MINISTRY OF SCIENCE AND HIGHER EDUCATION OF RUSSIAN FEDERATION
P.N. LEBEDEV PHYSICAL INSTITUTE OF RAS
NATIONAL MEDICAL RESEARCH CENTER OF RADIOLOGY
OF THE MINISTRY OF HEALTH OF RUSSIA
NATIONAL NUCLEAR RESEARCH UNIVERSITY MEPhI

International Scientific Conference «Innovative Technologies of Nuclear Medicine and Radiation Diagnostics and Therapy» October 24-26, 2022

International Youth School «Innovative nuclear physics methods of high-tech medicine» October 27-28, 2022

Programme
Book of absracts

Moscow, Russia

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The I International Scientific Conference "Innovative Technologies of Nu-clear Medicine and Radiation Diagnostics and Therapy" and III International Youth School «Innovative nuclear physics methods of high-tech medicine» are held within the framework of the project "Development of new technologies for the diag-nosis and radiation therapy of socially significant diseases with proton and ion beams using binary nuclear physics methods" with the support of the Federal Scientific and Technical Program "Development of synchrotron neutron research and Research Infrastructure for 2019-2027" Ministry of Education and Science of the Russian Federation

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International Scientific Conference
Innovative Technologies of Nuclear Medicine and Radiation Diagnostics and Therapy

The I International Scientific Conference "Innovative Technologies of Nuclear Medicine and Radiation Diagnostics and Therapy" is held within the framework of the project "Development of new technologies for the diagnosis and radiation therapy of socially significant diseases with proton and ion beams using binary nuclear physics methods" with the support of the Federal Scientific and Technical Program "Development of synchrotron neutron research and Research Infrastructure for 2019-2027" Ministry of Education and Science of the Russian Federation.

The conference topics are devoted to the application of nuclear physics methods in nuclear medicine, radiation diagnostics and therapy, nanoteranostics technologies, binary radiation therapy technologies, technologies of combined action of ionizing radiation of various types, mathematical methods of modeling the growth of cancer tumors, optimization of proton and ion therapy methods, development of proton tomography, modernization of the Russian proton therapy complex Prometheus in order to implement the developed technologies, production of modernized complexes and their installation in clinics of the Russian Federation.

I International Scientific Conference "Innovative Technologies of Nuclear Medicine and Radiation Diagnostics and Therapy" will be held on October 24-25, 2022 at the Physical Institute. P.N. Lebedev RAS.

Important information
- The venue - Lebedev Physical Institute of the Russian Academy of Science
- Official language - English
- The conference will be held in a face-to-face format with the possibility of remote connection
- Without registration fee

Website: https://protonconf.lebedev.ru/

E-mail: protonconf@lebedev.ru

International Youth School
Innovative nuclear physics methods of high-tech medicine

III International Youth School "Innovative Nuclear Physics Methods of High-Tech Medicine" continues the cycle of annual Schools dedicated to advanced methods of nuclear medicine, radiation diagnostics and therapy, accelerator technologies, nanoscale technologies of high-tech medicine.

The school is held within the framework of the project "Development of new technologies for the diagnosis and radiation therapy of socially significant diseases by proton and ion beams using binary nuclear physics methods", implemented with the support of the with the support of the Federal Scientific and Technical Program "Development of synchrotron and neutron research and research infrastructure" of the Ministry of Education and Science of Russia.

III International Youth School will be held on October 27 and 28, 2022 at the Physical Institute. P.N. Lebedev RAS.

Topic III School: "Combined methods of therapy in oncology."

The lecturers of the School are leading Russian and foreign scientists in the field of nuclear medicine, radiation diagnostics and therapy.
The school is designed for young scientists, graduate students, master's, specialist and bachelor's students, schoolchildren.

Important information:
• Format of the School - lectures by leading scientists
• The official language of the School is Russian
• The school will be held in a full-time format with the possibility of remote connection for non-resident and foreign participants
• The program of the School for full-time participants includes coffee breaks, memorable gifts and photos
• Without registration fee

Website: https://protonschool.lebedev.ru/

E-mail: protonschool@lebedev.ru

ORGANIZERS

P.N. Lebedev Physical Institute of RAS

National Research Nuclear University MEPhI

National Medical Research Center for Radiology of the Ministry of Health of the Russian Federation

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PROGRAMM
I International Scientific Conference
«Innovative Technologies of Nuclear Medicine and Radiation Diagnostics and Therapy»

	October 24, Monday
	Pillared Hall LPI, Moscow, Leninsky prospect 53
10.30 – 12.00	***Registration of participants. Coffee.***
12.00 – 12.30	***Opening ceremony***
	Session 1 - Chairman Kolobov A.V.
12.30 - 13.00	***Samoylov Alexander Sergeevich***
	Burnasyan Federal Medical Biophysical Centre of FMBA
	Radiopharmaceuticals and radiation technologies in the diagnosis and therapy of socially significant diseases
13.00 – 13.45	***Deev Sergey Mikhailovich***
	Institute of Bioorganic Chemistry of RAS
	Oncoteranostics: problems and prospects
13.45 – 14.15	***Zavestovskaya Irina Nikolaevna***
	LPI RAS, MEPHI
	«Development of new technologies for the diagnosis and radiotherapy of socially significant diseases by proton and ion beams using binary nuclear-physics methods». Project of Ministry of science and higher education of Russian Federation
14.15 – 15.00	***Lunch***
	Session 2 - Chairman Ryabov V.A.
15.00 – 15.30	***Udalov Yury Dmitrievich***
	Online
	FSCCRO of FMBA, Dimitrovgrad
	Implementation of the federal project and ramp-up of the

"closed cycle" oncology center to the planned capacity

15.30 – 16.00	***Shirkov Grigory Dmitrievich***
	Joint Institute for Nuclear Research, Dubna
	History and development of proton therapy at JINR Dubna
16.00 -16.30	***Chernyaev Alexander Petrovich***
	Lomonosov MSU, Moscow
	Development of nuclear-physical methods for medicine
16.30 – 17.00	***Coffee-break***
	Session 3 - Chairman Kurashvili Yu.B.
17.00 – 17.45	***Paras Prasad***
	Online
	University Baffalo, USA
	Interfacing Nuclear and Radiation physics with Nanoparticle Technology to Advance Nuclear Medicine and Radiation Diagnostics
17.45 – 18.15	***Rykalin Viktor Vladimirovich***
	ProtonVDA, USA
	Aspects of proton radiography and tomography
18.30	***Furshet***

October 25, Tuesday

Pillared Hall LPI,
Moscow, Leninsky prospect 53

9.30 – 10.30	***Registration of participants***
	Session 4 - Chairman Saburov V.O.
10.30 – 11.00	***Kolobov Andrey Vladimirovich***
	LPI RAS
	Influence of angiogenesis on tumor growth, progression and therapy. Analysis by mathematical modeling methods
11.00 – 11.30	***Bagulya Alexander Vasilievich***
	LPI RAS
	Geant4 simulation of alpha-particles production by protons
11.30 – 12.00	***Krylova Tatiana Alekseevna***
	N.N. Blokhin Oncology Center, JSC "NIITFA" (Rosatom)
	Radiotherapy complex "ONIKS": status of development and prospects
12.00 – 12.30	***Coffee-break***
	Session 5 - Chairman Bagulya A.V.
12.30 - 13.00	***Akulinichev Sergei Vsevolodovich***
	INR RAS, Troitsk
	Research of the Flash effect at the proton accelerator of the INR RAS
13.00 – 13.30	***Shemyakov Alexander Evgenievich***
	LPI RAS
	Proton therapy facility «Prometheus» status and research directions
13.30 – 14.00	***Belikhin Mikhail Alexandrovich***

	LPI RAS
	Optical- and bioimpedance- based respiration monitoring systems for spot scanning proton therapy
14.00 – 15.00	***Lunch***
	Session 6 - Chairman Zavestovskaya I.N.
15.00 – 15.30	***Saburov Vyacheslav Olegovich***
	A.Tsyb Medical Radiological Research Center
	Quality assurance procedures on the Prometheus proton therapy complex
15.30 – 16.00	***Roy Indrajit***
	Online
	University of Delhi, India
	Multifunctional nanoparticles in nuclear medicinal applications for cancer diagnosis and therapy
16.00 - 16.30	***Popov Anton Alexandrovich***
	MEPHI
	Laser-ablative synthesis of perspective nanomaterials for radiology
16.30 – 17.00	***Krishnan Sunil***
	Online
	Center for Physical Energy Therapeutics, UTHealth Center, USA
17.00 – 19.00	***Poster session. Coffee.***

October 26, Wednesday
Pillared Hall LPI,
Moscow, Leninsky prospect 53

9.30 – 10.30 ***Registration of participants***

Session 7 - Chairman Fronya A.A.

Denisova Natalya Vasilievna
NSU, ITAM SB RAS

10.30 - 10.50 **Computational Phantoms for Nuclear Medicine**

Kudryashov Iliya Anatolievich
Lomonosov MSU, LPI RAS

10.50 - 11.10 **Charged Particle Detection Method for Studying Targeted Technologies of Proton Therapy Using Advanced Nano-particles at Proton Synchrotron Complexes of the Prometheus System**

Popov Anton Leonidovich
ITEB RAS

11.10 - 11.30 **Gadolinium-based theranostic agents for mri-monitoring mesenchymal stem cells**

Kasatova Anna Ismagilovna
Budker Institute of Nuclear Physics, Novosibirsk

11.30 - 11.50 **Lithium neutron capture therapy as a new strategy for cancer treatment**

Vinogradov Sergei Leonidovich
LPI RAS

11.50 - 12.10 **Feasibility of Time-of-flight PET/Prompt Gamma Imaging based on Silicon Photomultipliers for in-Beam Hadron Therapy Monitoring**

Ovsenyov Alexander Evgenievich
Online
National Research Tomsk Polytechnic University

12.10 - 12.30 **Construction of a mathematical model of the channel of the cyclic accelerator R7-M in the phyts software package for boron-neutron capture therapy**

12.30 - 12.50 ***Coffee-break***

Session 8 - Chairman Kasatova A.I.

12.50 - 13.10	***Demidova Anna Mikhailovna*** FSCCRO of FMBA, Dimitrovgrad **Optimization of the validation procedure for the dosimetry model of proton pencil beam scanning**
13.10 - 13.30	***Kovalev Ivan Vladimirovich*** Burnazyan Federal Medical Biophysical Center of the FMBA of Russia **Innovative approach to the treatment of squamous cell skin cancer**
13.30 - 13.50	***Kurachenko Yuri Alexandrovich*** RIRAE **Methods of numerical investigation of radiation protection of the proton therapy center**
13.50 - 14.10	***Tskhay Vladimir Sergeevich*** LPI RAS **Neutral networks for event reconstrution in monolithic PET detectors**
14.10 - 14.30	***Gynevskyi Dmitry Alekseevich*** Burnazyan Federal Medical Biophysical Center of the FMBA of Russia **Modeling of space-time distribution of a drug agent in biological tissue**
14.30 - 14.50	***Petriakova Anastasia Valerievna*** Online Saint Petersburg Research Institute of Radiation Hygiene after P.V. Ramzaev **Phantom and patient-based approaches to evaluate image quality in positron emission tomography**
14.50 - 15.00	***Closing of the Conference***

PROGRAMM
International Youth School
«Innovative nuclear physics methods of high-tech medicine»

October 27, Thursday

Pillared Hall LPI,
Moscow, Leninsky prospect 53

09.00 – 13.00	***Excursion at NMRRC***
13.00 – 14.00	***Registration of participants. Coffee.***
	Session 1 - Chairman Grigoryeva M.S.
14.00 – 14.15	***Opening ceremony***
14.15 – 15.00	***Melerzanov Alexander Viktorovich*** *Online* Centre of collective usage "Applied genetics", MIPT **Multidisciplinary education in the healthcare industry**
15.00 – 15.45	***Lipengolts Alexey Andreevich*** N.N. Blokhin NMRCO **Binary technologies of radiation therapy**
15.45 – 16.30	***Aliyev Ramiz Avtandilovich*** NRC "Kurchatov Institute" **New approaches to the creation of targeted radiopharmaceuticals**
16.30 – 17.00	***Coffee-break***
17.00 – 17.45	***Koryakin Sergey Nikolaevich*** A. Tsyb Medical Radiological Research Centre **Combined methods of radiation therapy**
17.45 – 18.30	***Gritsenko Sergey Efimovich*** FSCCRO of FMBA, Dimitrovgrad **Proton radiation therapy as a technological cycle at the FSCCRO of FMBA of Russia**

October 28, Friday

Pillared Hall LPI,
Moscow, Leninsky prospect 53

09.00 – 13.00	***Excursion at the LPI RAS for schoolchildren***
13.00 – 14.00	***Registration of participants. Coffee.***
	Session 2 - Chairman Oginov A.V.
14.00 – 14.15	***Opening remarks***
14.15 – 15.00	***Foitik Anton***
	Online
	Czech Technical University in Prague
	NANOtechnology against Viruses
15.00 – 15.45	***Bugai Alexander Nikolaevich***
	Joint Institute for Nuclear Research, Dubna
	Innovative methods of radiation therapy: radiobiological fundamnetals
15.45 – 16.15	***Coffee-break***
16.15 – 17.00	***Kasatov Dmitry Aleksandrovich***
	Online
	Budker Institute of Nuclear Physics of RAS, Novosibirsk
	Boron neutron capture therapy
17.00 – 17.45	***Kurashvili Yulia Borisovna***
	JSC "Rusatom Overseas"
	Hardware-software expert-analytical solutions for assessing and predicting radiation risks of patients with multiple X-ray radiological examinations
17.45 – 18.00	***Closing of the School***

Poster session
October 25, Tuesday
Offline session
Pillared Hall LPI

1. ***Belikhin Mikhail Alexandrovich***
   LPI RAS
   STUDY OF COMBINED PLASTIC-METAL FIDUCIAL MARKERS FOR PROTON THERAPY
2. ***Bessarabova Kseniia Sergeevna***
   MEPhI
   EVALUATION OF CTV TO PTV MARGIN FOR HEAD AND NECK CANCER WITH DAILY SETUP USING MVCBCT IMAGING
3. ***Boyko Nadezhda Sergeevna***
   MEPhI
   GAGG AS A PERSPECTIVE SCINTILLATOR FOR AN INTRAOPERATIVE GAMMA PROBE AND ITS EXTENTIONS
4. ***Detkov Georgy Viktorovich***
   ITEC LLC
   INNOVATIVE METHODS OF THERAPY USING QUANTUM DOTS
5. ***Galechian Gevorg Yurievich***
   I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University)
   INVESTIGATION OF PHYSICO-CHEMICAL PROPERTIES OF MODIFIED CARBON NANOTUBES AS POTENTIAL DRUG NANOCARRIERS
6. ***Griaznova Olga Yurievna***
   Skoltech / IBCh RAS
   HYBRID FE-AU NANOPARTICLES FOR DUAL MRI/CT IMAGING AND PHOTPTHERMAL THERAPY
7. ***Grigoriev Andrey Andreevich***
   LPI RAS
   RADIOFREQUENCY HEATING OF NANOPARTICLES FOR THERAPEUTIC APPLICATIONS
8. ***Kolmanovich Danil Denisovich***
   Institute for Theoretical and Experimental Biophysics RAS
   POLYMER-COATED BiOCl NANOSHEETS FOR X-RAY IMAGING: COMPREHENSIVE CYTOTOXICITY ANALYSIS

9. ***Kolmanovich Danil Denisovich***
Institute for Theoretical and Experimental Biophysics RAS
RIBOFLAVIN-FUNCTIONALIZED HAFNIUM OXIDE NANOPARTICLES FOR SELECTIVE TARGETED DELIVERY TO TUMOR CELLS

10. ***Kopylova Ekaterina Aleksandrovna***
MSU
EFFECTIVNESS OF RESCANNING IN PROTON THERAPY: A SHORT REVIEW

11. ***Korotkikh Sofya Konstantinovna***
MSU
RADIOSENSITIZATION BY BISMUTH-BASED NANOPARTICLES USING PROTON BEAMS

12. ***Kutlubulatova Irina Aleksandrovna***
MEPhI
MOLECULAR DYNAMIC SIMULATION: INVESTIGATION OF THE INFLUENCE OF POROUS SILICON TARGET STRUCTURE ON THE THRESHOLD AND RATE OF LASER ABLATION

13. ***Matchuk Olga Nikolaevna***
A. Tsyb MRRC
ANTAGONISTIC AND ADDITIVE EFFECTS OF PROTON AND NEUTRON RADIATION ON THE CANCER STEM CELLS OF MCF-7 AND MDA-MB-231

14. ***Popov Anton Leonidovich***
Institute of theoretical and experimental biophysics RAS
SELECTIVE ACTION OF 5-AMINO-2,3-DIHYDROPHTHALAZINE-1,4-DIONE, SODIUM SALT (TAMERON®) UNDER RADIATION-INDUCED OXIDATIVE STRESS

15. ***Popov Anton Leonidovich***
Institute of theoretical and experimental biophysics RAS
RADIOSENSITIZING EFFECT OF BISMUTH NANOPARTICLES IN VITROAFTER PROTON BEAM IRRADIATION

16. ***Popova Nelli Rustamovna***
Institute of theoretical and experimental biophysics RAS
GUANOSINE-5-MONOPHOSPHATE AFFECTS THE X-RAY INDUCED LEVEL OF GENE EXPRESSION

17. ***Rudyi Alexandr Vladimirovich, Ul'yanov Yaroslav Vladimirovich***
MEPhI
OPTICAL PROPERTIES OF SEMICONDUCTOR NANOPARTICLES SYNTHESIZED BY PULSE LASER ABLATION IN A GAS

18. ***Shakhov Pavel Vladimirovich***
MEPhI
CHARACTERIZATION OF COLLOIDAL BORON NANOPARTICLES SYNTHESIZED BY LASER ABLATION IN WATER
19. ***Shemyakov Alexander Evgenevich***
PTC LPI RAS
PROTON THERAPY FACILITY «PROMETHEUS» STATUS AND RESEARCH DIRECTIONS
20. ***Shpakov Konstantin Viktorovich***
LPI RAS
METHODOLOGY OF FAST AUTOMATED DATA PROCESSING OF CHARGED PARTICLE TRACK DETECTORS
21. ***Siksin Viktor Valentinovich***
LPI RAS
CALCULATIONS AND CREATION OF COMPOSITE SHADOW PROTECTION FOR A THERAPEUTIC CHANNEL USING A NEUTRON BEAM
22. ***Sinitsyna Anastasia Pavlovna***
MEPhI
DELIVERY OF NANOPARTICLES INTO THE CELL USING ISOLATED MITOCHONDRIA
23. ***Stepanova Ulyana Alexeevna***
A. Tsyb MRRC
THE AUTOMATED SOFTWARE FOR MULTI-LEAF COLLIMATOR CONFIGURATION FOR HEAVY CHARGED PARTICLES
24. ***Taskaeva Iuliia Sergeevna***
Budker Institute of Nuclear Physics
"CELL DOSIMETER": A NEW APPROACH FOR MEASURING THE SUM OF FAST NEUTRON DOSE AND NITROGEN DOSE FOR BNCT
25. ***Tikhonowski Gleb Valerievich***
MEPhI
LASER-SYNTHESIZED BI NANOPARTICLES FOR MULTIMODAL THERANOSTICS: STUDY OF POLYMORPHIC TRANSFORMATION AND IN VITRO TOXICITY
26. ***Zakharchuk Ivan Aleksandrovich***
Bauman Moscow State University
MgB_4O_7-BASED TISSUE-EQUIVALENT STORAGE PHOSPHORS FOR IMAGE PLATES

