LABORATORY OF RADIATION BIOLOGY

In 2013, the Laboratory of Radiation Biology (LRB) continued activities within the framework of Theme 04-9-1077-2009/2014 "Research on the Biological Effect of Heavy Charged Particles with Different Energies" in the following fields: fundamental radiobiological and radiation genetics research with heavy charged particles; research on the effect of accelerated heavy particles on the nervous system and eye structures; molecular dynamics research; mathematical modeling of radiation-induced effects; and radiation research and radiation protection of JINR's basic facilities and the environment. Work was started on Theme 04-9-1112-2013/2015 "Research on Cosmic Matter on the Earth and in Nearby Space; Research on the Biological and Geochemical Specifics of the Early Earth".

RADIATION GENETICS AND RADIOBIOLOGY

Research was continued on the regularities and mechanisms of the induction and repair of DNA double-strand breaks (DSBs) in human cells under exposure to ionizing radiations of different quality. With the use of the fluorescent microscopy method involving immunocytochemical staining of γ-H2AX and 53BP1 proteins in human fibroblast nuclei, a comparative analysis of the specifics of DNA DSB formation was performed

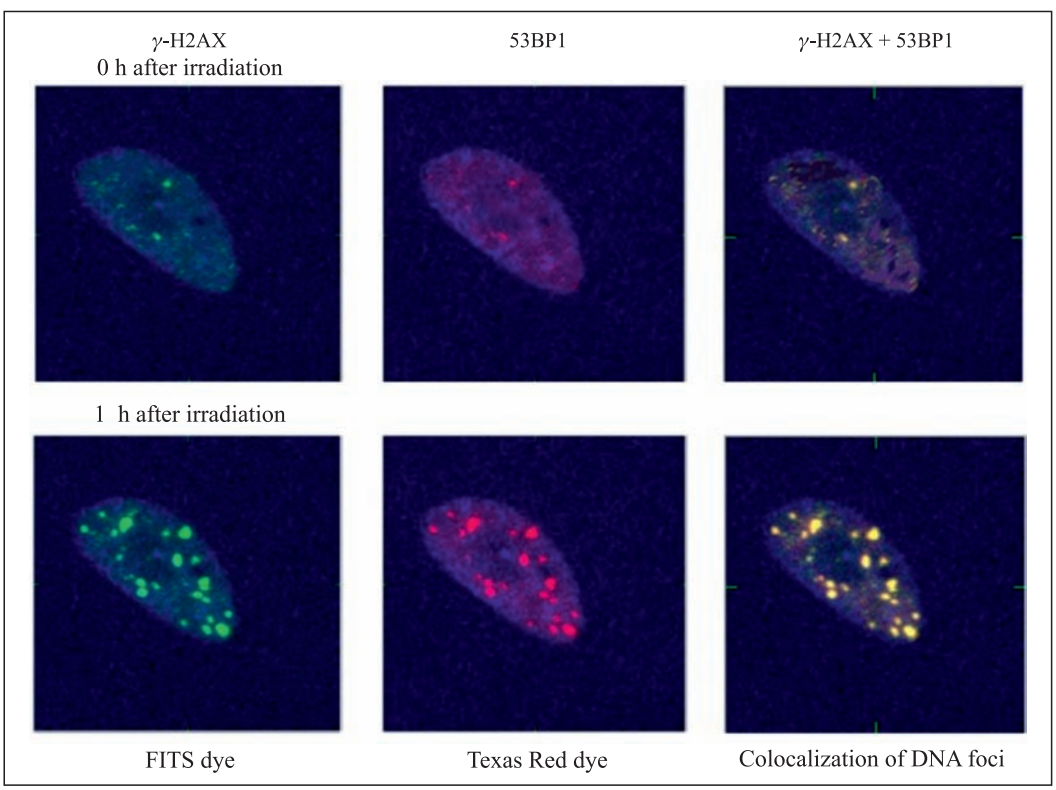

Fig. 1. Colocalization of γ-H2AX and 53BP1 DNA foci in human skin fibroblast nuclei 1 h after irradiation with ^{60}Co γ rays at 1 Gy

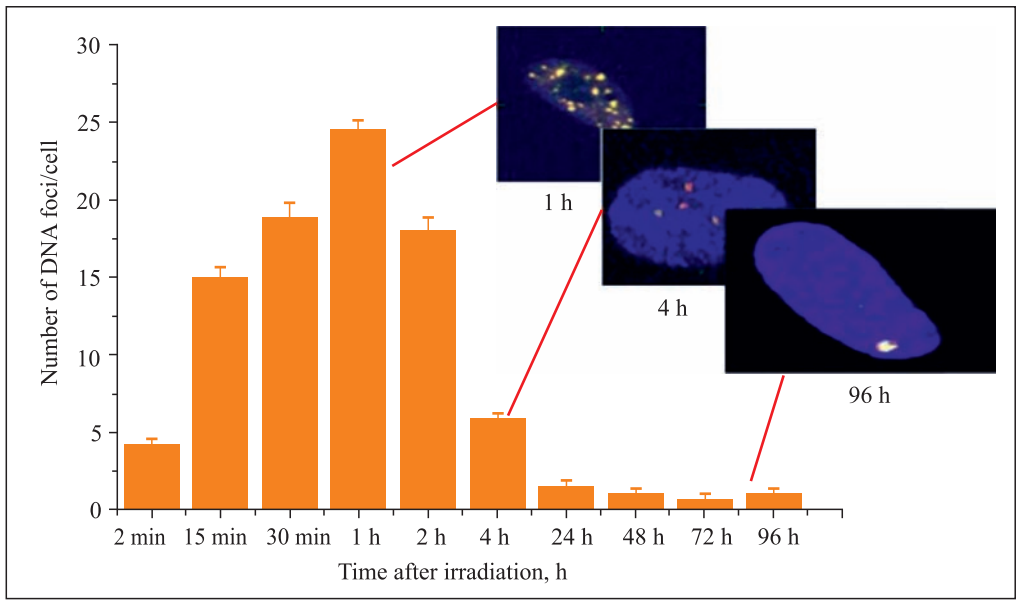

Fig. 2. DNA DSB repair kinetics in human fibroblasts after irradiation with ^{60}Co γ rays at 1 Gy

and the kinetics was studied of the repair of this type of damage induced by ^{60}Co γ rays and accelerated ^{20}Ne ions (50 MeV/nucleon energy and linear energy transfer (LET) of 130 keV/μm) [1–4]. The kinetics of the formation of radiation-induced DNA foci was studied for γ irradiation at 1 Gy. It was shown that the formation of radiation-induced DNA foci begins in the first minutes and peaks one hour after exposure (Fig. 1). Four hours after exposure, the number of DNA foci sharply drops, which points to the efficient DNA DSB repair. Some of the DNA foci, though, remain in cells for up to 96 h of post-irradiation incubation (Fig. 2). Most likely, those are the most severe DNA lesions that are part of DNA focus clusters.

