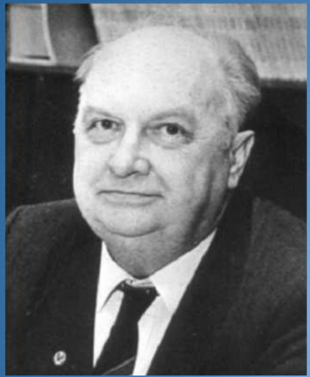


DUBNA

LRB

JINR

Accelerated heavy ions as a tool for solving problems in fundamental and space radiobiology

E. Krasavin

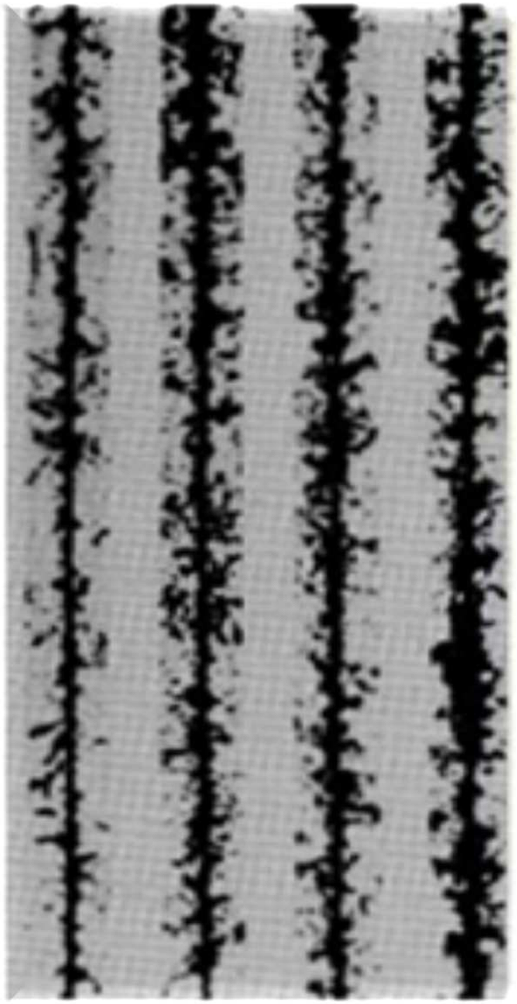
2012 Baldin Seminar

On the Earth: heavy charged particle accelerators

The sources of high-energy heavy ions

In the space: cosmic rays from the Galaxy

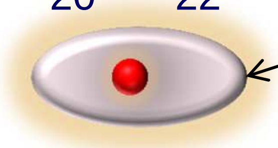
Heavy ion tracks in a nuclear emulsion



Si Ca Ti Fe

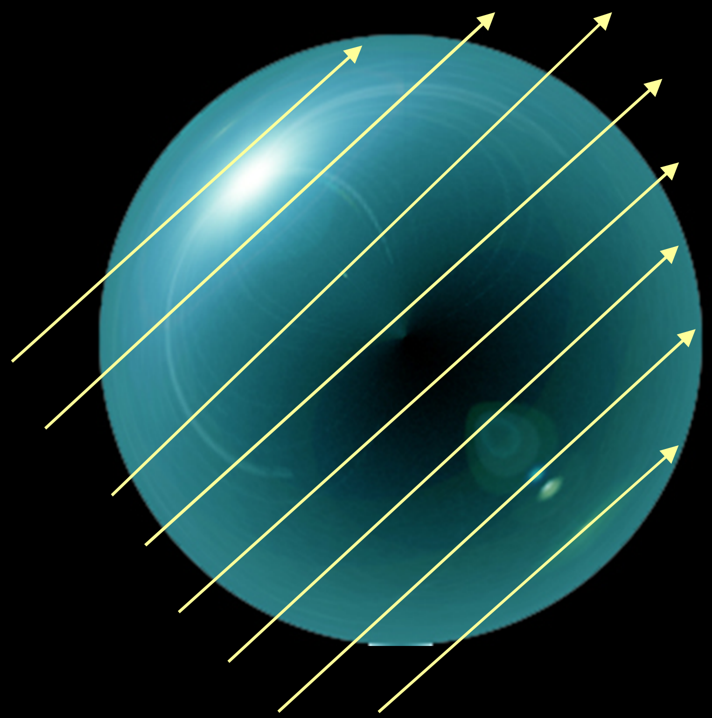
Z =14 20 22 26

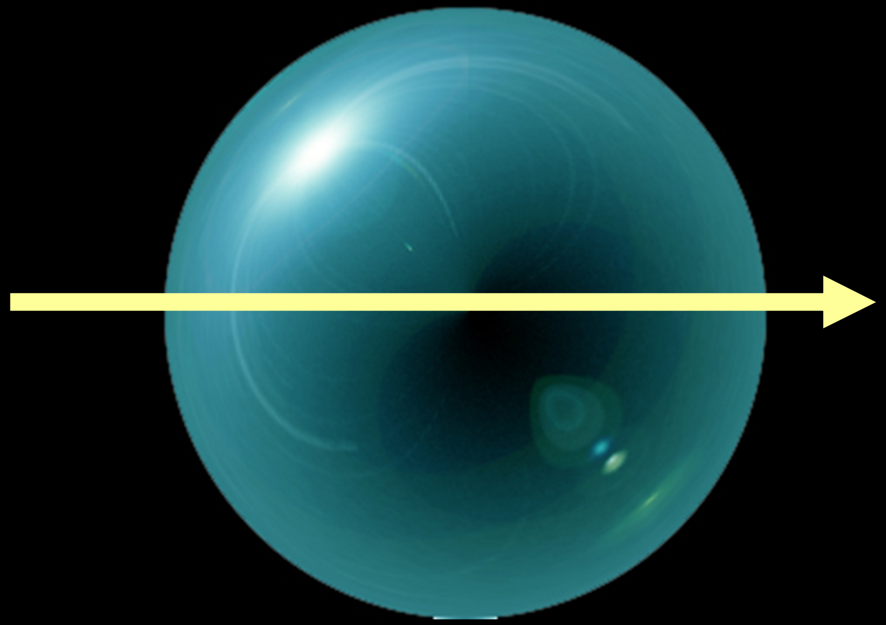
Z = 70



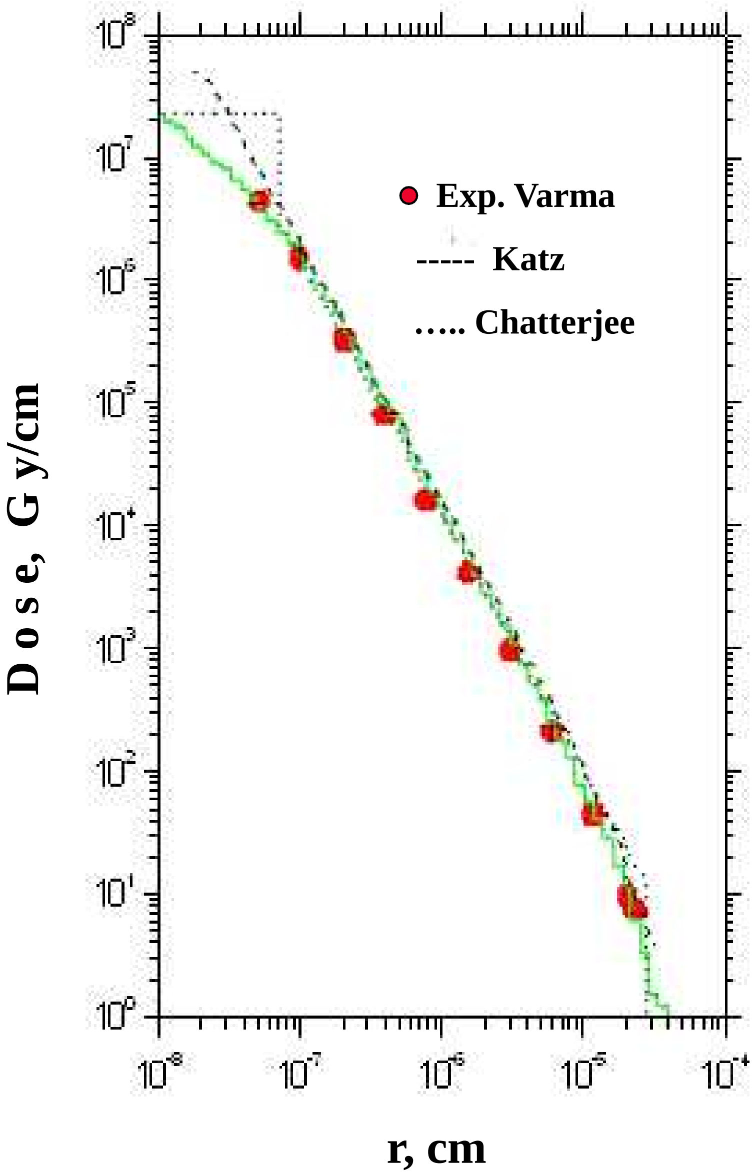
Mammalian cell

The radiation dose distribution in matter





Radial dose distribution

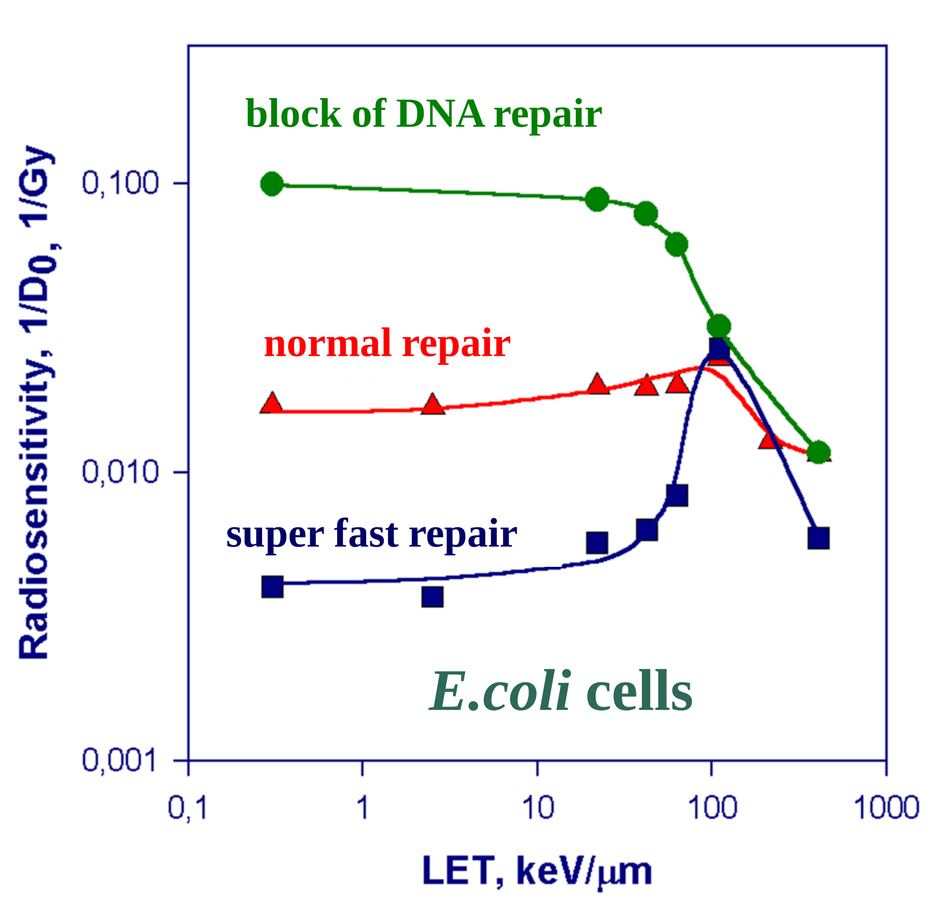


Radial dose distribution in a heavy ion track (^{12}C, 2.57 MeV/u)

What radiobiological problems can be solved with the use of accelerated heavy particles?

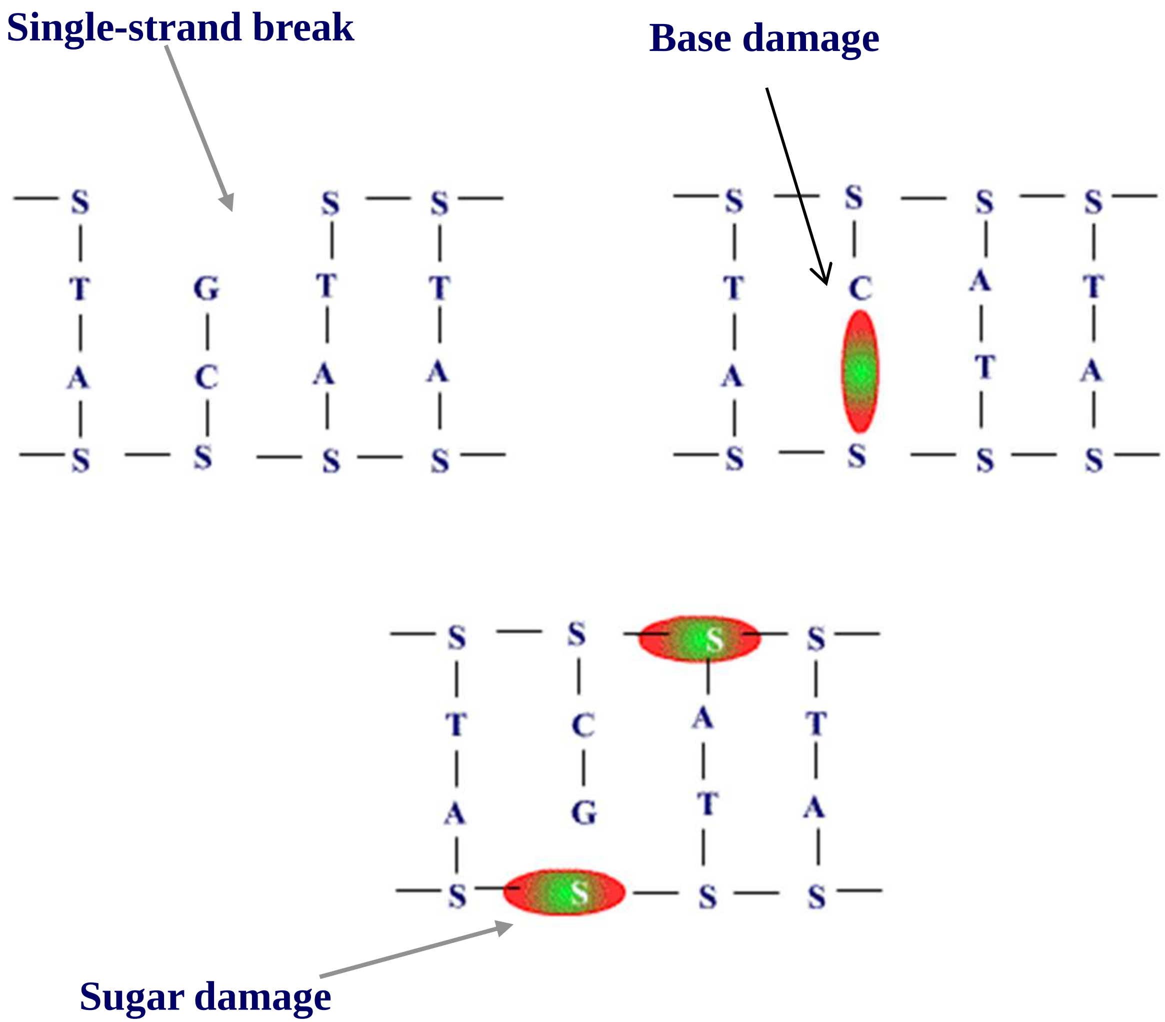
A.
Heavy ions are a powerful tool for solving problems in radiation genetics

The RBE problem

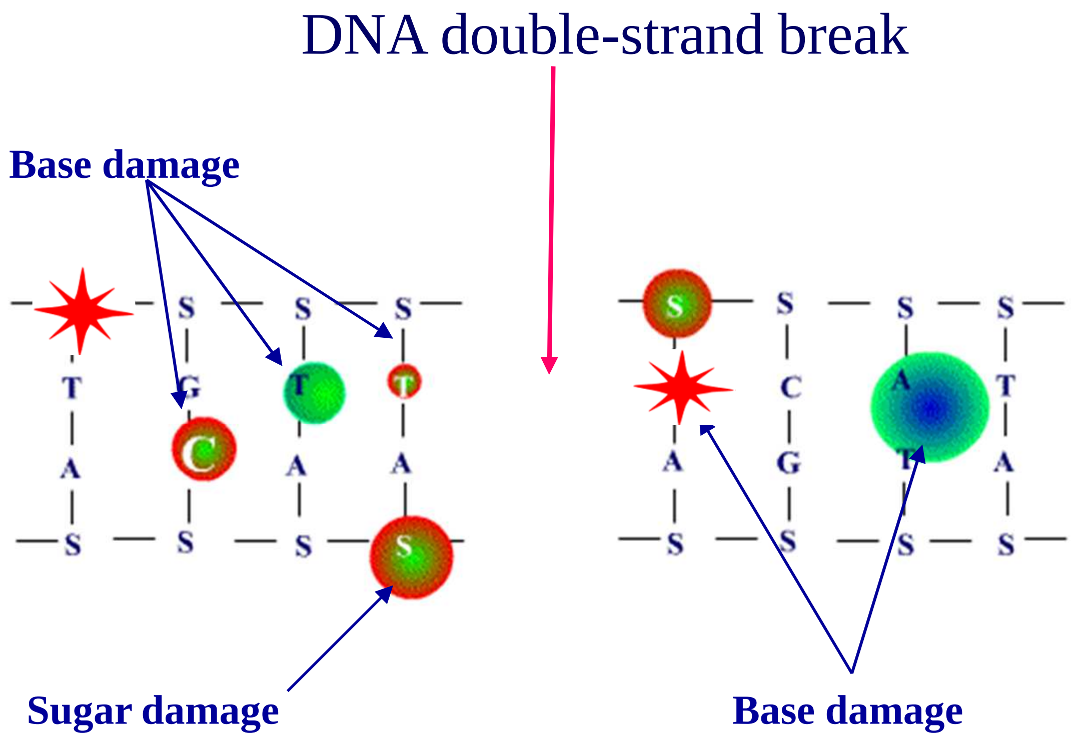


The ***DNA repair capacity*** of the living cells determines the type of the RBE dependence on LET

