Radiobiological research at JINR: applications in radiation medicine and space exploration

Aleksandr Bugay
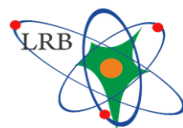
JINR Infrastructure for Life Science Research

U-400M cyclotron
heavy ions 50 MeV/u

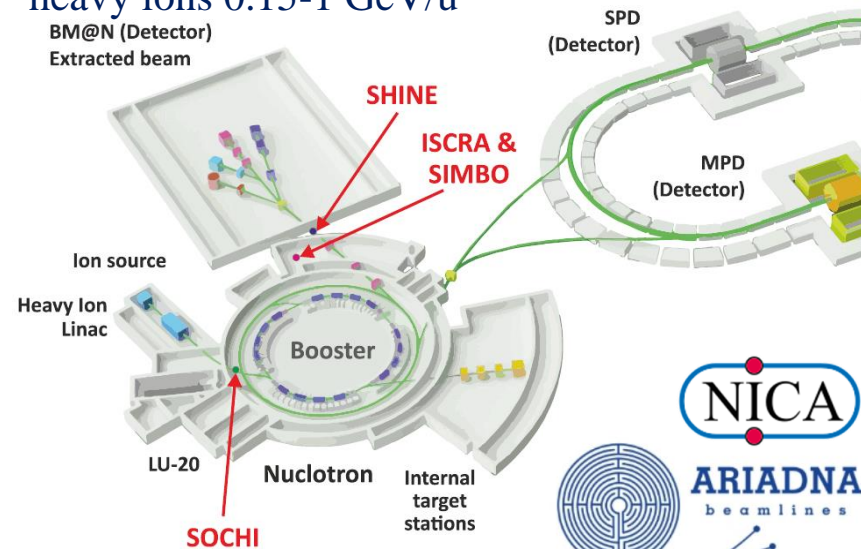**Infrastructure
for cellular and animal research**
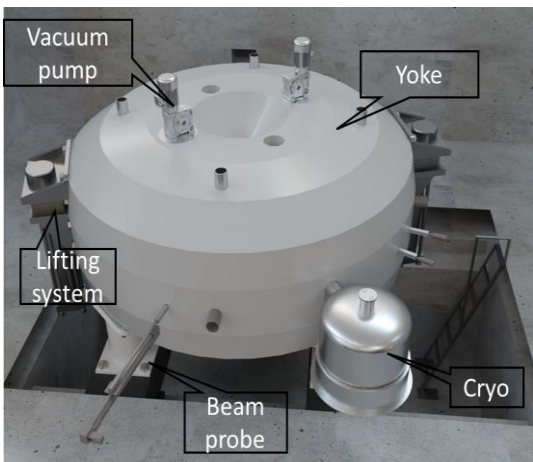
Microscopy
Tomography
OMICS

Vivarium

Nuclotron
heavy ions 0.15-1 GeV/u
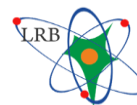

BM@N (Detector)
Extracted beam

SPD (Detector)

SHINE

ISCRA & SIMBO

MPD (Detector)

Ion source

Heavy Ion Linac

Booster

NICA

ARIADNA
beamlines

LU-20   Nuclotron   Internal target stations

SOCHI

MSC230 cyclotron
protons 230 MeV

Linac200
electrons
20-200 MeV

MICC
Supercomputer

SARRP X-ray

IBR-2, IREN neutrons

Vacuum pump

Yoke

Lifting system

Cryo

Beam probe
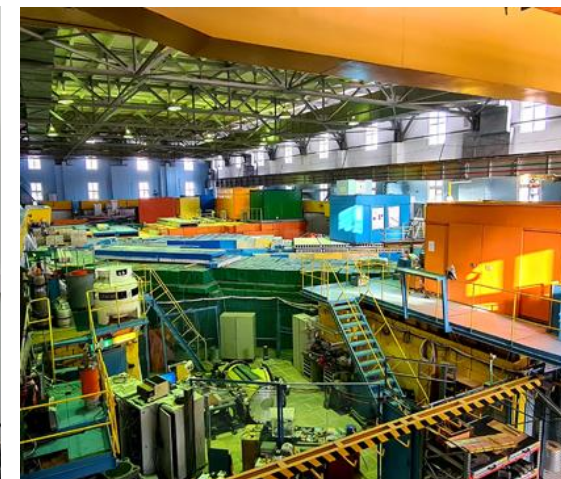
Interlaboratory cooperation

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

NICA   ARIADNA beamlines

- 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
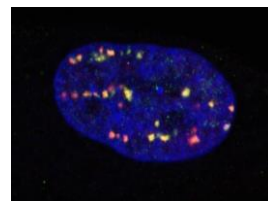- Radionuclides synthesis for radiation medicine

JINR Laboratory of Radiation Biology

MAIN RESEARCH FIELDS:

Molecular Radiobiology

Clinical Radiobiology

Mathematical Modeling

Radiation Genetics

Radiation Physiology

Radiation Research
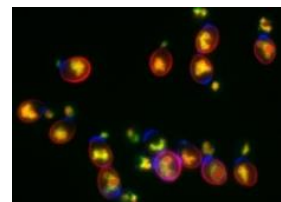
Radiation Cytogenetics
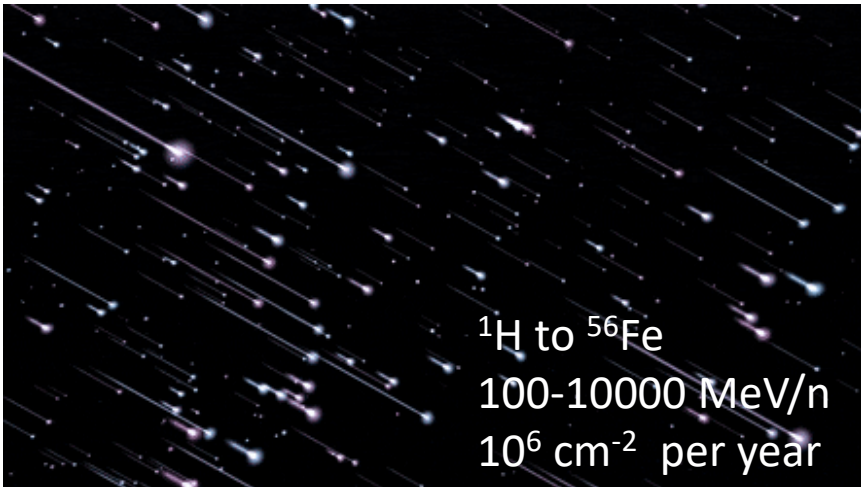