The use of different repair inhibitors (wortmannin, benzamide, and NU 7026) allowed evaluating the contribution of non-homologous end joining to the total repair of DNA DSBs in human lymphocytes induced by ^{60}Co γ rays. It was established that for γ irradiation, DNA DSB yield in control and in the presence of the repair inhibitor wortmannin is practically the same (Fig. 3, *a*). In the presence of wortmannin, as opposed to control, DNA DSB yield increases for up to 6 h of post-irradiation cell incubation, which indicates that non-homologous repair makes the main contribution to the overall DNA repair process in human lymphocytes (Fig. 3, *b*).

Research on the regularities and mechanisms of radiation-induced apoptosis in human lymphocytes was continued. Different apoptosis pathways (receptor-mediated, mitochondrial, caspase-independent, etc.) are initiated by a number of factors. In particular, radiation-

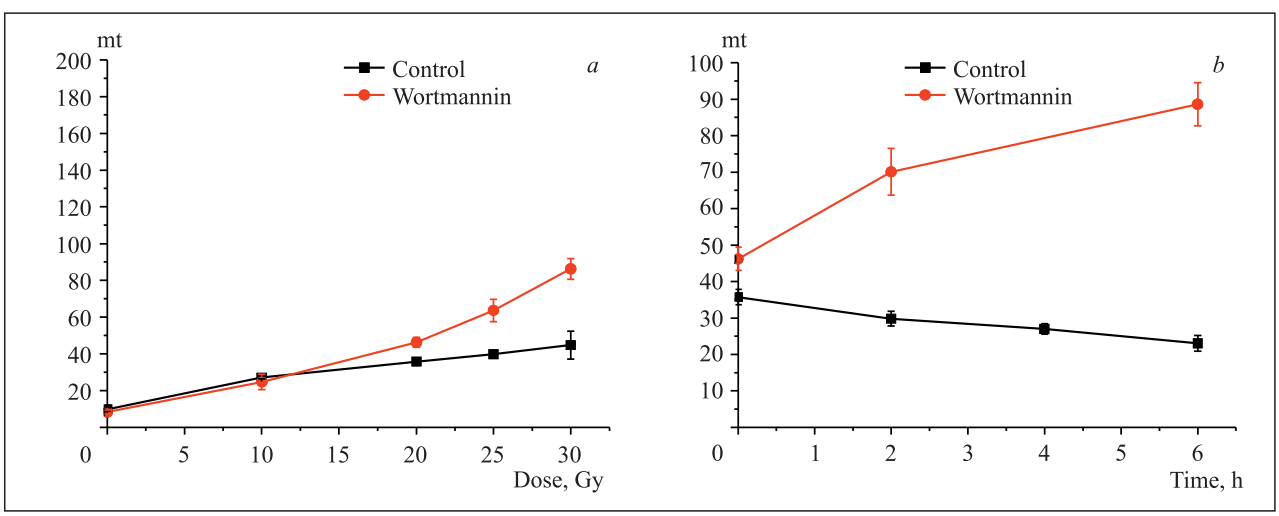

Fig. 3. A dose dependence of DNA DSB formation (*a*) and repair kinetics (*b*) in human lymphocytes in the presence of the non-homologous end joining inhibitor wortmannin (10 μM) after exposure to ^{60}Co γ rays at 20 Gy

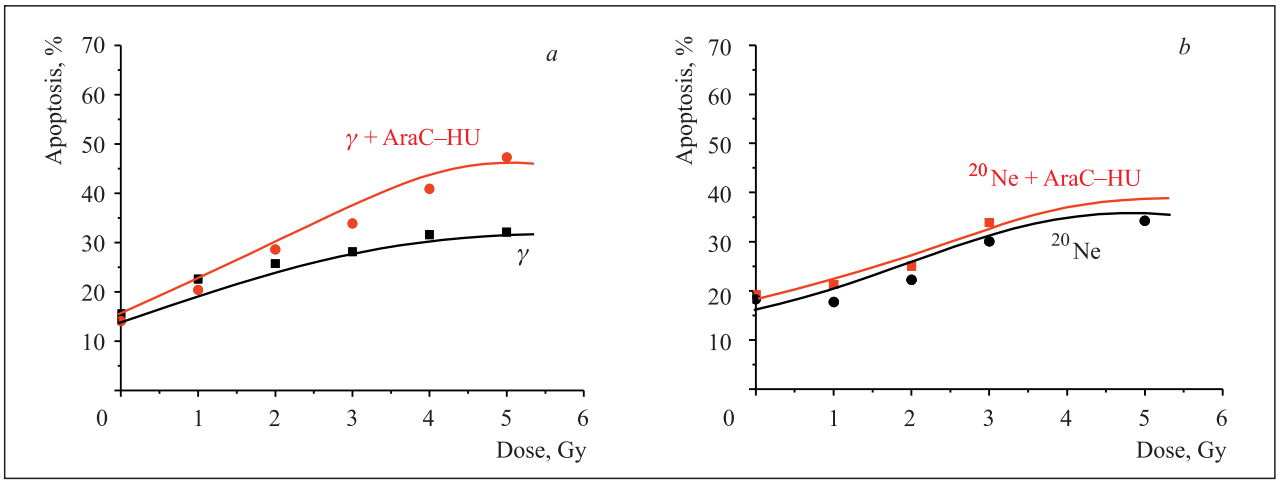

Fig. 4. A dose dependence of apoptosis induction in human lymphocytes 24 h after exposure to ^{60}Co γ rays and accelerated ^{20}Ne ions

induced apoptosis is initiated by DNA DSBs. There is no detailed knowledge of the relations between the different stages of programmed cell death that are its main independent stages: initiation, the effector phase, and degradation. Also, data on the influence of densely ionizing radiations on apoptotic death induction are practically absent. Of great interest is thus studying apoptosis induced by radiations with different LET in the presence of different repair and apoptosis protein inhibitors. With increasing LET, a significant attenuation of the radiosensitizing effect of the used inhibitors is observed, which seems to be connected with a change in the spectrum of the DNA lesions forming with increasing LET and a decrease in the yield of lesions from which, in the presence of inhibitors, enzymatic DNA DSBs can emerge that initiate radiation-induced apoptosis (Fig. 4).