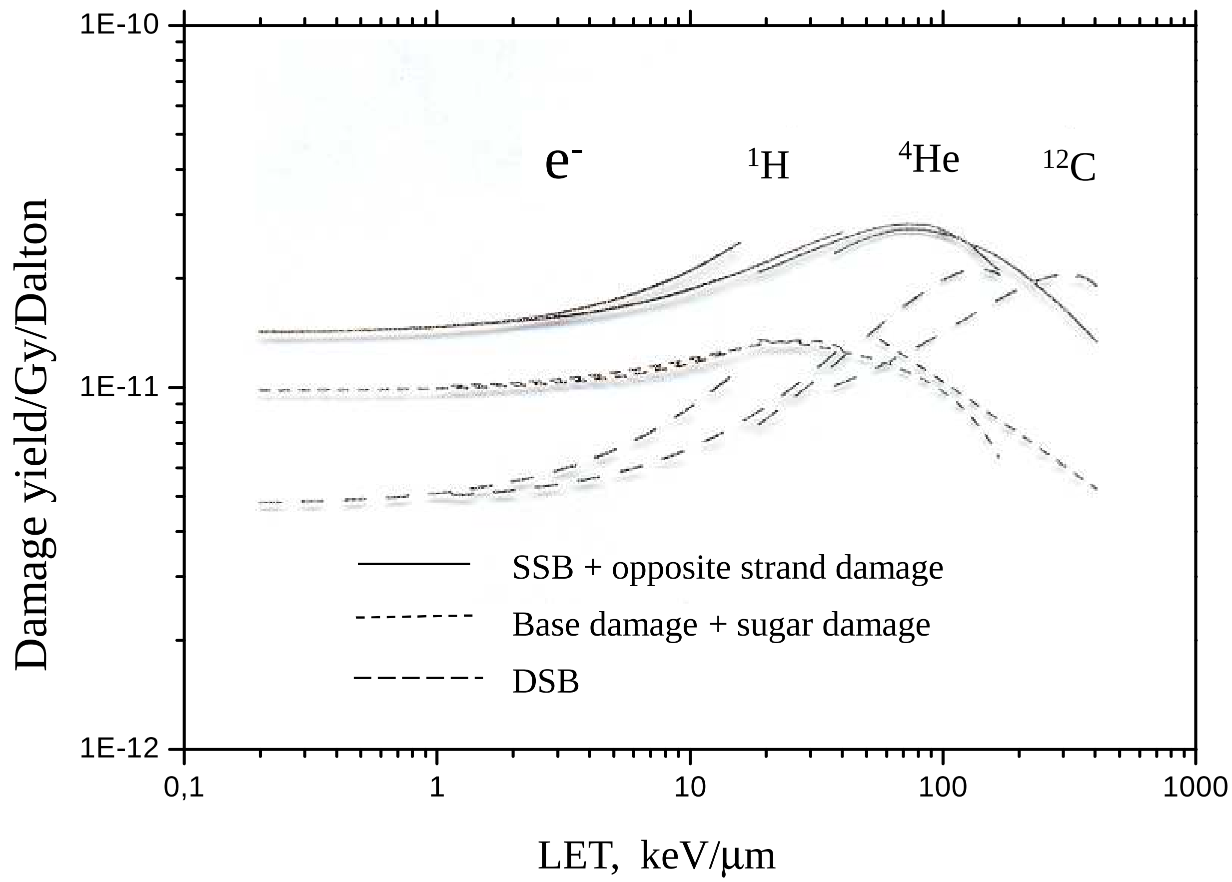
Single DNA damage



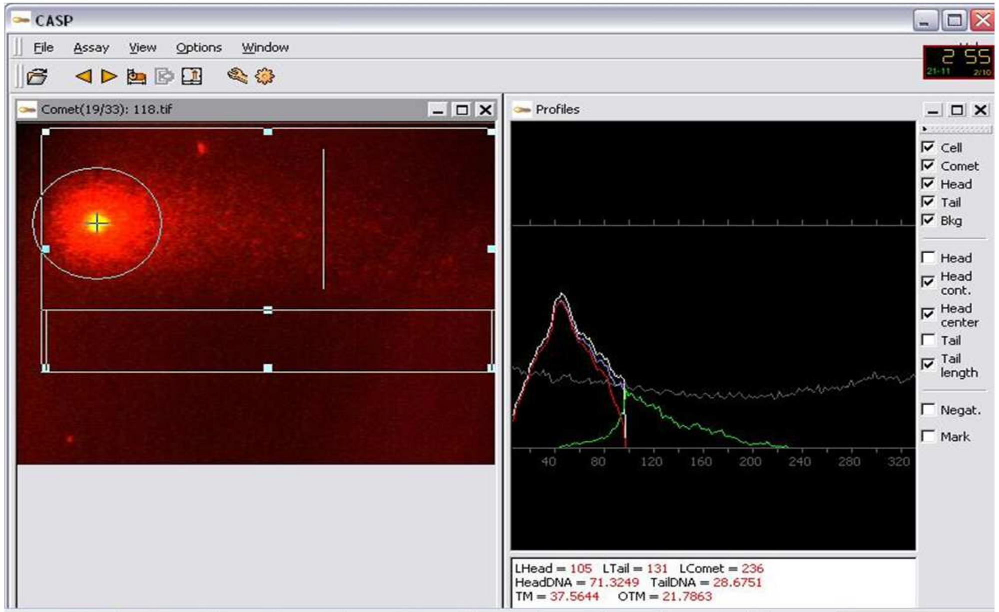
Clustered DNA damage

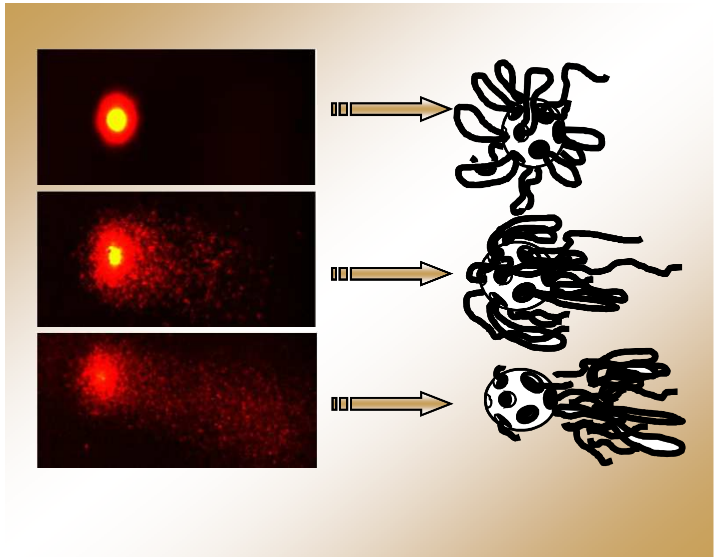


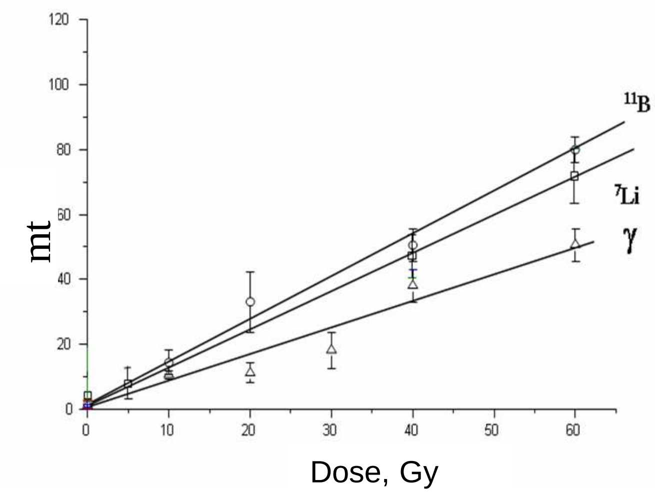
Clustered DNA damage yield as a function of LET

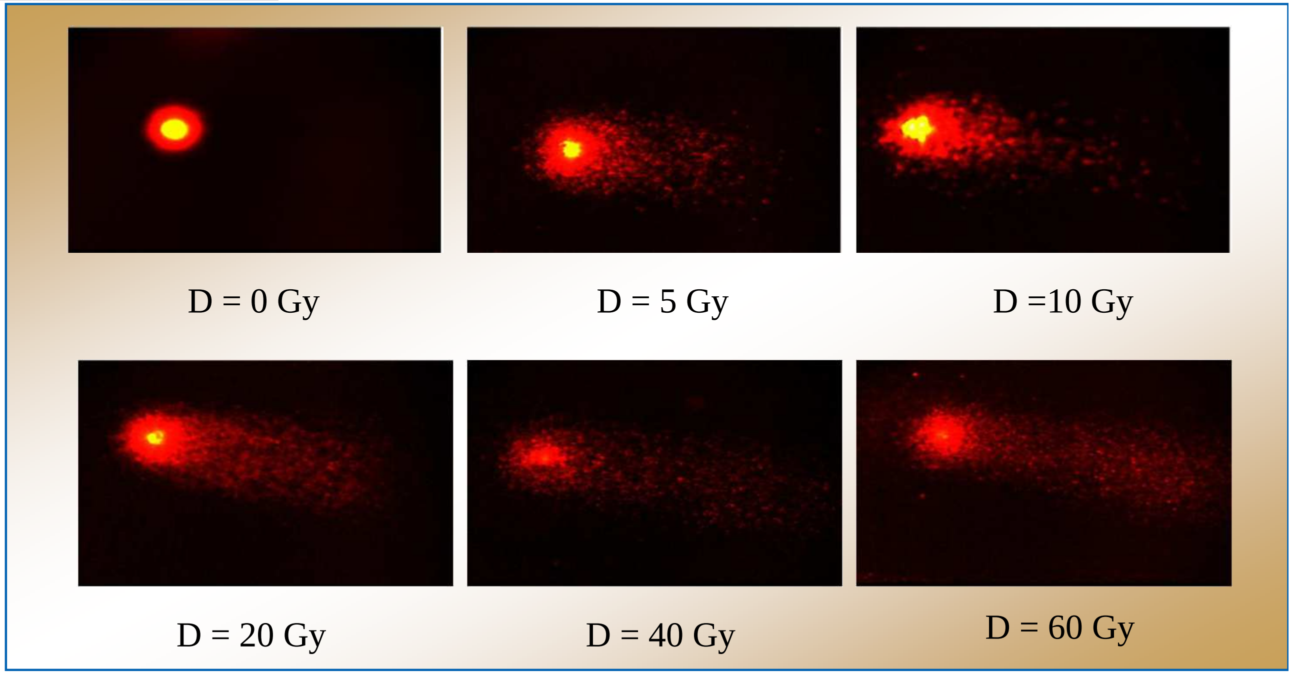


“Comet assay” for the detection of DNA lesions

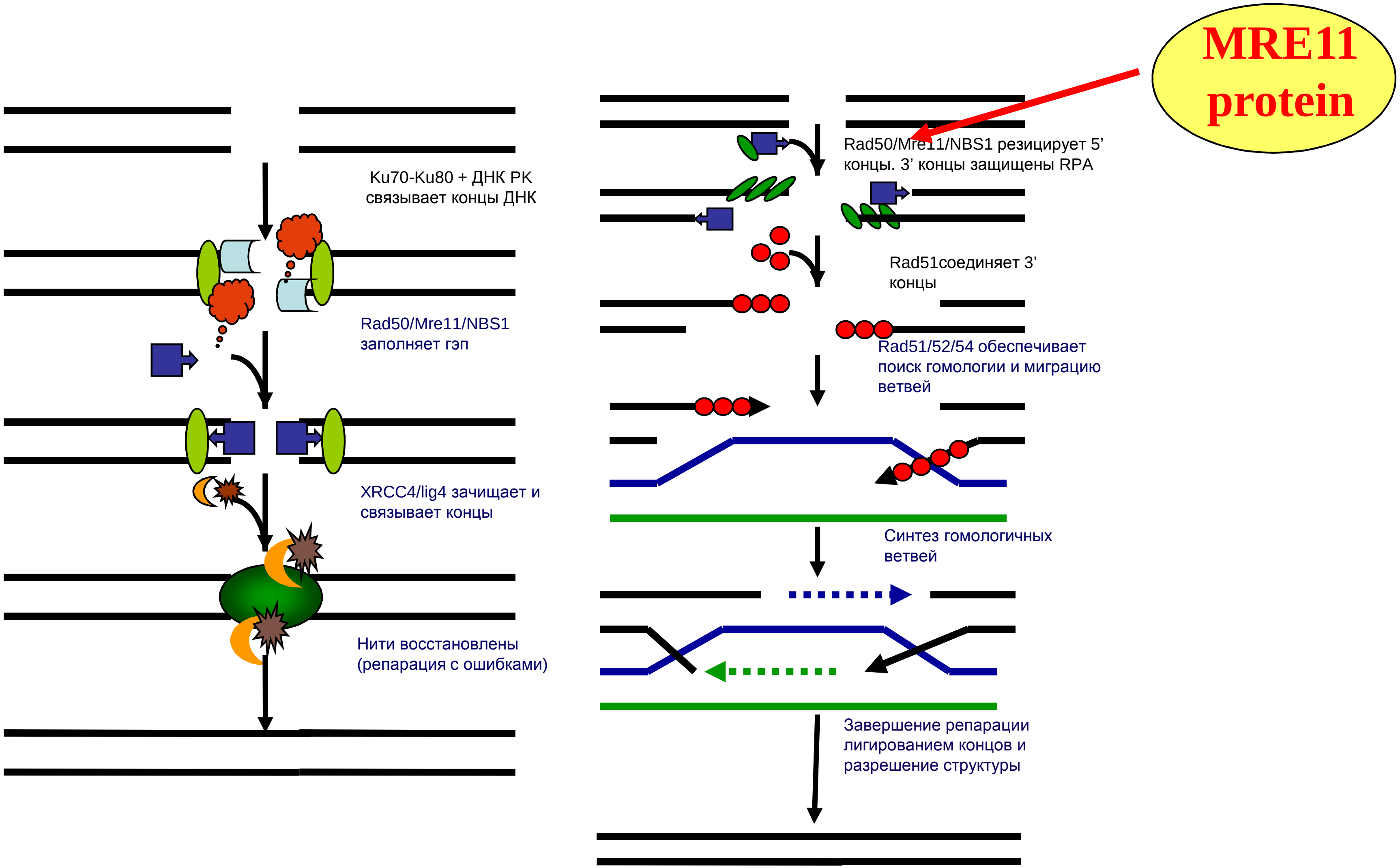




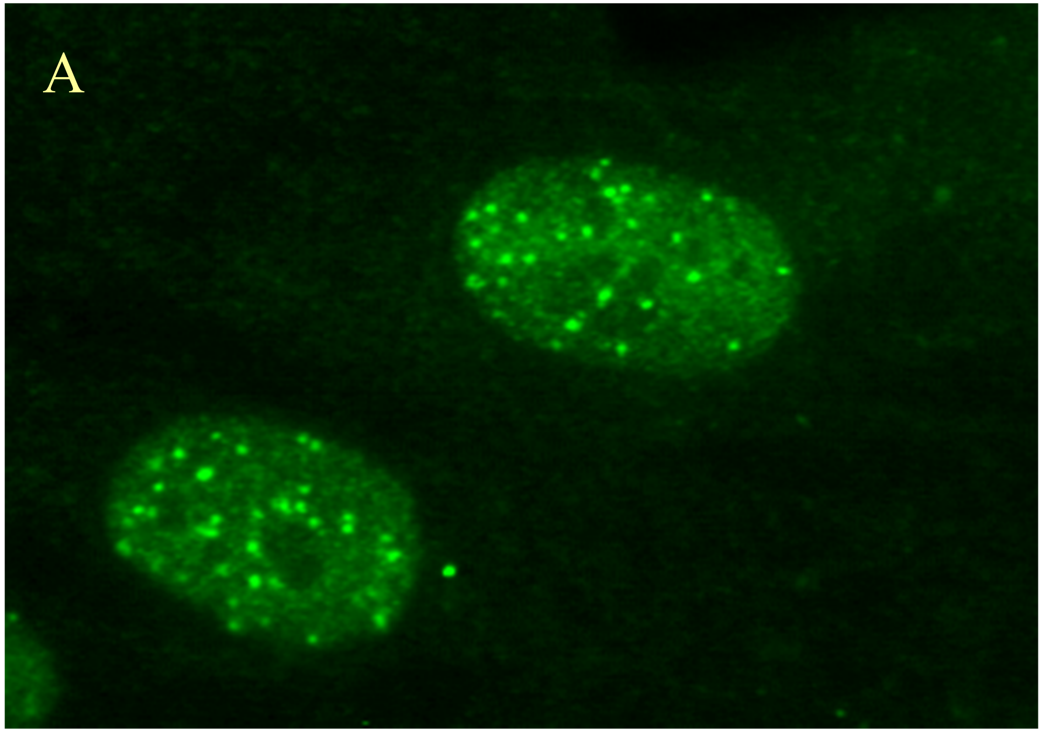


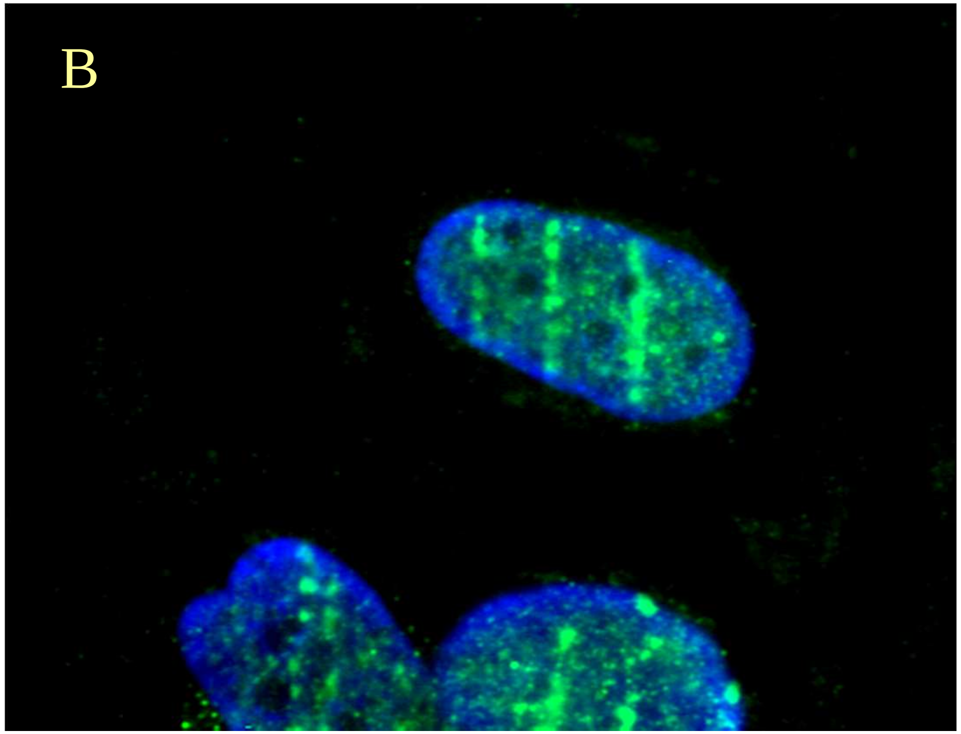


The mechanism of DNA DSB repair in human cells



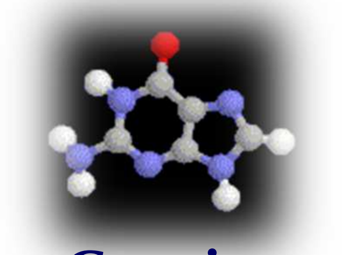
DSB (γ-H2AX) in human cells after X-ray (A) and heavy ion irradiation (B)





