JOINT INSTITUTE FOR NUCLEAR RESEARCH

2008-19

E. A. Krasavin, G. N. Timoshenko

RESEARCH PROGRAMME OF THE LABORATORY OF RADIATION BIOLOGY: ITS PERFORMANCE IN 2007 AND THE PROGRAMME FOR 2008

Report to the 103rd Session
of the JINR Scientific Council
February 21–22, 2008

Dubna 2008

1. Scientific research programme for 2007

The research programme of the Laboratory of Radiation Biology (LRB) determined by the 1st priority theme was concentrated in 2007 on the following main directions: fundamental radiobiological and radiation genetic research with heavy charged particle beams, investigation of molecular photo- and radiobiological processes in eye structures, research in the field of molecular dynamics, radiation research and radiation protection at the basic nuclear facilities of the JINR and its environment.

2. Execution of the 2007 programme

2.1. Radiobiological and radiation genetic research

The researches of induction of molecular damages in DNA in human lymphocytes after γ- and heavy ion irradiation were continued in group of molecular radiobiology. The regularities of formation and repair of double strand breaks (DSB) of DNA were studied by using comet-assay method after irradiation with γ-rays ^{60}Co and ^{11}B ions (linear energy transfer 40 keV/μm). The cell distribution on a DNA lesion level are received at γ- and heavy ion irradiation. It was shown that biological effectiveness of heavy ions on the criterion of DSB induction was greater in comparison with γ-irradiation. As can be seen the the linear relationship induction of DSB as a function of a dose of γ-rays and boron ions was obtained (Fig. 1). The value of relative biological efficiency of the accelerated boron ions is 1.7±0.1.

The experiments with human lymphocytes under PGA stimulation for initiation of cell cycle were carried out. The cells have been irradiated by γ-rays ^{60}Co and protons with energy 250 MeV in Brag peak with 1 – 4 Gy. The regularities of formation of DSB induction in various phases of a cell cycle (G_0, S, G_1 and G_2) were studied after proton irradiation. It is shown (Fig.1b) that the greatest yield of DSB in cells is observed in S-phase of a cell cycle. The kinetics of DSB repair in lymphocytes under PGA stimulation was studied in different period after irradiation (24, 48, 72 and 96 h). It is established that the number of DSB decreases exponentially during

the postirradiating period. The control level of DSB was observed up to 24 h after irradiation. This level is kept up to 96 h.

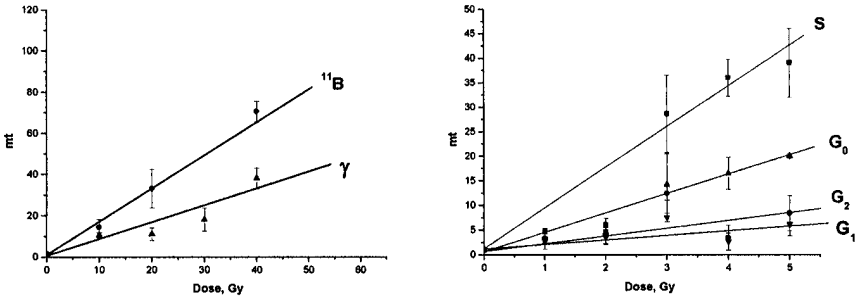

Fig. 1 The dependence of the induction of DSB in human lymphocytes on the dose of γ-rays 60Co and accelerated boron ions with linear energy transfer 40 keV/μm (a); DSB induction in human lymphocytes in different stages of cell cycle after irradiation b by protons in Bragg peak (b). Ordinate: mt – momentum tail of the comets, abscissa: dose of irradiation, Gy

The regularities of induction of apoptosis in human lymphocytes on the different stages of the cell cycle after irradiation by protons in Bragg peak were studied (Fig. 2). It was shown that formation of apoptotic cells in population of lymphocytes increases linearly for all stages of cell cycle at the doses of protons up to 5 Gy. The most sensitivity of cells on this criterion was revealed for G_2 and S stages of cell cycle. The investigations of chromosome aberrations induction in human peripheral blood lymphocytes by low doses of ionizing radiation with different LET have been continued. Based on the recently published phenomena observed at the low dose range of ionizing radiation such as bystander effects, genetic instability, hypersensitivity and adaptive response, the major role of ROS formation in all these effects was hypothesized. The elevated intracellular ROS level termed persistent oxidative stress was demonstrated in the progeny of irradiated and bystander cells for many cell generations, a year after single exposure in vivo. Persistent oxidative stress was found to exist in human lymphoblast clones derived from X-irradiated cells for about 20 generations after exposure and in primary mouse cells 2 weeks after X-ray exposure. Close

relation between oxidative stress and instability was proved in the cells that exhibit an unstable phenotype, i.e. the progeny of the irradiated cells possess an elevated level of ROS compared with their stable counterparts. Mitochondrial oxidative stress was shown to lead to a loss of genetic stability in the nucleus while anti-ROS conditions (addition of ascorbic acid) relieve genetic instability.