To clear up the P53 protein role in the process of the apoptotic death of human lymphocytes, the PFT-α inhibitor was used. Dose dependences of apoptotic cell induction were studied for ^{60}Co γ rays and accelerated ^{20}Ne ions (Fig. 5). In the presence of the PFT-α inhibitor, an effective decrease in apoptotic cell induction is observed compared with control for both γ rays and accelerated heavy ions [5].

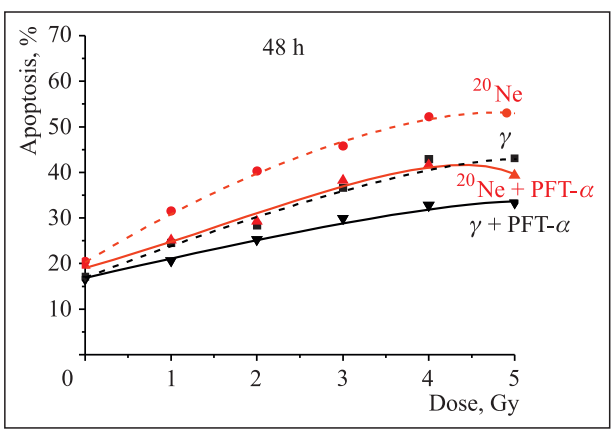

Fig. 5. Apoptosis induction in human lymphocytes 48 h after irradiation with ^{60}Co γ rays and accelerated ^{20}Ne ions in the presence of the PFT-α inhibitor of the P53 protein

To evaluate the effect of the inhibitors cytosine arabinoside (AraC) and hydroxyurea (HU) on apoptosis induction in human lymphocytes, a dependence of the dose change factor (DCF) on LET was plotted for the radiations used in the study (Fig. 6).

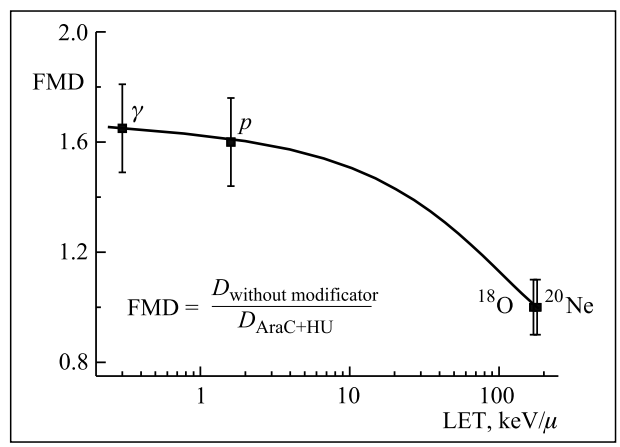

Fig. 6. The AraC and HU modifying effect on apoptosis induction in human lymphocytes under exposure to radiations with different LET

The yield of reactive oxygen species (ROS) was estimated in Cal 51 cells of human breast carcinoma after exposure to ^{60}Co γ rays at 0.5, 1, and 3 Gy. As a ROS indicator, the fluorescent dye CM-H_2DCFDA was used. The survival rate S was determined as the ratio of the dye fluorescence intensity (in relative fluorescence units, RFU) in the irradiated samples to that in the non-irradiated samples. Fluorescence intensity was measured with a Synergy H1m microplate reader during 24 h after irradiation. It was found that irradiation

induces long-lived ROS, the yield of which increases with the dose (Fig. 7). The highest ROS level was observed after 15–24 h incubation. These data indicate that low doses can cause oxidative stress in the cell, which is considered to be the main factor responsible for the delayed consequences of irradiation.

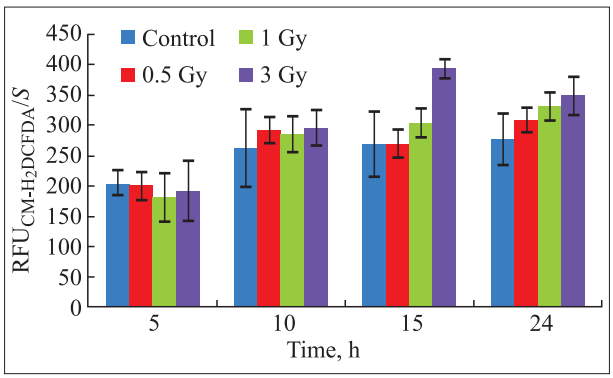

Fig. 7. Radiation-induced ROS yield in Cal 51 cells after exposure to ^{60}Co γ rays. The abscissa axis shows post-irradiation cultivation time; the ordinate axis shows CM-H_2DCFDA fluorescence intensity for wavelengths of 485 nm (ex) and 528 nm (em) normalized to the survival rate S

In experiments on mammalian cells, research was continued on radiation-induced mutagenesis under densely ionizing radiations. For accelerated ^{20}Ne ion exposure at 0.5, 1, and 2 Gy, it was established that its manifestations depended on the time of irradiated cell seeding (mutation expression time) in a selective nutrient medium with 6-thioguanine. Figure 8 shows the frequency of radiation-induced mutants for different seeding times and the frequency of similarly grown spontaneous mutants. After 4-day expression, the spontaneous and radiation-induced mutagenesis frequency was $1.2 \cdot 10^{-5}$. When the expression time was increased to 10–12 d, a decrease in the mutagenesis level was observed. At longer times, an increase was observed in the frequency of mutant colonies of cells irradiated in the studied dose range. The maximal mutagenesis level of $3.2-3.6 \cdot 10^{-5}$ was observed for the expression time of 20–26 d, which corresponds to approximately 40–50 cell generations (the Chinese hamster cell division cycle lasts 10–12 h). Further, the radiation-induced mutant frequency decreased. When seeding was done 30–45 d after, it was on the level of spontaneous mutagenesis. Earlier research allows suggesting that the increased level of radiation-induced mutagenesis is determined by increased chromosome and genome instability of the irradiated cell population.

