

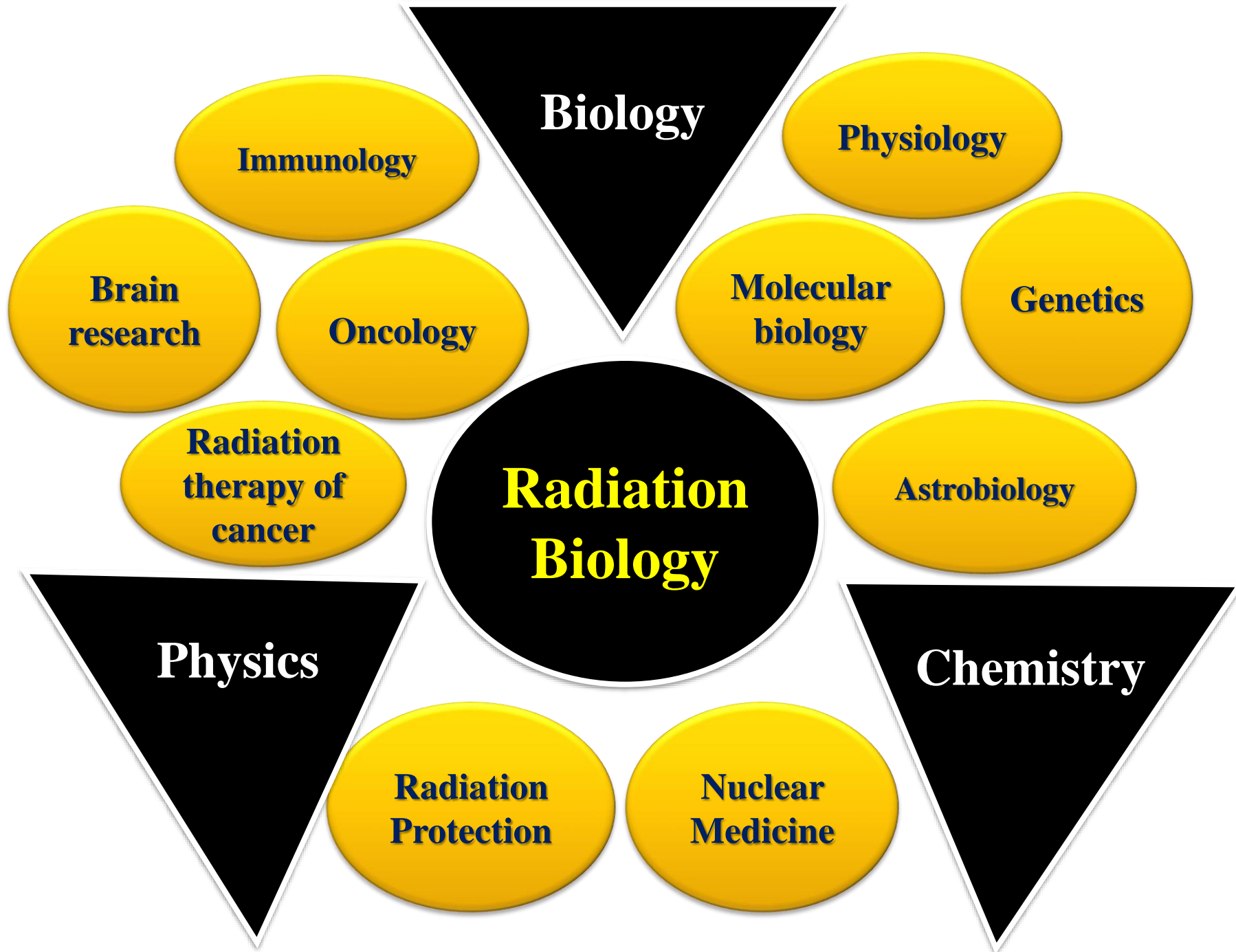
**Radiation Biology @ JINR:
Fundamental Research and
Applications in
Nuclear Medicine**



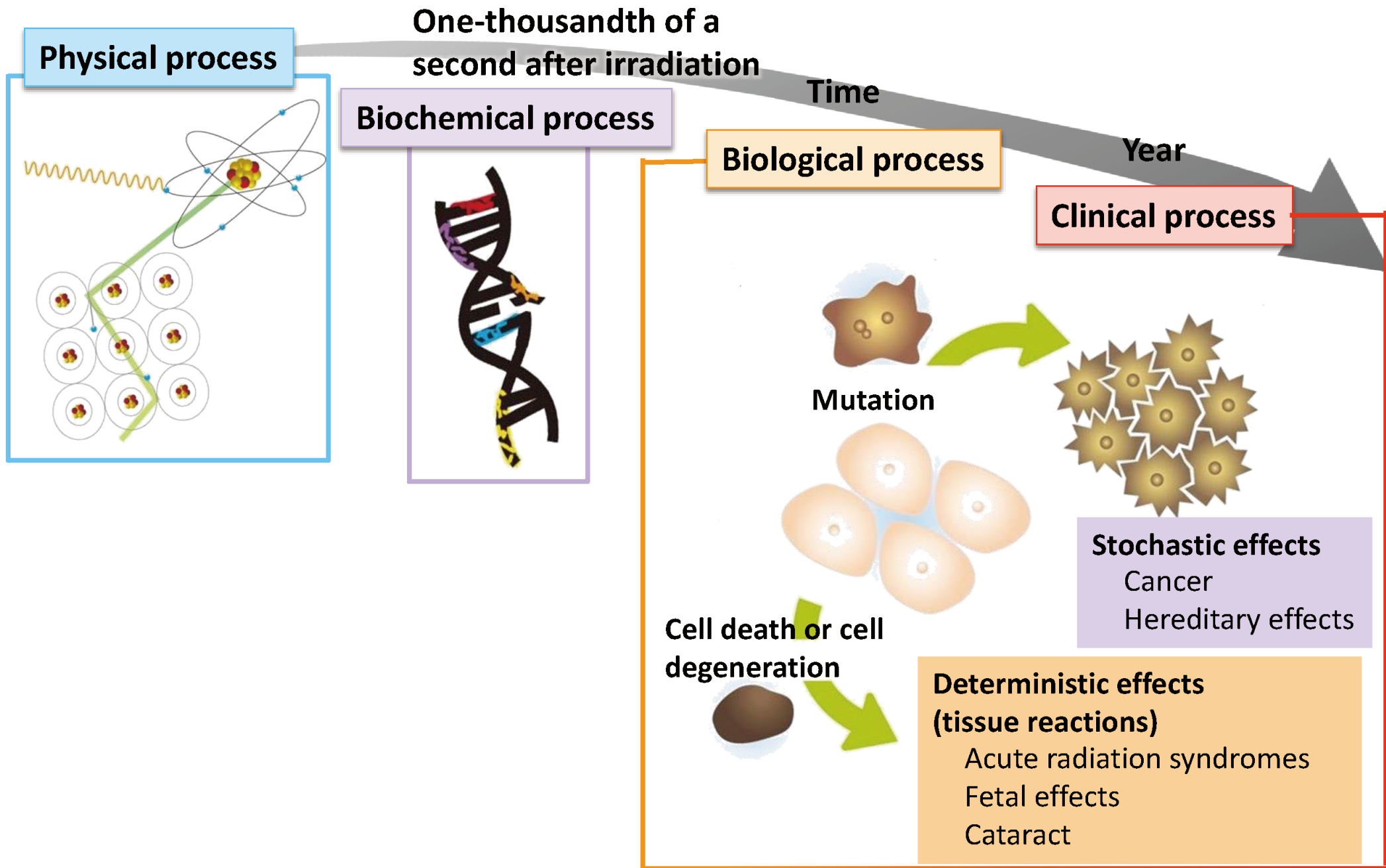
Aleksandr Bugay
**Laboratory of
Radiation Biology**

bugay@jinr.ru

Mathematics and computing



Ecology



DUBNA

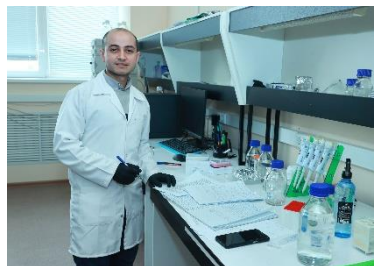
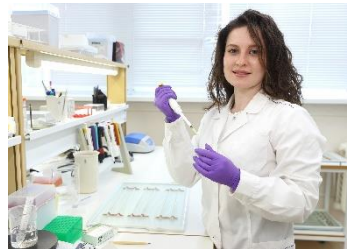
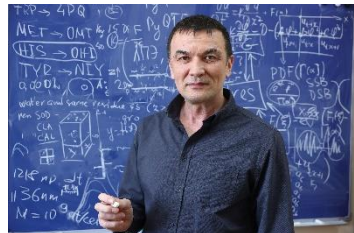


JINR

Laboratory of Radiation Biology

lrb.jinr.ru

- 1959 - first radiobiological experiments
- 1978 - Biological Research Sector
- 1988 - Biological Division at DLNP
- 1995 - The Department of Radiation and Radiobiological Research
- **2005 - Laboratory of Radiation biology**



Milestones:

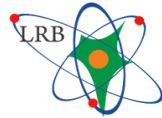
- role of DNA damage repair in relative biological effectiveness (RBE) of particle beams
- mechanisms of radiomodification: oxygen effect, radioprotectors, repair inhibitors
- radiation-induced mutagenesis after accelerated charged particle exposure
- new concept of radiation risk for deep space flights: CNS damage
- radiation-induced catalysis of prebiotic compounds in astrobiology context

Interlaboratory cooperation



Dzhelepov Laboratory of Nuclear Problems

- Proton therapy of cancer
- Genetics
- Detectors and Tomography



Laboratory of Radiation Biology

- Fundamental Radiobiology
- Radiation Neuroscience
- Clinical Radiobiology
- Mathematical Modeling
- Radiation Research
- Astrobiology

Infrastructure for molecular, cellular and animal research



Veksler and Baldin Laboratory of HEP



- Heavy ion beamlines for space radiobiology, technologies for beam therapy



Frank Laboratory of Neutron Physics

- Analysis in the structural biology and pharmacology
- Ecology



Mecheryakov Lab. of Information Technologies

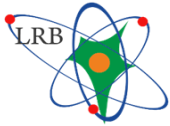
- High performance computing
- System for biological data storage and processing
- Bioinformatics, Machine Learning



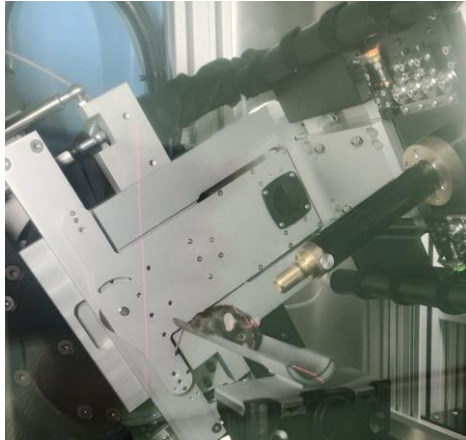
Flerov Laboratory of Nuclear Reactions

- Ion beams for cellular research
- Radionuclides synthesis for radiation medicine

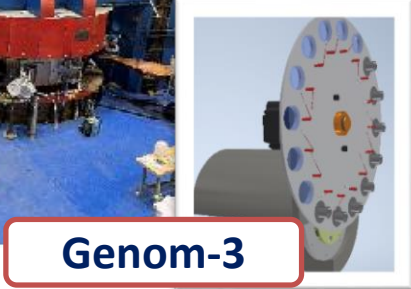
Research Infrastructure for the Irradiation of Biological Samples



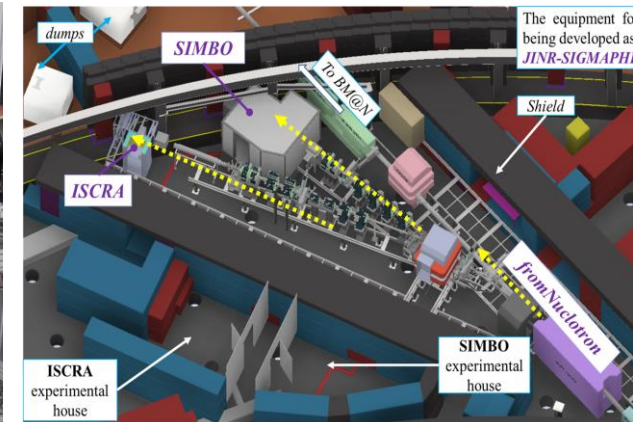
SARRP X-ray



U-400M cyclotron
Ions, Li – Ar, 50 MeV/u



Nuclotron
Ions (C, Ar, Fe, Kr) 0.3-1 GeV/u



Linac200
electrons 20-200 MeV



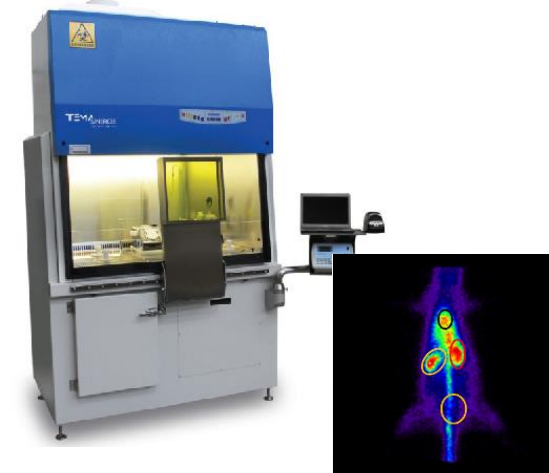
new MSC230 medical cyclotron
protons 230 MeV, **FLASH regime**



IBR-2, EG-5M neutrons



Radiopharmaceuticals



LRB Research Equipment



**Aberrior
confocal microscope
STED / FLIM**



**CYTEK Aurora CS
Cell Sorter | Flow Cytometer**

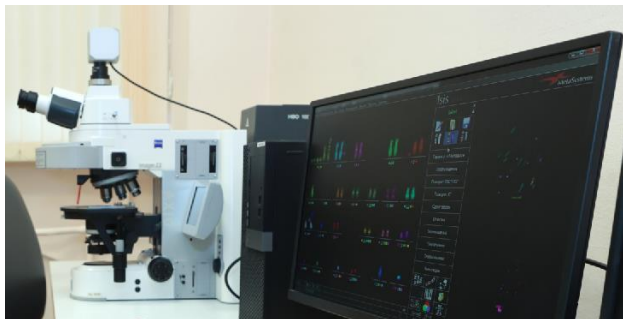


**SARRP (Small Animal Radiation
Research Platform)**



Kubtec Xcell 320

**METASYSTEMS
microscopy system for mFISH**



**AGILENT LC-MS
triple quadrupole**

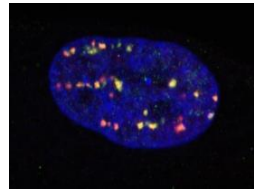


Scanning Electron Microscope

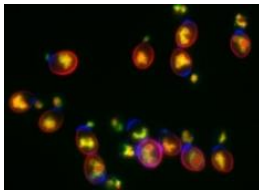
**Vivarium (up to SPF grade cages)
Tomography Units**



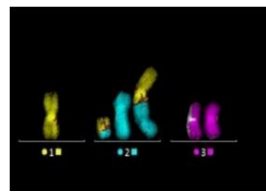
Strategy of Scientific Research



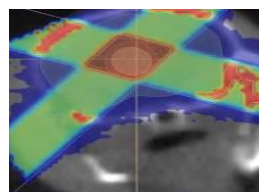
Molecular Radiobiology



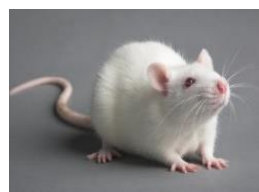
Radiation Genetics



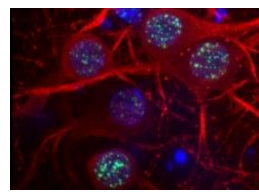
Radiation Cytogenetics



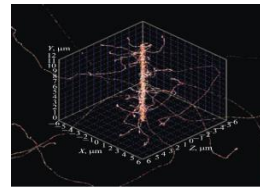
Clinical Radiobiology



Radiation Physiology



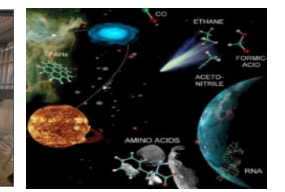
Radiation Neuroscience



Mathematical Modeling



Radiation Research



Astrobiology

Fundamental Research

Radiation Medicine

Radiation Risks

Radiation Factors

Biological Pathways

Space Radiobiology

X-ray therapy

proton and ion therapy

neutron-capture therapy

radionuclide therapy

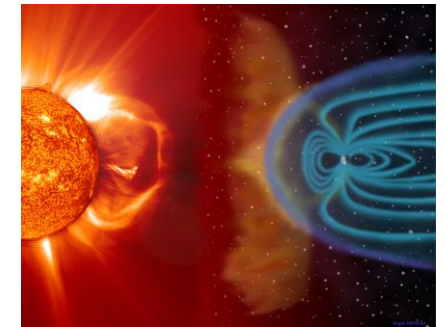
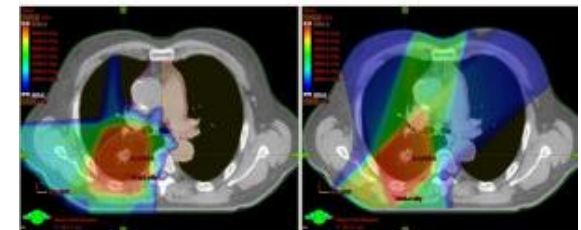
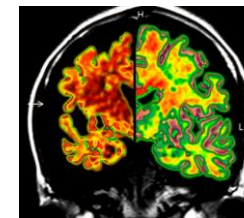
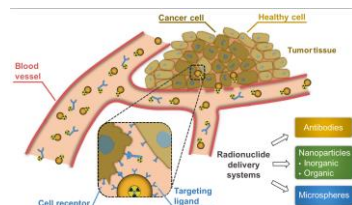
Radiosensitizers

Radioprotectors

Targeted drug delivery

Side Effects of Radiotherapy

Radiation Neuroscience



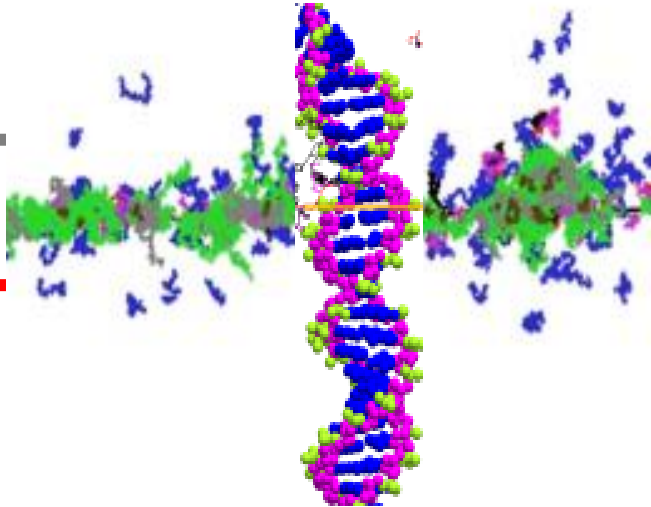
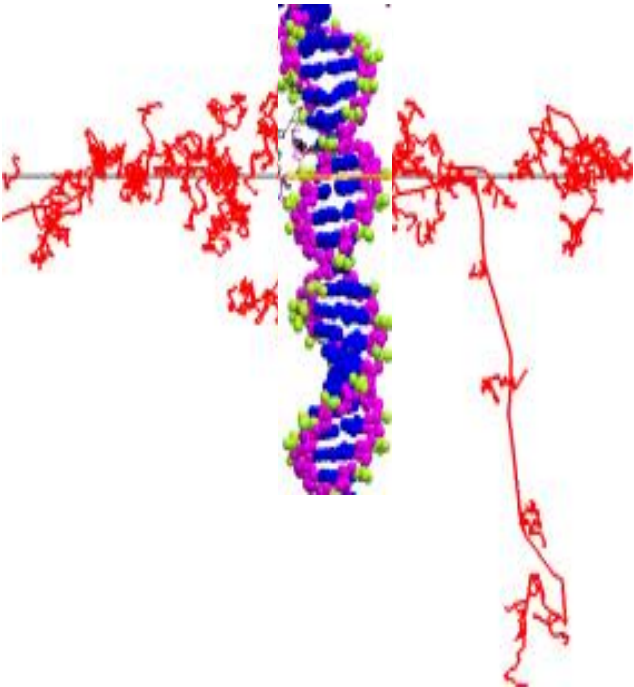
Biological efficiency of ionizing radiations

Molecular basis

Ionization, bond breakage

Radical attack, indirect lesion

DNA lesions



- e_{aq}^-
- $\cdot OH$
- H_3O^+
- H^\cdot
- OH^-
- H_2
- H_2O_2



Double strand break (DSB)

