Form 24

RESEARCH ON THE BIOLOGICAL EFFECT OF HEAVY CHARGED PARTICLES OF DIFFERENT ENERGIES

CODE OF THEME 04-9-1077

LIST OF AUTHORS IN THE ALPHABETICAL ORDER
WITH INDICATION OF INSTITUTES, COUNTRIES AND TOWNS OF LOCATION

Dubna, LRB JINR
Aksenova S.V., Alejnikov V.E., Bazlova T.N., Batova A.S., Bezhanyan T.Zh., Beskrovnaja L.G., Bogdanova Ju.V., Boreyko A.V., Bugay A.N., Budennaya N.N., Chausov V.N., Chernyak O.O., Chizhov A.V., Fadeeva T.A., Filatova A.S., Glebov A.A., Gordeev I.S., Gurjeu D.-N., Dushanov Je.B., Enjagina I.M., Ivanov A.A., Ignat E.-M., Il'ina E.V., Isakova M.D., Khramko T.S., Kovalenko M.A., Kozhina R.A., Kokoreva A.N., Kolesnikova E.A., Kolesnikova I.A., Koltovaja N.A., Komarov D.A., Komova O.V., Komochkov M.M., Korogodina V.L., Koshlan I.V., Koshlan N.A., Krasavin E.A., Kruglyakova E.A., Krupnova M.E., Krylov V.A., Kuz'mina E.A., Kutsalo P.V., Lalkovichova M., Lesovaya E.N., Lhagvaa B., Lhasuren P.-O., Lyakhova K.N., Mel'nikova L.A., Munkhbaatar B., Nasonova E.A., Nosirova M.A., Nurkasova A., Ostrovskij M.A., Pavlik E.E., Pavlova A.S., Panina M.S., Parhomenko A.Ju., Petrova D.V., Pronskih E.V., Severyuhin Ju.S., Shamina D.D., Shvaneva N.V., Smirnova E.V., Timoshenko G.N., Tiunchik S.I., Tudjevdorzh T., Turanova D.I., Utina D.M., Vasil'ev L.A., Vasil'eva M.A., Vinogradova Ju.V., Zadneprjanec M.G., Zhuchkina N.I.

Armenia, Yerevan, YSU
Harutyunyan R.M., Harutyunyan S.G.

Belarus, Minsk, Institute of Physiology NASB
Kulchitsky V.A.
Minsk, IBCE NASB
Antonevich N.G.
Minsk, SPMRC NASB
Khasanov O.Kh., Gusakov V.E.

Bulgaria, Sofia, IE BAS
Avramov LA
Sofia, NCRRP
Khadzhidekova V.
Sofia, Institute of Microbiology. Stefana Angelova BAS
Danova S., Tsakov I.

Cuba, Havana, CENTIS
Gonzalez I.

Czech Republic, Brno, IBR ASCR
Kozubek S., Falk M.
Řež, NRI
Stefanik M.

Germany, Darmstadt, GSI
Durante M.

Italy, Naples, INFN
Blaha P.
Udine, UNIUD
Ambesi F.

Mongolia, Ulaanbaatar, NUM
Lhagva O.

Poland, Krakow, INP PAN
Swakon J., Waligorski M., Olko P., Miszczyk J., Grzanka L.
Szczecin, SU
Czerski K., Kowalska A.

Romania, Bucharest, UMF
Verga N.
Bucharest, IFIN-HH
Radu M.
Cluj-Napoca, UBB
Pasca H.
Iași, IBR
Vochita G., Mihai C.-T.

Russia, Moscow, IBMP RAS
Orlov O.I., Shtemberg A.S., Il'in E.A.
Moscow, SF IPh
Kudrin V.S.
Moscow, MSU
Latanov A.V., Poletayeva I.I.
Moscow, SINP MSU
Panasyuk M.I.
Moscow, IKI RAN
Mitrofanov I.G.
Moscow, IHNA Ph RAS
Aseyev N.A.
Moscow, N.N. Blokhin NMRCO
Lipengolts A.A.
Moscow, Skoltech
Popova E.P.
Moscow, FBMC
Osipov A.N., Rozhdestvenskiy L.M.
Obninsk, A.F. Tsyb Medical Radiological Research Centre
Zamulayeva I.A., Khvostunov I.K., Evstratova Ye.S.
Pushchino, ITEB RAS
Gaziyev A.I.
Sochi, SRI MP
Klots I.N.

Serbia, Belgrade, INS “VINČA”
Adžić M., Zdravković S, Nešković N., Čevizović D.
Belgrade, Institute for Oncology and Radiology of Serbia
Stanojković T.

Slovakia, Bratislava, CU
Dubnickova M.

South Africa, Cape Town, iThemba Labs
Vandevoorde C.

Vietnam, Hanoi, INPC VAST
Wu Thi Ha, Trinh Thi Thu Huong
Hanoi, ITRRE VINATOM
Le Thi Mai Huong

PROJECT LEADERS

Evgeny Aleksandrovich KRASAVIN

Alexander Nikolaevich BUGAY

DATE OF SUBMISSION OF THE PROJECT PROPOSAL TO SOD _____

DATE OF THE LABORATORY STC 15.05.2020 DOCUMENT NUMBER 137

STARTING DATE OF PROJECT _____

(FOR EXTENSION OF PROJECT — DATE OF ITS FIRST APPROVAL) _____

Form 25

PROJECT ENDORSEMENT LIST

RESEARCH ON THE BIOLOGICAL EFFECT OF HEAVY CHARGED PARTICLES OF DIFFERENT ENERGIES

CODE OF THEME	04-9-1077
PROJECT LEADERS	E. A. Krasavin A. N. Bugay

APPROVED BY JINR DIRECTOR _____ _____

ENDORSED BY

JINR VICE-DIRECTOR _____ _____

CHIEF SCIENTIFIC SECRETARY _____ _____

CHIEF ENGINEER _____ _____

HEAD OF SCIENCE ORGANIZATION DEPARTMENT _____ _____

LABORATORY DIRECTOR _____ _____

LABORATORY CHIEF ENGINEER _____ _____

PROJECT LEADER _____ _____

PROJECT LEADER _____ _____

ENDORSED

PAC FOR CONDENSED MATTER PHYSICS _____ _____

RESEARCH ON THE BIOLOGICAL EFFECT OF HEAVY CHARGED PARTICLES OF DIFFERENT ENERGIES

Introduction

Accelerated heavy charged particles are a powerful tool for addressing fundamental issues of modern radiobiology and genetics. Evaluation of their biological effectiveness is essential for solving radiation medicine problems. As is known, radiation therapy with proton and carbon ion beams is one of the most efficient ways of treating hard-to-reach malignant neoplasms — in particular, brain tumors. Besides, high-energy protons and heavy ions are the largest component of space radiation and would present the highest radiation risk to the crews of the manned missions beyond Earth's magnetosphere. In this connection, **particle beam therapy of tumors and ensuring the radiation safety of the future manned interplanetary flights** are the top priorities of modern radiobiology.

The availability of a wide range of radiation sources at JINR's basic facilities, including heavy ion beams of different energies, offers a unique opportunity for carrying out research in these fields. The experiments planned at JINR's accelerators will be aimed at studying the mechanisms of the action of heavy ions at the molecular, cellular, tissue, and organismal levels of biological organization. Special focus will be placed on new ways of increasing the biological effectiveness of radiation therapy with charged particle beams and the analysis of damage to experimental animals' central nervous system in order to estimate the radiation exposure risk to crews on interplanetary flights and to take into account the possible side effects of the radiation therapy of malignant neoplasms.

The scientific and methodological rationale for the theme

Unlike the electromagnetic ionizing radiations, whose energy is distributed uniformly over the volume of the irradiated cell's nucleus, in the case of accelerated heavy ions passing through matter, energy is deposited along the particle's track, inducing complex clustered DNA damage. In addition, compared with electromagnetic radiation, charged particles have an opposite depth — dose distribution: energy deposition is minimal at the beginning of the particle range (that is, when the particle passes through healthy tissues) and sharply increases near the end of the range (the Bragg peak).

Among the wide variety of different types of DNA damage induced by ionizing radiation, the most severe lesions that lead to cell death are the violations of the integrity of both DNA strands — DNA double-strand breaks (DSBs). The DSBs are formed either as a direct break of two complementary sections (direct DSBs (DDSBs)) due to energy transfer to a local DNA section or from other lesions as "repair costs" during repair enzyme functioning (enzymatic DSBs (EDSBs)). With increasing radiation's linear energy transfer (LET), changes are observed in the spectrum of the induced cell DNA damage. At low LET values, base lesions and DNA single-strand breaks (SSBs) are the most frequent damage types. High-LET heavy charged particles induce mainly DSBs — predominantly DDSBs, while the SSB yield decreases. The yield of radiation-induced DNA EDSBs

depends on a number of physical and biological factors.

These fundamental features of accelerated charged particles' action on biological objects have to be taken into account when addressing the topical issues in modern radiobiology.

As is known, **the strategy of radiation therapy** is based on providing the conditions for the following principles to be observed. **The first principle** is that the irradiation of the target (the tumor) must be conformal: the necessary energy of the radiation used must be deposited to the most extent in the tumor tissues, while causing the least damage to the adjacent healthy tissues. In comparison with electromagnetic radiations, Bragg peak proton beam therapy of deeply located tumors ensures the highest possible exposure of the tumor along with decreased exposure of the adjacent healthy tissues and critical organs. Yet greater differences between absorbed doses at different parts of the Bragg curve are typical of the accelerated carbon ions. **The second principle,** which is linked with the first, is that it is necessary to cause the heaviest damage to the tumor cells. As has been shown, this is achieved by using the specific physical features of charged particles' energy transfer to matter. A sharp increase in charged particles' LET observed when they lose their energy near the Bragg peak causes an increase in the radiation damage yield in the exposed cells, which leads to the latter's death. The higher biological effectiveness of accelerated carbon ions than that of accelerated protons is due to the higher LET of heavy ions. For this reason, specialized carbon ion therapy centers were opened in a number of countries. It should be noted, though, that such accelerators are extremely expensive compared with proton machines; so there are still only few carbon ion therapy centers worldwide, and the treatment cost is also extremely high.

The biological effectiveness of the charged particle beams is determined by factors of different nature: the physical factor, which is connected with the character of energy deposition in the cells' sensitive targets (particles' LET, dose rate, etc.), and the biological factor, which determines the yield of the damage causing cell death (the cell's repair status, oxygenation, the cell cycle phase, the tumor microenvironment, etc.). The yield of radiation-induced DNA EDSBs can be influenced by a certain modification of DNA repair processes. In particular, in an *in vitro* research conducted at the Laboratory of Radiation Biology, JINR, it has been found that, in the presence of the DNA synthesis inhibitors 1-β-D-arabinofuranosyl cytosine (Ara-C) and hydroxyurea (HU), after γ-ray and accelerated proton exposure the DNA DSB yield significantly increases during post-irradiation incubation of cells due to the transformation of nonlethal DNA damage to EDSBs. A preliminary *in vivo* study, in which a melanoma tumor transplanted into mice was exposed to accelerated protons in the presence of Ara-C, has shown a threefold decrease in the tumor growth rate in the post-irradiation period compared with a usual proton exposure (Fig. 1). Further development of the proposed approach will probably bring much closer to each other the therapeutic fields of use of proton accelerators and much more expensive carbon ion accelerators and increase the efficiency of the therapeutic use of photon radiation

sources.

