# Radiobiological research at JINR

# LABORATORY OF RADIATION BIOLOGY

lrb.jinr.ru

**The Joint Institute for Nuclear Research** (JINR) is a unique international scientific center with a wide range of ionizing radiation sources — above all, accelerated heavy ion beams of different energies.

JINR's infrastructure provides unique opportunities for conducting interdisciplinary life sciences research. To carry out fundamental and applied research on the effects of radiation on living organisms, in 2005, by decision of the JINR Directorate and Scientific Council, JINR's seventh laboratory was established: the **Laboratory of Radiation Biology** (LRB).

### *History of radiobiological studies at JINR:*

**1959.** The first radiobiological experiments began. A number of tasks were solved related to the radiation safety of the first manned space flights.

**1967.** The first proton medical beam in the USSR was constructed for cancer treatment. Research in medical radiobiology began.

**1980's.** The central problem of radiation biology was solved: the problem of the relative biological effectiveness of ionizing radiation with different physical characteristics.

**1990's.** The mechanisms of the mutagenic effect of accelerated heavy charged particles on prokaryotic cells were determined. The key role of inducible SOS repair and the dependence of its effectiveness on radiation LET were shown.

### *Research fields*

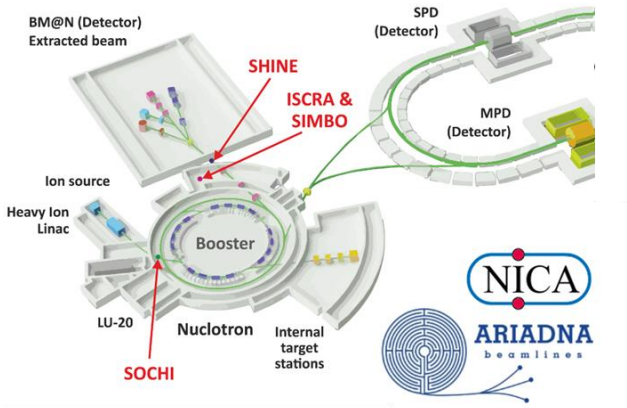
Radiobiological experiments are aimed at studying the action of ionizing radiation with different physical characteristics at the molecular, cellular, tissue, and organismal levels of biological organization.

Special attention is paid to the development of new approaches to increasing the effectiveness of the radiation therapy of cancer and research on radiation-induced functional disorders of the brain.

Astrobiological research is aimed at solving the problem of the origin and spread of life in the Universe with nuclear physics methods.

# RADIATION SOURCES

## Heavy ion beams

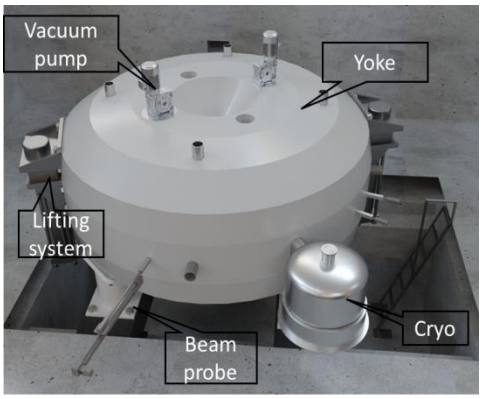



Laboratory of High Energy Physics
SIMBO station at the applied channels of the NICA complex (400–800 MeV/n)

Laboratory of Nuclear Reactions
Genome-3 facility at the U400M cyclotron (50 MeV/n)

## Protons

## Neutrons




Laboratory of Nuclear Problems
MSC230 superconducting proton cyclotron for R&D in radiotherapy