Radiation Neuroscience

Astrobiology

Relative biological effectiveness of charged particles
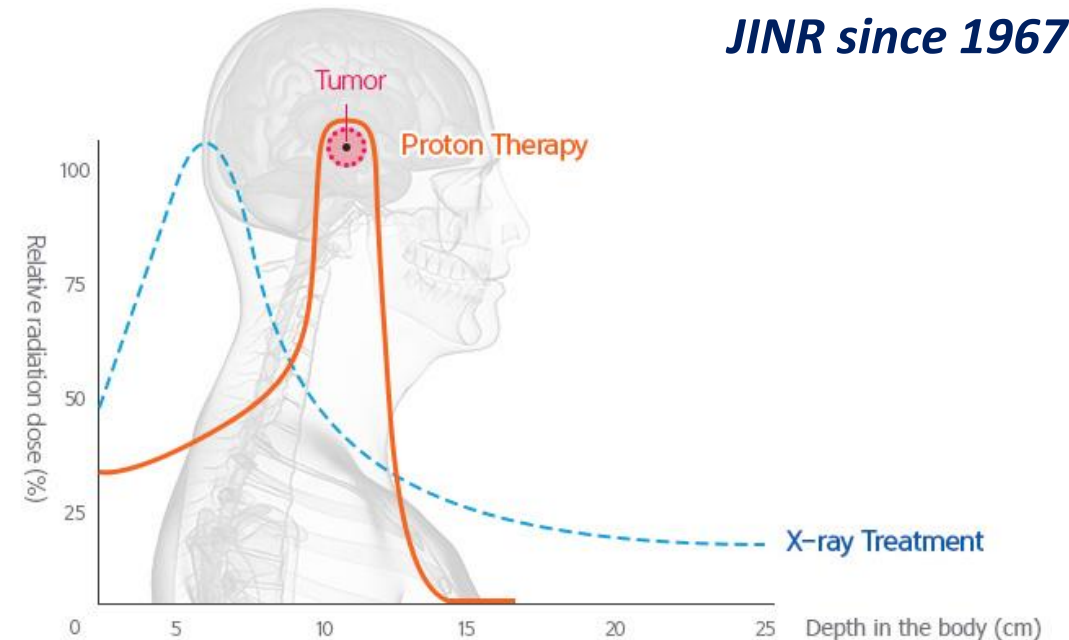# Radiation-induced mutagenesis

JINR since 1959

Radiation risk in deep space

JINR since 1959

^1H to ^{56}Fe
100-10000 MeV/n
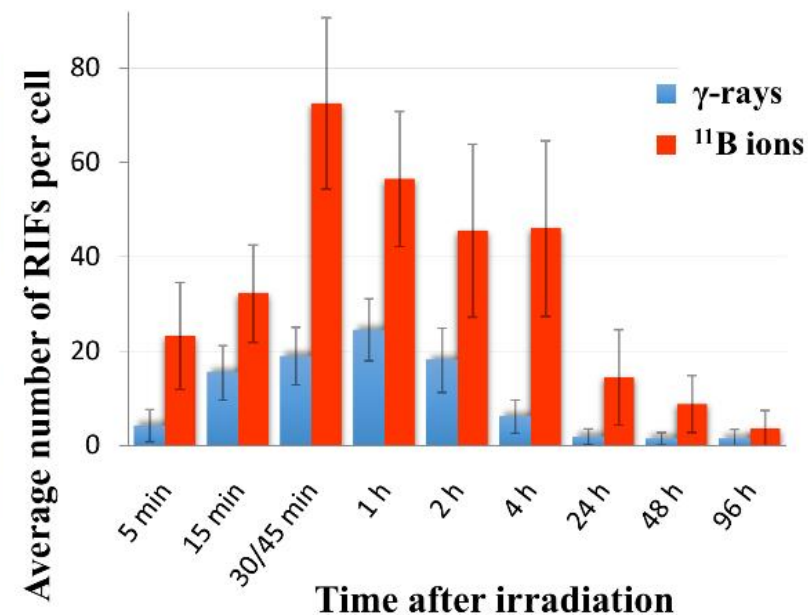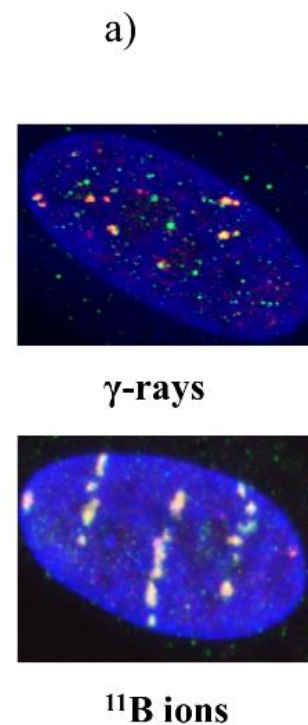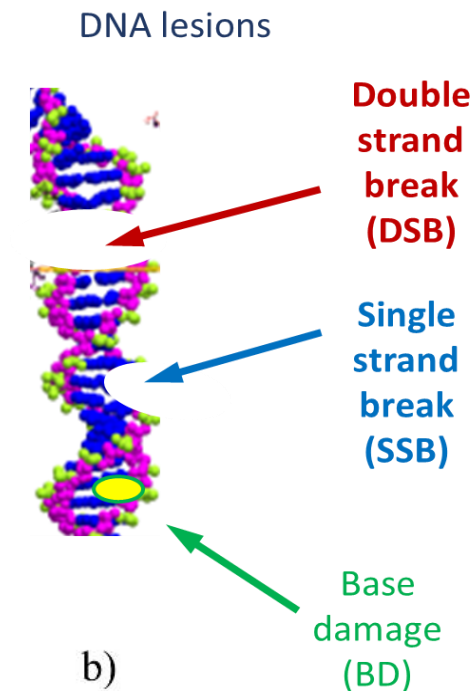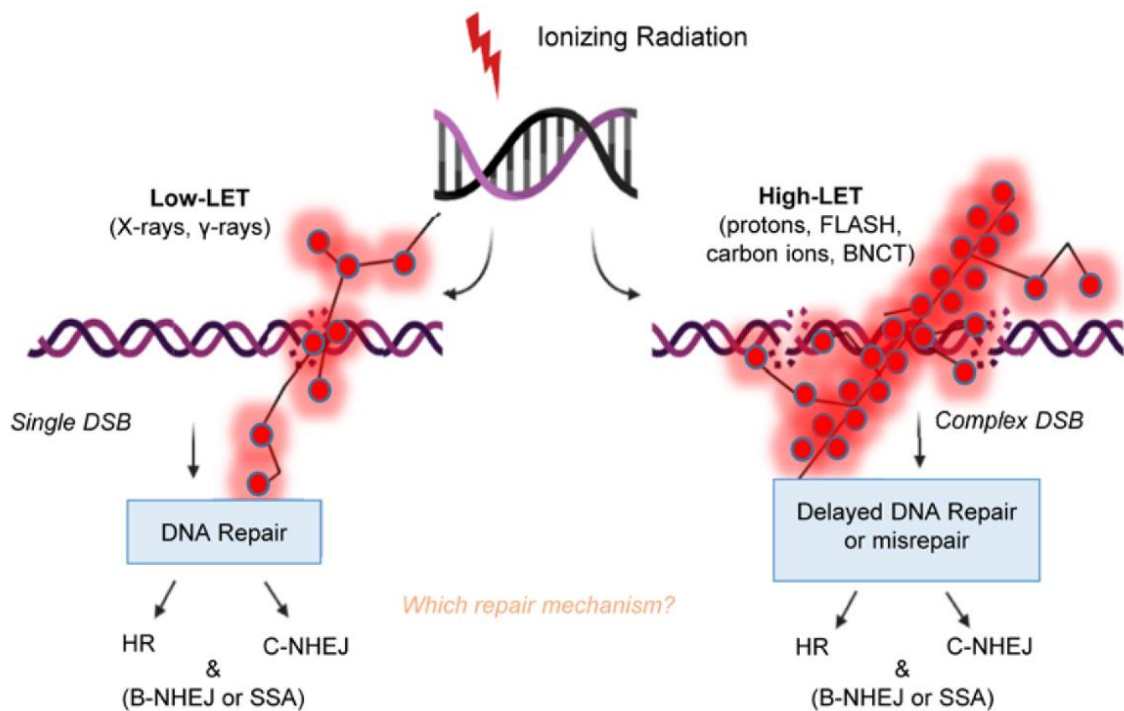10^6 cm^{-2} per year