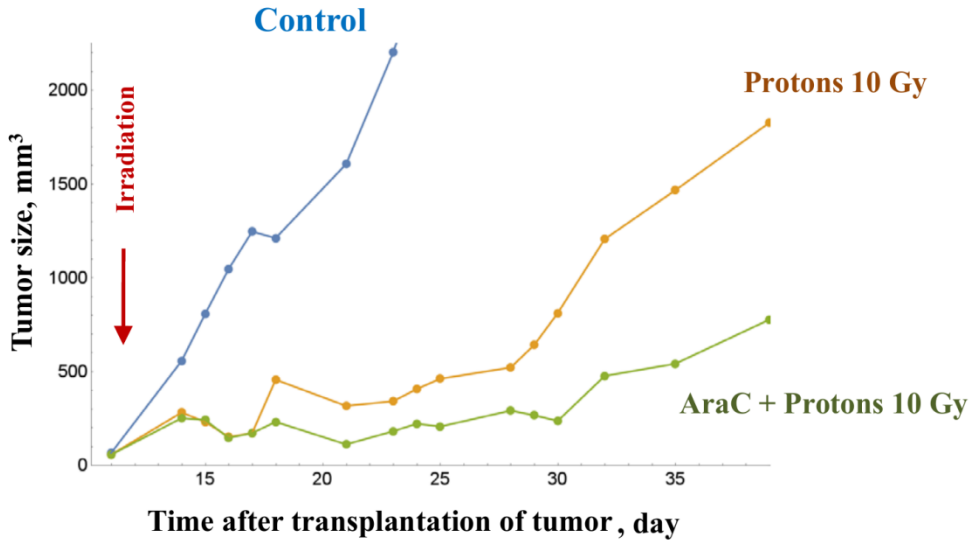

Fig. 1 The growth kinetics of a melanoma tumor transplanted into mice: The control (non-exposed) animal data are shown in blue; Bragg peak proton exposure of mice at a dose of 10 Gy in the presence and without Ara-C are shown in green and orange, respectively.

The idea of manned deep space missions involves new challenges to specialists in **space radiobiology.** The spectrum of the galactic cosmic rays (GCR) consists of high-energy protons and highly charged high-energy ions. The latter, despite their low fluence values, contribute hugely to the radiation risk to the crews due to their high biological effectiveness. Most of current knowledge about GCR action is based on terrestrial experiments at charged particle accelerators. From this perspective, JINR's basic facilities offer ample opportunities to model the biological action of space radiation. The modern concept of the radiation risk of the manned interplanetary flights considers the whole mission-long ergonomic risk determined by damage to the central nervous system (CNS) to be of the first importance. Here, the main task is to study in detail the character and mechanisms of the action of accelerated heavy charged particles, first, on cultures of nervous system cells — especially, cells with high proliferative activity; second, on laboratory animals' CNS structures and behavior.

In view of the above, solving the related fundamental and practical problems urgently requires the continuation of detailed research on the mechanisms of the action of accelerated heavy charged particles at the molecular, cellular, tissue, and organismal levels of biological organization. Studying molecular damage to genetic structures is important, first of all, for the analysis of the induction of the most severe DNA lesions: double-strand breaks (DSBs). An efficient method of the three-dimensional analysis of clustered DNA DSBs (the DNA foci method), which has been developed and introduced at the LRB, will allow studying the formation of the heaviest damage to the genetic apparatus caused by exposure to accelerated multi-charged ions and make it possible to conduct research on the formation and repair of genetic damage in proliferating tissues and in highly differentiated elements of the

nervous system. Finding out the mechanisms of response to the action of accelerated charged particles of different energies will lay the ground for understanding the tissue reactions of highly differentiated cell systems — structures of different parts of the CNS — to radiation exposure. In turn, this research will allow evaluating CNS integrity violations: disorders of cognitive functions and behavior. The practical character of such complex research is absolutely clear from the point of view of a number of applied areas — first of all, solving the problems of human space radiobiology.

During the conduction of the planned research, of special importance will be finding out the mechanisms behind increasing the biological effectiveness of proton and photon beams on radioresistant tumor cells and studying radiation action on tumors transplanted into experimental animals. Earlier results on the modifying effect of agents like cytosine arabinoside in combination with other drugs on DNA DSB yield for ionizing radiations of different quality, along with the possible prospects for the clinical use of DNA synthesis inhibitors of this type and ionizing radiation, point to the necessity of further research within the scope of the proposed Theme.

A review of research on the Theme

During the previous stage of the Theme, with the use of JINR's accelerators, a number of principal issues have been resolved concerning the mechanisms of the biological action of accelerated charged particles in a wide range of linear energy transfer (LET). Research has been focused mainly on genetic damage to cells of different origin and radiation-induced physiological disorders in mammalian organisms.

In *radiation genetics* experiments at JINR's basic facilities, formation and repair kinetics of DNA double-strand breaks (DSBs) induced by accelerated heavy ions has been studied in detail. Dose dependences of clustered DNA damage formation frequency in human cells have been obtained. Accelerated heavy charged particles have been found to be highly efficient in inducing clustered damage. It has been shown that the structure, size, and shape of clustered damage depend on ions' linear energy transfer (LET). It has been found that after accelerated multi-charged ion exposure, the elimination kinetics of radiation-induced genetic damage in cells is slower than after γ-ray exposure, which points to a decrease in DNA DSB repair efficiency. A series of works entitled "Research on molecular damage formation in genetic structures of human and mammalian cells after exposure to low and intermediate-energy accelerated heavy ions" won JINR's First Prize in 2020. Along with molecular aspects of the biological action of accelerated heavy ions, the mutation process has been studied in mammalian cells. In a wide LET range, the mutant clone yield has been studied at different times after exposure. It has been established that in the post-irradiation period the highest mutant clone yield depends on particles' LET and post-irradiation time.

In *radiation physiology research*, morphological and functional changes have been studied in

the retina and different parts of the brain in rodents. It has been found that the retina is highly radioresistant as evaluated based on morphological and functional damage in the post-irradiation period. Quantitative regularities have been established in the development of morphofunctional disorders in different brain parts after accelerated proton and carbon ion exposure; pharmacological action of nootropic drugs (Fig.2) on radiation exposure effects has been evaluated (in 2018, patent for an invention No. 2666937 was received). Behavioral disorders in exposed animals have been studied with different test systems in the post-irradiation period. In cooperation with specialists of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences (RAS) and RAS Institute of Biomedical Problems, the action of high-energy (500 MeV/nucleon) carbon ions on the metabolism of the key neuromediators of the rodent brain has been evaluated. The most radiation-sensitive parts of the brain have been identified, where metabolism changed at shorter and longer times after exposure.

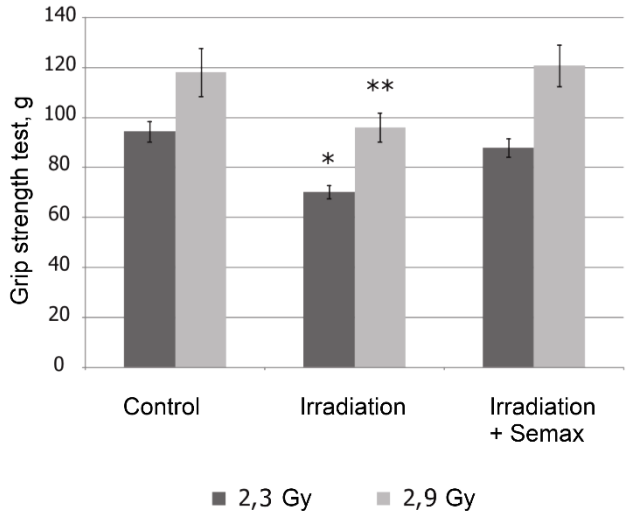

Fig. 2 The influence of the Semax drug on mice's forelimb grip strength on the 8th day after accelerated proton exposure.

A new *concept of the radiation risk for manned interplanetary flights* has been proposed and justified. The concept links the radiation risk to cosmonauts mainly to the action of the heavy nuclei of galactic cosmic rays on the central nervous systems' structures. During the flight, this exposure can affect the brain's highest integrative functions and result in the disruption of the crew members' operator activity. The new paradigm requires a change of the main fields of space radiobiology research and indicates the necessity of the development of new regulations on the radiation safety of the manned deep space flights.

Along with experimental research, a significant amount of theoretical work has been done on the *mathematical modeling of radiation-induced effects.* Methods have been developed of calculating the formation of DNA damage of different types in charged particle tracks passing through brain cells and structures. A molecular dynamics approach has been proposed to the quantitative account of the

action of mutations in hippocampal neurons' genes on the condition of synaptic receptors. The influence has been modeled of radiation-induced effects on the functioning of the brain's neural networks.

Molecular radiobiology research on the effect of some modifiers on the DNA DSB yield in the case of exposure of human normal and tumor cells to radiation in a wide LET range has shown that in the presence of some drugs the yield of DNA DSBs — the damage that leads to cell death in the post-irradiation period — is modified to different degrees. These modifiers include the officinal drugs 1-β-D-arabinofuranosyl cytosine (Ara-C) and hydroxyurea (HU). In the presence of these modifying agents, after γ-ray and accelerated proton exposure, the DNA DSB yield significantly increased during post-irradiation incubation of cells. After high-LET heavy ion exposure, the radiomodifiers' influence sharply weakened. Research on the mechanism of these agents' amplifying effect on cells' radiosensitivity has shown that Ara-C is kind of a Trojan horse at the molecular level. With the use of immunocytochemical methods, it has been found that, in the presence of the modifiers, after cell exposure to accelerated protons, the DNA DSB yield increases, and cells' radiosensitivity sharply rises to the level that is observed in the case of carbon ion beam exposure. An increase in the DNA DSB yield in the presence of Ara-C and HU is explained by an increase in the yield of enzymatic DNA DSBs which developed from single-strand breaks. Using the discovered phenomenon can be considered an efficient approach to improving radiation therapy techniques (in 2019, patent for an invention No. 2699670 was received).

Description of the proposed research

Molecular radiobiology

For a number of years, using different techniques, the Laboratory of Radiation Biology (LRB) has been conducting research on the molecular damage induced by electromagnetic and particle radiation in the genetic structures of mammalian and human cells. For these investigations, immunocytogenetic and immunohistochemical techniques have been widely used in recent years. These methods allow not only the quantitative analysis of genetic disorder formation, but also taking into account the spatial distribution of damage in cells' genetic structures. It is an important fact, which makes it possible to answer the question: Does cells' capability of repair depend on the distribution of different types of DNA damage, and if yes, how? Finding out how different proteins detect clustered damage, how fast the identification of different DNA damage types is, and which proteins are the first to reach the DNA damage location is essential for solving many fundamental problems of cytology and genetics. DNA DSB induction in certain parts of the cell's genome causes a specific phosphorylation of the H2AX histone in chromatin surrounding the lesion, which shows up as the formation of the so-called γH2AX foci. The internal structure of these radiation-induced foci (RIF) is a

network of biochemical pathways triggered by cells in response to the appearance of a DNA lesion to restore DNA integrity. The planned studies of RIF nanostructure using fluorescent and confocal microscopy (Fig.3) and single molecule localization microscopy — high-resolution nanoscopy — will allow finding out how radiation's physical characteristics and chromatin structure at a local DNA DSB formation site affect RIF micro-and nanostructure and, on the other hand, how the micro- and nanostructure of damaged chromatin and RIF affects the choice of a damaged site repair pathway and, further, repair kinetics and efficiency. Of special interest is the comparative analysis of the patterns and mechanisms of the induction and repair of DNA molecule damage in normal cells and radioresistant tumor cells exposed to γ-rays, protons, and heavy ions of different energies.