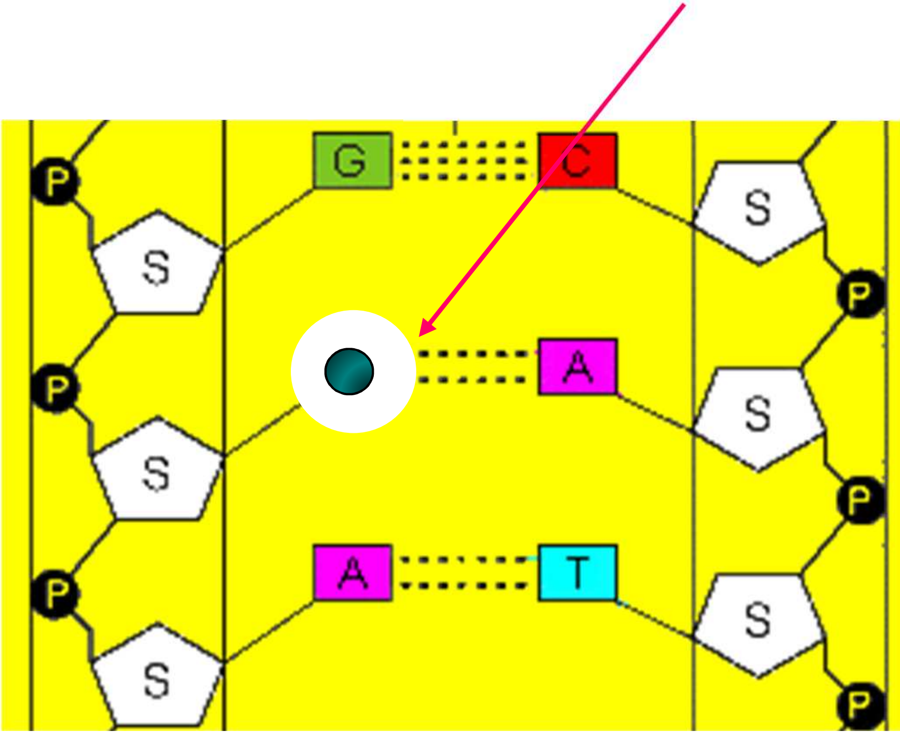
Radiation-induced mutagenesis

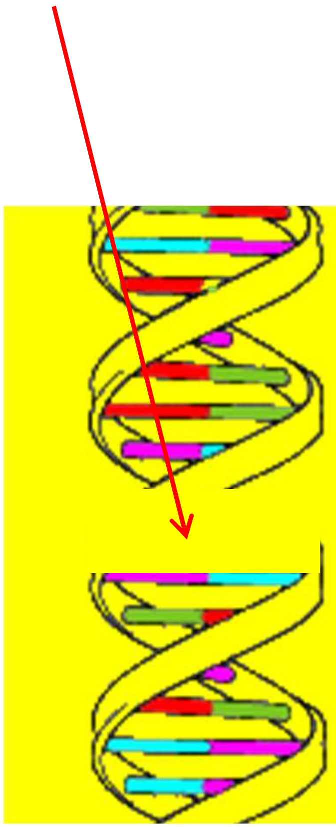
Gene mutation



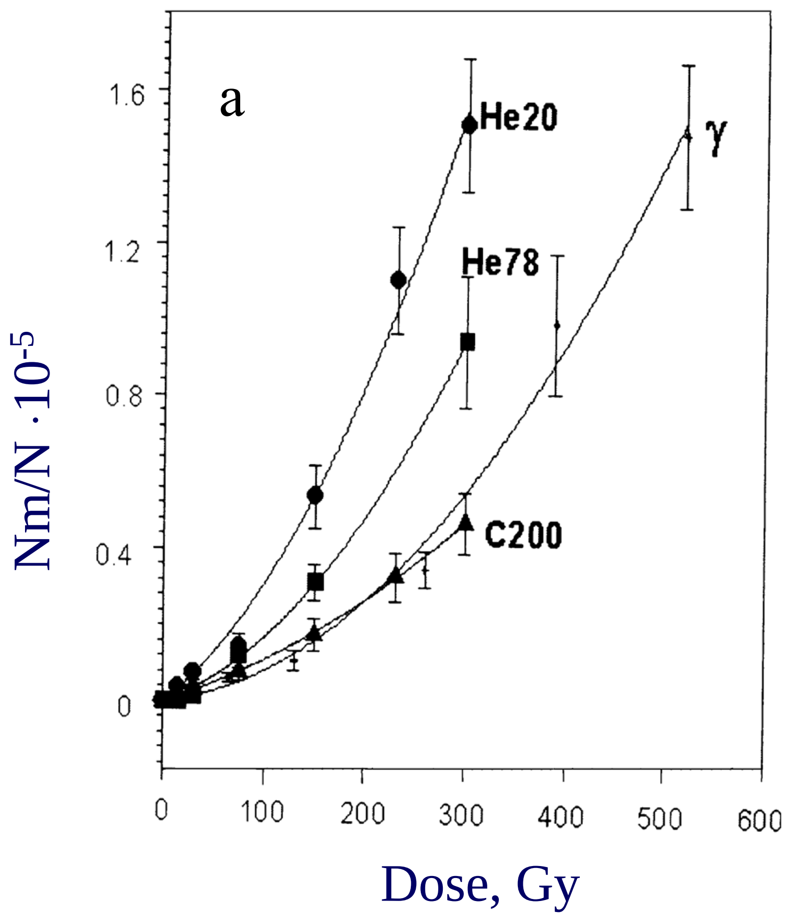
Guanine

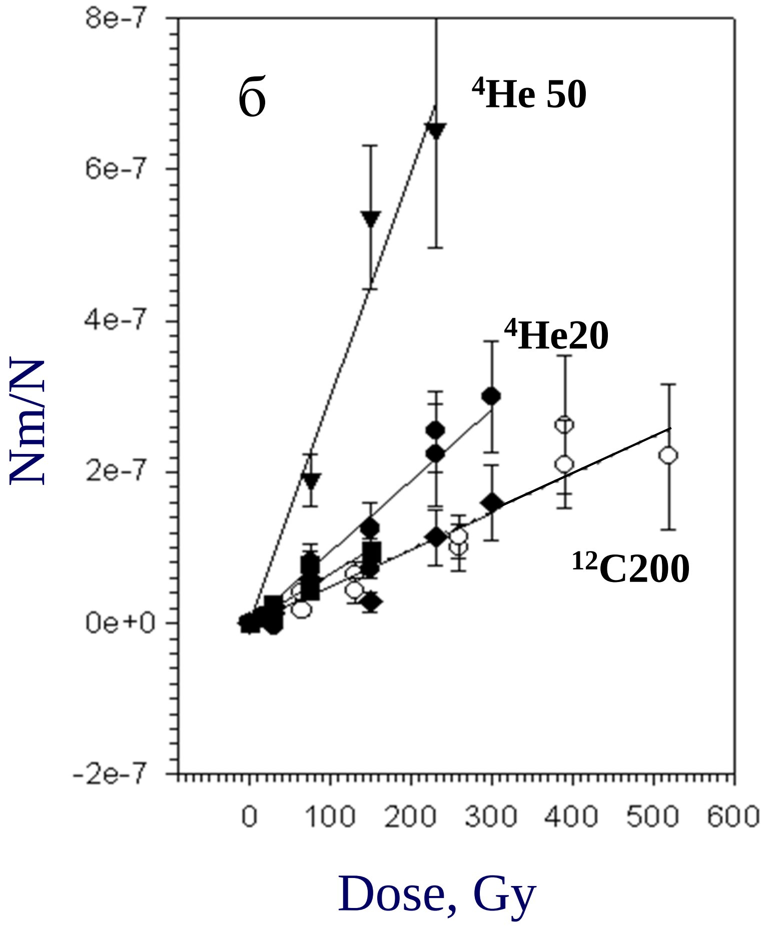
Structural mutation



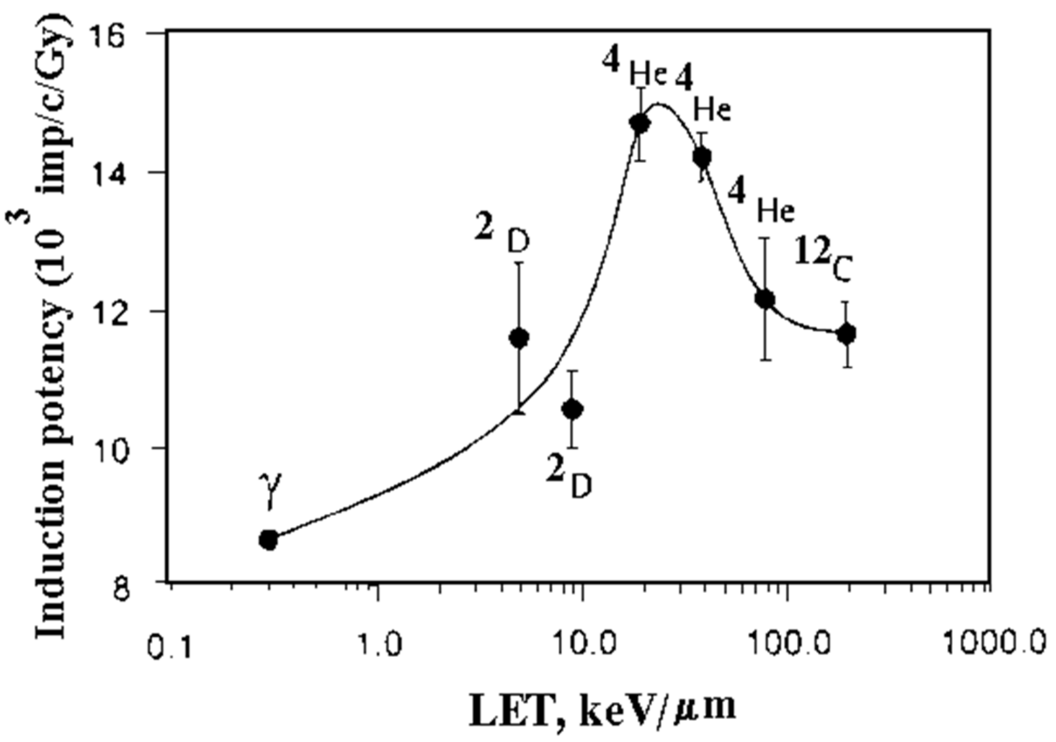


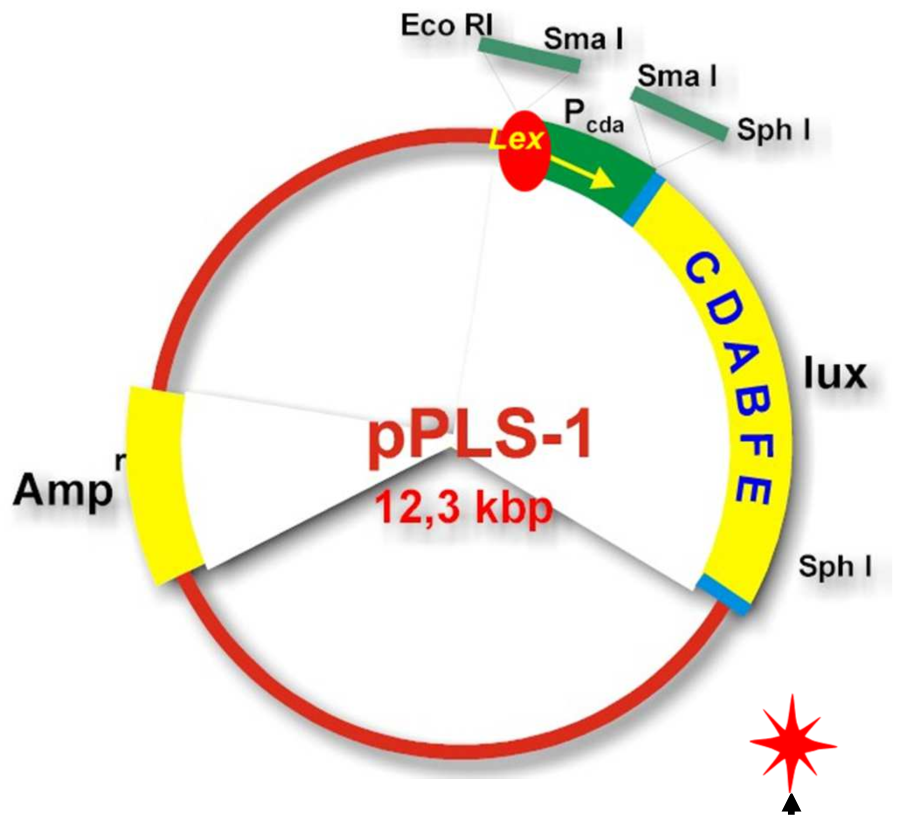
The frequency of gene and structural mutation induction after γ-ray and heavy ion irradiation





Induction of mutagenic DNA repair by heavy ions

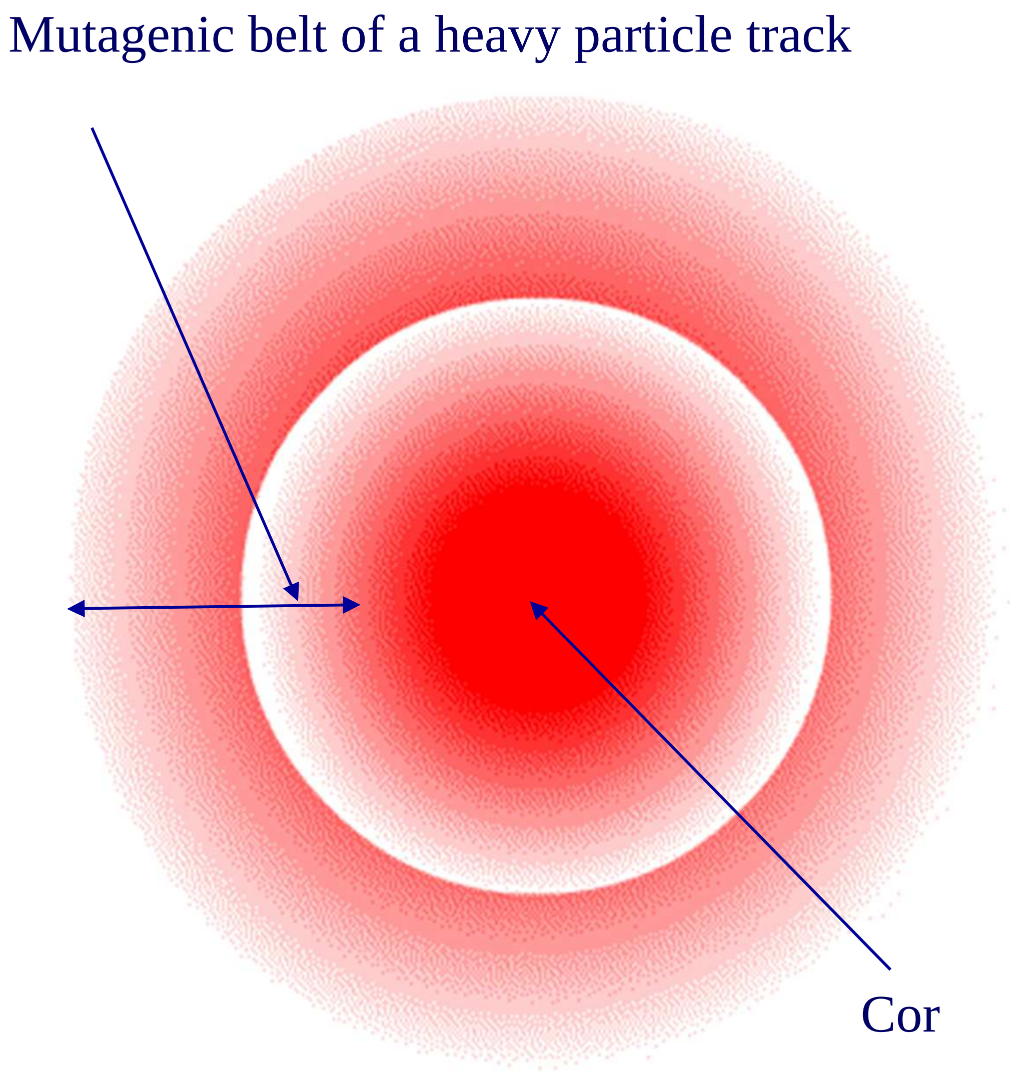




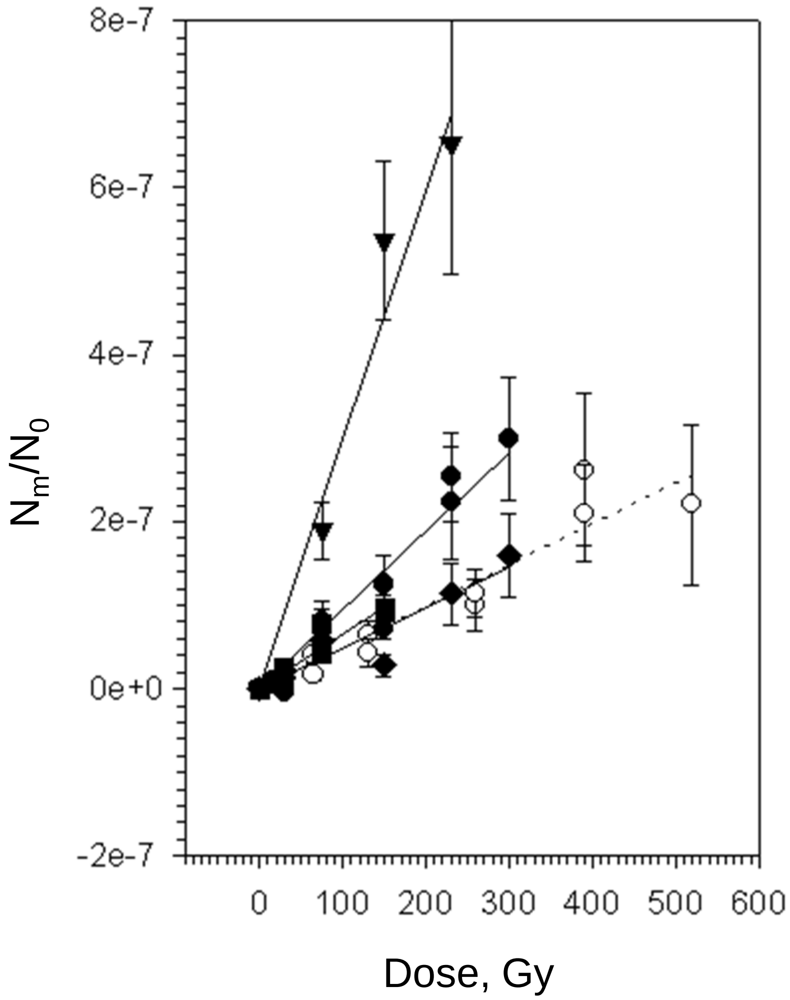
luciferase

$FMNH_2 + RCHO + O_2 \rightarrow FMN + RCOOH + H_2O + h\nu$

Mutagenic belt



Induction of deletion mutations by heavy ions



○ - γ-rays;

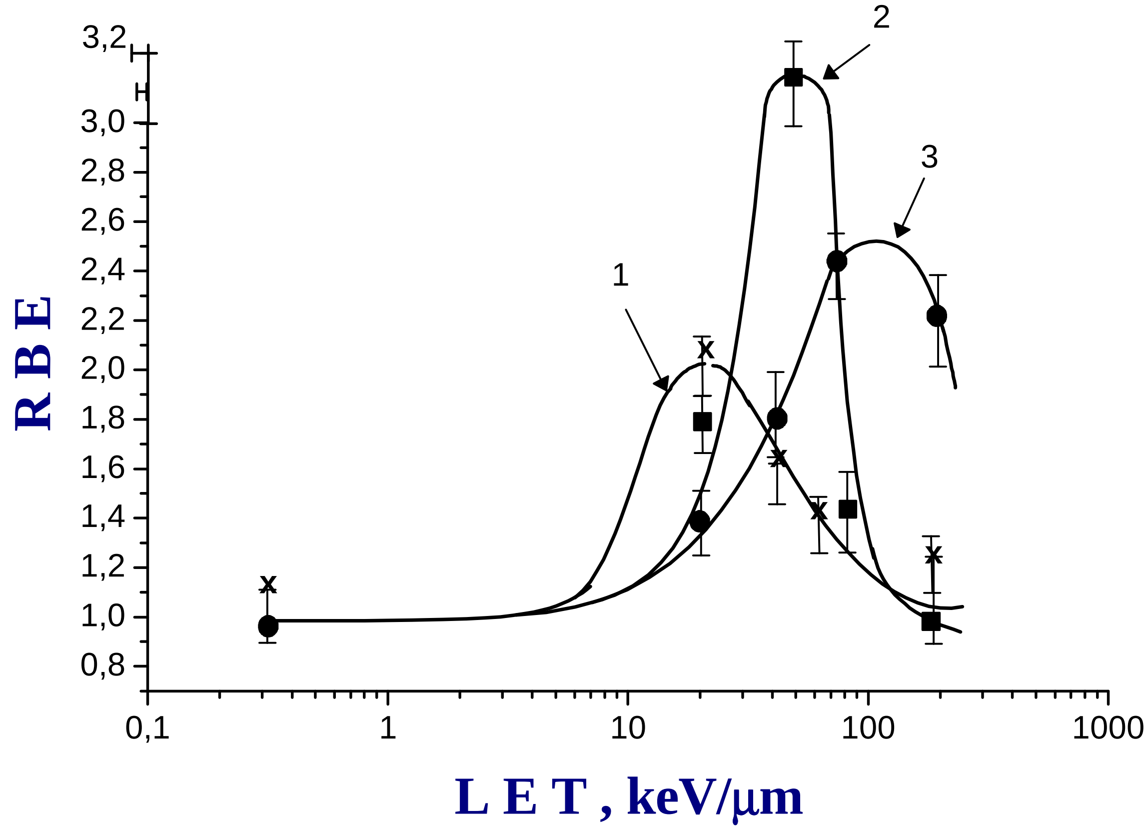
● - ^{4}He (20 keV/µm);

▼ - ^{4}He (50 keV/µm);

■ - ^{4}He (78 keV/µm);

♦ - ^{12}C (200 keV/µm)