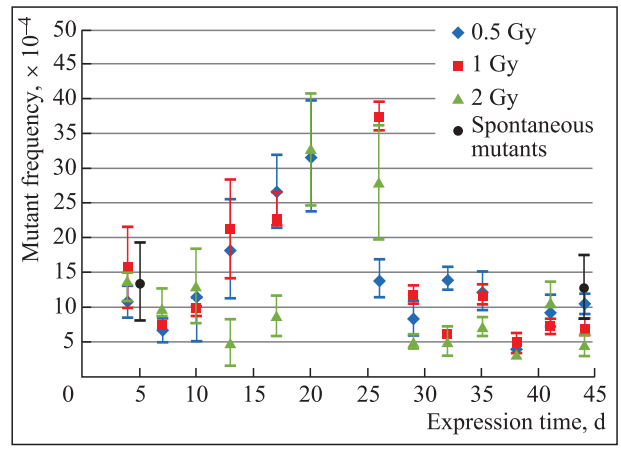

Fig. 8. Spontaneous and radiation-induced mutagenesis levels after accelerated ^{20}Ne ion exposure at 0.5, 1, and 2 Gy versus mutant expression time

In cooperation with the National Institute of Cancer in Naples and University of Udine, Italy, research was started on the radioprotective properties of the recombinant form of manganese-containing superoxide dismutase (rMnSOD). Preliminary results, which were obtained for 170 MeV proton irradiation of mice at 4 Gy, indicate that rMnSOD has a certain therapeutic effect. The effect was evaluated by bone marrow cellularity

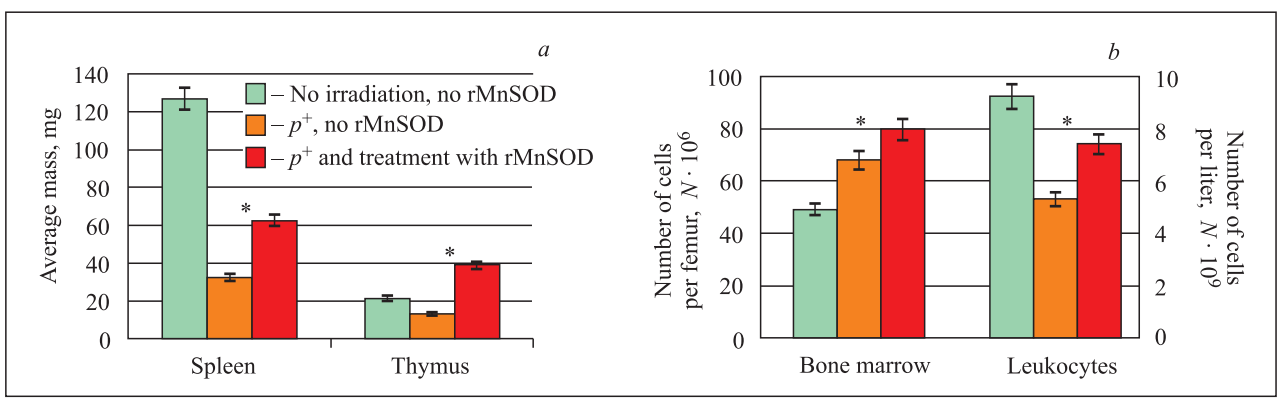

Fig. 9. The influence of rMnSOD on spleen and thymus mass (*a*) and bone marrow cellularity and the leukocyte level (*b*) in mice 7 d after 170 MeV proton irradiation at 4 Gy ($p \leqslant 0.01$)

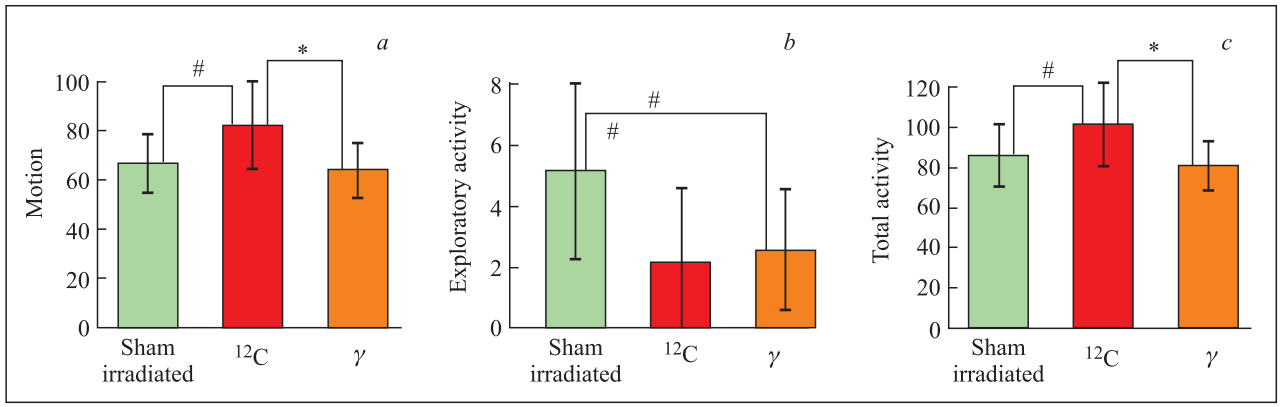

Fig. 10. Open field test indicators 30 d after animal irradiation with 500 MeV/nucleon ^{12}C ions and γ rays at 1 Gy ($\pm$SD; #$p \leqslant 0.05$; $^{*}p \leqslant 0.01$ against the Mann–Whitney U-criterion): *a*) motion activity measured by the number of sector border crossings; *b*) cognitive activity evaluated by the number burrow reflex manifestations; *c*) total animals' activity indicator

indicators, the leukocyte level in peripheral blood, and spleen and thymus mass, which were measured in parallel with regular introduction of the preparation during 7 d after irradiation (Fig. 9).

In cooperation with specialists of the Institute of Higher Nervous Activity and Neurophysiology of the Russian Academy of Sciences (RAS) and the RAS Institute of Biomedical Problems, an experiment was performed to evaluate the behavioral reactions of rats long after irradiation with ^{12}C ions (500 MeV/nucleon $\sim$ 10 keV/μm) at 1 Gy. The results of the open field test measurements are comparable with the γ-irradiation data. The measurements indicate that there are differences between the effects observed 30 d after irradiation with heavy nuclei and γ rays at the same dose. The effect of accelerated carbon ions consisted in increasing motion activity and inhibiting cognitive activity of the animals, while γ irradiation had a significant effect concerning only the latter indicator (Fig. 10, *a, b*). The rats' total activity increased by 18% after irradiation with ^{12}C ions, but γ irradiation caused no significant differences from the control values. Considerable differences were observed between the results obtained with sparsely and densely ionizing radiations (Fig. 10, *b, c*).