27. ***Zamyatina Elizaveta Aleksandrovna***
Institute of Theoretical and Experimental Biophysics of RAS
THERANOSTIC SYSTEM CONTAINING RARE-EARTH NANOPARTICLES IN RADIATION THERAPY: CHARACTERI-ZATION AND CYTOTOXITY ASSESSMENT

28. ***Kurilenkov Yuri Konstantinovich***
LPI RAS
NANOSECOND SOURCE OF α-PARTICLES AND DD NEUTRONS FOR CALIBRATION OF DETECTION SYSTEMS

29. ***Sedov George Evgenevich***
THE DETECTOR AND PREAMPLIFIER OF THE NUCLEAR REACTION PRODUCTS SPECTROMETER FOR LOW ENERGY PROTONS AND LIGHT NUCLEI ACCELERATORS (50 KEV - 1 MEV)

Poster session
October 25, Tuesday
Online session

1. ***Abduvaliev Azizbek Abdukhakim ugli***
Joint institute for nuclear research
SPREAD-OUT BRAGG PEAK FOR PASSIVE AND DYNAMIC IRRADIATION METHOD

2. ***Afanasev Leonid Leonidovich***
N.N. Petrov National Medicine Research Center of oncology
ASSESSMENT OF PATIENT ORGAN DOSES FROM RADIONUCLIDE THERAPY WITH 225AC PSMA

3. ***Aleksandrova Oksana Pavlovna***
Rosatom Technical Academy
RADIOBIOLOGICAL MODELS FOR DOSIMETRIC PLANNING OF RADIOIODINE THERAPY FOR THYROID DISEASES

4. ***Anikina Victoriia Alekseevna***
Institute of Theoretical and Experimental Biophysics of RAS
DEVELOPMENT OF A MODEL OF RADIATION DERMATITIS IN MICE

5. ***Bushmina Elizaveta Alekseevna***
Tomsk Polytechnic University
THE MEDICAL ELECTRON BEAM SHAPING BY 3D-PRINTED PLASTIC COLLIMATOR

6. ***Chernova Olga Sergeevna***
Tomsk Polytechnic University
INVESTIGATION OF 3D-PRINTED SAMPLES FOR PROTON RADIOTHERAPY APPLICATION
7. ***Dontsova Sofya Alexandrovna***
School number 1420, Moscow
COMPUTED TOMOGRAPHY, HISTORY OF CREATION AND DEVELOPMENT
8. ***Fadeev Maxim Nickolaevich***
The TITAN-2 construction holding
VERIFICATION OF THE METHODOLOGY FOR CALCULATING THE BIOLOGICAL PROTECTION OF THE MEDICAL HIGH-ENERGY LINEAR ACCELERATOR BLOCK
9. ***Ismailova Akylai Anarbekovna***
MEPhI
INVESTIGATION OF THE INFLUENCE OF ERRORS IN THE CLINICAL RADIATION DELIVERY SYSTEM ON THE QUALITY OF RADIATION THERAPY DOSIMETRIC PLANS
10. ***Knysh Aleksandr Aleksandrovich***
MEPhI
COMPOSITE MATERIALS BASED ON PEROVSKITE CsPbBr3 NANOCRYSTALS FOR APPLICATION IN X-RAY DIAGNOSTIC STUDIES
11. ***Snigirev Evgeniy Vyacheslavovich***
I.I. Leypunsky Institute of Physics and Power Engineering
COMPLEX SCHEME FOR DOSIMETRIC PLANNING OF RADIONUCLIDE THERAPY IN PATIENTS WITH BONE METASTASIS
12. ***Snigirev Evgeniy Vyacheslavovich***
I.I. Leypunsky Institute of Physics and Power Engineering
DEVELOPMENT OF A DOSIMETRIC TECHNIQUE FOR BRACHYTHERAPY OF LIVER CANCER WITH MICROSPHERES LABELED 90Y
13. ***Snigirev Evgeniy Vyacheslavovich***
I.I. Leypunsky Institute of Physics and Power Engineering
ANTHROPOMORPHOUS MODELS FOR THE PROBLEMS OF RADIATION MONITORING, RADIONUCLIDE DIAGNOSIS AND RADIONUCLIDE THERAPY
14. ***Sorokina Aida Arsenovna***
National Research Tomsk Polytechnic University
DEVELOPMENT AND TESTING OF A PLASTIC BOLUS FOR GAMMA THERAPY

15. ***Troshina Marina Viacheslavovna***
A. Tsyb MRRC
THE FREQUENCY OF CHROMOSOME ABERRATIONS INDUCED IN MAMMALIAN CELLS BY COMBINED EXPOSURE TO CARBON IONS AND PROTONS

16. ***Zelepukin Ivan Vladimirovich***
Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry RAS
X-RAY DIAGNOSTICS WITH PERORALLY DELIVERED BiOCl NANOSHEETS

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International Scientific Conference «Innovative Technologies of Nuclear Medicine and Radiation Diagnostics and Therapy» October 24-26, 2022

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INVITED REPORTS

RADIOPHARMACEUTICALS AND RADIATION TECHNOLOGIES IN THE DIAGNOSIS AND THERAPY OF SOCIALLY SIGNIFICANT DISEASES

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An analysis of the global radiopharmaceuticals market shows not only a stable level of clinical application of this technology, but also builds a very impressive forecast for the percentage increase in the number of diagnostic procedures performed.

Most of these drugs were developed at the Federal Medical Biophysical Center named after Avetik Ignatievich Burnazyan. And the development of new radiopharmaceuticals of this class also continues.

The gallium-68 generator, developed in our Center, is now produced by CJSC Cyclotron and is available for domestic consumers. However, today this generator, for reasons of production organization, does not meet modern GMP requirements in the field of medical devices.

With the participation of the SRC-FMBC this generator was registered complete with an imported synthesis module as a medical product, which for a certain time facilitated the use of gallium-68 preparations in clinics. However, the registration period has expired, and today the issue of creating and organizing the production of a pharmaceutical grade gallium-68 generator is particularly acute.

Among the recent developments of radiopharmaceuticals with gallium, it is worth mentioning our work in the field of folates. Folate receptors overexpressed by cells of a number of malignant tumors, including tumors of the ovaries, cervix, endometrium, lungs, kidneys, and so on, are a promising target for the creation of radiopharmaceuticals.

Folate-based radiopharmaceuticals have been in the zone of increased interest of researchers since it was shown that the level of expression of the folate receptor correlates with the degree of aggressiveness of a number of malignant tumors. The main disadvantage of this type of compounds is their high accumulation in the kidneys, since the only healthy tissue where folate receptor overexpression is observed is the proximal tubules of the kidneys. This fact is the main limiting factor in the active introduction of folate-based radiopharmaceuticals into clinical practice.

Together with Lomonosov Moscow State University, we have synthesized fundamentally new vectors for folate receptors containing a fragment that modifies pharmacokinetics. Experiments in vivo have shown that the new compound not only accumulates less in non-target organs and tissues, which significantly increases the visualization contrast, but also has an accumulation in the tumor 1.5-2 times more compared to the unmodified analogue. This work is ongoing.

Zirconium-89 deserves special attention among PET-emitting radionuclides. This radionuclide, due to its nuclear-physical properties, opens up a separate area of кadionuclide diagnostics - immunoPET. The half-life of zirconium ideally coincides with the period of accumulation of highly specific antibodies in pathological foci, and the low energy of the emitted positrons allows obtaining images with high contrast and resolution. The list of antibodies specific to various pathologies available for labeling with zirconium opens up great prospects for further development of immunoPET. In the world there are more than 30 clinical studies in the active phase of radiopharmaceuticals based on zirconium and various antibodies. In the context of these studies, preclinical studies of a drug intended for long-term monitoring of pathological changes in the musculoskeletal system using positron emission tomography based on zirconium-89 were performed at the SRC-FMBC. Work is planned to continue.

The Center also conducts active research in the field of radiopharmaceuticals based on alpha emitters: radium-223, actinium-225, bismuth-213. In particular, we have begun work with a very promising radionuclide for RNT - thorium-227.

The following areas of radiation technologies are being developed in our center: 1) Development of new radiomodifiers for radiation therapy of malignant neoplasms; 2) Planning and clinical dosimetry of ionizing radiation; 3) Research in the field of proton and neutron therapy.

In our center, research work was carried out and a prototype drug based on gold nanoparticles was obtained, for which computer simulation of the dosimetric characteristics of nanoparticles was carried out when irradiated with photons in the X-ray energy range. The effect of coating nanoparticles with a polyethylene glycol shell on the yield of secondary electrons has been studied, and the optimal sizes of nanoparticles have been found.

The analysis of X-ray dose distributions for various models of tumors contrasted with gold was carried out. The modeling method has shown that the addition of nanoparticles leads to a decrease in the dose load on the normal tissues surrounding the tumor. The results obtained can later be used in the development of a method for dosimetric planning of X-ray therapy, taking into account the nanoradiosensitizer.

We conducted in vitro cytotoxicity studies on 5 cell lines and determined the time of maximum accumulation of gold nanoparticles in tumor cells. The data obtained made it possible to increase the efficiency of irradiation up to 8 times in a model of colorectal cancer cell cultures. The mechanisms of cell death in the presence of gold nanoparticles and irradiation were also studied on this cell line. The study of the radiomodifying effect of gold nanoparticles in vivo was carried out on 2 tumor models, for tumors of various sizes, during irradiation at installations with different spectral composition of X-ray radiation, and various methods of drug administration were studied. In all the cases considered, the “contrasting” of the tumor with the help of nanoparticles enhanced the biological effect of irradiation. For example, intratumoral administration of a drug containing nanoparticles made it possible to increase the average life expectancy by 4 days, and the rate of tumor growth inhibition over 6 days was more than 70% compared to the control tumor, which indicates a high efficacy of the study drug. The formulation is now ready for preclinical testing.

In addition to research in the field of radiobiology, we are also developing areas related to computer methods of dose calculation in the field of clinical dosimetry.

Densely ionizing radiation, such as protons and neutrons, is effectively used in the treatment of radioresistant, inoperable tumors. It should be noted that, due to the complexity and dimensions of accelerators, large proton centers are rather resource-intensive projects. Neutrons proved to be effective in the treatment of a number of radioresistant anoxic and deeply hypoxic tumors: carcinoma of the mammary gland, salivary gland, osteogenic sarcoma. When using fast neutrons, it is possible to create a compact complex for wide distribution. Such a radiotherapy device is currently being developed at the Dukhov All-Russian Research Institute of Aviation Administration based on the NG-24 compact fast neutron generator and is undergoing clinical trials at the Tsyba MRRC, a branch of the National Medical Research Center for Radiology of the Ministry of Health of Russia.

The 3D dosimetric planning system is an important part of the complex for radiotherapy. In our Center, together with AO NIITFA, within the framework of the program for the development of nuclear medicine EOTP of the State Corporation Rosatom, a project is being carried out to develop such a system for radiation therapy with fast neutrons. Since modern requirements for patient safety during treatment are very high, the planning system will be similar in its functionality to the most advanced planning systems for photon radiation therapy in this segment. The program will allow a medical physicist to work with various diagnostic images, perform image segmentation, structure contouring, and for each structure, coefficients will be set that take into account the specifics of interaction with neutron radiation.

To calculate three-dimensional dose distributions, two approaches will be used to choose from: a thin beam model algorithm, and it will also be possible to carry out calculations using the Monte Carlo method. Now the prototype is undergoing primary verification using the NG-24 fast neutron generator. In the future, when a clinical source appears, the system can go through the verification procedure for a specific device.

We conduct research in the field of dosimetry of ionizing radiation not only for promising future areas of radiation therapy, but also deals with topical issues of photon radiation therapy. In the last two decades, new technologies for external beam radiation therapy have been intensively developed: intensity modulated radiation therapy, stereotactic radiosurgery and stereotactic body radiation therapy. Unlike conventional radiotherapy, which operates on fields larger than four square centimeters, for which generally accepted absolute and relative dosimetry procedures have been established, these radiation techniques operate on fields smaller than four square centimeters, the so-called. small fields. Small field dosimetry has a number of technical features: photon spectra different from the case of traditional fields and accuracy of detector positioning, lack of electronic equilibrium, and averaging of detector readings over volume. In addition, placing the detector in a small field can cause noticeable perturbations in the beam. All these features of IAEA low-field dosimetry for the area of static low-field dosimetry with photon energies up to 10 MeV (megaelectronvolts). Therefore, our task was to study the high-energy region of photons up to 20 megaelectronvolts, which are also used in clinical practice.

Using the Monte Carlo simulation method, various characteristics of the photon beam were studied, and correction factors were found for a number of ionization chambers, solid-state detectors, and radiochromic films widely used in practice. It was shown that errors for a number of detectors at a photon energy of 10 megaelectronvolts can reach up to 70%, which is a critical deviation and unacceptable for clinical dosimetry. This work has a direct practical application, since the results obtained by medical physicists can be used in the procedure of dosimetry of small photon fields.

Another promising area in the field of radiotherapy and diagnostics is the use of artificial intelligence.

To date, the field of radiation medicine is one of the most high-tech, however, the use of artificial intelligence dangerous to health requires improvement in the accuracy of the methods used. One of the directions in this area is the transition to adaptive methods of radiation therapy, that is, the adjustment of treatment plans daily before a treatment session. This requires new approaches to planning and diagnostic methods. One possible solution is the use of artificial intelligence and machine irradiation.

This year, we launched a project, together with MEPhI and RFNC VNIIEF, to study the possibility of using artificial intelligence in nuclear medicine. Image contrast and the dose delivered to the patient are critically dependent on the energy spectrum of the beams used. The energy spectrum is also important for characterizing the dosimetric properties of the beam, quality control of therapeutic and diagnostic X-ray equipment.

A new approach to solving this problem may be the use of artificial intelligence: neural networks, machine learning, and so on. Based on the inverse mapping of the output data to the input data in the presence of some a priori information, for example, the typical shape of the spectrum and X-rays, together with a fixed position of the peaks of the characteristic radiation.

At the first stage, we taught the neural network to reconstruct the X-ray spectrum based on the presented dose distribution.

As a training set, we used 5100 spectra reconstructed as described above and the anode materials corresponding to them. 2048 spectra randomly selected from them were used as validation spectra and were not used in training. The accuracy of spectra reconstruction turned out to be close to 100%.

DEVELOPMENT OF NEW TECHNOLOGIES FOR THE DIAGNOSIS AND RADIOTHERAPY OF SOCIALLY SIGNIFICANT DISEASES BY PROTON AND ION BEAMS USING BINARY NUCLEAR PHYSICS METHODS

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The results of the Project of Ministry of science and higher education of RF (2021-2023) are presented. The project is carried out on the base of the LPI RAS and the co-executors of the project – National Medical Research Radiological Centre of Radiology and MEPhI.

The project aim is in solving new fundamental problems and major applied developments in the field of binary nuclear-physics methods for creating new technologies for diagnostics and radiation therapy using proton and ion beams to solve the problem of current interest – the treatment of socially significant diseases.

The work will be carried out using the infrastructure of high-tech Russian-made accelerator facilities. Two proton therapy complexes (PTC) of the Prometheus system with a scanning beam and energy from 30 to 250 (330) MeV: research proton synchrotron (LPI RAS, Protvino branch), medical PTC (Tsyb Medical Radiological Research Centre, Obninsk); charge particle accelerator U-70 (NRC «Kurchatov Institute» – IHEP, Protvino cityr) as well as a neutron radiation source with an energy of 14-15 MeV, located in Tsyb Medical Radiological Research Centre, Obninsk.

The Prometheus PTC is a unique domestic development. It is a compact (outer diameter is 5 m, weight is 15 tons) synchrotron for protons with low energy consumption (up to 100 kW). Currently, such proton synchrotrons of Russian production by ZAO «PROTOM» are being put into operation for use in the treatment of patients in several places in Europe and the United States. Combining rapid acceleration (<300 ms to maximum energy) with an extraction cycle of up to a few seconds, a high duty cycle of the Prometheus PTC is achieved. PTC «Prometheus» can operate in a special proton beam extraction mode, in which single protons are released for each revolution, that allows such facilities to work effectively in tomographic mode.

Research is currently underway in the field of proton therapy for moving tumors. Main studies: Influence of intrafractional motion on dose distributions at various time and amplitude parameters of motion; Quality assurance of proton therapy of moving tumors; Treatment planning for moving targets; Possibilities of rescanning and gating.

Others directions: technologies of combined action of various hadron beams (protons-neutrons, protons-ions, multi-ion therapy), methods of binary nuclear-physical technologies aiming at the development of targeted proton therapy technologies using promising nanoparticles and their-based systems as sensitizers of therapy and active agents for diagnostics.

The latter area involves a significant development of the field of modern nuclear medicine through integration with nanomedicine, which uses unique properties of nanoparticles for cancer diagnosis and therapy. These properties include passive/active delivery, high load capacity, large cross-section of interaction with biological tissues, unique surface properties of nanomaterials, giving them many functional capabilities and combining many capabilities within a single nanoformulation. Experiments on irradiation with protons of various energies of cells with boron 11 nanoparticles obtained by laser ablation methods have shown that the presence of boron nanoparticles leads to increased cell culture death.

The results obtained in the course of the project, will allow us to prepare recommendations on the use of new technologies for diagnostics and therapy based on proton and ion beams for the medical community of the Russian Federation.

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IMPLEMENTATION OF THE FEDERAL PROJECT AND RAMP-UP OF THE "CLOSED CYCLE" ONCOLOGY CENTER TO THE PLANNED CAPACITY

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The implementation of the federal project and ramp-up of the "closed cycle" oncology center to the planned capacity is accomplished through the qualitative interaction of all departments of the Federal Scientific Clinical Center for Medical Radiology and Oncology of FMBA of Russia (FSCCRO of FMBA of Russia, the Center). The most important and responsible component of this process is smooth and well-coordinated work of the proton and photon center, the nuclear medicine center, the clinical hospital and the polyclinic of the Center.

The patient throughput capacity of the proton center in the FSCCRO of FMBA of Russia is 1200 patients per year. The diagnostic service, including the PET/CT center, provides more than 10,000 studies per year. More than 1,200 patients per year are treated in the radionuclide therapy department. Over 11,000 and 124,000 patients receive medical treatment in clinical inpatient hospital and polyclinic, respectively. In 2021, the number of patients treated in radionuclide therapy department according to high tech medical care group 24 (26) was 509, and, during 9 months of 2022 - 407 patients.