RBE dependence on LET

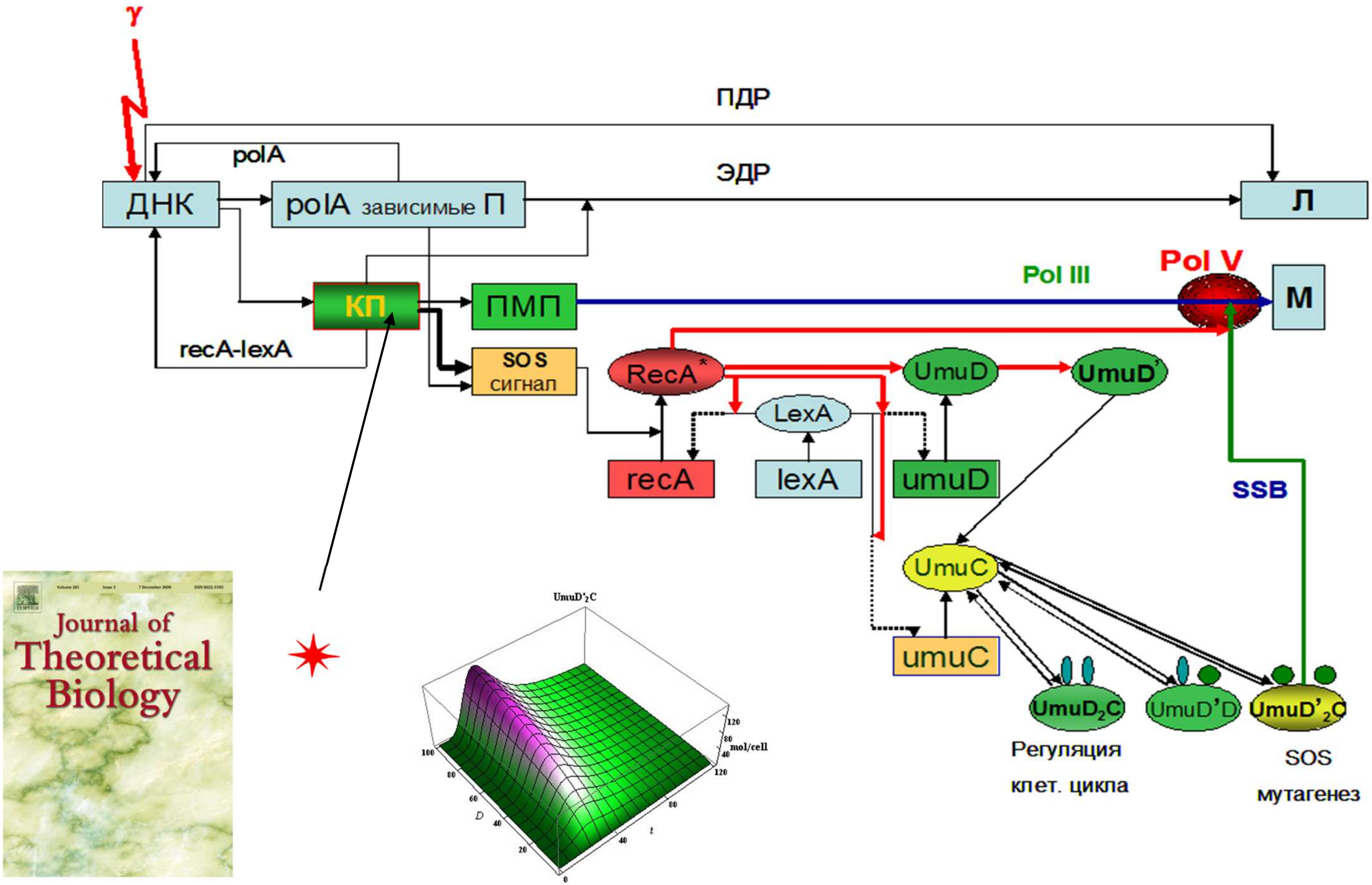


1 – gene mutations

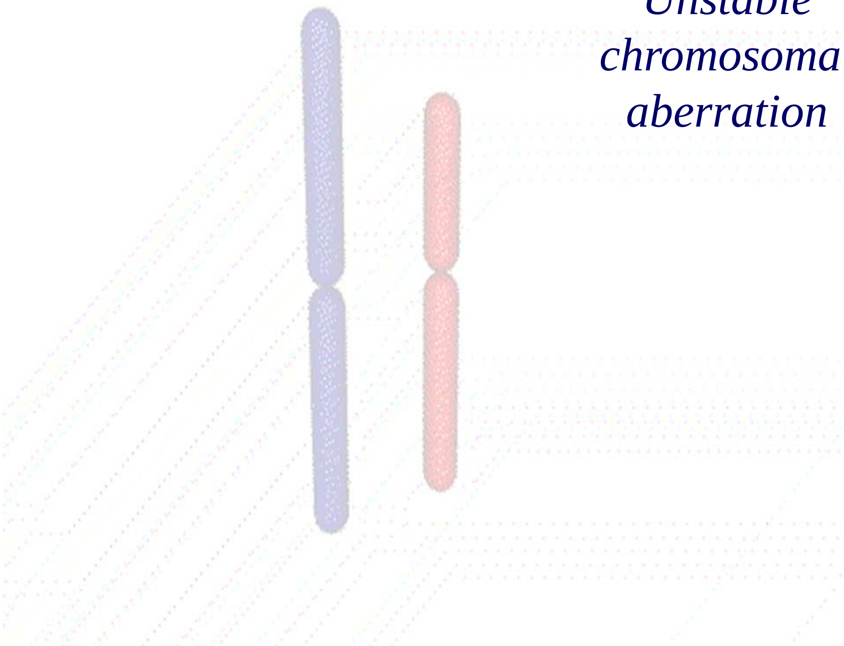
2 – deletions

3 – lethal effect

The model of gene mutation induction in E.coli cells

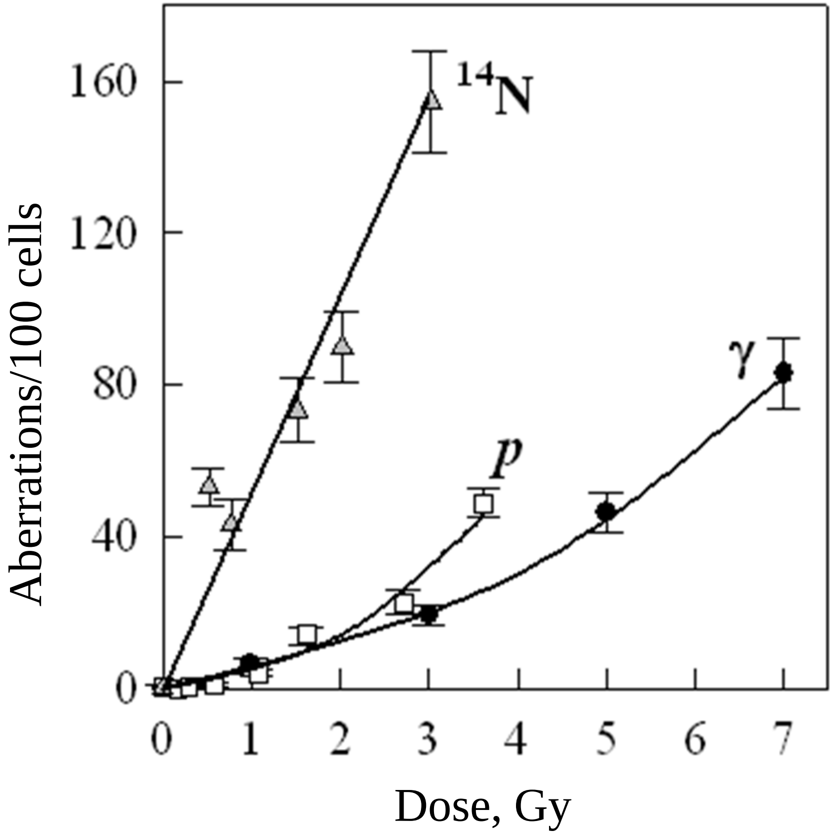


Formation of unstable chromosomal aberrations in human cells after heavy ion irradiation

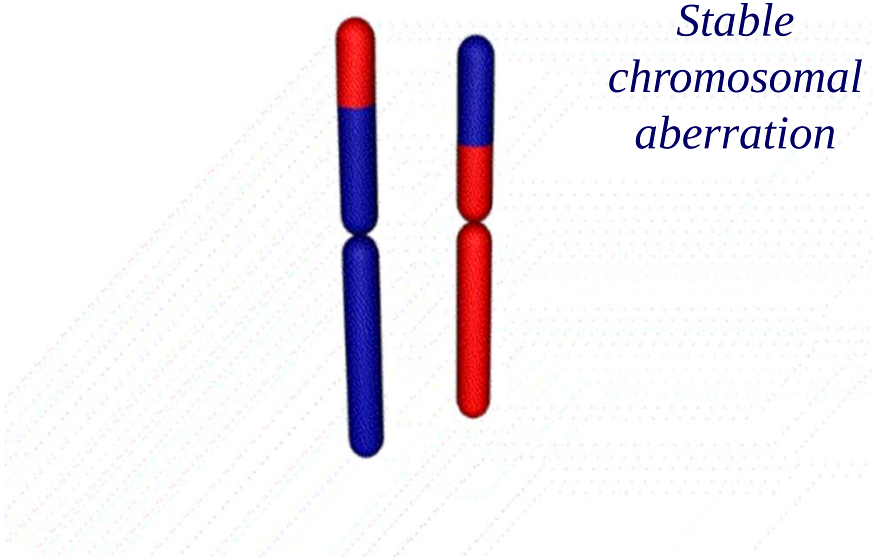


Unstable chromosomal aberration

Cell division blocking

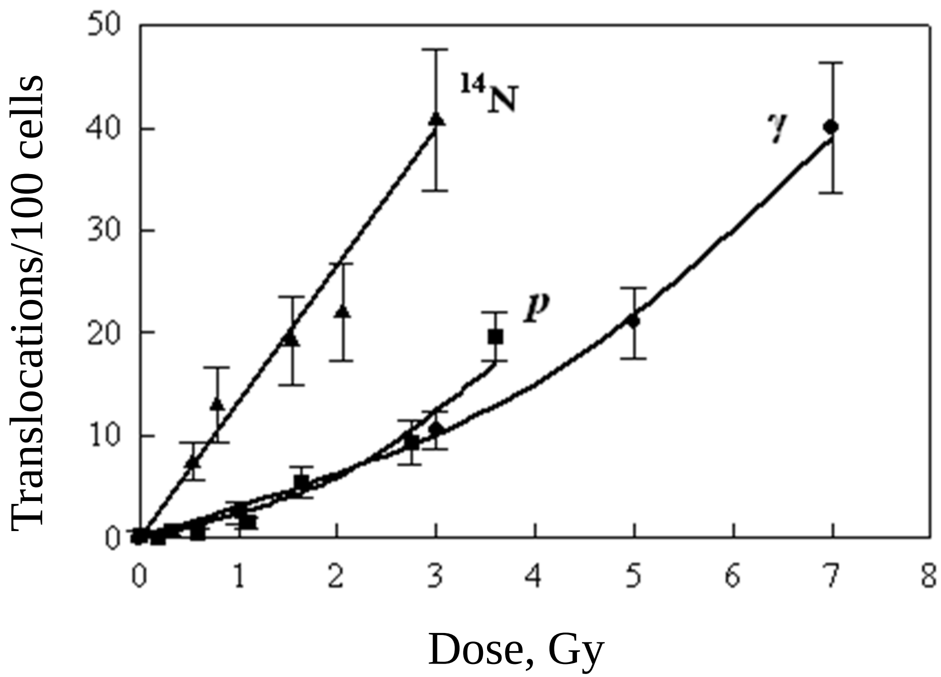


Formation of stable chromosomal aberrations in human cells after heavy ion irradiation



Successful cell division

Chromosome № 1



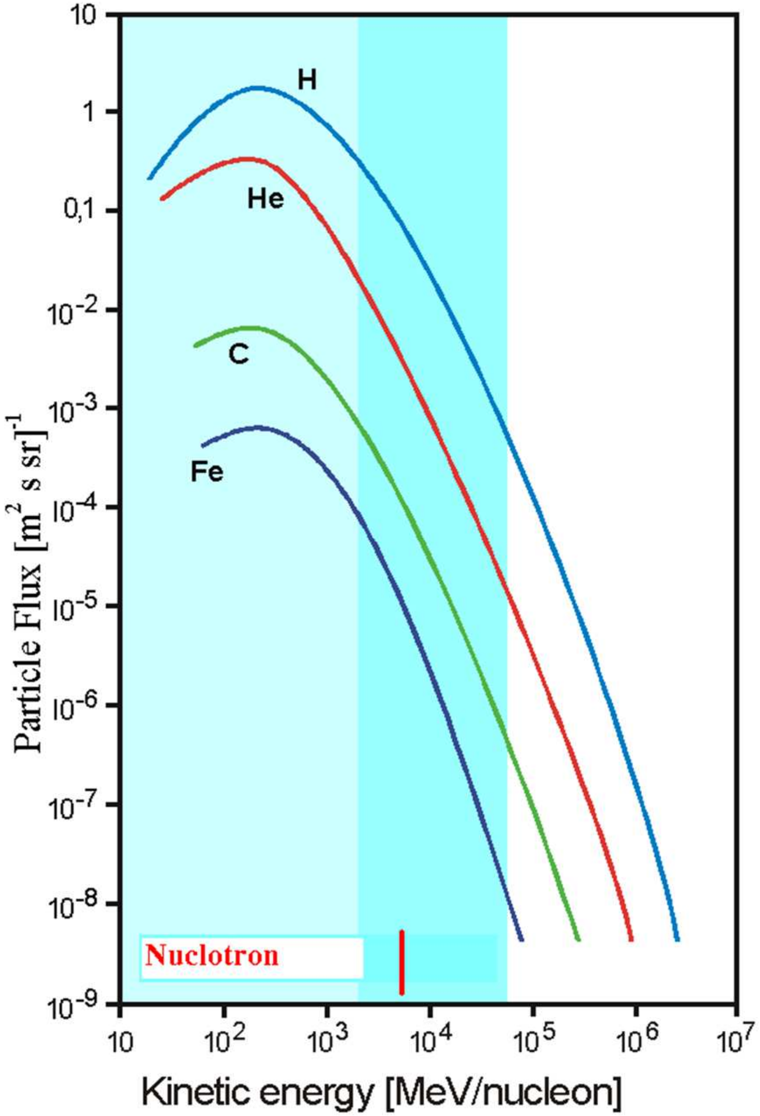
B.
Accelerated heavy ions as a tool for modeling the biological action of space radiation

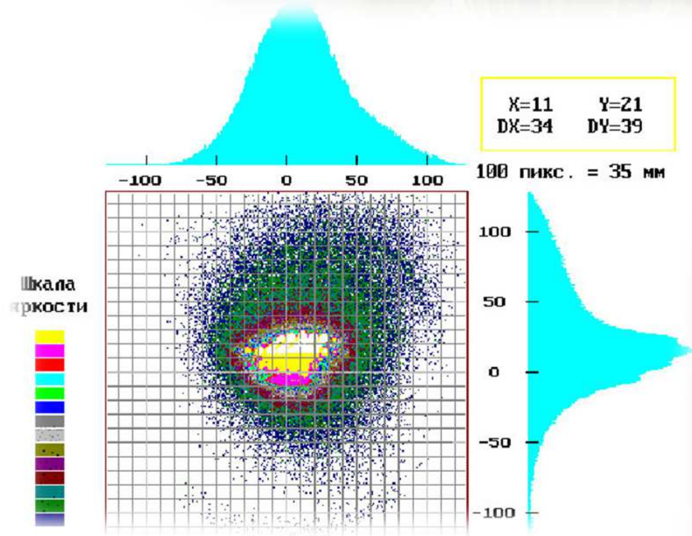
The GCR flux

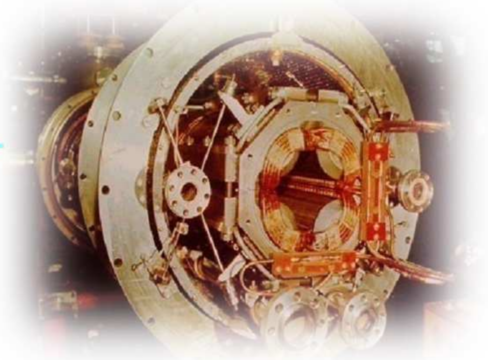
The integral flux of the GCR particles of the carbon and iron groups is ***10^5 part/cm^2 per year***

Flux density of particles with $z \geq 20$ in the interplanetary space: 160 per day per cm^2

GCR and Nuclotron energy spectra



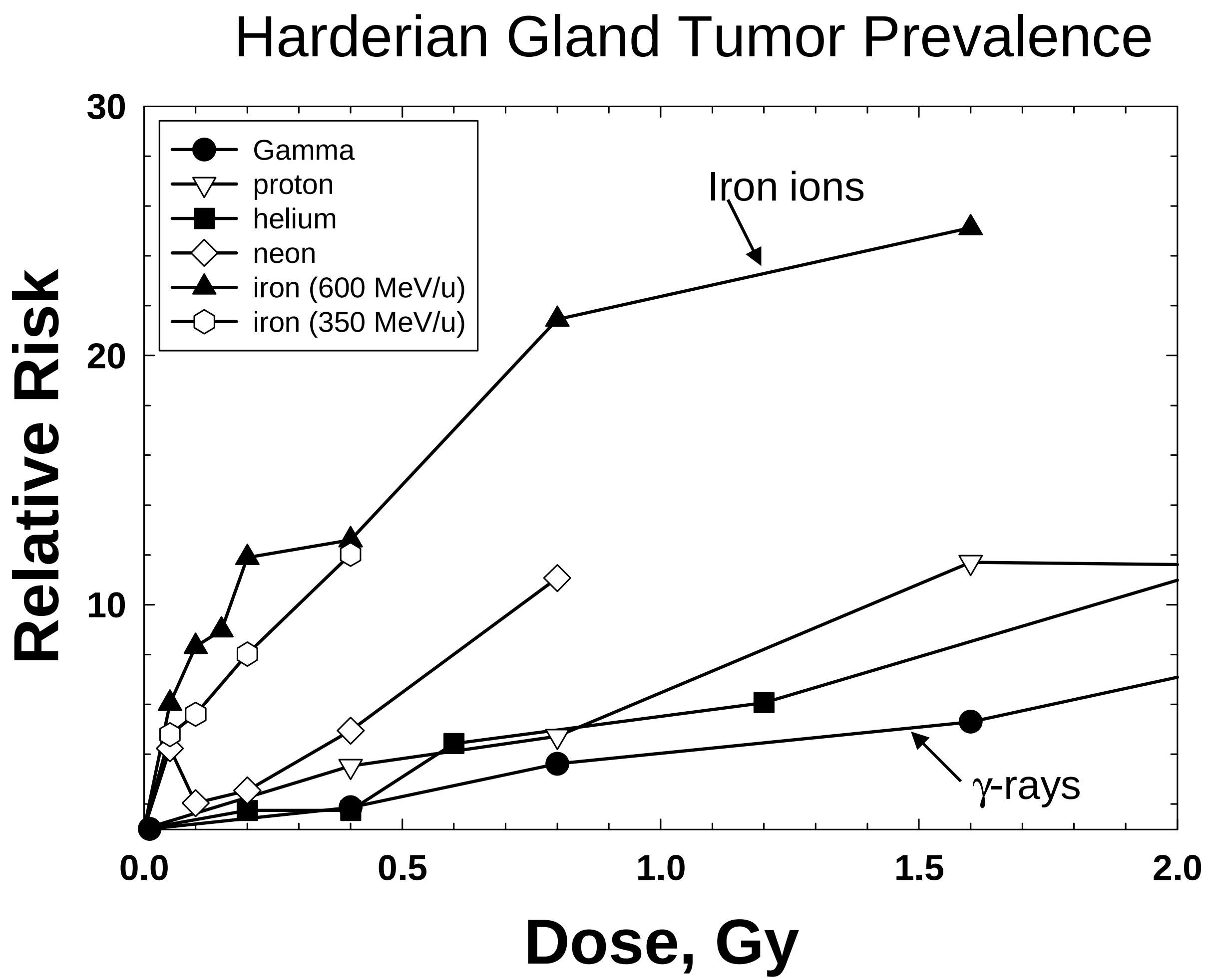




Effects of exposure to galactic heavy ions

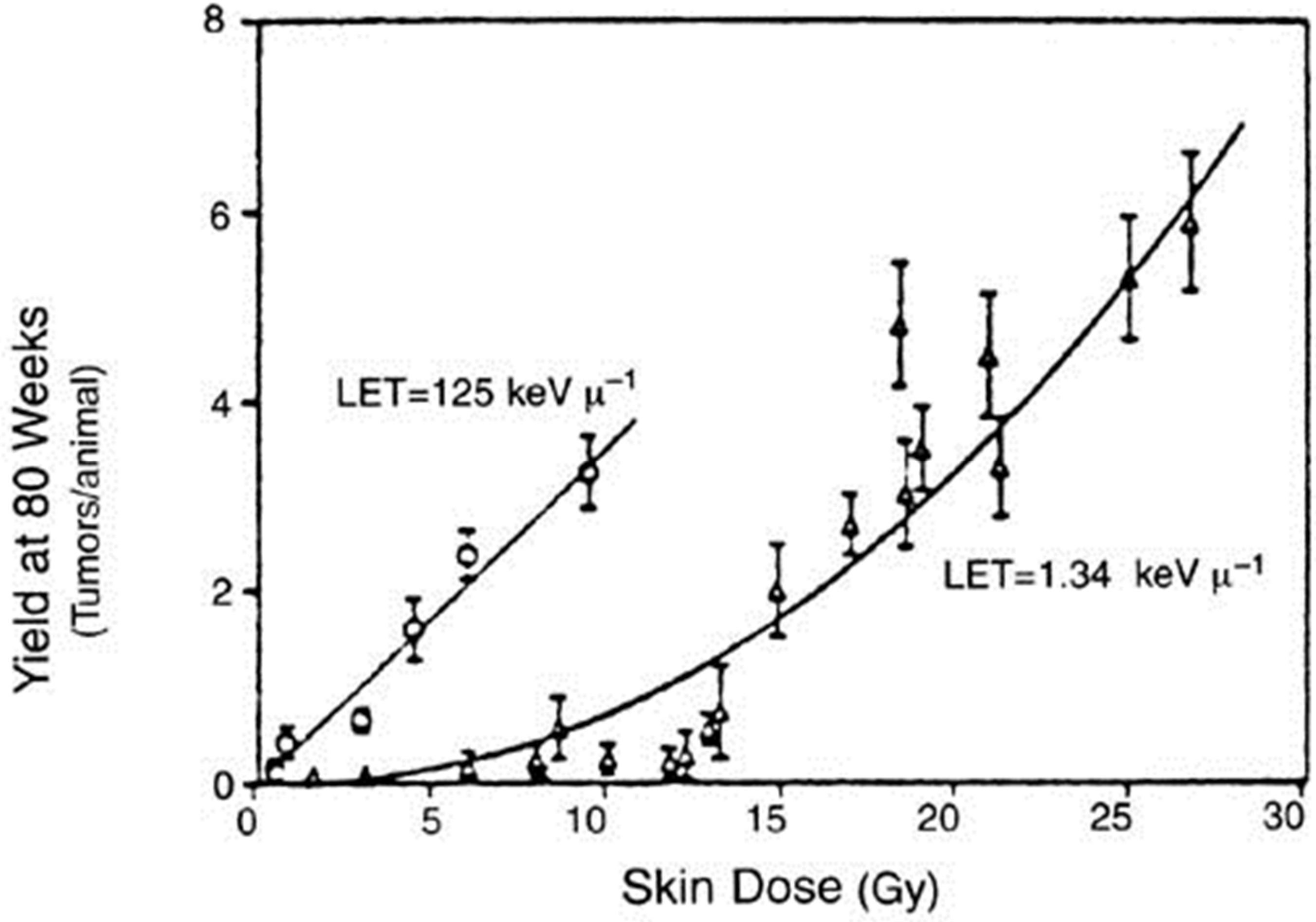
- **C**ancer induction;
- formation of gene and structural mutations;
- visual function disorders:
  - *retina lesions;*
  - *cataract induction*
- CNS disorders