Laboratory of Neutron Physics
IBR-2 research reactor,
IREN facility

## Photons

## Electrons

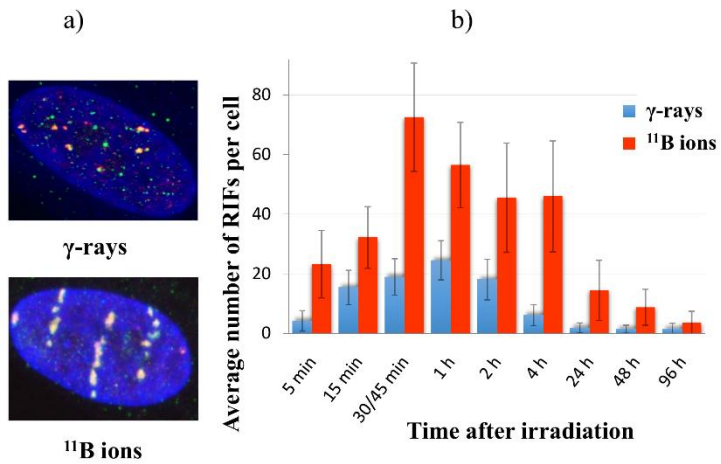
Laboratory of Radiation Biology
SARRP facility for modeling conformal radiation therapy on laboratory animals

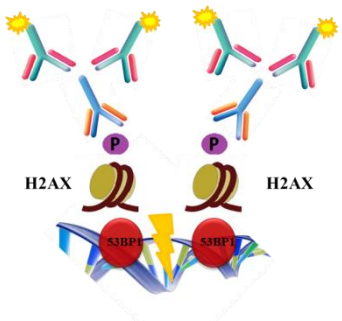
Laboratory of Nuclear Problems
LINAC-200 linear accelerator (20–200 MeV)

# MOLECULAR RADIOBIOLOGY

***Studies of the formation and repair of clustered DNA damage induced by radiation of different quality in normal and tumor cells of mammals and humans***

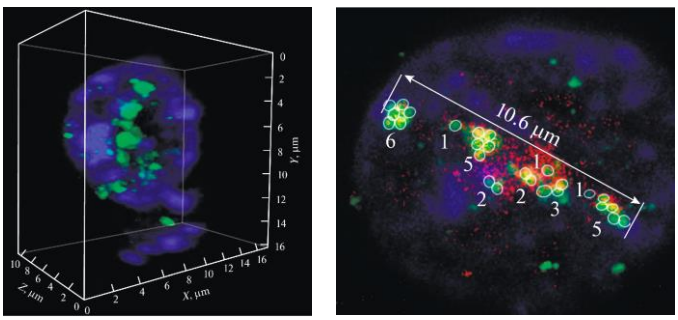
Molecular disorders in the genetic structures of normal and tumor cells induced by accelerated heavy ions are studied using high-resolution immunofluorescence microscopy methods, which make it possible not only to quantitatively assess the formation and repair of DNA damage (radiation-induced foci (RIF)), but also to take into account its spatial distribution in genetic structures.

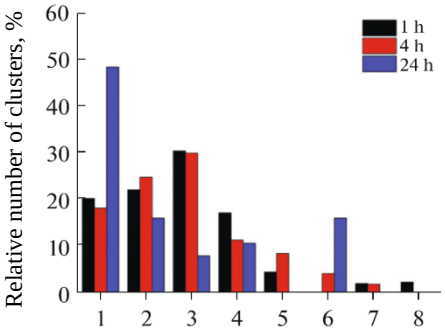



Visualization of γH2AX/53BP1 foci *(a)* and kinetics of their repair *(b)* after exposure to γ-rays and 50 MeV/nucleon $^{11}$B ions.

Based on a differential analysis of individual DNA foci in three-dimensional images reconstructing the entire volume of the cell nucleus, a detailed analysis of the structure and number of complex damage clusters in accelerated ion tracks has been carried out and their repair patterns have been studied.



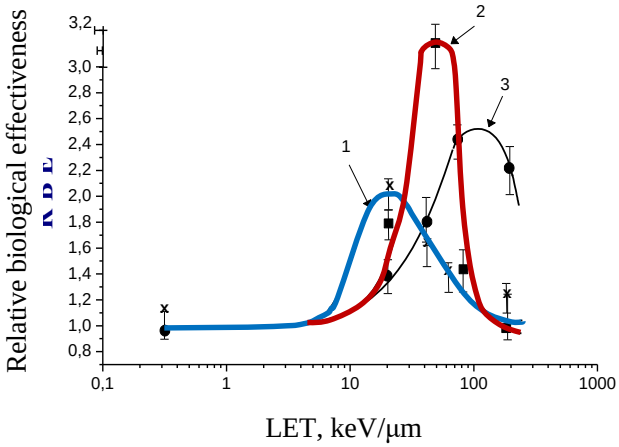

Visualization and quantitative composition of RIF in rat brain neurons irradiated with 2.58 GeV/nucleon $^{78}$Kr ions.