The most advanced technologies of radiation therapy support and treatment are applied in the Center along with various planning systems. A system of graphic scheduling of treatment sessions has been created and is successfully operating, enabling effective treatment planning schedule and well-timed delivery of patients. All this makes it possible to ensure high patient throughput capacity of the Center without loss of quality of treatment.

The FSCCRO of FMBA of Russia has accumulated certain experience in proton therapy treatment of more than 1,500 patients with various localizations of the tumor process. In 2021, 831 patients received proton beam therapy. Of these, 20% were diagnosed with prostate cancer, 18% - breast cancer, 17% - bowel cancer, 13% - CNS tumors, 10% - head and neck neoplasms, 7% - tracheal, bronchial and lung neoplasms, 4% - neoplasms of the urinary system, 2% - neoplasms of the esophagus and 2% - bone neoplasms. In all patients after proton beam therapy, with high treatment efficiency, no grade 4 adverse toxic reactions were observed.

In the first half of 2022, 453 patients received proton beam therapy. The gender distribution is as follows: 58.2% - male, 41.8% - female. Pediatric group is 1.3%. The largest group of patients was among 60-74 year olds - 48.1%. The group of working age patients (18-59 year olds) - 41.8%. The distribution of patients by localization has not fundamentally changed compared to 2021, but the number of patients who received proton beam therapy for brain and liver metastatic foci has increased. A group of 27.34% of the total number of patients received proton beam therapy for the treatment of metastatic lesions.

Clinical analysis of treatment outcome of patients undergoing proton beam therapy has not yet been finalized. Further data collection and constant clinical database updating are carried out with the help of a special unique software “Creating and maintaining a database of patients undergoing proton therapy for cancer in the FMBA of Russia system” ("Protoregistry-21"), which acts as a tool for improving cancer treatment.

The main perspective directions of research and clinical activities of the FSCCRO of FMBA of Russia are: the application of modern proton therapy treatment planning systems, including pediatric cancer patient treatment, combined proton-photon therapy, PET planning of proton therapy, the study of hypoxia of tumor formations, the development and introduction into clinical practice of new radiopharmaceuticals for diagnostic purposes, as well as for the treatment of socially significant diseases.

GEANT4 SIMULATION OF ALPHA-PARTICLES PRODUCTION BY PROTONS

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Proton (ion) therapy is becoming more and more popular for the cancer treatment. A number of methods was proposed to enrich the energy deposition in the Bragg peak, in particular to utilize reaction [1]

$$p+{}^{11}B \rightarrow \alpha+{}^{8}Be^{*},\ {}^{12}C^{*} \rightarrow 3\,\alpha + 8.7(9)\ MeV \qquad (1)$$

In this work a new Geant4 model for the reaction (1) is described.

On the base of the new model a simulation of an experiment of proton beam interaction with Boron target was performed. Preliminary results of the simulation are in satisfactory agreement with experimental data.

In addition, the Geant4 predictions for the alpha yield background are discussed. A contribution of different Geant4 physical processes to the yield is considered.

According to the Geant4 cascades 100-200 MeV protons produce remarkable amount of alpha particles (much more in total compared with special model for ${}^{11}B$). It is assumed that the Geant4 nuclear evaporation process is responsible for the result.

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RESEARCH OF THE FLASH EFFECT AT THE PROTON ACCELERATOR OF THE INR RAS

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Recent radiation therapy studies have shown the better sparing of normal cells at dose rates above 40 Gy/s (flash mode), referred as the Flash effect. A series of cell irradiation experiments was carried out at the proton accelerator of the INR RAS at dose rates from conventional values of less than 1 Gy/s up to 10^5 Gy/s in the single-pulse flash (splash) mode [1]. The lines of human colon adenocarcinoma (HT-29), human colon cancer (HCT116) and normal fibroblasts were considered.

The cell response to proton irradiation was performed using flow cytometry and real-time PCR. The expression of genes BAX, PUMA, CDKN1A and p53 was studied using quantitative PCR.

The preliminary results of cytometry show increased flash effect at the level of apoptosis in the splash mode. The PCR analysis shows significant difference in the levels of expression of apoptosis genes and some other important genes in the flash and splash modes of irradiation compared to the conventional mode.

The work is supported by the Russian Science Foundation grant No. 22-25-00211 “Investigation of cell response to the impact of record powerful ultrashort proton pulses.”

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PROTON THERAPY FACILITY «PROMETHEUS» STATUS AND RESEARCH DIRECTIONS

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The proton therapy facility "Prometheus", developed by the Physical Institute. P.N. Lebedev Institute of the Russian Academy of Sciences and manufactured by Protom Ltd. is a high-tech medical device for treatment of cancer patients using the most advanced method of external beam radiation therapy used in clinical practice. Currently, this unit is the most affordable and compact medical facility for radiation therapy with a scanning proton beam. The complex is fully developed, produced and assembled on the territory of the Russian Federation. Unlike its foreign analogues the domestic complex uses the proton synchrotron as its main tool.

The key feature of proton therapy relative to other methods is the accuracy of dose delivery [1-2]. The technology of active scanning by a narrow "pencil" beam is implemented at Prometheus. Beam size in the orthogonal plane is no more than 6 mm for 150 MeV. And the ability to change the energy of the extracted beam ensures millimeter accuracy of beam delivery in each cycle.

Complexes of proton therapy "Prometheus" are focused on installation in any hospitals and oncological clinics, and do not require the construction of separate buildings and specialized infrastructures. The complex provides an opportunity to use proton beams not only for medical practice [3], but also for radiobiological research on various biological objects [4-5].

Since 2021, FIAN specialists start working on the development and implementation of new technologies in the Prometheus proton therapy complex as part of the project "Development of new technologies for the diagnosis and radiation therapy of socially significant diseases with proton and ion beams using binary nuclear physics methods." The key directions of this work is improvement of X-ray system for targets visualization, the implementation of new techniques for moving targets irradiation [6] and proton tomography (the latest experimental development that can make proton therapy even more accurate). The maximum achievable energy of 330 MeV makes it possible to use it for proton tomography of the entire human body [7].

This report presents current data on accelerator researches and developments of Physical-Technical Center and Protom Ltd.

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OPTICAL- AND BIO-IMPEDANCE- BASED RESPIRATION MONITORING SYSTEMS FOR SPOT SCANNING PROTON THERAPY

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External surrogate motion monitoring systems [1] are widely used in radiation therapy for real-time tracking of respiratory-induced intrafractional tumor motion. These ones are non-invasive, non-ionizing, comfortable for a patient, relative low cost and easy to use. Such systems are usually based on optical or electromagnetic principles. These systems monitor of thorax or abdomen surface and form a respiratory signal. The signal is correlated with actual tumor motion using 4DCT. After such correlation, it is possible to irradiate a moving tumor by gating, tracking or DIBH techniques by synchronizing with the respiratory signal. However, correlation between the respiratory signal and actual tumor motion is a difficult task, and the correlation function may be instability during treatment that is disadvantage of all such monitoring systems. Nevertheless, external motion monitoring systems are actively used in conventional photon therapy and transferred into particle therapy.

In this paper, two monitoring systems are considered: optical- and bio-impedance- based. These systems are novel developments and are units of the Prometheus proton therapy complex [2]. Their main technical characteristics are demonstrated: noise, signal-to-noise ratio, accuracy, temporal delay, etc. and compared with the characteristics of existing commercially available and experimental respiratory monitoring systems.

The considered novel systems have good technical characteristics and have the potential to be used in the clinical practice of spot scanning proton therapy for moving tumors.

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LASER-ABLATIVE SYNTHESIS OF PERSPECTIVE NANOMATERIALS FOR RADIOLOGY

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Nanomedicine profits from applying functional nanoparticles (NPs) for the therapy and diagnosis of important diseases such as cancer and others. Depending on their physico-chemical properties NPs can be employed in different tasks of radiology. As an example, strong absorption of X-rays and proton beams makes NPs of elements with high atomic numbers (Au, Bi, etc.) promising for radioimaging and radiotherapies. Furthermore, many inorganic NPs can provide additional functionalities or combine several modalities within one NP for multimodal theranostical modalities.

For successful in vivo applications NPs should be biocompatible, free of any residual contaminations, have uniform size, shape, and surface properties. Conventional methods of colloidal chemistry cannot satisfy these requirements. Pulsed laser ablation in liquids (PLAL) profits from a natural generation of nanoclusters under laser irradiation of a solid target, submerged into an ultrapure liquid, which excludes any toxic contaminations. This method provides access to the synthesis of a variety of appealing nanomaterials for radiology. Here we present our recent results [1,2] on PLAL synthesis of colloidal NPs for radiology.

This work was financially supported by Ministry of Science and Higher Education of Russian Federation (project No 075-15-2021-1347).

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COMPUTATIONAL PHANTOMS FOR NUCLEAR MEDICINE

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An overview of computational anthropomorphic phantoms for research in the field of medical imaging, radiation dosimetry and radiotherapy planning is presented. In nuclear medicine, experimental research methods are limited due to radiation exposure, therefore, great efforts of researchers are directed to the development of a computer simulation method. Computational phantoms are used in simulations as "virtual patients". This new path of research in medicine opens up huge opportunities in the development of high technologies. There are several leading groups in the world that have received licenses for the use of computational phantoms for diagnostics, radiation dosimetry and therapy. The review analyzes the work of almost all major developers of computational phantoms in the world. The development of computational phantoms for nuclear medicine in Russia is also considered [1].

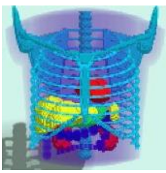
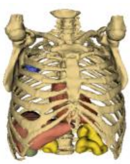
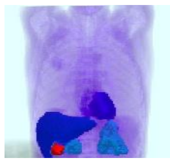

Fig.1. Examples of computational phantoms developed at the Khristianovich Institute of Theoretical and Applied Mechanics.

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CHARGED PARTICLE DETECTION METHOD FOR STUDYING TARGETED TECHNOLOGIES OF PROTON THERAPY USING ADVANCED NANOPARTICLES AT PROTON SYNCHROTRON COMPLEXES OF THE PROMETHEUS SYSTEM

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The work is devoted to the development and testing of silicon detectors and readout electronics for them to measure p+B^{11} reaction cross section at the Prometeus proton accelerator complex. This reaction is being actively studied as a possible tool for a binary technology for the treatment of oncological diseases [1]. The products of being absorbed by the target, they significantly increase the local energy release, relative to the energy release of a single proton. To measure the cross section of this reaction in the energy range corresponding to the Braga peak, the authors created silicon detectors with an effective area of 1 cm^2 with a charge-sensitive preamplifier, readout electronics, and a software package for data analysis. The silicon detector is optimally suited for solving problems of this type, since it simultaneously has sufficient energy resolution and a suficient sensitive surface area. At present, individual elements of the system are being tested at the Prometheus accelerator complex (using the proton-boron reaction) and the HELIS ion accelerator (using the d+d reaction).

At the HELIS facility, the results obtained are consistent with measurements made by a diamond detector [2] (Fig.1). The obtained results testify to the readability of the read path.

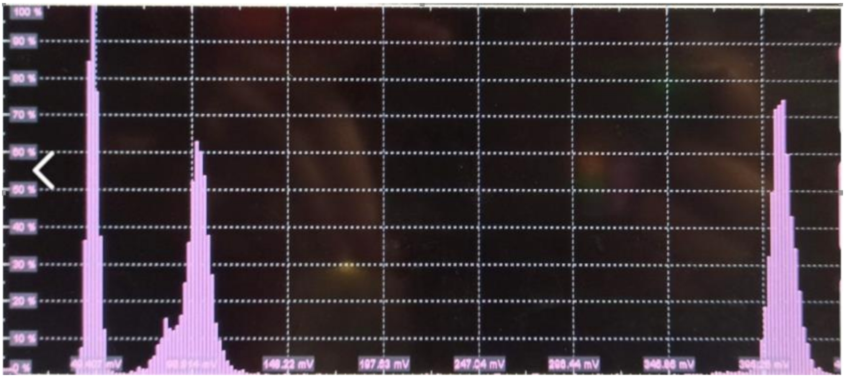

Fig1.Response to charged particles and the spectrum of measured reaction components obtained during testing of the detector at the HELIS facility

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GADOLINIUM-BASED THERANOSTIC AGENTS FOR MRI-MONITORING MESENCHYMAL STEM CELLS

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Recently, human mesenchymal stem cells (hMSc) attracted a great deal of attention as a potential therapeutic agent in the treatment of various socially significant diseases. The use of non-invasive methods for tracking stem cells in the body is very important for analyzing their distribution in tissues and organs, as well as for ensuring control of their lifetime after injection. The use of MSCs as delivery systems for therapeutic agents opens up new possibilities for cancer therapy [1]. It was also shown that bone marrow MSCs delivered to the tumor site and forcibly overexpressing IFN-beta inhibited the growth of malignant cells in vivo. Importantly, this effect required integration of MSCs directly into the tumor and could not be achieved with systemically delivered IFN-beta or IFN-beta produced by MSCs at a site distant from the tumor [2]. Thus, the ability of MSCs to invade tumor tissues and specifically locate in them, affecting tumor cells, suggests their potential use as a delivery vehicle for various anticancer agents, and *in vivo* MSCs imaging methods will be required to control the effectiveness of such therapy.

Here, we continued the research aimed at the creation of a new type of gadolinium-doped cerium oxide nanoparticles ($Ce_{0.8}Gd_{0.2}O_{2-x}$) as an MRI contrast agent for MSCs monitoring and presented a comprehensive study of their cytotoxicity.

We synthesized the citrate-stabilized gadolinium doped ceria ($Ce_{0.8}Gd_{0.2}O_{2-x}$) nanoparticles via hydrothermal method. Cell viability was assessed using MTT assay after 24, 48 and 72 h. The cell growth rate after incubation with nanoparticles was estimated by counting the number of the cells stained with Hoechst 33342. The ratio of live and dead cells in the culture was evaluated using LIVE/DEAD BacLight Bacterial Viability Kit (Invitrogen). The level of intracellular reactive oxygen species (ROS) was determined using dichlorofluorescein (DCF).

$Ce_{0.8}Gd_{0.2}O_{2-x}$ nanoparticles have not shown any cytotoxic effects in all the range of concentrations (0.3–5 mg/mL), these results corroborate previously reported negligible cytotoxicity of citrate-stabilized ceria nanoparticles. The introduction of low concentrations (0.3–1.25 mg/mL) of the gadolinium-doped cerium oxide nanoparticles expectedly did not result in an increase in the number of dead cells upon 24, 48 or 72 h of cultivation. No reliable effect of citrate-stabilized nanoparticles on the intracellular ROS level was observed.

Thus, $Ce_{0.8}Gd_{0.2}O_{2-x}$ nanoparticles can be considered as a safe theranostic agent for monitoring human MSCs.

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LITHIUM NEUTRON CAPTURE THERAPY AS A NEW STRATEGY FOR CANCER TREATMENT

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Boron neutron capture therapy is a form of binary radiation therapy based on the ability of nonradioactive ^{10}B isotope accumulated in the tumor tissue to capture a thermal neutron, resulting in the formation of an α-particle and a lithium nucleus, the path length of which is comparable to the cell size and makes it possible to selectively destroy malignant tumor cells [1].

One of the main issues in the development of boron delivery drugs is their tumor-specific targeting. Thus the implementation of ^{6}Li, which also has high thermal neutron capture cross section, instead of ^{10}B may be perspective alternative for neutron capture therapy of cancer. The advantage of LiNCT is the absence of γ-rays emitted in BNCT which may affect surrounding healthy cells. The Li neutron capture reaction results in α-particle and hydrogen isotope ^{3}H with a higher yield of ^{6}Li(n,α)^{3}H nuclear reaction. Moreover, ^{6}Li delivery agents can be synthetized in Russia due to existing technologies. Lithium carbonate which was used in our study is well investigated as the drug for treatment of mental deceases. There is a hypothesis according to which lithium replaces sodium and changes the concentration of intracellular calcium, so it can be suggested that lithium will be retained in cells [2].

Li uptake by tumor cells and its biodistribution *in vivo* is practically unexplored but plays a great role in possibility of application of LiNCT. The aim of this study was to determine the Li accumulation in tumor, blood and organs of interest and to evaluate acute Li nephrotoxicity after single doses administration in mice with B16 melanoma xenografts.

Lithium carbonate at doses of 300 (Li-300) and 400 (Li-400) mg/kg was introduced *per os*. Lithium concentration in tumor, blood, kidney, brain and skin was measured by the inductively coupled plasma atomic emission spectroscopy (ICP-AES) method 15 min, 30min, 90 min, 180 min и 7 days after drug administration. The tumor/blood lithium concentration ratio was highest at 30 minutes' time point for both groups and was 1.86 for Li-300 group and 2.01 for Li-400 group. The maximum tumor/surrounding normal tissue lithium concentration ratio ranged from 1.74 to 2.34. 7 days after lithium carbonate administration Li concentration in all organs of interest did not differ from the background in control group, which indicates the complete elimination of lithium. The absolute maximum uptake of lithium among all the studied organs was observed in the kidneys. Nevertheless, pathomorphological study and PAS reaction of kidney showed that a single administration of lithium carbonate at doses of 300 or 400 mg/kg does not lead to any acute kidney disorder.

Conclusion: ^{6}Li can be an alternative to ^{10}B in neutron capture reaction. Our study revealed safety of implementation of lithium carbonate and showed good tumor/blood and tumor/ surrounding normal tissue ratios. Further experiments are needed to determine the effect of LiNCT.

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FEASIBILITY OF TIME-OF-FLIGHT PET/PROMPT GAMMA IMAGING BASED ON SILICON PHOTOMULTIPLIERS FOR IN-BEAM HADRON THERAPY MONITORING

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Silicon photomultipliers (SiPMs) were developed in Russia in the 1990s–2000s and worldwide recognized as a new generation of photon detectors with a unique photon-number and time-of-flight (TOF) resolution [1]. Since the 2010s, the SiPMs provided a breakthrough in performance of scintillation and Cherenkov detectors for high energy physics (calorimeters in DESY, T2K, CERN) and nuclear medicine (TOF PET scanners by General Electric, Philips, Siemens). Promising SiPM application is also anticipated to be an in-beam in vivo monitoring and verification of an absorbed dose range in the hadron/proton therapy [2].

A new approach combining modalities of well-established TOF PET technology for intra-spill (and beam-off) acquisition of 511 KeV gammas with an in-spill TOF prompt gamma imaging (PGI) to utilize excellent time resolution of the SiPMs has been proposed in 2016 [3].

In contrast with a prompt gamma timing (PGT) which relies on a mean (center of gravity) of the TOF distribution, the TOF PGI approach is based on a full analytical model of TOF PGI spatial and temporal distributions in an array of detectors as shown in Fig.1. The model provides a closed-form expression for the absorbed dose profile reconstruction, and its correctness has been validated by the analytical modeling. Let us note, the TOF PGI based on SiPMs with Cherenkov radiators has recently been re-proposed by our colleagues [4].