PHOTORADIOBIOLOGICAL RESEARCH

The effect of genotoxic factors (methylnitrosourea (MNU) and ionizing radiation) on the mouse retina was studied. It was found that the retina is able to recover spontaneously its functional activity and provide the adaptive response of its photoreceptors *in vivo* after genotoxic exposures. A preliminary retina exposure to a non-toxic MNU dose makes it more resistant to a further cytotoxic dose of the agent. It was shown that the retina's adaptive response to MNU is associated with the suppression of effector apoptotic caspase-3 and a decrease in the photoreceptor death level in the retina. Proton irradiation of the mature retina at 1 Gy also leads to an adapting effect: the retina becomes resistant to a further cytotoxic exposure to MNU. The effect of the retina's radiation hormesis shows up as a decrease in the apoptosis frequency in the nuclear layer of photoreceptors and goes along with an increase in DNA DSB repair efficiency in retinal cells [6, 7].

MATHEMATICAL MODELING OF RADIATION-INDUCED EFFECTS

Mathematical modeling of DNA DSB repair in mammalian and human cells was continued. Models were developed of the three main damage repair mechanisms: non-homologous end joining (NHEJ), homologous recombination (HR), and single-strand anneal (SSA) through direct repeats. The proposed model approach was applied to the description of the kinetics of the repair of DNA DSBs induced by X rays, γ rays, and accelerated oxygen, silicon, and iron ions in a wide LET range of 0.2–440 keV/μm. The models allowed generalization of a large amount of experimental data on the time characteristics of specific stages of NHEJ, HR, and SSA. In particular, quantitatively described were the kinetics of the Ku70/80 complex binding with

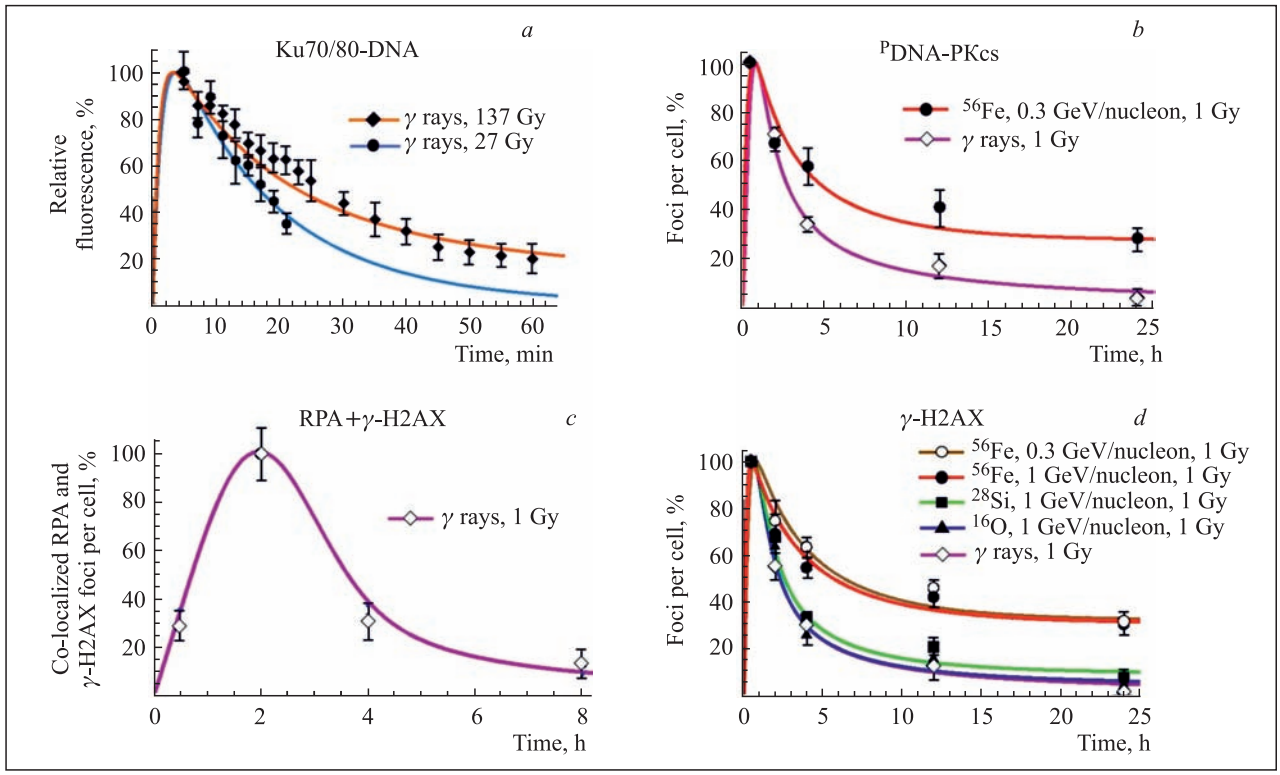

Fig. 11. Estimation of the kinetics of specific stages of the repair of DNA DSBs induced by ionizing radiations with different physical characteristics: *a*) the kinetics of the Ku70/80 complex binding with DNA DSBs in an XR-V15B Chinese hamster fibroblast culture (the dots are experimental data (Reynolds et al., 2012)); *b*) DNA-PKcs level change in a HSF42 human skin fibroblast culture (the dots are experimental data (Asaithamby et al., 2008)); *c*) RPA and γ-H2AX focus colocalization in a GM637H culture of embryonic lung fibroblasts (the dots are experimental data (Balajee and Geard, 2004)); *d*) γ-H2AX focus level change in a HSF42 human skin fibroblast culture (the dots are experimental data (Asaithamby et al., 2008))

DNA DSBs and the change of the level of phosphorylated DNA-dependent protein kinase (DNA-PKcs) and the RPA, Rad51, and γ-H2AX foci in cells of different organisms (Fig. 11). With the use of the proposed approach, it seems to be possible to predict the efficiency of DNA DSB repair for ionizing radiations with different physical characteristics.

Results were published of research carried out in collaboration between specialists of Cairo University (Egypt) and JINR's Laboratory of Radiation Biology and Laboratory of Information Technologies. The work was concerned with the mathematical modeling of mismatched DNA base repair (MMR) and evaluation of its role in the induced mutation process in bacterial cells [8, 9]. The mathematical model proposed in this research allowed establishing interrelation between the molecular mechanisms responsible for the removal of the nucleotides that were wrongly inserted by DNA polymerase V during SOS response and determining the MMR position in the hierarchy of the repair systems connected with the induced mutation process.