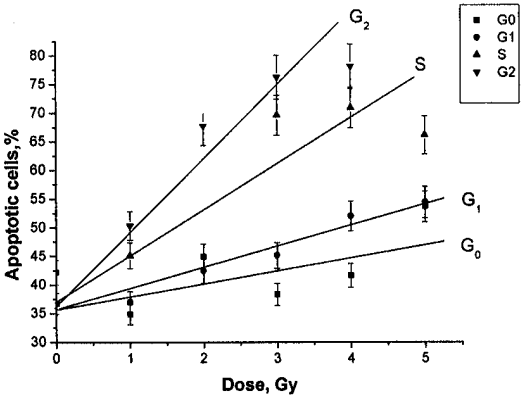

Fig. 2 The "dose-response" dependence on the induction of apoptotic lymphocytes at the different stages of cell cycle after irradiation by protons in Bragg peak. Ordinate: the number of apoptotic cells, %; abscissa: dose of irradiation, Gy

It is obvious that the elevated ROS level persisting for many cell generations after radiation exposure has endogenous nature. ROS are continuously generated in mitochondria as leakage from the respiratory chain and are believed to cause most spontaneous DNA damage. It was shown recently that radiation drastically increases the mitochondrial oxidative stress due to ROS amplification via reversible mitochondrial permeability transition (MPT). On the other hand adaptive response shown by irraidated cells as well as increased radioresistance observed after peak of hypersensitivity is the evidence of activation of cellular cytoprotective pathways which leads to decrease of oxidative stress rather then to activation of repair mechanisms and checkpoints. One of the cytoprotective proteins is erk-1, mitogene-activated protein kinases of early response, activation

of which prevents amplification of ROS via blocking MPT. Based on this the goal of present investigation was to prove:

- the role of ROS in phenomenon of hypersensitivity (HRS) using cytogenetic criteria (chromosomal aberrations)
- protective role of erk-1.

The cells of breast carcinoma Cal 51 cultured in DMEM medium supplemented by 10 % foetal calf serum were used for the experiments. Asynchronous cell cultures were exposed to 1-200 cGy γ-irradiation ^{60}Co (18 cGy/min) at room temperature. 10μM of PD98059 – inhibitor of erk-1 was added 30 min before irradiation, 2 % of DMSO – free radical scavenger – immediately after exposure. Both modifiers left in the culture until fixation 10h post irradiation. Cells were fixed and stained with acetoorsein. Anaphases were analyzed (typically 800-1600 for every data point) and amount of aberrant cells was evaluated including cells with bridges and fragments. The statistical uncertainty of the number of aberrations per cell was calculated as $\sqrt{n}/N$, where n is the frequency under consideration and N is the number of cells analyzed.

The dose dependence of frequency of aberrant cells has a nonlinear shape characterized by high radiosensitivity at very low doses with a peak around 1-3 cGy termed HRS. With the following increase of dose the yield of aberrant cells decreases significantly demonstrating the reverse dose dependence. At ≥50 cGy the dose-effect curve becomes linear with a less steep slope compared to the initial one (IRR). Previously we observed HRS/IRR on several mammalian and human cells lines including human lymphocytes using different cytogenetic methods (anaphase, metaphase analysis, micronucleus test). Only quantitative differences in amplitude and position of HRS peak were found.

We supposed that at low dose range besides DNA damaged resulted from direct targeting of DNA by ionizing track the additional factor exists causing aberration formation and HRS. At higher doses its action can be masked by high level of induced chromosome damage and at the doses ≥ 3cGy activation of cellular cytoprotective pathways occur leading to IRR.

The frequency of aberrant cells decreased in dose range of 1-10 cGy in the presence of DMSO (Table 1) and most importantly, neutralization of ROS in the presence of DMSO leads to disappearance of HRS at 1-3 cGy. DMSO was added to the medium immediately after exposure thus, it didn't affect the products of water radiolysis induced by radiation. These results confirm the role of endogenous ROS in HRS and marginally the role of radiation-induced mitochondrial stress in atypically high effectiveness of low doses. The direct testing of these assumptions can be done using inhibitors the respiratory chain of mitochondria.