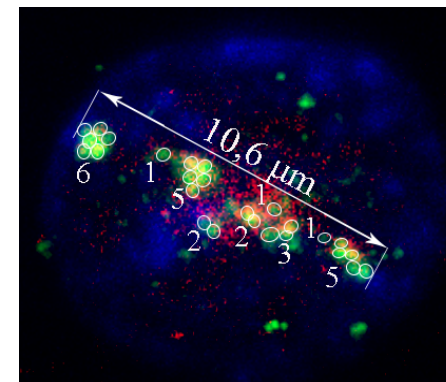
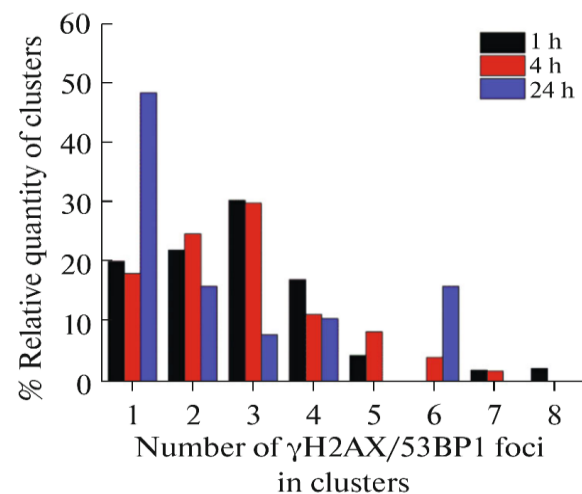
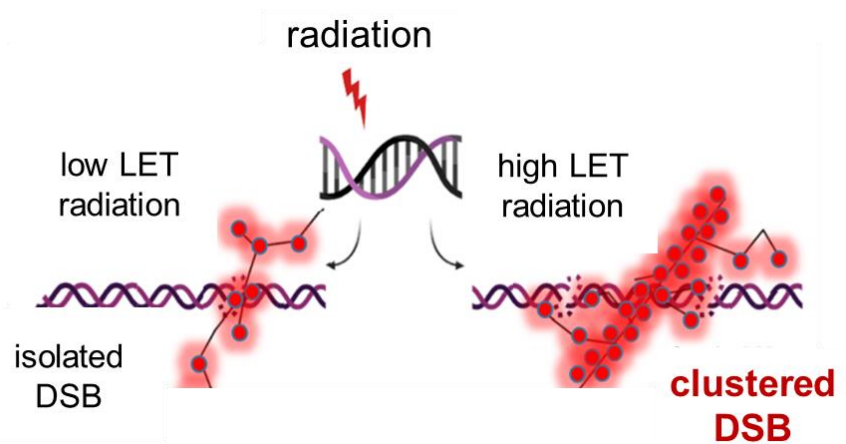
Single strand break (SSB)

Base damage (BD)

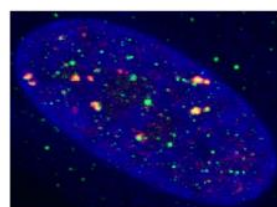
Apoptosis, chromosome aberrations, mitotic catastrophe, cell death

Molecular Radiobiology

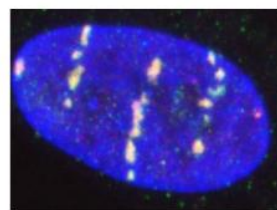
- Induction and repair of radiation-induced clustered DNA damage in normal, tumor and neural cells



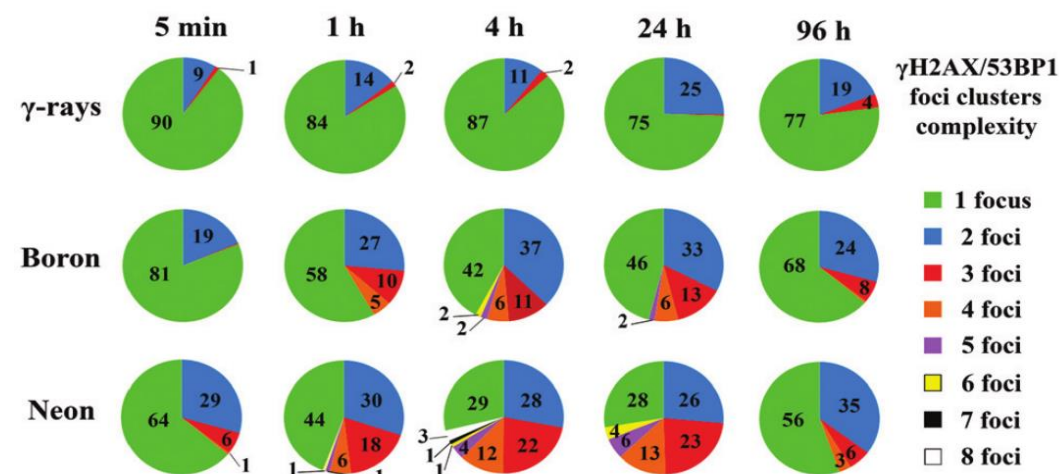
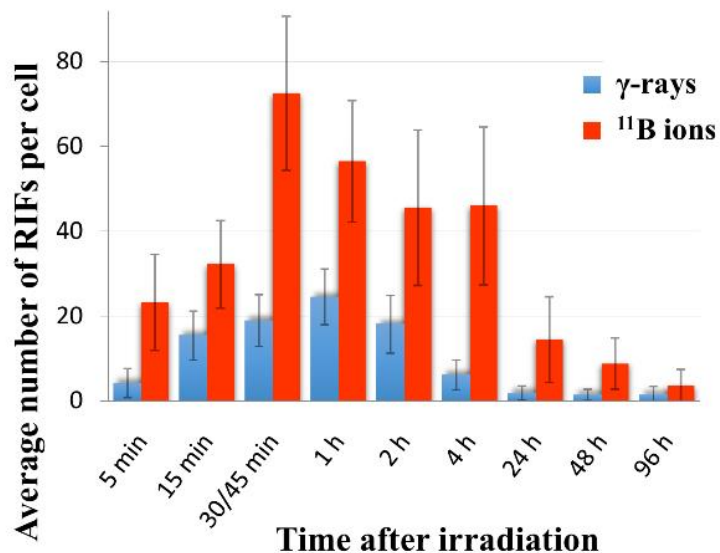
DNA damage in the rat hippocampus cells 1 hour after exposure to ^{78}Kr ion beam



γ -rays

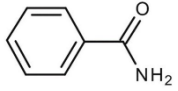


^{11}B ions

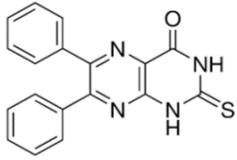


Molecular Radiobiology

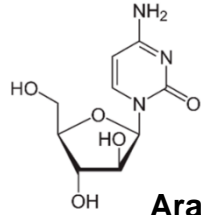
➤ Molecular and cellular mechanisms of radiomodification



Benzamide
PARP1 inhibitor

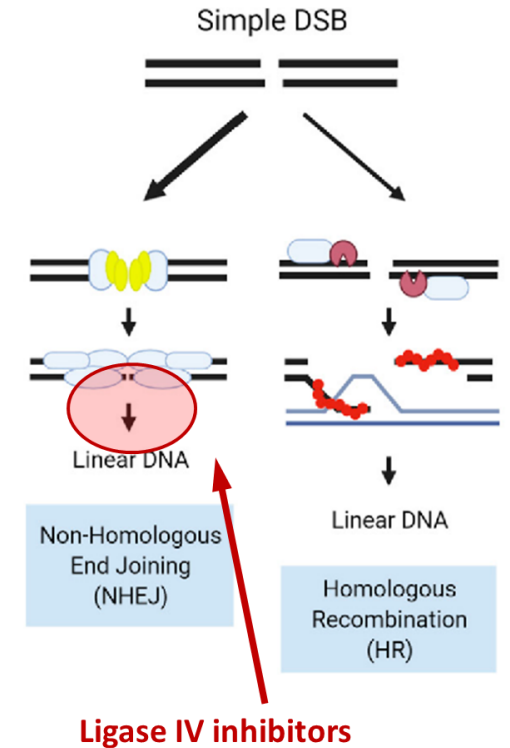
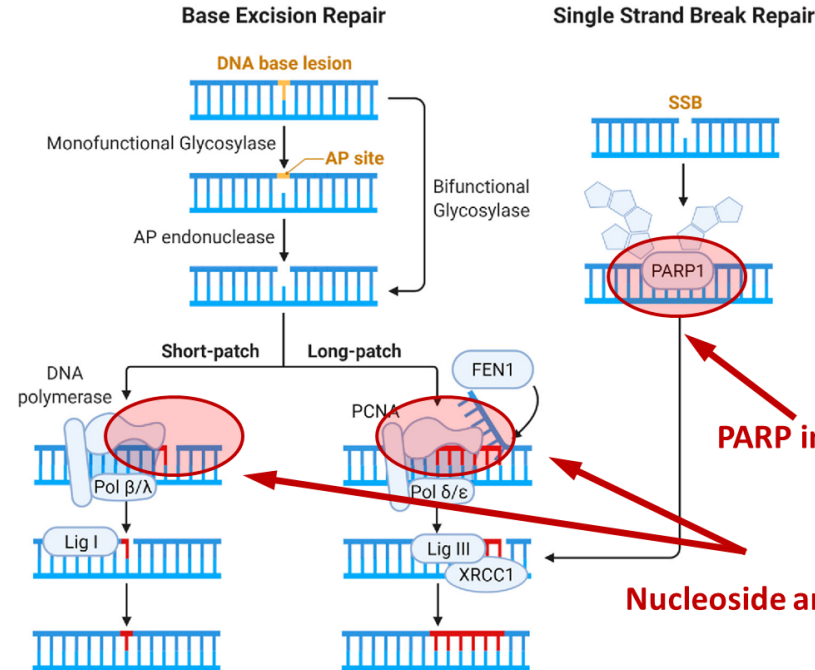
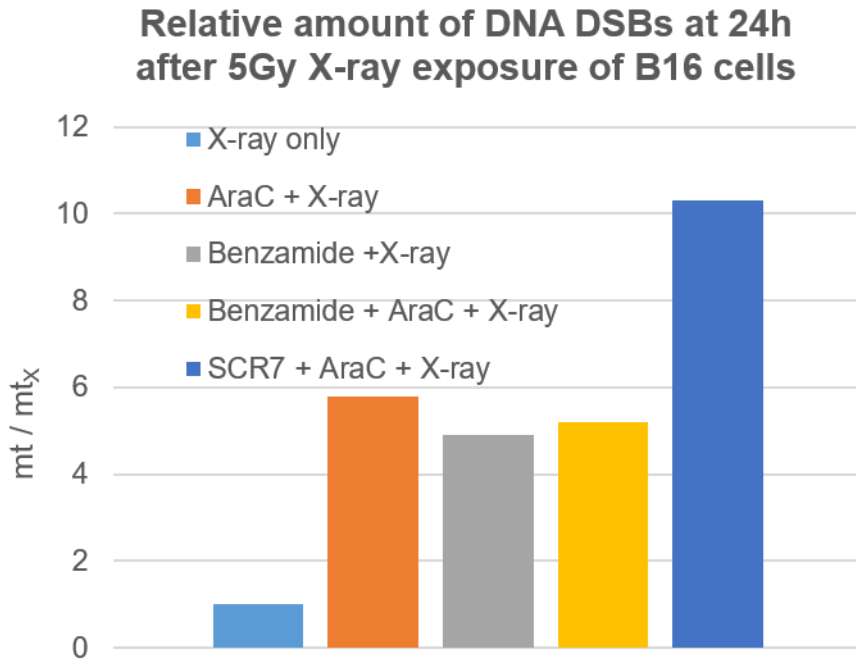
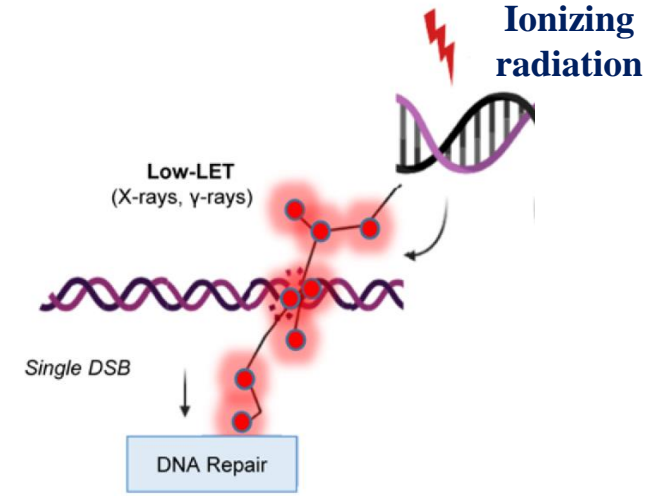


SCR7 pyrazine
ligase IV inhibitor



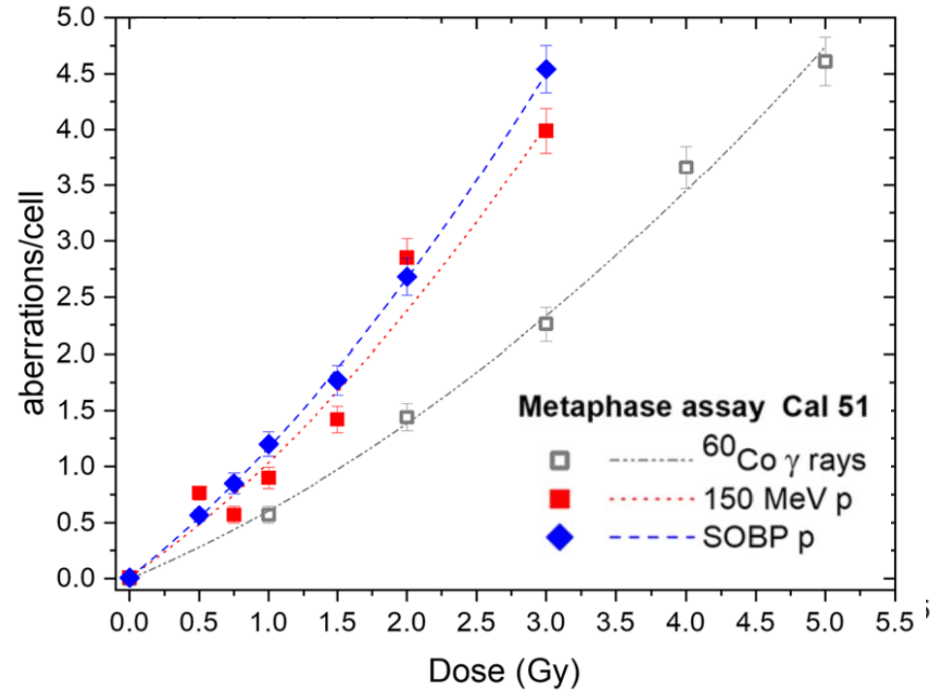
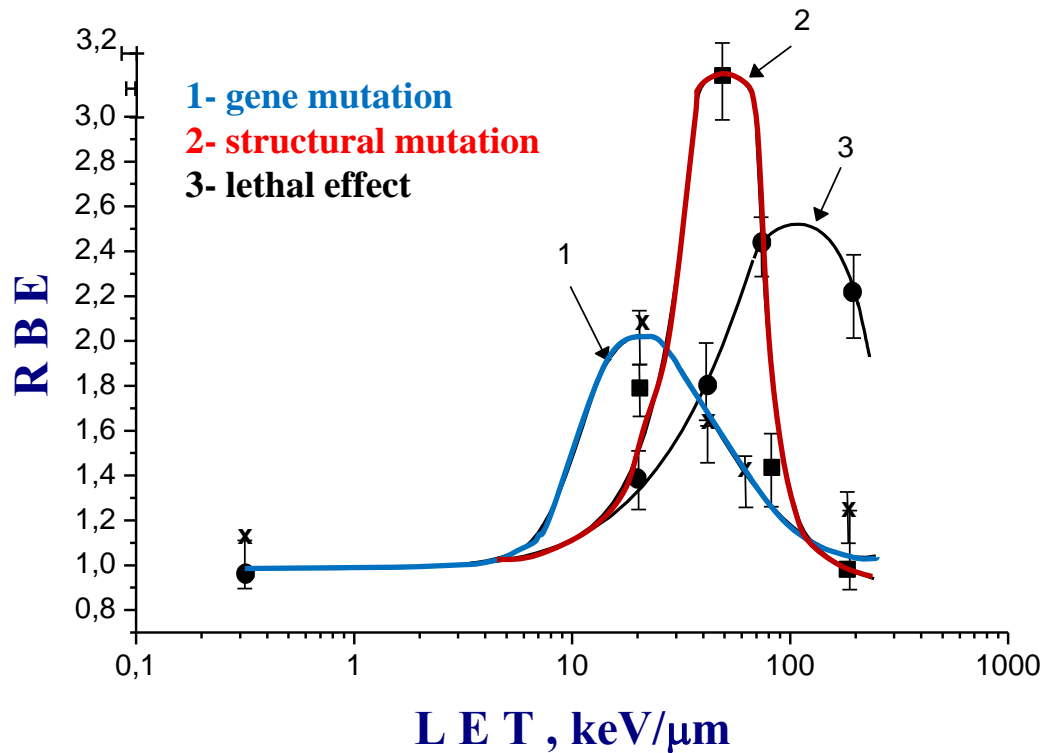
AraC
nucleoside analog

Comparison of molecular radiomodifier complexes



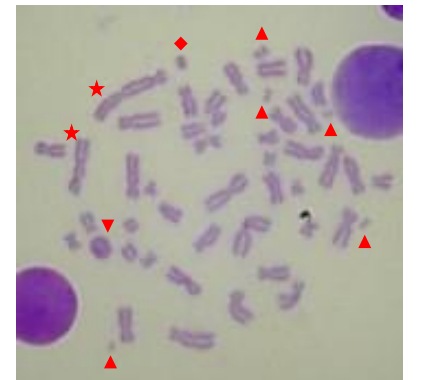
Radiation Genetics

- Evaluation of **complex chromosome aberrations** in normal and tumor cells
- **Long-term effects** of ionizing radiations with different characteristics

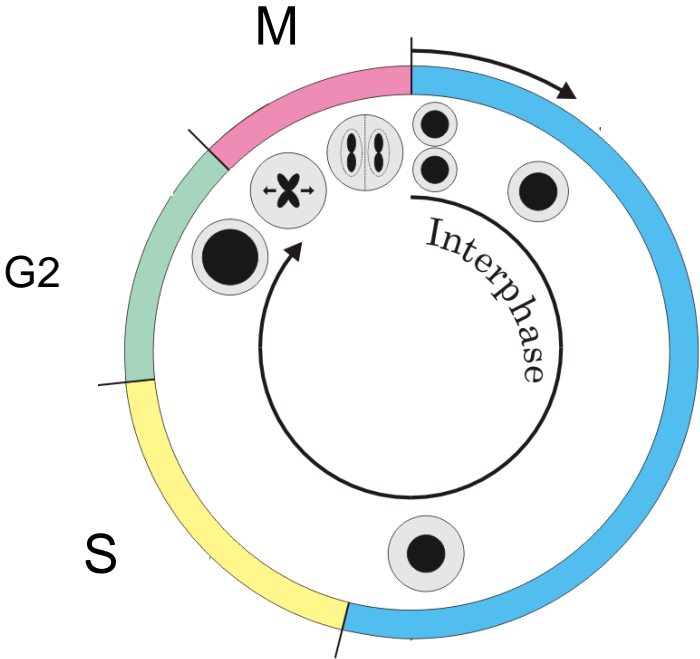


Dose dependence of mean number of chromosome aberrations per cell induced by gamma-rays and protons

(SOBP – spread out Bragg peak)

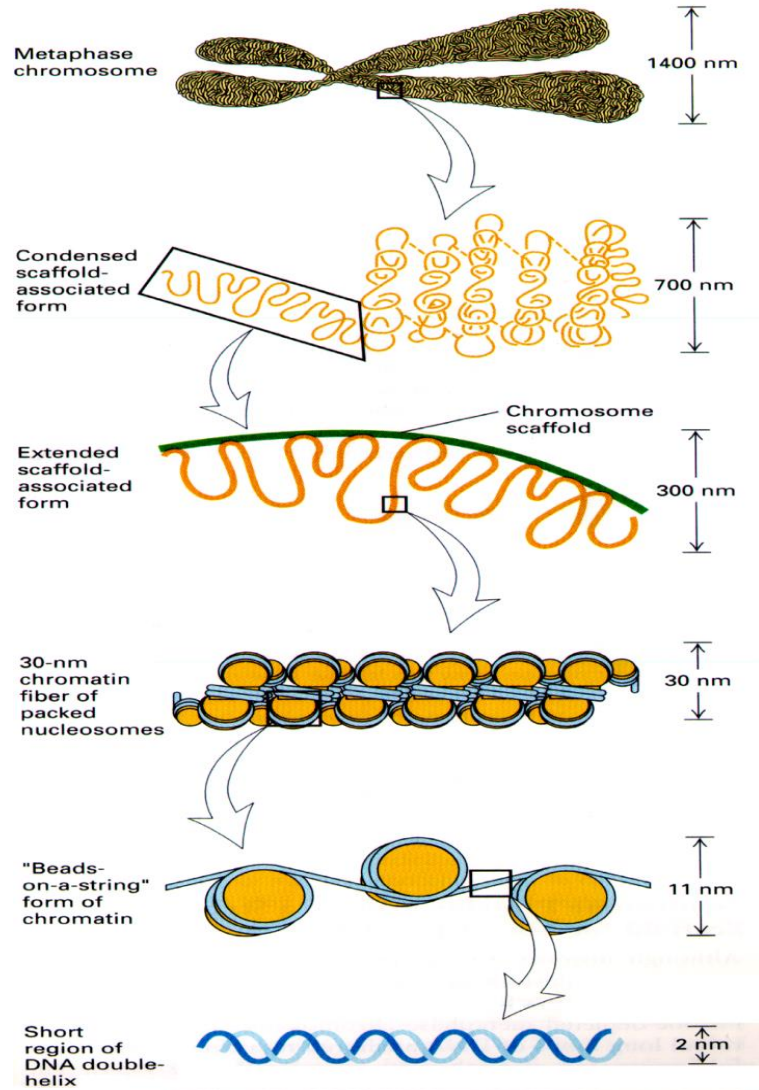
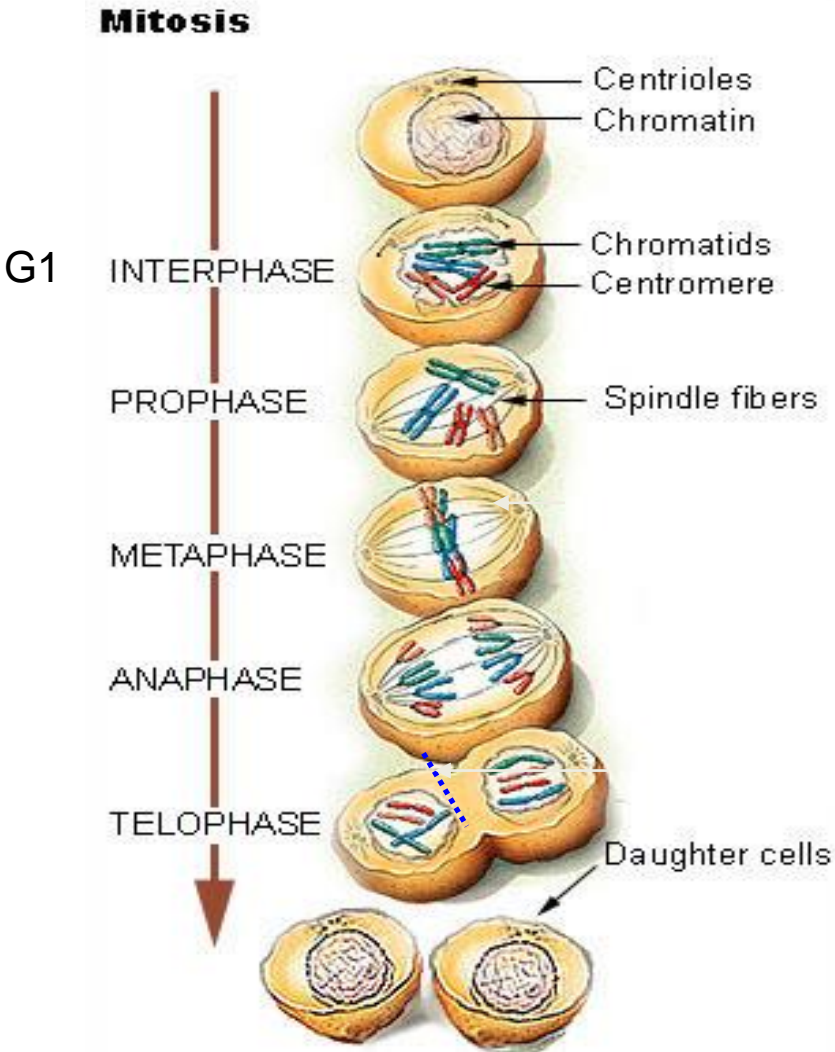


What is chromosome?