With the use of the cluster analysis algorithms proposed before, energy deposition in separate brain neurons of rats irradiated with accelerated ^{12}C ions at 1 Gy was calculated. The energy and dose distribution was evaluated for solid models of pyramid neurons of the CA1 region of the hippocampus (Fig. 12). For microdosimetric calculations, solid models of neurons of different types were developed based on experimental data on brain cell morphology [10–12].

Results were obtained on the mathematical modeling of electrophysiological characteristics of brain neurons for varying different parameters of synaptic transmission. With the use of a post-tetanic efficiency model of the dendritic spine of neurons in the CA3 region of the hippocampus (Murzina G. B., Silkis I. G., 1997), the synaptic potential of the membrane was evaluated for different values of the Ca^{2+} ion gradient, which can change under exposure to different chemical and physical agents, including, presumably, ionizing radiations (Fig. 13).

Changes in the conductivity of ion channels were calculated depending on the Ca^{2+} membrane potential. The modeling results are expressed as the values of the gate variables m, n, and h of the Hodgkin–Huxley equation (Fig. 14).

Along with the NMDA receptor expression model that was proposed earlier, these results can be used for clearing up the molecular mechanisms responsible for

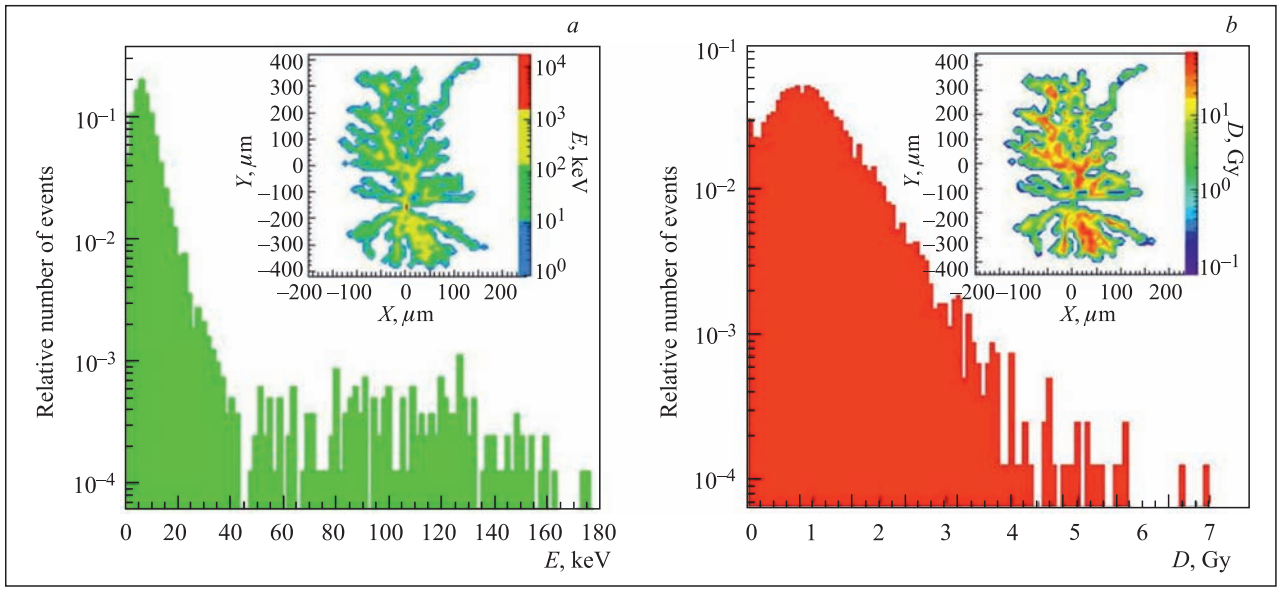

Fig. 12. Calculated distributions of energy E (*a*) and dose D (*b*) in the solid model of a pyramid neuron in the CA1 region of the rat hippocampus for irradiation with 500 MeV/nucleon ^{12}C ions. The insertions show energy and dose distributions in the neuron body in the XY plane. The projectile particle direction is the Z axis

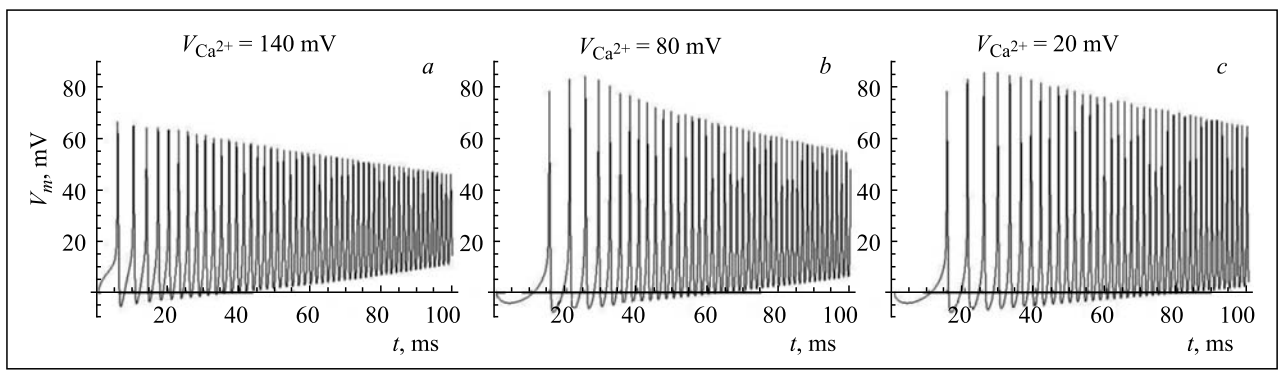

Fig. 13. Membrane potential change on the membrane of the dendritic spine of a pyramid neuron of the CA3 region of the hippocampus for different calcium ion gradient V_{Ca}^{2+} values

