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Invited lectures

others

Perspectives in BNCT and open research problems

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Boron Neutron Capture Therapy (BNCT) is facing an exciting new era with the development of accelerator-based neutron sources that can be place in hospitals and will favor the increasing of clinical trials worldwide. With the new developments, there is the possibility of improving BNCT in different aspects.

One of them is the reduction of unwanted radiation in the beam, such as gamma and fast neutron radiation, which contributions may differ depending on the particle energy selected and the beam shaping assembly designed. They will also play a role in radiation protection and in the whole body effective dose received by the patient.

Another very important problem is the reduction of uncertainties in dosimetry and treatment planning, from (i) the measurement of some reaction cross section not well known, (ii) the determination of more accurate and tissue-dependent radiobiological dose weighting factors, (iii) the description of the statistical distribution of the cellular boron uptake, and (iv) the development of real time imaging and dose monitoring during treatments. All these research topics will be discussed in this talk.

Of course, the development of more effective boron compounds and nanoparticles is probably the most active field of research in BNCT. Here it will be shown our work for testing them in vitro.
Finally, the project NeMeSis (Neutrons for Medicine and Sciences) of the University of Granada and the University Hospital Virgen de las Nieves for Pre- and Clinical BNCT will be described.

others

Current Status of Xiamen Humanity Hospital BNCT Center

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The Xiamen Humanity Hospital (XHH) BNCT Center represents a landmark in the evolution of accelerator-based Boron Neutron Capture Therapy (AB-BNCT) within China and globally. As the inaugural AB-BNCT facility operating within the nation, XHH also holds the distinction of being the first to administer human irradiation outside of Japan. Established in 2018 and achieving groundbreaking status in 2019, the center successfully generated its first neutron beam in 2021, culminating in the initiation of human irradiation trials in 2022.

The center utilizes the NeuPex AB-BNCT system, an innovative solution developed by Neuboron Medical Group. The system integrates an accelerator derived from the BINP VITA technology and is complemented by a stationary solid lithium target. Leveraging a proprietary Beam Shaping Assembly (BSA), NeuPex is capable of delivering an epithermal neutron flux exceeding 1 x 10^9 n cm^{-2} s^{-1} with a proton beam energy of 2.35 MeV and current of 10 mA. This translates to an exceptional neutron conversion efficiency exceeding 5 x 10^7 n cm^{-2} s^{-1} kW^{-1}, setting a new standard for efficiency in neutron generation for therapeutic purposes.

Clinical deployment commenced on October 9, 2022, under the aegis of an Institutional Review Board-approved study at XHH. Over the subsequent six months, the center administered therapy to 14 patients via 18 irradiation sessions. Boron carriers Neuboron NBB-001 (also known as BPA) and NBB-002 (^{18}F-BPA) were employed for treatment and patient screening. Treatment planning was meticulously orchestrated using the NeuMANTA Treatment Planning System (TPS) in conjunction with the Monte Carlo-based dose engine, COMPASS.

The NeuPex system has gained entry into the Green Channel of the National Medical Products Administration (NMPA) of China and is currently undergoing medical device registration testing. Anticipated to commence official Phase I trials by the second quarter of 2023, further insights into the technological and clinical milestones will be elaborated upon during the presentation.

neutron source

The development progress of the high current tandem accelerator for BNCT in KIRAMS

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KIRAMS (Korea Institute of Radiological & Medical Sciences) decided to ride the wave of AB-BNCT research in 2018. Cyclotron was considered for the very first model but proton energy over 10 MeV was not allowed in KIRAMS facility. In late 2019 the accelerator was change to electrostatic(ES) accelerator. A 1.5 MeV single-ended electrostatic deuteron accelerator was considers at the beginning. Accordingly technology transfer for an in-air operating 240 kV ES accelerator was carried out from CNEA (Argentina) for fast track. This accelerator was planned accelerate the deuteron to 1.5 MeV after upgrade. But the pandemic of COVID-19 made slower this project. In the meantime, for not wasting the time, KIRAMS started to develop a tandem accelerator by own efforts with the help of BINP(Russia) and NEC(USA). Both accelerators were successful but the final accelerator will be the tandem accelerator because it is more suitable for hospitals with limited area. An in-air ES accelerator is easy to access but needs sufficient space for isolate high voltage over 1,000 kV. The tandem accelerator will place in a smaller SF_6 tank for isolation the high voltage. And deuteron accelerator needs more radiation shield area for security because the D-D reaction during acceleration should be considered. A prototype of 250 kV tandem accelerator with Ar gas stripping terminal was constructed and successfully proton beam of 500 keV / 6 mA was injected. In this year 1,200 kV tandem accelerator for accelerating proton to 2.4 MeV / 10 mA will be constructed and investigate the high voltage isolation performance.

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others

Lithium-Neutron Capture Therapy

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One of the most promising methods of target tumor elimination is boron neutron capture therapy (BNCT) which is based on the uptake of isotope ^{10}B by cancer cells and the subsequent irradiation with an epithermal neutron beam. Particles from the $^{10}B(n,\alpha)^{7}Li$ nuclear reaction are characterized by short-range and high linear-energy transfer and are restricted mainly to the tumor cell which leads to local damage of the tumor. In 93.9% of cases, nucleus ^{7}Li is emitted in an excited state and emits a 478 keV photon, which takes away 16% of energy of the reaction.

Isotope ^{6}Li also has a large thermal neutron absorption cross section and may be used instead of boron for neutron capture therapy (NCT). In the $^{6}Li(n,\alpha)^{3}H$ reaction, only particles with a high linear-energy transfer are emitted: a tritium nucleus and an α-particle, thus 100% of the energy is released in tumor cells containing lithium. The data accumulated to date on the pharmacokinetics of lithium allow to effective monitoring of lithium concentrations to prevent the development of side effects. According to theoretical calculations, the concentration of ^{6}Li in the tumor required for the successful lithium-neutron capture reaction should be ≥ 20 μg/g.

In vitro experiments showed that cytotoxicity of lithium salts was observed in lithium concentrations of 160 μg/ml and more, thus, lithium salts can be safety used in lithium concentrations minimally required for successful NCT. ICP AES study revealed that lithium accumulation in cancer cells was higher than boron accumulation after incubation with lithium and boron containing drugs in concentrations of 40 μg/ml.

In vivo experiments revealed the maximal lithium accumulation in the tumor in mice with skin melanoma B16 30 minutes after lithium carbonate administration at a dose of 400 mg/kg which was 22.4 μg/g. The tumor/skin lithium concentration ratio at this time point was 1.5; tumor/blood ratio – 2. Thus, lithium uptake by tumor tissue was quite effective, furthermore, the single administration of high doses of lithium carbonate did not cause the structural changes in the kidney. The expression of protein markers of acute kidney injury Kim1 and NGAL was increased 30 and 90 minutes after an administration of lithium carbonate and was gradually decreased to the control values after 7 days. Thus, lithium carbonate may be used in future experiments in lithium neutron capture therapy.

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others

BNCT implementation in an existing clinical facilities – preliminary experience of Blokhin National Medical Research Center of Oncology

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Most known AB-BNCT facilities are situated in newly built, specially designed and standalone buildings. However, constructing a new building is very expensive, time demanding and in some cases is even not possible or allowed. In N.N. Blokhin National Medical Research Center of Oncology, the leading oncological institution in Russia, it was decided to install VITA accelerator based neutron source, developed by Budker Institute of Nuclear Physics for BNCT, in an existing room for distant beam radiotherapy (RT), which originally was meant for radiotherapy linear electron accelerators up to 24 MV. Placing VITA AB neutron source to the existing RT canyon requires significant rearrangement and reconstruction of the canyon. A corresponding engineering project was developed. Radiation safety assessment showed that VITA AB neutron source can be safely installed in an existing RT room. Serious issue for operating AB neutron sources with lithium target in a conventional radiotherapy department is recycling the used lithium target which gets highly radioactive while operating.

For prognostic evaluation of BNCT efficacy for a particular patients and thus proper selection of patients for BNCT Clinical Trials 18F-boron-phenylalinine (18F-BPA) is being introduced to the clinical practice as radiopharmaceutical for positron emission tomography (PET). A laboratory manufacture regulations were developed and preclinical studies of 18F-BPA as radiopharmaceutical has been performed.