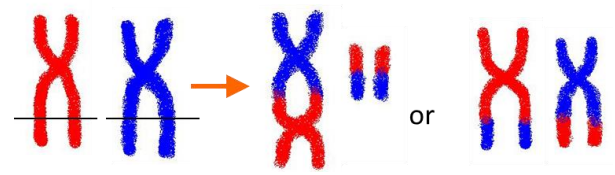


Mitotic cell

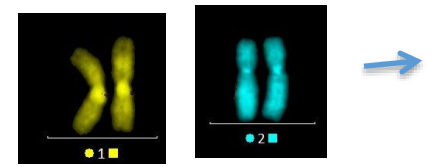
Interphase cells



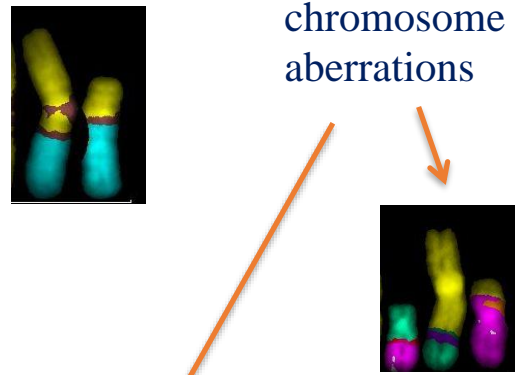
Cytogenetic evaluation of Relative Biological Efficiency (RBE) and long-term effects



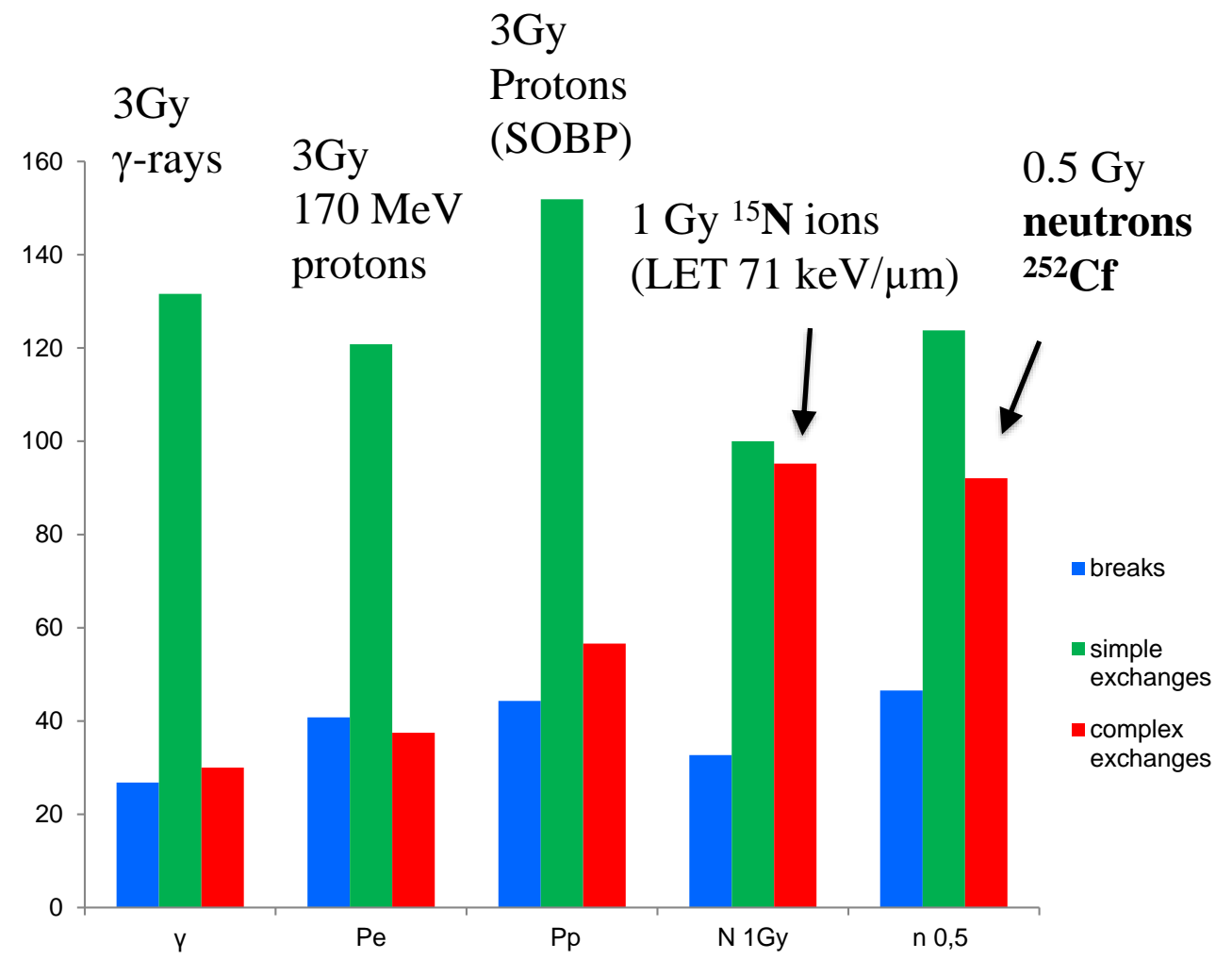
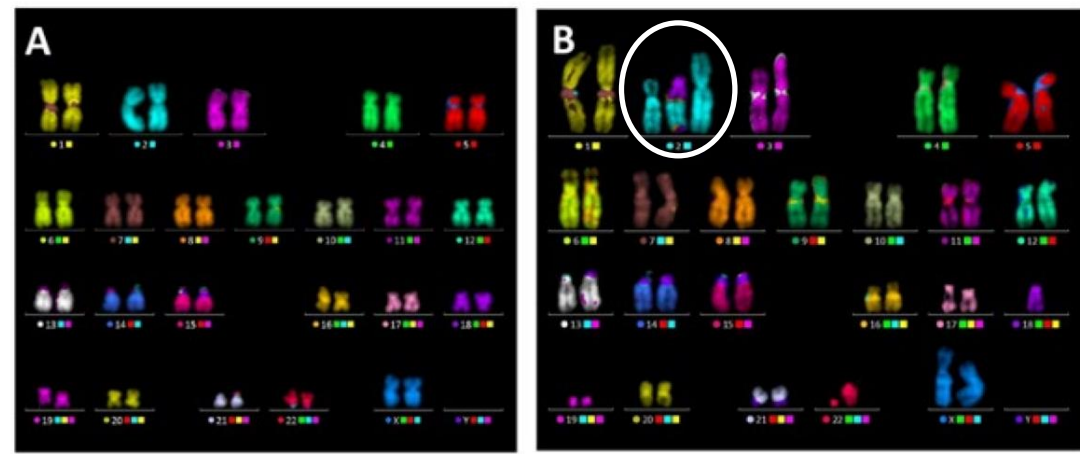
Example of simple chromosome aberrations



Complex chromosome aberrations



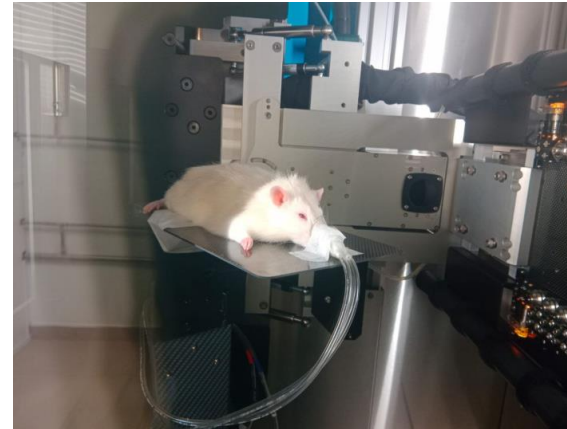
Normal karyogram



Level of complex chromosome aberrations induced by gamma-rays, protons, heavy ions and neutrons

Radiation Physiology

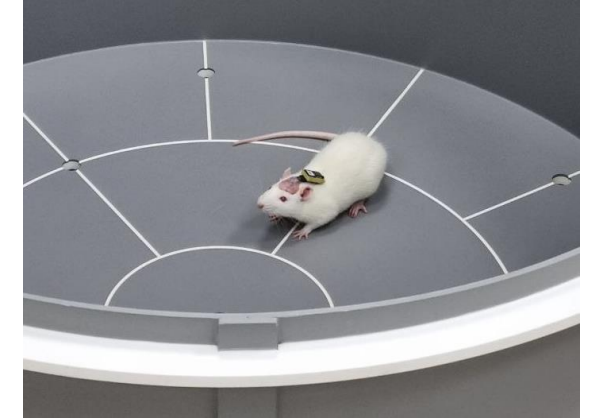
- Studies of behavioral disorders and pathomorphological changes in irradiated animals under normal conditions and under the influence of radioprotectors



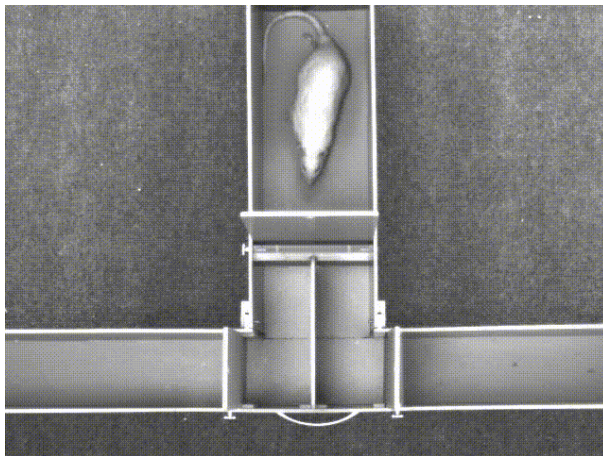
Animal irradiation



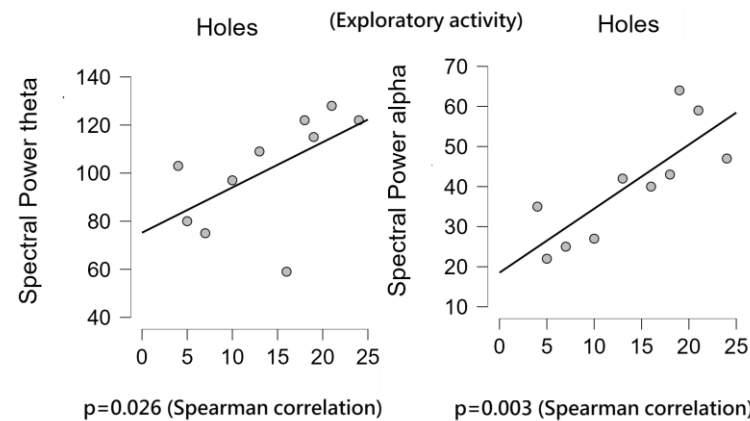
Treatment planning



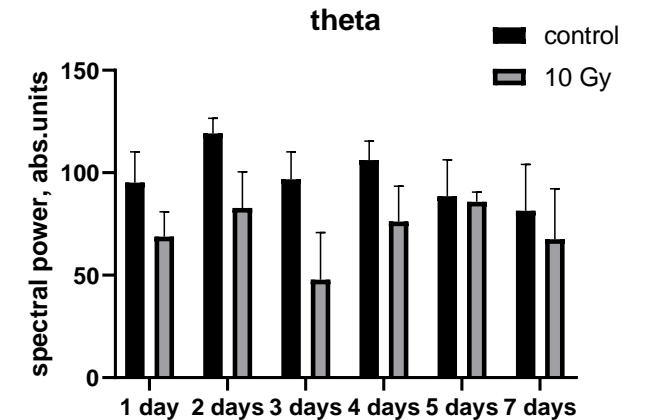
Behavior analysis



Behavior Test Systems



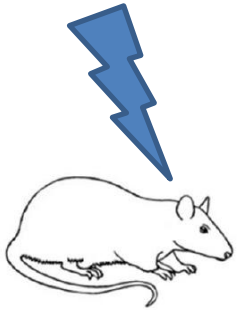
Correlation of behavioral disorders and electrical rhythms of the brain (EEG)



Radiation Physiology

➤ Research into the mechanisms of radiation-induced neurodegeneration and the development of brain diseases

Irradiation



Dose: 1 Gy
LET: 0.2 keV/μm (gamma ray)
0.5 keV/μm (170 MeV protons)
1 keV/μm (70 MeV protons)

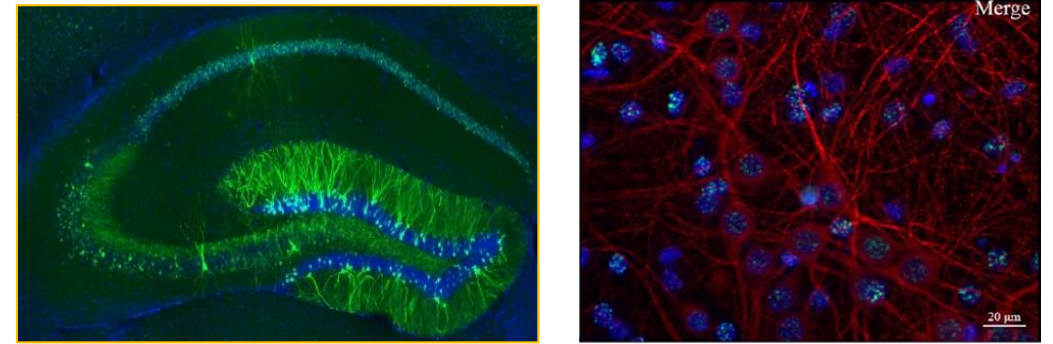
↓ *after 1 month*

Behavioral reactions:

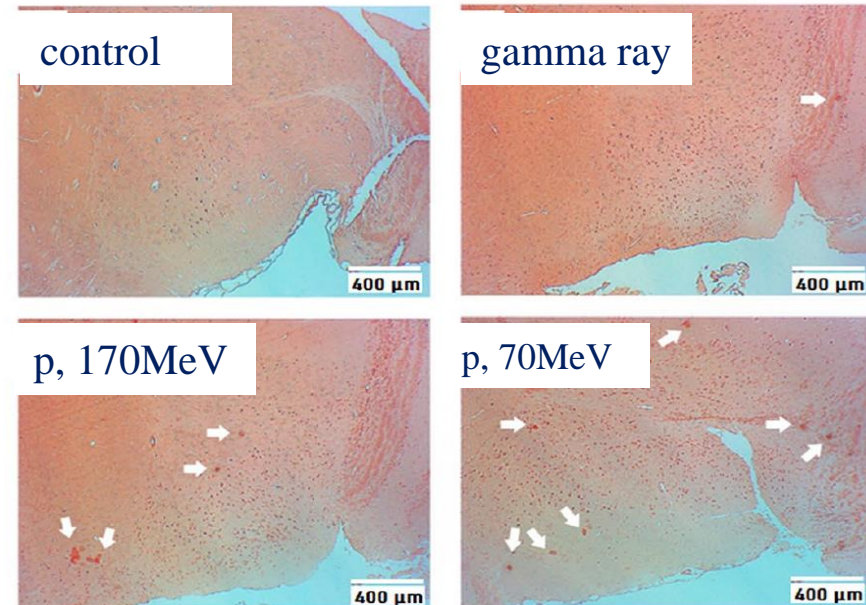
- impaired short-term memory
- decrease in overall motor activity
- decrease in exploratory behavior

Morphological changes in the brain:

- early amyloidosis
- autolysis of the ependymal layer
- neuronal hypertrophy
- increased dystrophic changes



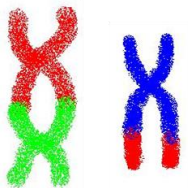
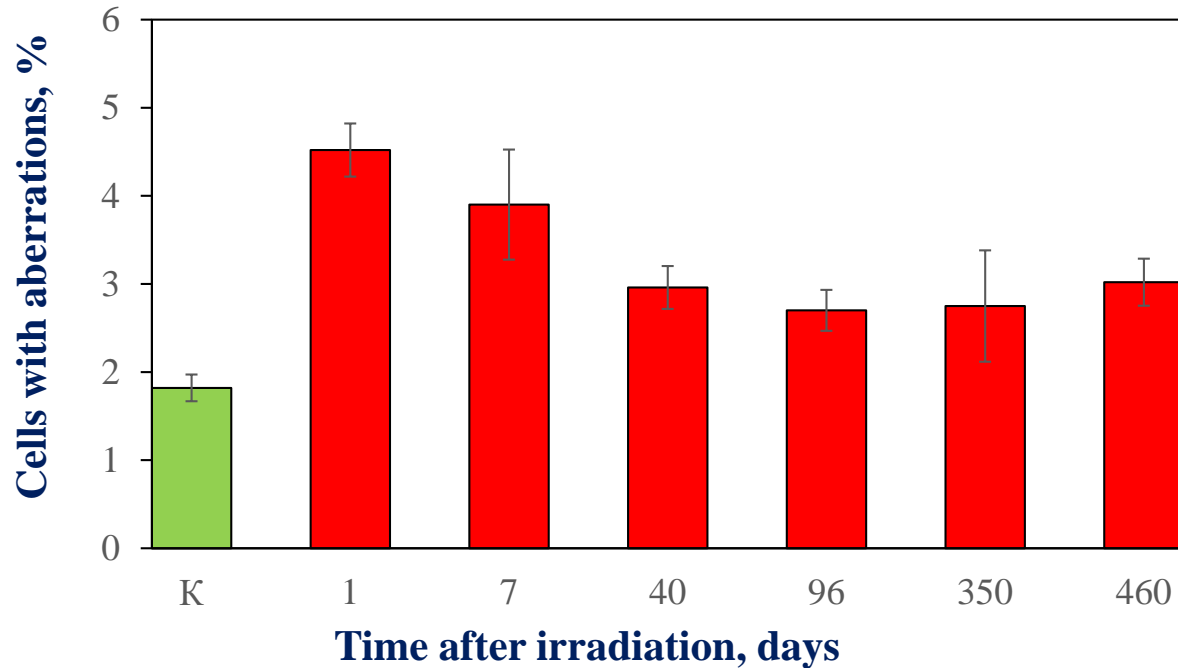
Visualization of cell viability in a hippocampal slice (right) and DNA damage in a hippocampal cell culture (left)



Amyloid plaques in the forebrain of rats (marked with white arrows)

