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# RESEARCH PROGRAMME OF THE DEPARTMENT FOR RADIATION AND RADIOBIOLOGICAL RESEARCH: ITS PERFORMANCE IN 2003 AND THE PROGRAMME FOR 2004

Report to the 95th Session
of the JINR Scientific Council
January 15–16, 2004

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## 1. Scientific research programme for 2003

In 2003 the main lines of the investigation were concentrated on:

- Neutron spectrometry and radiometry; radiation monitoring at the JINR nuclear installations and in environment;
- Physical support of radiobiological experiments;
- Shielding calculations and design;
- Study of the regularities and mechanisms of stable and unstable chromosome aberrations induction in human cells after irradiation by high energy heavy ions;
- Problem of low doses of radiation with different LET and sell recovery;
- Investigation of the heavy charged particles radiation effects on rodopsin and isolated retina of an eye;
- Clinical testing of the radiopharmaceutical preparation "methilen blue – $^{131}$I" developed for target radiotherapy of human pigment melanoma.

In 2003 the theme "Radiation and Radiobiological Investigations at the JINR Basic Facilities and in Environment" was prolonged to 2008.

## 2. Execution of the 2003 programme

### 2.1. Radiation researches

*The development of radiation protection measures* of the Cylab cyclotron complex (Slovakia) was continued. The radiation protection requirements needed for all nuclear and medical technologies to be used at the complex were specified. The following aspects of radiation protection were considered: criteria of radiation protection design, possible radiation sources, radiation shielding, skyshine problem, radiation monitoring, waste management, possible radiation accidents and others.

The radiation shielding of Cylab cyclotron complex was optimised based on principle ALARA. The comparison between Monte Carlo and phenomenological methods of calculation of neutron effective dose attenuation by concrete shield was carried out for verification of calculation technique. Model of isotropic punctual neutron source with energy 5, 20, 50 and 100 MeV at 5 m from shield was used thereto.

*The physics support of the biological experiment* with the protons, $^{12}$C, $^{24}$Mg, $^{40}$Ar and $^{56}$Fe beams at LHE nuclotron was carried out. The new modes of the nuclotron operation (acceleration of $^{40}$Ar and $^{56}$Fe ) allow to extend the range of a linear energy transfer of relativistic nuclei in radiobiological experiments from 0.2 keV/μm (protons) to 200 keV/μm (Fe nuclei).

The measuring instrument of laser light relaxation in pattern during its irradiation was developed for study of the charged particles impact on the lens proteins (crystallins) aggregation.

*The experimental studies of solid state track detector characteristics* were continued in the nuclotron experiments. Sensitivity of CR-39 solid state track detector to heavy nuclei of C, Mg, Ar and Fe with energy 500 MeV/nucleon was measured. The dependence of track size on LET of the particles was obtained as well.

*The prognostication of the radiation environment at the SAD installation* was continued. The first estimations of the SAD shielding and induced radioactivity of ground were done. The initial radiation situation in place of the SAD allocation was measured.

*The modification of multisphere neutron spectrometer* was carried out for expansion of measurable energy range. The heterogeneous (polyethylene and lead) spherical moderator was developed for this purpose. The calculation of neutron detection efficiency of the HEND neutron spectrometer on basis of stilbene detector (Mars Odyssey project) was started.

*Area and occupational personnel radiation monitoring* in the field of the JINR nuclear installation was continued.

**2.2. Radiobiological researches**

The study of mutagenic action of radiation with different LET on the human and mammalian cells and microorganisms was continued. The first experiments were performed on the nuclotron for exposure of the human blood lymphocytes to 1 GeV protons and $^{12}C$ and $^{24}Mg$ ions with energy of ~ 470 MeV/nucleon. Their LET values were of 0,218; ~ 12 and 42.7 keV/μm. The dependence of the frequency of aberrant cells from doses was linear after irradiation by all investigated radiation types. The power dependence of total chromosome aberration from doses was observed after irradiation by protons. It modifies in linear one after exposure to $^{12}C$ and $^{24}Mg$ ions. But at their highest doses the effects decrease, that was shown at the lower doses for earth radiation and a dependence of their LET. It was a result of mitoses delay of the cells with a great number of chromosome aberrations. Obtained data show that 1 GeV protons don't differ essentially in efficiency from γ-rays and their RBE values are not far 1. The heavy ions are more effective. At different cytogenetical test and $^{24}Mg$ ions -1.4-1.7 RBE values for $^{12}C$ ions were 1.2-1.3.