Radiation therapy of cancer

JINR since 1967

Molecular Radiobiology

Molecular radiobiology

DNA damage, repair and regulatory mechanisms in normal and tumor cells, molecular mechanisms of radiosensitivity (radioprotectors, sensitizers for cancer treatment)


DNA lesions

Double strand break (DSB)

Single strand break (SSB)

Base damage (BD)

Ionizing Radiation

Low-LET (X-rays, γ-rays)

High-LET (protons, FLASH, carbon ions, BNCT)

Single DSB

Complex DSB

DNA Repair

Which repair mechanism?

HR   C-NHEJ
&
(B-NHEJ or SSA)

Delayed DNA Repair or misrepair

HR   C-NHEJ
&
(B-NHEJ or SSA)

a)

γ-rays

^{11}B ions

b)

Average number of RIFs per cell

Time after irradiation

γ-rays
^{11}B ions

5 min, 15 min, 30/45 min, 1 h, 2 h, 4 h, 24 h, 48 h, 96 h

DNA damage complexity

A

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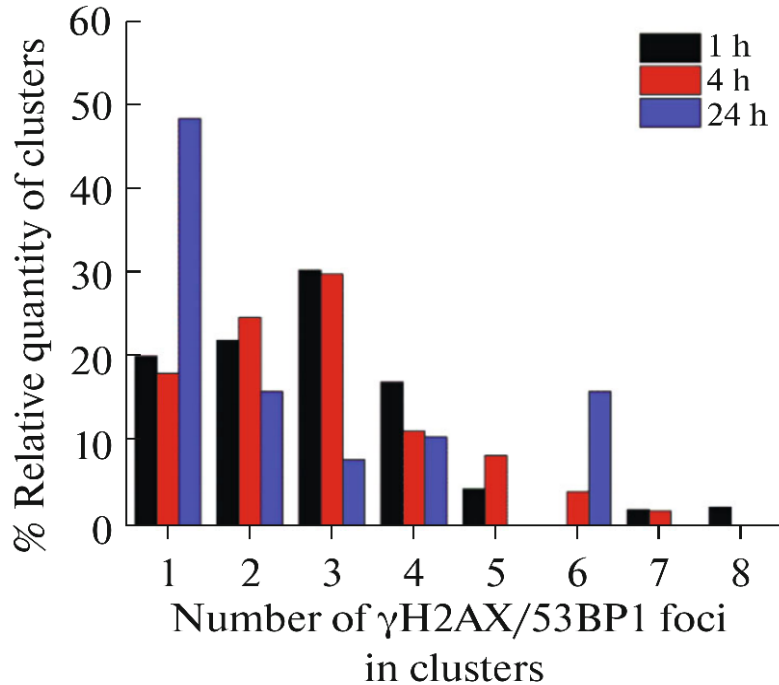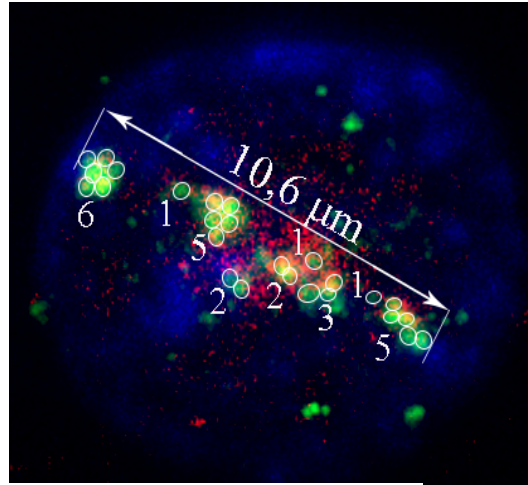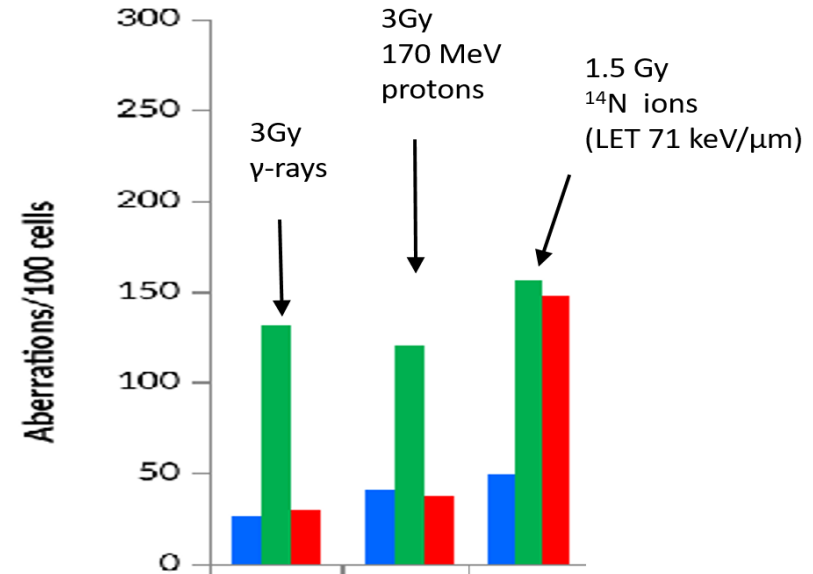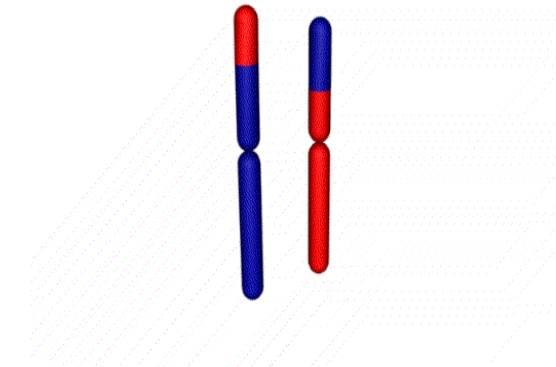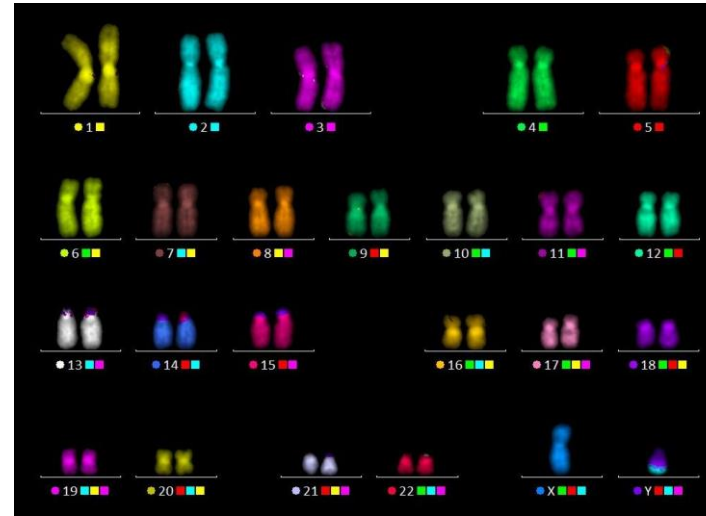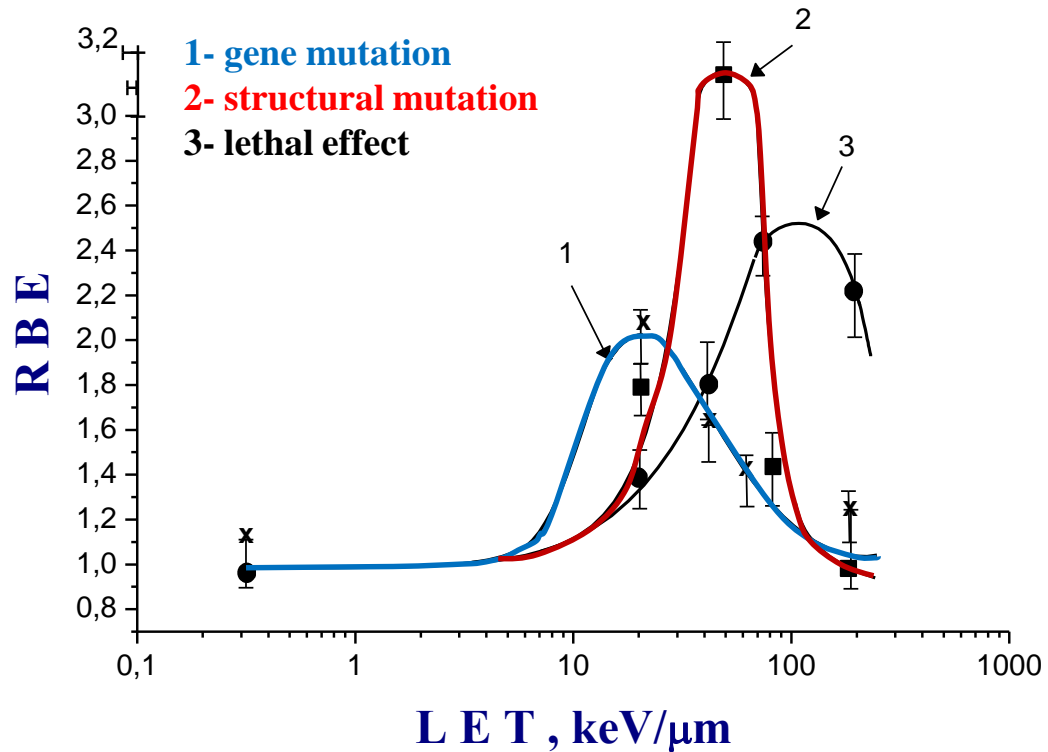

B
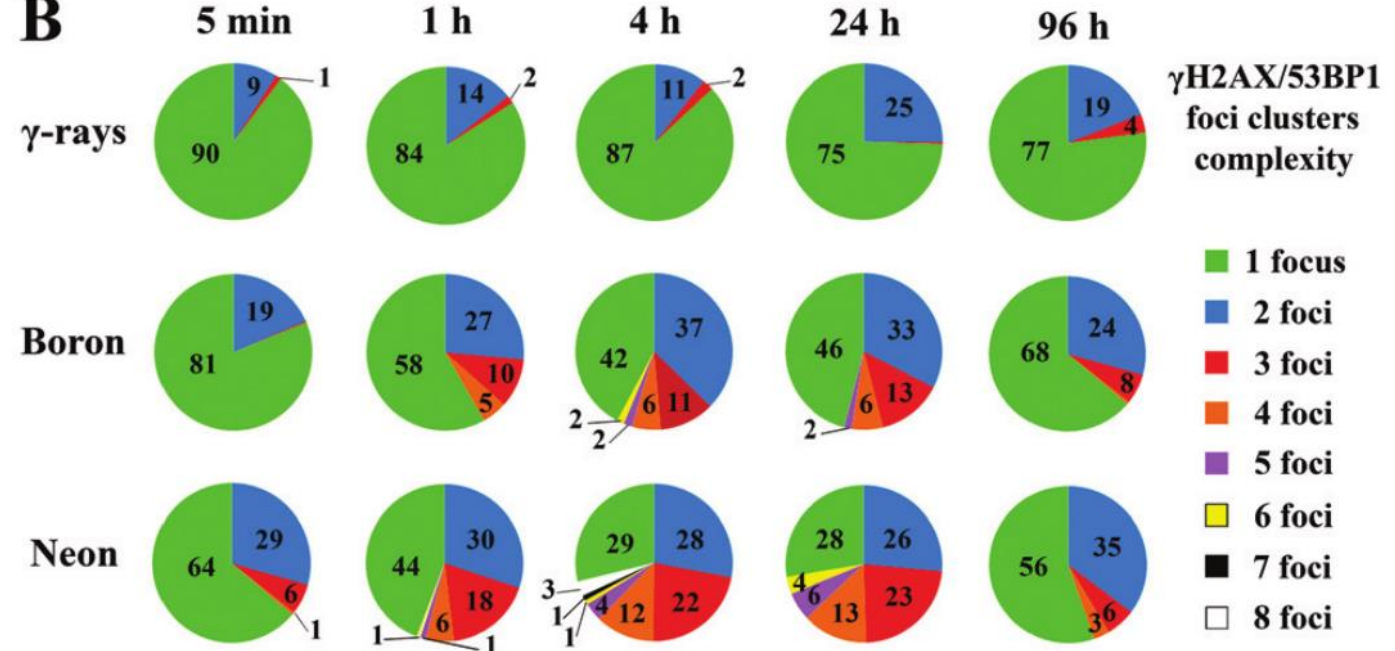
Ions with similar LET (~130 keV/mkm) generate foci clusters of different complexity