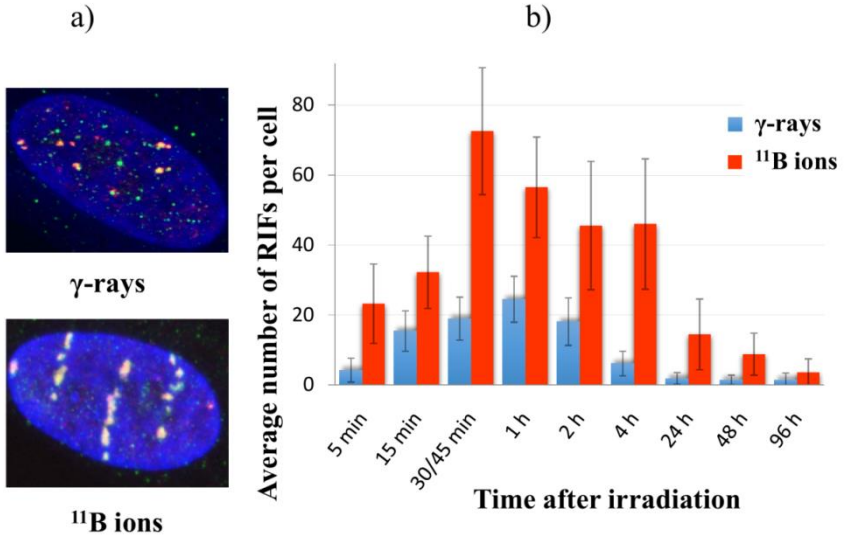

Fig. 3. RIF visualization *(a)* and repair kinetics *(b)* after γ-ray and 50 MeV/nucleon ^{11}B ion exposure

As is known, the main DNA DSB repair pathways are non-homologous end joining (NHEJ) and homologous recombination (HR). It is important that the repair pathways in the cancer cells are often deregulated, which makes them DNA DSB repair-defective. Using the immunocytochemical method with different RIF formation markers (H2AX, 53BP1, Rad51, etc.) will allow the analysis of the chromatin structure on a damaged site, its change kinetics, and determining which repair type makes the main contribution to damage elimination. On the basis of these data, the regulation mechanisms will be identified that determine the repair pathway choice depending on the chromatin structure on a local site, cell type, cell cycle phase, and ionizing radiation's physical characteristics.

Research will be performed not only on normal and tumor cell cultures, but also on neuronal cell cultures and histological sections of tissues of different parts of irradiated animals' central nervous system.

Within the framework of further research, it is planned:

- to study patterns of the formation of clustered DNA DSBs in human skin fibroblast nuclei and radioresistant U87 tumor cells after exposure to accelerated heavy ions;
- to find out whether the distribution of different DNA damage types affects the cells' ability for repair; if yes, how.
- to find out how different proteins identify clustered damage; how fast the identification of different DNA damage types is; and which proteins are the first to head towards the DNA damage location;
- to study the post-irradiation repair kinetics of clustered DNA DSBs in human skin fibroblast nuclei and radioresistant U87 tumor cells;
- to find out how the radiation's physical characteristics and the chromatin structure at a local DNA DSB formation site influence RIF microstructure and nanostructure;
- to study how the micro- and nanostructure of damaged chromatin and RIF affects the choice of the damaged site repair pathway and, later, repair kinetics and efficiency — in normal cells and radioresistant tumor cells exposed to γ-rays, protons of different energies, and accelerated heavy ions;
- using different RIF formation markers — γH2AX, 53BP1, RAD51, etc. — to analyze the chromatin structure at a damaged site and evaluate how it changes with time; and to find out which repair type makes the greatest contribution to damage elimination.

Radiation genetics

The mutagenic action of ionizing radiation of different quality — especially, accelerated heavy ions — on mammalian and human cells have still been poorly studied. It is planned to continue the research that has already been underway at the LRB on the efficiency of the induction of different types of gene and structural mutations depending on the radiation's dose and LET (Fig. 4), repair status, and oxidative stress development, as well as to clarify the mechanisms behind genetic stability.

It is obvious that studying the mechanisms of the induction of gene mutations in human cells by accelerated charged particles of different energies is extremely difficult. For this purpose, mammalian and eukaryote cell cultures are good model objects. The yeast *Saccharomyces cerevisiae* is a unicellular eukaryotic organism, in which the genetic control and molecular mechanisms of fundamental cell processes like replication, repair, and transcription have been investigated most comprehensively. Haploid tester strains are used to detect different molecular events, including base pair changes, omissions of one nucleotide, deletions, and recombinational rearrangements. The direct gene mutation testing system employed at the LRB allows detecting any gene mutations on a long section — in particular, 1.8 kbp-long arginine permeases, which emerge within the gene. It is planned

to continue research on the mutagenic action of sparsely and densely ionizing radiations using these tester systems; to determine more precisely mutations' molecular nature, induced point mutation sequencing and the electrophoretic and restriction analysis of deletion mutants are going to be used.

Besides nuclear DNA, there is mitochondrial DNA (mtDNA) in cells. The latter's mutagenesis and functional importance are still poorly studied. The ease of manipulating mtDNA in yeasts make them an ideal object for studying the role of mitochondria and mtDNA in radiation's mutagenic effect — in particular, as regards respiration and iron metabolism. It is planned to investigate the development of mitochondrial mutations and the influence of mitochondrial respiration-deficient mutations on the lethal and mutagenic action of radiation.

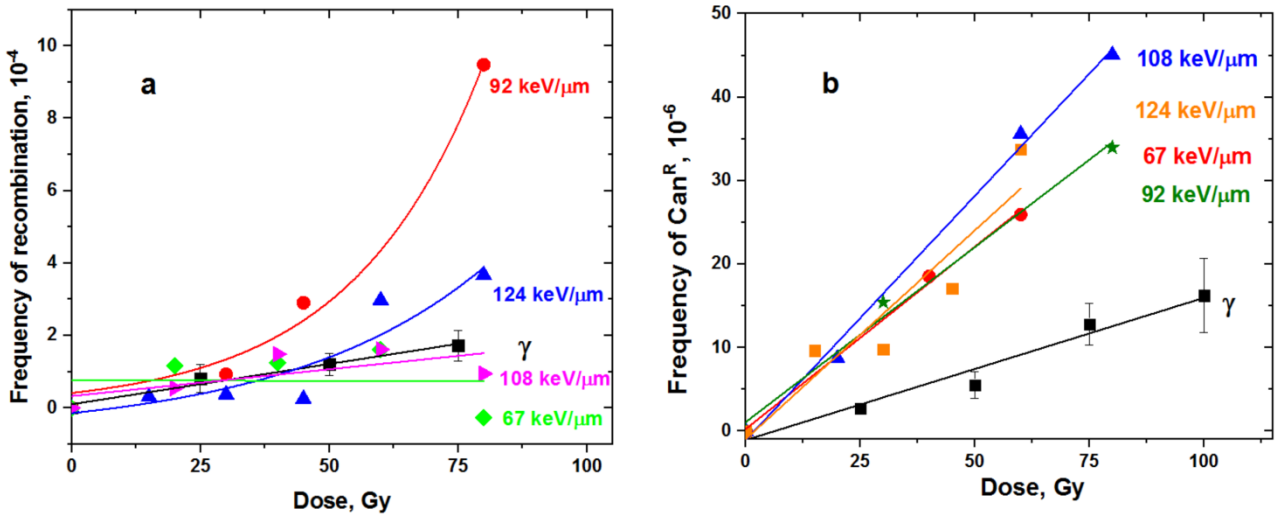

Fig. 4. Frequency of recombination (a) and forward mutations (b) in haploid yeast cells irradiated by beams of accelerated nitrogen ions with different LET.

Undoubtedly, of special interest are the mechanisms that increase radioresistance and suppress mutagenesis. At the LRB, a nuclear mutation was earlier obtained and genetically characterized that has a wide action spectrum — in particular, it increases cells' radioresistance and affects genetic stability. It is planned to study the radioresistance mechanism, to map this mutation, and to analyze the mutation's influence on genome expression. The preliminary protein electrophoresis data show that the mutation is localized in the regulatory gene.

Concerning repair and mutagenesis, of extreme importance is nucleotide balance. It is planned to continue the analysis of human inosine triphosphate pyrophosphohydrolase hITPA, which ensures the balance of the quantity of non-canonical nucleotides in the cell. In humans, the enzyme's inactivation changes sensitivity to medicines; in microorganisms, the gene's destruction leads to genetic instability. *In silico* experiments have shown that the bond between the mutant subunits becomes weaker, but it is unknown whether it is the reason for a decrease in the enzyme's activity. Further *in vitro* research is needed on the model organisms of yeasts and human cells (the yeast gene

ham1 and the human gene *itpa*). It is planned to investigate the mechanism of phosphatase activity regulation and the influence of the enzyme's inactivation on radiosensitivity, cell cycle regulation at the checkpoints, apoptosis, and ageing.

In the course of research on radiation-induced mutagenesis in V79 Chinese hamster cells, genome instability has been discovered in the HPRT mutants throughout numerous generations of a mutant cell. The mutants have been shown to be heterogeneous by a number of cytogenetic indicators. In particular, radiation-induced mutants have been found with a decreased, compared with the spontaneous, chromosomal damage yield. It points to a possibility of the "stabilization" of the genome that was exposed to accelerated ions. The analysis of structural damage in the *hprt* gene in descendants of a mutant cell will allow understanding possible mechanisms behind genome instability.

Within the framework of further research, it is planned

- to continue investigation of the induction of point mutations and structural rearrangements using accelerated ion beams;
- to study the influence of respiratory impairment caused by mitochondrial DNA damage on sensitivity to the damaging and mutagenic action of radiation;
- to study the radioresistance mechanism in a yeast mutant;
- to analyze the influence of the *ham1* mutation on yeast cells' sensitivity to the damaging and mutagenic action of radiation;
- to analyze checkpoint activation in the S phase and DNA damage accumulation in Itpa-deficient cells;
- to examine the possibility of phosphatase's enzymatic activity regulation due to chemical modifications in yeast and human cells;
- to perform a PCR analysis of structural damage to the *hprt* gene in descendants of irradiated V79 cells;
- to compare structural and chromosomal damage spectra in radiation-induced mutants at different times after exposure.

Radiation cytogenetics

Chromosomal aberrations have been studied for more than half a century, but there are still many unanswered questions in this area. The state-of-the-art technique of multicolor (or multiplex) fluorescent *in situ* hybridization (mFISH), which is now used at the LRB, allows identifying each pair of human and animal chromosomes by DNA chromosome hybridization with probes labeled with unique combinations of five fluorochromes. The main advantage of this method is that it is possible to study complex chromosomal aberrations (three and more breaks in two and more chromosomes).