Thought boron-phenylalanine (BPA) is well known as a boron carrier for BNCT all around the world, however it does not present in Russian drugs registry and thus for the Russian Healthcare it is a brand new drug. Any new pharmaceutical requires preclinical studies to be approved for usage in Clinical Trials. This studies were performed in N.N. Blokhin National Medical Research Center of Oncology.

Clinical protocols and operating procedures of BNCT conducting yet must be developed and approved by local scientific and ethic committees.

neutron source

The role of neutron therapy in the treatment of progressing primary cerebral anaplastic astrocytoma.

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The objective: The main objective of this research is establishing the role of neutron therapy as well as selecting the optimal treatment strategy approach to treating patients with progressing cerebral anaplastic astocytomas.

Materials and methods: The research includes 60 patients with progressing cerebral anaplastic astrocytoma who received treatment at the State Budgetary Health care Institution 'Chelyabinsk Regional Clinical Centre of Oncology and Nuclear Medicine' and the centre of neutron therapy in the city of Snezhinsk within the period from 2006 to 2021. The average age of the patients is 42,9±12,2 years. The male/female ratio is 1,5:1. The main treatment strategies for the first-degree prolapses included: combining surgical treatment with temozolomide chemotherapy (10 patients) or with radiotherapy (8 people); monochemotherapy using temozolomide (12 patients); regimen of autonomous radiotherapy (23 patients) or chemoradiotherapy (7 patients). On the whole radiotherapy was conducted on 40 out of 60 patients (66,7%): 10 patients (25%) received remote photon therapy on linear accelerators; 10 patients received a monoregimen of neutron therapy and 6 patients have undergone a regimen of combined photon and neutron therapy (the total percentage of neutron therapy is 40% of all radiotherapy treatment strategies); 14 patients were subjected to stereotactic radiotherapy (35% of cases).

The results: As the result of the conducted research it can be marked that the median overall survival (OS) of the patients under study is 48 months. The number of 1-year overall survival is 94,7%, 2-years OS is 78,6%, 3-years overall survival is observed in 63,7% of the cases and 5-years OS is seen within 37,4%. The median progression-free survival without after treating of the relapse is 24 months. The overall median survival for patients operated after the relapse is 58 moths, while for those who have not been operated – 48 months. The difference is not statistically significant. Alongside with this the best median progression-free survival index is noted either with reoperation with the following radiotherapy – 35 months or with autonomous radiotherapy (without

surgical interference) – 24 months. The difference between these cases is 0,897. The median progression-free survival indexes using other treatment strategies are significantly lower.

Among the radiotherapy strategies the highest indexes of the median overall survival (84 months) and the median progression-free survival (47 months) are noticed among the patients who have undergone the regimen of combined photon and neutron therapy.

Conclusions: Thus, the factors that have a positive impact on the indexes of the median overall survival and the median progression-free survival are conducting a surgical reoperation, combined neutron and photon therapy regimen and the patient's age lower than 50 years old. Reconducting a regimen of combined neutron and photon therapy can be an essential treatment component in treating patients with progressing cerebral anaplastic astocytoma.

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

cell research

BNCT with Laser-synthesized boron nanoparticles

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Boron neutron capture therapy (BNCT) is one of most appealing radiotherapy modalities. We explore the use of elemental boron nanoparticles (BNPs) fabricated by the methods of pulsed laser ablation in liquids as sensitizers of BNCT.

Depending on conditions of laser-ablative synthesis, the used NPs were amorphous (a-BNPs) or partially crystallized (pc-BNPs) with the mean size of 20 nm or 50 nm, respectively. Both types of BNPs were functionalized with polyethylene glycol polymer to improve colloidal stability and biocompatibility.

The NPs were efficiently absorbed by U87 glioblastoma and SW-620 colorectal adenocarcinoma cells and did not initiate any toxicity effects up to concentrations of 100 μg/mL, as followed from results of MTT and clonogenic assay tests.

The cells with BNPs incubated at 10B concentration of 40 μg/mL were then irradiated with a thermal neutron beam for 30 min. We found that the presence of BNPs led to a radical enhancement of cancer cell death, namely a drop of colony forming capacity of SW-620 cells down to 12.6% and 1.6% for a-BNPs and pc-BNPs, respectively, while the relevant colony-forming capacity for U87 cells dropped down to 17%. The effect of cell irradiation by neutron beam uniquely was negligible under these conditions.

To estimate dose and regimes of irradiation for future BNCT in vivo tests, we studied bio-distribution of boron under intratumoral administration of BNPs in immunodeficient SCID mice and recorded an excellent retention of 10B in tumor.

The obtained data unambiguously evidenced the effect of a neutron therapy enhancement, which can be attributed to efficient B NPs-mediated generation of α-particles.

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boron compounds

New Approaches to the Synthesis of Boron-containing Biologically Active Compounds for Boron Neutron Capture Therapy

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At the present time the main field of application of boron compounds in medicine is Boron Neutron Capture Therapy for Cancer (BNCT). In this presentation the principles of BNCT and main boron-containing biologically active compounds used for BNCT will be shown [1,2]. The successful treatment of tumors by BNCT requires selective delivery of the boron moiety into the tumor cells. One of the ways to solve this problem is attachment of boron fragment to different tumor-specific targeting molecules.

Literature data of novel boronated amino acids, and our recent results on the preparation and design of different conjugates of boron-containing biologically active compounds with tumor-seeking molecules, like cholesterol [3], curcumine [4], acridine [5] will be presented. Conjugates of cholesterol with *closo*-dodecaborate and cobalt bis(dicarbollide) can be used as liposome precursors for the selective delivery of boron into tumor cells for boron neutron capture therapy for cancer. Boronated curcumines are considered to be potential BNCT candidates because they can accumulate in the tumor cells, therefore, the report will show the synthesis of curcumin derivatives with cobalt bis(dicarbollide), as well as their antiproliferative activity and intracellular accumulation. Recently, researchers have paid attention to DNA-binding BNCT agents, such as acridine, so the report will consider examples of the synthesis of conjugates of acridine with cobalt bis(dicarbollide) and will present biological studies of the resulting new derivatives.

The synthesis of boron-containing biologically active compounds as potential candidates for BNCT was mainly carried out via the Cu(I)-catalyzed 1,3-dipolar [3 + 2] cycloaddition reaction of alkynes to azides (“click” reaction) and the ring-opening reactions of the cyclic oxonium derivatives of polyhedral boron hydrides with various nucleophiles.

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References:

1. A. Raitano, T. Martin, C. Zhang, et al. Boronotyrosine, a borylated amino acid mimetic with enhanced solubility, tumor boron delivery, and retention for the re-emerging boron Neutron Capture Therapy Field. *J. Med. Chem*. **2023**, 66, 19, 13809-13820.
2. T.Nomoto, Y. Inoue, Y. Yao, at al. Poly(vinyl alcohol) boosting therapeutic potential of p-boronophenylalanine in neutron capture therapy by modulating metabolism. *Sci. Adv*., **2020**, 6, eaaz1722- eaaz1732.
3. R. Dubey, A. Sarkar, Z. Shen, et al. Effects of linkers on the development of liposomal formulation of cholesterol conjugated cobalt bis(dicarbollides). *J. Pharm. Sci*. **2021**, 110, 1365-1373.
4. L. Dezhenkova, A. Druzina, Yu. Volodina, et al. Synthesis of Cobalt Bis(Dicarbollide) – Curcumin Conjugates for Potential Use in Boron Neutron Capture Therapy. *Molecules* **2023**, 27, 4658-4667.
5. A. Druzina, N. Dudarova, I. Ananyev, et al. New boron containing acridines: synthesis and preliminary biological study. *Molecules* **2023**, 28, 6636-6649.