We expect that TOF PGI is compatible with TOF PET with the same detectors and acquisition electronics. Certain mismatches of the combined detector requirements (1–8 MeV of prompt gammas vs. 511 KeV of annihilation ones) as well as other challenges are estimated to be resolvable due to modern advances in fast SiPM timing techniques including an estimation of the ultimate time resolution of SiPM-based scintillation detectors [5]. Overall, we anticipate high efficiency and accuracy of the bimodal TOF PET/PGI system.

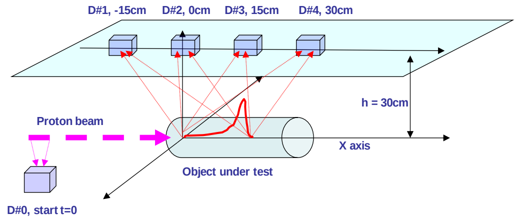

Fig.1. TOF PGI formation by a proton beam in an object under test (patient tissue) along X-axis and its detection by SiPM-based scintillation detectors D#0 – D#4.

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CONSTRUCTION OF A MATHEMATICAL MODEL OF THE CHANNEL OF THE CYCLIC ACCELERATOR R7-M IN THE PHYTS SOFTWARE PACKAGE FOR BORON-NEUTRON CAPTURE THERAPY

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Currently, it is impossible to conduct modern large-scale experiments without modeling physical processes without the use of software systems. For conducting various mathematical calculations, there are such software packages as: MCU, PHITS, GEANT, MCNP. For mathematical modeling of boron-neutron capture therapy-related processes, the PHITS software package is most preferable [1].

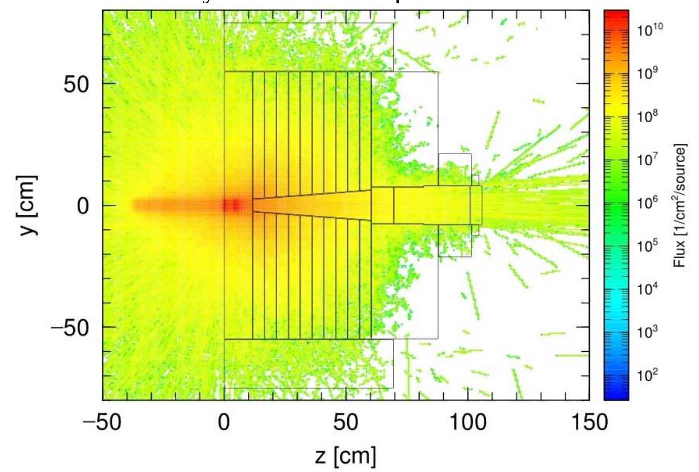
Boron neutron capture therapy (BNCT) is a form of bi-nuclear radiation therapy, which uses the uniquely high ability of the non-radioactive boron-10 nucleus to absorb a thermal neutron. The cross section of the neutron absorption reaction, described as $B^{10}(n,\alpha)Li^{7}$, is 3835 barns for thermal neutrons and decreases inversely proportional to the increase in the neutron velocity.

To obtain the necessary neutron flux for the BNCT procedure, two neutron sources are mainly used: nuclear reactors and accelerators of various types. However, charged particle accelerators are the most preferred in the field of BNCT. Interactions of various charged particles with neutron-generating targets are used to form the neutron flux density. The most common reactions are the interaction of protons with the lithium target $Li^{7}(p,n)Be^{7}$ and the interaction of deuterons with the beryllium target $Be^{9}(d,n)Be^{10}$. The neutron flux density required by the energy range for conducting BNCT lies in the range from 0.5 eV to 10 keV [2].

Tomsk Polytechnic University has a cyclic accelerator that can be used for conducting BNCT procedures. The initial characteristics of the neutron flux density at the outlet of the channel are

6.5-10^9 n/steradian·mkA·s and an energy of 4-11.8 MeV [3]. Using various moderator materials, such as: Fluental, MgF_2, AlF_3, D_2O, CaF_2, it is possible to achieve the necessary characteristics of the neutron beam for conducting BNCT.

In this paper, it is assumed that mathematical modeling is carried out in the PHITS software package to compare data between physical experiments and program calculations. Figure 1 shows the distribution of the neutron flux in the experimental channel of the cyclic accelerator R7-M during mathematical modeling. Then, the PHITS software package needs to perform calculations with various moderator materials in order to select one material that will form the most suitable energy spectrum of the neutron flux density for the BNCT procedure.



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OPTIMIZATION OF THE VALIDATION PROCEDURE FOR THE DOSIMETRY MODEL OF PROTON PENCIL BEAM SCANNING

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New technologies are constantly being introduced in various fields, including medicine. Specialists face the problem of commissioning new therapeutic devices and methods of treatment. One such example is the proton therapy system at the FSBI FSCCRO of the FMBA of Russia [1].

The validation of dosimetry model (VDM) of a thin pencil beam scanning (PBS) is a primary tool of quality assurance (QA) and a very important stage of commissioning of the proton therapy (PT) that emphasizes its practical significance. Its development is an urgent problem that arises for specialists in the field of medical physics during the first commissioning, since there are no strict and regulatory requirements for VDM of PT systems [2]. The aim of the work is to optimize VDM PBS during the commissioning of the treatment planning system (TPS). VDM PBS was carried out as part of the treatment room commissioning at the proton center of the FSBI FSCCRO of the FMBA of Russia according to the recommendations of the TPS vendors [3].

When first put into clinical operation, this process took a considerable time due to the ambiguity of the wording of the recommended tests, excessive requirements, or the inability to reproduce the conditions of dosimetry tests on this configuration of the PBS delivery system. With the repeated experience of putting a new TPS into clinical operation, it became necessary to optimize the procedure of VDM PBS.

In order to carry out the VDM PBS, it was necessary to calculate the dose distribution under given conditions [4]. But if, at the first commissioning of the TPS, the distribution of several calculation plans was modeled using a verifiable PBS model, then with repeated experience with a new TPS, the conditions of dosimetry tests were modeled in one universal calculation plan. In the process of obtaining dosimetry data, the following dosimetry equipment for PT was used to compare with the data calculated by the TPS: Lynx (IBA Dosimetry), Zebra (IBA Dosimetry) and Giraffe (IBA Dosimetry).

The result of the work is the optimization of the VDM PBS procedure, which has led to cutting time of a new TPS commissioning from 6 months to 3 months with the preservation of the quality and safety of delivery PBS [5].

Thus, it is not enough for VDM PBS to calculate several localizations and measure dosimetry plans, the so-called end-to-end test, because this test will be ineffective and not indicative due to the small number of estimated parameters. For PT, a more detailed testing of the PBS delivery system is necessary, but with the balance of time spent on this type of dosimetry work. Therefore, the optimization of VDM PBS is of great importance at the stage of commissioning of clinical irradiating equipment and new TPS.

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NEURAL NETWORKS FOR EVENT RECONSTRUTION IN MONOLITHIC PET DETECTORS

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Recent developments in Positron emission tomography (PET) show a gradual shift towards monolithic systems. The key characteristic of monolithic PET detectors is that monolithic systems use one, or a relatively small number of large scintillator crystals coupled with arrays of silicon photomultipliers, instead of large amounts (usually thousands) of smaller crystals used by classical PET systems. Such approach allows for significant cost reduction, as less mechanical processing is required for a small number of larger crystals. Monolithic systems also allow the use of special reconstruction algorithms that allow higher precision than classic systems. This work demonstrates the high precision attainable when using neural networks to reconstruct the point of interaction of 511 KeV gamma in monolithic scintillator PET detectors.

PHANTOM AND PATIENT BASED APPROACHES TO EVALUATE IMAGE QUALITY IN POSITRON EMISSION TOMOGRAPHY

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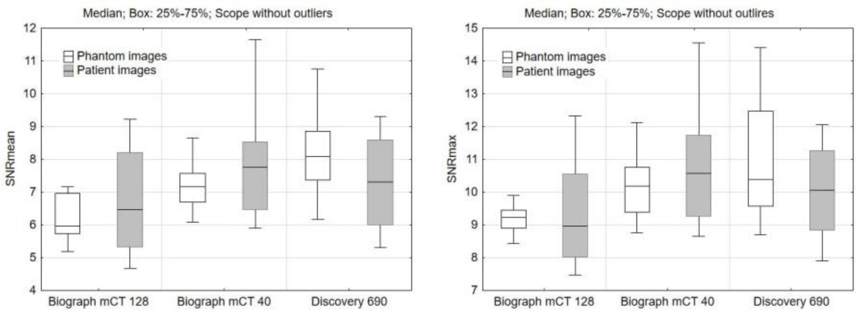
Image quality in positron emission tomography (PET) is one of the main characteristics to achieve the high quality and accuracy of the PET diagnostics. Comparison of the image quality gives an opportunity to compare and optimize the scanning and reconstruction protocols. The aim of this study was to compare two approaches of the evaluation of PET image quality by quantitative analysis: based on phantom images [1] or based on patient images [2].

NEMA IEC Body phantom with spheres with different diameters simulates the patient body with variety of lesions [1]. Phantom was filled with an aqueous solution of ^{18}F-FDG, and then was scanned on clinical protocol. 45 images (15 images on each scanner) of patients without liver pathologies who underwent the whole-body PET/CT with ^{18}F-FDG were obtained retrospectively.

Both phantom and patient PET images were obtained on three PET/CT scanners: Siemens Biograph mCT 128, Siemens Biograph mCT 40, GE Discovery 690.

Signal-to-noise ratio (SNR) was chosen as the parameter for quantitative analysis of phantom and patient images [3]. SNR was defined as a ratio between mean or maximum activity concentration and standard deviation measured in region of interest in phantom background and patient liver. Mean and maximum activity concentration on phantom images were calculated considering the decay.

SNR values measured on phantom and patient images for each PET/CT scanner are performed on Figure 1. Significantly differences between SNR values of phantom images and patient images was not established (Mann-Whitney U test, $p>0.05$).



(a) (b)

Fig.1. Distributions of SNRmean (a) and SNRmax (b) values of phantom images versus values of patient images

The results were demonstrated the consistency of approach based on evaluation of the phantom image quality and approach based on evaluation of the patient image quality. Both approaches are applicable to compare image quality in terms of comparison and optimization of the scanning and reconstruction protocols.

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MULTIDISCIPLINARY EDUCATION FOR THE HEALTHCARE INDUSTRY

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Major challenges for the development of modern healthcare in Russia are relatively low investment - 121 place in the World (WHO) [1] and rigid system of training for physicians and other healthcare professional towards the scientific and digital aspects. The underestimated role of researchers and technical personnel leads to the development and implementation of digital tools slowing down.

Despite of the good understanding of the needed measures for development of the healthcare basic issues are not addressed by the Governmental programs. The major issue is a lack of multidisciplinary programs facilitating integration of novel biomedical digital technologies into clinical practice. Estimation of nationwide needs for medical physicists falls far behind ones announced by China and the USA. Same situation with other digital healthcare (non MD) professions.[2]

The other issue is implementation of Artificial Intelligence (AI) tools into modern health care. Digital transformation of healthcare is impossible without properly trained in these regards medical personnel. There are two parts of this complex problem: lack of common language between researchers and physicians and a full responsibility of physicians for the final decision based on the AI based Physicians Decision Making Support Systems.

Ethical and legal issues of the AI based systems are well observed by a lot of researchers.[3] Major problem of trust and responsibility is yet to be solved.

In order to solve the problem of lack of common language for physicians and researchers the pilot project of joint education of researcher and physicians for digital healthcare was implemented by MIPT and

Sechenov University. [4,5] The project allowed future physician to obtain quality education in technical science and for researchers - basic medical disciplines. Extrapolation of this pilot with a simultaneous change of legislation including professional standards change and increasing of financial support will irradiate the barrier on digital transformation of healthcare.

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PROTON RADIATION THERAPY AS A TECHNOLOGICAL CYCLE AT THE FSCCRO OF FMBA OF RUSSIA

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The implementation of the technological cycle of proton beam therapy is accomplished through the interaction of all departments of the Federal Scientific Clinical Center for Medical Radiology and Oncology of FMBA of Russia (FSCCRO of FMBA of Russia). The most important and responsible component of this process is smooth and well-coordinated work of the proton and photon center, as well as compliance with the quality assurance program during radiation therapy.

The FSCCRO of FMBA of Russia has accumulated certain experience in proton therapy treatment of more than 1,500 patients with various localizations of the tumor process.

The main element of the proton center is the C235-V3 cyclotron manufactured by IBA, which generates a beam with a constant energy of 235 MeV. On the degrader plates, protons are decelerated to the required energy. The energy of the beam supplied for the clinical use in treatment rooms is in the range of 100-226.1 MeV.

Two full gantry treatment rooms work in two shifts. They implement the IMPT technology using pencil beam scanning (PBS) method.

The most advanced technologies of radiation therapy support are applied in the FSCCRO of FMBA of Russia along with various planning systems. These tools can compare irradiation plans, as well as choose the optimal one for each patient.

A system of graphic scheduling of treatment sessions has been created and is successfully operating, enabling effective treatment planning scheduling and well-timed delivery of patients.

All this makes it possible to ensure high patient throughput capacity of the FSCCRO of FMBA of Russia without loss of quality of treatment and the optimization of radiation therapy treatment modes.

NANOTECHNOLOGY AGAINST VIRUSES

Foitik Anton
Czech Technical University in Prague

Target was against HIV virus. Virus is very small, much less (1000 times) then bacteria or mould. Virus could be very clever conceal and hidden; we must also use such a clever unusually smart technology to attack him.

I have spoken about the way, how we proceeded. Nanotechnology is not regularly biological tool.

We must fine the way, how to use nanotechnology against the viruses, with success, effective, and possible. We have done some tests at "Czech Laboratory against HIV virus", with very positive results, bout 20% effectivities. Try to tie up on this way, as possible, for to defense and for to protection. In this way we used Nano fibers, fibers with big surface and surface modifications with biological actives molecules, against the viruses. How to do, explain technology and possible practical applications for the biological using.

We working not for obtain vaccine; we try to get possibilities for defense and protection against virus at the way, using Nanotechnology.

Defense and protection, that's our way. I like bring a small drop, for this afford. Maybe should be useful.

Nanotechnology is getting still more attention and is becoming emerging topic of recent days. Its biological and medical approaches and applications are opening novel, unpredicted and efficient ways of solving health issues that is why the extraordinary field of bio nanotechnology is shaping into one of the leading sciences of the 21st century…

Goal of the project is to functionalize $Fe3O4$ magnetic nanoparticles, which according to chemical groups attached at the surface, are able to bond to special pathogens (bacteria or virus) and being easily manipulated by magnetic field, they can be removed from the system taking the pathogens with them as well.

Nanoparticles are produced by 'wet' chemical way under special conditions, (last time also using the laser technology). Final product is tens of nanometers in diameter and possesses special superparamagnetic properties, which give it ability to be manipulated (with magnetic forces) while working in complex biological systems such as human body. Shape and size of nanoparticles are evaluated using AFM, magnetic properties measured by Mossbauer Spectroscopy and Superconducting Quantum Interference Device (SQUID). Surface of the particles is stabilized and treated, so that they maintain their unique properties and remain stable and separated. Certain chemical groups, proteins or residues are attached onto the surface to functionalize it. Particles are then ready to play a key role in recognition of the pathogens bonding to the surface of nanoparticles and following applied magnetic field to get out of the system.

Magnetic nanoparticles offer many attractive possibilities in the fields of biology and medicine.

The authors declare no conflict of interest.

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HARDWARE-SOFTWARE EXPERT-ANALYTICAL SOLUTIONS FOR ASSESSING AND PREDICTING RADIATION RISKS OF PATIENTS WITH MULTIPLE X-RAY RADIOLOGICAL EXAMINATIONS

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The use of ionizing radiation (IR) in medicine, especially with multiple x-ray studies (XRS), may lead to undesirable consequences for the health of patients, including the socalled stochastic or probabilis-tic effects. Number of multicenter studies have shown an increase in the risk of oncological morbidity for individuals who underwent repeated CT examinations in childhood. These and other similar data have caused increased attention to the procedures of prescribing, justi-fying and performing X-ray radiological imaging, especially multiple studies.

As a result, at the international and national levels, the regulations and requirements for assessing the risk of possible stochastic ef-fects and informing the patient when planning and justifying a medi-cal XRS were clearly defined (Requirement 36, paragraph 3.150 of the IAEA International Basic Safety Standards; international standards for radiation protection by UNSCEAR, ICRP).

Therefore, one of the directions of the implementation of the state policy of the Russian Federation in the field of ensuring nuclear and radiation safety is "the development and application of tools and methods for assessing radiation risks when using radiation technologies for medical purposes, nuclear medicine and radiopharmaceuticals, as well as in visual ionizing radiation” (section III, paragraph 13a Decree of the President of the Russian Federation of October 13, 2018 “On approval of the Fundamentals of State Policy in the field of ensur-ing nuclear and radiation safety for the period up to 2025 and beyond”) .

With the support of the State Enterprise Rosatom, collaboration of the Russian Scientific Commission on Radiation Protection (RSCRP) and the National Radiation and Epidemiological Register of the Ministry of Health of the Russian Federation, the Information System (IS) was finalized and tested for assessing, predicting and registering the in-di-vidual risk of development of unfavorable stochastic consequences of medical exposure during multiple XRS in the interactive mode; additional function of automatic compilation of an analytical report of effective doses.

There are currently no analogues in Russia and abroad, which determines the high export potential and the validity of including IP in the comprehensive proposal of the Rosatom State Corporation for non-energy nuclear technologies (RIVER-MED).

The basis of the IS includes validated methods for assessing medical stochastic risks in multiple RRIs, approved by the Russian Federal Service for Supervision of Consumer Rights Protection and Human Welfare in the "Guidelines" (MR 2.6.1.0098-15 /2.6.1.0215-20) and "Guidelines" (MUK 2.6 .7.3652-20); as well as international standards of the NCDR, IAEA and ICRP.

Pilot sites for refinement, implementation, as well as technical and clinical trials, trial operation, validation were determined by the State Budgetary Institution of Health "Scientific and Practical Clinical Center for Diagnostics and Telemedicine Technologies of the Department of Health of the City of Moscow" and a number of clinics in Moscow.

Methodological recommendations "The system for assessing the personal radiation risks of patient exposure when justifying the appointment of x-ray and radionuclide studies" based on the results of the implementation of the IS, were developed and approved by the Department of Health of Moscow; MR-No. 122; Application of analytical information systems, section 1; Best practices of radiation and instrumental diagnostics; Moscow 2020; ISSN 2618-7124.