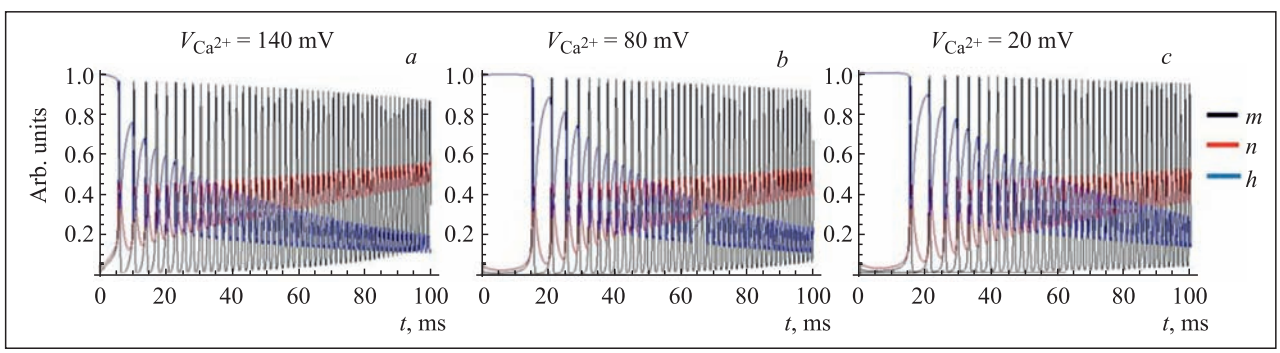

Fig. 14. Estimation of changes in the gate variables $m, n,$ and h of the Hodgkin–Huxley equation for different calcium ion gradient V_{Ca}^{2+} values

disorders in the functional activity of neurons after exposure to heavy charged particles.

The influence was studied of radiation or chemical exposure-caused heterogeneities in synaptic bonds on pulse propagation. An interaction between a pulse and an heterogeneity can result in pulse delay, reflection, compression and decomposition down to its decay [13].

In the course of nonlinear DNA model research, soliton conformational excitation types were identified

that had not been known before: localized sections with an increased spiral twist. It is suggested that such solitons can participate in the regulation of DNA unwinding by topoisomerases [14].

A nonlinear dynamics model of cell cytoskeleton microtubules was proposed. A mathematical apparatus was developed for studying such systems. Both analytically and numerically, the main solution types were obtained that describe nonlinear localized oscillations and the propagation of structure transitions in a microtubule ensemble. The found solution types allow clearing up the picture of the mechanisms of the transfer of energy and transport proteins along microtubules during intracellular processes [15].

COMPUTER MOLECULAR MODELING OF BIOPHYSICAL SYSTEMS

With the use of molecular dynamics (MD) methods, the structural and functional properties of the DNA photolyase enzyme were studied [16]. DNA photolyase is a light-activated enzyme that repairs a UV-induced cyclobutane–pyrimidone dimer in damaged DNA. A series of MD calculations was performed in which 3D protein models of DNA photolyase in a water solution were built, and the topology of the intermolecular potential field of cofactors (the FAD and MHF chromophores) was preliminarily reconstructed (Fig. 15). The modeling results point to the high mobility of the FAD molecule in comparison

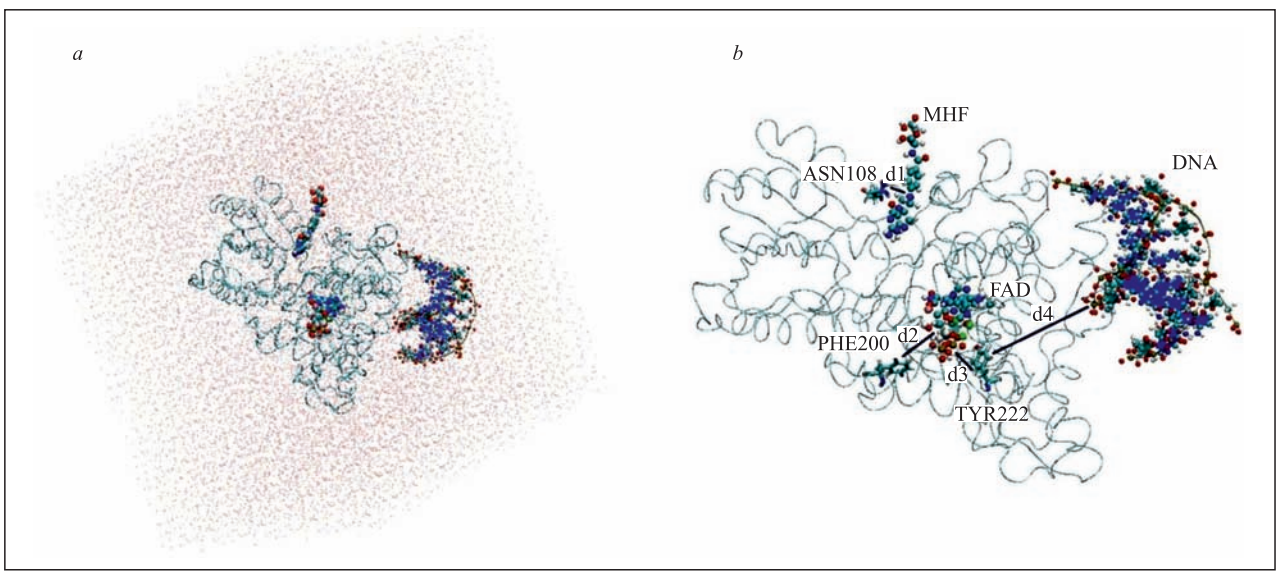

Fig. 15. *a*) A molecular dynamics model of the DNA photolyase enzyme with two chromophore cofactors. The enzyme is solvated in a periodic cubic cell. *b*) The d1–d4 distances show the locations of different parts of the system during their molecular dynamics changes and interactions