biology

Targeted agents based on aptamers for the delivery of the 10B isotope in BNCT

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Glioblastomas are the most common type of malignant brain tumors, characterized by high aggressiveness and resistance to almost all currently existing methods of therapy. A promising approach to the treatment of such tumors is boron neutron capture therapy (BNCT), based on irradiation of tumor cells saturated with the boron-10 isotope with a neutron flux of a certain energy range. We have proposed a new strategy for boron isotope delivery based on the use of oligonucleotide aptamers of structured synthetic DNA and RNA fragments capable of selectively binding and penetrating tumor cells. A quantitative assessment of the level of boron achieved in tumor cells upon specific delivery in the form of a conjugate with the 2'-F-RNA aptamer was carried out [1]. For this purpose, two independent methods were used: quantitative real-time RT-PCR and inductively coupled plasma atomic emission spectrometry. The results obtained by both methods are in good agreement with each other. Aptamer-mediated delivery achieves intracellular levels of boron that exceed those required for effective BNCT (10^9 atoms/cell) [2]. The biodistribution of boron-containing GL44 2'-F-RNA aptamer conjugates was studied in SCID mice bearing subcutaneous U-87 MG human glioblastoma xenografts *in vivo*. For this purpose, methods of intravital fluorescence imaging and atomic emission spectroscopy were used. Fluorescence imaging did not reveal significant differences between the experimental and control groups. However, studying the distribution of boron in individual organs of model animals revealed higher levels of boron in the tumor xenograft. The results obtained on inhibition of tumor growth, survival and tumor node weight allow us to preliminary evaluate the effect of the aptamer conjugate GL44-5B12 as specific. The results obtained allow us to draw a preliminary conclusion about the specific effect of the boron-containing aptamer conjugate on the in vivo tumor model. Undoubtedly, to confirm this effect, study it in detail and select the optimal dosage and irradiation regimen, improving the pharmacokinetic characteristics of aptamer conjugates, further additional experiments will be required, which will be the development of this work. We have demonstrated the low toxicity of 2'-F-RNA conjugates with closo-dodecaborate, the specificity of their interaction with tumor cells *in vitro* and *in vivo*, the ability to deliver the amount of boron required for BNCT into cells, as well as the positive results of model experiments on BNCT confirm the promise of such studies.

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References:

1. Vorobyeva M.A.; Dymova M.A.; Novopashina DS, et al. Tumor Cell-Specific 2′-Fluoro RNA Aptamer Conjugated with *Closo*-Dodecaborate as A Potential Agent for Boron Neutron Capture Therapy. *Int. J. Mol. Sci.* 2021, *22*, 7326.
2. Novopashina DS, Dymova MA, Davydova AS, et al. Aptamers for Addressed Boron Delivery in BNCT: Effect of Boron Cluster Attachment Site on Functional Activity. Int J Mol Sci. 2022. 24(1):306.

veterinary studies

Experience of neutron capture therapy for malignant tumors of cats and dogs and prospects for the development of the method

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Malignant tumors show radioresistance to varying degrees when using traditional methods of radiotherapy with low linear energy transfer. The use of ionizing radiation with high linear energy transfer in this aspect is considered more promising. One type of ionizing radiation with high linear energy transfer is neutron capture therapy. Considering the binary nature of the method, it is possible to use both different elements with a high neutron capture cross-section and different forms of drugs that differ in pharmacokinetic properties and selectivity of accumulation in tumor cells. To evaluate the effectiveness of neutron capture therapy, the most approximate model at the preclinical stage is spontaneous malignant tumors in cats and dogs, which largely repeat the nature of malignant tumors in humans.

We treated spontaneous soft tissue tumors in cats and dogs using neutron capture therapy using drugs enriched with boron-10 - sodium borocaptate (BSH) and boronophenylalanine (BPA), nanoparticles of elemental boron, as well as a drug with natural gadolinium content - gadopentetic acid. Therapy sessions were carried out at the Tandem-BNCT accelerator neutron source at the Budker Institute of Nuclear Physics (Novosibirsk) as well as on the horizontal channel "GEK-1", the IRT-T research reactor, Tomsk Polytechnic University. The selection of animals for treatment was carried out in accordance with the inclusion criteria. Animals with tumor recurrence after surgical treatment, chemotherapy, and also in cases where it was impossible to carry out alternative treatment options were subjected to neutron capture therapy.

After boron-neutron capture therapy, in most cases, a partial tumor response was noted, an improvement in the overall clinical condition and an increase in the expected duration and quality of life of the animals, while after gadolinium-neutron capture therapy there was no significant response of tumors to treatment. It was noted that toxic effects associated with drug infusion, as well as post-radiation reactions, were mild and reversible.

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dosimetry

Prompt Gamma-ray Spectroscopy for Boron Dose Measurement

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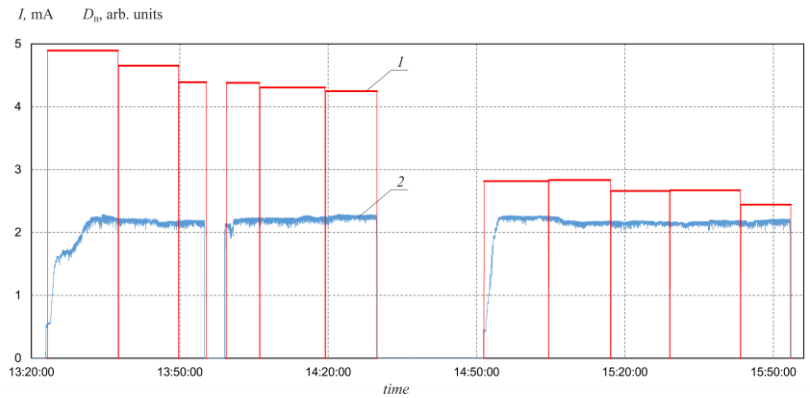
The $^{10}B(n,\alpha)7Li$ reaction itself provides a direct way to measure the boron dose, since one of the products of this nuclear reaction, the lithium nucleus, emits a photon with an energy of 478 keV in 93.9% of cases. Registration of such photons provides direct information about the number of nuclear reactions, i.e. about boron dose. Of course, this method of prompt γ-spectroscopy is well known [1], but has not been implemented for practical use in therapy.

The difficulty of implementation is that the γ-radiation spectrometer must be located in a neutron flux and have good energy resolution. It should be taken into account that photons with the same energy are emitted from the lithium target as a result of inelastic scattering of protons on lithium atomic nuclei. If we use a γ-spectrometer, which is relatively stable in a neutron flux, then the energy resolution does not allow us to separate the 478 keV line from the more powerful 511 keV line. The HPGe γ-spectrometer separates these lines, but it is not resistant to neutrons.

The report presents the results of a study that made it possible to measure the time dependence of boron dose in the treatment of a pet cat with adenocarcinoma in the nasal cavity. The study was carried out at the accelerator based neutron source VITA [2]. The figure shows the measured dependence of boron dose (*1*) and proton beam current (*2*). The results obtained made it possible to determine the absolute value of the absorbed dose, which is important for assessing the result of therapy.



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

References:

1. T. Kobayashi, K. Kanda. Microanalysis system of ppm order B-10 concentrations in tissue for neutron capture therapy by prompt gamma-ray spectrometry. Nucl. Instrum. Methods Phys. Res. 204 (1983) 525–531.
2. S. Taskaev, *et al*. Neutron Source Based on Vacuum Insulated Tandem Accelerator and Lithium Target. Biology 10 (2021) 350.

Oral presentations

boron compounds

Development of albumin-based theranostic conjugates for combining chemotherapy with boron-neutron capture therapy

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Boron-neutron therapy is a method of treating cancer tumors that is developing in Russia. Despite the obvious advantages of this method, such as the possibility of local therapeutic effects, to implement more effective therapy within the framework of BNCT, new therapeutic constructs are needed. For the effective therapy the constructs should combine a sufficient amount of boron, a signaling molecule that allows visualization of the construct within the body and a chemotherapeutic residue for enhancing BNCT with chemotherapeutic effect.

On the platform of human serum albumin, we have created therapeutic constructs carrying boron-containing residues (derivatives of cobalt bisdicarbolide and *closo*-dodecarborate), signaling molecules (Cy5, Cy7, trifluoro acetyl group) and chemotherapeutic residues (analogues of gemcitabine and inhibitors of tubulin synthesis - auristatins MMAE and MMAF). To create the constructs, «click» - chemistry methods were used with application of the polyfunctional reagent homocysteine thiolactone.