Analysis of chromosome damages in human lymphocytes after exposure to low doses of protons (0.05-0.7Gy) has shown that the complex nonlinear dependencies of the frequency of chromosome aberration formation from doses are observed. Dose-effect dependence curves differ from analogous ones obtained after extrapolation of high dose effects to low doses ones. "The hypersensitivity" of the lymphocytes reveals in super low doses region (0.05-0.1). The frequency of aberrant cells and total chromosome aberrations were in ~ 4-5 times more as compared to effects for corresponding extrapolation curves. Observed effects were a result of chromosome fragmentation and mainly a formation of chromatid and chromosome fragments. Among them the chromatid fragments prevail and their fraction was to 70-80 % from total number of fragments. The effects decreased in the region of ~ 0.2 Gy and corresponded to extrapolation curves values. At following increased of doses its increase again up to a level at the doses of 1 Gy. Obtained date show an incompetence



of estimation for influence of estimation for influence of sparsely radiation low doses on the human cells proceed from extrapolation effect values on the basis of high radiation doses.

The chromosome damages induced by low doses of $^{60}Co$-irradiation in human peripheral blood lymphosytes has been studies using different cytogenetic assays. Despite of quantitative differences in the amount of chromosome damage by different methods all of them have demonstrated complex nonlinear dose dependence of the frequency of aberrant cells. At the dose range of 0,01-0,05 Gy called hypersensitivity region (HRS) the cells have shown the highest radiosensitivity. HRS peak is completely formed by chromatid aberrations. At the dose of 0,5-1,0 Gy the dose-effect curves become linear with the decreasing slope compare to initial one by factors of 5 to 10 for different criteria reflecting the higher radioresistance of cells.

It was found at low dose range the high interdonor variability in the extent and position of HRS peak as well as intradonor variability when two experiments were performed on the lymphocytes of the same donor in some time.

So due to complex relation of dose and effect extrapolation of high dose effect to low doses is unreliable as well as biodosimetry at doses below ~ 0,5 Gy. High inter- and intradonor variability also complicates and tasks of biodosimetry.

Mechanisms underlying HRS may differ from classical model of formation of radiation-induced chromosome damage as we concluded from the analysis of aberration spectra induced at low dose range.

The investigations of α- and β-emitters combined with methylene blue (MTB) application in target diagnostic and therapy of pigmented melanoma are continued. Significant success have been achieved in investigation of $^{131}I$-MTB biodistribution in mice with pigmented melanoma. Gamma-camera imaging as well as direct measuring of radioactivity, accumulated in different organs of mice, shows primary accumulation of the compound in pigmented melanoma and the radioactivity clearance through gastro-intestinal and urine systems. Experiments on therapeutic action of $^{131}I$-MTB are carried out as well. All the results allow to conclude $^{131}I$-MTB to be suitable for the diagnostic and therapy and open a way for clinical experiments in the nearest future. Experiments with $^{211}At$-MTB show inadequate binding stability of the compound. That makes necessary further works in this field.

The study of induction of different type mutations by ionising radiation in yeast *Saccharomyces cerevisiae* as model of eucariotic cells was continued. A new method was developed to test extended deletions on plasmid bearing a cluster of yeast genes (two negative selection markers, the *CAN1* and *CYH2* genes, and three positive selection markers, the *URA3*, *TRP1*, and *LEU2* genes). We suppose to use this system for investigation of efficiency of deletion production on ionising radiation with different physical characteristics.

The study of genetic control of DNA damage-induced arrest of cell cycle progression, named checkpoint control, was continued along with Institute of Molecular Genetics RAN (Moscow). We have studied interactions between checkpoint genes *RAD17* and *RAD53*. It was shown epistatic interactions between these genes in relation of γ-ray sensitivity. So RAD17 and RAD53 genes act in the same pathway determining the sensitivity of yeast cells to radiation.

DRRR and University of Perugia (Italy) are started the investigation of involvement of checkpoint control and DNA polymerases δ and ε in spontaneous and induced mutagenesis in nondivided cells.

Analysis of genetic characteristics of *SRM* genes was continued. We have investigated the effect of *srm* mutations on induced mitochondrial rho- mutagenesis.

The study of charged particles influence on the lens proteins – crystallins was started. Previous we shown that the analysis of kinetics of UV-light-induced photo-aggregation of proteins is an effective way to reveal the differences between them. Using this approach, we were able to discover the different behaviour of recombinant normal and amino-arm truncated βA3-crystallins to UV-light-induced photo-aggregation. Now we have observed the latent radiation defects of crystalline. The preliminary results of our first experiments with accelerated helium ions (500 MeV/nucleon) have shown that the irradiation of bovine βL-crystallin by relative low doses of helium ions (8.2 Gy) does not induce detectable changes of light scattering of protein solution. However, the comparison of kinetics of UV-light-induced photo-aggregation of helium ions irradiated and control, non-irradiated βL-crystallin samples demonstrates that the irradiated βL-crystallin is more sensitive to photo-aggregation than the non-irradiated one. In contrast of UV-light-induced photo-aggregation results, the study of aggregation induced by heating at 60°C did not show any difference between helium ions irradiated and non-irradiated samples. Also, we did not reveal any differences between the samples using Na-SDS electrophoresis technique both at normal and reducing conditions (150 mM DTT). One can propose that the irradiation of bovine βL-crystallin by relative low doses of accelerated helium ions induces the latent radiation defects in the native structure of protein. The changes are probably in the tiny dimerization of βL-crystallin molecules. Actually, the gel-filtration profile (Sephacryl S200) demonstrates slightly wider peak of helium ions irradiated βL-crystallin in comparison with control, non-irradiated one. Thus, the UV-light-induced photo-aggregation revealed the latent defect of βL-crystallin irradiated by rather low doses of accelerated helium ions like it took place in case of recombinant genetically modified amino-arm truncated βA3-crystallin.