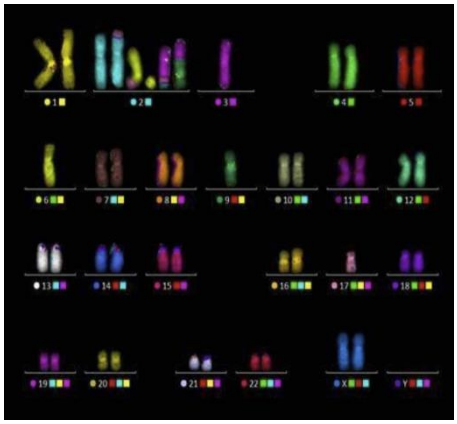
Research at the Nuclotron has yielded unique results on the induction and repair of clustered DNA damage after irradiation of laboratory animals with accelerated heavy ion beams.

# RADIATION GENETICS

***Studies of the formation of gene, structural, and complex mutations in mammalian and human cells after exposure to radiation with different characteristics***

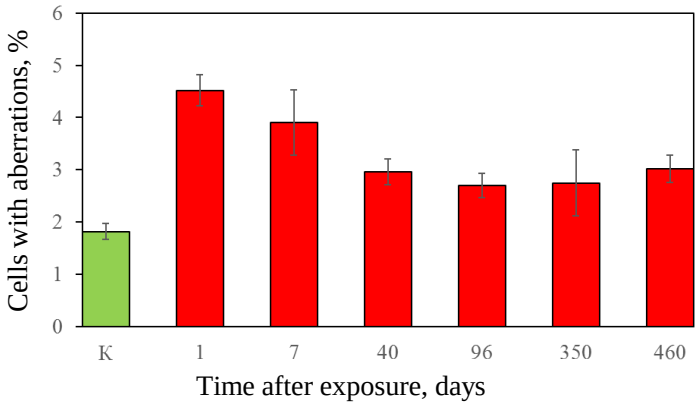
Induction of gene and structural mutations depending on radiation's linear energy transfer (LET):
(1) gene mutations;
(2) structural mutations;
(3) lethal effect.



mFISH karyotype of human lymphocytes irradiated with 2 Gy of Bragg peak protons, containing a complex aberration that includes 6 breaks in 5 chromosomes.

Biodosimetry methods based on the analysis of the yield of chromosomal aberrations make it possible to estimate the radiation dose received during radiation incidents, medical diagnostics, and cancer radiotherapy. The mFISH method developed at the LRB makes it possible to identify each pair of chromosomes in human and animal cells and analyze all their possible rearrangements, including complex chromosomal aberrations (three or more breaks in two or more chromosomes), which are not detected using routine methods.



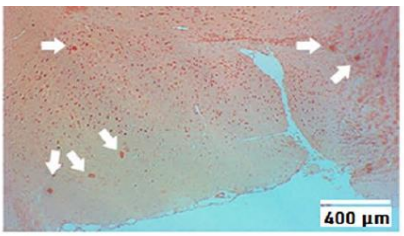

Level of chromosomal aberrations in peripheral blood lymphocytes of monkeys exposed locally to 3Gy of 2.6 GeV/nucleon krypton ions at different observation times.

LRB scientists monitor the condition of monkeys irradiated with accelerated heavy ions. Long-term after irradiation of certain areas of the monkey brain with 3 Gy of accelerated krypton ions, a persistently high level of chromosomal aberrations was observed.