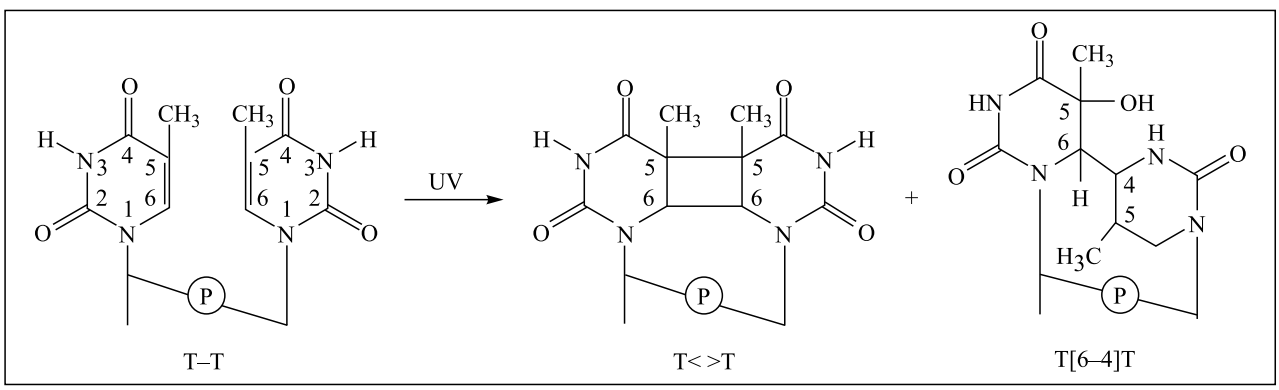

Fig. 16. Two main DNA lesions as a result of UV irradiation: (1) T<>T merging of two neighboring nucleotides — thymines — in the DNA structure, i.e., cyclobutane–pyrimidone dimer formation; (2) T[6–4]T pyrimidine–pyrimidone photoproduct

with other fragments of the protein complex of DNA photolyase.

The reconstruction of the relaxed structure of the FAD molecule points to a transition of its conformational state from the U-closed to the I-open shape. Such behavior of the FAD molecule inside the enzyme's chromophore centre can be one of the key factors in the process of damaged DNA structure repair, which is followed by the formation of a "wrong" cyclobutane: the pyrimidone dimer (Fig. 16). The high mobility of the FAD chromophore and the role of enzyme binding in the region of the interaction of the FAD molecule with the damaged DNA section (T<>T cyclobutane–pyrimidone dimer) can determine the process of DNA repair by the DNA photolyase enzyme. The obtained results are conductive to the solution of the problem of identifying the mechanisms of DNA repair by this enzyme.

Research was continued on the photochemical and photophysical properties of the G-proteins, in particular, the visual pigment rhodopsin [17–19].

PROTECTION PHYSICS AND RADIATION RESEARCH

Two radiobiological sessions were conducted at the 52 MeV/nucleon ^{20}Ne ion beam of the MC-400M cyclotron of the Flerov Laboratory of Nuclear Reactions. For automated irradiation of a large number of thin biological samples, the ACCULINNA separator-based Genome-M facility was used. During these sessions, the facility was calibrated and methods of ion beam quality control were worked out. The irradiated samples included human peripheral blood lymphocytes, mammalian and human cell cultures, and yeast cells. The interest in ^{20}Ne ions is determined by high values of their linear energy transfer (120–150 keV/μm), inducing severe clustered damage in biological structures.

A radiobiological session was held at the 500 MeV/nucleon ^{12}C ion beam of the Nuclotron, the Veksler and Baldin Laboratory of High Energy Physics. A large experimental programme was fulfilled, which included, in particular, irradiation of laboratory rats and primates for studying the effect of heavy ion exposure on animals' cognitive functions. The urgency of this research is determined by the prospects of long-term manned flights beyond the Earth's magnetosphere.

Work was continued on the prediction of the radiation conditions at the planned booster synchrotron of the NICA complex using the Monte Carlo based MCNPX code for calculating radiation transport in matter. The spatial distributions of skyshine neutrons and γ rays around the Nuclotron were measured (Fig. 17). Neutron spectra were measured beyond the shielding of the MC-400M cyclotron experimental hall for acceleration of ^{20}Ne ions up to 52 MeV/nucleon.

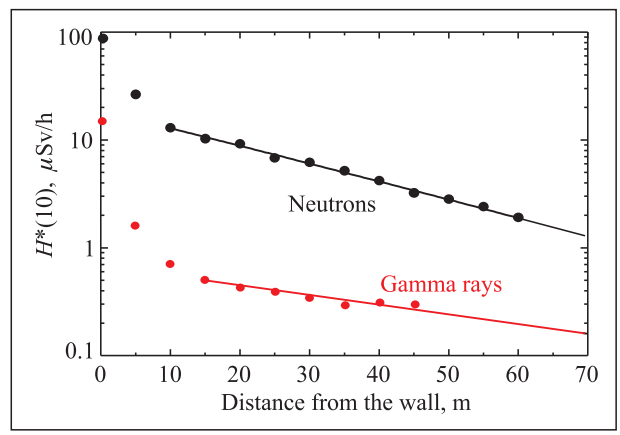

Fig. 17. Radial distributions of the ambient equivalent dose rate of skyshine neutrons and γ rays from the Nuclotron for deuteron acceleration up to 4.1 GeV/nucleon

RESEARCH ON COSMIC MATTER ON THE EARTH AND IN NEARBY SPACE

Reactions were analyzed of chemical compound synthesis from formamide NH_2COH (an HCN hydrolysis product) under ionizing radiation. The reactions were realized under 165 MeV proton irradiation at the Phasotron (the Dzhelepov Laboratory of Nuclear Problems, JINR) in the presence of different catalysts isolated from meteorites of different classes. Based on these experiments, an important conclusion was made that in the system "formamide – meteorite matter + ionizing radiation", prebiotic compounds (precursors of nucleic acids, proteins, metabolic cycles, and metabolism) emerged in notable amounts. Under exposure to UV and/or heating, no prebiotic compounds were produced. This research can shed light on the origin of life not only on the Earth, but also in the Universe.

CONFERENCES AND EDUCATION

In 2013, LRB staff members participated in nine conferences in Russia and five conferences abroad.

Jointly with the Physiology and Fundamental Medicine Department of the Russian Academy of Sciences (RAS), RAS Council on Heavy Ion Physics, and RAS Institute of Biomedical Problems, a two-day conference was held entitled "Neurophysiological Aspects of the Radiation Risk. On the Problem of Interplanetary Flight Safety". The conference was concerned with the following issues: the effect of high-energy heavy charged particles on the structures and functions of the central nervous system; neurophysiology of higher nervous activity; mathematical modeling of the molecular mechanisms of the synaptic transmission of the nervous system signals; and evaluation of the radiation risk of manned interplanetary flights.

The Biophysics Department of Dubna University continued its education activity. Total enrollment in the Human and Environmental Radiation Safety specialty is 48 students; four postgraduates attend the Radiobiology specialty programme. In 2013, eight new students were accepted to the Department. Ten students successfully completed their graduate programmes and received engineer-physicist diplomas. The Department of Cemistry, Geochemistry, and Cosmochemistry offers a Molecular Dynamics course to graduate students of Dubna University.

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