The successful preparation of boron-containing polyfunctional constructs has been confirmed by various physico-chemical methods. The toxicity of the created constructs was studied in relation to human glioma cell lines.

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biomagnetic sensing

Biomagnetic Sensing with Nitrogen-Vacancy Centers in Diamonds plates modified by proton beams

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The Nitrogen vacancy (NV) center is a novel solid-state sensor for detecting magnetic fields with high sensitivity and high spatial resolution at room temperature. Such a magnetometer has potential applications in a variety of fields, including biomedicine, neuroscience, and nanoscale magnetic resonance microscopy. compared to the Earth's static magnetic field, which at its surface ranges from 25 to 65 uT, brain magnetic fields strengths are measured to be between 8 and 9 orders of magnitude smaller. Moreover, magnetic noise generated by electrical devices and moving magnetic objects, encountered in a typical laboratory environment, is usually a thousand times stronger than any magnetic signal induced by the activity of neurons within the brain [1,2]. As such, in order to sense the really weak biomagnetic signals, very sensitive magnetometers are needed.

A diamond irradiated with protons can provide greater sensitivity than if irradiated with electrons. the possibilities for ensemble magnetometers of high density [3] determine the sensitivity, the development of such magnetometers requires reliable production of diamond samples with NV concentration control. Proton irradiation can create a denser distribution of such defects. For example the effect of double refraction in diamonds was used to study mechanical tensions. Pronounced changes are observed on plate S#1. In the center of this place, there is a cross, visually transparent. Figure 1 shows the distribution of internal stresses. The scale is dimensionless, char-acterizes the anisotropy of internal tensions |sinδ|.

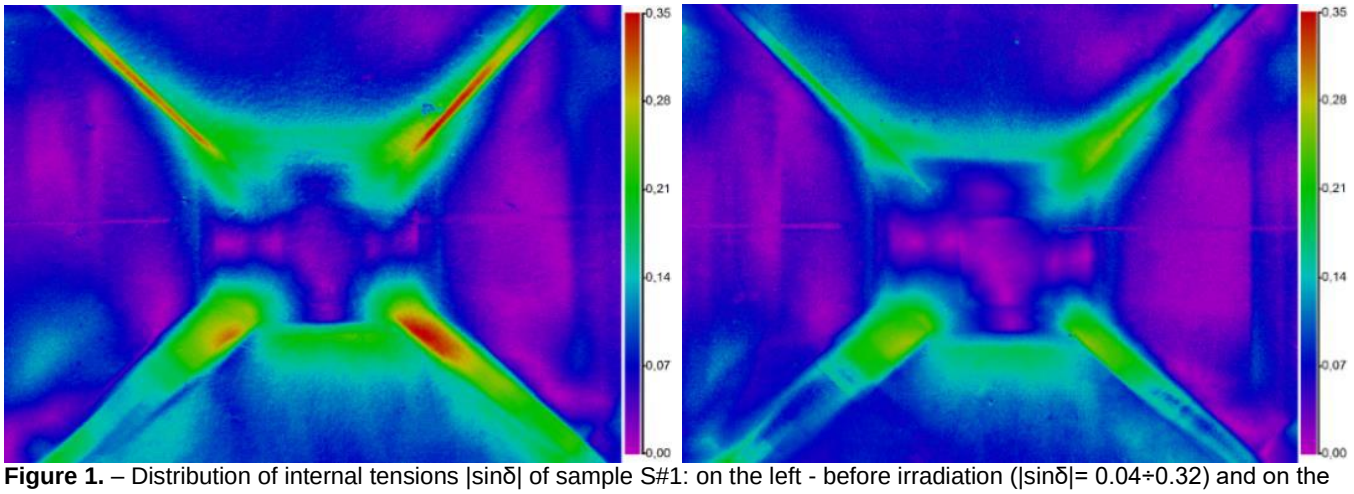

Figure 1. – Distribution of internal tensions |sinδ| of sample S#1: on the left - before irradiation (|sinδ|= 0.04÷0.32) and on the right - after irradiation in combination with subsequent annealing at 900 °C for two hours in vacuum (|sin δ| = 0.02÷0.25)

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References:

1. J Vrba. “Magnetoencephalography: the art of finding a needle in a haystack”. In: Physica C: Superconductivity 368.1-4 (2002), pp. 1–9.
2. Peter Hansen, Morten Kringelbach, and Riitta Salmelin. MEG: an introduction to methods. Oxford university press, 2010
3. Mrózek, M.; Schabikowski, M.; Mitura-Nowak, M.; Lekki, J. Marszałek, M.; Wojciechowski, A.M.; Gawlik, W. Nitrogen-Vacancy Color Centers Created by Proton Implantation in a Diamond. Materials. 2021. 14, 833. https://doi.org/10.3390/ma14040833

Posters

boron compounds

Synthesis and study of the properties of carboranyl-containing hydrindones

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Requirements for potential drugs that can be used in BNCT are low toxicity, high chemical and biological stability, high selectivity to tumor cells, the maximum possible amount of boron in the molecule in relation to other elements, and solubility in water. Among the variety of boron compounds potentially suitable for BNCT and actively investigated in many research centers, carboranes occupy a special place. Various compounds of benzylidene malonic ester with isopropylorthocarborane have been studied previously [1]. In this study, carborane derivatives, hydrindones, were synthesized. Developing this topic, diethyl 2-(4-(dimethylamino) benzylidene) malonate with lithium-o-carborane was synthesized for the first time. The reaction scheme is presented in Figure 1.

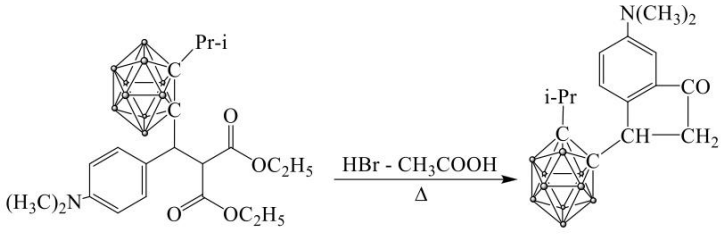

Figure 1 – The scheme of 2,3-(4-dimethylaminophenyl)-4-(isopropyl-o-carboranyl)hydrindon synthesis

We have found that this reaction occurs regardless of different conditions, mixing methods, and amounts of initial reagents and always results in a product containing the conjugate coupling of a carboranyl-substituted malonic ester. To determine the chemical properties, reactions with amines of different basicities (allylamine, ethylenediamine, piperidine, morpholine) were studied. With highly basic amines, Schiff bases are formed, and the product yield also increases. The toxicity of the obtained compound was also studied using T98G human glioblastoma, F98 rat malignant glioma, and CT26 murine colorectal carcinoma cell lines. The compound exhibited dose-dependent cytotoxicity and was well tolerated by all cells in equivalent boron concentrations in the medium ranging from 0 to 150 μg/mL. To verify the compound efficacy in BNCT, further in vitro and in vivo accumulation and irradiation studies are required.

The study was carried out within the framework of the BR20081011 program, funded by the Ministry of Energy of the Republic of Kazakhstan.

References:

1. Korolkov I.V., Zibert A.V., Lissovskaya L.I. Boron and Gadolinium Loaded Fe3O4 Nanocarriers for Potential Application in Neutron Capture Therapy. Int. J. Mol. Sci. 2021, 22, 8687.

boron compounds

Study of boron accumulation in mice with U87 human glioblastoma xenografts after administration of elemental boron nanoparticles using inductively coupled plasma atomic emission spectrometry

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For the successful implementation of boron-neutron capture therapy, targeted boron delivery agents are needed. There are several criteria for an “ideal” boron-containing drug: firstly, its use must be safe; secondly, the accumulation of boron should be tumor-specific and its concentration in tumor tissue should be 20-50 μg/g or more; thirdly, boron delivery drug should excrete relatively rapid from blood and normal tissues, and persiste in tumor for at least several hours during neutron irradiation. Therefore, conducting studies to assess the accumulation of boron in tumors and organs after administration of a boron-containing drug is an important step in planning therapy. The purpose of the study was to evaluate the accumulation of boron in organs and tissues after intratumoral administration of elemental boron nanoparticles obtained by laser ablation and coated with polyethylene glycol [1] in mice with U87 human glioblastoma xenografts.