Table 1 Dose dependence of aberrant cells frequency

Dose	**% aberrant cells**		
	Without modifiers	*+DMSO*	*+PD98059*
0 cGy	4.4 ±0.53	3.8±0.68	
1 cGy	4.9 ±0.76	3.8±0.68	
3 cGy	6.3±0.85	4.7±0.7	4.8±0.54
5 cGy	3.9±0.48		6.0±0.83
7 cGy	4.8±0.54		5.9±0.8
10 cGy	9.2±1.0	7.0±0.9	

The treatment of cells with PD98059 – inhibitor of protein kinases erk-1 leads to the increase of frequency of aberrant cells at the doses ≥ 3cGy as it was expected. These results confirm the idea that erk-1 activation causes IRR, i.e. plays cytoprotective role in oxidative stress conditions caused by irradiation. Unexpectedly, it caused also to the decrease of frequency of aberrant cells at 3cGy. However, it was recently demonstrated that PD98059 in addition to inhibition of protein kinases erk-1 may also increase the production of free radical scavenger glutathione and thus, acts similar to DMSO. To avoid this contradiction the inhibitor UO126 which doesn't affect the glutathione production should be used.

The analysis of data obtained in the set of experiments investigating chromosomal damage and proliferation perturbations induced in human peripheral blood lymphocytes by irradiation with accelerated carbon ions of different energy has been finished.

Experiments were performed in collaboration with biophysics group of GSI (Darmstadt, Germany).

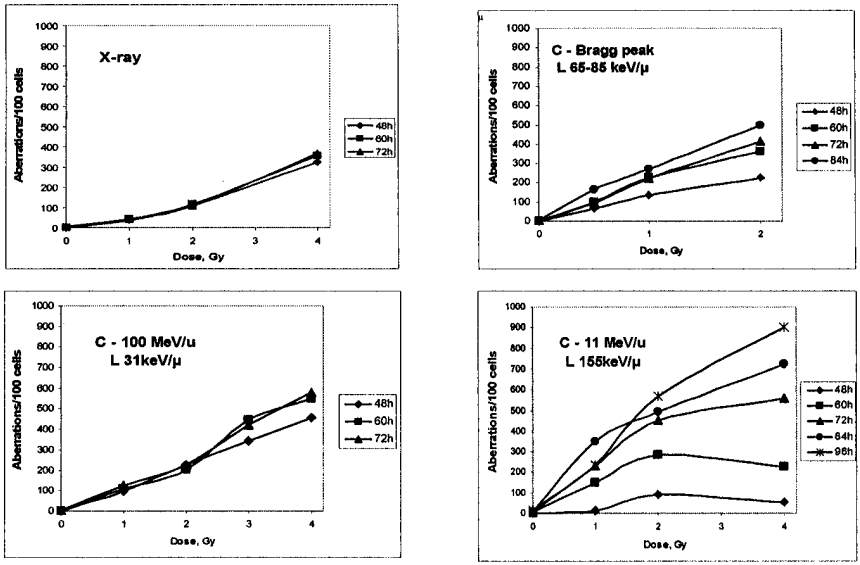

Fig. 3 Time-course of registered chromosomal aberration frequency induced by carbon ions of different energy in human peripheral blood lymphocytes

The cytogenetic consequences of carbon particle beams of different energy have to be known for both, space research and heavy ion tumor therapy. An increasing number of cancer patients is treated with charged particles due to the advantage of the dose-depth profile and their greater biological effectiveness compared to photons. At present radiotherapy with carbon ions is performed at three facilities at Chiba (Japan) since 1994, GSI (Germany) since 1997 and Hyogo (Japan) since 2002; several new facilities are already approved. High energy ions (100 MeV/u) used in the present study are similar to those affected healthy tissues of patient during cancer therapy while tumor volume is treated by carbon ions at Bragg peak (SOBP – spread-out Bragg peak) and ions with low energy (11 MeV/u). Moreover, high-energy carbon ions are the part of galactic cosmic radiation (GCR) which is known to be an important limiting factor for manned space missions. Thus, to estimate the health risk posed to astronauts the

biological action of carbon ions as well as other charged particles of GCR has to be examined in detail.