The main purpose of the IS is to support the implementation of the “principle of validity”: information on the accumulated radiation medical risk is used by both the attending physician and the radiologist to make a decision on conducting subsequent examinations of the patient with additional radiation exposure and processing in accordance with the standards and requirements in the field of health protection and radiation safety (RS) of citizens of the Russian Federation of mandatory medical documents: “Informed voluntary consent” or “Motivated refusal”.

Integration of IS as a component with the Unified State Health Information System (USHIS) both in the Russian Federation and abroad will allow:

• implemention of the requirements of national and interna-tional norms of health protection and the Republic of Belarus;

• providing the support for making medical decisions when justifying the appointment of medical diagnostic exposure, including repeated; optimization of research protocols and choice of imaging method;

• creation of the unified database of personalized radiation risks of medical exposure at the national level.

POSTER REPORTS

SPREAD-OUT BRAGG PEAK FOR PASSIVE AND DYNAMIC IRRADIATION METHOD

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Proton beams are more effective than photons in cancer treatment because their dose peaks at the end of the depth range ("Bragg peak") and quickly decreases to a minimum outside the range; this feature allows avoiding radiation dose to important healthy tissue [1]. However, the sharpness of the Bragg peak for a mono-energetic proton beam means that a very high dose can be obtained over a depth range of only a few millimeters. To extend the treatment depth range, a "Spread-out Bragg peak" (SOBP) is created by slightly varying the energy of the incident proton beam, using appropriately weighted different energies to produce a flat dose plateu. (Such a single dose that covers the tumor is required.) There is a suitable passive and dynamic irradiation method for generating SOBP [2-3]. This work demenstrates the possibility of obtaining SOBP for passive and dynamic method using FLUKA [4] and Geant4 [5] Monte Carlo codes. Corrected weight factor can be useful in theoretical calculations and may be important in determining weights for proton beams used in cancer treatment.

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DEVELOPMENT OF A MODEL OF RADIATION DERMATITIS IN MICE

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To increase the effectiveness of therapy of cancer, depending on the type and localization of the tumor, different types of ionizing radiation (X-ray and gamma radiation, protons, etc.) are used. In the last decade, radiation therapy with heavy ions, including protons, has become a priority due to their high LPE, low penetrating power and the ability to direct the maximum radiation energy directly into the tumor based on the Bragg peak, which minimizes damage to healthy tissues and organs. However, regardless of the type of radiation used, 95% of patients develop a side effect in the form of radiation dermatitis [1].

Thus, a global problem of modern radiation biomedicine is finding and developing of new effective and specific methods for prevention and treatment of radiation dermatitis. At the same time, for drugs analysis, it is necessary to develop and obtain an experimental model of radiation dermatitis in vivo. Therefore, the purpose of this study is developing a model of radiation dermatitis in vivo in mice.

A model of radiation dermatitis induced by ionizing radiation (protons) was obtained on male white outbred mice of the SHK mice (30-35 g), which were kept in polycarbonate cages of 5 mice in the vivarium of the ITEB RAS. In the experiments, ethical guidelines for working with laboratory animals were followed [2]. Irradiation of animals was carried out in the proton therapy complex "Prometheus" of the LPI Physico-technical Centre (Protvino), which is a high-tech medical device of Russian production for the treatment of tumors in cancer patients using the remote radiation therapy. The basis of this complex is a compact proton synchrotron capable of accelerating protons in the energy range from 30 to 330 MeV [3].

To obtain a model of radiation dermatitis, a series of experiments were conducted, on the basis of which optimal conditions were selected. The estimated dose on the surface of the animal was 50 Gy. The coverage area (95%) with given dose is 15 x 15 mm. The beam energy at the output of the accelerator is 88.5 MeV. The irradiation is pulsed, with a cycle of 2 seconds. The proposed technique makes it possible to obtain radiation-induced skin damages and determine the duration of periods of radiation dermatitis in mice. In addition, such a model allows for a comparative analysis of periods of radiation damage to the skin or a decrease in the severity of damage in various experimental groups and, therefore, can be used to evaluate the effectiveness of therapeutic agents intended for the prevention and treatment of radiation-induced skin damage.

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EVALUATION OF CTV TO PTV MARGIN FOR HEAD AND NECK CANCER WITH DAILY SETUP USING MV-CBCT IMAGING

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The definition of CTV to PTV margin [1] remains an urgent issue in each RT department. According to the approach [2], margin value is affected by the movement of the target, the inaccuracy of structures delineation and patient positioning, the usage of fixation devices, the imaging system and the accuracy of RTT [3]. That is why it is necessary to analyze the CTV to PTV margin for different groups of patients: with tumors of a specific localization, with a certain type of fixing devices, as well as the technique and frequency of visualization.

In the tunnel accelerator Halcyon type 2 before each fraction the patient is fixed in a thermoplastic mask up to shoulders, set up with markers, after which MV-CBCT is applied by reconstruction from a portal device. The quality of obtained images allows you to adjust them with the planning CT image. An online protocol is implemented, so positioning correction is performed every fraction.

Using the Offline Review section of the Eclipse treatment planning system, an additional adjustment was performed for 35 patients with head and neck tumors treated with Halcyon (30-35 fractions). The adjustment was carried out according to bone structures: the base of the cranium, the mandible and C1-C3 vertebrae.

Based on the results of additional adjustment, the difference between the values of the displacements obtained online and offline was found. Based on these values, the CTV to PTV margin, which takes into account daily imaging, was calculated (table 1).

Table 1. CTV to PTV margin values calculated according to Offline Review data.

	Vrt [cm]	Lng [cm]	Lat [cm]
CTV-PTV_{diff}	0,24	0,21	0,25

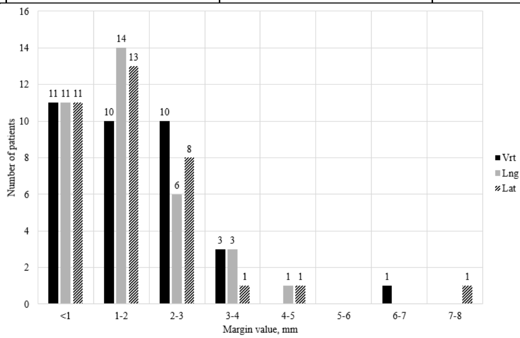

Fig. 1. Histogram of individual CTV-PTV margins for 35 patients with head and neck cancer during offline offset analysis

On the histogram of individual CTV to PTV margins (fig. 1), upward variations from 5 mm margin used in unit were registered for two patients. This fact shows the need for routine practice of working in Offline Review to identify problematic cases. The resulting margins are small, but we do not consider the reduction to 2.5 mm justified, since there are additional errors that were not taken into account in this work (intrafraction movement and equipment parameters).

In prospect, we plan to estimate the displacement of the vertebrae, starting from C4, relative to the base of the cranium and calculate separately margins for the neck area.

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GAGG AS A PERSPECTIVE SCINTILLATOR FOR AN INTRAOPERATIVE GAMMA PROBE AND ITS EXTENTIONS

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Intraoperative gamma probe [1] is a powerful device for sentinel nodes search and diagnostics in breast cancer. The detector for the gamma probe should meet specific requirements. It should be small enough to fit to the incision, possess high gamma-ray detection efficiency and energy resolution, be easy and safe in use. An example of gamma probe by Neomed company is present at figure 1.

Fig. 1. Gamma probe by Neomed company.

The detector based on recently developed scintillator GAGG ($Gd_3Al_2Ga_3O_{12}$) coupled to silicon photomultiplier (SiPM) meets the requirements listed above. The main characteristics of GAGG can be found in table 1. GAGG appears a good alternative to LYSO due to high light yield and absence of self-radioactivity.

The SiPMs are the silicon photomultipliers that has very small size and low power supply voltage and compete with classical PMTs by amplification, efficiency and noise level. They appear the best solution for such miniature devices [2].

The Cs-137 spectrum obtained with the GAGG scintillator of 3x3x10 mm^3 by OJSC "Fomos Materials" (Moscow) coupled to SiPM SensL FB30020 is present at figure 2. The peak at the beginning of scale is the 32 keV from Ba-137. The measured energy resolution @662 keV is 8.5%.

	LYSO	LaBr3(Ce)	GAGG
Z_{eff}	63	45	51
Density, g/cm^3	7.1	5.1	6.6
Light yield, photons/keV	32	65	38
Luminescence decay time, ns	41	16	80
Energy resolution @662 keV, %	7	3	5
Hygroscopicity	-	+	-
Self-radioactivity	+	+	-

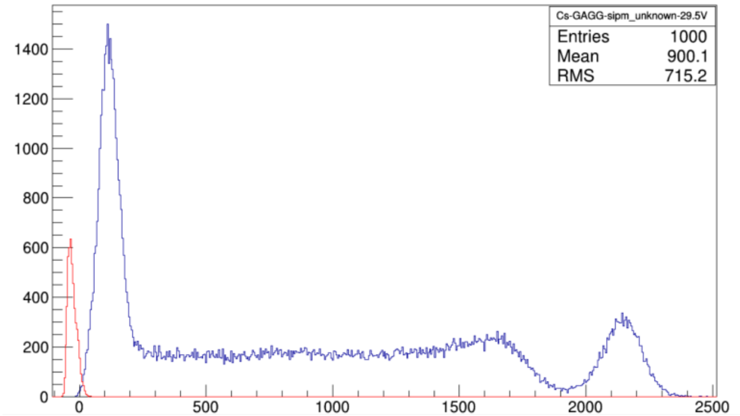

Fig. 2. Measured spectrum of Cs-137.

This detector has wide range of applications in medical diagnostics and imaging systems. One possible application could be the extension of well-known gamma probe to the device for endoscopic search of tumors located in deep seated biological tissues.

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THE MEDICAL ELECTRON BEAM SHAPING BY 3D-PRINTED PLASTIC COLLIMATOR

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Cancer of the nasal mucosa and paranasal sinuses accounts for 3% of all cases of head and neck tumors. Electron beam therapy allows achieving good therapeutic results in the treatment of locally distributed malignant tumors of the nose and sinuses [1, 2].

To improve the procedure of electron beam therapy, it is necessary to use additional means of shaping an electron beam. In this paper, it is proposed to use the 3D-printing method for the manufacture of such shaping devices. 3D-printing is the process of creating three-dimensional products from digital models with high precision. In addition, the speed of manufacturing products on 3D-printers is one of the key qualities of this method. This approach is effectively used in radiotherapy applications [3, 4].

3D-printing technologies can improve the process of radiation therapy planning, facilitate immobilization of patients, create a more accurate radiation field, or compensate for patient radiation dose. A special role is given to collimators made by additive technologies, which are then used to form radiation dose fields in radiotherapy. The existing approaches of creation of metal collimators (cutting and melting) have a number of the following limitations: expensive equipment, availability of specially trained staff and facilities [5].

Therefore, in this work, a 3D-printing method was chosen for the manufacture of a modular collimator for the tumors of the nose and sinuses.

As part of the study, it was shown that the developed design of the collimator is universal and allows the formation of four different configurations of an electron beam field. The ease of use and manufacture of a plastic collimator will allow it to become a popular device in electron beam therapy.

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INVESTIGATION OF 3D-PRINTED SAMPLES FOR PROTON RADIOTHERAPY APPLICATION

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The radiation therapy is one of the main approaches for oncological diseases treatment. It is based the destruction of tumor tissues by ionizing radiation. One of the effective methods is proton beam therapy. The planning of therapeutic procedures using tissue-equivalent dosimetric phantoms is a necessary part of effective treatment due to protons interaction features with a substance [1].

In this study the numerical simulation of medical proton beams interaction with plastics suitable for 3D-printing methods using the Geant4 toolkit and the Monte Carlo method was carried out. As a result deep dose distributions of the proton beams in the studied plastics and biological tissues were obtained.

Also, the experimental studies were carried out at the A. Tsyb Medical Radiological Research Centre on a medical proton beam. Based on the results obtained, the plastic objects were evaluated for equivalence to biological tissues in relation to their interaction with protons.

This work was supported by a grant from the Ministry of Science and Higher Education of the Russian Federation under agreement 075-15-2022-620 (project No. MK-26.2022.1.2).

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INNOVATIVE METHODS OF THERAPY USING QUANTUM DOTS

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Quantum dots (QD) are semiconductor nanocrystals with a size in the range of 1-10 nanometers. They are created on the basis of inorganic semiconductor materials Si, InP, CdSe, etc., and are coated with a stabilizer monolayer. QD have unique optical, electrical, electrochemical, and catalytic properties. The crystal core of a quantum dot contains about 100–100,000 atoms [1]. Quantum dot size is comparable to the wavelength in the material on the basis of which it is made. Inside quantum dot, the potential energy of an electron is lower than outside it, and thus the motion of the electron is limited in all three dimensions. The energy levels of electrons inside quantum dot are discrete and are separated by regions of forbidden states. The behavior and properties of these objects are described not by classical physics, but by quantum mechanics [2].

The current review focuses on applications of QD such as providing high-quality bioimaging of tumors in vitro and in vivo; visualization of drug transportation; targeted drug delivery; photothermal and photodynamic therapy; cell sorting activated by fluorescence [3]; use in biosensors [4]. Emphasis is placed on the technology of accurate detection and inhibition of SARS-CoV-2 using quantum dots [5].

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HYBRID FE-AU NANOPARTICLES FOR DUAL MRI/CT IMAGING AND PHOTOTERMAL THERAPY

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Nanoparticles for biomedical applications are studied for over three decades. The introduction of laser-synthesized nanoparticles enabled to overcome most problems of conventional chemical synthetic methods, since these materials have low size-dispersion under a controllable mean size, exceptional chemical purity, and low toxicity *in vivo*. [1]

Hybrid Fe-Au nanoparticles have plasmon properties with absorption in near-infrared region. Illumination of nanoparticles by 808-nm light lead to a strong photo-hyperthermia effect capable of efficiently killing cancer cells. Due to composite structure of iron and gold, these hybrid bimetallic nanoparticles can be used for multimodal imaging. Nanoparticles were efficiently targeted by magnetic field in the mammary adenocarcinoma tumors and following successful MRI and CT contrasting of tumor borders *in vivo*. Our results give a promise for the development of novel phototherapy and imaging modalities profiting from superior properties of laser-synthesized Fe-Au nanoparticles. [2]

This work is supported by the Ministry of Science and Higher Education of the Russian Federation, agreement no. 075-15-2020-773.

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RADIOFREQUENCY HEATING OF NANOPARTICLES FOR THERAPEUTIC APPLICATIONS

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In the current conditions, new methods of treating oncological diseases are needed. One of these methods is local hyperthermia of a tumor by Joule heating by electromagnetic radiation in the radio frequency range using nanoparticles as sensitizers [1]. To develop this technique, it is necessary to build an adequate mathematical model that describes the physical processes that occur during the interaction of a solid-state nanoparticle with radio emission in the environment of the human body. Based on the proposed model, the dependences of the heat release around nanoparticles on the frequency of the external field and the nanoparticle material are obtained.

The proposed model can be further applied to calculate the optimal parameters of nanoparticles and radiofrequency electromagnetic radiation for use in hyperthermia of malignant tumors.

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INVESTIGATION OF THE INFLUENCE OF ERRORS IN THE CLINICAL RADIATION DELIVERY SYSTEM ON THE QUALITY OF RADIATION THERAPY DOSIMETRIC PLANS

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With the advent of increasingly complex methods of dose planning and delivery in radiotherapy (for example, VMAT and IMRT), quality assurance (QA) for a specific treatment plan has become an integral procedure in the process of preparing a clinical plan and its delivery. Quality control and safety assurance for intensity-modulated radiation therapy (IMRT) and volume-modulated arc therapy (VMAT) programs have been reviewed in various guidance documents that propose the implementation of appropriate quality assurance programs for specific clinical tasks [1]. The purpose of individual quality control of IMRT and VMAT plans is to ensure that all plan parameters are correctly transferred from the planning system to the treatment apparatus, and that the measured plan exactly corresponds to the plan predicted by the treatment planning system (TPS). This is usually achieved by comparing the planned calculations with measurements made using an ionization chamber, film and/or detector array. The most frequently used method for comparing dose measurements and calculations performed in the planning system is gamma analysis [2], which combines the distance to coincidence (DTA) and the percentage difference of doses (%Diff) into one indicator, γ. However, despite the prevalence of the use of gamma analysis is some uncertainty in the analysis of the indicators of the resulting gamma criteria. The user cannot interpret the results of QA checks based on gamma analysis with sufficient clarity, since this indicator does not have a clear connection with clinically unacceptable criteria, for example, a violation of uniformity, insufficient coverage of the target volume (PTV) or an excess dose to a critical organ (OAR).

To conduct a study to identify the gamma criteria most sensitive to clinical errors, a common clinical localization was selected - prostate cancer. This choice is optimal, as it has the following advantages: ease and speed of planning, the presence of risk organs located close to the target volume and established clinical criteria for evaluating plans due to extensive experience in the treatment of prostate cancer with remote radiotherapy. One of these clinical criteria will be the average dose to the risk organs and the amount of coverage of the clinical dose of the target volume (D_{mean}= 18 - 19 Gy and D(95%)≤V(95%).

MLC (multileaf collimator) positioning errors for each field were introduced into the received plans. Moreover, the errors varied in absolute value (from 0.1 mm to 1 mm) for each plan, since the ultimate goal was to obtain precisely a violation of clinical criteria, that is, an increase in the average dose to the risk organs (bladder and rectum) or undercoverage of PTV.

The MatLab software package was used to introduce errors into dicom plans. A plan file was opened in the program console, after which errors were introduced using a loop in the desired data tree storing the absolute values of the MLC coordinates.

All plans were measured on the same day with the same positioning of the dosimetric phantom in compliance with all the positioning rules recommended by the manufacturer. In addition, detector calibration procedures and absolute dose values were carried out before the measurements.

During the analysis, false positive indicators (P=95%) of convergence were revealed for all gamma criteria with the Global parameter. Criteria without correction for the Global parameter has fewer false positive results. To a greater extent, the indicator of 2mm/2% showed the most realistic picture (10 plans with errors had a convergence of less than 90%), and the criterion of 3mm/2% also performed well (8 plans with errors had a convergence of less than 90%).

In the future, it is planned to expand the statistics and conduct a more accurate analysis for specificity and sensitivity.

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COMPOSITE MATERIALS BASED ON PEROVSKITE $CsPbBr_3$ NANOCRYSTALS FOR APPLICATION IN X-RAY DIAGNOSTIC STUDIES

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Perovskite semiconductor nanocrystals (PNCs), such as $CsPbBr_3$, represent a new class of materials that can be used in optoelectronic devices due to their high optical absorption coefficients and high fluorescence (FL) quantum yield (QY). PNCs can fluoresce in any region of the visible and near-IR spectrum by modifying their composition by varying the precursors during their synthesis. [1] The widespread use of PNCs in applied areas is limited due to their internal structural instability and deterioration of photophysical properties when exposed to moisture, light, and air.[2] PNCs $CsPbBr_3$ are of particular interest for use in new types of light-emitting diodes (LEDs) and photodetectors. [3] Scintillators based on PNCs $CsPbBr_3$ are a promising new imaging tool for X-ray radiography. PNCs $CsPbBr_3$ as a scintillator have better energy resolution (E ~ 1.4%) and faster scintillation decay times than NaI(Tl) which is used in most detectors. [4] The characteristic average lifetime of the luminescence kinetics (τ) for $CsPbBr_3$ PNCs is about 5÷30 ns, while for NaI(Tl), which is used in most detectors, this value is around 230 ns. To use PNCs $CsPbBr_3$ as a detector scintillation layer, it is necessary to achieve uniform coverage of the PNCs layer.