Nanoparticles were injected intratumorally once in a volume required to achieve a concentration of 40 μg/g in the tumor site. The study used boron with natural isotope content: 20% ^{10}B, 80% ^{11}B. Tumor, blood, skin, kidneys, liver, spleen, brain and muscle were collected for subsequent ICP AES analysis [2].

The accumulation of boron in the tumor 30 minutes after administration was 56 μg/g, and after 90 minutes – 82 μg/g. The content of boron in the blood was significantly lower and amounted to 4 μg/ml after 30 minutes and 3.5 μg/ml after 90 minutes, respectively. Thus, the accumulation of boron in the skin was at the level of the values obtained in the control group. The resulting accumulation of boron in the tumor is sufficient for successful BNCT in the case of boron enrichment with the ^{10}B isotope.

Acknowledgments:
This research was funded by Priority 2030 program.

References:

1. A.I. Pastukhov *et al.* Laser-ablative aqueous synthesis and characterization of elemental boron nanoparticles for biomedical applications. Sci. Reports. 2022. 12(1):9129.
2. Tsygankova A. R. *et al.* Determination of boron by inductively coupled plasma atomic emission spectrometry. Study of the biodistribution of ^{10}B in the organs of mice. News of the Academy of Sciences. Chemical series. 2020. no. 3. pp. 601-607.

others

Study of the reaction ^{11}B(p,α)αα in the 0.3-2.15 MeV proton beam energy range

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The credible value of the ^{11}B(p,α)αα reaction cross-section is essential for the proton therapy of cancer, the thermonuclear fusion, and the nuclear astrophysics. Despite the relevance, the mechanism of the reaction is still an open question. The goal of the study consists in acquiring new knowledge about the reaction, modernization and clarification of the preliminary studies data in the 0.3-2.15 MeV proton beam energy range.

To achieve the aim, a thick boron-containing target was irradiated with protons at the Vacuum Insulated Tandem Accelerator (VITA) at the Budker Institute of Nuclear Physics in Novosibirsk, Russia. The spectra of the emitted α-particles and backscattered protons were measured using the silicon semiconductor α-spectrometer PDPA-1K (Institute of Physical and Technical Problems, Dubna, Russia) at 135° with respect to the beam moment. Using SIMNRA version 7.03 (Max Planck Institute for Plasma Physics, Germany), we modeled the interaction of a proton beam with the boron-containing target and succeeded to reveal the accurate composition of the irradiated target. The obtained results proved that the reaction ^{11}B(p,α)αα has two channels - ^{11}B(p,α_1)^{8}Be* and ^{11}B(p,α_0)^{8}Be with different cross-sections which agrees with the nowadays conceptions.

In future we plan to study a thin boron target to measure the cross sections of each channel.

Acknowledgments:
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others

COBALT 1,2-DICARBOLIDE PLGA NANOPARTICLES FOR BORON-NEUTRON CAPTURE THERAPY

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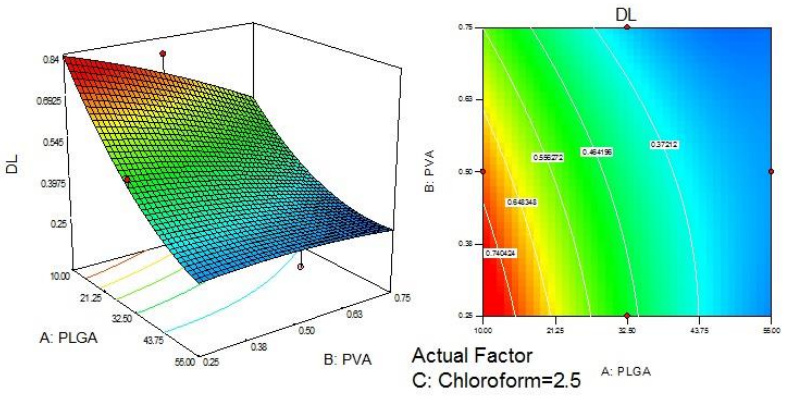
Boron-neutron capture therapy (BNCT) is a rapidly developing treatment for cancer. One of the challenges for therapy is achieving a concentration of the boron isotope ^{10}B in tumor cell ~20 μg. The development of new nanoscale delivery systems will solve this problem. This paper presents the results of optimizing the synthesis of nanoparticles based on copolymer of lactic and glycolic acids (PLGA) with cobalt 1,2-dicarbollide using the design of the Box-Behnken experiment.

Cobalt bis(1,2-dicarbollide) sodium Na[8,8′-I-3,3′-Co(1,2-$C_2B_9H_{10})_2$] was chosen as the drug for incorporation into nanoparticles because of its large number of boron atoms and hydrophilic properties.

For the synthesis of nanoparticles the double emulsion method was used, changing the amounts of polymer, chloroform as solvent and polyvinyl alcohol (PVA) as stabilizer while keeping the amount of cobalt 1,2-dicarbollide constant. Box-Behnken plans were used to plot drug loading (DL) and average nanoparticle diameter at different parameters.



Picture 1. Two and three-dimensional DL response surface diagram

An analysis of the diagrams made it possible to determine the optimal conditions for the synthesis of nanoparticles with a total content of drug 8 wt. % and the smallest average diameter is 228±27 nm.

The obtained parameters of nanoparticles are optimal for effective BNCT, and further *in vivo* and *in vitro* experiments are planned.

фармакокинетика

Изучение накопления и распределения изотопа бора-10 в составе борфенилаланина – агента для бор-нейтронозахватной терапии

Study of the accumulation and distribution of the boron-10 isotope in the composition of borphenylalanine, an agent for boron neutron capture therapy

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Бор-нейтронозахватная терапия (БНЗТ) является перспективным методом терапии различных злокачественных нозологий. Для эффективной процедуры БНЗТ концентрация ^{10}B в опухолевой ткани должна находиться в пределах 20-35 мг на 1 кг ткани [1]. Поэтому проведение доклинических исследований биораспределения L-борфенилаланина (BPA) в организме мыши является важным шагом в разработке инновационного метода лучевой терапии.

Цель: оценка биораспределения ^{10}B после внутривенного введения препарата BPA в организме здоровых мышей и с аллотрансплантантом клеток колоректального рака мыши CT26.

Материалы и методы. Материалом для исследования послужили органы и ткани мышей, изъятые через 1,5, 3, 6 и 24 часа после инъекции BPA. Концентрацию ^{10}B в тканях определяли методом масс-спектрометрии с индуктивно-связанной плазмой. Для оценки токсического действия борфенилаланина проведено гистологическое исследование опухоли, печени и кишечника мыши.

Результаты. Максимальное содержание бора в опухоли составило 142,0±4,4 мкг/г через 1,5 часа после внутривенного введения, затем оно экспоненциально снижалось и через сутки составило 3,1±0,1 мкг/г. Минимальная концентрация бора в опухоли достигается через 5,25 часа после введения BPA, что позволяет эффективно проводить нейтронное облучение до указанного периода. Отношение содержания BPA опухоль/кровь через 1,5 часа составил 4,4, в других органах этот показатель находился в диапазоне 1,3-4,5. По результатам гистологии дегенеративные изменения внутренних органов отсутствуют.

Таким образом, облучение мышей BALB/c с опухолевым аллотрансплантантом CT26 возможно в течение примерно 5 часов после внутривенного введения BPA. Однако проводить облучение оптимально через 2-3 часа после инъекции.

References:
1. Joel, D.D. et al. / Neurooncol, 1999. Vol. 41. P. 213-221.