# RADIATION PHYSIOLOGY

***Studies of behavioral disorders and pathomorphological changes in different brain structures and critical organs and systems of irradiated animals under normal conditions and in the presence of radioprotectors. Research on the mechanisms of neurodegeneration under exposure to ionizing radiation of different quality.***

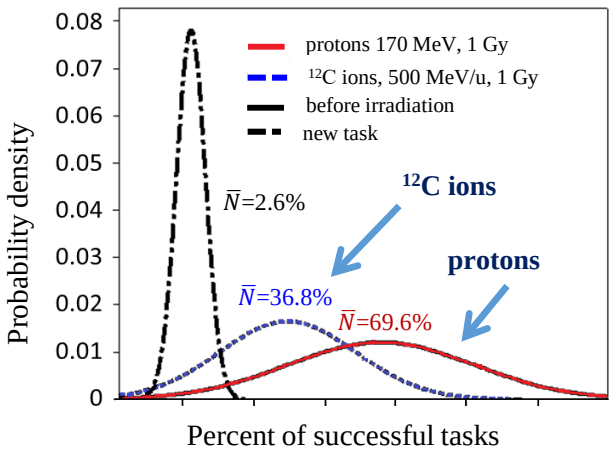
Test systems for studying rodent behavior




Amyloidosis in the brain of rats after irradiation with 70 MeV protons

Radiation-physiological research is aimed mainly at studying disorders in the behavioral reactions of irradiated animals, bioelectrical activity of the brain, and pathomorphological changes in various critical organs and systems, primarily in the central nervous system. Studies have revealed a number of behavioral disorders and pathomorphological changes in the brain of rodents after irradiation with heavy charged particles.

In a series of pioneering studies on primates conducted at the LRB, a significant decrease in cognitive functions was revealed after irradiation with accelerated carbon ions, while irradiation with gamma rays or protons did not cause such effects.



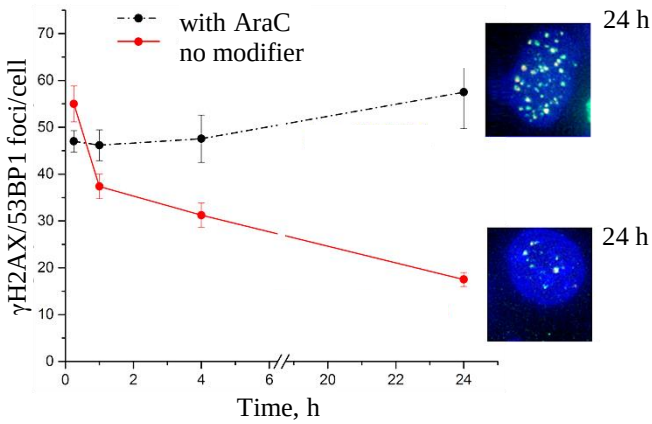

In the long term after irradiation with accelerated krypton ions (460 days or more), most of the irradiated monkeys developed stable deviations from the standard behavior. The most pronounced pathology was manifested in the form of episodic tilting of the head up and uncharacteristic pendulum movements of the body.

As a result of research conducted in cooperation with specialists from a number of institutes of the Russian Academy of Sciences, **a new concept of radiation risk for manned interplanetary flights** was proposed and justified, in which the radiation risk for astronauts is associated with the effect of heavy nuclei of galactic cosmic rays on the structures of the central nervous system.

# CLINICAL RADIOBIOLOGY

***Development of new approaches to increasing the biological effectiveness of the radiation therapy of tumors***

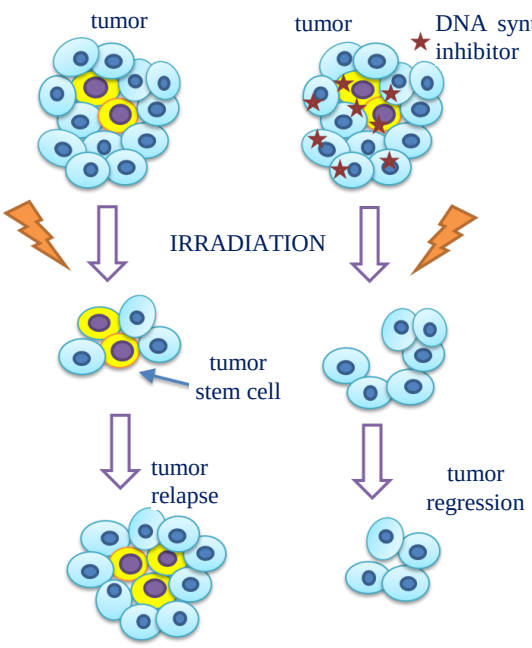
**The LRB has developed and patented a fundamentally new approach to increasing the biological effectiveness of therapeutic proton beams with preliminary introduction of certain radiomodifiers before irradiation.**