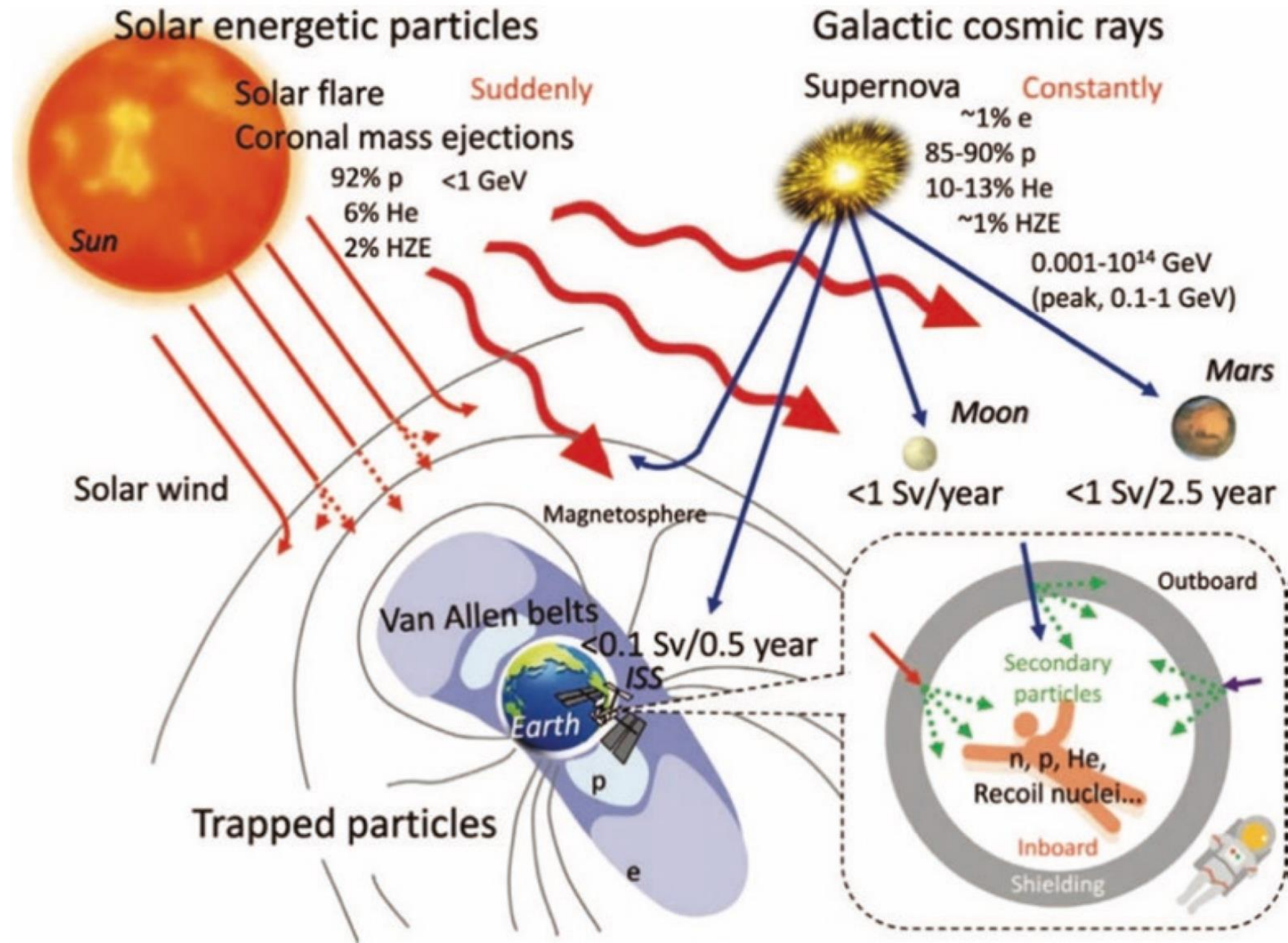
Radiation Physiology

Long-term cytogenetic, neurochemical and behavioral disorders in monkeys after brain irradiation with accelerated heavy ions



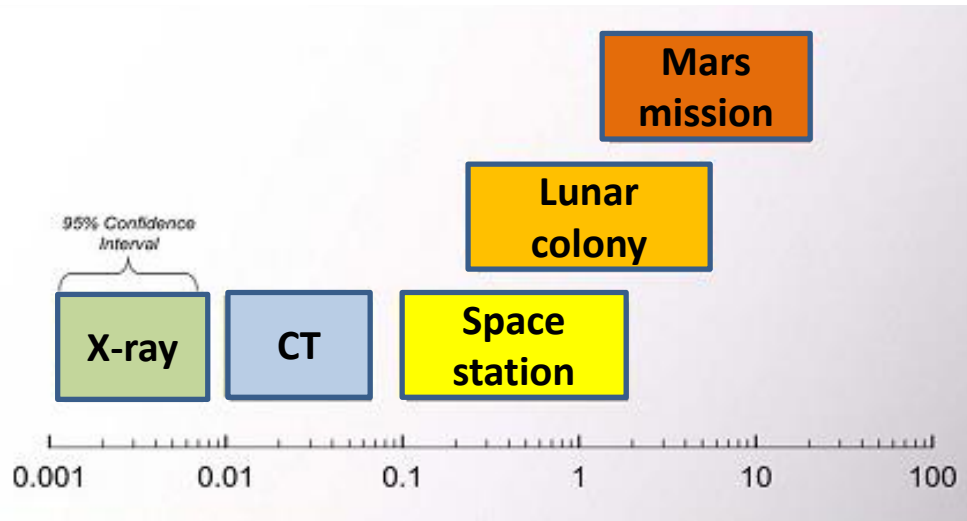
The level of chromosomal aberrations in peripheral blood lymphocytes of monkeys subjected to local action of accelerated krypton ions with an energy of 2.6 GeV/nucleon at a dose of 3 Gy at different periods of observation.

In the long term after irradiation of *certain areas of the brain of monkeys* (the hippocampus), most of the irradiated monkeys developed stable deviations from the standard behavior of animals which **persisted for 5 years** of the study.



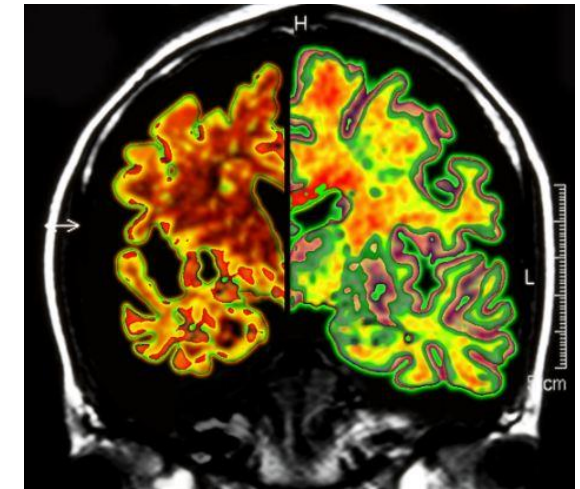
New concept of radiation risk for deep space flights: Damage to the central nervous system (CNS)

*Grygoriev, Krasavin, Ostrovskii,
Bulletin of RAS 2017*



% Risk of cancer death

Paradigm shift



Radiation Neuroscience

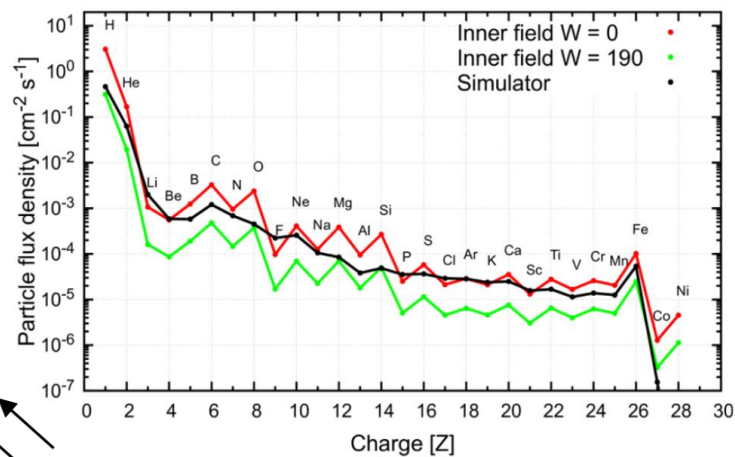
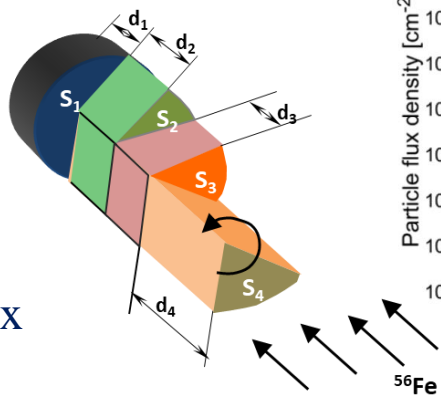
Radiation Research

➤ Modeling of mixed radiation fields

- *A new concept of accelerator-based simulator of mixed cosmic radiation fields* for NICA complex

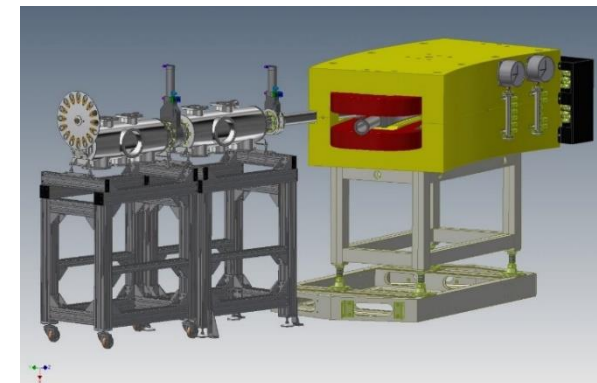
- Calculation and modeling of the radiation field inside a spacecraft outside the Earth's magnetosphere

➤ *Radiation protection at JINR* development of neutron dosimetry

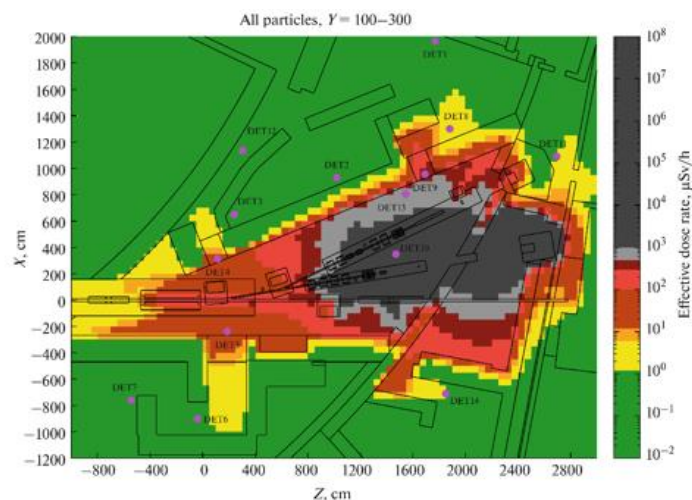
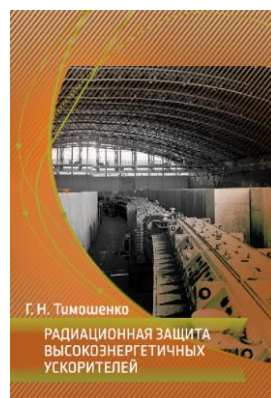
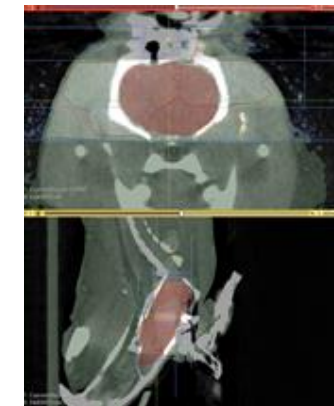


Comparison of measured and simulated galactic cosmic ray spectra

➤ Organization of irradiation of biological samples



➤ Implementation of new visualization and tomography systems

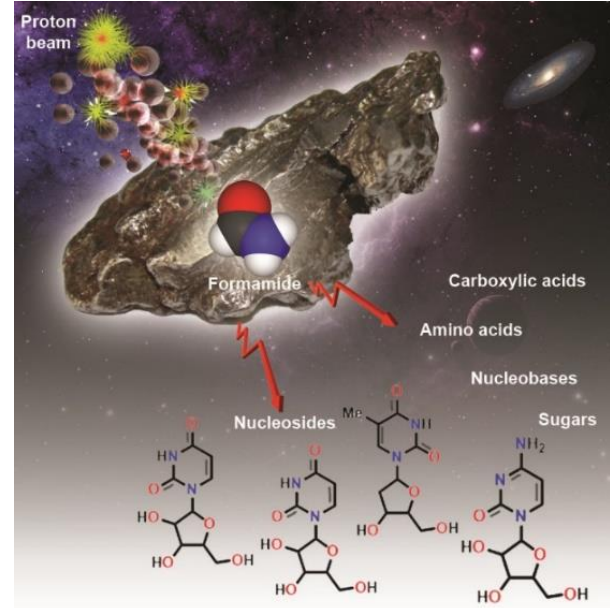
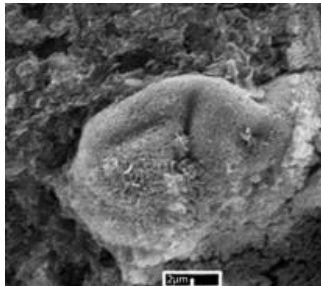


Modeling of radiation environment at NICA complex

Astrobiology

Discovery of mechanisms responsible for *prebiotic chemistry* in meteorites initiated by charged particle irradiation

The world's first illustrated atlas of fossilized microorganisms found in the Orgei meteorite using electron microscopy



A scheme of prebiotic synthesis



A prototype for simulation of prebiotic synthesis in comet matter



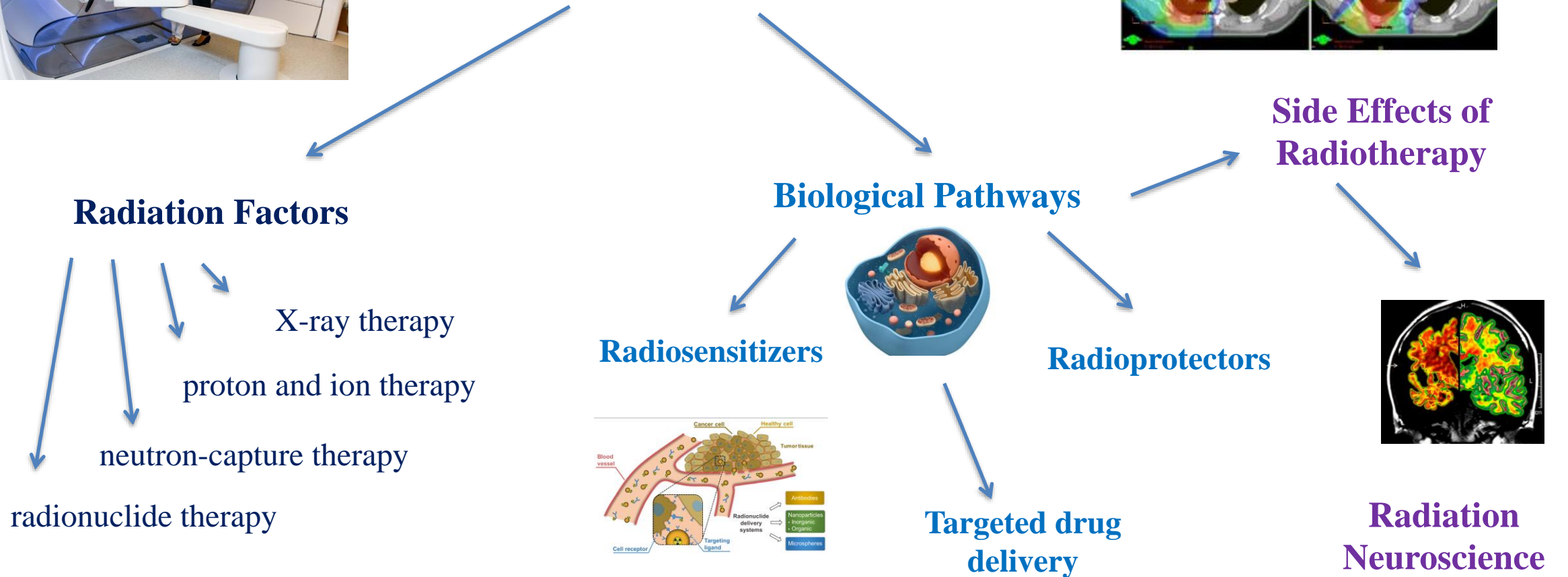
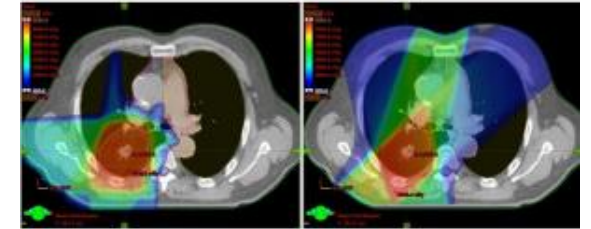
New book on Astrobiology



Atlas of microfossiles

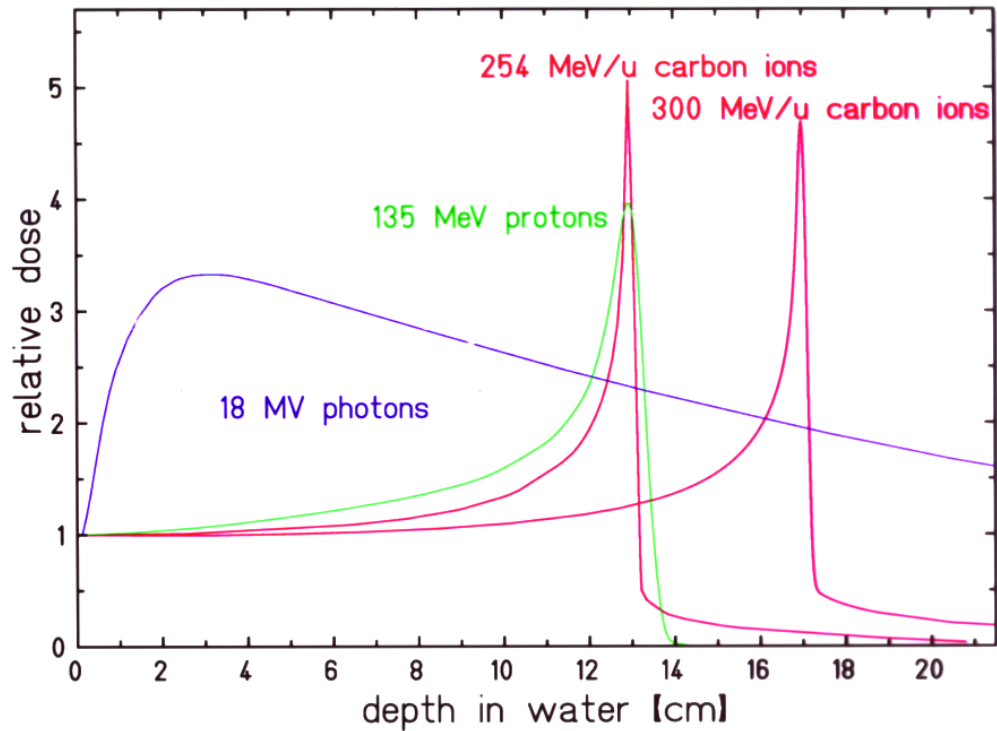
- Pathways of abiogenic **prebiotic synthesis after radiation exposure**
 - different radiations
 - deep insights into radiation catalysis mechanisms
 - special irradiation setups mimicking space conditions
- **Structural and elemental analysis** of microfossils and organic compounds in meteorites using nuclear physics methods