Using mFISH made it clear that many aberrations that were considered simple are in fact part of a complex, which includes breaks in several chromosomes and their interaction. The introduction of mFISH thus leads to the necessity of the revision of all postulates of classical cytogenetics and changes the current concept of chromosomal aberrations, their spectrum, and their distribution over cells. As an example, one of the first discoveries made with 2–3-color FISH can be mentioned: it has been found that the well-known linear quadratic dependence of the dicentric yield on the dose of sparsely ionizing radiation is determined by complex aberrations, while the dicentric yield evaluated by the classical technique depends on the dose linearly.

Accordingly, mFISH analysis is proposed to be used, first of all, for evaluating complex chromosomal aberrations induced by radiations of different quality (Fig.5). Now, it is clear that complex aberrations are the marker of densely ionizing radiation, indicating a narrowly localized clustered DNA damage. Even at low doses of densely ionizing radiation, up to 80% of the induced aberrations are complex. However, their adequate evaluation can be done only with mFISH because 2–3-color FISH exposes only some part of the complex due to a limited number of the stained chromosomes, which leads to data distortion and a loss of a significant amount of information. Using mFISH will provide new insights into the mechanisms of radiation-induced aberration formation. In radiation cytogenetics, the induction of complex chromosomal aberrations by accelerated protons and intermediate energy heavy ions (tens of MeV/nucleon) has still been poorly studied — such beams are available at JINR's basic facilities. It is planned to conduct research on the action of such particles on human and mammalian normal and tumor cells.

The mFISH method is also promising for studying the long-term consequences of the radiation exposure of the organism as it allows evaluating translocations — inherited symmetric aberrations that can survive for a long time in irradiated cells' progeny. In this connection, it is planned to study in experiments on small laboratory animals (mice and rats) the chromosomal aberration yield in bone marrow cells and blood lymphocytes for acute and chronic γ-ray and accelerated proton and heavy ion exposure. The residual chromosomal damage in bone marrow cells and blood lymphocyets are planned to be examined during 6–8 months after exposure by both mFISH and the standard metaphase method; in parallel, the radiation-induced response of the hematopoietic, immune, and other regulatory systems of the organism will be studied, which is very important for solving problems of space radiobiology and radiation oncology.

The technique of premature chromatin condensation, which allows measuring the initial yield of radiation-induced DNA breaks, will be used for a comparative evaluation of chromatin break induction and repair in human normal and tumor cells.

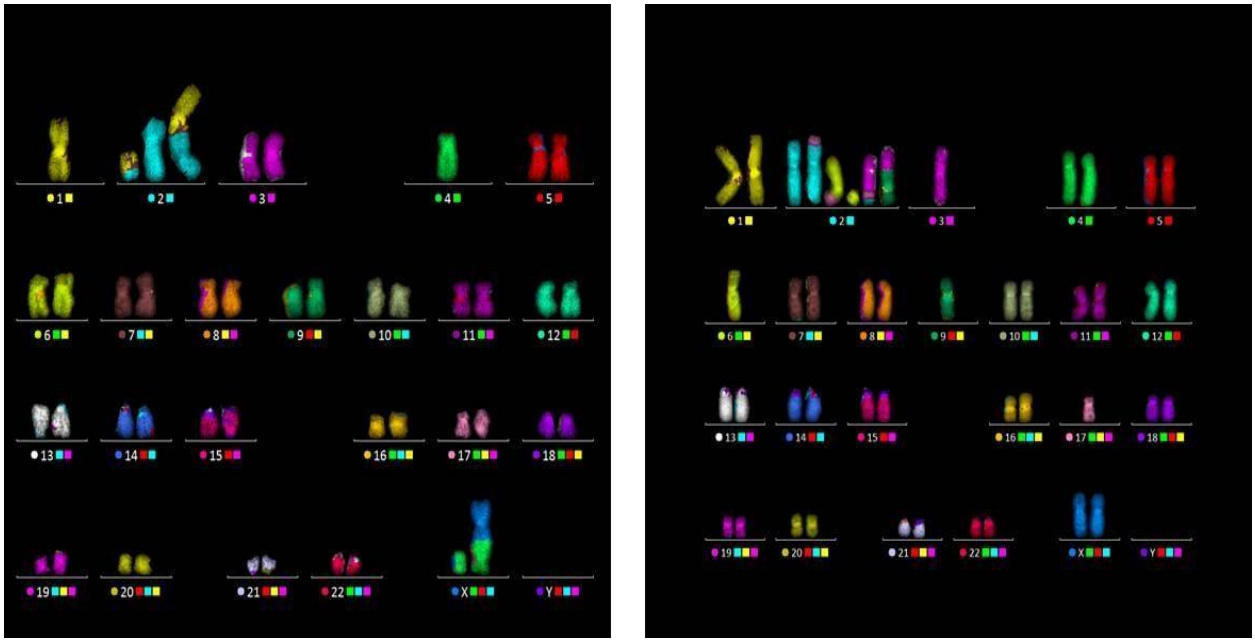

Fig. 5. An mFISH image of the karyotype of human lymphocytes exposed to 2 Gy of ^{60}Co γ-rays, containing two simple exchanges (dicentrics) which involve four chromosomes (left) and 2 Gy of Bragg peak protons (right), containing one complex aberration which involves six breaks in five chromosomes.

Using mFISH in combination with the standard metaphase method will also allow addressing in detail the problem of genome instability, which is connected with chromosomal rearrangements. Here, heavy charged particle beams will be used as an instrument for identifying the corresponding mechanisms. For this purpose, research will be conducted on spontaneous and radiation-induced chromosomal aberrations in different cultures of mammalian and human cells.

Within the framework of further research, it is planned

- to study *in vitro* the induction of complex chromosomal aberrations in human normal and tumor cells by densely ionizing radiations;
- to evaluate *in vivo* the acute and long-term consequences of radiation exposure. In experiments on animals to assess the action of radiations on nervous system structures, to study, in parallel, the chromosomal aberration yield in bone marrow and lymphocytes for acute and chronic exposure;
- to perform an mFISH study of the induction of complex and symmetric inherited chromosomal aberrations in human cells by exposure to different radionuclides used in cancer therapy;
- to do an analysis of karyotypes and evaluate the genetic stability of different lines of stem cells cultivated *in vitro;*

- to perform a comparative premature chromatin condensation analysis of the induction and repair of chromatin breaks in human normal and tumor cells after exposure to photons and accelerated protons and ions;
- to evaluate with the metaphase method chromosomal aberrations in lymphocytes of primate blood induced by a local exposure of the animal's head to accelerated ions of different energies.

Radiation physiology

In the coming period, radiation physiology research will be focused mainly on behavioral reaction disorders in irradiated animals and pathomorphological changes in different structures of the brain, spinal cord, and critical organs and systems of rodents. The evaluation of behavioral reactions is going to be made using the whole set of modern zoopsychology techniques and equipment, including test systems for assessing long-term and short-term memory, emotional reactivity, the anxiety level, and motor reflexes. Behavior parameters will be analyzed with modern video tracking tools. To study pathologies in the animal organism caused by radiation exposure, it will be necessary to use delicate techniques of surgical intervention and catheterization. With this purpose, the research program includes the introduction of systems for laboratory animals' anesthesia, electrophysiological and hematological analysis, and internal organ perfusion. Pathomorphological changes in tissues will be studied with modern histological and immunohistochemical methods using light, and fluorescent microscopy instruments.

There are practically no data on densely ionizing radiation-induced effects in microglia, oligodendrocyets and their precursors, and myelin sheath. However, it is known that accelerated multi-charged ions impair laboratory animals' mental and motor functions more heavily than electromagnetic radiation — even at much lower exposure doses.

To clarify the possible mechanisms of radiation-induced damage to the central nervous system (CNS) and cognitive functions, it is planned to investigate the extremely important role of glial cells in this process. As one of the most probable causes of ionizing radiation-induced cognitive deficit, considered is demyelination — the destruction of axons' myelin sheath due to oligodendrocyte death.

In the development of cognitive disorders in irradiated mammals, a no less important role is played by microglia, which is the basis of CNS immune defense under the normal physiological conditions. But microglia’s activation by radiation exposure causes a chronic neuroinflammation and, as a result, development of cognitive disorders.

Both mechanisms — demyelination and neuroinflammation —play key roles in the CNS functional disorders in the course of neurodegenerative diseases like multiple sclerosis, Huntington's, Parkinson's, and Alzheimer's. However, there have been no advances in understanding the basis of

radiation-induced cognitive disorders. Therefore, using radiations with different physical characteristics can be considered as an approach to research on the interplay between cognitive disorders and changes in the glial cell population and myelin structure as well as to evaluating the risks of densely ionizing radiation exposure to the CNS.

Within the framework of further research, it is planned

- to develop pharmacological protection and therapy for particle radiation exposure;
- to continue studying effects of exposure to accelerated protons and secondary radiation generated by protons passing through spacecraft elements and space base construction materials;
- to continue studying primary and long-term morphological and functional changes in the CNS of SD rats and CD-1 mice after accelerated proton exposure;
- to study the action of particle radiations of different LET on pathogenesis in organs and tissues of small laboratory animals;
- to study the secretion of inflammatory cytokines in mouse brain homogenates after irradiation;
- to study the myelin basic protein (MBP) level in irradiated mouse brain homogenates at different times after exposure;
- using fluorescent markers, to study the yield of oligodendrocyte and MBP precursors in irradiated mouse brain sections at different times after exposure.

Molecular radiobiological aspects of radiation therapy

Earlier LRB's research showed that, in the presence of the DNA synthesis inhibitors 1-β-D-arabinofuranosyl cytosine (Ara-C) and hydroxyurea (HU), the DNA double-strand break (DSB) yield in the cells exposed to γ-rays and high-LET particles is modified in the post-irradiation period to different degrees (Fig. 6). In the presence of the modifying agents, after γ-exposure, the DNA DSB yield significantly grew during post-irradiation incubation of human lymphocytes and other cells in culture. For accelerated heavy ion exposure, however, the agents' modifying effect was weaker. Their influence on DNA DSB formation is determined by Ara-C being an efficient inhibitor of DNA α-polymerase and, to a lower degree, β-polymerase, which perform DNA repair synthesis. HU, being a ribonucleotide reductase inhibitor, affects the intracellular pool of nucleotides (in particular, cytosine), and diminishes it. As the result, prolonged fixation of the emerging direct DNA single-strand breaks (SSBs) or SSBs that are forming during excision repair takes place. Such lesions can become sites of enzymatic DNA DSB formation caused by S1 nucleases attacking the thread opposite to the damaged site. As Ara-C and HU are officinal drugs used for the treatment of acute and chronic leukemia, and,

as part of combined or complex therapy, HU is used for the treatment of different tumors (head and neck tumors, skin melanoma, and the colon, rectum, uterine neck, kidney, and prostate cancer), it seems essential to study their effect on the molecular damage formation in human cells after spread-out Bragg peak proton exposure. The current clinical use of these drugs is based on inhibiting the S phase of the cell cycle. Taking into account the LRB's earlier results on the modifying effect of these agents on the DNA DSB yield for exposure to ionizing radiations of different quality and the possible prospects for their practical use, it is necessary to conduct further research on the influence of these agents on the biological effectiveness of proton beams on different tumor cell cultures and tumors transplanted into mice.