In this work, PNCs $CsPbBr_3$ were synthesized as a material for fabricating the scintillation layer of the detector. The stability of the material used was evaluated by measuring the dynamics of τ and QY values of thin films of PNCs with characteristic thicknesses of the order of 20–40 nm. Perovskite TFs were created on a glass substrate using the spin – coating method. In addition to thin films, samples with characteristic thicknesses of about 2 mm were also prepared and studied, for which encapsulated in a polydimethylsiloxane matrix. The obtained samples have a stable value of τ over time. The advantage of these samples is the absence of contact between PNCs and the external environment, which eliminates the influence of factors such as moisture and oxygen. Finally, so that more effectively eliminate the influence of the environment, it was decided to encapsulate the PNCs in polystyrene through the radical polymerization of styrene. The produce samples have characteristic dimensions of the order of 0.5÷2.0 cm and have a stable QY FL value. For the latest, the amplitude characteristics of scintillation were studied in order to isolate samples (manufacturing technologies) with the maximum light output.

The fabricated bulk composite samples can be considered the most promising for use as a scintillation coating for X-ray and gamma-ray detectors.

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POLYMER-COATED BiOCl NANOSHEETS FOR X-RAY IMAGING: COMPREHENSIVE CYTOTOXICITY ANALYSIS

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Among the main radiotherapy and medical research methods, X-ray computed tomography (CT) occupies a leading position and belongs to the methods of medical imaging. CT allows the diagnosis of a large number of pathological diseases. However, to visualize the majority of pathological foci, contrast agents are needed based on atoms of chemical elements that can absorb X-rays more efficiently than the surrounding tissues of the body. Such contrast agents may include substances containing atoms with high atomic density. In this work, we studied the cytotoxicity of polymer-coated bismuth oxychloride (BiOCl) nanosheets synthesized by hydrolysis of bismuth chloride under alkaline conditions. The resulting nanoplates had radiopaque properties, more pronounced (about 2.55 times) than the classic contrast agent in CT examination of the gastrointestinal tract - barium sulfate.

The size of the synthesized nanosheets was 178.5 ± 45.4 nm, and the thickness was about 26.0 ± 11.5 nm. The nanoplates were additionally coated with a biocompatible polymer, carboxymethyldextran, and the zeta potential was about –34 ± 20 mV. The study of cytotoxic properties was carried out on five cell lines: the MNNG/HOS human osteosarcoma, the EMT6/P mouse breast carcinoma, the B16/F10 mouse melanoma, the NCi/ADR human ovarian cancer and mesenchymal stem cells (MSCs) isolated from the human tooth pulp. The cytotoxicity of polymer-coated bismuth oxychloride (BiOCl) nanosheets at concentrations of 10, 50, 100, and 200 μg/mL was assessed after 24 and 72 hours of incubation with nanosheets via MTT assay, which allows assessing the cell metabolic activity, and by fluorescence microscopy using a wide range of fluorescent dyes: NucView Caspase-3 (Biotium) for apoptotic cell analysis, LumiNuc LUCS 13/propidium iodide fluorescent dye mixture for differential cell staining (Live/Dead assay), and Hoechst 33342 for nuclei staining.

The MTT assay results did not reveal a significant decrease in the metabolic activity of cells after 72 hours of co-cultivation with polymer-coated bismuth oxychloride (BiOCl) nanosheets for all the studied cell cultures. Analysis of the ratio of the number of dead and apoptotic cells revealed that cultures of EMT6/P and MNNG/Hos showed a significant increase in the number of apoptotic cells at a concentration of 50 μg/mL after 24 h. It should not be noted that high concentrations of nanosheets (above 50 μg/mL) aggregated on the cell surface, covering them with a thin layer, which caused some artifacts when analyzing their metabolic activity using the MTT assay. Thus, it can be concluded that the synthesized polymer-coated bismuth oxychloride (BiOCl) nanosheets are biocompatible, do not cause death of human MSCs even at high concentrations, and can be toxic to mouse carcinoma and human osteosarcoma MNNG/Hos cells at concentrations above 50 μg/mL.

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RIBOFLAVIN-FUNCTIONALIZED HAFNIUM OXIDE NANOPARTICLES FOR SELECTIVE TARGETED DELIVERY TO TUMOR CELLS

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Radiation therapy is still one of the most common methods of treating tumor diseases. It is used in 70% of oncology cases and can be used alone or in combination with chemotherapy and/or surgery. Despite the ubiquity of radiation therapy, side effects after the application of this method of tumor therapy dramatically reduce the effectiveness of treatment. In this regard, the search for methods to increase the effectiveness of radiation therapy does not stop. One of the promising approaches to improve the efficiency of radiation therapy of tumors can be the use of nanosized agents based on chemical elements with high atomic number, also known as high Z elements. One of the promising nanomaterial is hafnium (Hf), or rather its oxide. Relatively low toxicity, extremely stable oxidation state (+4), and high atomic density make hafnium oxide an excellent candidate for medical applications. The issue of targeted delivery of hafnium oxide to increase the effectiveness of radiation therapy still remains unresolved. To date, there are many substances that can provide intratumoral internalization of various nanoagents. Among them, it is worth noting riboflavin mononucleotide (vitamin B2). Some types of tumors are known to overexpress certain riboflavin transporter proteins (RFTV family), for example, squamous cell lung cancer overexpresses the riboflavin transporter protein type 3 (RFTV 3) 187 times above normal. Thus, surface modification of nanodispersed hafnium oxide with riboflavin can provide its targeted delivery directly to tumor cells.

We synthesized hafnium oxide nanoparticles and functionalized them with flavin mononucleotide. Such an organic-inorganic nanocomposite had a hydrodynamic radius of about 4 – 6 nm. The radiosensitizing properties of the obtained nanoparticles were studied on U251 human glioblastoma cells and on the NCTC cline L929 mouse cell line using the MTT test and fluorescence microscopy, using a mixture of SYTO9 fluorescent labels and propidium iodide (PI), for differential staining of live and dead cells. The assessment of radiosensitizing properties was carried out after 72 hours after cell irradiation. Before irradiation, cell cultures were incubated with nanoparticles for at least 12 hours.

The MTT assay showed a pronounced decrease in the viability of U251 glioblastoma cells already at a concentration of 300 μg/mL after irradiation at a dose of 15 Gy. At the same time, in relation to L929 cells, a decrease in the level of dehydrogenase activity was revealed, which did not exceed 0.5 times in relation to the control group after irradiation with X-ray radiation at a dose of 15 Gy at a concentration of nanoparticles of 2.5 mg/mL. The results of the study of the ratio of dead to living cells using fluorescence microscopy confirmed the results of studies using the MTT assay and demonstrated a clear dose-dependent radiosensitizing effect in relation to tumor cell lines of glioblastoma, which was expressed in a sharp increase in the number of dead cells, at the same time in relation to cells line L929, this effect was expressed to a much lesser extent. Thus, the synthesized organic-inorganic nanocomposite can be considered as a promising theranostic agent in the framework of radiation therapy for oncological diseases.

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EFFECTIVNESS OF RESCANNING IN PROTON THERAPY: A SHORT REVIEW

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Organ motion is one of the major obstacles in charged particle therapy. From a geometric point of view, the movement of the target leads to a blurring of dose gradients and can lead to the inclusion of a therapeutic beam when the tumor is outside the field of the beam [1]. In addition to these geometric effects, the movement of organs in the target area and within the beam path can change the length of the radiological path and, consequently, the distribution of the deposited dose. In order to be able to treat mobile tumors with active, scanned proton therapy, adequate motion mitigation techniques have to be applied. Repainting is one of the techniques of motion compensation [2]. It consists in multiple repeated irradiations of the entire volume or individual iso-energy layers with the dose that is a multiple of the prescribed dose. As a result, the dose is averaged which leads to an increase in the homogeneity of the dose field. Some groups have compared different techniques of rescanning for plan parameters (number of fields, field directions, number of re-scans) as well as in respect to different motion parameters (motion amplitude, motion starting phase) [3][4]. In this review, we investigate the limitations and possibilities of rescanning.

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RADIOSENSITIZATION BY BISMUTH-BASED NANOPARTICLES USING PROTON BEAMS

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Nanoparticles (NPs) of high atomic number (Z) materials can act as radiosensitizers to enhance radiation dose delivered to tumors.

For X-ray irradiated nanoparticles dose enhancement is often attributed to photoelectrons and Auger electrons. Photoelectrons are highly energetic, have a long range (up to hundreds of microns) in surrounding water, and deposit a small fraction of their energy near the nanoparticle. On the contrary, Auger electrons have lower energy and shorter range (less than 1 μm), allowing most of the energy to be deposited close to the nanoparticle. [1]

The aim of this report is to overview the theoretical and experimental data on application of bismuth-based nanoparticles in proton radiotherapy.

Numerous studies [1-3] have shown that bismuth NPs cause maximum dose enhancement compared to gold NPs, platinum NPs and superparamagnetic iron oxide NPs (Fig.1). There are a number of advantages of using bismuth-based nanomaterials as radiosensitizers [2]. Firstly, due to bismuth's larger atomic number (Z = 83) compared to gold (Z = 79), Bi-NPs enhance the effects of low-energy X-rays. Secondly, bismuth and most of its compounds are considered harmless. Thirdly, bismuth-based NPs can be readily prepared in various well-defined shapes and sizes. Finally, bismuth is the least expensive of the high atomic number (Z) elements.

Protons' interaction mechanism differs from the one for X-rays. The majority of proton energy is deposited at the end of proton range (Bragg

Peak) in a targeted volume. Thus, the tissues beyond the tumor receive minimal dose. The inclusion of high Z metallic NPs in the target leads to the local increase of ionization energy loss. Coulomb collision of protons with nanoparticles causes ionization of the atomic electrons generating characteristic X-rays and Auger electrons. Energy deposition by electrons hydrolyzes water molecules surrounding cells and their nuclei, producing reactive oxygen species (ROS) that induce DNA damage, eventually leading to cell death.

A proton beam can be utilized to irradiate nanoparticles with a single Bragg peak set to occur inside a tumor volume (fully absorbed) or to occur after the beam had traversed the entire body. The experiments on mouse tumors [4] show a significant increase in complete tumor regression with single BP-based PIRT (particle-induced radiotherapy) compared with proton irradiation alone.

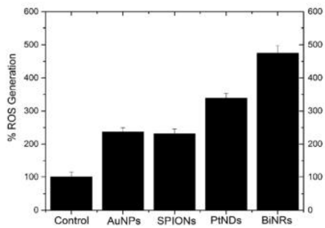

Fig.1 Percentage ROS generated by AuNPs, SPIONs, PtNDs and BiNRs [0]

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NANOSECOND SOURCE OF α-PARTICLES AND DD NEUTRONS FOR CALIBRATION OF DETECTION SYSTEMS

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Compact and powerful sources of fast particles and X-rays are in demand in various fields from medicine to materials science and non-destructive testing. This work presents the push button source of neutrons and α-particles based on nanosecond vacuum discharge (NVD) of low energy (≈ 1 J), where the inertial electrostatic confinement (IEC) scheme with reverse polarity have been used [1,2]. PiC modeling within the full electrodynamic code KARAT revealed the key role of the formation of a virtual cathode (VC) and the corresponding potential well (PW) in the interelectrode space of NVD. Generally, it provides in the interelectrode space both confinement and acceleration of protons and deuterons to energies of tens keV, and multicharged boron ions up to hundreds of keV. This turns NVD into a kind of microreactor of "collisional" nuclear synthesis, including an aneutronic proton–boron (pB) one. The neutron yield estimated in isotropic approximation changes from shot to shot and is about $(10^5 - 10^7)/4\pi$, ≈1 J, 40 ns. NVD scheme (fig.1a,b) involves automatic injection of electrons into the anode space when the high voltage is applied, and corresponding formation of a very small VC (with radius $r_{VC} \sim 0.1$ cm) and PW related (with depth $\varphi_{PW} \sim 100$ kV). Deuterons can oscillate in the PW, and at the moments of their collapses at the PW bottom, the main DD synthesis takes place. In a result, periodic oscillations of deuterons in PW are leading to the pulsating yield of DD neutrons [1]. At the same time, the PW constantly holds the oscillating deuterons, since the energy they gain in the VC field is always insufficient to leave the well. This type of confinement should be referred to as electrodynamic or oscillatory one (OSCO) [2].

By analogy with DD synthesis, PiC modeling showed that pB reaction (p + $^{11}B \rightarrow \alpha + ^{8}Be^{*} \rightarrow 3\alpha$ + 8.7 MeV) can also be achieved by accelerating and confining protons and boron ions by the field of VC in NVD. In the process of their oscillations in PW, head-on collisions of a part of protons and boron ions with energies of ~100 -500 keV lead to pB reaction. The specifics of OSCO in pB case is that the oscillation periods of boron ions and protons are differ (fig.1c) due to the difference in their masses and charges. On average, the yield of α-particles registered recently from pB fusion was about 250 α-particles per one shot (≈ 1 J, voltage pulse U ≈ 100 kV, duration $\tau \approx 20$ ns) in a given series of demonstration experiments [2]. In a better geometry of electrodes we have to obtain at least ~ $10^3/4\pi$ α-particles per one shot. If to use pulse-periodic high voltage generator and solve heat dissipation problem, the yield will depend of total duration of work, for example, at ~ 10^4 kHz it would be ~ 10^7 α-particles/s.

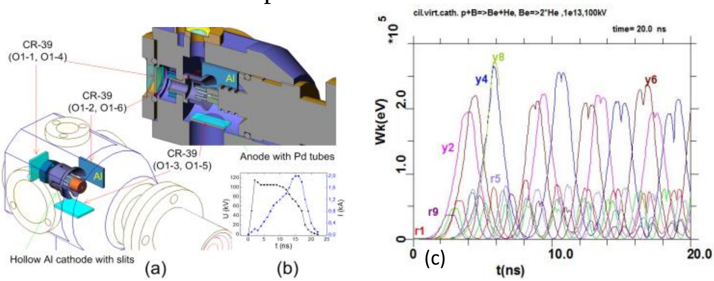

Fig.1. **(a)** Sectional diagram of the discharge chamber with CR-39 detectors around the anode composed of Pd tubes and a hollow Al cathode **(b)** V-A characteristics of the voltage pulse-periodical generator **(c)** Energy of groups of protons (*r*) and boron ions (*y*) as a function of time in the process of their oscillations in the potential well.

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MOLECULAR DYNAMIC SIMULATION: INVESTIGATION OF THE INFLUENCE OF POROUS SILICON TARGET STRUCTURE ON THE THRESHOLD AND RATE OF LASER ABLATION

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The relevance of the study is determined by the growth in the last decade of the use of porous silicon nanostructures in various fields of biomedicine, which is associated with its unique properties. For example, porous nanosilicon is able to luminesce in the visible range of the spectrum, which makes it promising for use in bioimaging technologies [1–3]. In addition, it has excellent biocompatibility and biodegradability and can be used as sensitizers of the therapeutic action of physical fields [4].

For biomedical applications, silicon nanoparticles must be ultra-pure and non-toxic. The most promising method for the production of such nanoparticles is the laser ablation method, which makes it possible to obtain a narrow size distribution of produced nanoparticles both in air and in colloidal solutions [5].

In the present work, the process of laser ablation of a porous silicon target in air under irradiation with ultrashort laser pulses is simulated using the molecular dynamics approach. The number of ablated atoms was calculated for targets of various degrees of porosity and pore size upon irradiation at a wavelength of 1030 nm at pulse durations of 100 and 270 fs. It has been shown that the laser ablation threshold decreases with an increase in porosity from 0 to 70%, while the ablation rate decreases significantly. The simultaneous drop in both the ablation threshold and its productivity with an increase in porosity leads to the need to optimize the porosity of the initial target for each specific problem of nanoparticle synthesis. The minimum ablation threshold and the maximum rate are observed at a substrate porosity of 60–65%. For samples with a small pore size (1 nm), the ablation threshold is reduced by almost 60% relative to samples with large pores with a size of 5 nm. Despite the decrease in the ablation threshold, the rate of ablation with a small pore size is significantly lower than with the ablation of targets with a large pore size.

The modern approaches and methods of theoretical and numerical studies used have made it possible to obtain new results on revealing the patterns that occur during laser ablation of porous silicon films depending on its thermodynamic characteristics and the degree of porosity.

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ANTAGONISTIC AND ADDITIVE EFFECTS OF PROTON AND NEUTRON RADIATION ON THE CANCER STEM CELLS OF MCF-7 AND MDA-MB-231

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In recent years, proton therapy has been widely used, including in the field of breast cancer. In radiotherapy, organs at risk include the heart, lungs, and contralateral breast. Proton beam therapy decrease the risk of radiation-induced damage, including the development of secondary tumors, compared with standard photon radiotherapy with γ- or x-rays. However, the biological effectiveness of proton radiation in terms of elimination of malignant neoplasms is relatively low and only 1.1–1.3 times higher than the efficiency of photon radiation [1]. High linear energy transfer ionizing radiation (fast neutrons, etc.) is much more effective in the fight against radioresistant tumors, but their use has a number of limitations - it is associated with a high risk of late radiation complications in normal tissues surrounding the tumor, for example, compared with proton therapy.

It can be assumed that the combination of neutron and proton radiation will significantly increase the effectiveness of radiotherapy in compliance with all quality assurance requirements. However, the radiobiological effects of sequential irradiation of tumor cells with neutron and proton beams have not been practically studied, including effects on cancer stem cells (CSCs), which are known to be more resistant to anticancer therapy [2, 3].

Thus, the aim of this work was to assess changes in the pool of breast CSCs and expression of genes that control stemness of these cells after neutron or proton irradiation and their combined exposure at isoeffective doses in vitro.

We studied the radiation response of two cell lines: MCF-7 (luminal A-subtype ER+PrR+HER2neu-) and MDA-MB-231 (triple negative subtype ER-PrR-HER2neu-). The cells were exposed to a beam of fast neutrons at a dose of 0.7 Gy; irradiation of cells with protons at a dose of 2.0 Gy was performed in a spread-out Bragg peak (proton energy 67–83 MeV); gamma irradiation at a dose of 4.0 Gy was performed from a ^{60}Co source at the Agat-R facility.