The values of relative biological efficiency (RBE) of carbon ion beams of different energy were estimated as well as influence of cell proliferation alterations, i.e. radiation-induced cell cycle delay, on the registered yield of chromosomal aberrations induced in healthy human lymphocytes. No differences in aberration yield were found at different fixation times (48, 60 and 72 h postirradiation) after X-irradiation and 100 MeV/u carbon exposure. After irradiation with spread-out Bragg peak carbon ions (LET 65-85 keV/μ) aberration yield increases twice between 48 and 84 h postirradiation. The drastic increase of aberration frequency was found after 11 MeV/u carbon ions (LET 155 keV/μ): by factor of 15-17 from 48 to 96 h after exposure. Thus, RBE estimated at different single fixation time varied from 0 at 48 h to 6.0 at 84 h postirradiation (Fig. 3). This is the result of severe cell cycle delay of heavily damaged cells which is more pronounced for low energy and high-LET ion beams. Thus, using of single fixation time point at 48 h may lead to pronounced underestimation of RBE values of high LET radiation.

In collaboration with biophysical group of Institute of Biology (Keltce, Polska) the series of experiments was continued for study individual radiosensitivity of lymphocytes of peripheral human blood after exposure by high LET radiation.

As was shown in the experimental data analysis that is important to consider a radiation-induced cell cycle delay. Total quantity chromosomal aberrations modify from donor to donor and against demonstration individual radiosensitivity.

The study structural chromosome aberrations in the human cells after irradiation therapeutic proton beam (E = 150-170 MeV, LET ~0.49 keV/μ). We used the lymphocytes of peripheral human blood as model. The samples were irradiated at two different depth points: at the entrance to the object and in the Break peak region of proton beam. The positions of experimental irradiation correspond to the irradiation of healthy surrounding tissues along the beam path and tumor tissue. The Relative Biological Effectiveness (RBE) of protons

beam at Bragg peak is ~1.25, at entrance to tissue and after γ-irradiation this is equal ~1.

It is possible higher proton beam efficiency in the Bragg peak region, because tumor tissue cells are in mitotic cycle difference normal tissue cells. The radiation sensitivity is differing in various cell cycle phases.

High radiation sensitivity was found in G_2 phase irradiated lymphocytes, the phase is previous mitos (Fig. 4). Aberration type in lymphocytes irradiation in G_2 phase were analyzed, considerable increase chromatid aberration yields was found, they are about 70-75 % of the total number of aberrations.

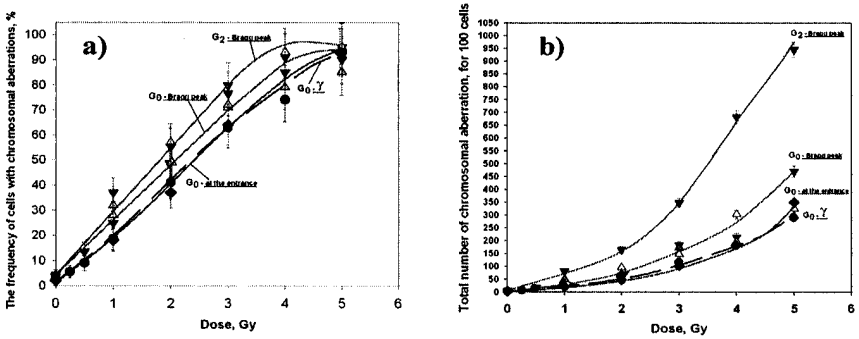

Fig. 4 Dose dependence number of lymphocytes with chromosomal aberrations (a) and total number of chromosomal aberrations (b) after irradiation therapeutic protons beam (LNP) at the entrance and in the Bragg peak region

Standard metaphase analysis didn't register any difference effects after irradiation lymphocytes in G_0, G_1, S phase. On the basis of frequency of PCC excess fragments, after irradiation in dose 5 Gy, radiation sensitivity is higher in G_1 phase then in G_0, after irradiation lymphocytes in S phase effect increased more then twice in comparison G_1 phase.

The first results show possibility rising RBE protons in Bragg peak region to 1.4, because part of cells in radiosensitive G_2 phase. Our investigation confirms the high efficiency of the proton beams for the use in radiation therapy. Either evidence possibility lowering the dose for radiotherapy patients.