клеточные исследования

Оценка *in vitro* эффективности нового D-D генератора нейтронов для задач БНЗТ: пилотные исследования

In vitro evaluation of the effectiveness of a new D-D neutron generator for BNCT: pilot studies

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Бор-нейтронозахватная терапия (БНЗТ) является перспективным методом лечения злокачественных опухолей. Одной из наиболее существенных проблем, препятствующей широкому клиническому внедрению БНЗТ, является отсутствие компактных источников нейтронного излучения. В настоящее время в Институте прикладной физики РАН разработан новый дейтериевый генератор (D-D генератор) нейтронов для задач БНЗТ. Для оценки эффективности данного генератора на первом этапе необходимо определить его биологическую эффективность, где в качестве объекта выступают клеточные культуры.

Цель данной работы - оценить эффективность D-D генератора нейтронов для задач БНЗТ на клеточных культурах.

Материалы и методы. Клеточные линии: CT26 (колоректальный рак мыши), U87 (глиобластома человека), huFB (фибробласты человека). Препарат L-борфенилаланин (L-BPA). Оценка выживаемости: MTT-тест и анализ колониеобразующей активности.

Результаты. За 24 часа перед облучением клетки рассевали в 6-луночные культуральные планшеты по $2x10^5$ клеток на лунку, либо в питательной среде, либо в питательной среде с добавлением L-BPA (40 мкг/мл). Затем планшеты с клетками размещали в камере прибора непосредственно перед мишенью и на расстоянии ~10 см от мишени и облучали, согласно расчётам, была получена доза тепловых/эпитепловых нейтронов 10^{-4} Гр, быстрых 10^{-1} Гр. Было выявлено, что эффекты облучения зависят от расстояния до мишени. По результатам MTT-теста значимых эффектов для линий CT26 и huFB не наблюдалось. Однако для линии U87 в присутствии L-BPA было показано снижение жизнеспособности от контроля на 24,5 % для 1-ой пробы и на 38,4 % для второй пробы. Анализ колониеобразования показал незначительное снижение показателей для линий U87 и huFB, и увеличение числа колоний на 8,4±2,6 % для линии CT26.

Таким образом, установлена частичная эффективность исследуемого D-D генератора нейтронов. Более высокая токсичность для 1-ой пробы вероятнее всего связана с воздействием быстрых нейтронов, что указывает на необходимость оптимизации работы источника и проведение дополнительных исследований. Однако снижение выживаемости клеток U87 в присутствии L-BPA на 38,4 % указывает на перспективность дальнейших исследований.

BSA design, dosimetry

Bismuth collimator effect on beam shaping assemblies during dose measurements of thermal neutrons and gamma ray.

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Dosimetry in BNCT is more complicated than in conventional radiotherapy (photon and electron therapy). In BNCT, the total absorbed dose is the sum of four dose components: boron, nitrogen; fast neutron and γ-ray doses. The damage of tissue in BNCT is due to three types of ionizing radiation: low linear energy transfer (LET) gamma rays, high-LET protons and heavier high-LET charged particles ^{7}Li, ^{4}He and ^{14}C (Fig 1). A dosimeters for all these doses was developed and verified at the accelerator based neutron source VITA [1]. In order to improve BNCT and protect the patient, it is desirable that the useful dose (boron dose) exceed as much as possible the harmful dose (the sum of the fast neutron, gamma ray and nitrogen doses), where the ratio of useful dose to harmful dose is called the therapeutic factor. In this study, we will present the results of measuring the spatial distribution of boron dose and gamma radiation dose using a small polystyrene scintillator detector [2] in the presence of a bismuth collimator for two neutron beam shaping assembly, one containing moderator of magnesium fluoride and the other moderator made of plexiglass (PMMA) [3].

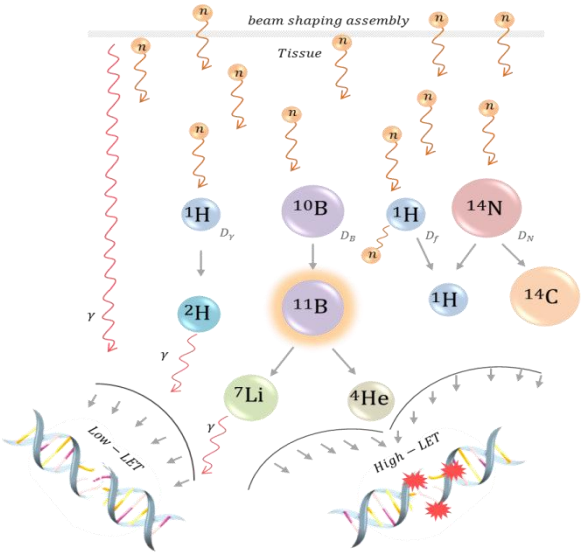

Fig 1

Acknowledgments:
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References:

1. Bikchurina M. et al. Dosimetry for Boron Neutron Capture Therapy Developed and Verified at the Accelerator based Neutron Source VITA //Frontiers in Nuclear Engineering. (2023): T. 2. – C. 1266562.
2. Bykov, T. A., et al. "Initial trials of a dose monitoring detector for boron neutron capture therapy." Journal of Instrumentation 16.01 (2021): P01024.
3. L. Zaidi, M. Belgaid, S. Taskaev, R. Khelifi. Beam shaping assembly design of 7Li(p,n)7Be neutron source for boron neutron capture therapy of deep-seated tumor. Applied Radiation and Isotopes 139 (2018) 316-324.

dosimetry

Realization of the program interface for displaying the results dosimetry calculations of the VITA dosimetry planning system for boron neutron capture therapy.

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Boron neutron capture therapy (BNCT) is currently regarded as one of the most promising methods of cancer treatment - it allows for the targeted destruction of cells of some malignant tumors by accumulation of stable isotope ^{10}B in tumor cells and subsequent irradiation of these cells with a stream of epithermal neutrons.

An original accelerator source of neutrons VITA[1] was proposed and developed at the Budker Institute of Nuclear Physics for the Blokhin National Medical Research Center of Oncology. In 2025 it is planned to put it into operation in Moscow and use it to treat patients. A VITA dosimetry planning system (VITA DPS) should be developed for therapy planning and treatment outcome assessment. Calculation of four dose components considered in VITA is supposed to be performed by Monte Carlo method using the neutron and γ-radiation transport code NMC.

This paper presents the results of implementation of the software interface for modeling the voxel model of the modified Snyder head phantom. Dosimetry calculations were performed using the NMC code and comparison of the obtained results with reference values obtained using the MCNP code [2] is presented. A program interface for displaying the obtained results in the form of a "dose-volume" histogram was implemented, and the possibility of layer-by-layer display of the obtained doses on the voxel model in the form of a heat map was realized.

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

References:

1. S. Taskaev, E. Berendeev, M. Bikchurina, T. Bykov, D. Kasatov, I. Kolesnikov, A. Koshkarev, A. Makarov, G. Ostreinov, V. Porosev, S. Savinov, I. Shchudlo, E. Sokolova, I. Sorokin, T. Sycheva, G. Verkhovod. Neutron Source Based on Vacuum Insulated Tandem Accelerator and Lithium Target. Biology 10 (2021) 350.
2. Goorley J.T., Kiger Iii W.S., Zamenhof R.G. Reference dosimetry calculations for neutron capture therapy with comparison of analytical and voxel models //Medical Physics. – 2002. – Т.29. – №. 2. – С. 145-156.

neutron source

Investigation of the characteristics of the neutron radiation beam of the R-7 M accelerator for the purposes of BNCT

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Boron-neutron capture therapy is a method of treating malignant neoplasms. The method is based on irradiation with a stream of thermal neutrons of a boron-containing drug located in a cancerous tumor [1].

The paper investigates the characteristics of the neutron radiation beam of the R-7M accelerator and the ratio of the data obtained experimentally in the PHITS software.

The main object of research is the fourth channel of a typical cyclic accelerator R-7M. Determining the neutron flux density is a key task. For this purpose, the method of irradiation of neutron activation foils is used. After irradiation, the activity of the irradiated foils is determined and the energy and density of the neutron flux are determined from the data obtained. The PHITS software tool is used to correlate the experimental data obtained in the software [2]. After the correlation, it will be possible to plan the experiment in the software before carrying out irradiation procedures for various biological tissues [3].