The relative number of $CD44^{+}CD24^{-/low}$ CSCs of the MCF-7 line increased by 1.7 times under the influence of γ-irradiation at a dose of 4.0 Gy ($p=0.047$ compared with the control). However, no significant changes were found in the relative number of CSCs and the expression level of *OCT4*, *NANOG*, and *SOX2* genes after neutron, proton beam irradiation or their combined action at a total equieffective dose of 4.0 Gy compared with the control in both cell lines. The absolute number of CSCs decreased under the influence of neutron or proton radiation compared with the control ($p<0.05$ for both cell lines). The effects of sequential exposures to neutron and proton radiation on the size of the CSC pool depended on the molecular subtype of cancer cells. Additive interaction was observed for MCF-7 line and antagonistic one for MDA-MB-231 line (coefficients of synergism were 0.96 and 0.45, respectively).

In this way, the combined use of protons and neutrons gives an advantage in terms of overcoming the resistance of CSCs, although the technique needs to be expanded and refined.

The work was supported by the Ministry of Education and Science of the Russian Federation (Agreement No. 075-15-2021-1347).

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RADIOSENSITIZING EFFECT OF BISMUTH NANOPARTICLES *IN VITRO* AFTER PROTON BEAM IRRADIATION

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One of the most promising approaches to increase the effectiveness of the therapeutic effect of a proton beam on tumor cells, including those that are radioresistant, is the use of selective radiosensitizers - substances that can effectively accumulate in a tumor and, interacting with protons, induce DNA damage and oxidative stress, leading to death. tumor cells. In the framework of this work, we studied the cytotoxicity and radiosensitizing properties of bismuth nanoparticles under the influence of a proton beam.

The study of the cytotoxic and radiosensitizing effect of bismuth nanoparticles (Bi-Pluronic) was carried out on the EMT6/P mouse mammary cell line. This type of cell line is used to test various drugs. The EMT6/P mouse mammary is drug resistant cell line. Irradiation of cell cultures was carried out in culture flasks (12.5 cm) on a therapeutic proton complex "Prometheus" based on the FTC Lebedev Physical Institute (Protvino, Moscow region) according to the scheme in the Bragg peak with doses of 1.5, 3 and 5 Gy. Studies of the cell metabolic activity 72 hours after proton beam irradiation were carried out using the MTT assay. Study of the clonogenic activity of EMT6/P cells in the presence of bismuth nanoparticles were carried out 9 days after irradiation. The quantitative analysis of caspase 3-positive cells and the number of dead cells was carried out by fluorescence microscopy 24 hours after irradiation.

According to the results of all research methods, the extreme toxicity of bismuth nanoparticles was revealed, which manifested itself in a sharp decrease in the level of dehydrogenase and clonogenic activity already at a concentration of 50 μg/ml. In the study of cells by fluorescence microscopy, a sharp decrease in the total density of the EMT6/P cell monolayer was observed in the presence of bismuth nanoparticles even without irradiation. Irradiation of cell cultures with a proton beam at a dose of 1.5 and 3 Gy in the presence of bismuth nanoparticles (1-10 μg/mL) led to a significant decrease (by 3.5 times) in the number of colonies and an increase in the number of apoptotic cells, which confirms a pronounced radiosensitizing effect. Thus, it has been shown that bismuth nanoparticles with concentrations below 25 μg/mL can act as an effective radiosensitizer after exposure to proton irradiation.

This study was supported within the Federal Scientific and Technical Program no. 075-15-2021-1347 of the Ministry of Science and Higher Education of the Russian Federation “Development of new technologies of diagnostics and beam therapy of socially diseases by proton and ion beams using the binary nuclear methods”.

GUANOSINE-5-MONOPHOSPHATE AFFECTS THE X-RAY INDUCED LEVEL OF GENE EXPRESSION

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Purine nucleosides and nucleotides exhibit antioxidant and radioprotective properties both in vitro and in vivo [1,2,3]. A possible mechanism for the protective action of purine compounds is the maintenance of a normal nucleotide pool in the cell. As is known, a pool of nucleotides is required for RNA transcription and replication of both nuclear and mitochondrial DNA [4, 5]. Of particular interest in this regard is the study of the mechanisms of the radioprotective action of purine nucleotides and their ability to act as a signal molecule.

In this work, we investigated the effect of GMP on gene expression in human mesenchymal stem cells (MSCs) under the action of X-ray radiation at a dose of 15 Gy. In this study, we evaluated changes in the expression of 94 genes distributed over 25 clusters involved in the regulation of processes associated with cell proliferation, differentiation, and death. We have identified 3 groups: 1 - irradiated human MSCs without guanosine-5-monophosphate (GMP); 2- irradiated MSCs incubated with GMP; 3 - non-irradiated human MSCs incubated for 1 hour with GMP.

It has been shown that incubation of MSCs with GMP (1 mM) for 1 h after irradiation leads to significant changes in the level of gene expression in the cluster of osteoblast differentiation markers SPP1, TNF, VDR; S phase markers (WEE1); phase markers G2 (CCNA2); proapoptotic markers (TNFRSF10). Expression patterns of genes of antiapoptotic markers (NOS2, BMP7) were especially distinguished. Also, an increased level of transcription is observed in the group of self-renewal markers (HSPA9), in the group of loss of stemness, the level of activation of FOXA2 gene expression was observed, relative to the control group.

After incubation of human MSCs with GMP (1 mM) without irradiation, patterns of expression of genes of osteoblast differentiation markers (SPP1, TNF, VDR) were especially distinguished; modulators of chromosomes and chromatin (KAT2A), as well as several genes of anti-apoptotic markers (NOS2, BMP7). The expression of the WEE1 gene of the S phase marker and the TNFRSF10 gene of the proapoptotic marker also increased. In the group of cell necrosis markers, activation of FOXI1 gene expression was observed.

Thus, the incubation of irradiated cells with GMP also activates the processes of cell differentiation and division, its self-renewal, and increases both pro- and anti-apoptotic activity. In addition, GMP affects the processes of self-renewal, reducing cell stemness. Compared to a group of irradiated cells without GMP, purine nucleotide reduces the expression of asymmetric cell division genes.

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OPTICAL PROPERTIES OF SEMICONDUCTOR NANOPARTICLES SYNTHESIZED BY PULSE LASER ABLATION IN A GAS

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In this paper, we analyze the results of studying two types of semiconductor nanoparticles: silicon and germanium. Nanoparticles were synthesized by pulsed laser deposition (PLD) in a gaseous medium in the form of films on a silicon substrate. The deposition experiment was carried out by the MBE-2000, PVDProduct system using a COMPexPro KrF excimer laser (248nm, 30ns, 1-105Hz) in a vacuum chamber. Air was pumped out of the chamber to a level of 10^{-7} Torr. After that, buffer gases (He, N2) were let into the chamber. During the deposition process, different proportions of gases in the mixture and a fixed total working pressure in the range of 0.5^{-5} Torr were provided. In the experiments, the sputtered target constantly rotated and was irradiated at an angle of 45 degrees with respect to the normal to the target surface. Constant rotation of the target was used to minimize the impact of laser radiation to the same point on the target surface. The material was deposited on a substrate, which was located 2 cm from the irradiated target. This distance was chosen as optimal for the given energy in the laser pulse and the operating pressure range. Nanostructured films in the process of pulsed laser ablation were formed during the action of several thousand (5000-7000) laser pulses. The thickness of the formed films was approximately 1 μm.

Additionally, for the structural, elemental, and phase composition of nanostructured films, such methods as scanning electron microscopy, X-ray diffraction, and Ramon spectroscopy were used. As a result of the analysis of the obtained experimental data, it was revealed that all samples contain nanosized germanium crystals. The data obtained by Raman spectroscopy indicate the formation of a crystalline form of germanium nanograins. A comparative analysis with silicon nanoparticles obtained in the same way is given. It is shown that the particles have a less structured shape and a greater tendency to conglomerate. Their size reaches 1 micron. It can be seen that silicon obtained in this way differs in its structure from germanium nanoparticles. Particles have a more structured shape, less prone to conglomeration. The quantitative elemental composition of the point spectra of germanium samples showed that oxygen is present in the samples. It is possibly present in the form of germanium oxide, which could have formed as a result of storage in air after sputtering. For all Ge samples on the Si substrate, broad photoluminescence was observed, which was excited at 350 nm. It can be seen from the spectra that the deposition conditions (gas pressure) do not affect the photoluminescence wavelength of the samples, while affecting the radiation intensity. All samples have a pronounced emission peak centered at 430 nm. There is a tendency for the intensity to increase with an increase in helium pressure ablation in a gaseous medium. When nitrogen is added, the intensity drops. Silicon nanoparticles obtained under similar conditions have more significant scatter in the spectra associated with the deposition conditions, which is explained by nitrogen passivation of silicon nanocrystals and attributed to radiative transitions between electronic states in amorphous silicon oxynitride a-SiNxOy formed on the surface of silicon nanocrystals. The spectra are presented under the same gas pumping conditions. Comparison clearly shows differences in fluorescence. Germanium has a more intense FL line, with a peak in the blue spectrum, silicon has a peak in the red zone.

The work was experimental in nature. It was important to compare silicon and germanium particles as potential biomedical applications.

THE DETECTOR AND PREAMPLIFIER OF THE NUCLEAR REACTION PRODUCTS SPECTROMETER FOR LOW ENERGY PROTONS AND LIGHT NUCLEI ACCELERATORS (50 keV - 1 MeV)

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Proton therapy is the fastest growing method of hadron therapy and a mainstay in the fight against cancer [1]. The work is devoted to the development and testing of silicon detectors and readout electronics for them to measure proton-boron fusion reaction cross section at the Prometeus proton accelerator complex:

$$p + B \rightarrow 3\alpha\ (7{,}8\ MeV)$$

The detector tract for recording α-particles and other light products of nuclear reactions in the energy range 0,5 MeV - 10 MeV is presented. The spectrometer has been tested at the HELIS facility for D-D nuclear fusion reaction.

The main results:

1. Two detector units were manufactured for the HELIS facility. One detector unit was manufactured for the Prometheus complex (also two detector boards for the «Amplitude» ADC were manufactured).
2. The detector units use the same silicon sensors 1*1 cm in size with a thickness of the inactive region on the surface (“entrance window”) of about 1 μm
3. The electronics of the detector units uses a charge-sensitive amplifier circuit, implemented on the AD4817 operational amplifier integrated circuit (high-frequency low-noise amplifier with low input current). To reduce the influence of the expected

"pedestal" from the Prometheus booster reset, a differentiating cell with a time constant of ~2μs is introduced into the circuit.

4. Some instrument parameters:
   - Range of registered signals - up to 10 MeV;
   - Intrinsic noise level - less than 100 keV
   - Dead time - from 2μs (adjustable upwards in some limits).
5. The amplitude spectrum obtained at the GELIS facility. The results obtained are consistent with measurements made by a diamond detector [2] (Fig.1).

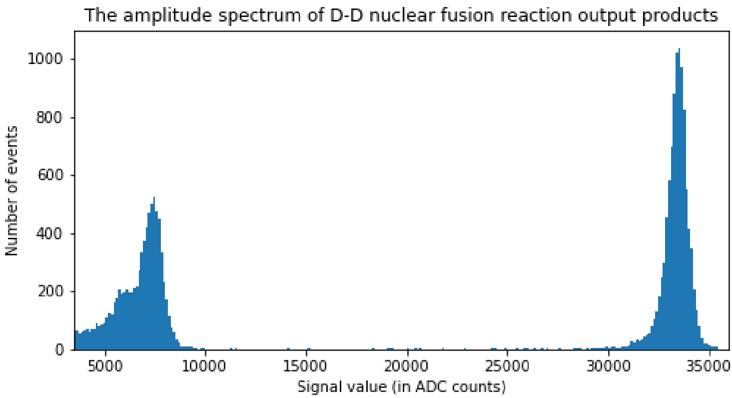

Fig1.Response to charged particles and the spectrum of measured reaction components obtained during testing of the detector at the HELIS facility

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CHARACTERIZATION OF COLLOIDAL BORON NANOPARTICLES SYNTHESIZED BY LASER ABLATION IN WATER

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Boron (B) and its compounds are widely used in engineering, microelectronics and in quantum dots synthesis [1]. B is also used in neutron capture therapy [2]. ^{10}B isotope has the second largest neutron capture cross section and can generate alpha particles, which damage DNA of nearby cells. However, to achieve a therapeutic effect, high concentrations of the ^{10}B isotope are required (approximately 20...35 μg/g or 10^9 B atoms per cell). An accumulation of this amount of ^{10}B in cancer cells is possible by the use of high doses of molecular B compounds, such as disodium mercaptoundecahydrododecaborate (BSH) or p-borophenylalanine (BPA), which cause toxicity issues to healthy tissues.

This problem can be solved by applying nanotechnology methods that have already proven their effectiveness in various fields. The use of B nanoparticles (NPs) instead of molecular compounds can significantly increase the therapeutic effect due to higher mass-concentration of B. The chemical synthesis of B NPs is complicated by the fact that toxic by-products are generally formed during the synthesis, and the size of the resulting NPs can exceed several hundred nanometres.

In contrast to chemical methods, there is a well-established physical alternative for the synthesis of colloidally stable NPs – laser ablation in liquids. The laser synthesized NPs are free from any residual contamination due to the synthesis in an ultrapure environment (deionized water) without using any additional chemicals [3]. We already used methods of laser ablation in water to produce aqueous colloidal solutions of elemental B NPs [4,5].

Here, we present our results on elaboration of femtosecond laser-ablative synthesis of ultrapure colloidally stable B NPs. We also report characterization of the obtained NPs by electron microscopy, dynamic light scattering and optical spectrometry.

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METHODOLOGY OF FAST AUTOMATED DATA PROCESSING OF CHARGED PARTICLE TRACK DETECTORS

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Track detectors are insensitive to gamma and electromagnetic radiation, which makes them a convenient solution for registering an integral particle flux in high-current devices. However, the main disadvantage of such detectors is the time-consuming manual processing and the lack of ready-made solutions for automation. This work describes the processing algorithm for CR-39 track detectors manufactured by Fukuvi Chemical Industry. In work [1], the calibration of these track detectors by alpha particles and protons of different energies is given.

After etching, the surface of the detectors was photographed using a Nikon L200 microscope with a 50x objective. For each detector, 100 photographs of the surface were taken in the form of a 10x10 matrix. The photos do not overlap. The size of each photo is 4908 x 3264 pixels (288 x 191.5 microns).

In different RGB channels, tracks have different contrast. In the green and red channels, the tracks have a uniform dark color and stand out well against the background, in contrast to the blue channel.

For further processing, we merge the red and green channels, and remove the blue. To increase the contrast between the tracks and the background, we use the levels tool, while the absolute values for the right (lights) and left (darks) borders are selected based on the histogram of a particular image.

The histogram shape for track detector photographs is an asymmetric bell. To lighten the background, we move the right border of the levels tool to the mark where the histogram drops to 0.1% of its maximum. Then, to darken the tracks, we move the left border of the levels tool to where the histogram rises to 8% of its maximum. The histogram shape for track detector photographs is an asymmetric bell. To lighten the background, we move the right border of the levels tool to the mark where the histogram drops to 0.1% of its maximum. Then, to darken the tracks, we move the left border of the levels tool to where the histogram rises to 8% of its maximum. Both percentages are selected empirically for each series of images in such a way as to minimize the darkening of the background and surface defects on the one hand and the highlighting of the tracks (reducing their areas) on the other hand.

The image is then converted to a black and white mask. The voids are filled (white highlights inside large tracks). Watershed separation is applied to touching circular areas (mostly tracks). After setting the scale to ~0.06 microns per pixel, the particle analyzer is invoked.

The microscopic image processing algorithm is implemented as a fully automatic script for the ImageJ2 script. At the output of the script, we get a csv file with a list of particle areas and an image with the boundaries of the found particles overlaid on the original image (for visual control).

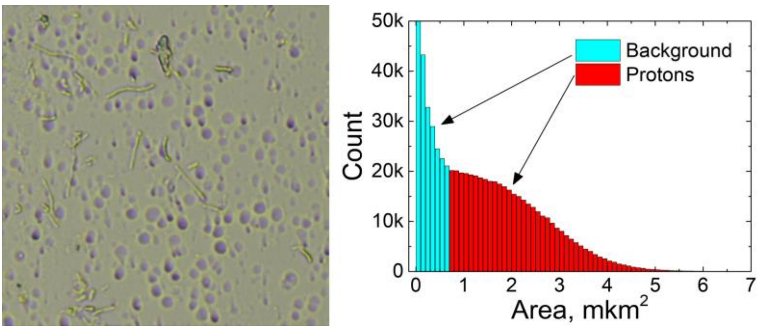

Fig.1. A fragment of the track detector image and a histogram for the entire series of 100 images.

After processing the obtained data, based on the characteristic dimensions of the track, it is possible to calculate the number and average flux of protons and alpha particles.

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CALCULATIONS AND CREATION OF COMPOSITE SHADOW PROTECTION FOR A THERAPEUTIC CHANNEL USING A NEUTRON BEAM

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Theoretical calculations have been carried out for multilayer protection of the formation of a medical channel based on a neutron beam source. The channel design is based on Monte Carlo calculations, using the example of selected protective materials - water, “Tivarobor” and W. The MIC camera [1] designed to work with a scanning proton beam at an accelerator “Prometheus” also allows measuring neutron beam profiles in the range of about 24 MeV. As one of the elements of the MIC camera, it can include a digital image acquisition detector (CDPI) [2]. Experimental measurements of attenuation coefficients for “Tivarobor” were carried out in [3]. Theoretical calculations of protection for a variant of the neutron channel in the form of cones made of composite material are carried out. The calculation by the FLUKA program [4] and the MCNP program [5] was carried out in accordance with Fig. 1.

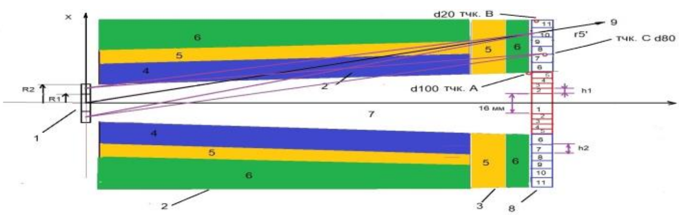

Fig. 1. Design of a neutron channel for calculating three-layer neutron protection.

Figure 2 shows the dose distribution in the annular zones of the MIC chamber. The calculation of this figure was performed by A.E. Chernukha with the MSNP program[5], for our geometry of the neutron channel construction in Fig.1.

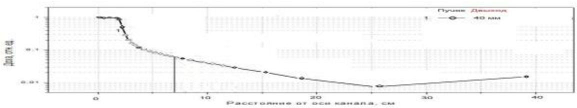

Fig. 2. Dose distribution in the annular zones of the integrated electrodes of the MIC chamber.

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DELIVERY OF NANOPARTICLES INTO THE CELL USING ISOLATED MITOCHONDRIA

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Nanoparticles are one of the promising means of therapy and diagnosis of various diseases.