Radiation Genetics

Genetic and cytogenetic effects of radiation: gene mutations, chromosome aberrations, genome instability, biodosimetry

1- gene mutation
2- structural mutation
3- lethal effect

3Gy γ-rays

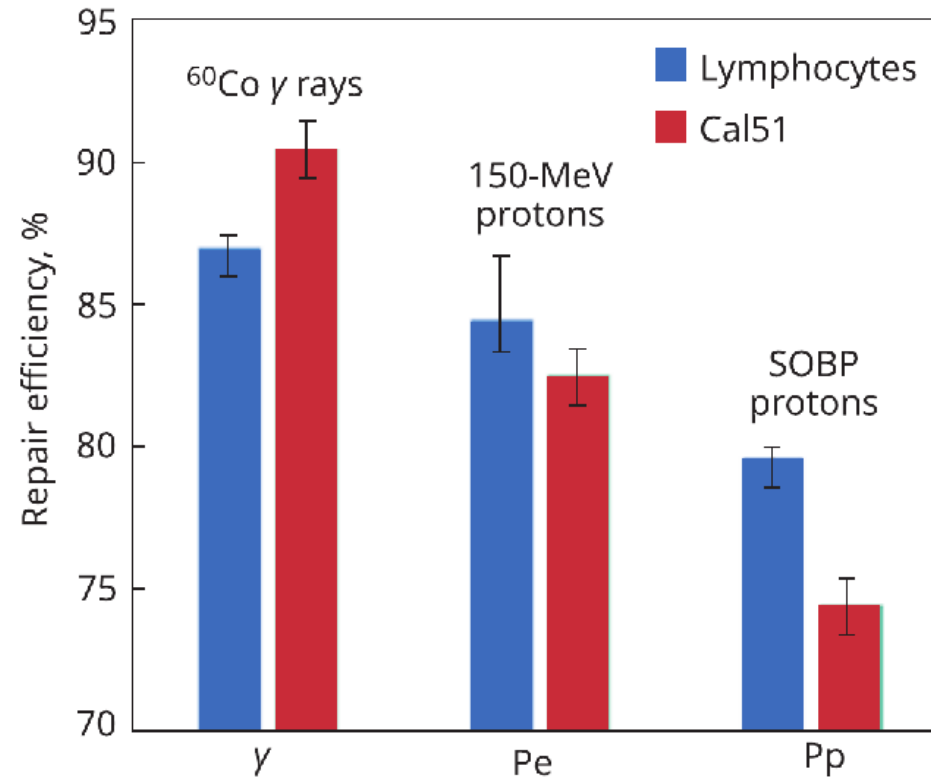3Gy 170 MeV protons

1.5 Gy ^{14}N ions (LET 71 keV/µm)

Complex chromosome aberrations (≥3 breaks)

Chromosomal radiosensitivity of human breast carcinoma Cal51
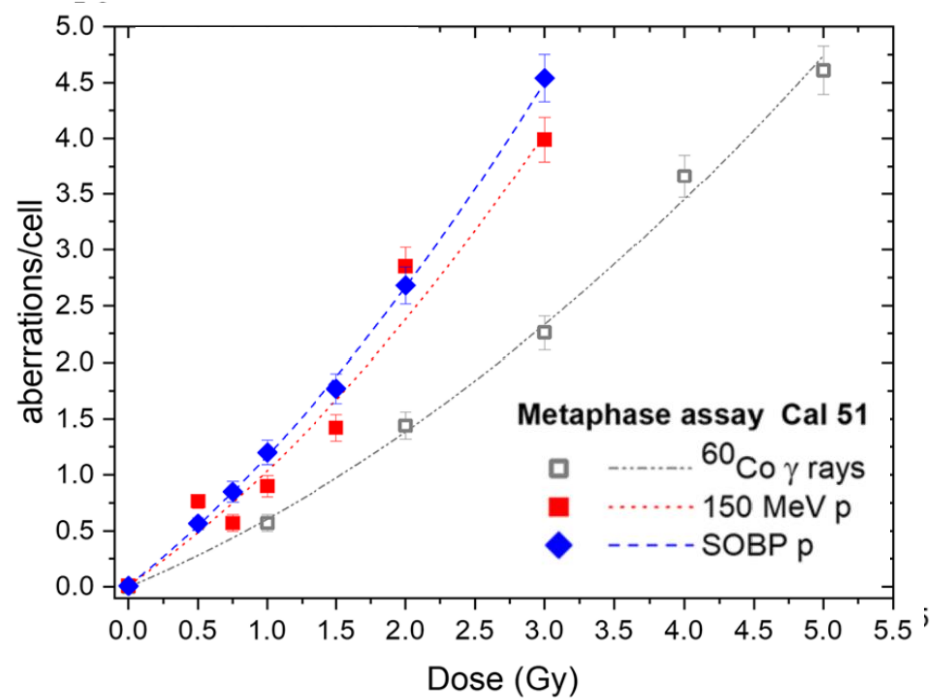
Dose dependence of mean number of chromosome aberrations per cell induced by gamma-rays and protons
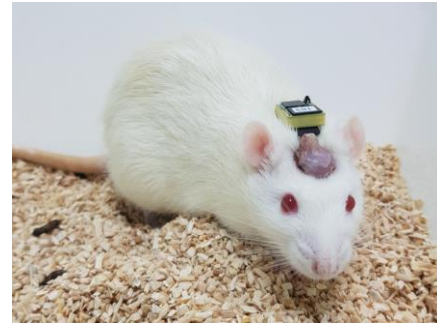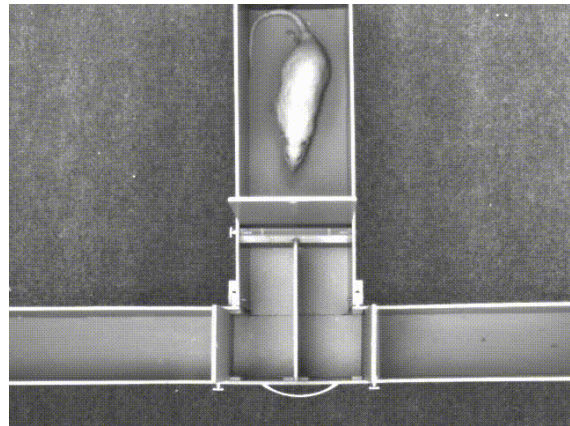
(SOBP –spread out Bragg peak)