Radiobiology for Nuclear Medicine

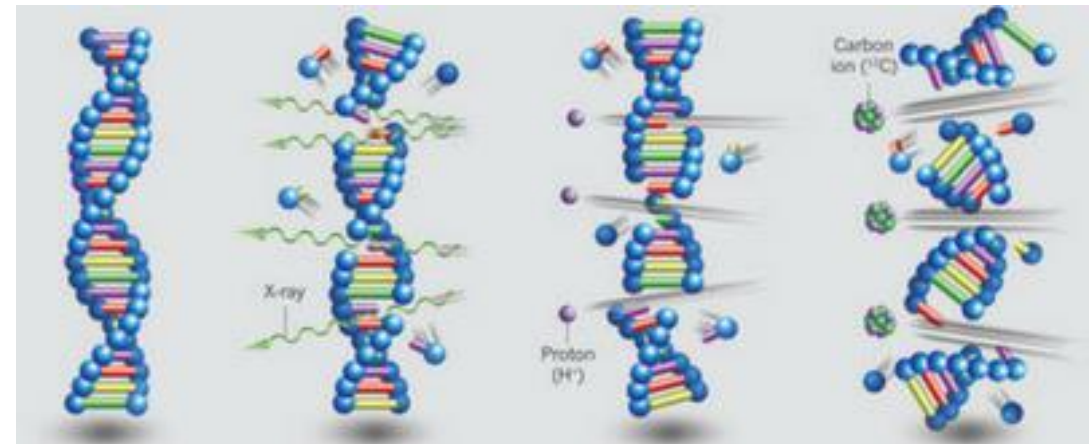


Principles of radiation therapy of cancer

1. Conformal irradiation



2. Biological effectiveness of radiation

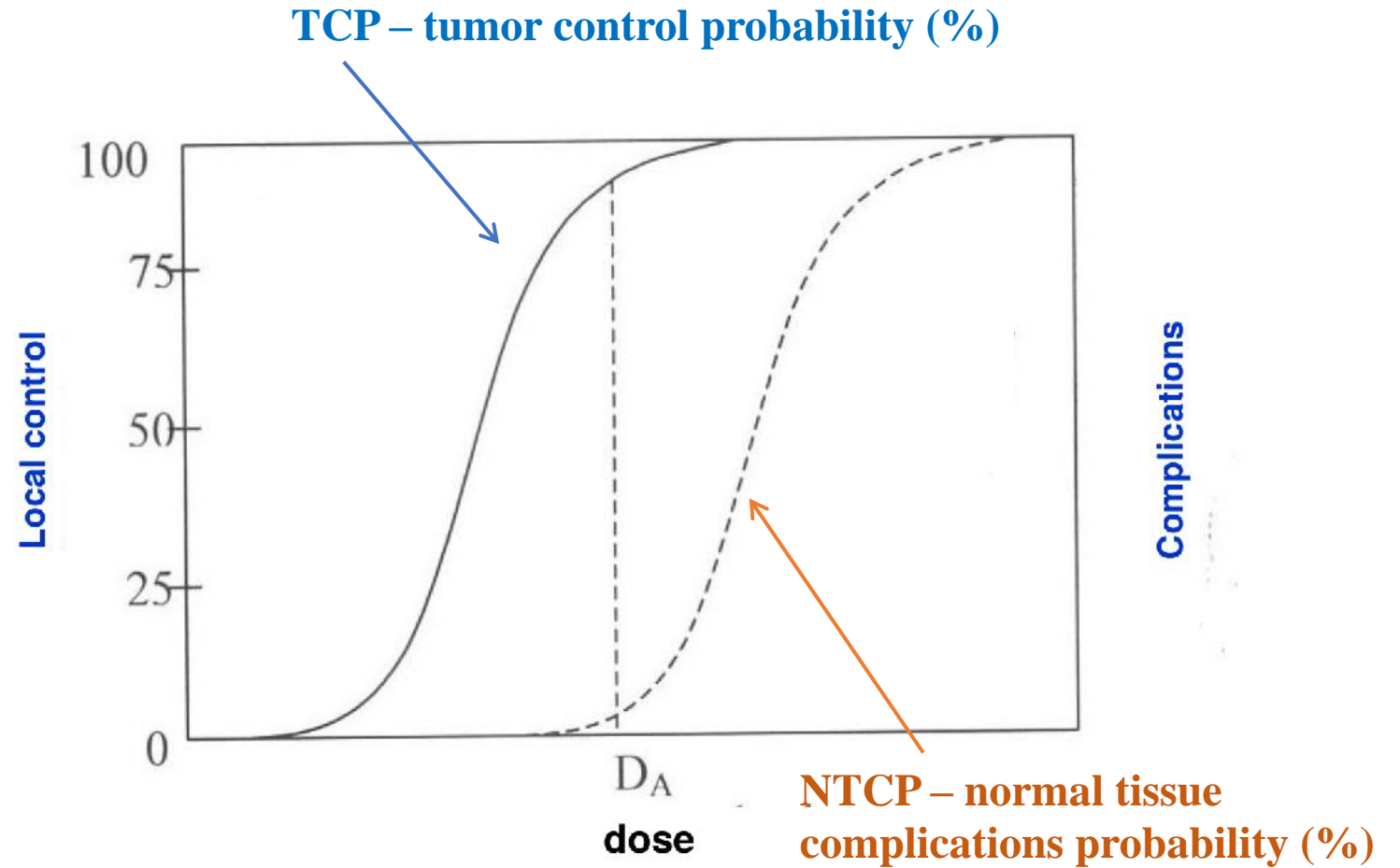
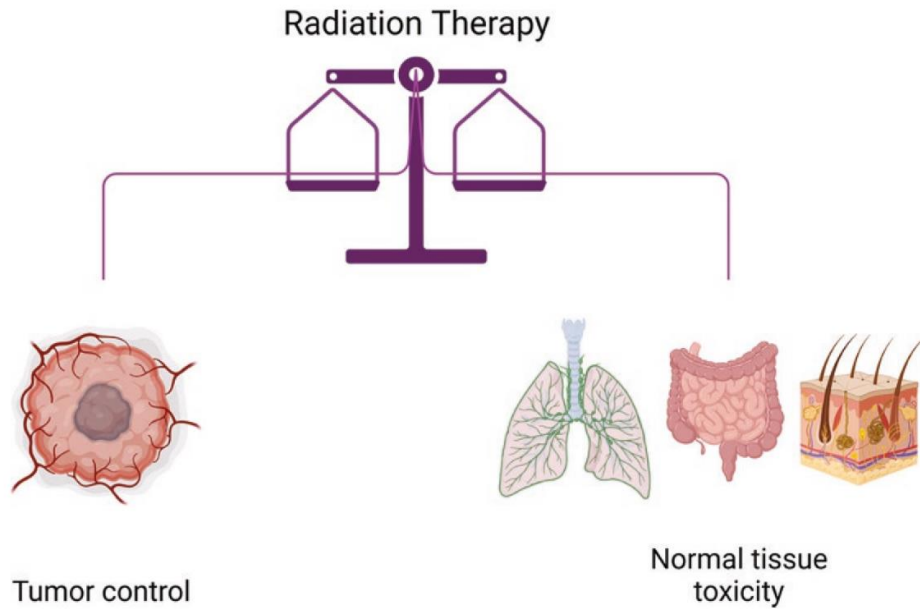


X-ray

protons

carbon ions

Treatment planning



Required dose in the treated volume – minimal dose to healthy tissue

JINR facility for preclinical research on X-ray 3D CRT

SARRP (Small Animal Radiation Research Platform)

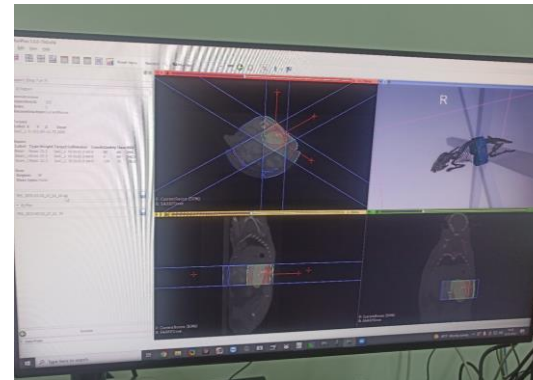


SARRP imitates modern X-ray radiation therapy systems for animal research



The 360° gantry and motorized stage allow for non-coplanar beam delivery from any angle.

Techniques utilizing planar static beams, parallel opposed beams, continuous arc therapies, multiple isocenter treatments, and non-planar arcs can all be planned, evaluated, and delivered with SARRP

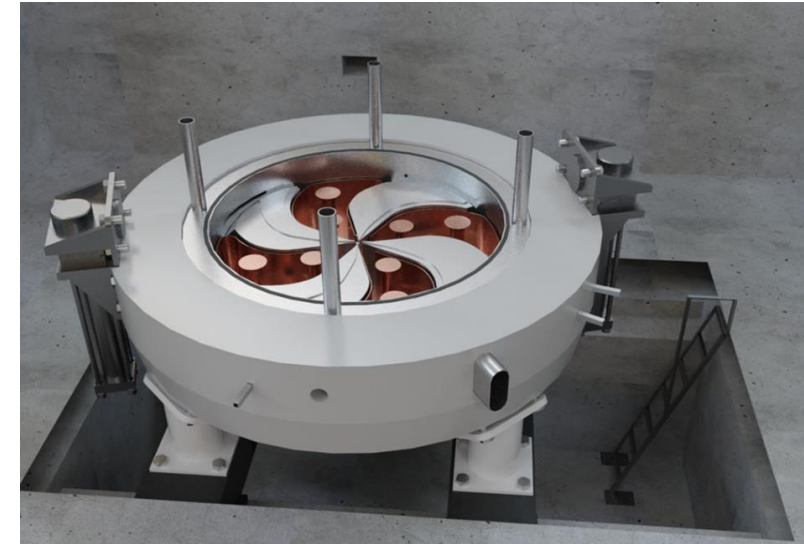
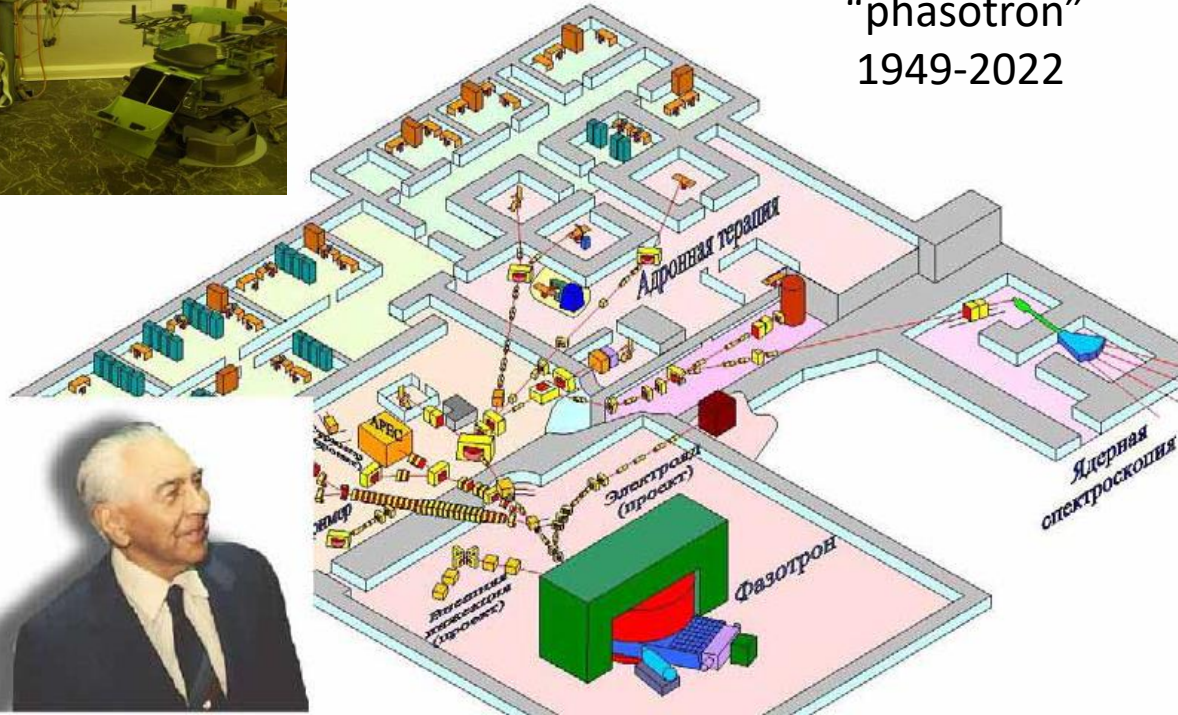


Experiments on mice tumor irradiation at SARRP

Proton therapy complex of JINR: past and future



Accelerator
“phasotron”
1949-2022



New superconducting medical proton cyclotron
MSC 230:

JINR Proton therapy center at Dzheleпов Laboratory of Nuclear Problems

First proton center in USSR, **1967**

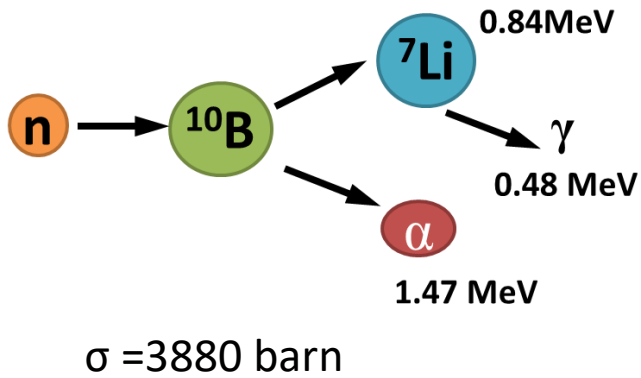
First 3D conformal treatment technique

More than 1300 patients treated (tumors of head and neck)

Compact, low power consumption
High current and dose rate suitable for FLASH regime (>40 Gy/s)

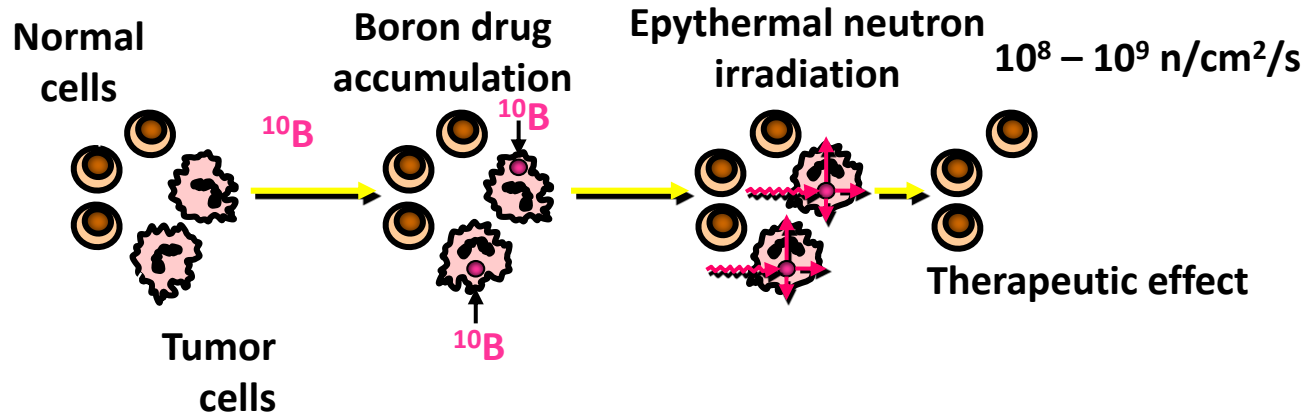
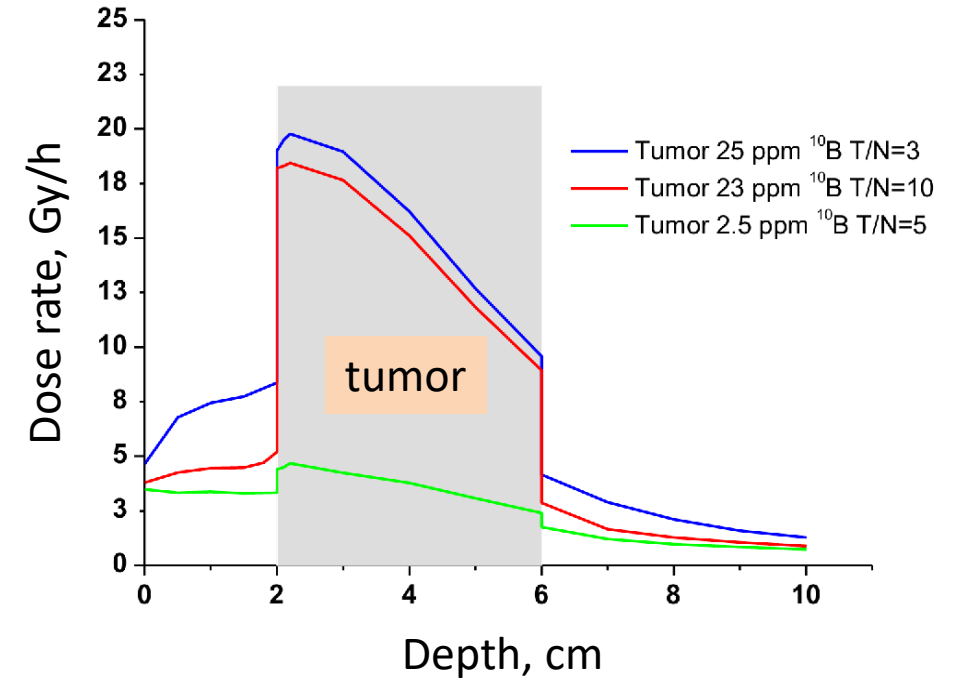
Neutron beams (towards neutron capture therapy)

neutron capture therapy



element	σ , barn
^{10}B	3880
H	0,332
O	0,27
N	0,075
C	0,0034

Dose deposition



^{10}B concentration in tumor	50 mkg/g
Ratio of ^{10}B concentration in tumor and normal tissue (T/N)	3

Radiopharmaceuticals

β -emitters

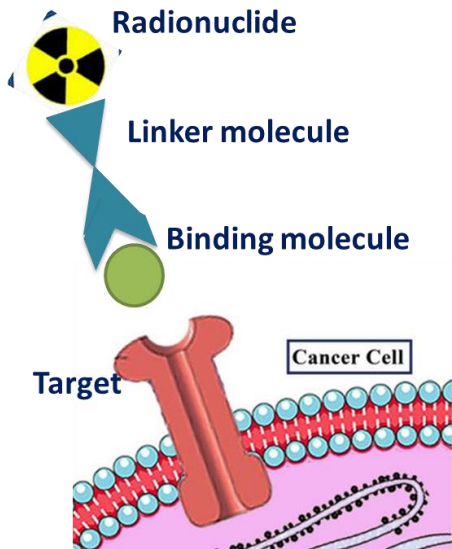
- + high variability, theranostic pairs
 - low RBE, low precision (long tracks)
- ^{99m}Tc , ^{177}Lu , ^{188}Re , ^{123}I , ^{47}Sc , ^{44}Sc , ^{67}Cu , ^{105}Rh

Auger-electron emitters

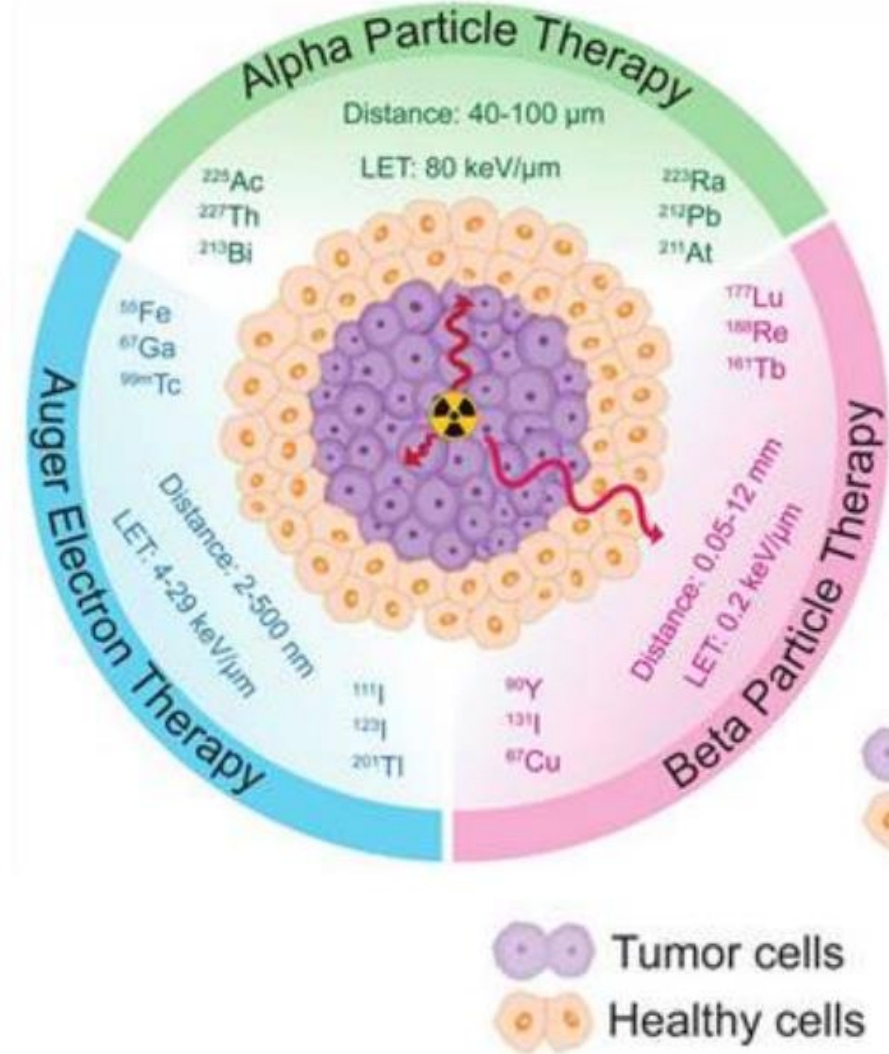
- + better RBE than β , high precision (short tracks)
 - not implemented
- ^{119}Sb , ^{195m}Pt , ^{239}Np , ^{111}In , ^{125}I , ^{67}Ga , ^{99m}Tc , ...