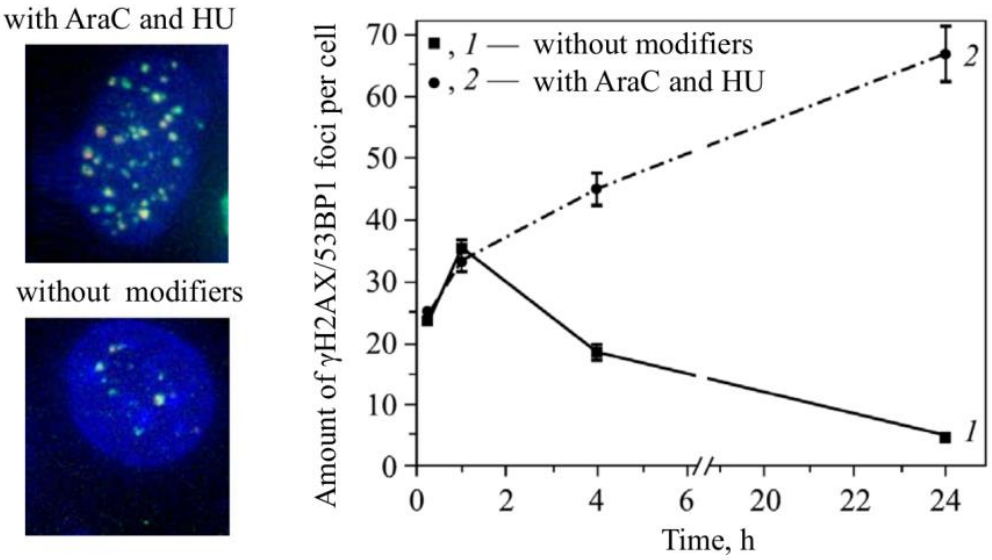

Fig.6 Images of individual RIF (γH2AX/53BP1) 24 h after exposure and their formation and elimination kinetics in human cell nuclei after exposure to 170 MeV Bragg peak protons at a dose of 1.25 Gy — under normal conditions and in the presence of Ara-C and HU.

Within the framework of further research, it is planned

- To study the effect of arabinosidcytosine on the survival of various human cell lines by the criterion of clone formation, the formation of apoptosis under the action of protons and γ-quanta;
- To study the kinetics of the formation and elimination of γH2AX / 53BP1 foci in the culture of U87 glioblastoma cells and other radioresistant lines when irradiated with protons at the Bragg peak and γ-quanta under normal conditions and in the presence of AraC;
- To study the patterns of the formation of double-strand DNA breaks in various parts of the central nervous system when irradiated *in vivo* with protons and γ-quanta without a radio modifier and in the presence of AraC;

- To study the contribution of double-strand DNA breaks repair to the radioresistance of tumor cells;
- To investigate the induction, kinetics of the formation and conversion of single-stranded DNA breaks into double-stranded breaks for various types of normal and tumor cells irradiated in the presence or absence of AraC (+/- HU);
- To study the effect of AraC (+/- HU) on the radiosensitization of normal and tumor cells under various radiation fractionation schemes and levels of cellular hypoxia;
- To check the effect of new radiosensitizers (4,6-dichloro-5-nitropyrimidine, etc.), similar in their mechanism of action to AraC;

Mathematical modeling of radiation-induced effects

Future work will be focused on the development of an hierarchy of models that would allow systematizing experimental data and studying the pathways of how radiation-induced pathologies develop at different organization levels (from molecules to cell populations) and time scales (acute and long-term radiation effects). It will require a wide range of computational methods from different areas of knowledge, including modeling charged particle transport in matter, molecular dynamics, polymer biophysics, genetic regulatory networks, modeling the dynamics of cell populations, and information procession and transmission in neural networks. Also, computational resources will be needed, including JINR's supercomputer.

As part of research within the framework of the Theme, typical radiation therapy scenarios will be modeled for different types of radiation: γ-rays and accelerated protons and carbon ions. Unlike using the common therapy planning software packages, this research will yield detailed distributions of DNA damage — not only the absorbed dose — over the tumor. The study will focus mainly on central nervous system (CNS) cells, which are a rather difficult target for such calculations due to their complex geometry. The formation and repair of the main types of DNA damage (first of all, double-strand breaks (DSBs) — both direct and enzymatic) will be modeled with the Geant4-DNA software package. Also, it will be possible to assess in more detail the damage to the healthy cells in the adjacent tissues.

Based on the obtained data on DNA damage, models of radiation-induced death of normal and tumor cells will be developed. They will be validated by known experimental data. These models will be used to calculate the dynamics of different cell populations: different tumor cells and radiosensitive CNS cells (neuronal stem cells and glial cells). Detailed tumor growth models will be developed, and post-irradiation tumor dynamics will be studied. This approach is going to be generalized to a number of promising mechanisms of increasing therapy efficiency. Examined will be the physical mechanisms that are already used to increase the biological effectiveness of charged particle beams (using

nanoparticles as a target increasing the effect) and the most promising biological mechanisms (using DNA synthesis inhibitors, which transform simple nonlethal DNA damage into lethal enzymatic DSBs). It is planned to work out an approach to choosing the optimal combined therapy parameters, including the concentrations of the active substances, beam parameters, therapeutic dose, its fractioning, etc.

It is also planned to assess charged particles' influence on the functioning of neural networks of the brain's critical parts — first of all, the hippocampus (Fig. 7). Scenarios will be examined of both acute local exposure (to evaluate radiation therapy safety) and total chronic exposure (to advance in the solution of the problem of space radiation action on cells during interplanetary flights). In the latter case, for the first time the action will be investigated of a spectrum of charged particles of different energies and fluences on the DNA damage yield and dynamics of cell populations. For further assessment of possible CNS pathologies after exposure, research will be conducted on different mutant and oxidized forms of the synaptic receptors determining interneural interaction and the dynamics of neurogenesis and gliogenesis. The obtained data will be systematized and used in modeling the functioning of the brain's neural networks. It will allow estimating the failure probabilities of different types of memory and learning, which is essential for the theoretical evaluation of the radiation risks.

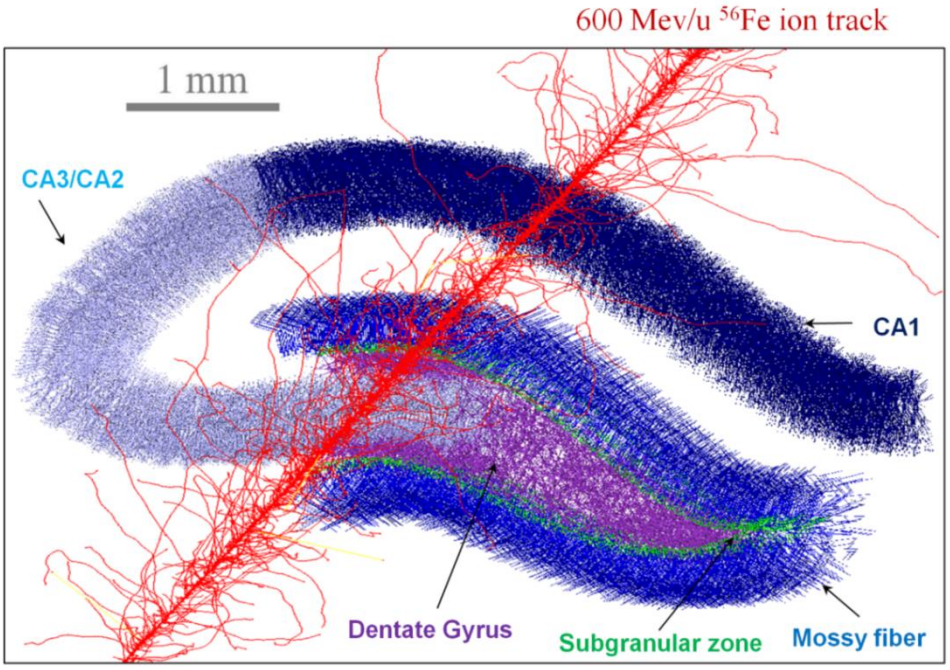

Fig. 7. A Monte Carlo simulation of a 600 MeV/nucleon ^{56}Fe ion track in a three-dimensional rat hippocampus model which includes the main parts of the hippocampus and cell types (shown in different colors).

Within the framework of further research, it is planned

- to develop mathematical models of the formation of the key types of DNA damage and their repair and the formation of mutations and chromosomal aberrations;

- to perform molecular dynamics modeling of impairments of the structure and functioning of mutant and oxidized forms of proteins;
- to develop mathematical models of radiation-induced tumor cell death and prediction of tumor growth in the course of applying promising methods of radiation therapy;
- based on mathematical models of neural networks, to perform a theoretical evaluation of radiation-induced CNS disorders taking into account synaptic receptor damage, oxidative stress, and impairments of neurogenesis and gliogenesis.

Improvement of accelerator-based radiobiological experiment procedures

It is planned, first of all, to provide scientific and technological support to radiobiological experiments at charged particle accelerators and to work towards constructing new and upgrading existing irradiation facilities. Within the framework of the NICA project, it is planned to continue the LRB's participation in the creation of the SODIB station (the Biological Station for Long-Range Ion Exposure) at the Nuclotron, JINR's Laboratory of High Energy Physics (LHEP), for radiobiological research at carbon, neon, argon, iron, and krypton ion beams with energies of 250–1000 MeV/nucleon. In cooperation with the LHEP, technical specifications will be developed for the SODIB station and positioning table; working designs will be agreed upon. Also, further upgrade will be continued of the LRB's Genom automated irradiation facility at the U-400M cyclotron, JINR's Laboratory of Nuclear Reactions. In particular, it is planned to replace the facility's electromechanical system with a stepper motor; to develop new control software; and to include in the facility units of time-of-flight ion energy measurement and monitoring the spatial distribution of the radiation field using a two-dimensional strip ionization chamber.

Radiation safety research will be focused on the LRB's participation in designing JINR's new nuclear physics facilities — first of all, the NICA accelerator complex. Documenting the evaluation of the radiation conditions at NICA will be completed; radiation safety calculations will be made to determine the buffer zone of the complex; and the radiation conditions at the complex will be calculated for accelerating and colliding 12.7 GeV protons.

Concerning research on radiation fields at JINR's nuclear physics facilities and in their environment, measurements will be continued of neutron spectra at the facilities and in places with the most complex radiation conditions.

In space radiobiology, Monte Carlo calculations of radiation transport in matter will be performed using the software toolkits GEANT4, FLUKA, and PHITS in order to make a realistic evaluation of the cosmonauts' effective doses depending on flight duration, solar activity, and radiation protection of the habitable module. It is planned to continue modeling galactic cosmic radiation (GCR) fields at high-energy accelerators for experimental space radiobiology research — in particular, to

study the possibility of modeling the GCR heavy ion field at the 1 GeV/nucleon iron ion beam at the Nuclotron.

As part of the joint research program with the Institute of Space Research of the Russian Academy of Sciences and JINR's Laboratory of Neutron Physics, the functioning of the DAN (Dynamic Albedo of Neutrons) experimental stand will be provided, and the LRB's participation will be continued in the design, fabrication, testing, and calibration of nuclear planetary science instruments for studying the elemental composition of the surface of Solar System's celestial bodies and the search for water ice.

Within the framework of further research, it is planned

- to upgrade the Genome facility at the MC400 cyclotron;
- to participate in the construction of the Nuclotron's radiobiological beam;
- to continue work on predicting the radiation conditions at the NICA complex;
- to explore the possibility of constructing a facility at the Nuclotron for modeling the GCR heavy ion field;
- to continue neutron spectrum measurements at JINR's nuclear physics facilities;
- to continue the joint work with the Institute of Space Research of the Russian Academy of Sciences and JINR's Laboratory of Neutron Physics on creating and testing nuclear planetary science instruments.