Average efficiency of PCC breaks elimination in Cal51 tumor cells after the irradiation

Radiation Physiology and Neuroscience

Radiation physiology: tissue and organismal pathologies, animal behavior
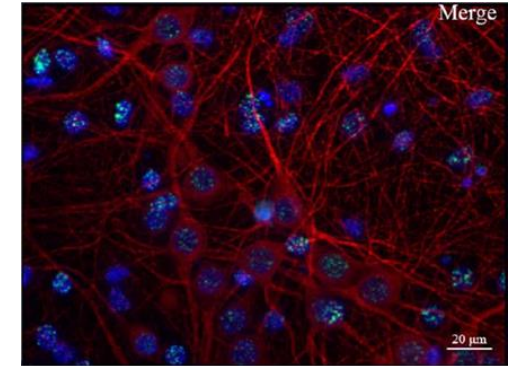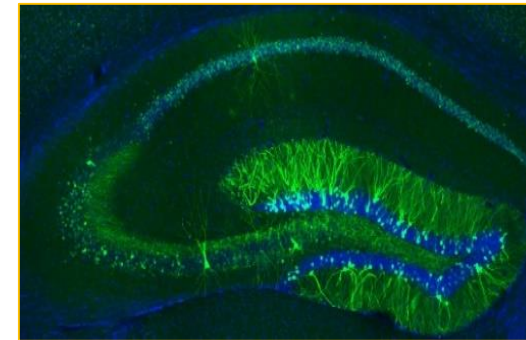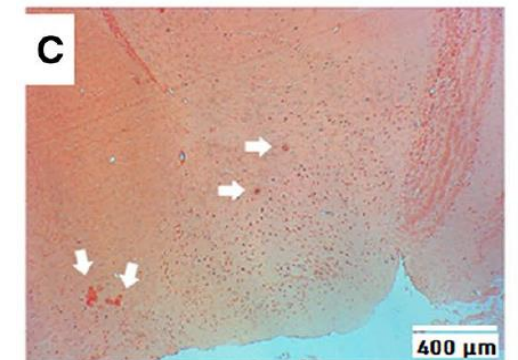

Behavioral tests

EEG records after irradiation

Radiation neuroscience: mechanisms of brain diseases and radiation-induced neurodegeneration

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

Amyloid plaques in the forebrain of rats after 170 MeV proton irradiation

Worldwide unique experiments with monkeys

Automated computer system for the simulation of operator activity during the flight

RAS Institute of Biomedical Problems,
RAS Institute of Medical Primatology,
RAS Institute of Higher Nervous Activity and
Neurophysiology,
Moscow State University

The monkeys were preliminarily trained to solve logical problems on a computer. The effect of exposure to 1 Gy of carbon ions with energy 500 MeV/u consisted in a significant suppression of the learning ability of monkeys.