α -emitters

- + highest RBE, high precision
 - difficult to produce, difficult to visualize
- ^{225}Ac , ^{211}At , ^{253}Es , ^{223}Ra , $^{212/213}\text{Bi}$, ^{212}Pb , ^{149}Tb , ^{227}Th

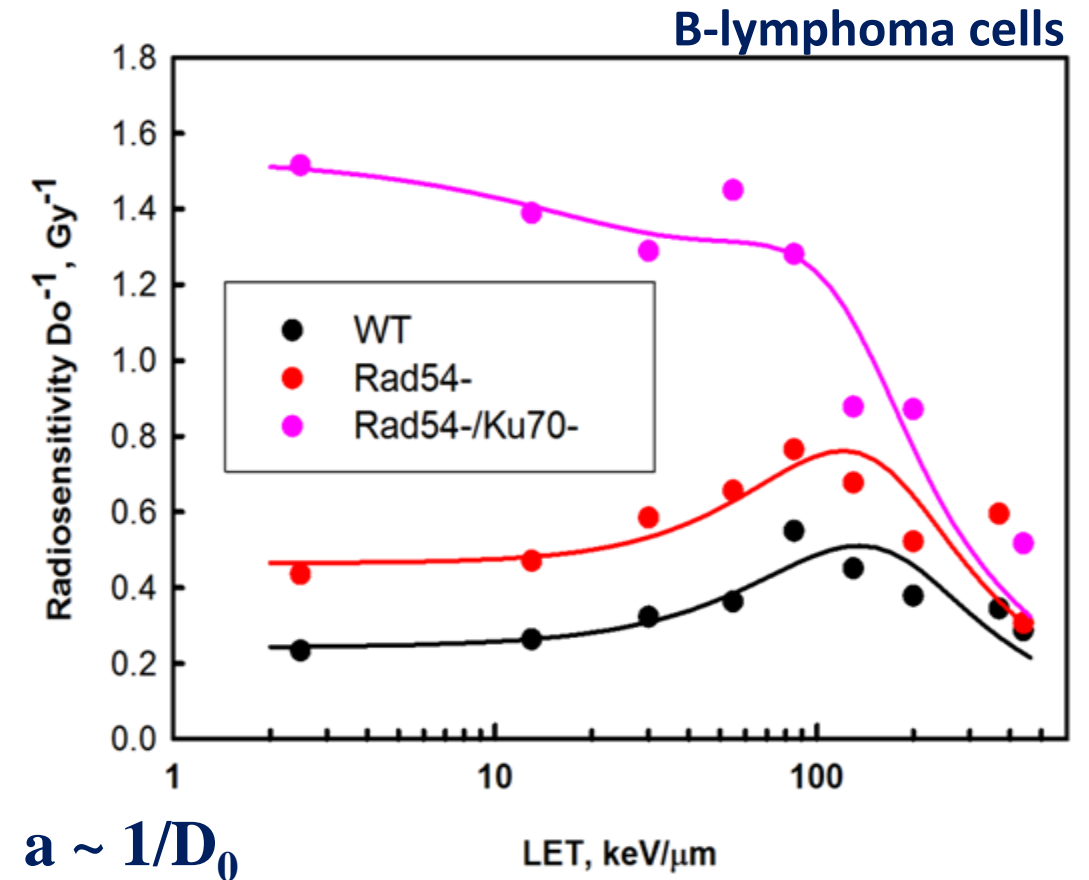
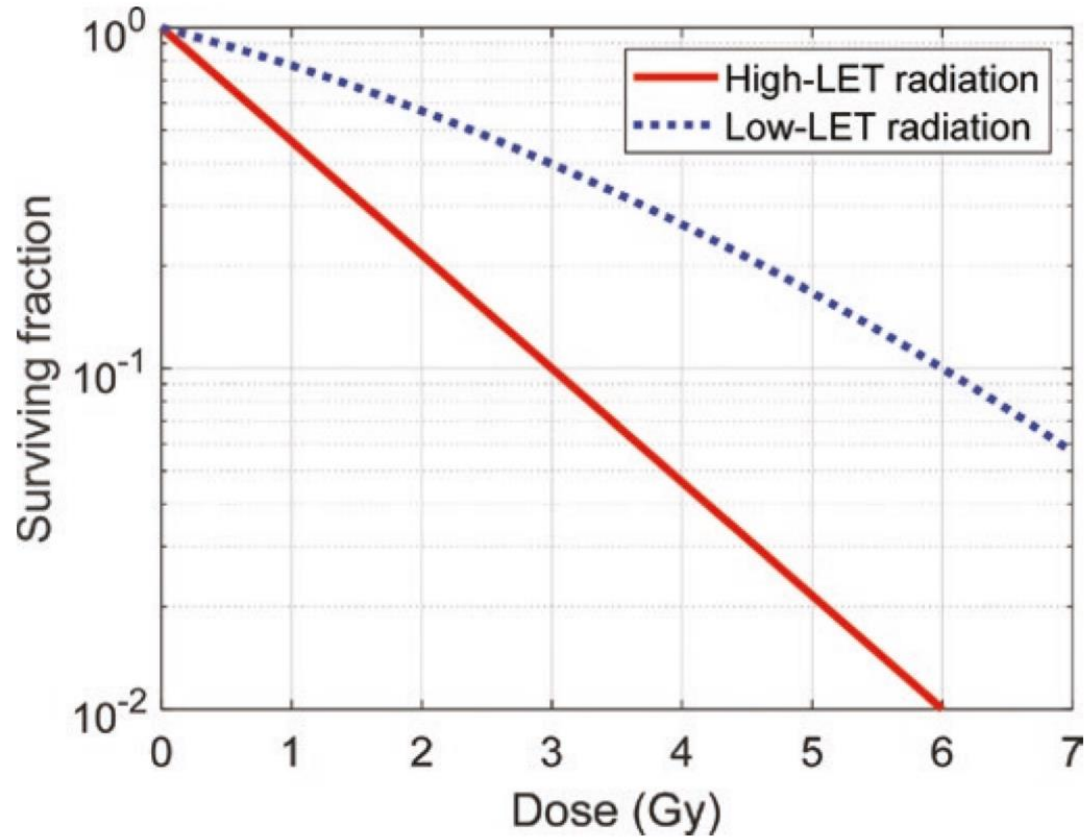


Radiopharmaceuticals for targeted therapy of cancer



Biological efficiency of ionizing radiations

Radiobiological basis



$$S = \exp[- aD - bD^2]$$

$$a_{\text{gamma}} < a_{\text{p, Bragg}} < a_{\text{ion, Bragg}}$$

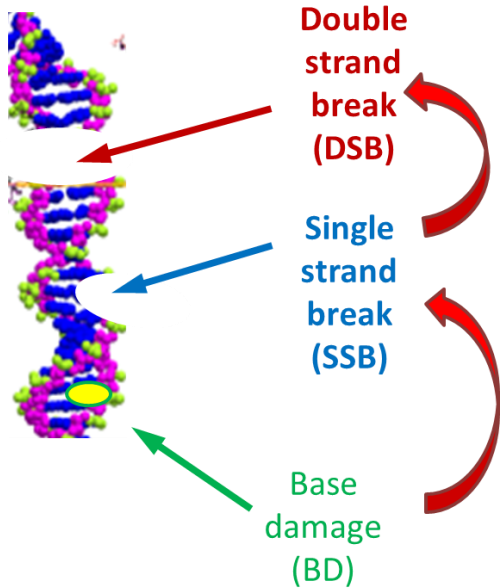
Radiosensitivity of tumor cells
can be modified

Data source: Furusawa 2013

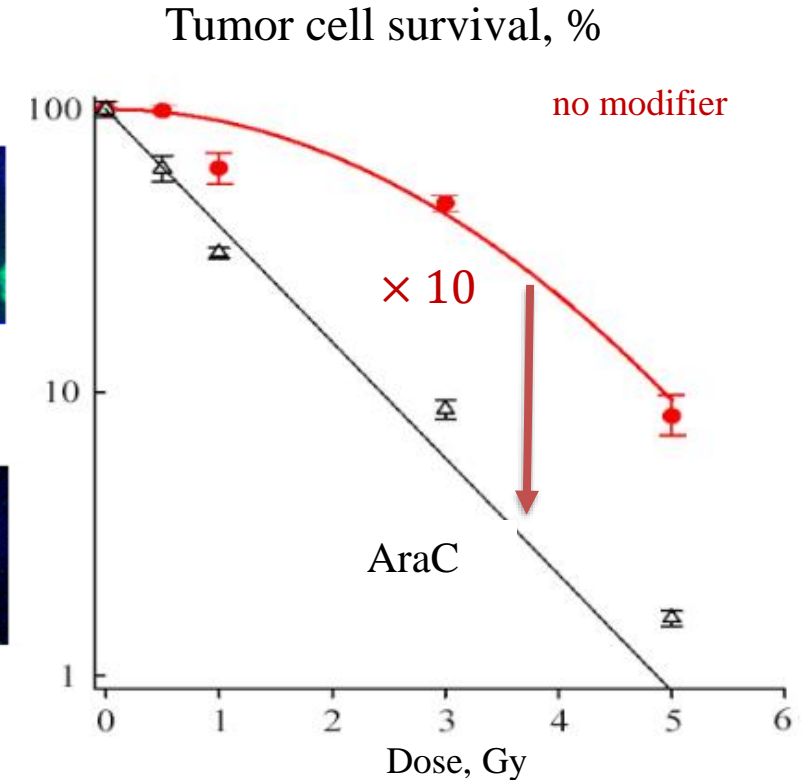
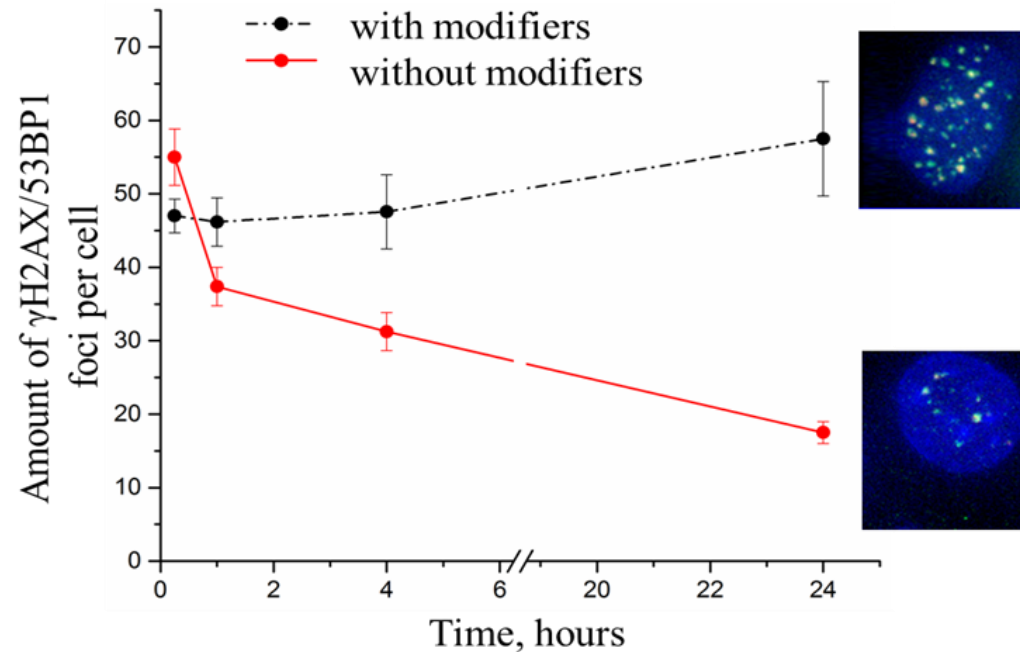
Clinical Radiobiology

- New approaches for increasing the efficiency of radiation therapy with molecular agents and complexes

1 DSB 10 SSB 100 BD
per unit dose



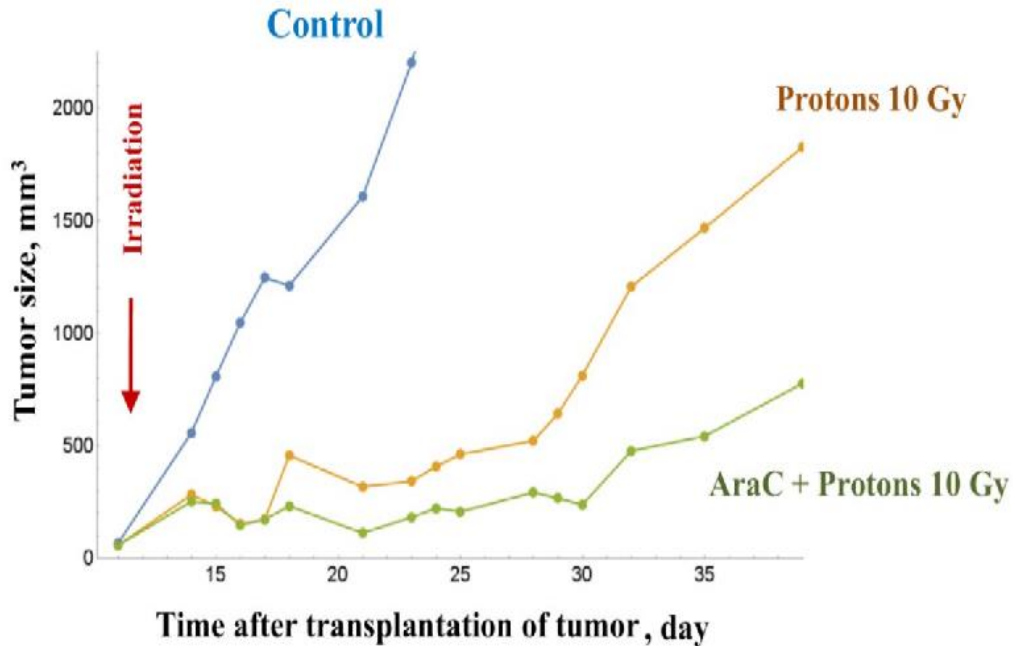
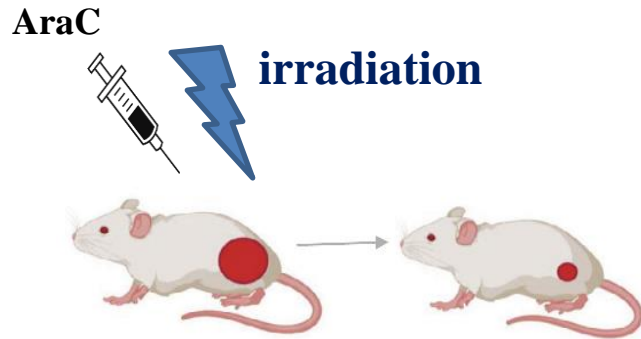
Glioblastoma tumor cells (U87)
irradiated by medical proton beam (1.25 Gy)



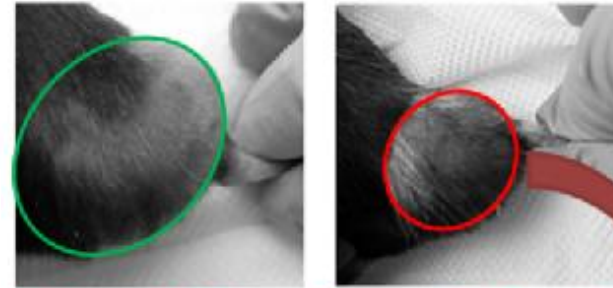
Clinical Radiobiology

- New approaches for increasing the efficiency of radiation therapy with molecular agents and complexes

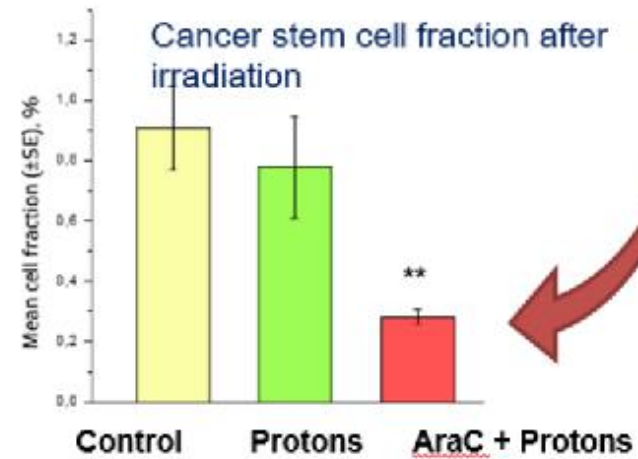
Patents No.
 2798733 (2023)
 2774032 (2022)
 2699670 (2019)



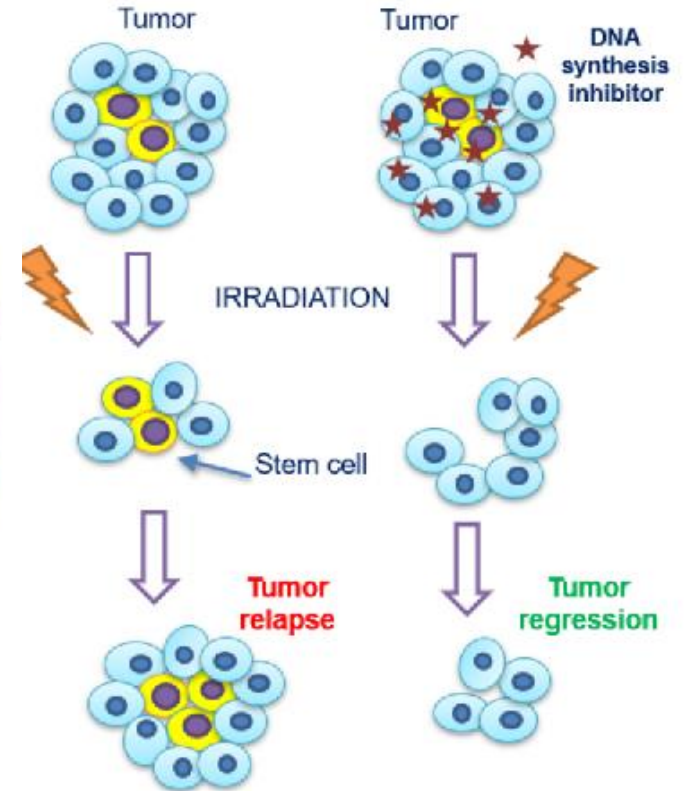
The size of the tumor on a mouse paw on the 18th day after irradiation



Protons 10 Gy Protons 10 Gy + AraC

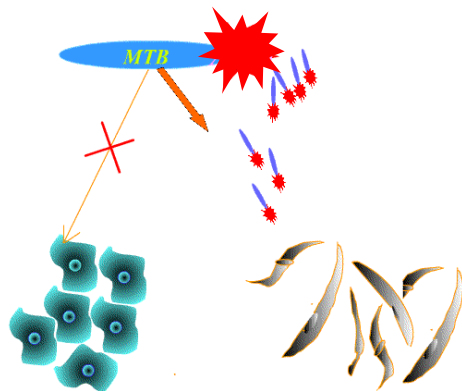
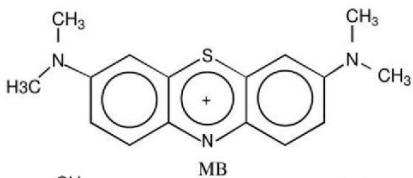


Tumor regression due to stem cell death



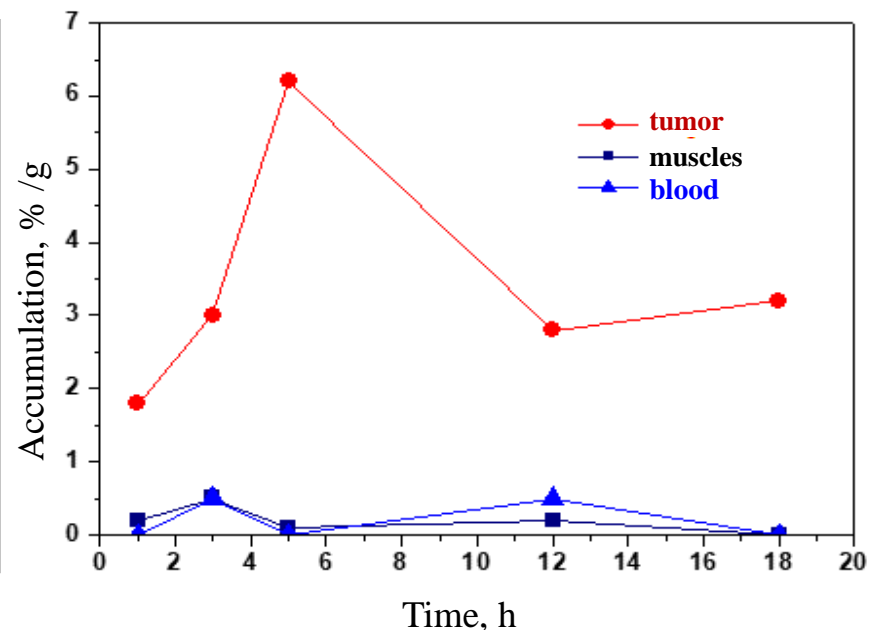
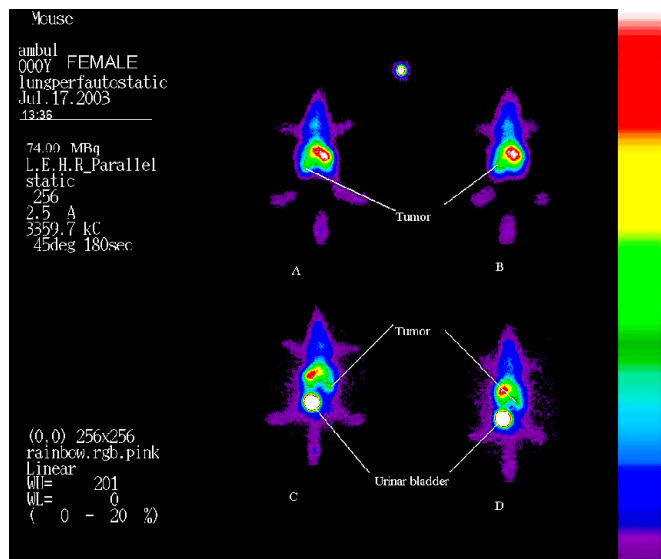
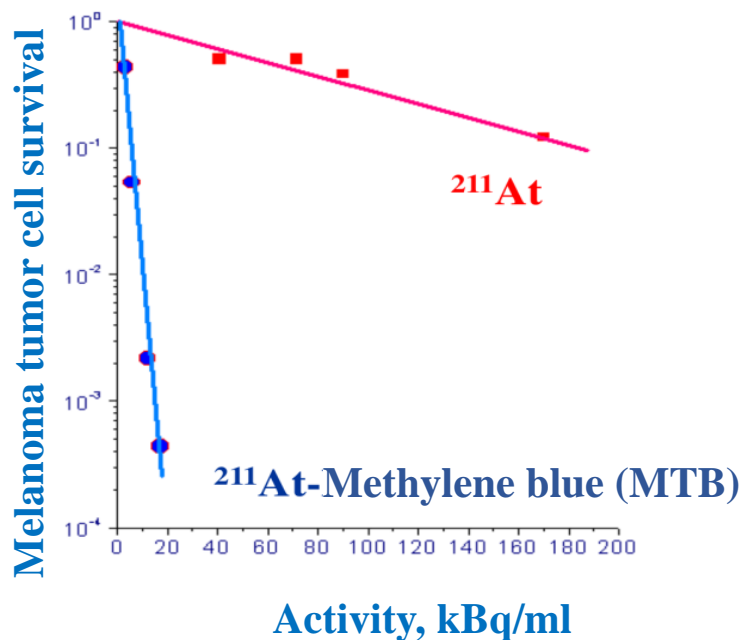
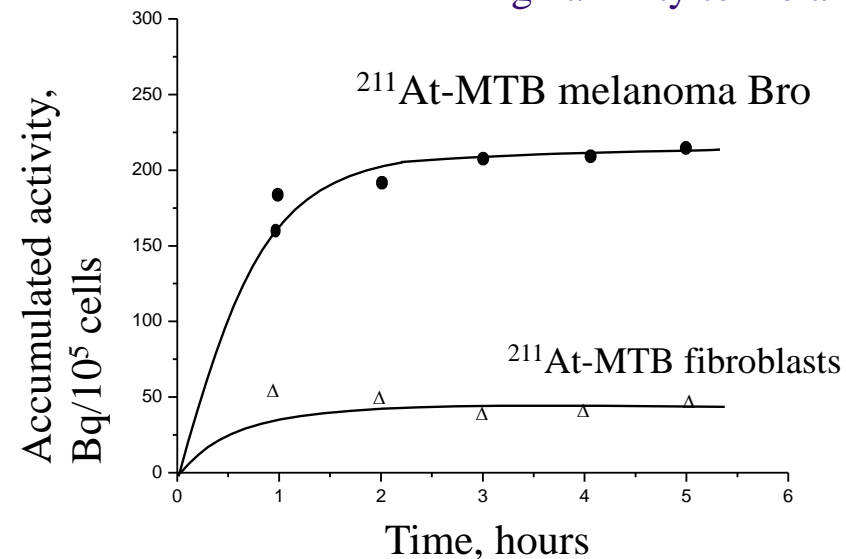
Clinical Radiobiology