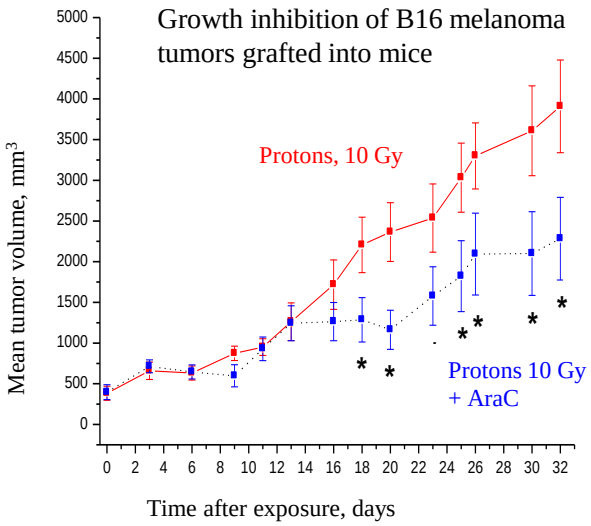

DNA damage yield in U87 glioblastoma cell culture irradiated with 1.25 Gy of spread-out Bragg peak protons

When the drug AraC is administered before irradiation of human cells with protons and gamma rays, single-strand DNA breaks are transformed into double-strand breaks — severe damage that leads to cell death. In the presence of the drug, the biological effectiveness of proton irradiation is comparable to that of irradiation with carbon ions.

**Tumor regression due to stem cell death**




The proportion of tumor stem cells was reduced threefold after combined exposure.




Specialists from the LRB JINR and Tsyb Medical Radiology Research Center have jointly studied this new approach on grafted tumors of murine melanoma B16. An almost threefold inhibition of tumor growth was observed with the preliminary administration of a non-toxic dose of the drug compared with proton irradiation alone.

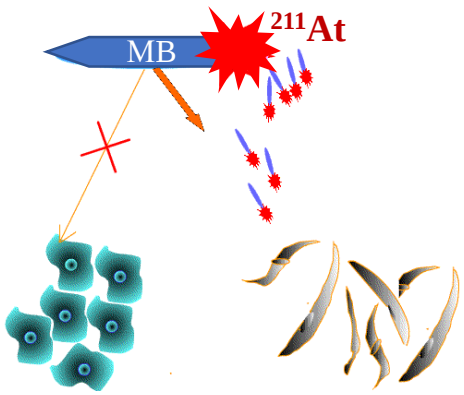
# CLINICAL RADIOBIOLOGY

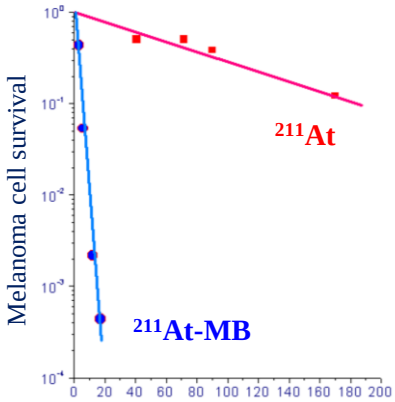
***Development of new methods for targeted therapy with radionuclides***

## A method for targeted delivery of the therapeutic alpha emitter $^{211}$At to a melanoma tumor and its metastases has been developed.

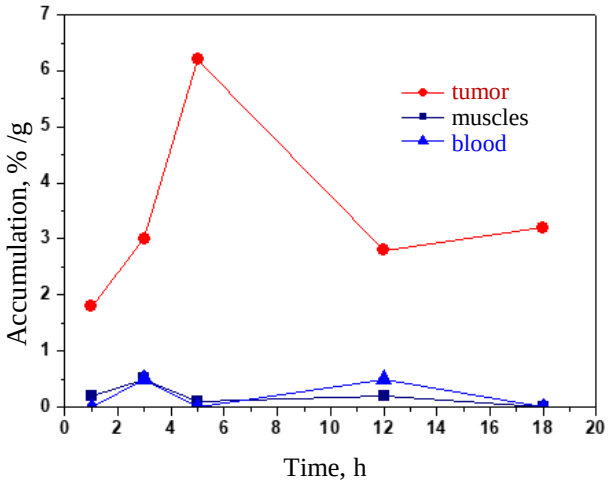
Scientists at JINR's LRB, FLNR, and DLNP, together with colleagues from the Burnazyan Federal Biomedical Center, conducted pioneering studies of the biological effect of the alpha emitter $^{211}$At and the possibility of its use in targeted cancer therapy.

