The Laboratory of Radiation Biology
Founders

Andrej Vladimirovich Lebedinskij

Vasilij Vasil'evich Parin

Oleg Georgievich Gazenko

Jurij Grigor'evich Grigor'ev
First radiobiological experiments on synchrocyclotron
History

1959 First experiments at Laboratory of Nuclear Problems (LNP)
1978 Biological Research Sector at LNP
1988 Biological Department at LNP

1995 The Department of Radiation and Radiobiological Research

2005 Laboratory of Radiation Biology

www.lrb.jinr.ru

Prof. E.A. Krasavin, Corr. Member of RAS
The LRB performs education programs for students and young researchers on modern equipment.
Main research topics

1. Research on the effect of accelerated heavy ions of different energies on **genetic structures**

2. Research on the effect of different doses of accelerated charged particles on the **retina**, study of **cataractogenesis**


4. **Mathematical modeling** of radiation induced effects in biophysical systems

5. Evaluation of the radiation environment and **radiation safety**

6. Solving problems of **astrobiology** (**in cooperation with Italy**)
JINR’s accelerators

Phasotron: protons 660 MeV

U-400: heavy ions 10 MeV/u

U-400M: heavy ions 50 MeV/u

Nuclotron: heavy ions up to 4 GeV/u
The dose distribution of radiation in matter

1 unit of the dose

X-rays

Fe ion

1 unit of the dose
The Galactic Cosmic Ray (GCR) energy spectrum

The integral flux of GCR particles of carbon and iron groups equals to \(10^5\) particles/cm\(^2\) per year

Particle flux density interplanetary space \(Z \geq 20\)
160 per day per cm\(^2\)
Consequences of Galactic heavy ion action

- Formation of gene and structural mutations;
- Induction of cancer;
- Violation of visual functions:
  - lesions of retina;
  - cataract induction;
- CNS violation
DNA damage
Isolated DNA damage

- Single strand break
- Base damage
- Sugar damage
Clustered DNA damage

Double strand break

Base damage

Sugar damage

Base damage
“Comet assay” for detection of DNA lesions

D = 0 Gy
D = 5 Gy
D = 10 Gy
D = 20 Gy
D = 40 Gy
D = 60 Gy

Comet assay

Dose, Gy
Visualization of damaged sites in DNA

1. Irradiation
2. Fixation of cells at different times post-irradiation (PI)
3. Visualization of induced DSBs (γH2AX/53BP1 foci)
4. Acquisition of images
5. 3D analysis of induced γH2AX/53BP1 foci

- Acquarium

**Diagram:**
- Secondary antibody with fluorescent dye
- Primary antibody
- γH2AX foci
- 53BP1 foci
- DSB DNA
- Merge
Human cells exposed to γ-rays and $^{11}$B ions

γ-rays (LET = 0.3 keV/μm) vs. $^{11}$B ions (LET = 135 keV/μm)

- **5 min**
- **1 h**
- **24 h**

- γH2AX
- 53BP1
- Chromatin (DAPI)
Human cells exposed to $^{11}$B ions at 10°
Kinetics of the formation and disappearance of γH2AX/53BP1 foci

Comparison of γH2AX/53BP1 foci: γ-rays and ¹¹B

Average number of γH2AX/53BP1 foci per cell

Time after irradiation

- γ-rays
- ¹¹Boron
Incidence of clusters of $\gamma$H2AX/53BP1 foci

Comparison of total clusters: $\gamma$-rays and $^{11}$B

Time after irradiation

Average number of clusters per cell

- $^{11}$Bor
- $\gamma$-rays
Monte-Carlo computer modeling of heavy ion tracks and cluster damage analysis

GEANT4-DNA
http://geant4.org
Mutagenesis and RBE
Radiation induced mutagenesis

Gene mutation

Structural mutation

Guanine
The frequency of gene and structural mutation induction after $\gamma$-ray and heavy ion irradiation

The graphs show the frequency of gene and structural mutation induction as a function of dose for different ions and radiation types. The y-axis represents the number of mutations per cell (Nm/N) in $10^{-5}$, and the x-axis represents the dose in Gy.
Induction of mutagenic DNA repair by heavy ions

\[ \text{FMNH}_2 + \text{RCHO} + \text{O}_2 \rightarrow \text{FMN} + \text{RCOOH} + \text{H}_2\text{O} + \text{hv} \]
RBE dependence on LET

1 – gene mutations
2 – deletions
3 – lethal effect
Formation of unstable chromosomal aberration in human cells after heavy ion irradiation

Block of cell division

Unstable chromosomal aberration

![Graph showing the formation of aberrations per 100 cells versus dose in Gy for different ions.](attachment:graph.png)

- **Aberrations per 100 cells**
- **Dose, Gy**

- **$^{14}$N**
- **p**
- **γ**
Formation of stable chromosomal aberrations in human cells after heavy ion irradiation

Successful of cell division

Stable chromosomal aberration

Translocations/100 cells

Dose, Gy

Chromosome № 1

\[ ^{14}\text{N} \]

\[ ^{p} \]
Cytogenetic effect of low doses of accelerated $^{24}$Mg ions

The frequency of cells with chromosome aberrations.