Radiobiology of alpha-emitter radionuclides



²¹¹At-MB for therapy
¹³¹I, ¹²³I-MB for diagnostic

High affinity to melanoma cells



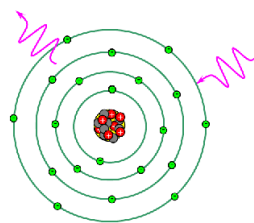
Clinical Radiobiology

Radiobiology of Auger-electron emitter radionuclides

^{67}Ga , ^{111}In , $^{99\text{m}}\text{Tc}$, ^{123}I , $^{124}\text{I}^*$, ^{125}I , $^{193\text{m}}\text{Pt}$

Auger- and conversion-electrons

- + very high local dose
- Very low range

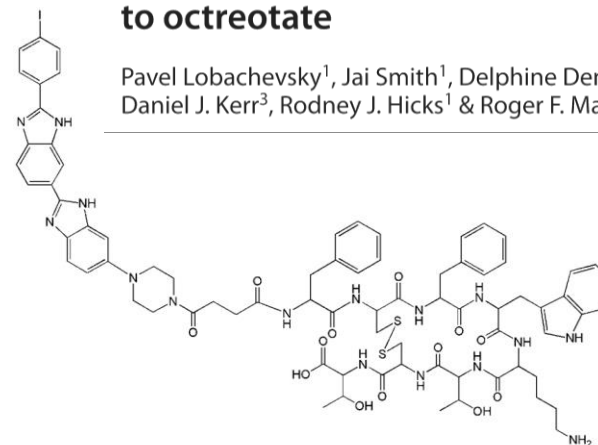


X-ray, γ

- low RBE
- Long range

Tumour targeting of Auger emitters using DNA ligands conjugated to octreotate

Pavel Lobachevsky¹, Jai Smith¹, Delphine Denoyer¹, Colin Skene², Jonathan White², Bernard L. Flynn³, Daniel J. Kerr³, Rodney J. Hicks¹ & Roger F. Martin¹



^{125}I



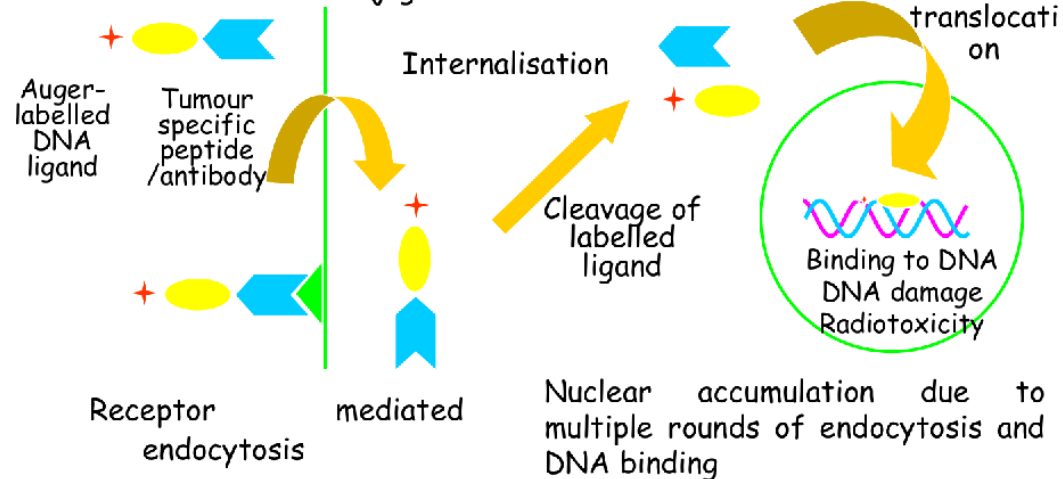
PIH

OCA

Dual targeting strategy

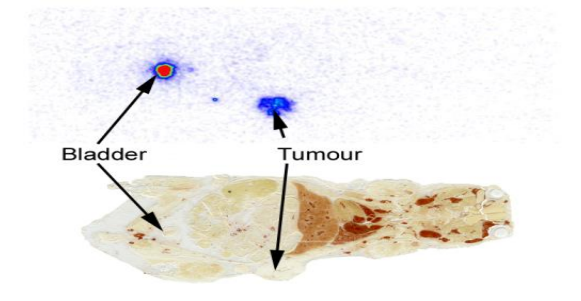
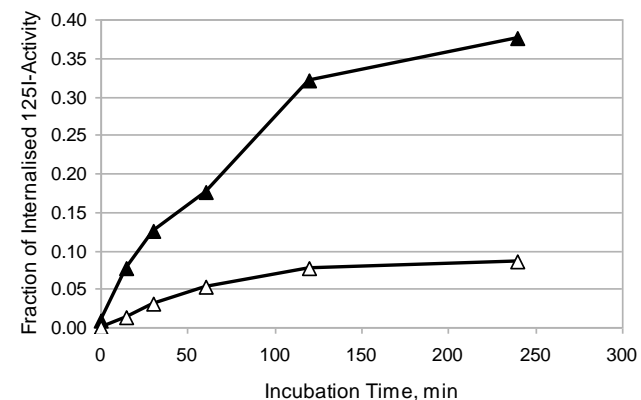
Step 1: Tumor cell delivery of conjugate

Step 2: DNA delivery of radiolabelled ligand



Three component conjugate (^{125}I -PIH-OCA)

Internalisation of PIHOCA Conjugate into A427-7 cells

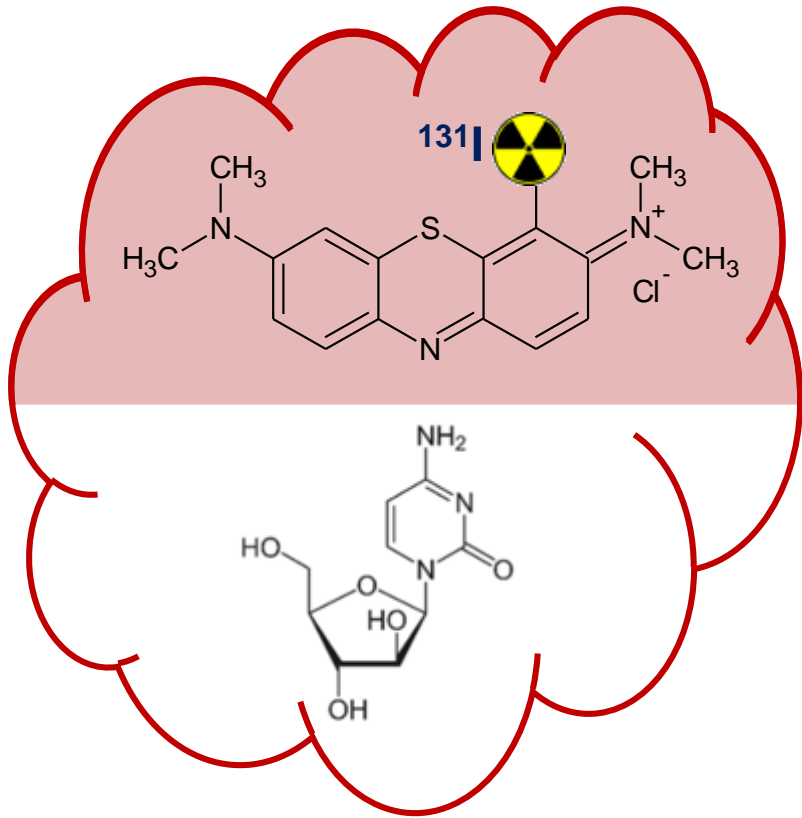


▲ 125I-PIHOCA
△ 125I-TOCA

Clinical Radiobiology

➤ Radiobiology beta-emitter radionuclides

A new approach to increase biological efficiency of **beta-emitter radionuclides**

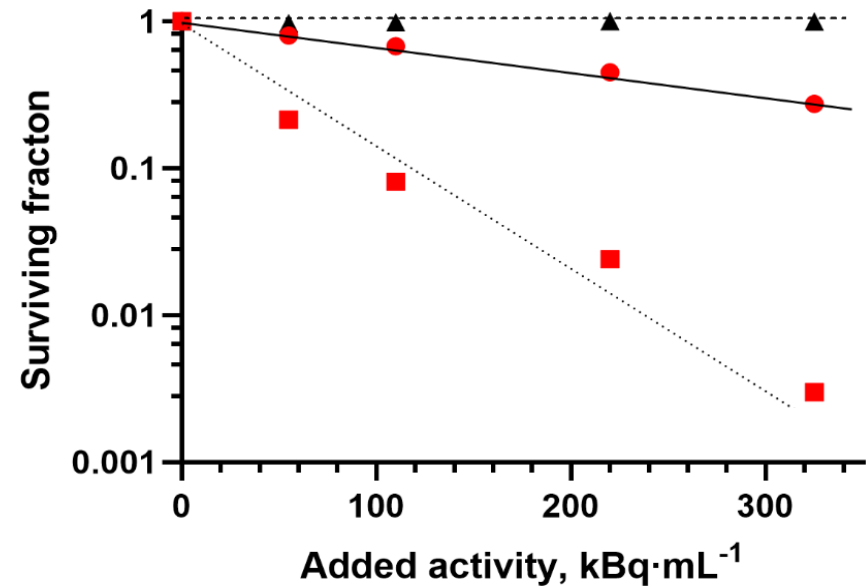


Metilene Blue (MB) – radiopharmaceutical for imaging and targeted therapy of melanoma (**halogen radioisotopes**)

AraC (nucleoside analog) – molecular radiosensitizer

Proof of principle experiment

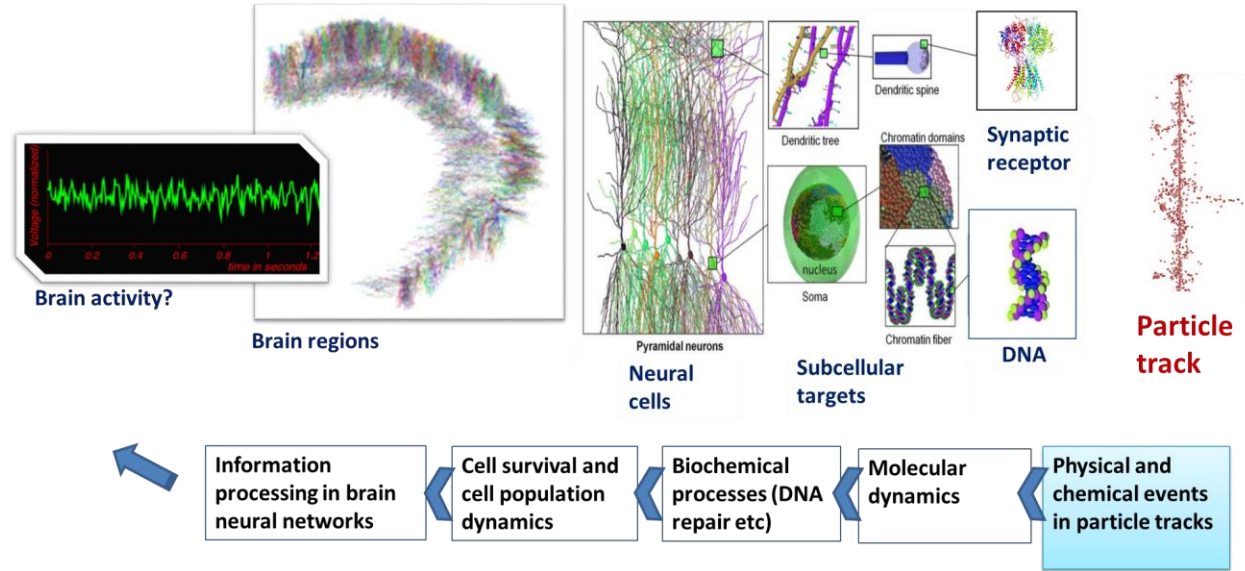
▲ [¹³¹I]NaI ● [¹³¹I]I-MB ■ [¹³¹I]I-MB + AraC



Tumor cell survival decreases **5 times** with respect to ‘standard’ ¹³¹I radiopharmaceutical

Mathematical Modeling

New mathematical approaches for *computation of brain damage* following particle irradiation

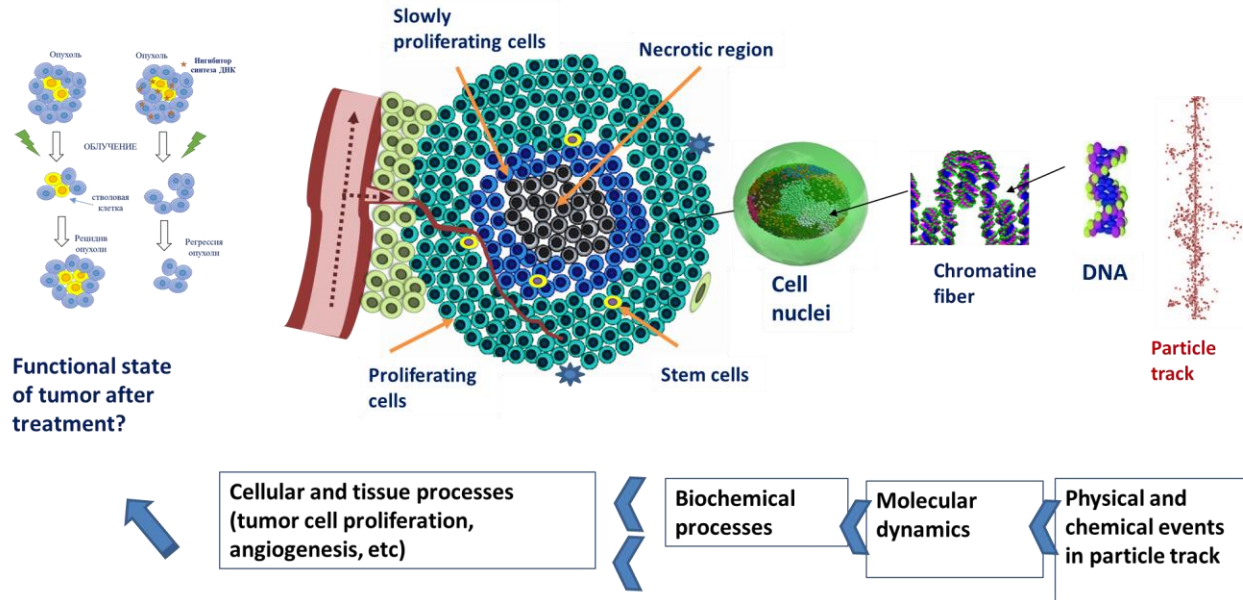


➤ A **hierarchy of mathematical models** to describe radiation-induced effects at different levels of biological organization and time scales

➤ Estimation of **radiation risks for normal tissues**

- space radiation safety
- side effects of radiation therapy

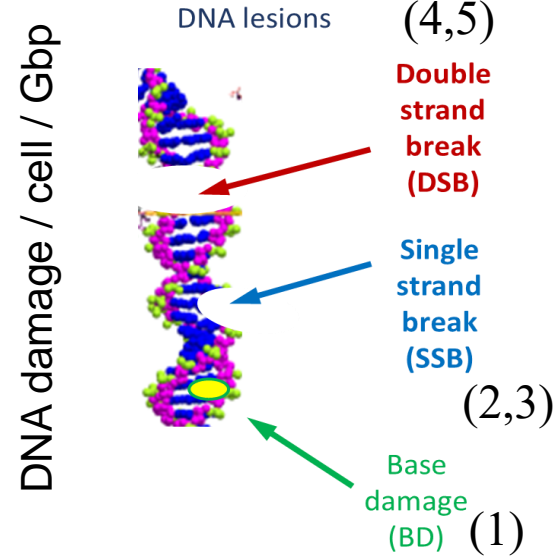
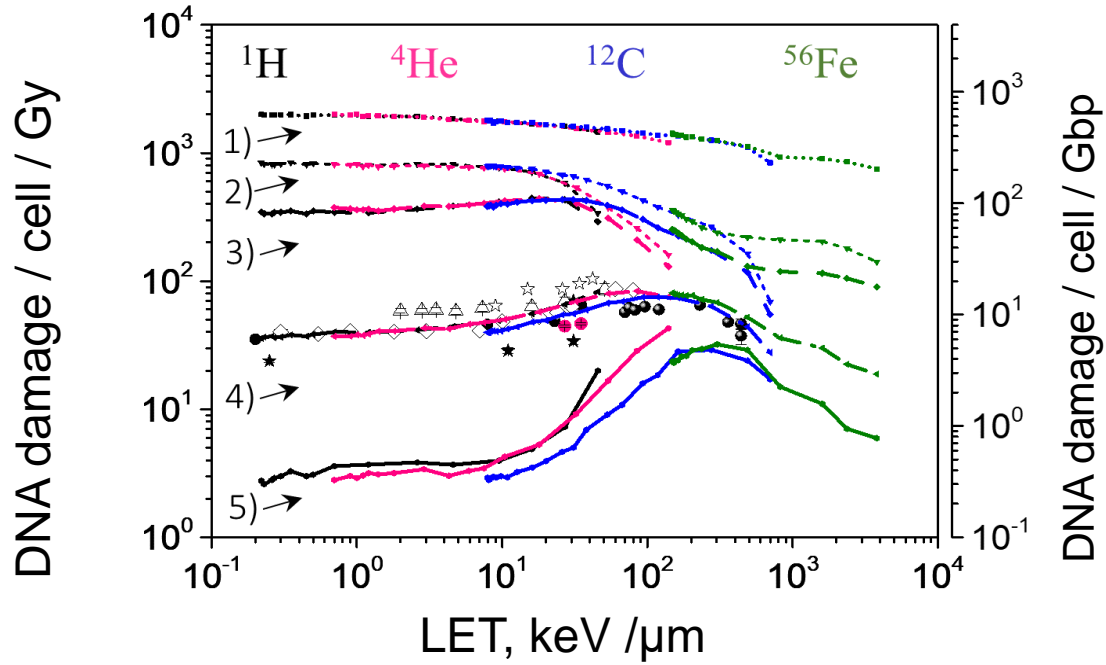
Models of structural and functional properties of *mutant proteins and their link to brain diseases*



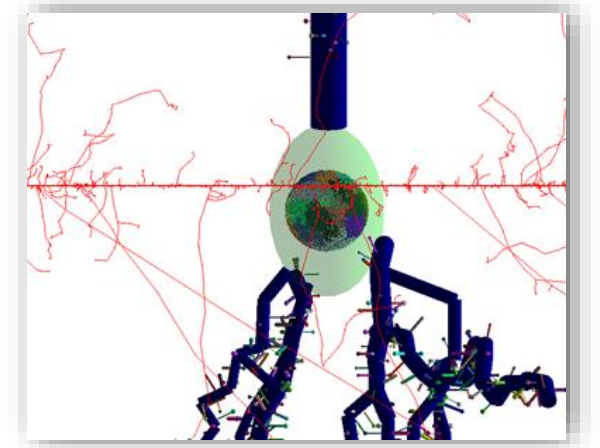
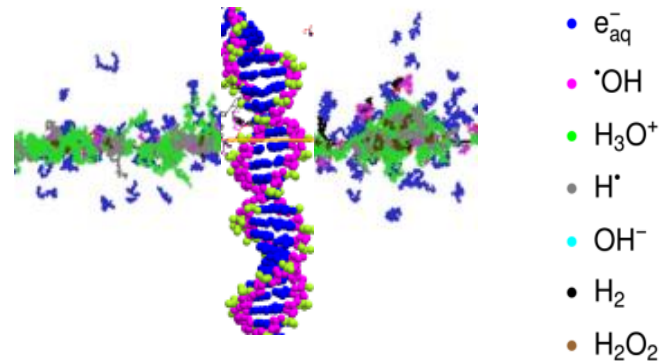
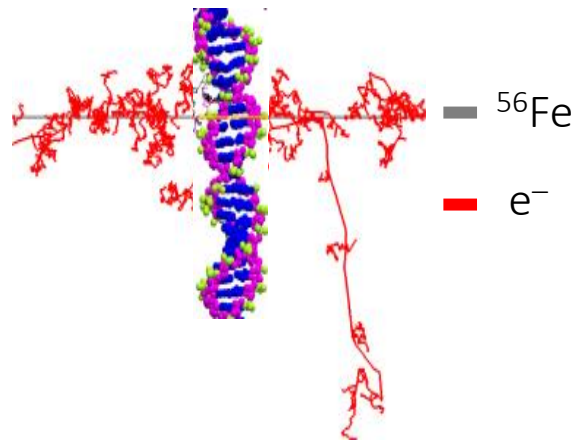
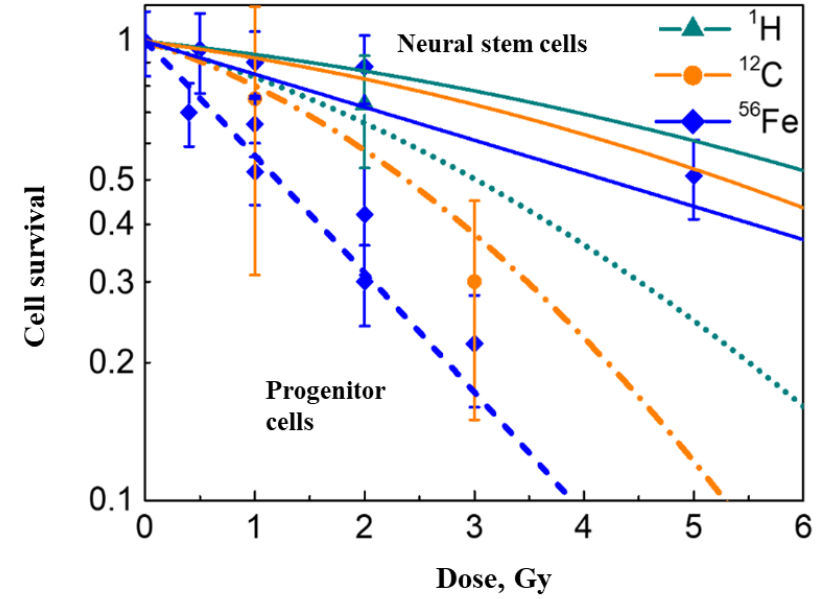
➤ Modeling of **tumor radiation response** for different modalities of particle and radionuclide therapy