One of the most aggressive forms of malignant neoplasms, melanoma, characterized by early and extensive metastasis, was chosen as a model. It is for the fight against micrometastases that the targeted effect of $^{211}$At is most appropriate. Its decay produces alpha particles with a range of 60 μm, which is several cell diameters. The $^{211}$At isotope was obtained at the FLNR JINR by irradiating a bismuth target with alpha particles — the reaction $^{207}$Bi(α,2n)$^{211}$At.




As a means of radionuclide delivery to tumor cells, a polycyclic compound was used known as methylene blue (MB), which is characterized by high binding ability to tumor cell melanin.




In an *in vitro* system, using human melanoma cells and normal non-pigmented cells, selective accumulation of the $^{211}$At-MB compound in melanin-containing tumor cells was shown, which caused killing 15–20 times more melanoma cells than normal cells.

Studies on mice with grafted melanoma tumors also showed selective accumulation of $^{211}$At-MB predominantly in the tumor area. Another MB-based drug for diagnostics was obtained, $^{131}$I-MB, which proved highly effective for visualizing melanoma and its metastases in animals with grafted tumors.

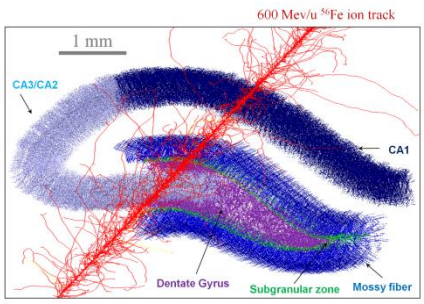
# MATHEMATICAL MODELING

***Development of new mathematical models and computational methods for radiobiology, bioinformatics, and radiation medicine***

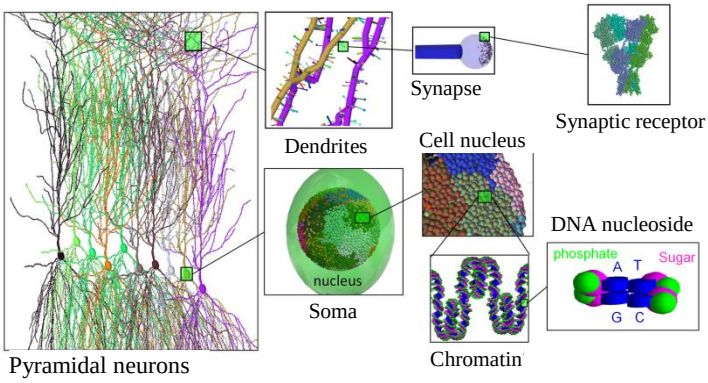
The main goal of the LRB's research in this area is to create a hierarchy of models that will make it possible to systematize experimental data and study the ways in which radiation-induced pathologies develop at different levels of organization (from molecules to cell populations) and over time (acute and long-term consequences).

## Problems

- models of DNA damage formation and repair;
- formation of mutations and chromosomal aberrations;
- prediction of the structure and functions of mutant proteins;
- tumor growth prediction models;
- theoretical assessment of radiation-induced brain disorders.

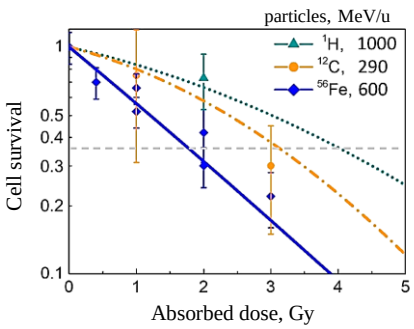



Rat brain hippocampus

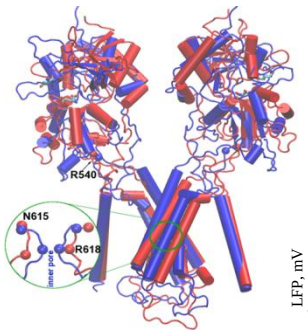



Pyramidal neurons

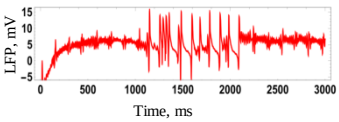
An example of a hierarchy of models in the study of damage in the rat brain due to the passage of 600 MeV/nucleon iron ions. The elements of the layer of pyramidal neurons and the main targets at the cellular level are shown.