One of the problems hindering the introduction of nanomaterials into medical practice is the lack of tools for their delivery into cells. We developed a new approach of transporting nanoparticles inside cells using isolated mitochondria. The choice of mitochondria as an instrument for the delivery was due to their low immunotoxicity in vivo and natural presence in the bloodstream of mammals.

Mitochondria were isolated from mouse liver by tissue homogenization and subsequent organelle separation by centrifugation. All manipulations were performed at 4 °C to avoid activation of damaging phospholipases and proteases [1]. The integrity of the organelles after the isolation was confirmed by scanning electron microscope.

Then we tested the viability of isolated mitochondria by measuring activity of membrane respiratory chains. Mitochondria were stained with dye Rhodamine 123, which is sensitive to the membrane potential. A decrease in relative fluorescence was observed with the addition of proton carriers (ascorbic, glutamic, succinic, malic acids in the presence of adenosine diphosphate ADP) and an increase with the addition of disconnectors and inhibitors of membrane complexes (FCCP, rotenone) due to changes in the membrane potential [2]. The above indicates the viability of isolated mitochondria and the absence of their significant damage during isolation.

Also, the possibility of delivering nanoparticles on the surface of mitochondria to cells in vitro was tested. The mitochondria were dyed with fluorescent nanoparticles, the excess of which was removed by centrifugation, and incubated with mouse epithelium cells and human tumor cells. Confocal microscopy in the dynamic showed the active penetration of the mitochondrial complex with nanoparticles into the cells.

The next step was the selection of nanoparticles to cover isolated mitochondria. Since the zeta potential of mitochondria is negative, the zeta potential of nanoparticles must be positive for better stability of the system. Nanoparticles from a copolymer of lactic and glycolic acids (PLGA) modified with chitosan were selected as particles. PLGA nanoparticles synthesized by the "water-in-oil-in-water" emulsion method.

Currently, work is underway to encapsulate magnetite citrate nanoparticles inside the PLGA. The magnetic properties of the latter will simplify the measurement of particle distribution in organs and circulation in the bloodstream.

Thus, it has been shown that coating isolated mitochondria with nanoparticles is a novel tool for delivering nanomaterials inside cells. The presented method makes it possible to deliver the drug intracellularly, which significantly reduces the drug load on the body and the probability of side effects of the treatment.

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DEVELOPMENT AND TESTING OF A PLASTIC BOLUS FOR GAMMA THERAPY

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The radioactive isotopes are widely used in many areas of human life. In particular in medicine there are used for the diagnosis and treatment purposes. For example, gamma-therapeutic devices containing ^{60}Co is used for external radiotherapy. The dosimetric planning is one of the main steps for preparation of irradiation. It is including the selection the treatment parameters in such way as to ensure the delivery of the necessary dose to the tumor while minimizing the radiation effects on healthy tissues. For superficially located neoplasms special devices called boluses used to form a deep dose distribution of a given configuration [1]. The boluses shape determined during the planning process with taking into account anatomical fitches of the patients. It is promising to use the three-dimensional printing method for the individual boluses manufacturing economically and quickly enough.

The purpose of this work was to develop and test of a 3D-printed plastic bolus for gamma therapy.

To calculate the geometric parameters of the tested bolus, it is proposed to use the Monte Carlo method. Within the framework of this research, numerical modeling was carried out in the software PCLAB [2]. The medical gamma-therapeutic device was used as a radiation source. The dose field formed by plastic bolus at the tissue equivalent phantom was simulated. In addition, the calculated data were compared with experimental one. It was obtained that the developed plastic bolus can be used for gamma therapy.

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THE AUTOMATED SOFTWARE FOR MULTI-LEAF COLLIMATOR CONFIGURATION FOR HEAVY CHARGED PARTICLES

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The external beam therapy using protons or carbon ions is a promising and actively developing trend in Russian healthcare system. The use of heavy charged particles makes it possible to achieve high conformity of irradiation of the target and is especially indispensable in the treatment of deep-seated tumors. This advantage simultaneously places increased demands on the process of planning radiation therapy and on technologies for ensuring the conformity of irradiation [1, 2]. These technologies include active and passive methods of beam shaping. One of the devices used in passive beam shaping system is a multi-leaf collimator (MLC) [1–3]. Our department has developed a special algorithm and dedicated software for automated MLC configuration determination.

The purpose of the development is to automate routine procedures and accelerate the MLC configuration calculation for proton and carbon ion therapy. This software allows to quickly calculate the shape of the MLC aperture for any beam entry angle, as well as for layer-by-layer irradiation with a given step by depth. At the moment, the program is designed for a specific collimator model. However, with a slight modification, it can be adapted to multi-leaf collimators of various models, both with horizontal and vertical arrangement of leaves, single-layer or double-layer, with any number and any width of leaves. The program also provides the ability to manually correct the resulting collimator configuration. This software can become a universal solution for various medical centers that are planned to be equipped with proton and ion beam therapy equipment with a passive type of beam forming using a multi-leaf collimator. It can be used as a stand-alone software product, as well as a module of a radiotherapy planning system.

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"CELL DOSIMETER": A NEW APPROACH FOR MEASURING THE SUM OF FAST NEUTRON DOSE AND NITROGEN DOSE FOR BNCT

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The biological effects observed under the influence of charged particles, neutrons and gamma quanta are due to the amount of absorbed energy and its spatial distribution, characterized by the linear energy transfer. In Boron Neutron Capture Therapy (BNCT), the total absorbed dose is the sum of four dose components with different RBE: boron dose; high-LET dose from the $^{14}N(n,p)^{14}C$ reaction ("nitrogen" dose); fast neutron dose; gamma-ray dose. The methods for measuring the fast neutron dose for BNCT are absent also, as the energy of neutrons, as a rule, is obviously lower than 1 MeV and, for example, fission ionization chambers are not applicable. Quite a lot of proven approaches are existed only for measuring gamma-ray dose. We present a new approach for measuring boron dose, nitrogen dose and fast neutron dose in BNCT. The idea of approach for measuring dose from high-LET particles is the following. The cell lines are exposed to g-radiation and mixed radiation (neutrons and g-radiation) measuring the dose of g-radiation. The doses of g-radiation which cause the same effect, for example cell surviving, are compared. The equivalent dose of high-LET particles was calculated by the formula: $D_n = D_{\gamma\ standard} - D_{\gamma\ mixed}$, where D_n – the equivalent dose of high-LET particles; $D_{\gamma\ standard}$ – the dose of γ-radiation when the cells were exposed to g-radiation; $D_{\gamma\ mixed}$ – the dose of γ-radiation when the cells were exposed to mixed radiation.

The human glioblastoma multiforme cells (line U251) were irradiated at an accelerator-based neutron source (Budker Institute of Nuclear Physics) in two modes: with energy of protons equal to 1.8 MeV and 2.05 MeV. In the first case, U251 cell line was irradiated for 1.5 h with photons produced in the $^7Li(p,p'\gamma)^7Li$ reaction at proton energy 1.800 ± 0.002 MeV and proton current 2.17 ± 0.03 mA. The dose absorbed by the cells was 5.21 Gy and the cell survival as a result of photon irradiation was 34 ± 4%. In the second case, to generate mixed radiation, gamma and neutron radiation, the proton energy was increased to 2.05 MeV – above the threshold of the $^7Li(p,n)^7Be$ reaction. At a current of 0.99 ± 0.02 mA, the survival fraction was 54 ± 7%, at 1.50 ± 0.04 mA - 31 ± 4%, and finally at 1.40 ± 0.05 mA the cell survival fraction was achieved exactly 34%. The proton energy was 2.050 ± 0.002 MeV and the dose absorbed by the cells was 3.98 Gy.

Since the survival rate of cells after irradiation with mixed radiation is the same as that of γ-radiation and the irradiation times were equal, the cells received the same equivalent dose – 5.21 Gy-Eq. When irradiated with mixed radiation, γ-radiation gave 3.98 Gy-Eq at this dose, which means that the remaining 1.23 Gy-Eq were due to recoil nuclei caused by the absorption of thermal neutrons and elastic scattering of fast neutrons.

The result obtained has the following practical value: it facilitates the assessment of the effect caused by irradiation, namely, when carrying out such irradiation, it is sufficient to measure only the dose of gamma radiation and assume that the sum of fast neutron doses and nitrogen doses is equal to 31 % of the γ-ray dose.

Thus, all four components of the equivalent dose can be measured: the γ-ray dose – with g-dosimeters, the boron dose – by a neutron detector with a polystyrene cast scintillator with boron, the sum of the fast neutron dose and nitrogen dose – by the method described above.

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LASER-SYNTHESIZED Bi NANOPARTICLES FOR MULTIMODAL THERANOSTICS: STUDY OF POLYMORPHIC TRANSFORMATION AND IN VITRO TOXICITY

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Nanoparticles (NPs) of high-Z elements are well known as efficient sensitizers of radiation and proton-based therapy [1].

Despite Bi have the highest atomic number of all non-radioactive materials (Z=83), Bi-based NPs also strongly absorb light over a broad spectral range extending to the NIR [2], which opens avenues for sensitization of photothermal therapy and photoacoustic imaging.

Bi NPs exhibit fast polymorphic transformation in an aqueous medium, which leads to dramatical decrease of colloidal stability and morphology change [2]. At the same time coating of the NPs with a biocompatible polymer protects them against the polymorphic transformation at neutral pH [2].

Here, we at the first time demonstrate the possibility of polymorphic transformation of laser-ablated Bi NPs in slightly acidic media (Fig. 1).

The kinetics of polymorphic transformation was determined by measure of NPs optical extinction spectra (Fig. 1a). It was found that increase of solution acidity results in decrease of the transformation time. Such unique ability of triggered transformation in low pH can be used to deliver NPs to cell cytoplasm via the endocytic pathway.

Also, we studied an in vitro toxicity of laser-ablated Bi NPs, covered with biocompatible polymer Pluronic F-127 on 3 cell lines (Fig. 2). It was found that Bi NPs have LD_{50} in the range of 62-125 ug/ml for L929 and B16 cell lines.

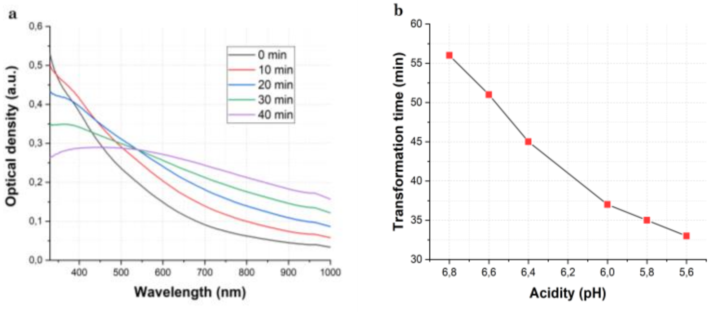

Fig.1. (a) Dependence of Bi NPs extinction spectra on time of incubation in low pH media and (b) transformation time on acidy of solution.

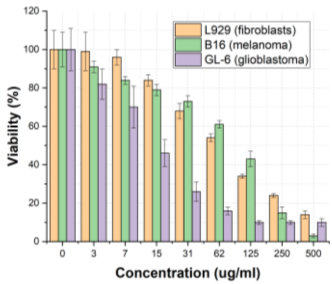

Fig.2. In vitro toxicity of laser-synthesized Bi NPs covered with Pluronic F-127.

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THE FREQUENCY OF CHROMOSOME ABERRATIONS INDUCED IN MAMMALIAN CELLS BY COMBINED EXPOSURE TO CARBON IONS AND PROTONS

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The particle therapy has unique advantages over photon therapy. One of them is the possibility of conformal irradiation of deep located tumors. The combination of different types of ions in one irradiation scheme allows improving the biological dose distribution [1]. The simultaneous irradiation by several ion beams can be implemented on special accelerators, which are a few in the world. Sequential irradiation can be carried out at different facilities (for example, proton and ion accelerators) located nearby. In this case, the biological endpoint will be depend by the effect of fractionation. In addition, the biological effect may depend on the sequence and contribution of different ions to the total dose [2].

This report presents preliminary results of cytogenetic studies, including different schemes of irradiation with protons and carbon ions beams.

Chinese hamster ovary cells were irradiated with carbon ions (A. Logunov IHEP, Protvino) and protons (A. Tsyb MRRC, Obninsk) in the sequence "carbon ions → protons". The linear energy transfer (LET) was 1 keV/μm for protons and 10-12 keV/μm for carbon ions. The time intervals between two fractions were 2 and 4 hours. Two dose levels were studied in this work, 0.5 Gy and 1.5 Gy. The dose contribution of carbon ions to the total dose was 50% and 75%. The cytogenetic effect was evaluated by metaphase analysis. The cell cultivating and preparing of the first mitosis metaphases were performed by the standard methods. All types of chromosome aberrations visible by Giemsa staining were taken into account.

The results of cytogenetic analysis show that the number of chromosome aberrations decreases with the increasing of time interval between two factions. The irradiation scheme with the contribution of 75% carbon ions was more effective for a total dose 0.5 Gy. However, no differences between contributions were found for a total dose of 1.5 Gy. The overall level of aberration yield after irradiation with carbon ions and protons in a total dose 1.5 Gy was 1.6-1.9 times lower than the expected from independent action, i.e. an antagonistic effect was shown. The efficiency coefficients of the combined effect for total dose of 0.5 Gy approximate to 1, i.e. there is a tendency to independent action.

The presented results are the preliminary stage of the study of cytogenetic effects induced by combined ion-proton irradiation.

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MgB_4O_7-BASED TISSUE-EQUIVALENT STORAGE PHOSPHORS FOR IMAGE PLATES

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Image plates for conventional roentgenoscopic investigations are based on the BaFBr:Eu phosphor [1] which is far from tissue equivalence. We discuss here tissue-equivalent MgB_4O_7-based phosphors as suitable materials to make image plates for proton therapy scheduling.

The most known among MgB_4O_7-based thermoluminescent detectors is MgB_4O_7:Dy,Na (TLD-580) [2] with good tissue equivalence. We regard MgB_4O_7:Dy,Na as possible candidate to make image plates and try to read MgB_4O_7:Dy,Na-based detectors (TLD-580n) by optical stimulation. Detectors have been produced in Laboratory of detectors of JSC "SNIIP" by prolonged annealing of a precursor (which was produced from acidic solution of initial compounds).

A surprising result of this study is a very efficient optical elimination of thermally stimulated luminescence (TSL) peaks, at which no detectable signal of optically stimulated luminescence (OSL) is observed. Moreover, photoluminescence of MgB_4O_7:Dy,Na demonstrates the lack of characteristic lines of Dy^{3+}, with the latter appearing only in the TSL spectra. This can be explained by the presence of only Dy^{2+}, before subjecting the sample to ionizing radiation. The same feature has been previously known for Tm in MgB_4O_7:Tm, where Tm^{3+} luminescence appeared after hole capturing by Tm^{2+} [3]. The absence of the OSL signal can be explained by only electron release at optical stimulation. The electrons released from traps recombine nonradiatively with trapped holes making TSL impossible. Such behavior is expected for any rare-earth impurity (RE) which is initially present in MgB_4O_7 as RE^{2+}, and vice versa, OSL may be effective for that present as RE^{3+}.

Hence, in order to create phosphors suitable for OSL readout, we should know the charge state of the RE in MgB_4O_7. This can be provided by P. Dorenbos technique [4]. The position of the RE^{3+} ground state can be found from the charge-transfer luminescence excitation bands. Knowing the ground state position for any of the RE^{3+} impurities, the others can be calculated. The 3+ state will be stable if it occurs well-above the Fermi level, otherwise the 2+ state will be preferable. We have built P. Dorenbos "zigzag curve" for RE impurities in MgB_4O_7. According to this diagram, only Ce^{3+}, Tb^{3+}, and Pr^{3+} can be stable and produce effective OSL. So, MgB_4O_7:Tb^{3+} and MgB_4O_7:Ce^{3+} can be best candidates to make image plates for proton therapy scheduling.

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THERANOSTIC SYSTEM CONTAINING RARE-EARTH NANOPARTICLES IN RADIATION THERAPY: CHARACTERIZATION AND CYTOTOXITY ASSESSMENT

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Radiation therapy is one of the main methods of cancer treatment. Radiation therapy is not a highly selective method, so the core task for the specialists is to increase the effectiveness of the method without increasing damage to healthy tissues [1]. Nanoparticles with diagnostic and therapeutic properties can be used as radiosensitizers, selectively increasing the sensitivity of cancer cells to radiation therapy, as well as for MRI imaging, making it possible to control the distribution of the radiosensitizing agent in the body [2]. Nanoparticles that simultaneously have a number of diagnostic and therapeutic properties are called theranostic agents. We proposed a theranostic system in the form of silica oxide nanoparticles loaded with cerium oxide nanoparticles doped with gadolinium.

In this work, we synthesized silica oxide nanoparticles loaded with cerium nanoparticles doped with gadolinium ions ($SiO_2 + Ce_xGd_xO_{2-x}$). The hydrodynamic radius, polydispersity index, and zeta potential were studied by dynamic light scattering and electrophoretic light scattering using a Zetasizer Nano ZS nanoparticle characterization system (Malvern Panalytical, UK). The shape of the nanoparticles was measured by transmission electron microscopy on a JEM-1011 electron microscope at an accelerating voltage of 100 kV. The synthesized $SiO_2 + Ce_xGd_xO_{2-x}$ nanoparticles have a spherical shape and a size of 146±31 nm, a zeta potential of -63 mV, and a polydispersity index of 0.2.

To study the cytotoxicity of nanoparticles, cell cultures of human osteosarcoma (MNNG/HOS), human fibroblasts (HF), and human mesenchymal stem cells (hMSc) were used using the MTT assay with viability analysis, determined using the method of fluorescent staining of living and dead cells. The studies were carried out in the range of nanoparticle concentrations from 6.7 μM to 0.67 M.

At concentrations of SiO_2 nanoparticles from 0.134 mM to 0.67 M, a decrease in the dehydrogenase activity of hMSc cells is observed compared to control values. Silica oxide nanoparticles loaded with $Ce_xGd_xO_{2-x}$ do not lead to a decrease in cell activity, which can be associated with the manifestation of the antioxidant activity of $Ce_xGd_xO_{2-x}$ nanoparticles, which provide the most favorable conditions for cell cultivation.

At concentrations of silica nanoparticles of 0.67 M, there is a decrease in the dehydrogenase activity of HF upon incubation for 48 and 72 hours to 85% compared with control values. The activity indices in the presence of silica oxide nanoparticles loaded with $Ce_xGd_xO_{2-x}$ are comparable with the control values.

At concentrations of silica oxide nanoparticles from 6.7 μM to 0.67 M, a decrease in the dehydrogenase activity of MNNG/HOS cells is observed during incubation for 24 h from 47 to 74%. The activity indices in the presence of silica oxide nanoparticles loaded with $Ce_xGd_xO_{2-x}$ are comparable with the control values.

The data obtained allow us to conclude that SiO_2 + $Ce_xGd_xO_{2-x}$ nanoparticles do not have a toxic effect on different cell cultures, and further work with X-ray exposure is expedient.

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