The investigations of the mutagenic action of ionizing radiation were continued. Using of several genetic systems allows to test of

mutagenic consequences of double strand breaks of DNA. Unrepaired breaks lead to chromosome loss and cells death. Breaks repair by homologous recombination (HR) or non-homologous end joining (NHEJ) with creations of rearrangements or deletions.

Model plasmid system allows to test deletions creating in results of NHEJ. The spontaneous rate of deletions in strains *RAD*$^+$ was (0.4±8.2) x 10^{-8}. Deletions induced effectively by γ-irradiation (Fig. 5). Under dose 100 Gy (survival 26 %) the frequency of deletions was (8.7±4.2) x 10^{-6}. The curve of mutagenesis was linear-quadratic in *RAD*$^+$ strains but *rad53* mutation inhibits of deletion inductions by γ-irradiation. So, gene *RAD53* participates in regulation of NHEJ.

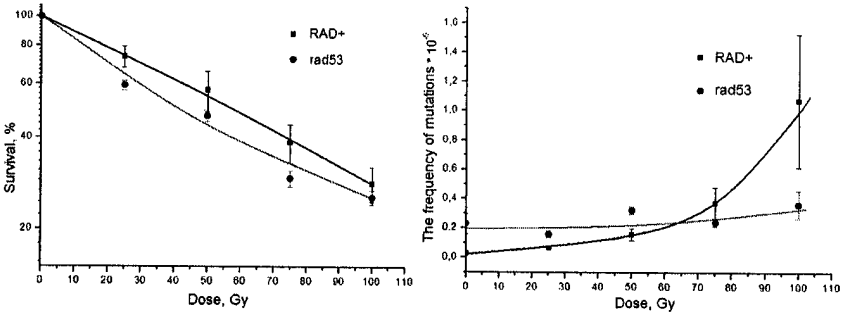

Fig. 5 Survival and induction of deletions in haploid strains of different genotypes by γ-irradiation

The genetic analysis of deletion mutants induced by ionizing radiation had shown that in the cell's population before irradiation the majority of deletions (~70 %) was formed by the smallest tested deletions covering two markers (*CYN2* and *CAN*). The rest part of mutants (~10 %) had large deletions covering four markers (*CYN2, CAN1, LEU2, TRP1*). With the rise of the radiation dose, the portion of mutants with large deletions has grown up to 30 %. Induction of the large deletions was less effective under irradiation of heavy ions.

Restriction analysis of the recombinant plasmids showed that the plasmids had deletions at various sites of the *CAN1-CYN2* region. The size of deletion, which covered two genes, *CAN* and *CYN2,* ranged from 1.0 to 2.8 kbp. Plasmid DNA from mutants with deletion of four genes didn't extracted. May be they had damaged regulation regions.

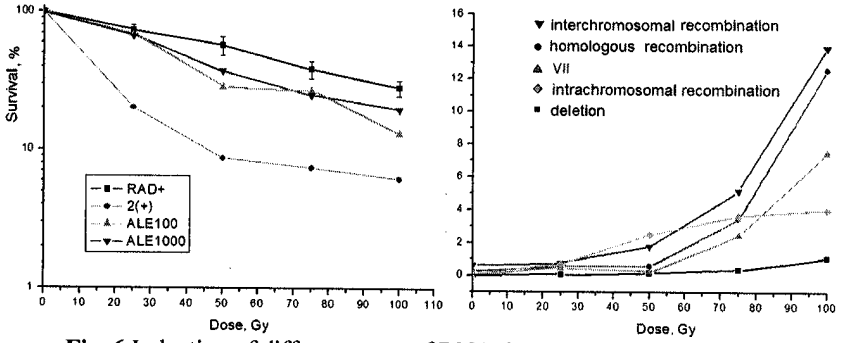

Fig. 6 Induction of different types of DNA damage on ionizing radiation
a) survival curves of analysed strains; b) frequency of different types of mutations

Ionizing radiation induced more effectively rearrangements as consequences of homologous recombination, chromosome loss and deletion (NHEJ) were induced with smaller frequency in haploid strains (Fig. 6).