An analysis of stochastic radiobiological effects of low-dose exposure of different biological objects has been carried out on the basis of the two-protection reaction model. The model leans upon the accepted scheme of the principal stochastic radiobiological process and uncontradictorily describes accessible data. The analysis shows that the yield of initial damages, in such structures as DNA, follows the linear no-threshold (LNT) relationship dose – effect. The resulting effect also follows the LNT relationship, provided that there is no reparation process or its suppress. The action of inducible or adaptive protective mechanisms, having restricted possibilities, leads to non-linear relationship dose – effect. The power of non-linearity is determined by the nature of the biological object, degree of damage, exposure conditions and level of the spontaneous effect.

The estimation of the excess of the relative risk (ERR) of cancer mortality for adult residents of contaminated regions of Belarus as result of the Chernobyl accident, has been carried out on the basis of the two protection reaction (TPR) model. With such estimation the testing of the model founded on the results of cancer mortality for survivors of Hiroshima and Nagasaki at low doses. The estimation of ERR has been



carried out on the basis of accumulated doses for adult residents of contaminated regions. The results show that the ERR of cancer mortality as a result of the Chernobyl accident is about 5 - 6 % during the whole life. This value is some times larger then value calculated on the basis of International commission radiological protection recommendations.

## 3. Scientific programme for 2004

**3.1. Radiation researches** in 2004 will be concentrated on the following main lines:

- *Shielding calculations and design.* It is planned to continue the shielding calculation and the prognostication of radiation environment for the Cylab cyclotron complex (Slovakia) and the SAD installation in JINR;
- *Physical support of radiobiological experiments.* The radiobiological experiments with heavy nuclei at nuclotron will be carried out for study of chromosomal aberration in human blood lymphocytes and for study of lens proteins aggregation dynamics under action of ionizing radiation with high LET;
- *Response Detectors Study.* The investigations of the responces of different type dosimeters and radiation detectors at the JINR basic facility will be continued.

**3.2. Radiobiological researches** in 2004 will be connected with:

- *Study of regularities of chromosomal aberration induction in human lymphocytes* by heavy ions in broad region of LET. The spectrum of induced aberrations in peripheral blood lymphocytes by heavy ions will be analyzed;
- *Investigation of the cytogenetic effects* on human blood cells and mammalian cells in culture from low dose of charged particles radiation with different physical characteristics will be continued;
- *Investigation of the heavy charged particles radiation effects on rodopsin and isolated retina of an eye* will be developed;
- *Target therapy.* The development of methods for target therapy of pigmented melanoma by using complex "methylthyonin chloride – Astatine-211" is planned;
- *Investigation of the structure of protein molecules* with using mathematical methods of the molecular dynamics will be started in newly founded theoretical DRRR sector.

## 4. Conferences and educational activity

The education process at the chair "Biophysics" of the International University "Dubna" was continued. 45 students are studied at the chair now. The first seven students will be graduated in 2004 on specialty "Radiation protection of people and environment".

The 2nd International COSPAR Colloquium "Radiation safety of manned Mars mission " took place in Dubna on September 28 – October 02. It was organized by the Russian Academy of Sciences (The Scientific Council of RAS on radiobiology and SRC RF – Institute for Biomedical Problems), Joint Institute for Nuclear Research and Branch of Skobeltsyn Institute of Nuclear Physics MSU.

More than 100 physicists and radiobiologists from Russia, JINR, some European countries and USA participated in the Colloquium. The main scientific objects of the Colloquium were:

- the radiation environment on the lane Earth – Mars– Earth and on the Martian surface;
- the radiobiological effects of the astronauts exposure (substantiation of the space radiation protection rules);
- the physical and methodical aspects of the radiation protection of the Mars mission crew.

The COSPAR Working Group meeting took place within two days after the Colloquium end.

## 5. Administration activity

**Personnel.** The total personnel of the DRRR were 76, including the Directorate staff.
**Finance.** Funding of research in the direction of radiation and radiobiological investigations in 2004 is shown in Table 1.

Table 1. Financing DRRR in 2004.

| Area | Financing plan (k$US) |
|---|---|
| 08-9-1015-96/2008 (1-st priority) | 265,8 |
| Infrastructure | 87,2 |
| Total: | 353,0 |