In experiments with gamma-rays and protons with energy 170 MeV at the same dose 1 Gy similar effect was not observed.
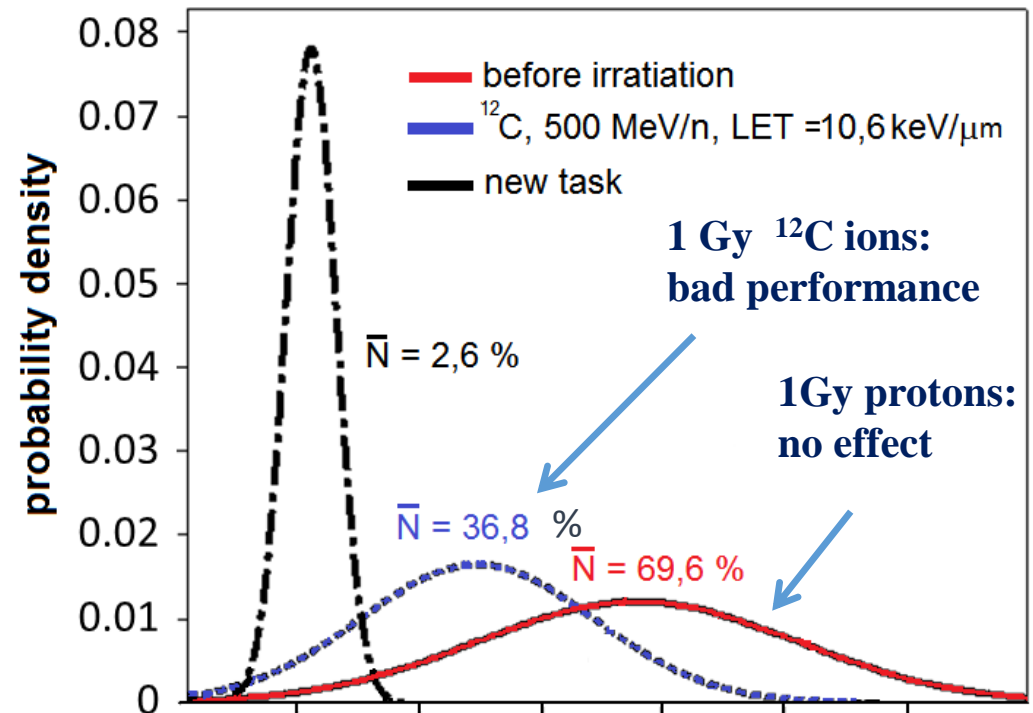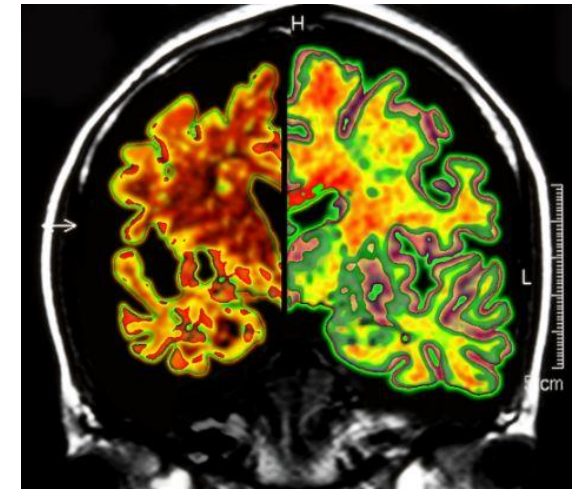
New concept of radiation risk for deep space flights: Damage to the central nervous system (CNS)
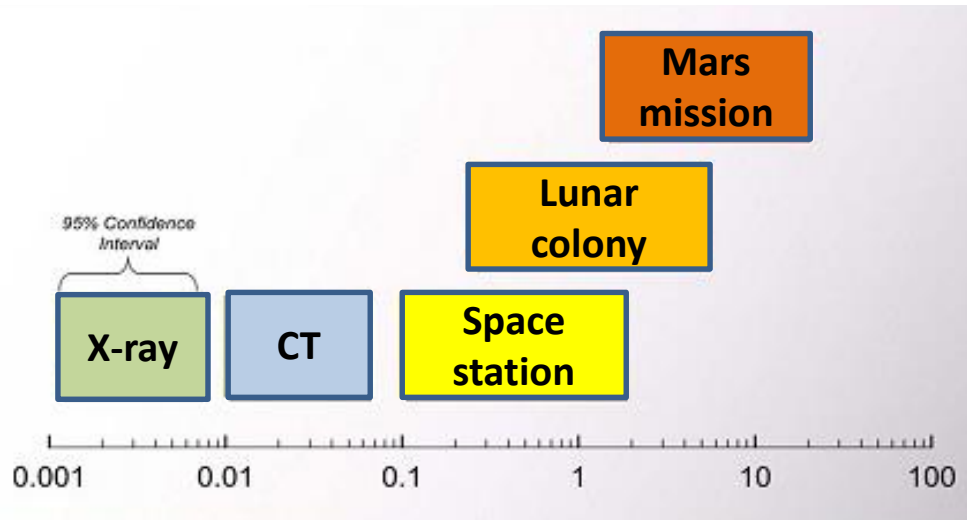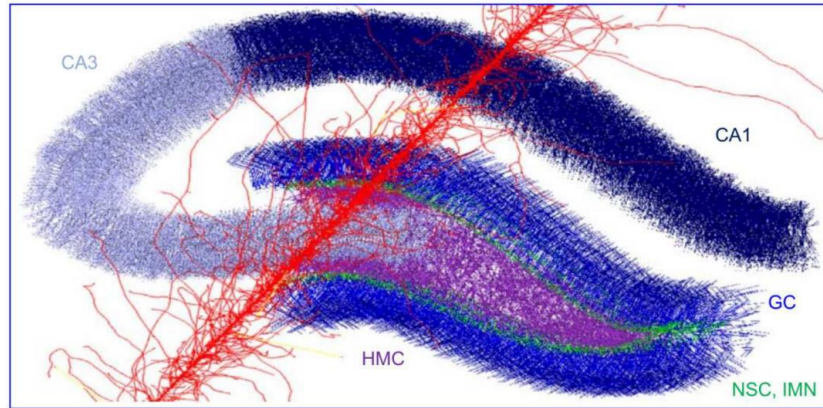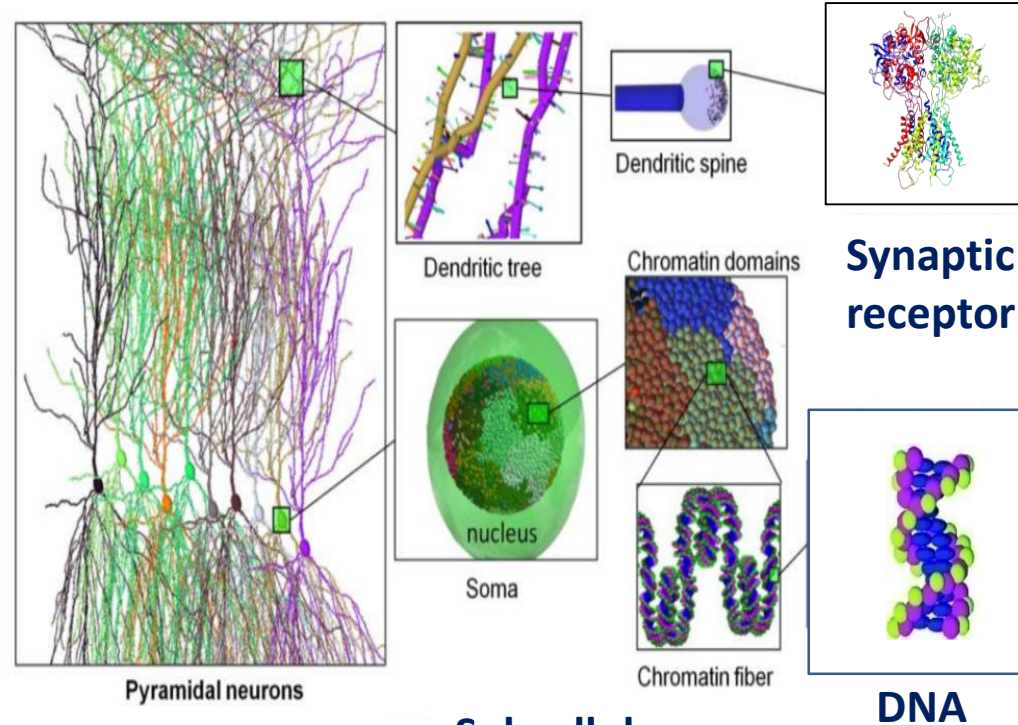

% Risk of cancer death

Paradigm shift

Radiation Neuroscience
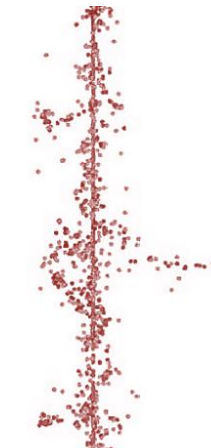
Radiation Neuroscience

