при БНЗТ в настоящее время используют 2 соединения: борфенилаланин (BPA) и боркаптат (BSH). Цель исследования – изучение влияния высоких доз облучения при БНЗТ на жизнеспособность клеток глиобластомы U87 in vitro в МТТ-тесте и клоногенном тесте. Материалы и методы. Клетки линии U87 инкубировали с BPA и BSH, а также с их комбинацией BPA + BSH в течение 24 ч в концентрации 40 ppm. Облучение проводили на тандемном ускорителе с вакуумной изоляцией (ИЯФ СО РАН). После облучения оценивали выживаемость клеток в МТТ-тесте и клоногенном тесте. Результаты. Было показано, что высокие дозы облучения при БНЗТ способны снизить количество живых клеток глиобластомы U87 до 41% при BPA и 45% при BSH после 2-х часового облучения по сравнению с контролем (100%). Сочетание 2-х используемых препаратов не приводило к значительному улучшению БНЗТ (45%) по сравнению с индивидуальным применением исследуемых соединений (Табл.1). В ходе анализа результатов клоногенного теста было выявлено наибольшее усиление эффекта БНЗТ при 2-х часовом облучении в сочетании BPA (17%) по сравнению с контролем (Табл.2). Заключение. Полученные результаты продемонстрировали необходимость увеличение дозы облучения и концентрации борсодержащих препаратов для повышения эффективности БНЗТ и достижения 100% гибели клеток глиобластомы U87.

МТТ-тест		
Жизнеспособность в %		
Время облучения /Группа	1 ч	2 ч
BPA	49% ± 7%	41% ± 6%
BSH	81% ± 7%	45% ± 8%
BPA + BSH	46% ± 2%	42% ± 3%
Облучение	82% ± 12%	67% ± 8%
Контроль	100% ± 12%	

Табл.1. Результаты МТТ-теста.

Клоногенный тест		
Пролиферативная способность в %		
Время облучения /Группа	1 ч	2 ч
BPA	44% ± 2%	17% ± 2%
BSH	93% ± 2%	39% ± 6%
BPA + BSH	65% ± 5%	52% ± 7%
Облучение	88% ± 7%	54% ± 12%
Контроль	100% ± 14%	

Табл.2. Результаты клоногенного теста.

boron compounds

Laser synthesis of boron nanoparticles for BNCT

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The use of boron nanoparticles (B NPs) in boron neutron capture therapy (BNCT) is a promising direction in radiotherapy [1, 2]. In our previous work [3] we showed that the use of B NPs in BNCT leads to a sharp increase in cancer cell death. The next logical step is to obtain B NPs with a high content of the ^{10}B isotope. In this work, we study the synthesis of elemental B NPs using pulsed nanosecond laser fragmentation of boron micropowder, enriched with the ^{10}B isotope, in isopropanol in flow cell. A solid-state Nd:YAG laser with a wavelength of 1064 nm, a pulse duration of 10 ns, a pulse repetition rate of 10 kHz, and a pulse energy of 1 mJ was used as a source of laser radiation in our experiments. The initial boron particles are not spherical in shape, but are fragments ranging in size from several hundred nm to several microns. Laser fragmentation of boron micropowder resulted in the formation of spherical NPs. Transmission and scanning electron microscopy studies shows that the average size obtained B NPs is 50 nm. Analysis of X-ray diffraction patterns shows that B NPs enriched with the ^{10}B isotope are amorphous. The isotopic composition measured on a secondary ion mass spectrometer of B NPs enriched with the isotope ^{10}B, shows a content ^{10}B of 82%. The obtained B NPs were functionalized with polyethylene glycol polymer to improve colloidal stability and biocompatibility in Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry. The obtained B NPs will be studied in BNCT researches at Budker Institute of Nuclear Physics.

Acknowledgments:
This research was funded by Russian Science Foundation, Grant № 24-62-00018.

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