Harderian tumors



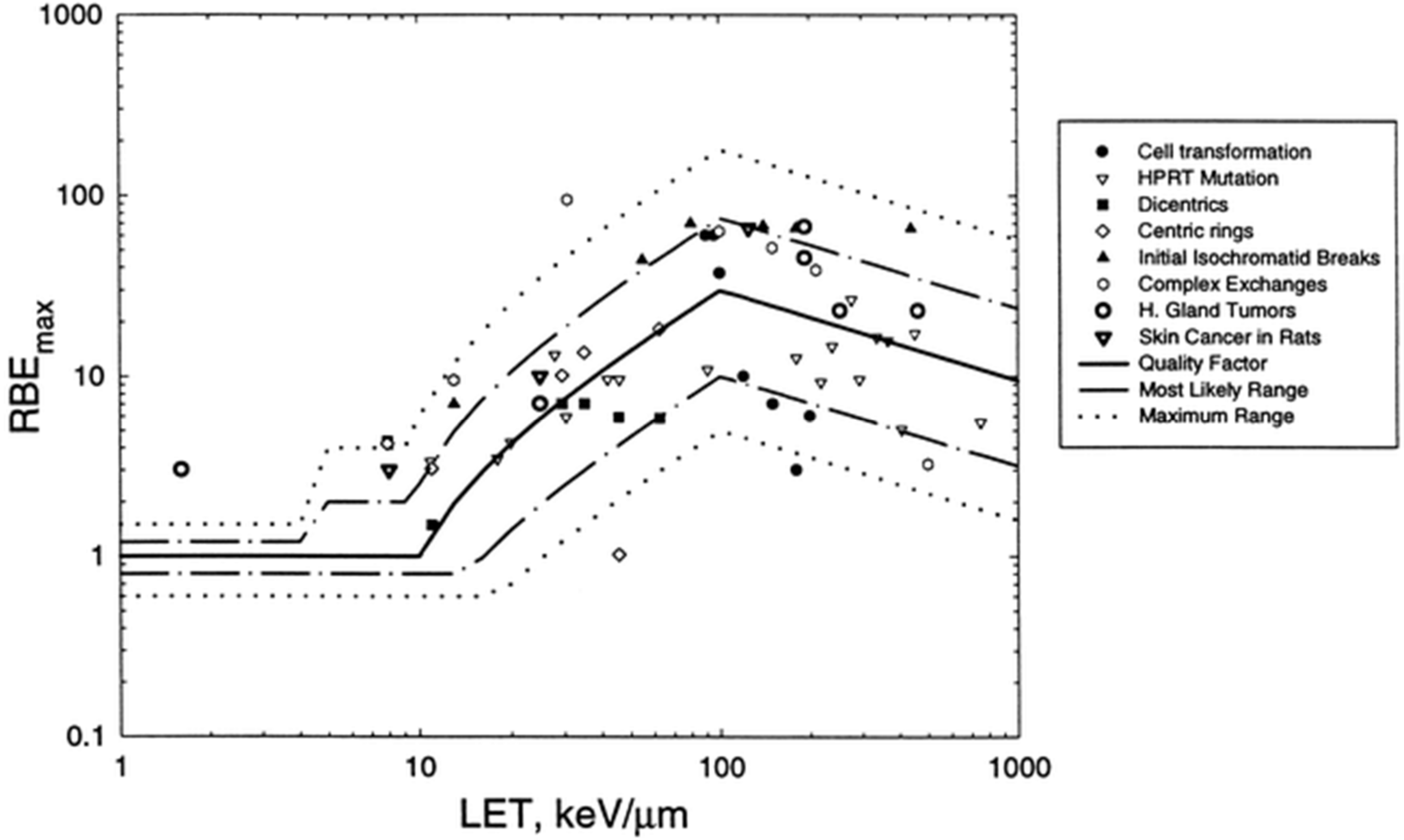
Nelson, 2006

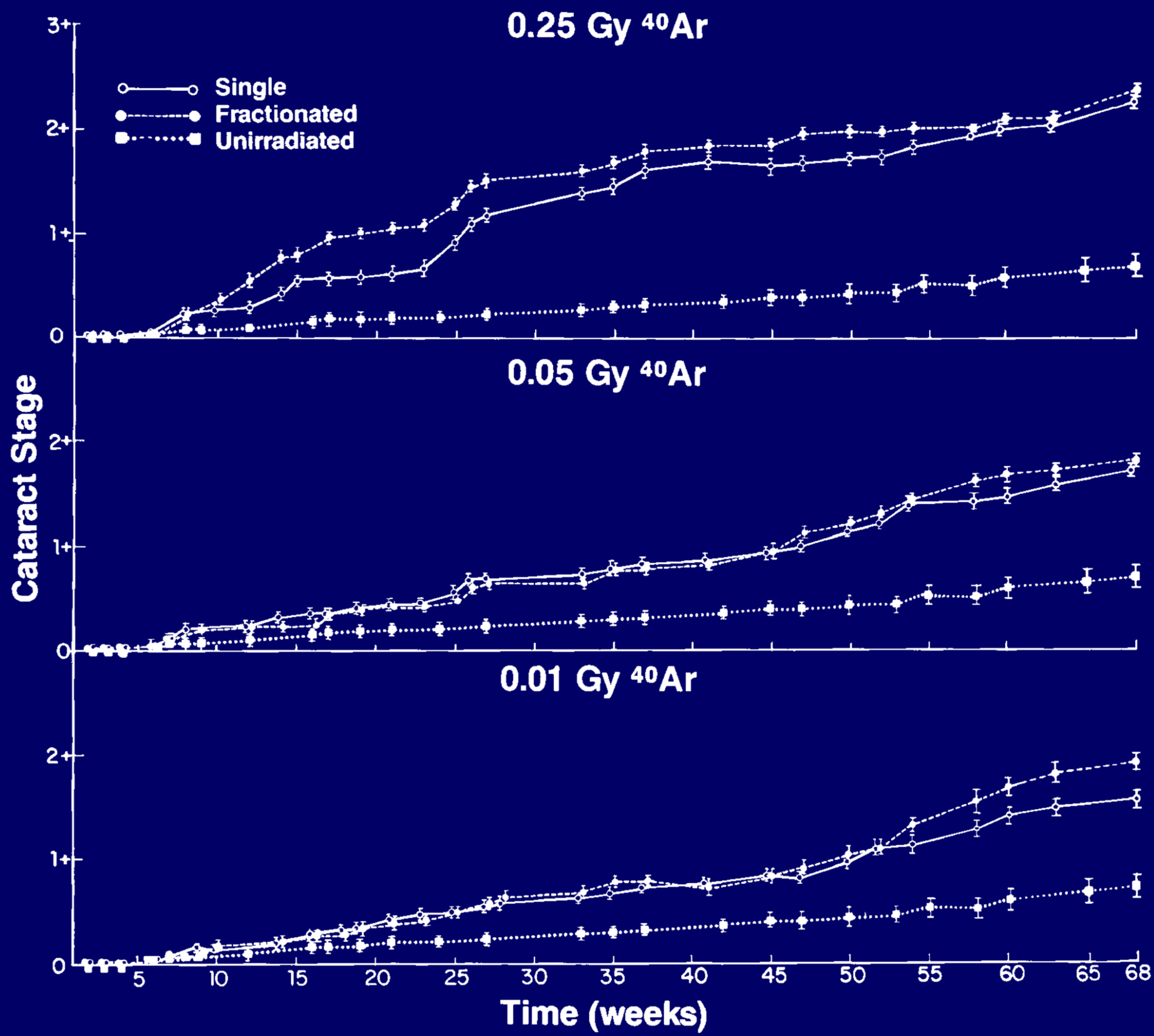
Skin cancer (rats)



Burns, Albert, 1986

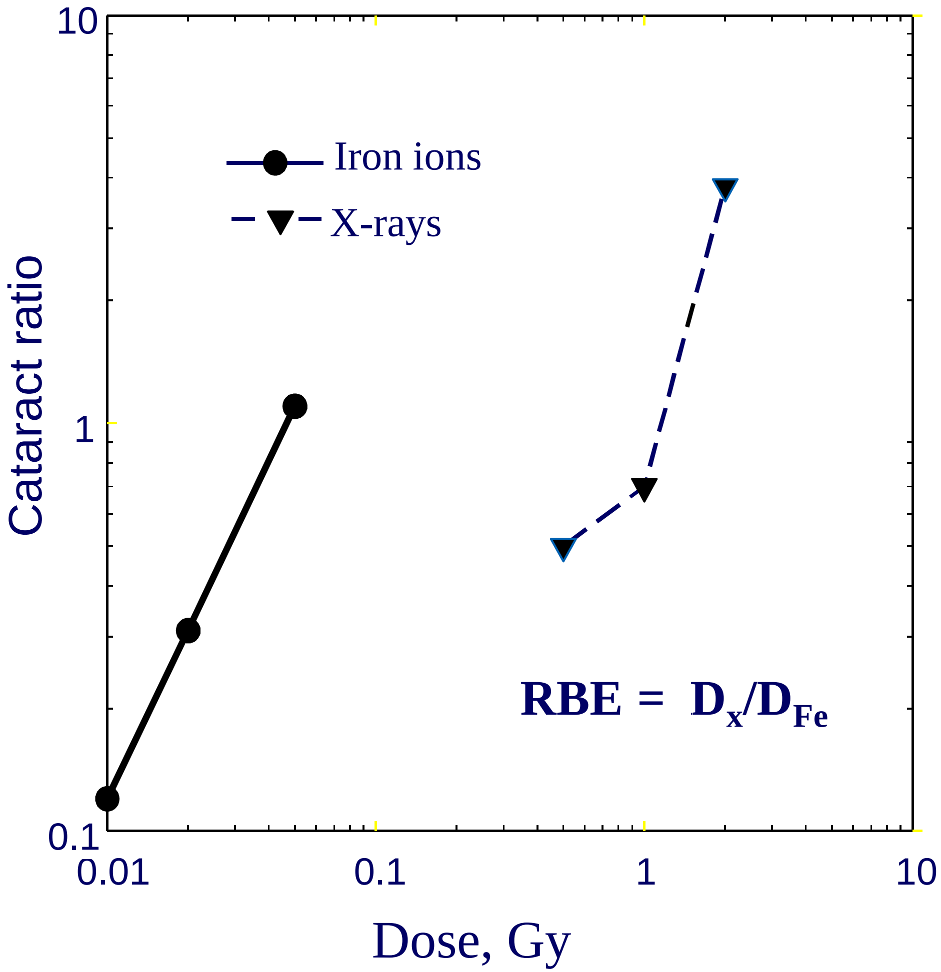
RBE of the carcinogenic effect of irradiation

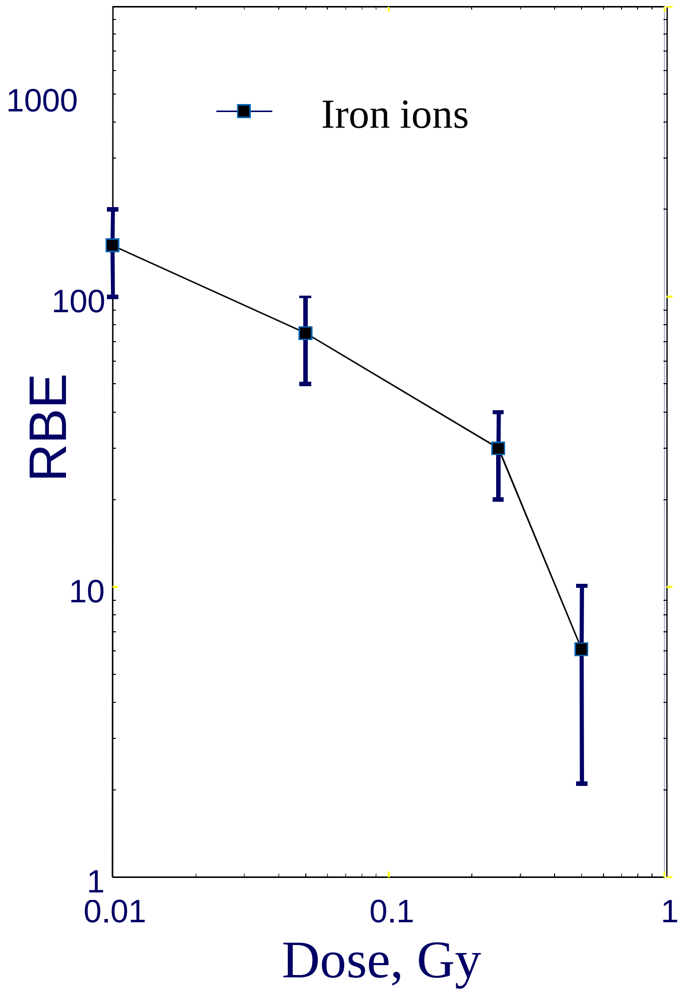




Worgul et al., 2006

Cataract ratio after irradiation by iron ions and X-rays



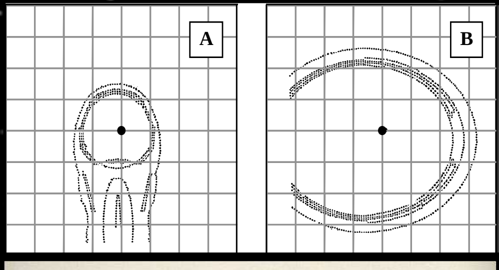


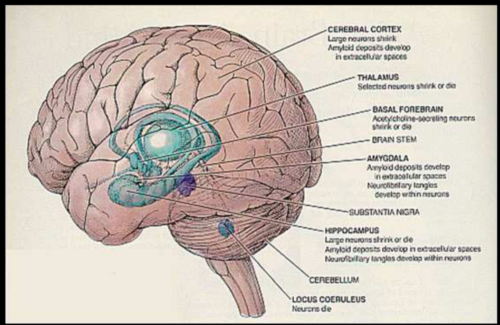
Worgul et al., 2006

Accelerated heavy ions and CNS

Cosmic ray hit frequencies in CNS critical areas

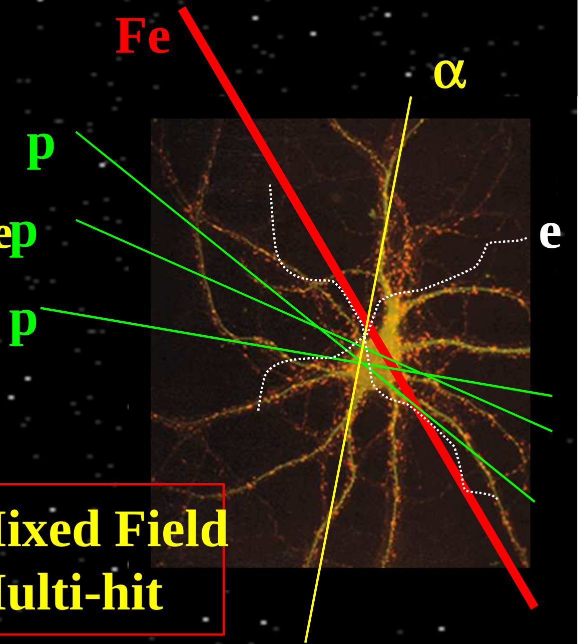
BROOKHAVEN NATIONAL LABORATORY





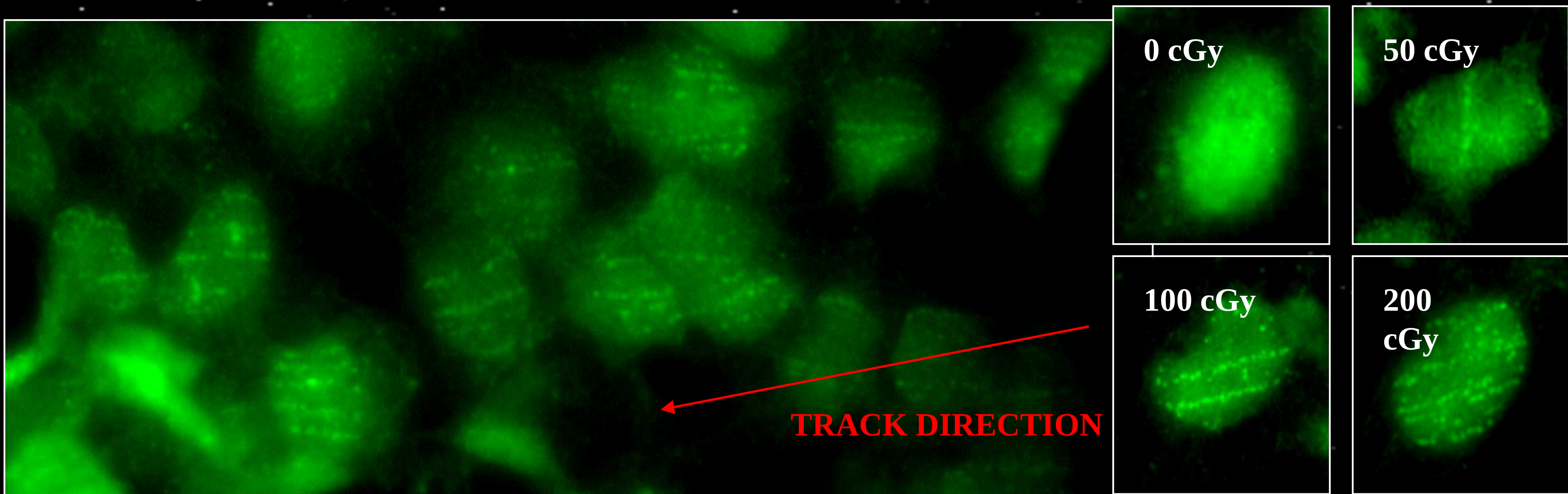
CNS in General

- 2 – 13% of the cells will be hit by at least one Fe particle
- 8 – 46% will be hit by at least one particle with Z≥15
- Every nucleus will be traversed by a proton once every 3 days and an alpha particle once every 30 days.

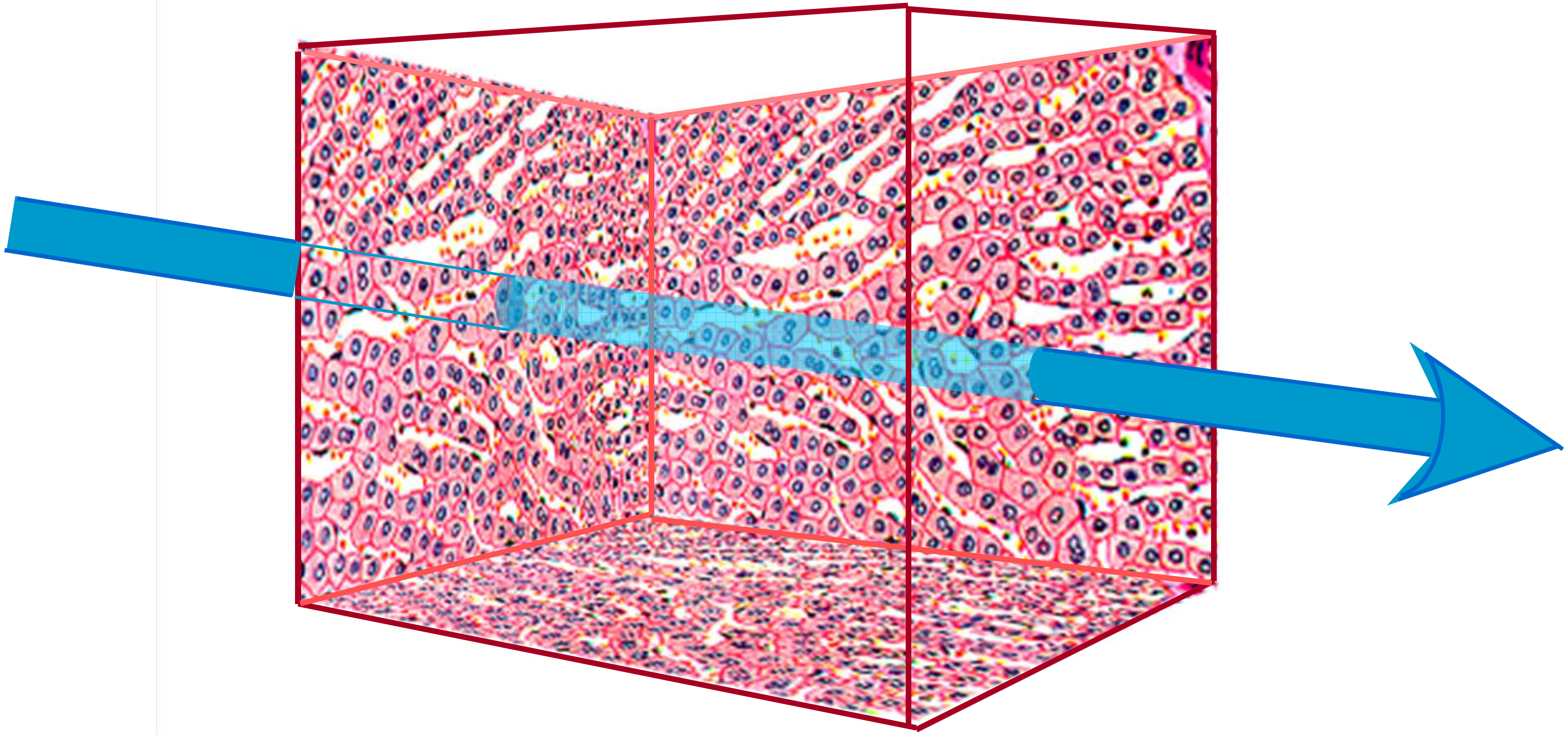


Mixed Field Multi-hit

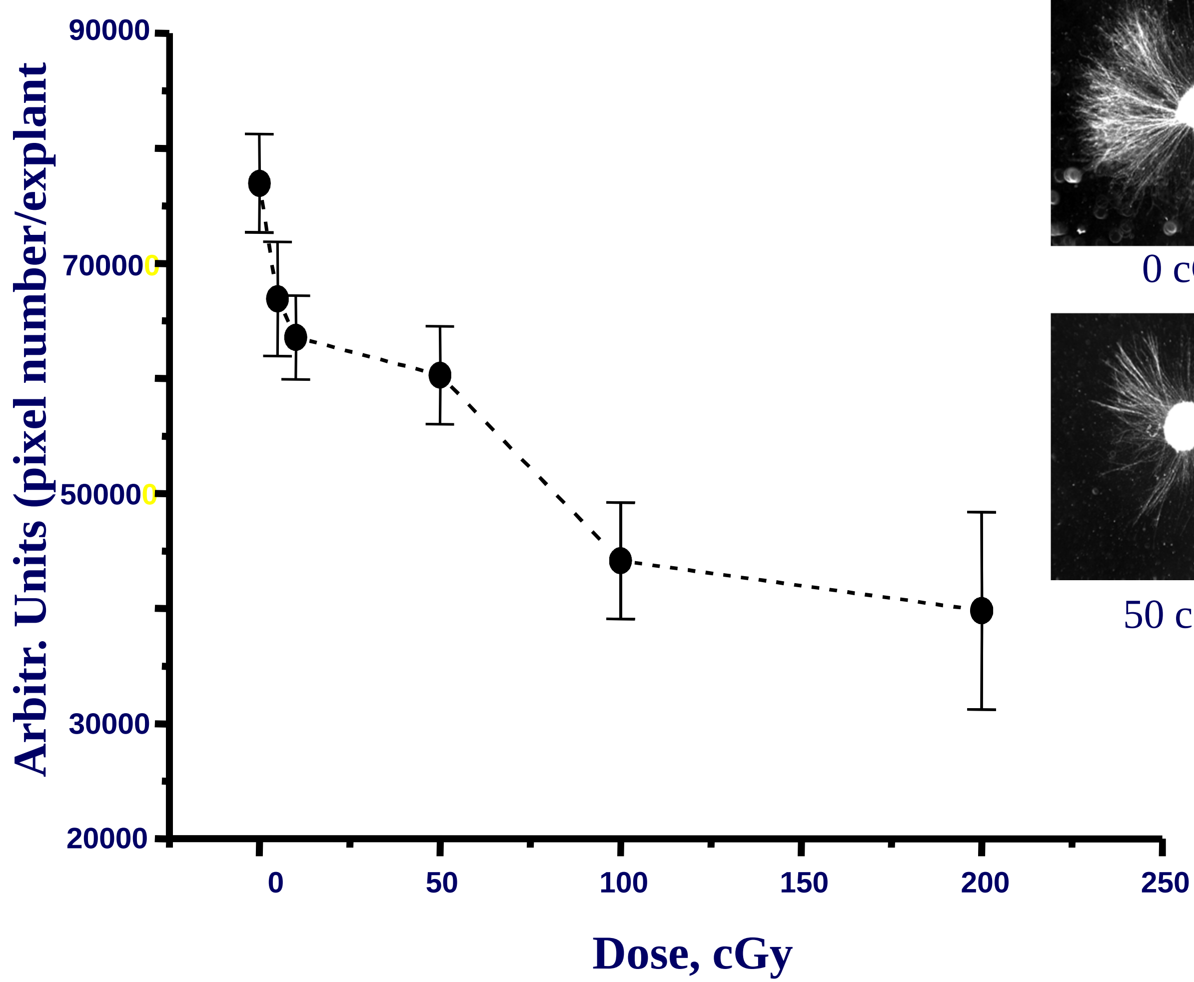
FE ION TRACKS VISUALIZED BY MARKERS OF DNA DSBs (γH2AX)