Model-based calculation of stem cell death in rat brain



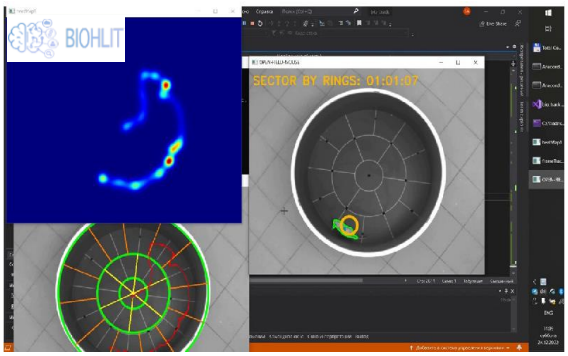

Mutant NMDA receptor structure and calculation of the EEG signal during the development of epilepsy caused by the p.ASN615LEU mutation




***Automation of biological experiment data processing using computer vision algorithms and artificial intelligence***

The LRB and Laboratory of Information Technologies, JINR, are jointly developing the **BIOHLIT information system** for processing

- video recordings of animal behavior,
- histological sections,
- confocal microscopy images.



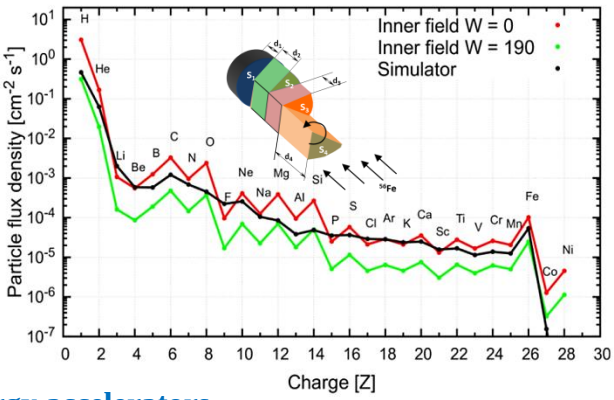
# RADIATION RESEARCH

***Development and upgrade of new facilities for radiobiological experiments. Predicting radiation conditions at nuclear physics facilities and spacecraft.***

## Improving methods of radiobiological experiments

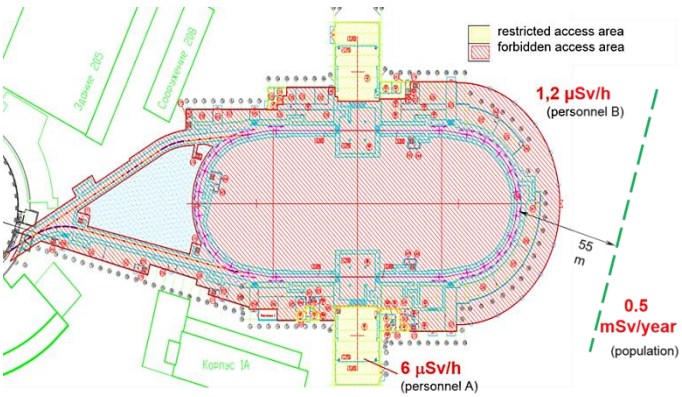
JINR's LRB has developed and patented a method for generating a mixed radiation field at heavy ion accelerators to simulate a multicomponent radiation field inside a spacecraft or on a celestial body.

A computer model of the simulator designed at the LRB in the version for a beam of 1 GeV/nucleon $^{56}$Fe nuclei reproduces in the correct ratio all components of the radiation field inside a spacecraft, averaged over solar activity.




## Predicting radiation conditions at high energy accelerators

Work is underway to predict the radiation conditions at JINR accelerators, primarily at the NICA complex, and in the environment; assess the induced activity of equipment; assess personnel exposure and develop radiation safety measures; and build up radiation monitoring systems.