Publications

1. *Depes D., Lee J.-H., Bobkova E., Jezkova L., Falkova I., Bestvater F., Pagacova E., Kopecna O., Zadneprianetc M., Bacikova A., Kulikova E., Smirnova E., Bulanova T., Boreyko A., Krasavin E., Hausmann M., Falk M.* Single-molecule localization microscopy as a promising tool for H2AX/53BP1 foci exploration // Eur. Phys. J. D., 2018, V.72. P.158.
2. *M.G. Zadneprianetc, A.V. Boreyko, T.S. Bulanova, L. Ježková, E.A. Krasavin, E.A. Kulikova, E.V. Smirnova, M. Falk, I. Falkova.* Regularities in the formation and elimination of γH2AX/53BP1 foci induced by γ-rays and accelerated heavy ions // Radiation Biology. Radioecology. 2018, Vol. 58, No. 2, pp. 146–156 (in Russian).
3. *M.G. Zadneprianetc, A.V. Boreyko, T.S. Bulanova, L. Ježková, E.A. Krasavin, E.A. Kulikova, E.V. Smirnova, M. Falk, I. Falkova.* Structure analysis of complex damage to DNA caused by accelerated ^{11}B ions and ^{60}Co γ-rays // Radiation Biology. Radioecology. 2018, Vol. 58, No. 3, pp. 229–237 (in Russian).
4. *Jezkova L., Boreyko A. V., Bulanova T. S., Davidkova M., Falkova I., Kozubek S., Depes D. Krasavin. E., Kruglyakova E., Smirnova E., Valentova O., Zadneprianetc M., Falk M. //*Nanoscale 2018. V.10(3). P.1162-1179.
5. *Zadneprianetc M.G., Boreyko A.V., Bulanova T.S., Ježková L., Krasavin E.A., Kulikova E.A., Smirnova E.V.* The Influence of Physical Characteristics of Accelerated Heavy Ions on the Formation and Repair of DNA Double-Strand Breaks // Physics of Particles and Nuclei Letters, 2018, Vol. 15, № 6, P. 693-699.
6. *Bobkova E., Depes D., Lee J.-H., Jezkova L., Falkova I., Pagacova E., Kopecna O.,*

Zadneprianetc M., Bacikova A., Kulikova E., Smirnova E., Bulanova T., Boreyko A., Krasavin E., Wenz F., Bestvater F., Hildenbrand G., Hausmann M., Falk M. Recruitment of 53BP1 Proteins for DNA Repair and Persistence of Repair Clusters Differ for Cell Types as Detected by Single Molecule Localization Microscopy // International Journal of Int. J. Mol. Sci., 2018. V.19, P.3713.

7. *Kulikova E., Boreyko A., Bulanova T., Ježková L., Zadneprianetc M., Smirnova E.* Visualization of clustered DNA damage along accelerated ions tracks. // EPJ Web of Conferences 2018. V. 177, P.06002.
8. *Bulanova T.S., Zadneprianetc M.G., Ježková L., Kruglyakova E.A., Smirnova E.V., Boreyko A.V.* Induction and Repair of DNA Double-Strand Breaks in Rat Cerebellar Cortex Exposed to ^{60}Co γ-Rays. //Physics of Particles and Nuclei Letters, 2018, V. 15, No. 1, P. 121-126.
9. *Boreyko A.V., Bugay A.N., Bulanova T.S., Dushanov E.B., Jezkova L., Kulikova E.A., Smirnova E.V., Zadneprianetc M.G., Krasavin E.A.* Clustered DNA Double-Strand Breaks and Neuroradiobiological Effects of Accelerated Charged Particles // Physics of Particles and Nuclei Letters, 2018, V. 15, No. 5, P. 551-561.
10. *Kozhina R.A., Chausov V.N., Kuzmina E.A., Boreyko A.V.* Induction and repair of DNA double-strand breaks in hippocampal neurons of mice of different age after exposure to ^{60}Co γ-rays *in vivo* and *in vitro* // EPJ Web Conf. EDP Sciences, 2018. Vol. 177. P. 06001.
11. *Bulanova T.S., Boreyko A.V., Zadneprianetc M.G., Krasavin E.A., Kulikova E.A., Smirnova E.V., Severiukhin Y.S., Timoshenko G.N.* Formation of DNA Double-Strand Breaks in Rat Brain Neurons after Irradiation with Krypton Ions (78Kr) // Physics of Particles and Nuclei Letters, 2019, V. 16, No. 4, pp. 402-408.
12. *Koltovaya N.A., Zhuchkina N.I., Koltovoyi N.A., Hlinkova E.* Effect of γ– and proton irradiation on algae Euglena. Scientific discussion. 2017. №11, V.1, p.10-20.
13. *Koltovaya N., Kokoreva A., Shvaneva N., Zhychkina N.* Mutagenic effects induced by accelerated ^{11}B ions with energy of 12-30 MeV/u on yeast *Saccharomyces cerevisiae*. // Rad. Applic. 2017. V. 2. Issue 2. P.82-85.
14. *Koltovaya N.A.* Molecular mechanisms of mutagenesis // Modern mycology in Russia. 2017. pp. 25–30.
15. *Koltovaya N., Kokoreva A., Shvaneva N., Zhuchkina N.* Kinetics of UV-induced gene and structural mutations. Journal of Radiation and Applications. 2017. V. 2. Issue 1. P. 10-13.
16. *Koltovaya N.A.* CDK1/CDC28 kinase and DNA integrity control in the yeast *Saccharomyces cerevisiae* // Radiatsionnaia biologiia, radioecologiia. 2017. Vol. 57, No. 6, pp. 573–590 (in Russian).
17. *Koltovaya N.A.* DNA damage-independent cell cycle arrests in the yeast *Saccharomyces cerevisiae* // Radiatsionnaia biologiia, radioecologiia. 2018. Vol. 58. No. 1. pp. 5–14.
18. *Bláha P., Koshlan N.A., Koshlan I.V., Petrova D.V., Bogdanova Y.V., Govorun R.D., Múčka V., Krasavin E.A.* Delayed effects of accelerated heavy ions on the induction of HPRT mutations in V79 hamster cells // Mutation Research. 2017. V. 803-805. P.35-41.
19. *Koltovaya N., Zhuchkina N., Lyubimova K.* All types of base pair substitutions induced by γ-rays in haploid and diploid yeast cells // J. Bioeng. Life Sci. 2018. V. 12. № 9.
20. *Koltovaya N., Lyubimova K., Zhuchkina N.* Genetic effects after irradiation of heavy ions in haploid and diploid yeast cells // Rad. Applic. 2018. V. 3. Issue 3. P.185-189
21. *Dushanov E.B., Koltovaya N.A.* Effect of substitution Pro32Thr on the interaction between dimer subunits of human phosphatase ITPA // Cur. Enzyme Inhibition 2019. V. 15. Issue 1. P. 46-54.
22. *I.V. Koshlan, N.A. Koshlan, P. Blaha, Yu.V. Bogdanova, D.V. Petrova, R.D. Govorun, E.A. Krasavina* Radiation-induced mutagenesis in mammalian cells after exposure to accelerated ions of different linear energy transfer // Physics of Particles and Nuclei Letters. 2020, V. 17, No. 1, P.573-588.

23. *Komova O. Krasavin E., Nasonova E., Mel'nikova L., Shmakova N., Cunha M., Testa E., Beuve M.* Relationship between radioadaptive response and individual radiosensitivity to low doses of gamma radiation: An extended study of chromosome damage in blood lymphocytes of three donors. // International Journal of Radiation Biology. 2017. V.94. P.1-27.
24. *Kowalska A., Czerski K., Nasonova E., Kutsalo P., Krasavin E.* Radiation dose-response curves: cell repair mechanisms vs. ion track overlapping? // Eur. Phys. J. D 2017 V.71. P. 332.
25. *Hartel C., Nasonova E., Fuss M., Nikoghosyan A., Debus J., Ritter S.* Persistence of radiation-induced aberrations in patients after radiotherapy with C-ions and IMRT. // Clinical and Translational Radiation Oncology. 2018 V.13. P.57-63.
26. *Kowalska A., Pereira W., Czersrki K., Nasonova E., Kutsalo P.* Fano Factor of chromosome aberrations and asessment of repair efficiency // Acta Phys. Pol. A 2018 V.133. P.225-227.
27. *Kowalska A., Nasonova E., Czerski K., Kutsalo P., Pereira W., Krasavin E.* Production and distribution of chromosome aberrations in human lymphocytes by particle beams with different LET // Radiation and Environmental Biophysics. 2019. V.58. P.99-108.
28. *Czerski K., Kowalska A., Nasonova E., Kutsalo P., Krasavin E.* Modeling of chromosome aberration response functions induced by particle beams with different LET // Radiation and Environmental Biophysics 2019, V.59. P.79-87.
29. *Kowalska A., Czerski K., Nasonova E., Kutsalo P., Krasavin E.* Initial radiation DNA damage observed in prematurely condensed chromosomes of G2-phase human lymphocytes and analytical model of ion tracks // Eur. Phys. J. D2020, V.74. P. 17.
30. *Pereira W., Kowalska A., Czerski K., Nasonova E., Kustalo P., Valerievich L.E.* Deviations from Poisson Statistics Observed in Chromosome Aberrations Induced by ^{252}Cf Neutrons // Acta Phys. Pol. B 2020. V.51. P.881.
31. *Severyukhin Yu.S., Budennaya N.N., Timoshenko G.N., Ivanov A.A., Krasavin E.A.* Morphological changes in Purkinje cells of the rat cerebellar cortex after irradiation with ^{12}C ions // Aviakosmicheskaia i ekologicheskaia meditsina, 2017, Vol. 51, No. 1, pp. 46–50 (in Russian)
32. *K.V. Belokopytova, O.V. Belov, Gaevsky V.N., V.B. Narkevich, V.S. Kudrin, E.A. Krasavin, A.S. Bazyan A.S.* Neuromediator exchange dynamics in rats at long times after ^{60}Co γ-ray exposure // Meditsinskaya radiologiya i radiatsionnaya bezopasnost (Medical Radiology and Radiation Safety). 2017, Vol. 62, No. 2, pp. 5–12 (in Russian)
33. *Ivanov A.A., Mitsyn G.V., Abrosimova A.N., Bulynina T.M., Gaevsky V.N., Dorozhkina O.V., Lyakhova K.N., Severyukhin Yu.S., Utina D.M., Krasavin E.A.* Radiobiological effects of the secondary radiation at the Phasotron, the Joint Institute for Nuclear Research // Aviakosmicheskaia i ekologicheskaia meditsina, 2017, Vol. 51, No. 3, pp. 46–53 (in Russian)
34. *Lyakhova K.N., Ivanov A.A., Molokanov A.G., Severyukhin Yu.S., Utina D.M, Krasavin E.A.* The effect of the Semax neuropeptide on proton-irradiated mice's cognitive behavioral activity indicators and skeletal muscle strength // Aerospace and Environmental Medicine. 2018, Vol. 52, No. 4, pp. 71–76 (in Russian)
35. *Kolesnikova I.A., Budennaya N.N., Severyukhin Yu.S., Lyakhova K.N., Utina D.M.* Analysis of the morphofunctional condition of experimental animals' brain structures in a long-term period after proton irradiation // Bulletin of New Medical Technologies. 2018, Vol. 25, No. 3. pp. 177–181 (in Russian)
36. *Lyakhova K.N., Kolesnikova I.A., Utina D.M., Severyukhin Yu.S., Budennaya N.N., Abrosimova A.N., Molokanov A.G., Lalkovičova M., Ivanov A. A. Morphofunctional* Indicators of the Effects of Protons on the Central Nervous System // Medical Radiology and Radiation Safety. 2019; 64(2):75-81. (Russian). DOI: 10.12737/article_5ca60c7bba45e9.77708543
37. *Lyakhova K.N., Kolesnikova I.A., Budennaya N.N., Severyukhin Yu.S., Utina D.M., Molokanov A.G., Ivanov A. A.* The action of the Semax drug on the vital status and

morphological changes in the brain of mice after accelerated proton exposure // Radiatsionnaya biologiya, radioekologiya. 2019, Vol. 59, No. 2, pp. 191–199 (in Russian)