Chinese hamster cells exposed to $^{24}$Mg ions with energy 500 MeV/nucleon
Genetic network model of induced mutagenesis in bacteria E.coli
Mathematical modeling of DNA repair systems in bacteria
Mathematical modeling of DNA repair systems in mammals and human
Action of radioprotectors
Influence of radioprotectors on bacterial cells after heavy ion irradiation

![Graph showing the effect of LET on bacterial cells with and without protector.](chart)

- **bacteria E.coli**
- **cysteamine**
- **without protector**

Parameter: $D_0^{-1} \times 10^{-2} \Gamma^{-1}$
Cancer
Gardner tumors

H a r d e r i a n  G l a n d  T u m o r  P r e v a l e n c e

Relative Risk

D o s e ,  G y

Iron ions

γ-rays

Iron ions

Iron (600 MeV/u)

Iron (350 MeV/u)

G a m m a

proton

helium

neon

Nelson, 2006
Skin cancer (rats)
RBE for carcinogenic effect of irradiation
Eyes and retina
Cataractogenesis

Eye lens and retina

UV-induced aggregation of $\beta_L$-crystalline under B$_{11}$

cytoplasm micro-vacuolization, fiber cell swelling, nuclear fragmentation

electroretinogram

Dysfunction after mutagen insertion
Cataract induction by iron ions and X-rays

\[ \text{RBE} = \frac{D_x}{D_{Fe}} \]

Worgul et al., 2006
Action of $^{56}$Fe ions on retina cells

Axon growth index vs $^{56}$Fe ion dose

Vazquez, 2006
Central Nervous System
Cosmic ray hit frequencies in CNS critical areas

CNS in General
- 2 or 13% cells will be hit at least one Fe particle
- 8 or 46% would be hit by at least one particle with $Z \geq 15$
- Every nucleus will be traversed by a proton once every 3 days and a alpha particle once every 30 days.

FE ION TRACKS VISUALIZED BY MARKERS OF DNA DSBs ($\gamma$H2AX)
Cognitive tests (Morris water maze)

$^{56}$Fe ions, 1 GeV/amu

Control

1.5 Gy

1 month after irradiation

M.Rabin, 2005
Persistent reduction in the spatial learning ability of rats after $^{56}$Fe ion irradiation

Results after 3 months

Delay, s

0 20 40 60 80 100 120 140 160

colour simulation 20 cGy 1 GeV/nucleon $^{56}$Fe

20 cGy
$\Phi \approx 10^5$/cm$^2$

R. Britten et al., 2012
First experiments with monkeys

Irradiation with a proton medical beam, 170 MeV

Irradiation with $^{12}\text{C}$ ions, 500 MeV/u, at the Nuclotron
Distinguishing visual stimuli on the sensory attributes

- color
- brightness
- configuration
- orientation

conditioned stimulus

refreshment

right response
Molecular targets at subcellular level

Myelin sheath degradation
Chiang et al (1993)

RRP in glutamate synapses
Machida et al (2010)
Britten et al (2014)

Levels of receptor subunits
Machida et al (2010)
Britten et al (2014)

Na\(^+\) currents

Membrane hyperpolarization
Rarefaction of Purkinje cell layer after irradiation by 645 MeV protons and $^{137}$Cs $\gamma$-rays

Krasavin E.A., 1979
Irradiation with 1 Gy of 500 MeV/u carbon ions

Radiation-induced decrease in the level of neurotransmitters is observed in the brain regions responsible for the *emotional and motivational state*

3 months after irradiation

![Graph showing concentration changes in Nucleus accumbens](chart.png)
Modeling of energy deposition events in CA1 pyramidal neurons
Modeling of cognitive tests by neural networks

Simulation of single neuron and network activity during WM task
The used risk concept

- Based on the introduction of a **generalized dosimetric functional** as the criterion and quantitative measure of radiation danger.

- **Generalized dose** $H_I$ and $H_D$ for the evaluation of, respectively, the *immediate adverse consequences* during the flight and the *delayed consequences* during the rest of life:

$$
H_I = (\sum_{i=1}^{n} D_i \times KK_{Ii} \times KB_{Ii} \times KP_{Ii}) \times KM_I
$$

$$
H_D = (\sum_{i=1}^{n} D_i \times KK_{Di} \times KB_{Di} \times KP_{Di}) \times KM_D
$$

- $KK_i$ – *radiation quality* coefficients;
- $KB_i$ – coefficient taking into account the *dose distribution over time*;
- $KP_i$ – coefficient taking into account the *dose distribution over the human body*;
- $KM$ – coefficients of the organism’s radiation response modification caused by *other factors* of the space flight.
The probability of successful mission implementation

\[ P = 1 - (P_{\text{rad. damage}} + P_{\text{non-rad. injury}} + P_{\text{techn. failure}}) \]

\[ P_{\text{rad. damage}} = P_{\text{CNS}} + P_{\text{immed. eff.}} + P_{\text{delayed eff.}} + P_{\text{other}} \]
Astrobiology
Formamide as Prebiotic Probe

“Simulations based on Density Functional Theory show that formamide is the most stable species with molecular formula “CHON”
Pauzat, F. et al. 6th EANA 2006

“This one-carbon molecule was detected in the gas phase of interstellar medium” Crovisier, J. Astrobiology: Future Perspectives, Kluwer Eds, 2004 Chapter 8, p. 179-203.


“in the solid phase on grains around the young stellar object W33A “ W.A. Schutte et al. Astr. Astrophys. 1999

Prebiotic chemistry in space conditions: the role of radiation on formamide system

Meteorites: Dohfar 959
Gold Basin
NWA1465
Chelyabinsk
NWA4482

Formamide irradiation at U400M cyclotron

In each tube:

**Absence of RADIATION**

- FORMAMIDE + METEORITE
  - NO PRODUCTS

**RADIATION**

- FORMAMIDE ALONE
- FORMAMIDE + METEORITE

**JINR-Cyclotron**

Few amounts
Thank you for the attention!