Radiation zoning at the NICA collider


## Instruments for nuclear planetary science

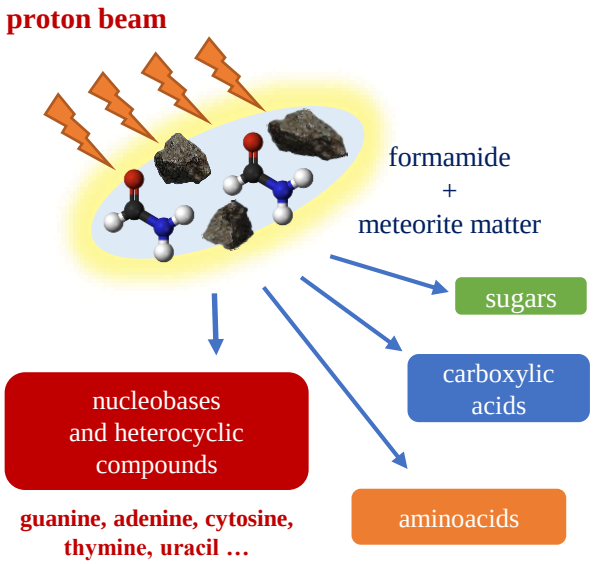
As part of a joint research program with the RAS Institute of Space Research and JINR's FLNP, the DAN experimental stand has been put into operation, and LRB's participation continues in the fabrication, testing, and calibration of nuclear planetary science instruments for studying the elemental composition of the surface of celestial bodies of the Solar System and searching for water ice.

# ASTROBIOLOGY

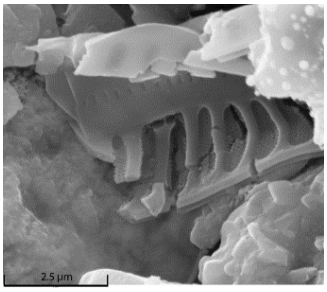
***Identification of the mechanisms of abiogenic synthesis of prebiotic compounds under radiation exposure and studying cosmic matter with nuclear physics methods; search for microfossils and organic compounds in meteorites.***

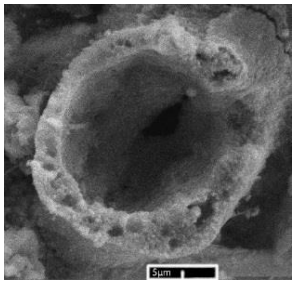
## Synthesis of prebiotic compounds under radiation exposure

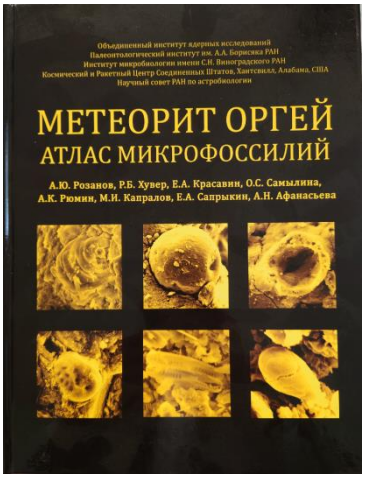
In pioneering experiments carried out by JINR's LRB jointly with colleagues from the University of Tuscia (Viterbo, Italy) on the irradiation of aqueous solutions of formamide with 170 MeV protons and 33 MeV/nucleon boron ions in the presence of meteorites as catalysts, the synthesis of a wide range of prebiotic compounds was observed for the first time: amino acids, carboxylic acids, sugars, nucleic bases, and even nucleosides. These compounds had not previously been detected in experiments with other types of exposures.




## Search for fossilized microorganisms in meteorites




Very promising in studying meteorite material is the use of nuclear physics methods, such as scanning electron microscopy, X-ray microtomography, neutron activation analysis, and X-ray spectral analysis. A major challenge is to compare microfossil finds in meteorites with terrestrial counterparts and confirm the absence of terrestrial contamination.

More than 30 meteorite and terrestrial rock samples were studied with an electron scanning microscope at the LRB Astrobiology Sector. Several hundred images of fossil microorganisms were obtained and analyzed, and the world's first atlas of finds in the Orgueil meteorite has been published.


International intergovernmental organization

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