38. *Severyukhin Y. S., Feldman T.B., Ostrovsky M.A. and Molokanov A.G.* Effects of Cranial Exposure to 170-MeV Proton Radiationat a Dose of 5 Gy on the Visual Behavior and Optomotor Response of Adults Rats // Biology Bulletin, 2019, Vol. 46, No. 12, P. 46–51.
39. *Cataldi S., Borrelli A., Ceccarini M.R., Nakashidze I., Codini M., Belov O., Ivanov A., Krasavin E., Ferri I., Conte C., Patria F. F., Traina G., Beccari T., Mancini A., Curcio F., Ambesi-Impiombato F.S., Albi E.* Neutral Sphingomyelinase Modulation in the Protective/Preventive Role of rMnSOD from Radiation-Induced Damage in the Brain // Int J Mol Sci. 2019. V.20 No.21. P.5431.
40. *E.A. Krasavin, A.V. Boreyko, V.N. Chausov. E.V. Ilyina, R.A. Kozhina, E.A. Kulikova, E.A. Kuzmina, E.V. Smirnova, G.N. Timoshenko, S.I. Tiounchik, M.G. Zadnepryanets.* DNA synthesis inhibitors' effect on the biological effectiveness of a modified Bragg peak proton beam // JINR Preprint, P19-2018-48, 2018 (in Russian)
41. *V.N. Chausov, A.V. Boreyko, T.S. Bulanova, E.V. Ilyina, L. Ježková, E.A. Krasavin, R.A. Kozhina, E.A. Kulikova, E.A. Kuzmina, E.V. Smirnova, S.I. Tiounchik M.G. Zadnepryanets.* Induction of direct and enzymatic DNA double-strand breaks by radiation of different quality in the presence of repair inhibitors // Particles and Nuclei, Letters. 2018, Vol. 15, No. 6 (218), pp. 573–588 (in Russian)
42. *Kuzmina E.A., Chausov V.N., Dubnickova M., Gaevsky V.N., Ilyina E. V., Kozhina R.A., Timoshenko G.N., Tiounchik S.I., Boreyko A. V.* Modifying effect of different forms of lipid A on the induction of DNA double-strand breaks in mice hippocampal cells after exposure to ionizing radiation of different quality in vitro // AIP Conference Proceedings. American Institute of Physics Inc., 2019. V. 2163. № 1. P. 050002.
43. *E.A. Krasavin, A.V. Boreyko, M.G. Zadneprianetc, E.V. Ilyina, R.A. Kozhina, E.A. Kuzmina, E.A. Kulikova, E.V. Smirnova, G.N. Timoshenko, S.I. Tiunchik, V.N. Chausov.* The action of DNA synthesis inhibitors on the biological effectiveness of a modified Bragg peak proton beam // Particles and Nuclei, Letters. Vol. 16, No. 2 (221), 2019, pp. 181–190 (in Russian)
44. *E.A. Krasavin, A.V. Boreyko, I.A. Zamulaeva.* A new method of increasing the efficiency of ionizing radiation action on tumor tissue cells // Proceedings of the 3rd Russian conference with international participation "Radiobiological Basis of Radiation Therapy" (Dubna, 17–18 October 2019). Dubna: JINR, 2019, pp. 84–85 (in Russian)
45. *Bugay A.N., Aru G.F., Dushanov E.B., Parkhomenko A.Yu.* Radiation Induced Dysfunctions in the Working Memory Performance Studied by Neural Network Modeling // Belgrade BioInformatics Conference Proceedings. University of Belgrade, 2017. P.18-28.
46. *Zdravković S., Bugay A.N., Parkhomenko A.Yu.* Application of Morse potential in nonlinear dynamics of microtubules // Nonlinear Dynamics 2017. V.90. P.2841-2849.
47. *Batmunkh M., Bugay A.N., Bayarchimeg L., Lkhagva O.* Radiation damage to nervous system: designing of optimal models for realistic neuron morphology // European Physical Journal Web of Conferences 2018. V.173. P. 05004.
48. *Zdravković S., Satarić M.V., Parkhomenko A.Yu., Bugay A.N.* Demodulated standing solitary wave and DNA-RNA transcription // Chaos 2018. V.28. P.113103.
49. *Batmunkh M., Aksenova S.V., Bayarchimeg L., Bugay A.N., Lkhagva O.* Optimized neuron models for estimation of charged particle energy deposition in hippocampus // Physica Medica 2019. V.57 P.88-94.
50. *Bayarchimeg L., Bugay A., Batmunkh M., Lkhagva O.* Evaluation of Radiation-Induced Damage in Membrane Ion Channels and Synaptic Receptors // Phys. Part. Nucl. Lett. 2019 V.16, P.54-62.
51. *Batmunkh M., Bayarchimeg. L, Bugay A.N., Lkhagva O.* Monte Carlo track structure simulation in studies of biological effects induced by accelerated charged particles in the

central nervous system //EPJ WoC. 204, 04008, 2019.
52. *Batmunkh M., Bugay A.N., Bayarchimeg. L, Aksenova S.V., Lkhagva O.* Computer Modeling of Radiation – Induced Damage to Hippocampal Cells // Mongolian Journal of Physics. 2019. V.5. P.76-82.
53. *Togotokhtur T., Lkhagva O., Batmunkh M., Bayarchimeg L., Lkhagvajav T.* The use of Einstein–Smoluchowski equation to study the chemical reaction-diffusions in neurons induced by a charged particle // Mongolian Journal of Physics. 2019. V. 5. P. 72-75.
54. *Batmunkh M., Bayarchimeg L., Bugay A.N., Lkhagva O.* Computer modeling of DNA damage formation in nerve cells under exposure to accelerated heavy charged particles // Aktual'nye voprosy biologicheskoi fiziki i khimii (Current Issues in Biological Physics and Chemistry). 2019. Vol. 4, No.2, pp. 214–219 (in Russian)
55. *Kolesnikova E.A., Bugay A.N.* Modeling the influence of heavy ion beams on neurogenesis and functioning of hippocampal neural networks // EPJ Web of Conferences, Vol. 204, 2019. P. 04007.
56. *Aksenova S.V., Batova A.S., Bugay A.N., Dushanov E.B.* The influence of mutant forms of the NMDA synaptic receptors on oscillations in neural networks // Aktual'nye voprosy biologicheskoi fiziki i khimii (Current Issues in Biological Physics and Chemistry). 2019. Vol. 4, No.2, pp. 209–213 (in Russian)
57. *Batova A.S., Bugay A.N., Dushanov E.B.* Effect of mutant NMDA receptors on the oscillations in a model of hippocampus // Journal of Bioinformatics and Computational Biology, 2019, V.17, №1, P. 1940003.
58. *Ivanov A.A., Mitsyn G.V., Timoshenko G.N., Bulynina T.M., Krylov A.R., Krasavin E.A.* Phasotron proton beam-based modeling of neutron fields generated inside a spacecraft // Aviakosmicheskaia i ekologicheskaia meditsina, 2017, Vol. 51, No. 2, pp. 20–25 (in Russian)
59. *Timoshenko G.N., Krylov A.R., Paraipan M., Gordeev I.S.* Particle accelerator-based simulation of the radiation environment on board spacecraft for manned interplanetary missions // Radiation Measurements 2017 V.107. P. 27-32.
60. *Beskrovnaia L.G., Guseva S.V., Timoshenko G.N.* Method for Monitoring of Neutron Fields near High-Energy Accelerators. // Physics of Particles and Nuclei Letters. 2018, V. 15, No. 3, P.336-341.
61. *Toan C.N., Beskrovnaia L.G., Latysheva L.N., Sobolevsky N.M., Timoshenko G.N.* Dosimeter for Measuring the Ambient Dose of Neutrons with Energy from 10^{-4} MeV to 1 GeV Based on a Cylindrical Polyetylene Moderator // Physics of Particles and Nuclei Letters. 2019, V. 16, No. 1, P.63-69.
62. *Timoshenko G.* Neutron spectrometry at JINR nuclear facilities // Nuclear Instruments and Methods A, 2019, V. 945, No. 21, P. 512-518.
63. *Timoshenko G., Belvedersky M.*Fluence-to-Effective Dose Conversion Coefficients for Male Astronauts // Journal of Radiological Protection 2019. V. 39, No 2, P. 511-521.
64. *Timoshenko G.N., Paraipan M., Krylov A.R., Gordeev I.S.* Radiation safety at the NICA complex // JINR Project Solutions. Dubna: JINR, 2019 (in Russian).
65. *Chan Ngok Toan, Beskrovnaya L.G., Timoshenko G.N., Latysheva L.N. Sobolevsky N.M.* Dosimeter for Measuring the Ambient Dose of Neutrons with Energy from 10^{-4} MeV to 1 GeV Based on a Cylindrical Polyethylene Moderator // Physics of Particles and Nuclei Letters, 2019, V.16, No. 1, P. 63-69.
66. *Mitrofanov I.G. et al.* Gamma spectrometry of compound targets — planetary matter analogs — at a JINR accelerator's proton beam using the labeled proton technique // Particles and Nuclei, Letters. 2019 (in press) (in Russian) // Письма в ЭЧАЯ. 2019. Т.16. №3 (222). С.233-239.
67. *Timoshenko G., Gordeev I.* Simulation of radiation field inside interplanetary spacecraft // Journal of Astrophysics and Astronomy. 2020. V.41. P.5.

Human resources

The team of participants includes 74 employees of JINR's LRB, of whom 20 are highly qualified specialists in radiation biology and radiation physics with many years of professional experience. Among them are a RAS Academician, a RAS Corresponding Member, six Doctors of Sciences, and 12 Candidates of Sciences. The number of young employees (under 35) is 39, which is 53% of the team.

For more than 20 years, the Biophysics Department of Dubna University has offered graduate and postgraduate programs in radiobiology. Many of those who completed them work successfully at the LRB. In addition, the LRB has a long tradition of attracting and employing graduates of Moscow State University and Moscow Engineering Physics Institute. All this provides sufficient reinforcement of the Laboratory with young staff.

In joint work with the LRB, research teams participate from Armenia, Belarus, Bulgaria, Cuba, the Czech Republic, Germany, Italy, Mongolia, Poland, Romania, Russia, Serbia, Slovakia, South Africa, and Vietnam. The LRB's membership in the International Biophysical Collaboration will allow attracting a larger number of participants from different countries to the project.