At the moment, neutron flux spectra have been obtained at a distance of 1 m from the source, depending on the energy of the deuteron beam. The angular distributions of the neutron flux at a distance of 10 cm from the source for the deuteron energy of 13.6 MeV are also obtained [4].

As the deuteron energy increases, the most probable neutron energy increases from 4.98 MeV to 6.06 MeV, the average energy increases from 4.33 MeV to 5.10 MeV. The anisotropy of neutron scattering of all energies increases to the most probable energy, and then decreases. At the same time, 66.02 % of radiation in the entire energy range and 69.2 % of radiation with an energy of 5.5 MeV propagates in the ± 20 degree sector. angular distributions correspond to the normal Gaussian distribution.

References:

1. E. L. Kuplennikov, A. N. Dovbnya, & Yu. N. Telegin, Puchki neytronov dlya terapii: obzor po ist. otech. i zarub. pechati za 1936-2010 gg //Kharkov: NNTs KhFTI. – 2011. – p. 31.
2. T. Sato et al. Recent improvements of particle and heavy ion transport code system: PHITS //EPJ Web of Conferences. – EDP Sciences, 2017. – T. 153. – C. 06008.
3. W. Sauerwein, A. Wittig, R. Moss, Y. Nakagawa (editors). Neutron Capture Therapy: Principles and Applications. – Springer, 2012. 553-558 pp.
4. Sauerwein W. A. G. et al. (ed.). Neutron capture therapy: principles and applications. – Springer Science & Business Media, 2012.

neutron source

Cockcroft-Walton generator for powering a vacuum-insulated tandem accelerator

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The accelerator neutron source VITA based on a vacuum insulated tandem accelerator operates at the Budker Institute of Nuclear Physics. At the accelerator source, when transporting a powerful (up to 10 kW/cm^2) beam of protons or deuterons to the target, neutrons with a wide range of energies are generated: cold, thermal, epithermal and fast. The transported beam or neutron flux is used for conducting research in the field of boron-neutron capture therapy, measuring the cross section of nuclear reactions ($^7Li(p,p'\gamma)^7Li$, $^7Li(p,\alpha)^4He$, $^6Li(d,\alpha)\alpha$, $^7Li(d,\alpha)^5He$, $^6Li(d,p)^7Li$ $^7Li(d,\alpha)\alpha n$), conducting materials science research together with INP, CERN, ITER and other applications.

The creation of a Cockcroft-Walton generator to power vacuum insulated tandem accelerator and their separation to a new neutron source is an urgent task, this will allow the treatment of malignant tumors by fast neutrons and radiation testing of promising materials. The generation of fast neutrons on an existing accelerator neutron source is complicated by the fact that a source of negative hydrogen ions and a bending magnet were calculated and produced for the generation and transportation of a proton beam. The installation being created will be designed to generate and conduct a deuteron beam, while the high-voltage and intermediate electrodes of the accelerator will be connected directly to the corresponding sections of the high-voltage power supply [1].

This study presents the concept of a powerful compact accelerator source of fast neutrons being developed; the results of numerical calculations, modeling and preliminary testing of the accelerator power source in air are presented and summarized; further steps of manufacturing and testing of the proposed power source are formulated.

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References:
1. S. Taskaev, I. Sorokin. Vacuum-insulated tandem accelerator. Patent for invention № 2653840, 15.05.2018.

boron compounds

Synthesis of biocompatible boron-nitride quantum dots

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Boron-neutron capture therapy (BNCT) is a binary radiotherapy based on the selective destruction of tumor cells by preliminary accumulation of the stable boron-10 isotope in them and subsequent irradiation with neutrons. Foremost challenge in this method is the synthesis and screening of new boron-containing drugs with high selectivity for tumor cells. There are three generations of boron-containing drugs [1]. The first-generation delivery agents represented by boric acid, borax and pentaborate were the lack of tumor targeting. Two well-known second-generation boron drugs – boronophenylalanine (BPA) and borocaptate (BSH) – and some of their derivatives are currently allowed to be used in clinical practice. However, they still have many shortcomings including a poorly water solubility, an insufficient tumor-to-normal cells boron concentration ratios, difficulties with the crossing the blood-brain barrier making them inappropriate for treatment of glioblastomas.

Boron-containing nanomaterials and boron-nitride quantum dots (BNQDs) belong to the third generation of boron-delivery agents. BNQDs have a graphene-like structure formed by six-membered rings comprising boron and nitrogen atoms in equal amounts. They (i) have nm-size, low-toxicity and penetrate biological barriers, (ii) unique photophysical properties provide the possibility for drug accumulation detection in tumor cells by fluorescence microscopy. It is worth emphasizing the possibility of functionalizing the surface and edges of the BNQDs to improve targeted delivery to the tumor [2]. So of great significance is the development of the one-step reproducible synthesis of biocompatible BNQDs as a promising boron delivery agent for BNCT.

In this work, we proposed hydrothermal synthesis of BNQDs by using boric acid and urea as a precursor of boron and nitrogen, respectively. The solvent system used was a mixture of the ethanol, liquid ammonia and distilled water. The presence of BNQDs in the prepared solution was confirmed by the fluorescence and IR-spectroscopy. It was found that when excited at a wavelength of 320 nm, synthesized BNQDs have intense fluorescence with a maximum of 400 nm. The IR spectra have typical absorption bands of B-N group in the regions: 1337-1300, 1420-1410 and 1630 cm^{-1}. The biocompatibility of BNQDs has been revealed by estimating the viability of Vero cells in the presence of nanoparticles.

References:
1. X. Cheng, F. Li, L. Liang. Boron Neutron Capture Therapy: Clinical Application and Research Progress. Curr Oncol., vol. 29 (2022), p. 7868-7886.
2. X. Zhang, L. An, C. Bai, *et al*. Hexagonal boron nitride quantum dots: Properties, preparation and applications. Mater. Today Chem., vol. 20 (2021), p. 100425.

biology

Study of the toxicity of boron nanoparticles *in vitro* and *in vivo*

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Nanoparticles (NPs) of elemental boron are a new generation of drugs for boron neutron capture therapy (BNCT). Compared to boron-containing drugs used in clinical practice, NPs differ in the content of a large number of boron atoms, which makes them promising objects of research [1]. The purpose of the study is to determine the toxicity of NPs *in vitro* and *in vivo.*

The NPs under study are a colloidal solution of boron NPs in hyaluronic acid with a concentration of 500 ppm. Human tumor cells were used: melanoma SK-Mel-28, intestinal carcinoma SW620 and glioblastoma U-87 MG, as well as “healthy” human fibroblasts BJ-5ta. Cells were cultured and tested using standard methods [2]. CD-1 mice were used at 6 weeks of age, ♂. The injection of NPs was carried out once, 1st group of mice intravenously at a dose of 10 mg/kg, 2d group intraperitoneally - 40 mg/kg, control group - intact. The condition of the animals was continuously recorded during the first hour after injection and then once a day. Mice were weighed before injection and then once a week. Cell cultures and laboratory animals were obtained at the SPF-vivarium center of the Institute of Cytology and Genetics SB RAS.

In vitro, in the MTT test, no cytotoxic effect of NPs was observed on any of the cell lines. An important result is the lack of toxicity of relatively “healthy” cells - human fibroblasts. The lack of suppression of tumor cell proliferation is not a negative result, since the most important thing is the accumulation of boron in cancer cells for subsequent BNCT. *In vivo*, there were also no signs of toxic effects of the studied NPs either on the day of injection or in further observations. The body weight of the animals did not decrease and did not differ from the control group throughout the entire observation period - 30 days.

The results obtained provide grounds for using the studied NPs as an agent for BNCT; however, to fully assess their effectiveness, it is necessary to study the accumulation of boron in the tissues of laboratory animals with grafted xenografts of human cancer cells, which is the next stage of our research.