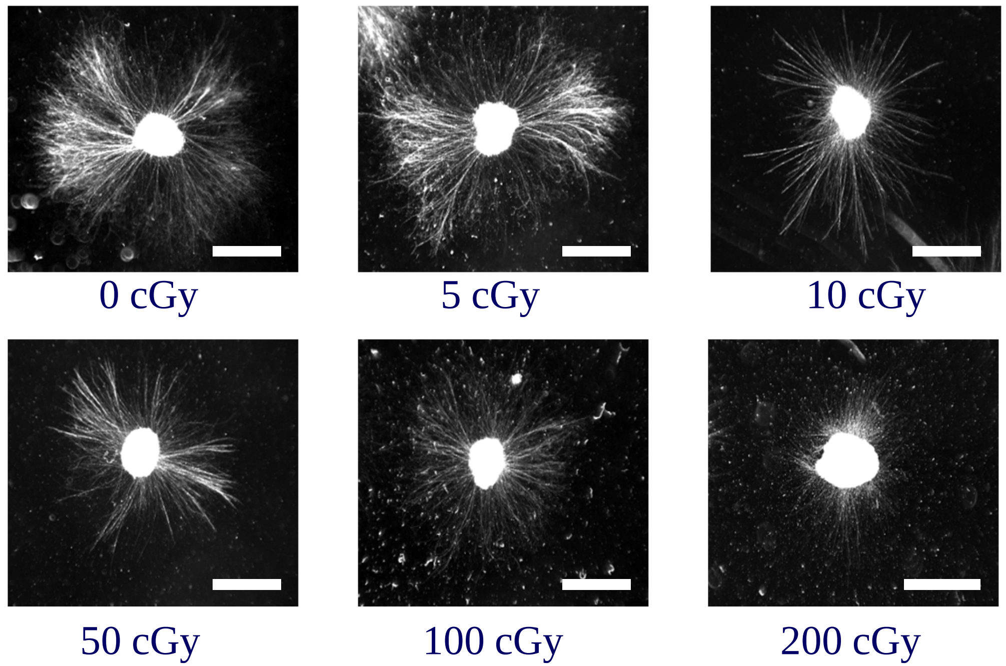


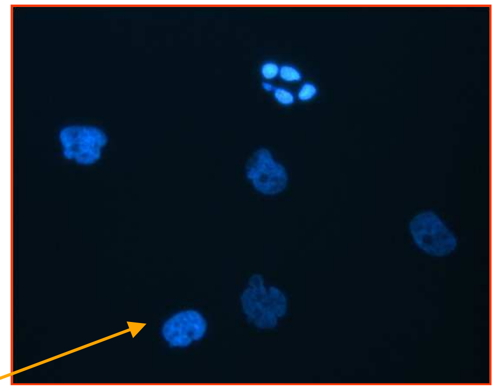
Damage of a large number of cells in a tissue by a single heavy ion track



In Vitro Neurotoxic Effects of ^{56}Fe Ions on Retinal Explants



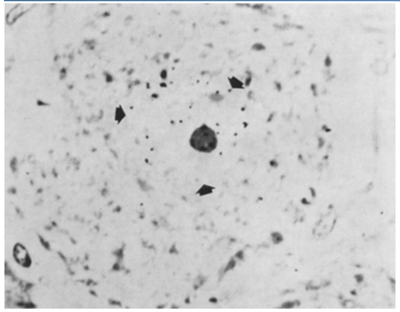


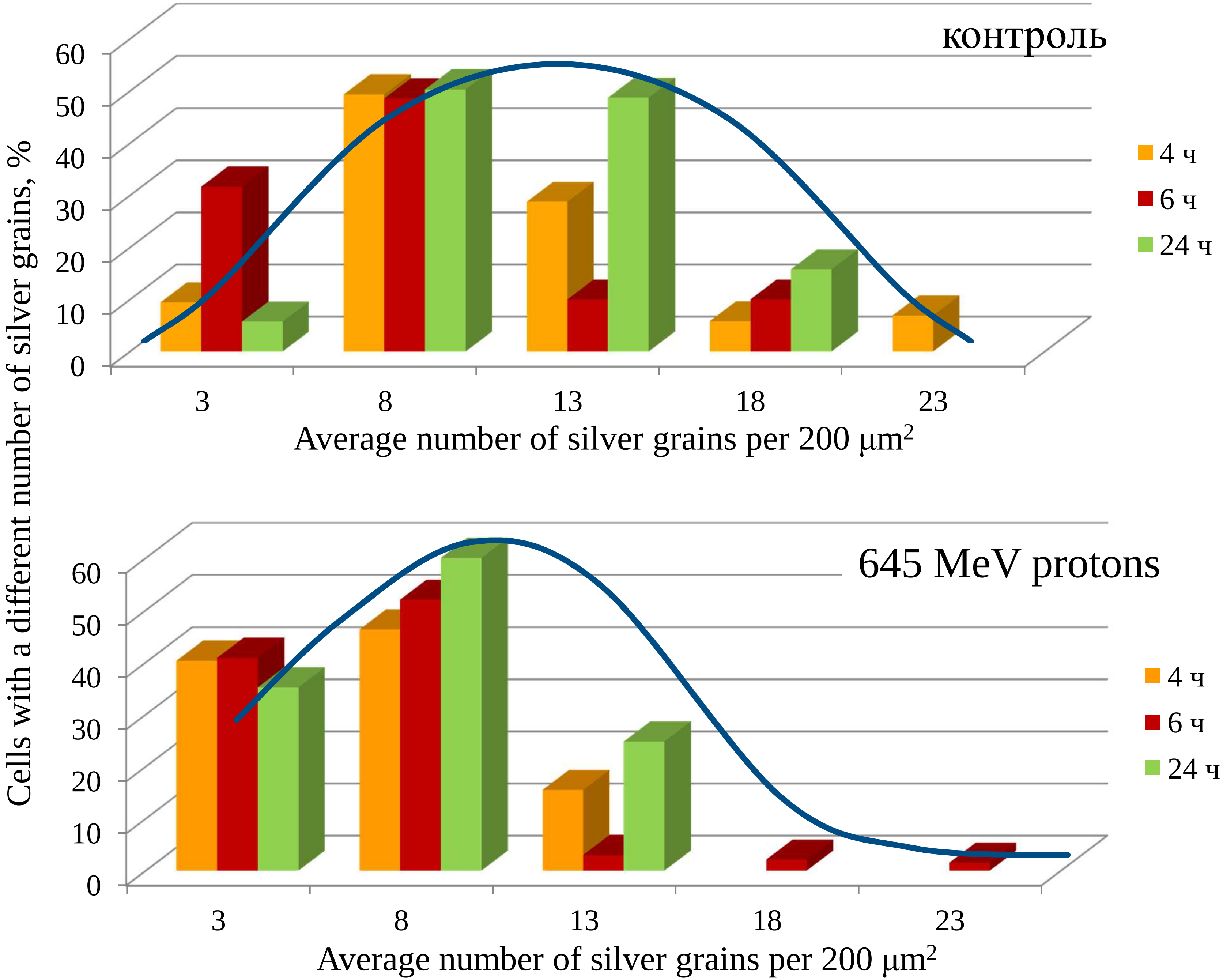


apoptosis

Vazquez, 2006

^{3}H-uridine uptake in rat spinal ganglions

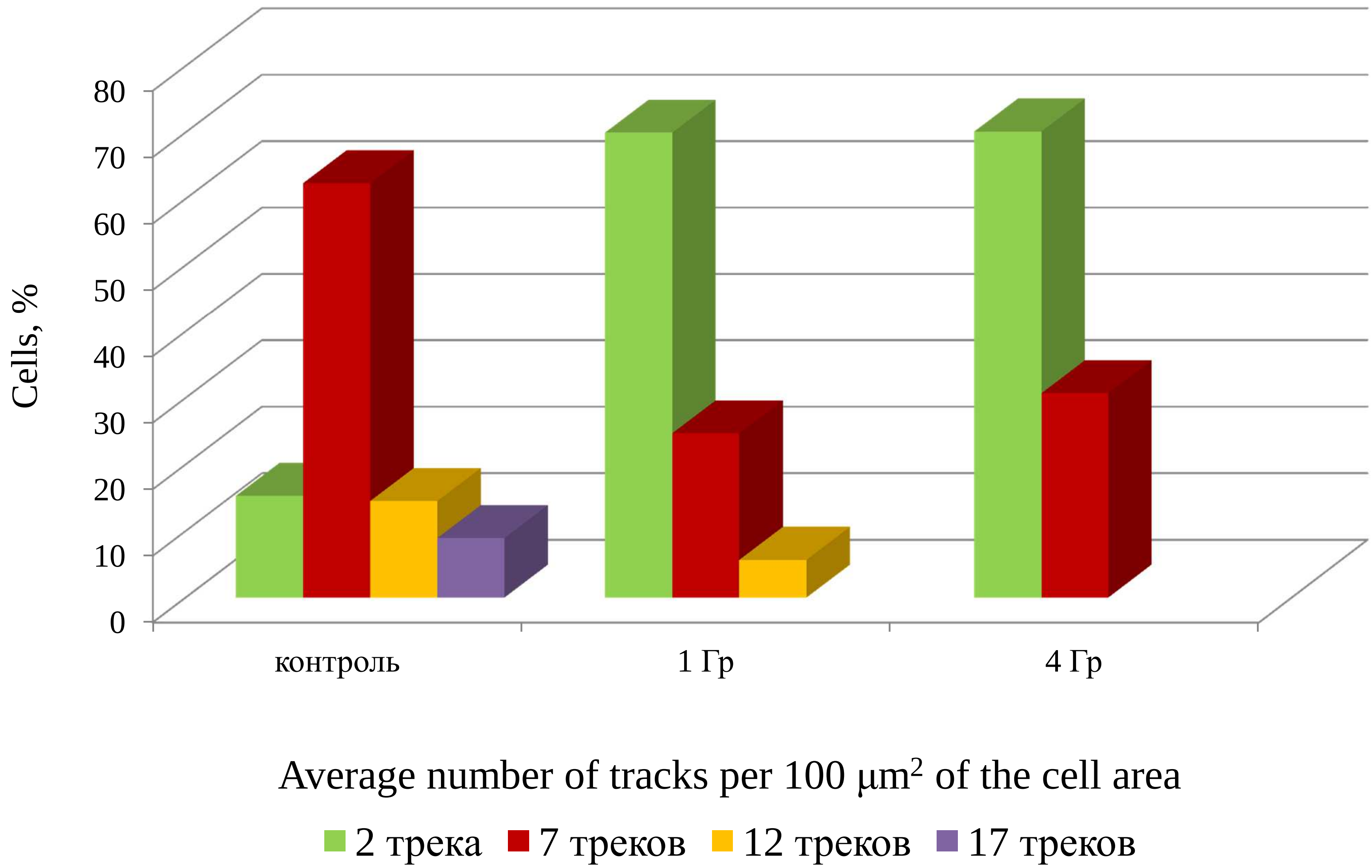




First 24 hours after irradiation

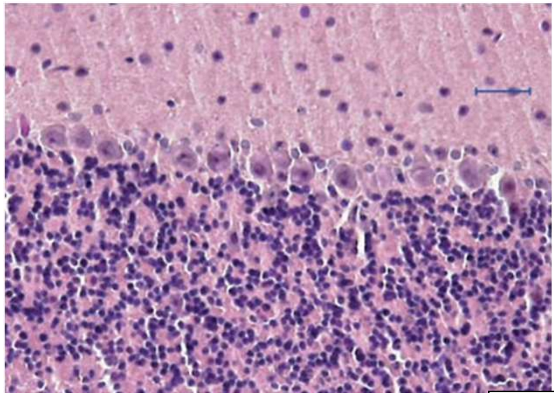
E.A. Krasavin

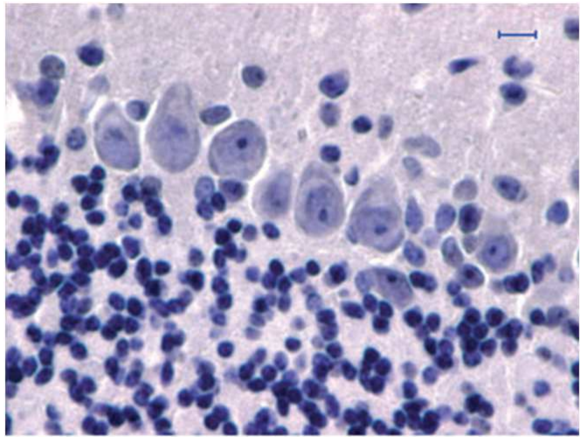
Distribution of Purkinje cells of the rat cerebellar cortex over the intensity of S^{35} methionine uptake one month after irradiation with 645 MeV protons



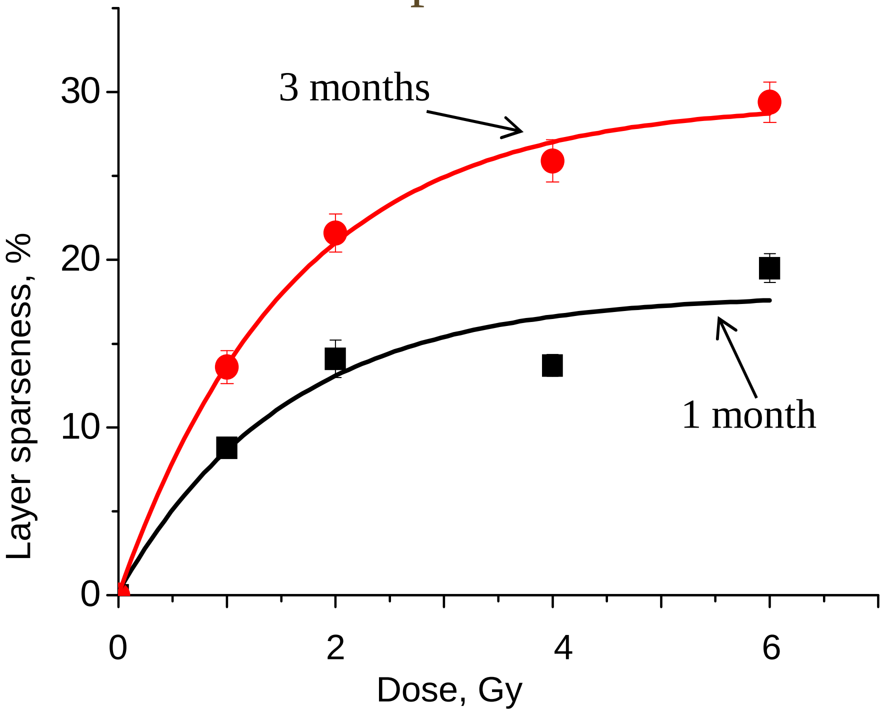
E.A. Krasavin,1979

Sparseness of the Purkinje cell layer at different times after irradiation with 645 MeV protons and ^{137}Cs γ-rays