Work schedule

	Main tasks and stages	Time frames (year, quarter)	
		Start	**End**
1	Finding out the patterns of clustered DNA double-strand break (DSB) formation in human skin fibroblast nuclei and radioresistant U87 tumor cells after accelerated heavy charged particle exposure.	2021-I	2023-IV
2	Analysis of the formation patterns and structure of complex clustered DNA damage by immunocytochemical staining of the repair proteins γH2AX, 53BP1, OGG1, and XRCC1 in human fibroblast nuclei after accelerated heavy ion exposure.	2021-I	2023-IV
3	Studying the kinetics of clustered DNA DSB repair in human skin fibroblast nuclei and radioresistant U87 tumor cells after accelerated heavy charged particle exposure.	2021-I	2023-IV
4	Studying the formation of different DNA damage types (single-strand breaks, base damage, and complex damage) in human fibroblast nuclei after accelerated heavy charged particle exposure.	2021-I	2023-IV
5	Assessment of the proportion of different DNA DSB repair pathways in human fibroblasts by immunocytochemical staining of the repair proteins RAD51 (HR) and DNA PKcs (NHEJ) after exposure to radiations of different quality.	2021-I	2023-IV
6	Research on the formation and repair kinetics of clustered DNA DSBs in neuron precursor cell nuclei and mature neurons and in glial cells of the mammalian central nervous system (CNS) after accelerated heavy charged particle exposure — using the cell subpopulation markers NeuN, doublecortin, GFAP, BrdU, and calbindin.	2021-I	2023-IV
7	Experiments to study the expression of the genes encoding the repair proteins (RAD51, DNAPKcs, NBS1, MRE11, etc.) in human skin fibroblasts after accelerated heavy charged particle exposure.	2021-I	2023-IV
8	Research on apoptosis induction in human skin fibroblasts and mammalian CNS neurons after accelerated heavy charged particle exposure.	2021-I	2023-IV
9	Experiments to study the expression of the genes encoding the proteins and caspases participating in apoptosis induction in human fibroblasts and nerve cells after accelerated heavy charged particle exposure.	2021-I	2023-IV
10	Studying *in vitro* the formation and elimination of DNA DSBs in the rat hippocampal cells using a primary hippocampal culture obtained from rats aged P0–P1.	2021-I	2023-IV

11	Finding out the patterns of DNA DSB formation in mammalian CNS neurons after γ-ray and accelerated heavy ion exposure.	2021-I	2023-IV
12	Research on clustered DNA DSB repair kinetics in mammalian CNS neurons after γ-ray and accelerated heavy ion exposure.	2021-I	2023-IV
13	Research on the expression of the genes encoding the repair proteins (RAD51, DNA PKcs, NBS1, MRE11, etc.) in human fibroblasts after exposure to ionizing radiations with different characteristics.	2021-I	2023-IV
14	Research on the induction of point mutations and structural rearrangements by accelerated ions.	2021-I	2023-IV
15	Evaluation of the action of respiratory impairment caused by mitochondrial DNA damage on sensitivity to radiation's damaging and mutagenic effects.	2021-I	2023-IV
16	Studying the characteristics of the mutation which decreases cells' radiosensitivity	2021-I	2023-IV
17	Analysis of the radiosensitivity, genetic stability, and biochemical specifics of the inactivated phosphatase of humans and yeasts.	2021-I	2023-IV
18	PCR analysis of structural damage in the *hprt* gene in descendants of irradiated V79 cells.	2021-I	2021-IV
19	Comparing structural and chromosomal damage spectra in radiation-induced mutants at different times after exposure.	2021-III	2023-IV
20	*In vitro* research on complex aberration induction in human normal (lymphocytes) and tumor (Cal 51 breast carcinoma) cells by photons, accelerated protons, and accelerated boron and nitrogen ions.	2021-I	2023-IV
21	mFISH and standard metaphase analysis of the induction and elimination (3–6 months after exposure) of chromosomal aberrations in animal bone marrow cells and blood lymphocytes.	2021-I	2023-IV
22	mFISH analysis of chromosomal aberrations induced in human peripheral blood lymphocytes by different types of radiation used in cancer therapy.	2021-I	2023-IV
23	mFISH karyotyping and analysis of structural and numerical chromosomal aberrations in different lines of human stem cells cultivated in vitro.	2021-I	2023-IV
24	Premature chromatin condensation research on the induction of chromatin breaks in human normal (lymphocytes) and tumor (Cal 51 breast carcinoma) cells by γ-rays and accelerated protons and ions at different times after exposure.	2021-I	2023-IV

25	Metaphase analysis of long-term consequences of accelerated carbon and krypton ion exposure of the head of *Macaca mulatta* monkeys.	2021-I	2022-IV
26	Research on morphological and functional changes in the CNS of SD rats and CD-1 mice after accelerated proton exposure.	2021-I	2021-IV
27	Development of radioprotector drugs based on new understanding of radiation damage pathogenesis, including radiation's action on the CNS and hematopoiesis.	2022-I	2022-IV
28	Research on the effects of exposure to accelerated protons and secondary radiation generated by protons passing through spacecraft elements and space base construction materials.	2023-I	2023-IV
29	Research on the influence of particle radiations of different LET on pathogenesis in organs and tissues of small laboratory animals.	2023-I	2023-IV
30	Studying inflammatory cytokine secretion in mouse brain homogenates after radiation exposure.	2021-I	2022-IV
31	Measurements of the myelin basic protein (MBP) level in irradiated mouse brain homogenates at different times after exposure.	2021-IV	2023-IV
32	Fluorescent marker-based evaluation of the yield of oligodendrocyte and MBP precursors in irradiated mouse brain sections at different times after exposure.	2023-I	2023-IV
33	Studying the effect of cytosine arabinoside (Ara-C) on the survival of different mammalian and human normal and tumor cell lines by the criteria of clone formation and apoptosis after exposure to accelerated protons and γ-rays.	2021-I	2023-IV
34	Studying the formation and elimination kinetics of γH2AX/53BP1 foci in cultures of U87 glioblastoma cells and cells of other radioresistant tumor lines after exposure to Bragg peak protons and γ-rays — under normal conditions and in the presence of Ara-C (±HU).	2021-I	2023-IV
35	Research on DNA DSB formation in different parts of rodent CNS after *in vivo* irradiation with accelerated protons and γ-rays without radiomodifiers and in the presence of Ara-C (±HU).	2021-I	2023-IV
36	Studying the kinetics of DNA single-strand break formation and transformation into DSBs for different types of normal and tumor cells irradiated in the presence and absence of Ara-C (± HU)	2021-I	2023-IV
37	Studying the influence of Ara-C (± HU) on the radiosensitizing of normal and tumor cells for different exposure fractionation schemes and different cell hypoxia levels.	2021-I	2023-IV

38	Examining the efficiency of new radiosensitizers (4,6-dichlor-5-nitropyrimidine, 5-nitro-2,4-dichloropyrimidine, etc.) which have the action mechanism similar to that of Ara-C	2021-I	2023-IV
39	Modeling DNA formation and repair after irradiation of normal and tumor cells with heavy charged particles of different energies.	2021-I	2023-IV
40	Modeling the induction of mutations and chromosomal aberrations in eukaryotic cells by irradiation with heavy charged particles of different energies.	2021-I	2023-IV
41	Modeling the growth of a tumor cell population after ionizing radiation exposure in the presence of DNA synthesis inhibitors.	2021-I	2023-IV
42	Modeling the growth of a tumor cell population after ionizing radiation exposure in the presence of metal nanoparticles.	2021-I	2023-IV
43	Modeling the action of a charged particle spectrum corresponding to galactic cosmic rays on DNA damage formation and elimination in nervous system cells.	2021-I	2023-IV
44	Molecular dynamics modeling of impairments of the structure and functioning of mutant and oxidized forms of proteins.	2021-I	2023-IV
45	Modeling radiation-induced neurogenesis and gliogenesis impairments and neuroinflammatory processes in CNS structures.	2021-I	2023-IV
46	Modeling accelerated heavy charged particles' action on the functioning of the brain's neural networks.	2021-I	2023-IV
47	Radiobiological experiments at Nuclotron ion beams.	2023-I	2023-IV
48	Radiobiological experiments at MC-400 ion beams.	2022-I	2023-IV
49	Radiobiological experiments at the Phasotron and Rocus-M.	2021-I	2023-IV
50	Research on predicting the radiation conditions at the NICA complex.	2021-I	2023-IV
51	An upgrade of the Genome irradiation facility.	2021-I	2022-IV
52	Radiation field research at JINR's facilities.	2021-I	2023-IV

PROJECT LEADERS

E.A. Krasavin

A.N. Bugay

Form 26

Schedule proposal and resources required for the implementation of the Project

Research on the Biological Effect of Heavy Charged Particles of Different Energies

Expenditures, resources, financing sources			Costs (thousand USD) Resource requirements	The Laboratory's proposals on the distribution of finances and resources		
				2021	2022	2023
Required resources	Standard hour	Nuclotron	72 h	-	-	72 h
		Cyclotron U400M	192 h	-	96 h	96 h
		Rokus-M	300 h	100 h	100 h	100 h
		Phasotron	300 h	100 h	100 h	100 h
Financing sources	Budget	theme 1077	548.2 $	204.2k$	163.2k$	180.8k$

PROJECT LEADERS

E.A. Krasavin

A.N. Bugay

Form 29

Estimated expenditures for the Project
Research on the Biological Effect of Heavy Charged Particles of Different Energies

	Expenditure items	Full cost (thousand USD)	1st year	2nd year	3rd year
	Direct expenses for the Project				
1.	Materials	240	70	70	100
2.	Equipment	158.2	84.2	43.2	30.8
3.	Payments for agreement-based research	-	-	-	-
4.	Travel allowance, including:	150	50	50	50
	a) non-rouble zone countries				
	b) rouble zone countries				
	c) protocol-based				
	Total direct expenses	548.2	204.2	163.2	180.8

PROJECT LEADERS

E.A. Krasavin

A.N. Bugay

LABORATORY DIRECTOR

A.N. Bugay

LABORATORY CHIEF ENGINEER-ECONOMIST

I.Yu. Lesninova

Strengths, weaknesses, opportunities, threats

Strengths

- Many years' experience of the main executors of the project in radiobiology; their prominence in the international scientific community.
- The project is headed by a Corresponding Member of the Russian Academy of Sciences (RAS), who has great authority and is widely recognized in science.
- Scientific and methodological support of the planned research by the RAS Council on Radiobiology.
- The project is planned to be implemented in cooperation with a wide range of highly qualified specialists from different countries, including members of the International Biophysical Collaboration.
- A large number of young specialists in the team.
- The planned research will be based on using accelerators at several JINR Laboratories.

Weaknesses

- The upgrade of multi-charged ion sources in 2021–22 limits the number of JINR-based experiments.

Opportunities

- The LRB's great scientific potential and modern equipment open broad prospects for attracting young specialists from JINR Member States.
- Implementing the project will enhance the scientific authority of JINR as one of the few organizations conducting cutting-edge fundamental and applied research in heavy ion radiobiology.
- The results of space radiobiology research enable an assessment of the safety of the future lunar and Martian mission crews.
- The results of research focused on the molecular biology aspects of improving the methods of the radiation therapy of cancer open prospects for increasing the efficiency of photon and proton therapeutic facilities and reducing costs and negative consequences of treatment.

Threats

- A delay in the construction and commissioning of applied research channels at the NICA complex may slow down part of the project.