Acknowledgments:
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References:
1. Boron nanoparticles in chemotherapy and radiotherapy: synthesis, current state and prospects. Uspenskii S.A., Khaptakhanova P.A.Russian Chemical Bulletin, 2022, No. 12.
2. Freshni R.Ya. Animal cell culture: a practical guide / R. Ya. Freshni; lane 6th English ed. – 4th ed., rev. and additional (el.). – M.: Knowledge Laboratory, 2018.

boron imaging, boron compounds, cell research

HSA-based theranostics promise to combine BNCT and chemotherapy

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For extremely aggressive tumors, as glioblastoma, where individual cancer cells can escape surgical/chemotherapeutic removal and reconstitute the tumor, BNCT must be of great use. Considering that under BNCT conditions, most of the ionizing energy transferred to tissues is localized to ^{10}B-loaded cells, it is the biodistribution of the boron compound that is the key to the effectiveness of BNCT. Unfortunately, the BNCT drugs used in clinical practice today (boron phenylalanine and sodium borocaptate) have difficulty achieving the lower threshold of accumulation criteria.

Recent developments in the field of boron compounds concern targeted delivery systems, including those based on albumin. Human serum albumin (HSA) has been shown to be capable of delivering therapeutic agents to tumor tissues [1]. We previously reported on the development of new boron-containing HSA conjugates that make it possible to monitor the accumulation of boron in a tumor in real time, as well as to provide a chemotherapeutic effect on tumor tissues due to the content of a cytostatic (gemcitabine) in the structure. Our albumin modification strategy does not reduce the protein's circulation time in the blood and allows pharmaceutical substance to programmed release in cancer tissues.

Our last BNCT experiments against the human glioblastoma T98G cell line show that the effectiveness of the new BNCT conjugate is close to that of boron phenylalanine, even when using the conjugate having natural boron (≈20% of ^{10}B, ≈80% of ^{11}B). Taking into account the proven dose-independent cytotoxicity of the conjugate against the T98G cell line without irradiation, the synergistic effect of gemcitabine and boron cluster residues takes place [2]. Thus, the conjugate is promising for combination therapy.

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References:

1. B. Bhushan, *et al*. Impact of albumin-based approaches in nanomedicine: Imaging, targeting and drug delivery. Advances in colloid and interface science. Vol. 246 (2017), 13-39.
2. V. Raskolupova, *et al*. Design of the new closo-dodecarborate-containing gemcitabine analogue for the albumin-based theranostics Composition. Molecules. Vol. 28 (2023), 2672.

boron compounds

Simulated radiation damage to tumor cells accumulated boron nitride quantum dots

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Boron neutron capture therapy (BNCT) offers a promising non-surgical radiotherapy approach for treating invasive chemoresistant malignant tumors. This method comprises two key stages: (i) the delivery of a drug containing the non-radioactive isotope boron-10 (^{10}B) to the tumor, and (ii) the irradiation of the patient tumor with epithermal neutrons. The interaction of neutrons with ^{10}B leads to the generation of alpha particles, 7Li nuclei, and high-energy gamma. The effectiveness of BNCT relies on the achieving the appropriate concentration of boron, with approximately 10^9 ^{10}B atoms per targeting cell [1]. Cell nuclei emerge as the primary target for BNCT due to their role as DNA storage sites. But, the optimal location of BNCT in cells may be not only the nucleus, but also the cytoplasm.

For optimal BNCT parameter determination, the theoretical evaluation of BNCT effectiveness utilizing boron nitride quantum dots (BNQDs) was performed. Various models of tumor cells, with different nucleoplasmic ratios (including a unified cell model, lymphoma, melanoma, and squamous cell carcinoma), were considered. The simulation of ion pair (^{7}Li and ^{4}He) interaction with cellular components was conducted using the Monte Carlo method implemented in SRIM [2]. The tracks and total energy release of alpha particles and lithium ions were calculated. At that, three different localizations of boron atoms and 14 possible models of interaction of ions with cell medium were formulated. By applying GEANT4-DNA toolkit, the focus of the study was to investigate how radiation damage to cells determined as the yield of double-strand breaks of DNA depends on the BNQD localization in various cellular compartments (intercellular space, membrane, cytoplasm, nucleus) and concentration (25-100 μg/g of 10B).

The neutron total absorption cross-section for boron were shown to exhibit its highest value at neutron energy of 0.0253 eV. The considerable damage to the nucleus of a unified cell occurs when BNQDs are localized in the cytoplasm of cells. When ^{10}B isotopes localize in the extracellular space, the efficiency of damage to the nucleus can decrease by 3-4 fold compared to localization in the cytoplasm. The highest yield of double-strand breaks of DNA (about 30 per Gy per Gbp) is defined when BNQDs are distributed within the nucleus of the cell and for neutron energies ranging from 0.0253 to 104 eV. The yield of double-strand breaks of DNA for BNQDs in cytoplasm is 2-fold lower.The results obtained from this study underscore the potential to enhance the effectiveness of BNCT by applying BNQDs that are specifically functionalized to accumulate near the nucleus.

References:

1. Coderre J.A., Morris G.M. The radiation biology of boron neutron capture therapy // Radiation Research. 1999. Vol. 151, № 1. P. 1–18.
2. Ziegler J. James Ziegler - SRIM & TRIM [Electronic resource]. 2017. URL: http://www.srim.org/

others

Разработка и внедрение системы автоматизации ионного источника D-Pace для ускорителя VITA

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В Институте ядерной физики СО РАН (ИЯФ СО РАН) разработан ускорительный источник эпитепловых нейтронов VITA [1], используемый для развития методики бор-нейтронозахватной терапии (БНЗТ) злокачественных опухолей [2, 3] и ряда других приложений. Для управления установкой, хранения и анализа данных ранее создана система автоматизации, позволяющая оператору обеспечивать длительное стабильное получение пучка нейтронов или дейтронов в широком диапазоне изменения энергии и тока, а научным сотрудникам получать экспериментальные данные и обрабатывать их в режиме реального времени.

Установка VITA рассматривается как наиболее перспективный источник эпитепловых нейтронов для лечения онкологических больных в клиниках БНЗТ. На первой коммерческой установке VITA, размещенной в г. Сямынь (Китай), осуществляется лечение больных с октября 2022 г.

В настоящее время ИЯФ СО РАН изготавливает ускорительный источник нейтронов VITA для Национального медицинского исследовательского центра онкологии им. Н. Н. Блохина в Москве, планируется ввести его в эксплуатацию в 2024 г. В отличие от работающей экспериментальной установки ИЯФ СО РАН вместо источника ионов, разработанного в ИЯФ СО РАН, будет использоваться источник ионов компании D-Pace (Канада). Ионный источник D-Pace отличается возможностью генерировать больший ток и способностью обеспечить высокую стабильностью работы. Для эксплуатации этого источника было разработано специальное программное обеспечение и внедрены устройства ввода-вывода. При помощи разработанной системы автоматизации на стенде в ИЯФ СО РАН удалось увеличить ток пучка с 5.9 до 13 мА со стабильностью 0.14%.

В работе представлена и обсуждается основная концепция системы управления ионным источником, обеспечивающая его первоначальный запуск на стенде в ИЯФ СО РАН и последующее включение в общую систему управления медицинской установкой в Москве. Отмечаются такие особенности, как: 1) расположение узлов автоматизации на разных потенциалах, которые нужно синхронизировать между собой с частотой 100 Гц и точностью 0.05% при помощи PID регулятора; 2) спецификой разрабатываемого ионного источника является его постоянная модернизация и внедрение новых диагностик, которые необходимо оперативно интегрировать в систему автоматизации.

1. S. Taskaev, E. Berendeev, M. Bikchurina, T. Bykov, D. Kasatov, I. Kolesnikov, A. Koshkarev, A. Makarov, G. Ostreinov, V. Porosev, S. Savinov, I. Shchudlo, E. Sokolova, I. Sorokin, T. Sycheva, G. Verkhovod. Neutron Source Based on Vacuum Insulated Tandem Accelerator and Lithium Target. Biology 10 (2021) 350.
2. Sauerwein W. A. G. et al. (ed.). Neutron capture therapy: principles and applications. – Springer Science & Business Media, 2012.
3. M. Ahmed, D. Alberti, S. Altieri, ... S. Taskaev, ... K. Tsuchida. Advances in Boron Neutron Capture Therapy. International Atomic Energy Agency, Vienna, Austria, June 2023, 416 p. CRCP/BOR/002, ISBN: 978-92-0-132723-9