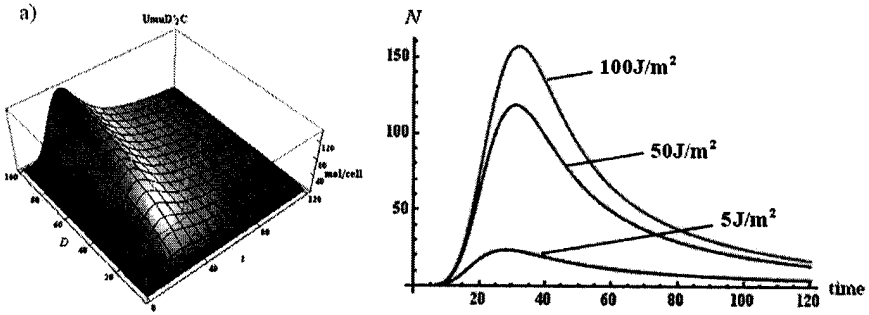

Fig. 7 The calculation of normalized concentration for UmuD'2C protein complex (DNA-polymerase V). a) The surface characterizing concentration of UmuD'2C protein depending on time and on dose of UV-irradiation. b) The range of curves characterized dynamics of UV-irradiation

On the basis of prior approaches the mathematical model describing kinetics of protein complexes which carry out the mechanism of translesion synthesis (TLS) in cells of bacteria *Escherichia coli* was developed. The dynamic models have been constructed for concentrations of *umuD* and *umuC* gene products, for dimer products of *umuD* gene, and for main regulatory complexes of SOS-system: $UmuD_2C$, $UmuD'_2C$ (DNA- polymerase V) (Fig. 6),

UmuDD'C. The parameters of models were calculated using experimental data. Also protein dynamics was analyzed subject to dose of UV-irradiation. Observed results in a good agreement with known experimental data and other theoretical modals.

The next steps of our research are improvement of presented approaches and development of integrated mathematical model for inducing mutagenesis in cells of bacteria *Escherichia coli.*

2.2. Photo-radiobiological research

Main aim of 2007-year research was *in-vivo* study of cataract formation upon combination of radioactive and UV irradiation. A single radioactive irradiation and UV irradiation prolonged was used. It was shown that combination of radioactive and UV irradiation was more effective then every factor separately.

Lens opacity (cataract) is the main parameter for characteristic of the damaging factors influence. At the same time it is well know that many unspecific factors could influence the cataract formation. For example age (senile cataract), trauma, some diseases (diabetes) causes lens opacity formation. Therefore the main task of our investigation was the true condition search. For prevention the age influence we used a F1 hybrid of C57Bl/CBA mouse, as this mouse hybrid does not form the senile cataract during 1 year.

The following experimental groups were formed: (1) control – 18 animals, (2) daily UV irradiation - 18 animals, (3) single 2 Gy γ-irradiation – 20 animals, (4) single 2 Gy γ-irradiation and daily UV irradiation – 20 animals, (5) single 4 Gy γ-irradiation – 22 animals, (6) single 4 Gy γ-irradiation and daily UV irradiation – 22 animals. 2 and 4 Gy radiation doses were used for special control of radiation cataract formation.

Slit-lamp examination of animals was blind and accomplished monthly. The following lens opacities were detected: post-cortical, needle, spot, net and diffuse. The diffuse opacities were discovered among all group animals; therefore, this parameter was used for cataract measure. On 6^{th} month γ-irradiation it was observed that UV irradiation increased lens opacity significantly ($P<0.001$, Mann-Whitney nonparametric U-test). It should be emphasized that expert

method data cannot be used for UV effect calculation. Only continuous data (graphic analysis data) could be used for such calculation. But graphic analysis of lens images is impossible as all groups' cataracts are low now. Therefore in-vivo experiment will be finished on 9th month post γ-irradiation.

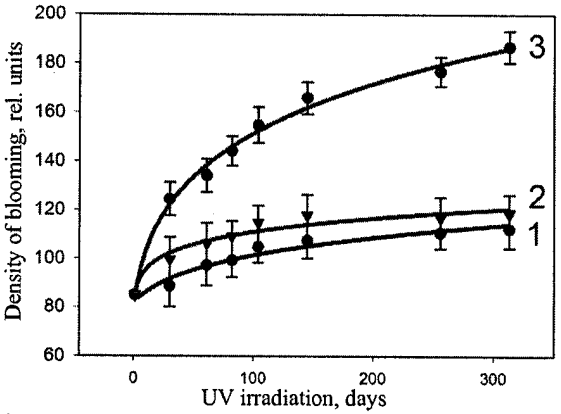

Fig. 8 The curative effect of new compound (N-acetyl carnozin + pantetin) on the cataract induction in mice by UV radiation

The researches of cataract formation by UV and ionizing radiation in sector of photo-radiobiology were continued (Fig. 8). The new compound (N-acetic-carnosine + pantethine) for prophylaxis and treatment of UV induced cataract was obtained in LRB. The high curative effect of the compound was shown in experiments with animals irradiated by UV light. The clinical trial of this compound will be started in 2008.