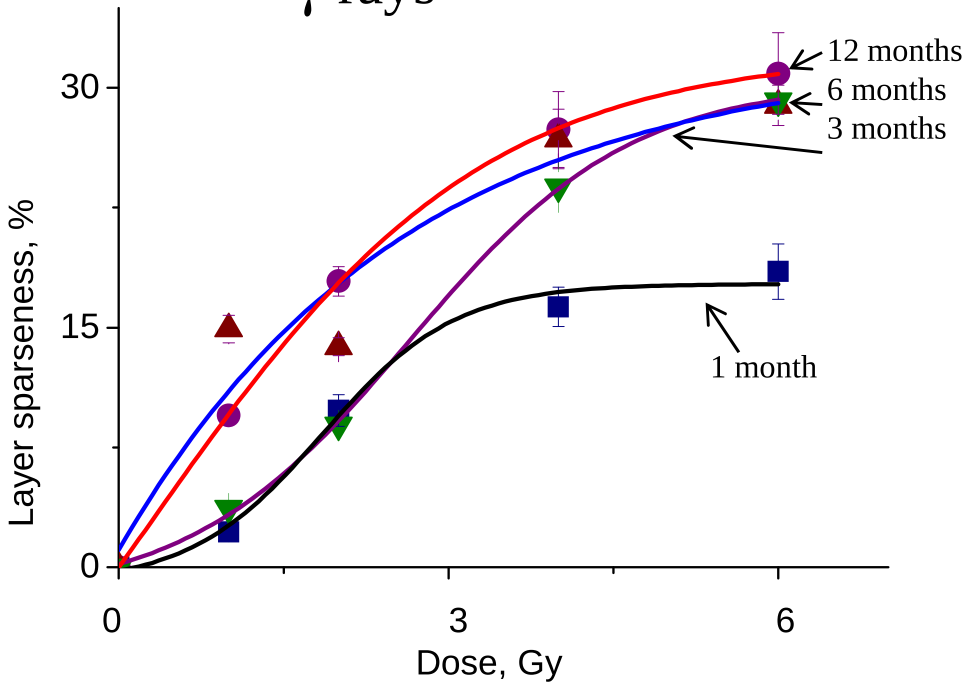




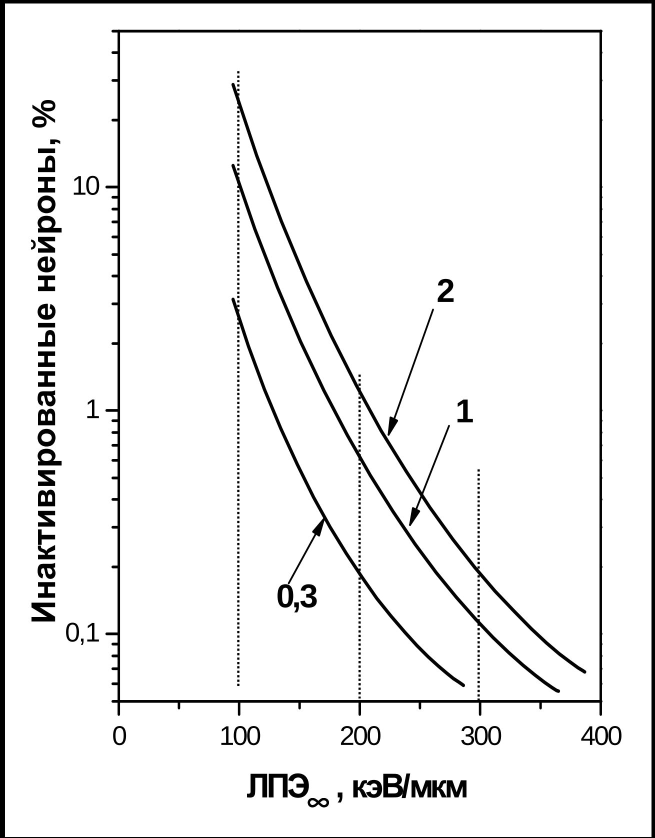
645 MeV protons

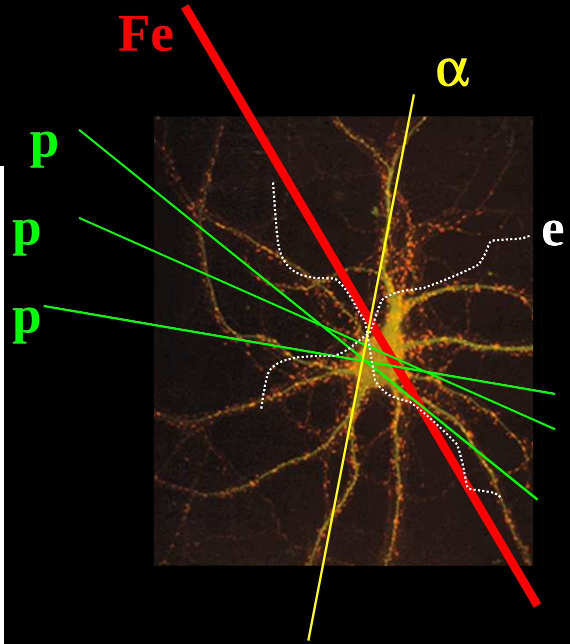


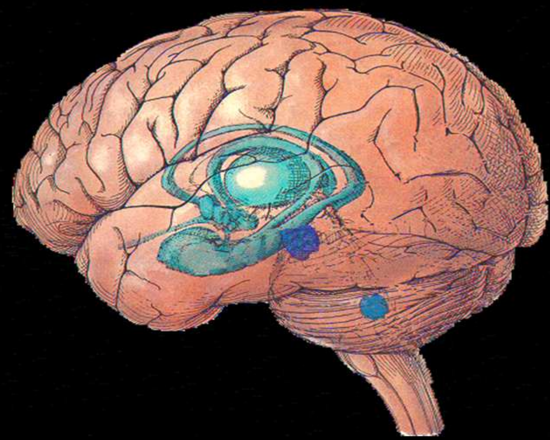
γ-rays



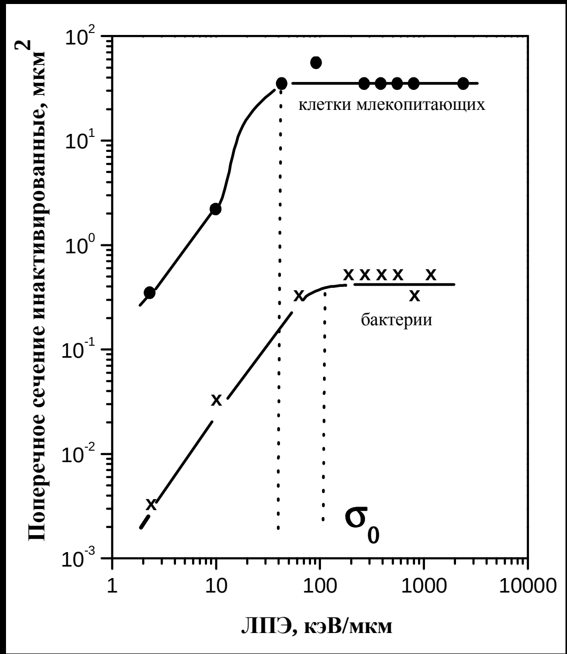
E.A. Krasavin







The number of the inactivated neurons with r=10μm depending on the threshold values of particle LET for different flight durations (0.3, 1, and 2 years)



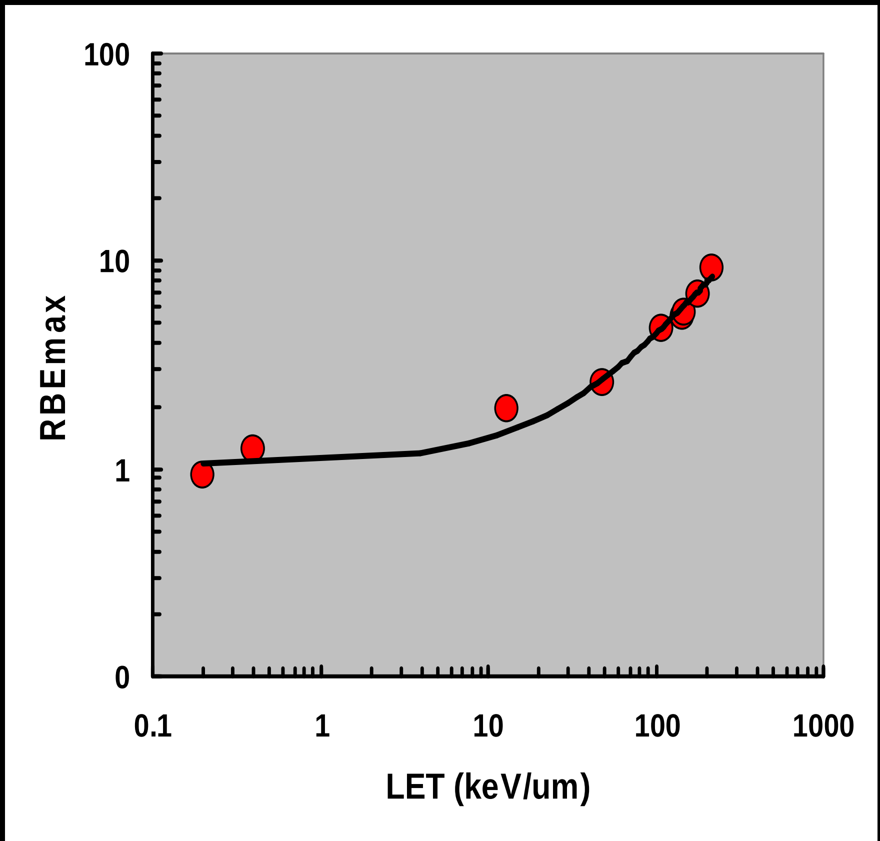
Dependence of the mammalian and bacterial cell inactivation cross-section on accelerated heavy ion LET

E.A. Krasavin, 1979

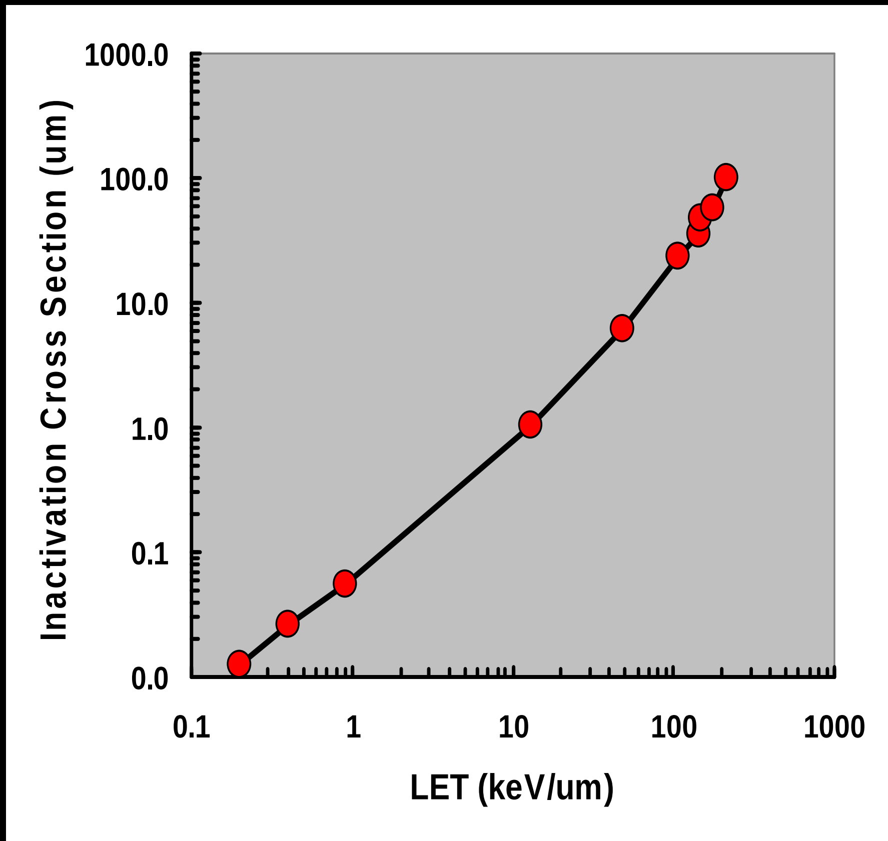
APOPTOSIS INDUCTION AT 48 hrs

NT2 Human Neural
Stem Cell

RBEmax/LET DEPENDENCE



INACT. CROSS SECT./LET DEPENDENCE



Vazquez, 2006

(The inactivation cross section based on the survival data was calculated using the following formula:
$\sigma(\mu m^2) = 0.16021 \times LET(keV/um)/D_{10}$ (Gy).

Morris Water Maze

Rat 214-126
Morris Water Maze
Learning Test #1

Tracking with:
Noldus Ethovision

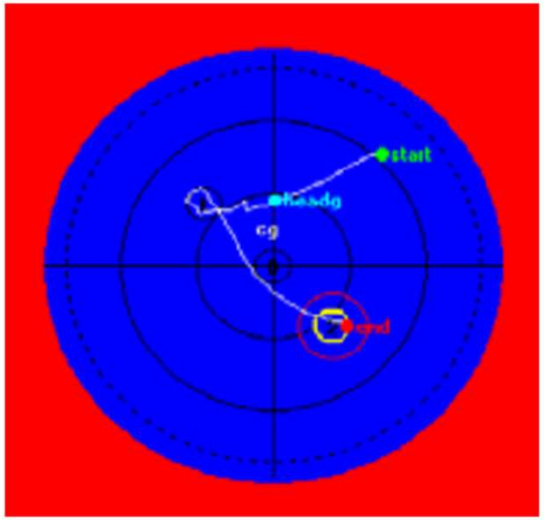
Cyclotron Research Center
University of Liege

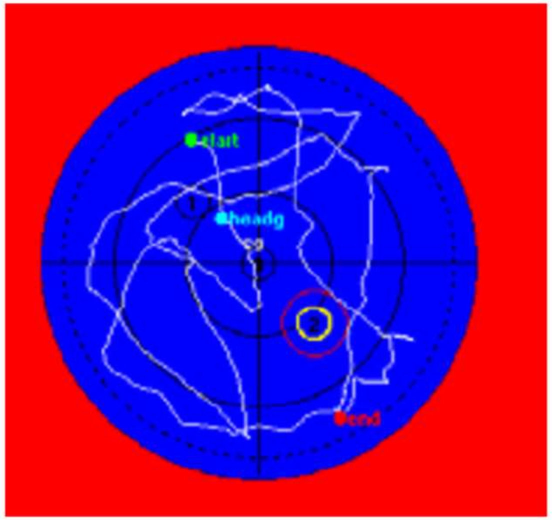
jepoirrier@ulg.ac.be
http://www.poirrier.be/~jean-etienne/

^{56}Fe ions: 1 GeV/nucleon,

Control

1.5 Gy

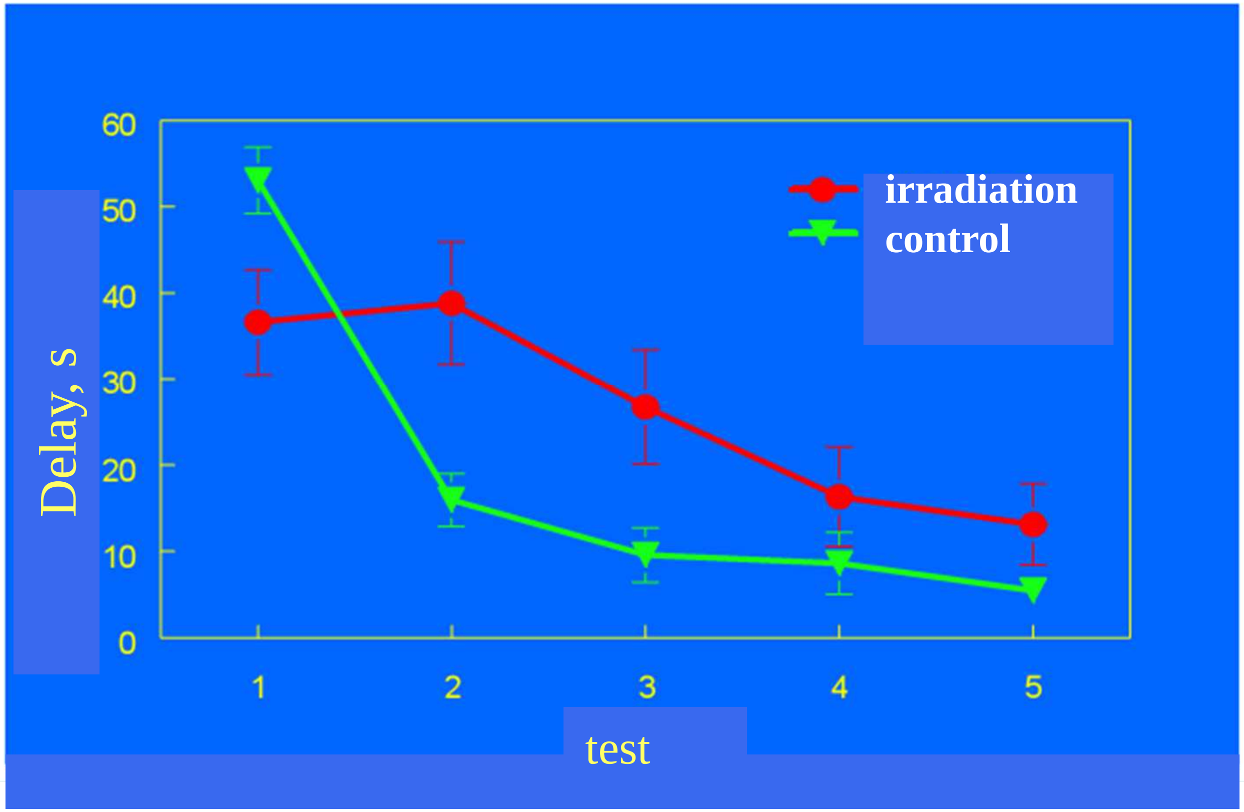




Cognitive tests

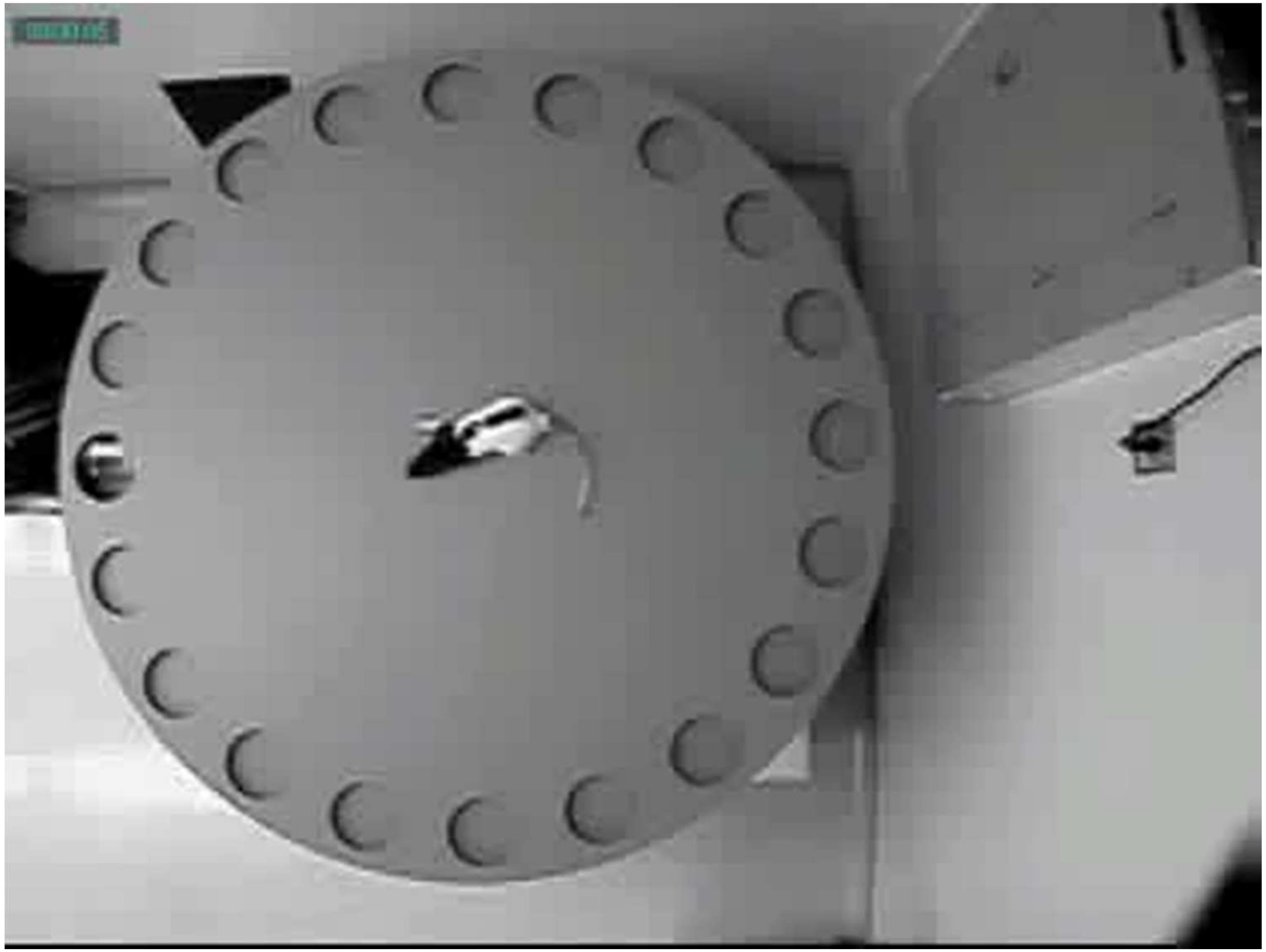
(Morris water maze, etc.)