➤ **Software for research and treatment planning**

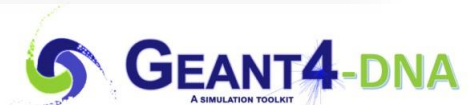
Mathematical Modeling



Computation of neural stem cell survival

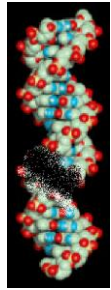


"neuron" package

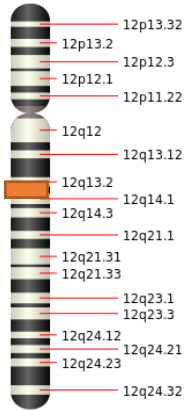


Mathematical Modeling

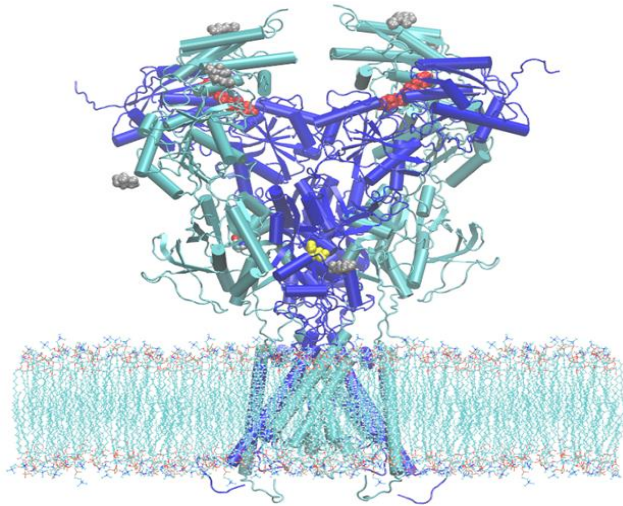
Genetic and molecular mechanisms of neurodegenerative diseases



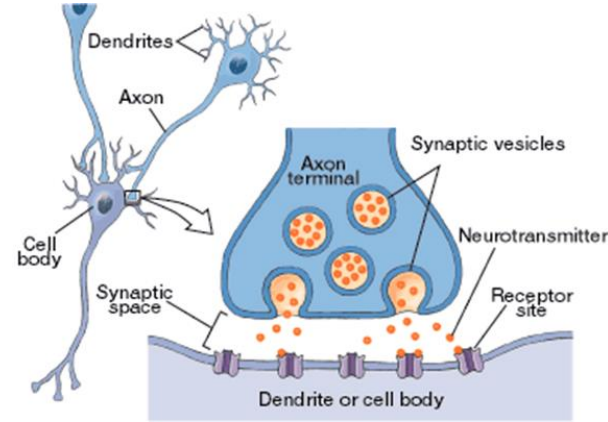
DNA damage



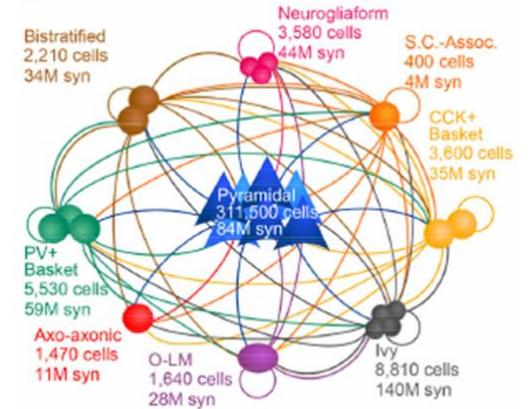
Chromosome 12
GRIN2B gene



NMDA synaptic receptor



Interconnections between neurons,



Brain neural networks

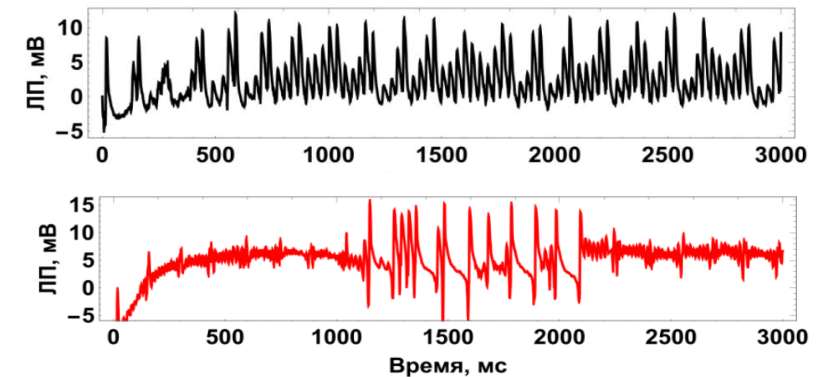
Multiscale simulation approach

- Monte Carlo simulations
- Bioinformatics
- Molecular dynamics
- Biochemical kinetics
- Neural networks

Mutation	Phenotype
p.Asn615Leu p.Phe671_Gln672del	West syndrome (epilepsy) Mild ID, Autism

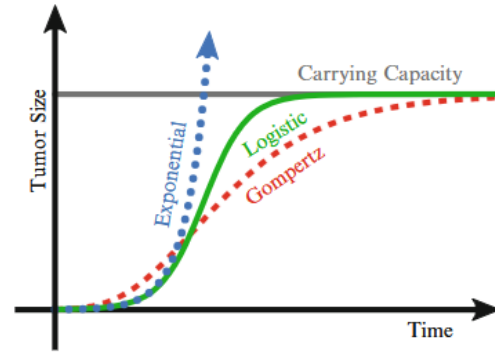
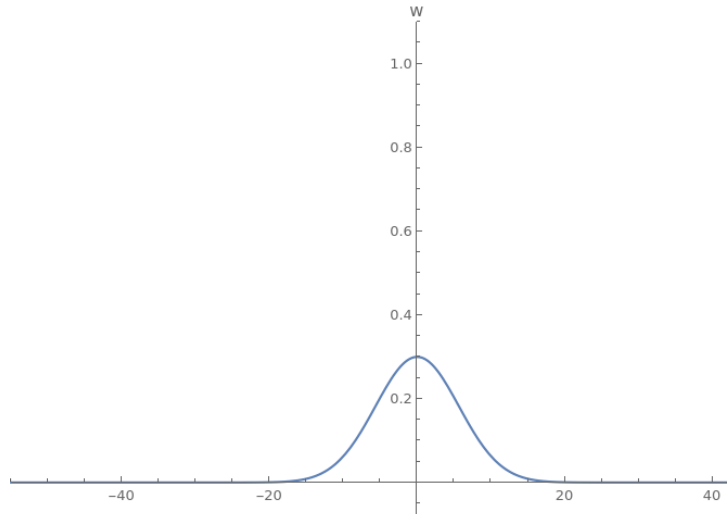
Native

p.ASN615LEU
Epileptic seizure

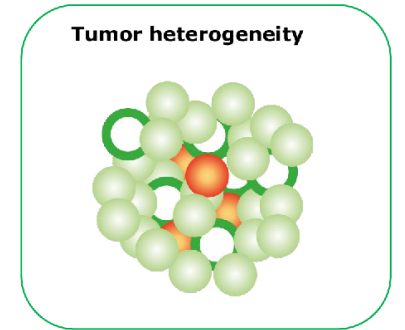


Mathematical Modeling

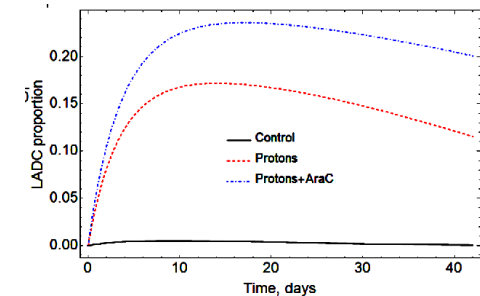
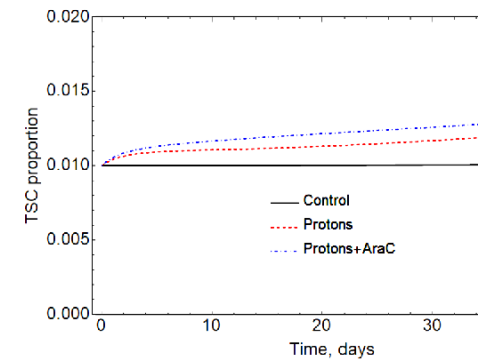
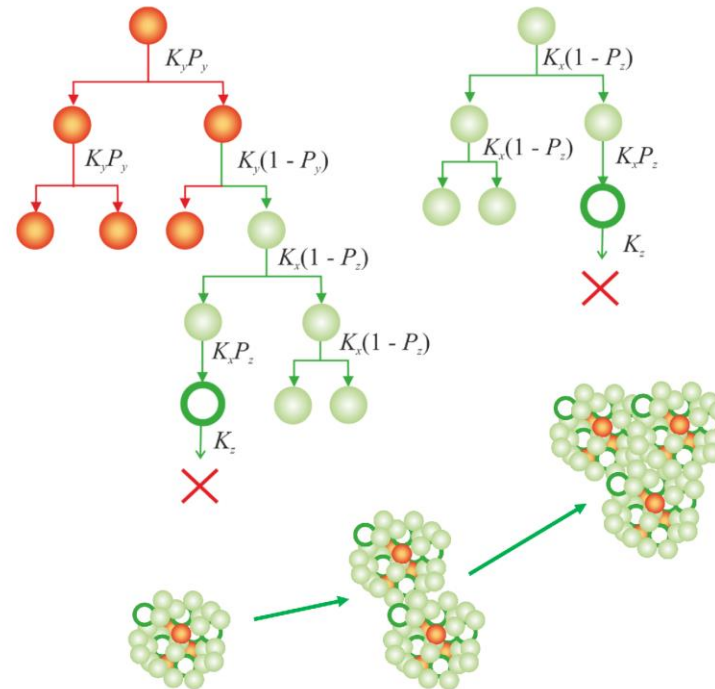
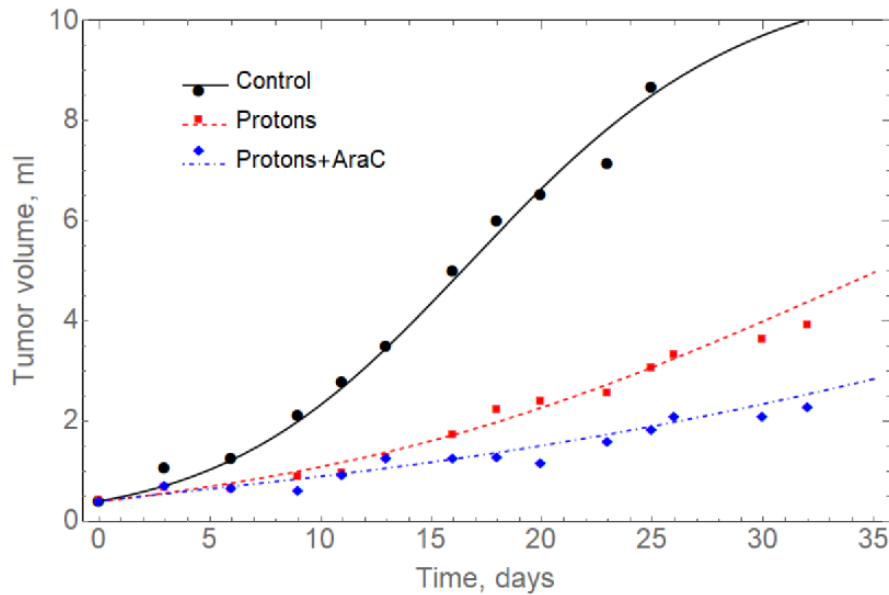
Modeling of tumor growth in radiation therapy



- - X - tumor cells (TC);
- - Y - tumor stem cells (TSC);
The smallest subpopulation.
Equilibrium proportion of TSC is about 1%
- - Z - cells lost the ability to divide (LADC)



$$\frac{\partial n_i}{\partial t} + \nabla \cdot (\mathbf{I}_i n_i) = \nabla \cdot (D_i \nabla n_i) + \lambda_i(\mathbf{n}, \mathbf{C})$$



Machine learning in biological data processing



BIOHLIT



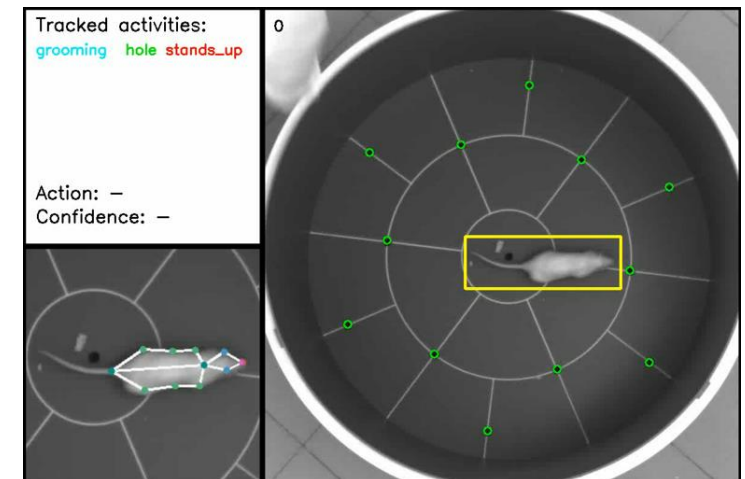
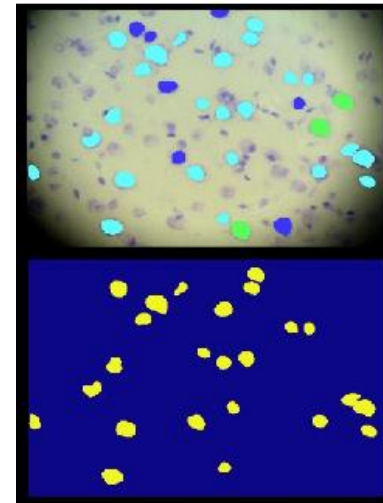
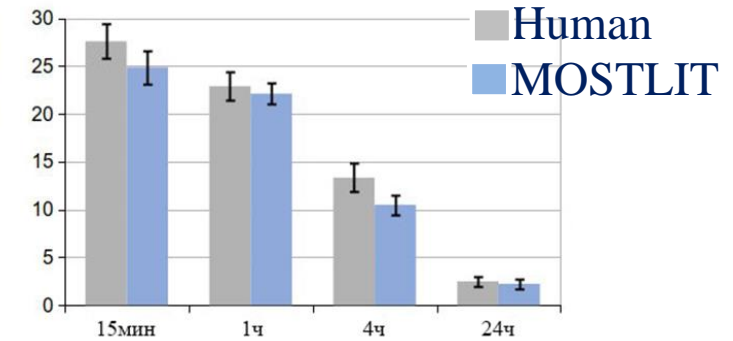
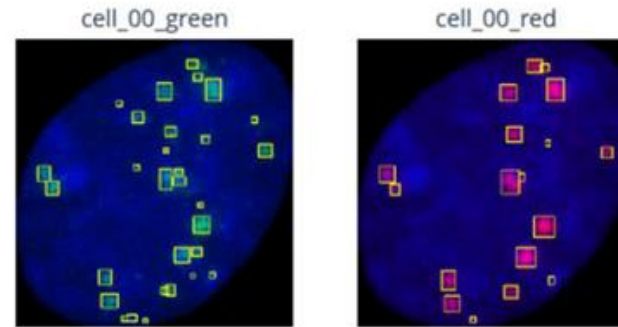
<https://it4bio.jinr.ru>

BIOHLIT information system

- computer vision algorithms based on machine learning and deep learning technologies;
- modern IT solutions for data storage, processing and visualization;

Data used

- video recordings of animal behavior
- photos of histological sections
- images of confocal microscopy



International Research Network

**50 scientific centers from 16 countries,
member of 4 international collaborations**

Geant4-DNA collaboration (2024)

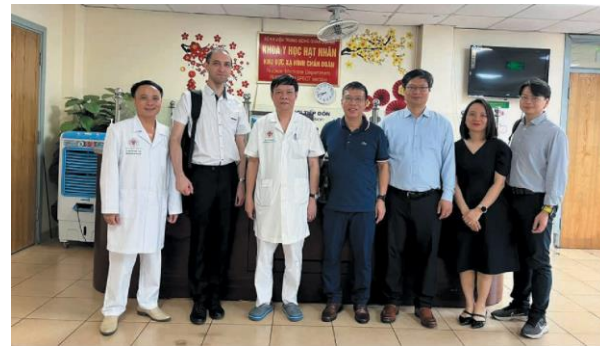


- ❑ International school NUMAR (Latin America, Asia, Africa)
- ❑ Annual international conference Modern Problems in Radiobiology (Dubna)
- ❑ Annual workshops and scientific schools on radiobiology

**Ongoing projects on cooperation programs:
Belarus, Bulgaria, Egypt, Vietnam, Serbia,
South Africa,**

International staff:

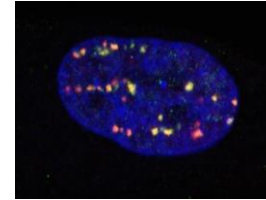
Mongolia,
Vietnam,
Belarus,
Cuba,
Kazakhstan,
Uzbekistan,
Egypt,
India



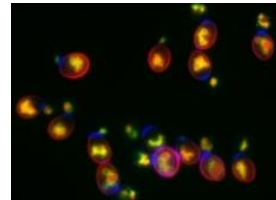
Research at the Laboratory of Radiation Biology

1. Establishment of integrative interrelations of **radiation-induced effects at different levels** of biological organization:
2. Identification of the mechanisms of the **radiations effects on brain** and the development of neurodegenerative diseases.
3. Assessment of **radiation risks** for various scenarios of manned space flights and mixed radiation fields of nuclear physics facilities.
4. Development of new methods to improve the **effectiveness of radiation and radionuclide therapy** of cancer.
5. Development of **new mathematical models** and computational approaches for radiobiology, bioinformatics, and radiation medicine.
6. Identification of mechanisms and pathways of **catalytic synthesis of prebiotic compounds** under the action of radiation.
7. Development of **new research protocols**, including omics technologies, bio-imaging, automated processing of biological data.

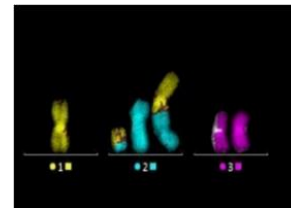
Molecular Radiobiology



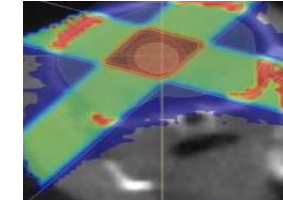
Radiation Genetics



Radiation Cytogenetics



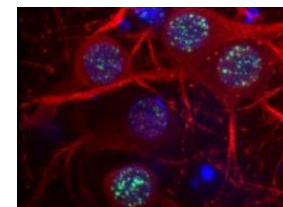
Clinical Radiobiology



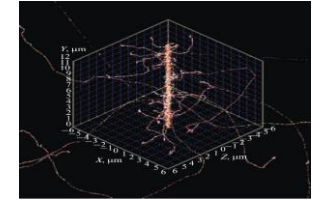
Radiation Physiology



Radiation Neuroscience



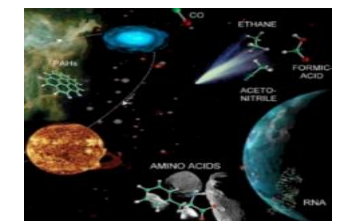
Mathematical Modeling



Radiation Protection



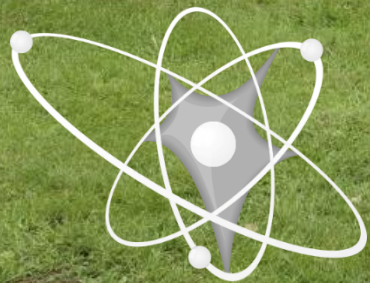
Astrobiology



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Thank you for the attention!