2.3. Computer molecular modeling of biophysical systems

In computer molecular modeling sector the simulation analysis have been continued in studying of the structural and functionality domains of the human and yeast protein kinases. We have built a yeast kinase tertiary structure using its homologs for a human kinase protein one. A comparative analysis of phenotypic manifestations for different mutations that are localized in CDC28 along with kinase structural behavior has been performed. The radio sensitivity, generation time and mutability level of mitochondrial genome in the yeast cells have

been demonstrated in correlation with the kinase structural destruction.

Molecular-dynamics simulations have been performed for the visual pigment rhodopsin in its native dark-adapted state. The analysis of the interaction of chromophore group (with 11-*cis* retinal) and the nearest amino acid residues surrounding the chromophore center has been done for the beta-ionone ring and protonated Schiff base regions.

Based on the computer molecular simulation method we have investigated the conformational dynamics of the rhodopsin protein as well as the free opsin with a special emphasize to the behavior of the chromophore (11-*cis* retinal) group for the dark-adapted state. The molecular dynamics trajectories were traced up to the time interval of 3000 picoseconds; thereby we have generated the $3x10^6$ discrete states of the free opsin and rhodopsin to perform the comparison of the rhodopsin and opsin structural conformation changes. The analysis of the chromphore retinal adaptation process in the opsin location center in correlation with the behavior of the surrounding amino acid residues have been carried out. From the analysis data we demonstrate the role of the amino acid residues for the keeping of a stressed twisted conformation of the chromphore retinal in the protein binding pocket. Based on the simulation results we discuss also the possible molecular mechanisms of the conformational adaptation of the chromophore in the protein that occur during the physiological regeneration of the visual pigment rhodopsin.

2.4. Radiation research

1. The first works concerning the NICA radiation protection design were started:

- The verification of the universal MC codes FLUKA and GEANT4 for radiation transport in matter calculation was done on the basis of the experimental data on the neutron yields from thick iron target irradiated by ^{238}U nuclei with energies 1 GeV/n (Fig. 9);
- The crucial criterion for radiation shielding design of the modernized nuclotron at ^{238}U nuclei acceleration was defined;
- The calculations of the effective dose rate radial distributions owing to the skyshine neutrons around the nuclotron without

upper shielding were carried out by FLUKA and GEANT4 codes for ^{238}U nuclei acceleration to 3,5 GeV/n energy;

- The calculations of the effective dose rate radial distributions owing to the skyshine neutrons around the nuclotron with upper shielding from different thickness concrete were carried out by FLUKA and GEANT4 codes for ^{238}U nuclei acceleration to 3,5 GeV/n energy (Fig. 10);

2. The investigations connected with the development, computer modelling and physical calibration of the Russian neutron detectors DAN and LEND assigned for the Mars and Moon surfaces research by the nuclear-physical methods were continued;

3. The technique for data correction of individual neutron albedo-dosimeters and neutron dosimeters with CNM-14 counter and moderator was developed on the basis of systematization of neutron spectra at nuclear facilities of JINR and other foreign scientific centers;

4. In the frame of Intergovernmental Russia-India scientific agreement on a new shielding material design the first investigation of the Indian TLD characteristics were began at the medical beam of the LNP phasotron.

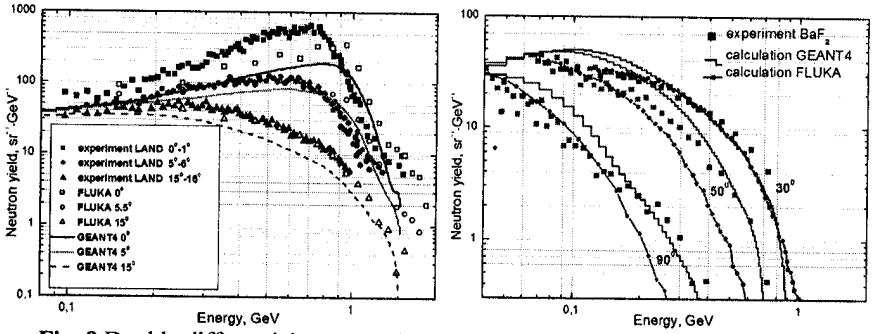

Fig. 9 Double differential neutron yields at small angles from thick iron target (20 cm length, 10x10 cm^2 cross-section) induced by ^{238}U nucleus with energy 1 GeV/n