1 month after irradiation

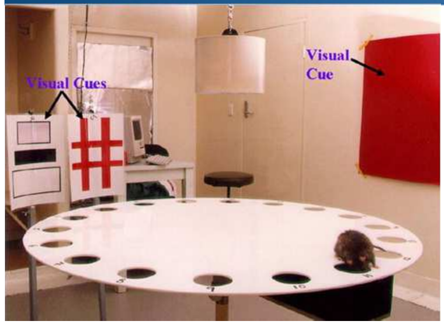


M.Rabin, 2005

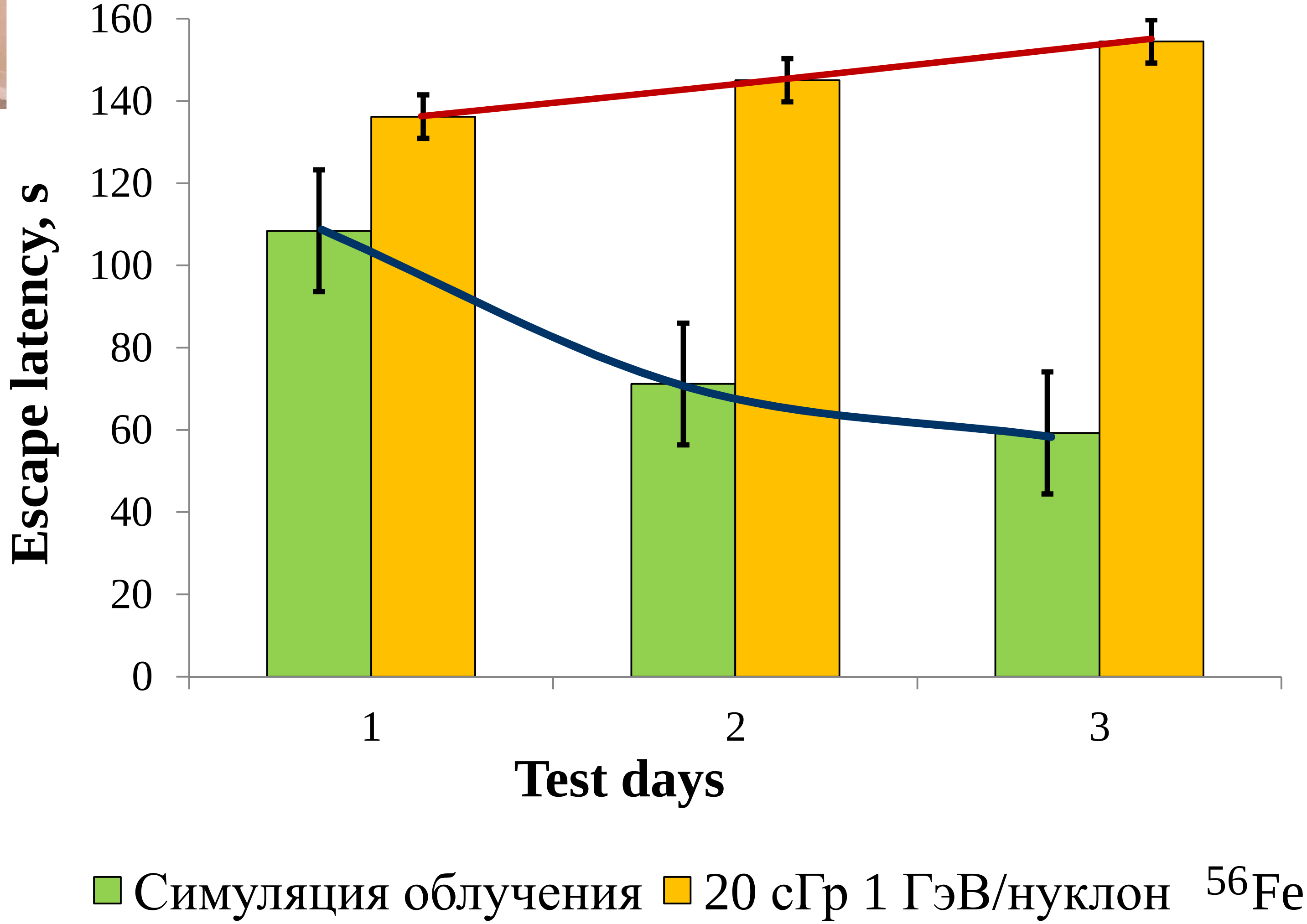
C. Barnes test



Spatial learning disorders under exposure to ^{56}Fe ions



3 months after irradiation



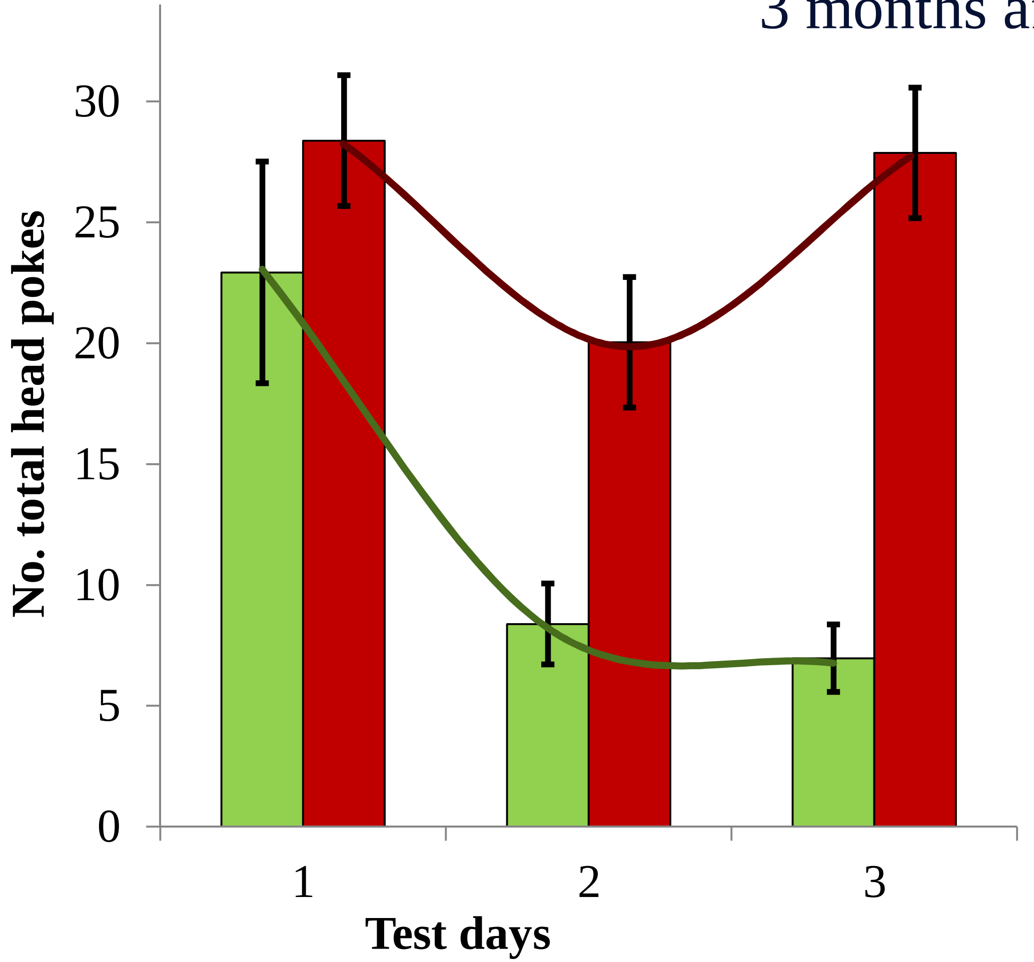
20 cGy

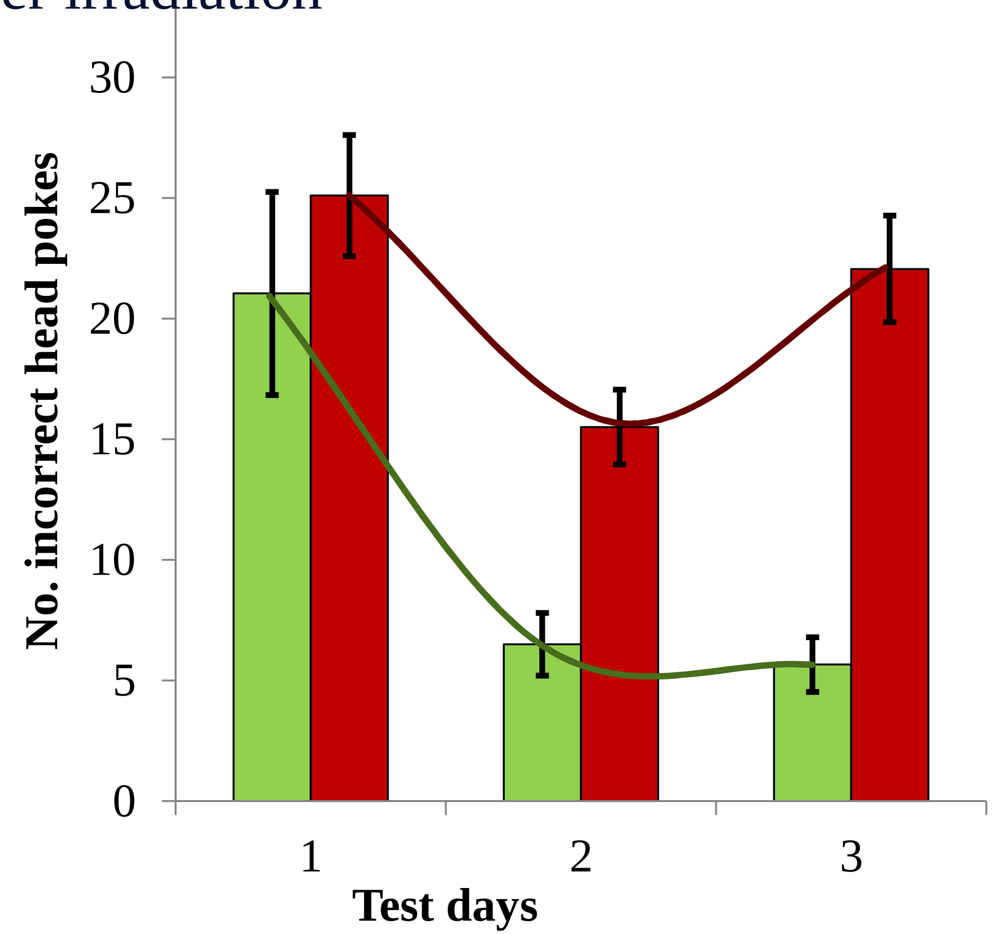
$\Phi \approx 10^5/cm^2$

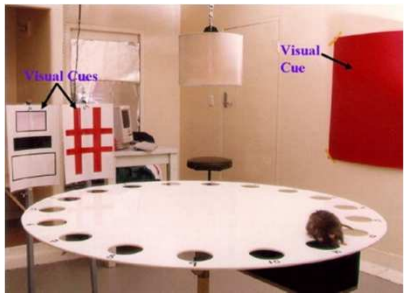
R. Britten et al., 2012

Spatial learning disorders under exposure to ^{56}Fe ions

3 months after irradiation





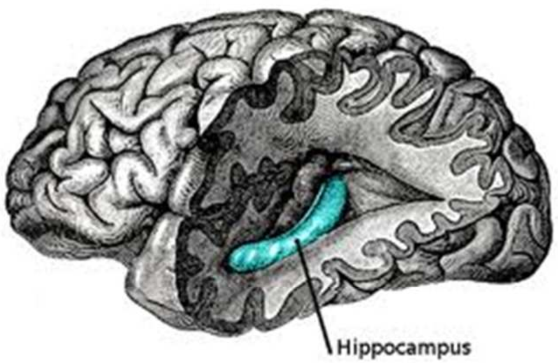


Irradiation simulation

^{56}Fe at 20 cGy, 1 GeV/nucleon

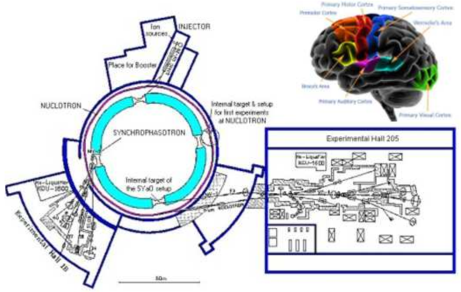
R. Britten et al., 2012

Spatial learning disorders

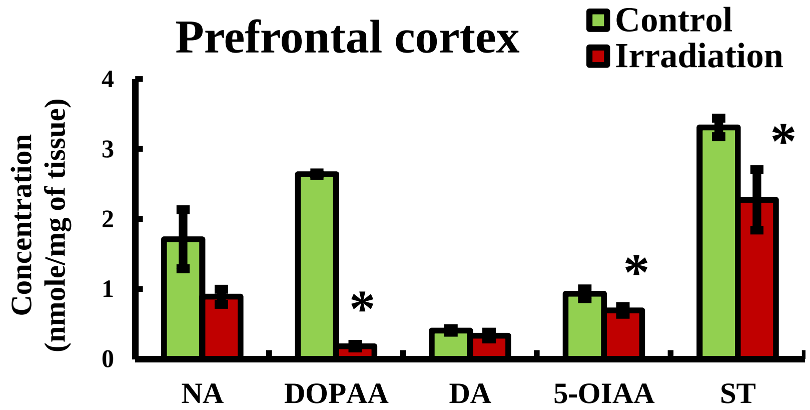


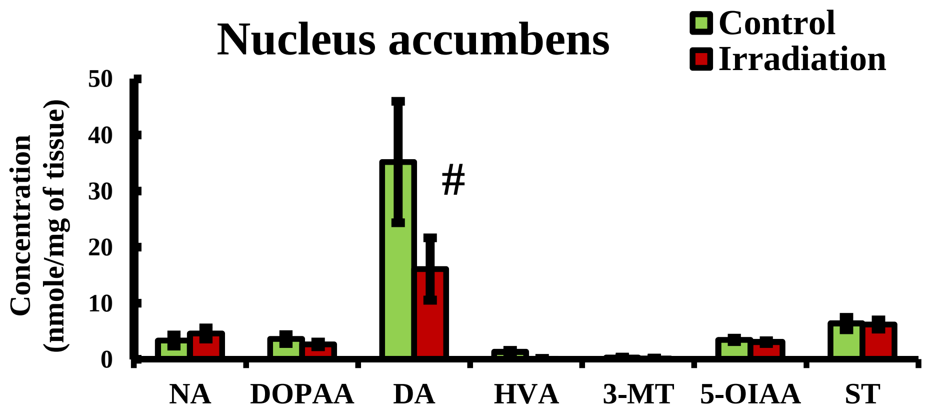
Disorder mechanism: the damage of glutamatergic transmission in hippocampus synaptosomes, which consists in a significant decrease in the expression of the NR1, NR2A, and NR2B subunits of the NMDA glutamatergic receptor.

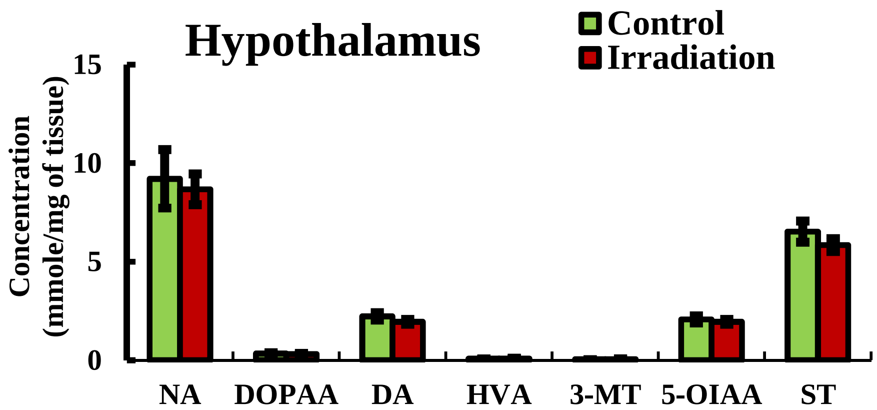
Initial radiobiological studies at Nuclotron-M

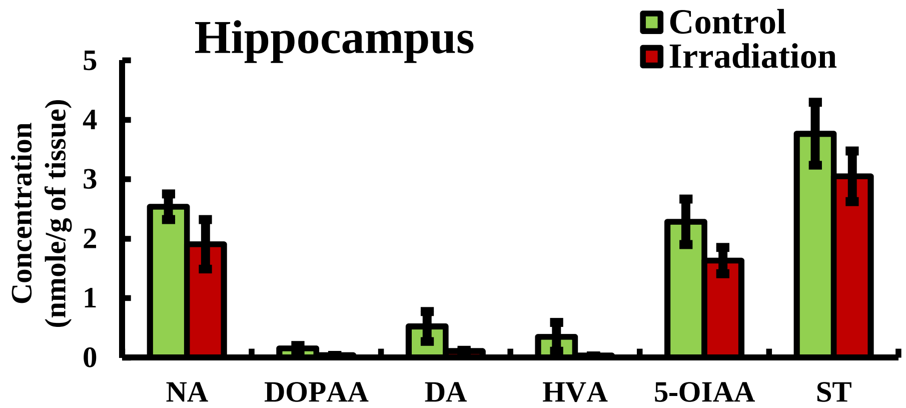


Studying the level of neurotransmitters in different brain areas of rats after irradiation with 1 Gy of 500 MeV/nucleon carbon ions

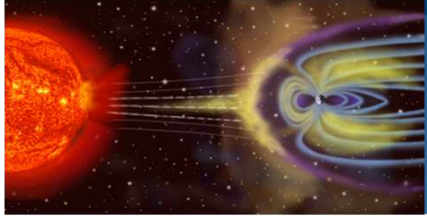








Decreasing in the level of neurotransmitters is observed after irradiation



The current risk concept

- The concept is based on the introduction of a *dosimetric finctional as the criterion* and quantitative measure of *radiation danger*.

- **Generalized dose** $\boldsymbol{H_G}$ and $\boldsymbol{H_E}$ for the evaluation of the immediate adverse consequences during the flight and the delayed effect during further life:

$$H_G = \left(\sum_{i=1}^{n} \overline{D}_i \times KQ_{Gi} \times KT_{Gi} \times KP_{Gi}\right) KM_G$$

$$H_E = \left(\sum_{i=1}^{n} \overline{D}_i \times KQ_{Ei} \times KT_{Ei} \times KP_{Ei}\right) KM_E$$

KQ_i – *radiation quality* coefficients;

KT_i – coefficients of the *dose distribution over time*;

KP_i – coefficients of the dose *distribution over the human body*;

KM – coefficients of the organism’s radioreaction modification caused by *other factors of the space flight.*

New risk concept

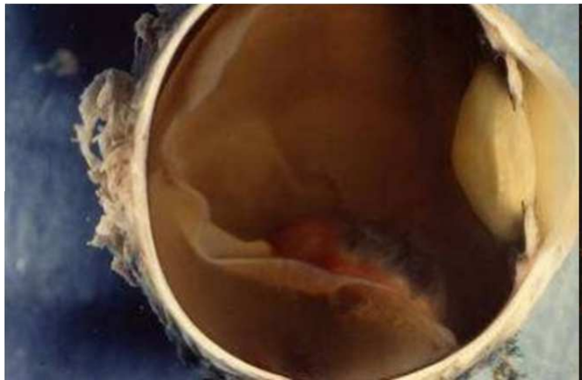
Introduction of the *probability* $\boldsymbol{P}$ *of the successful completion of the mission:*

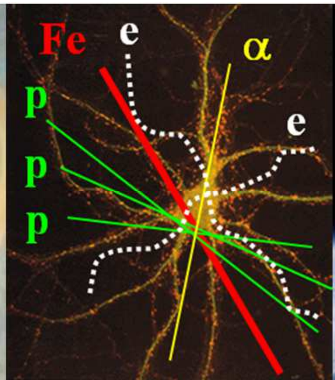
$$\boldsymbol{P} = 1 - (\boldsymbol{P}_{\mathbf{RAD}} + \boldsymbol{P}_{\mathbf{NONRAD}} + \boldsymbol{P}_{\mathbf{TECHN\ FAIL}})$$

$$\boldsymbol{P}_{\mathbf{RAD}} = P_{CNS} + P_{retina} + P_{cataract} + P_{oncol} + P_{other}.$$

$$\boldsymbol{P}_{\mathbf{NONRAD}} = P_{\text{ZERO-GRAVITY}} + P_{\text{CLOSED SPACE}} + P_{\text{PHYS TRAUM}} + P_{\text{INFECT}} + P_{\text{OTHER}}$$

$$\boldsymbol{P}_{\mathbf{TECHN\ FAIL}} = P_{\text{LAUNCH EARTH}} + P_{\text{INTERPL}} + P_{\text{MARS LANDING}} + P_{\text{MARS LAUNCH}} + P_{\text{EARTH LANDING}} + P_{\text{LIFE SUPPORT}}$$

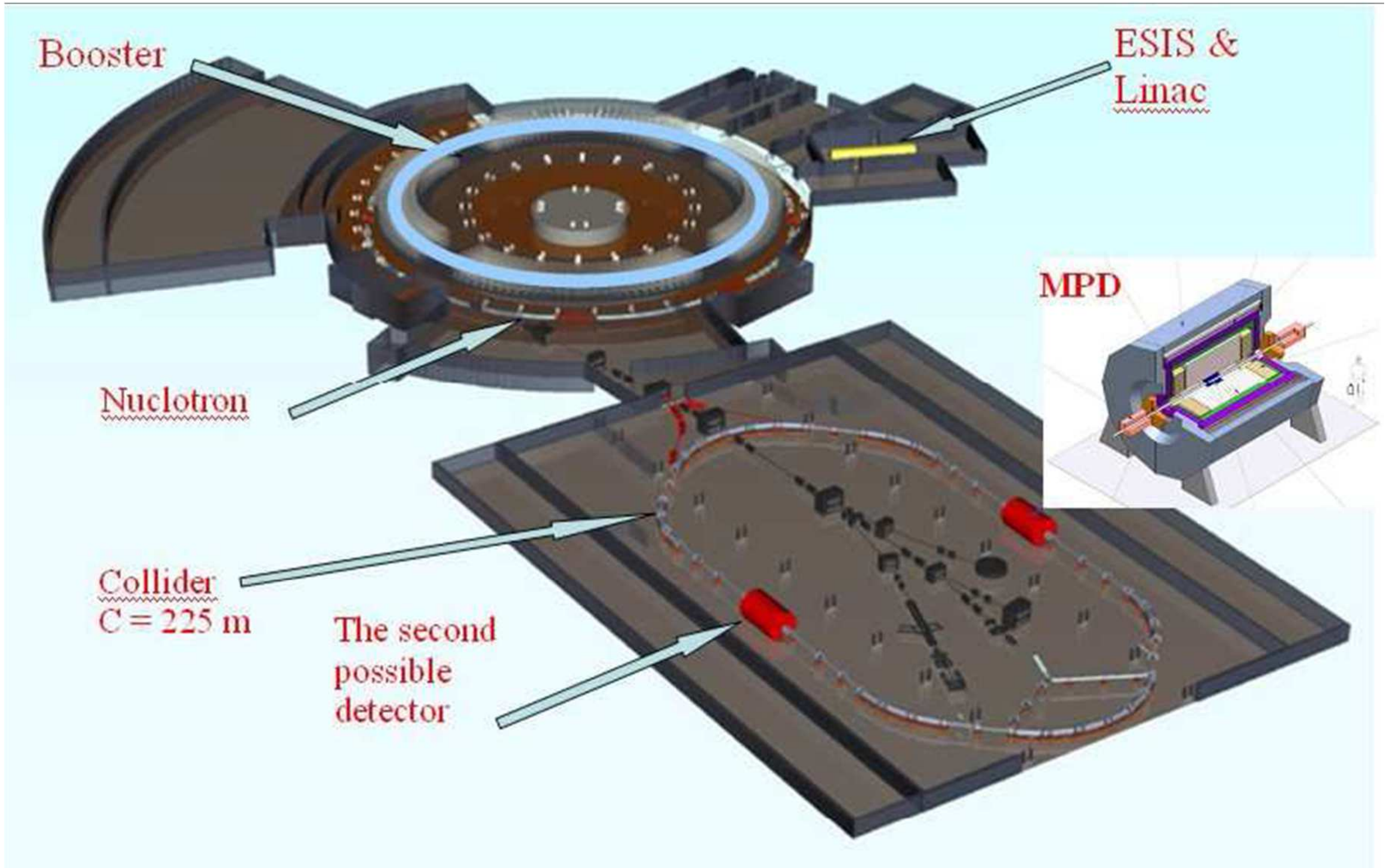




New risk concept

$$\boldsymbol{P}_{\mathbf{RAD}} = \boldsymbol{P}_{CNS} + \boldsymbol{P}_{retina} + \boldsymbol{P}_{cataract} + \boldsymbol{P}_{oncol} + \boldsymbol{P}_{other.}$$

NICA Project



Thank you for your attention