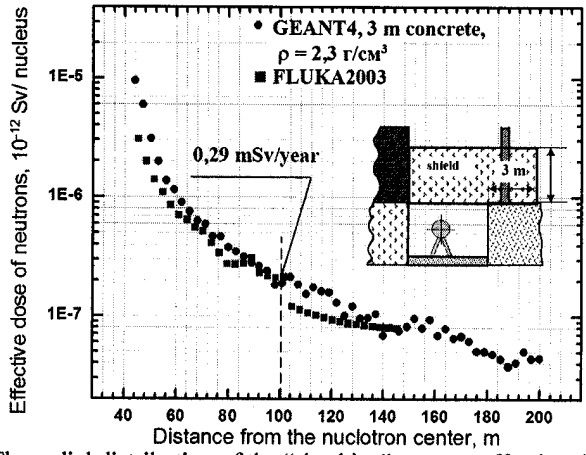

Fig. 10 The radial distribution of the "skyshine" neutron effective dose at the 3m concrete radiation shielding of the nuclotron

3. Scientific meetings and educational activity

On 24-28 January 2007, the Russian Academy of Sciences, the Division of Biological Sciences of the Russian Academy of Sciences, the Bach Institute of Biochemistry of RAS, the Russian State Scientific Centre "Institute of Biomedical Problems" of RAS, together with the Bunatian Institute of Biochemistry of the National Academy of Sciences of the Republic of Armenia, Yerevan State University, and the Joint Institute for Nuclear Research hold the III International Symposium "Problems of Biochemistry, Radiation and Space Biology" dedicated to the centenary of the birth of Academician Norair Sissakian.

The International Symposium "Modern spectroscopy methods in studying structure and function of biopolymers in biology and medicine", organized by Counsel on biophysics of RAS, Laboratory of Radiation Biology of Joint Institute for Nuclear Research and M.V. Lomonosov Moscow State University, took place from 28 May to 2 June 2007 at the International Conference House in Dubna. The symposium was supported by International Union for Pure and Applied Biophysics (IUPAB). Modern methods of spectroscopy are very effective in biopolymer research and have great advantage as non-invasive ones. They are successfully used for bioindication of

different diseases since they provide an opportunity to detect primary stages of various pathogenic changes. Diomedical spectroscopy is boundary area in biophysics where a great number of new results have been obtained for the last years. About 80 scientists from JINR, Russia, Armenia, Azerbaijan, Belarus, Bulgaria, Germany, Denmark, Canada, USA, France and Switzerland participated in the symposium. The symposium programme included 30 plenary reports on fundamental basis of spectral methods and the results of their application in biomedicine. Special attention was given to analysis of the primary processes of optical and ionizing radiation affects on biopolymers, as well as infrared spectroscopy methods, radiobiological methods, polarized fluorescence, acoustic methods, gamma-ray and optical spectroscopy and others techniques using in biomedicine.

During 22-26 October, 2007 International workshop of Multilateral Medical Operations Panel (MMOP) and Multilateral Radiation Health Working Group (MRHWG) was held in Dubna under the direction of LRB.

The education process at the chair "Biophysics" of the International University "Dubna" was continued. 80 students in sum are studying now on specialty - "Radiation protection of people and environment" and 19 new students were admitted in 2007 to the chair. The 4th graduation of the 9 students took place in 2007.

4. Administration activity

Personnel. The total personnel of the LRB were 80, including the directorate staff 16.

Finance. Funding of research in the direction of radiation and radiobiological investigations in 2008 is shown in Table 2.

Table 2. Financing LRB in 2008

Area	Financing plan (k$ USA)
08-9-1015-96/2008 (1st priority)	469.6
Infrastructure	121.4
Total	591.0

Отпечатано методом прямого репродуцирования
с подготовленного лабораторией оригинала.

Макет *Т. Е. Попеко*

Получено 11.02.2008. Подписано в печать 12.02.2008.
Формат 60 × 90/16. Бумага офсетная. Печать офсетная.
Усл.-печ. л. 1,43. Уч.-изд. л. 1,51. Тираж 115 экз. Заказ № 56057.

Издательский отдел Объединенного института ядерных исследований
141980, г. Дубна, Московская обл., ул. Жолио-Кюри, 6.
E-mail: publish@jinr.ru
www.jinr.ru/publish/