The rat hippocampus

CA3
CA1
GC
HMC
NSC, IMN

Brain regions

Computer simulations

Neural stem cells
- ▲ ^1H
- ● ^{12}C
- ◆ ^{56}Fe

Cell survival

Progenitor cells

Dose, Gy

Dendritic spine
Dendritic tree
Chromatin domains
nucleus
Soma
Chromatin fiber

Synaptic receptor

DNA

Particle track

Pyramidal neurons

Neural cells

Subcellular targets

| Cell survival and cell population dynamics | ◁ | Biochemical processes (DNA repair etc) | ◁ | Molecular dynamics | ◁ | Physical and chemical events in particle tracks |
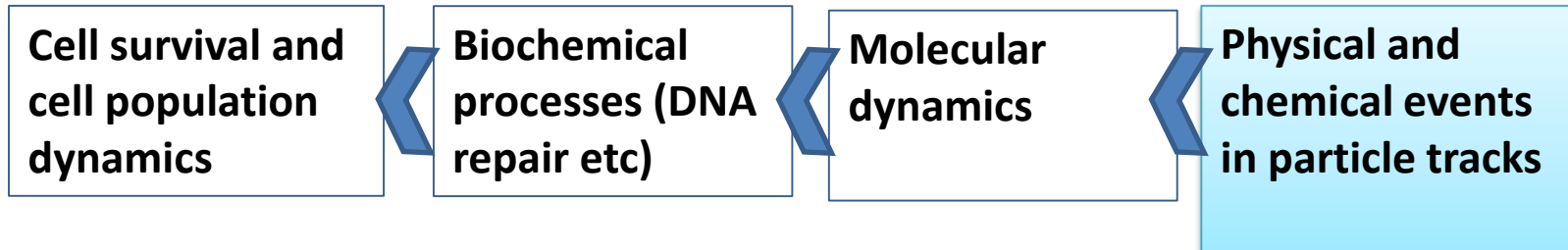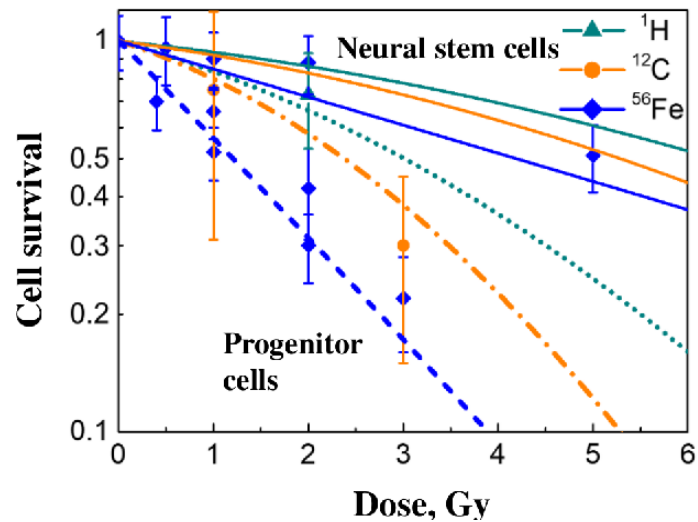
Radiation Neuroscience

Genetic and molecular mechanisms of neurodegenerative diseases

DNA damage

Chromosome 12
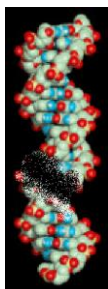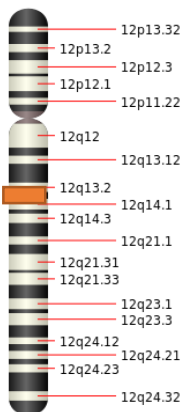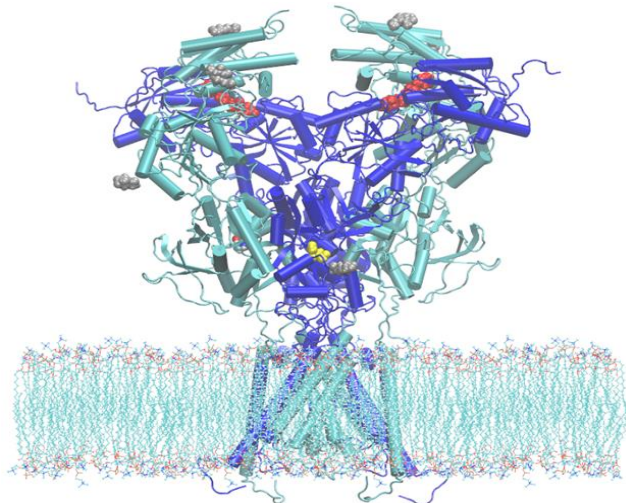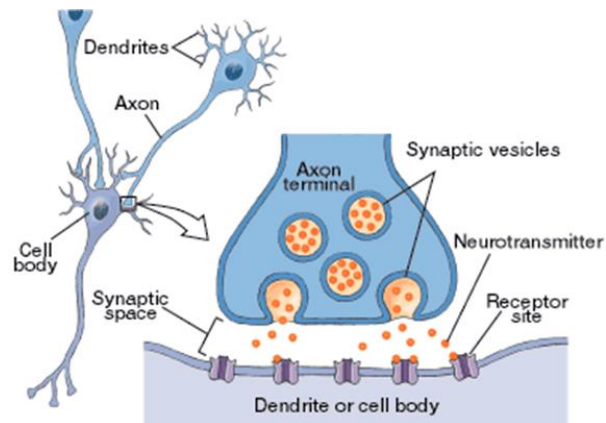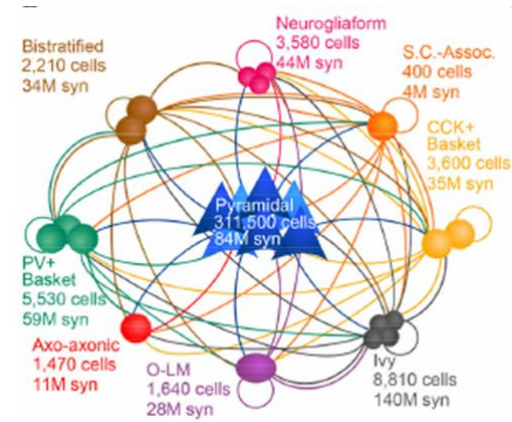*GRIN2B* gene

NMDA synaptic receptor

Interconnections between neurons,
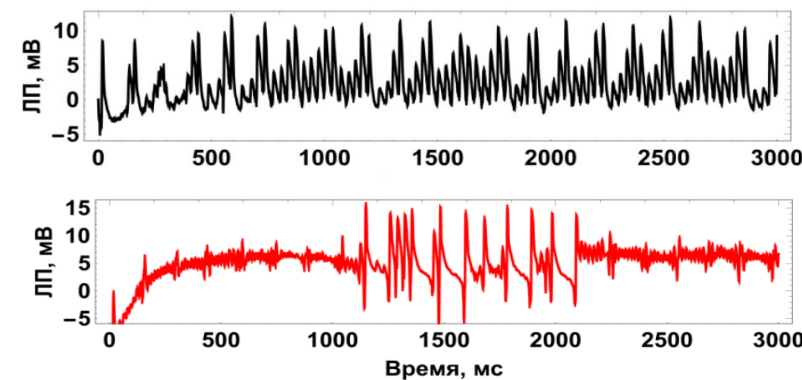
Brain neural networks

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

Machine learning and data processing
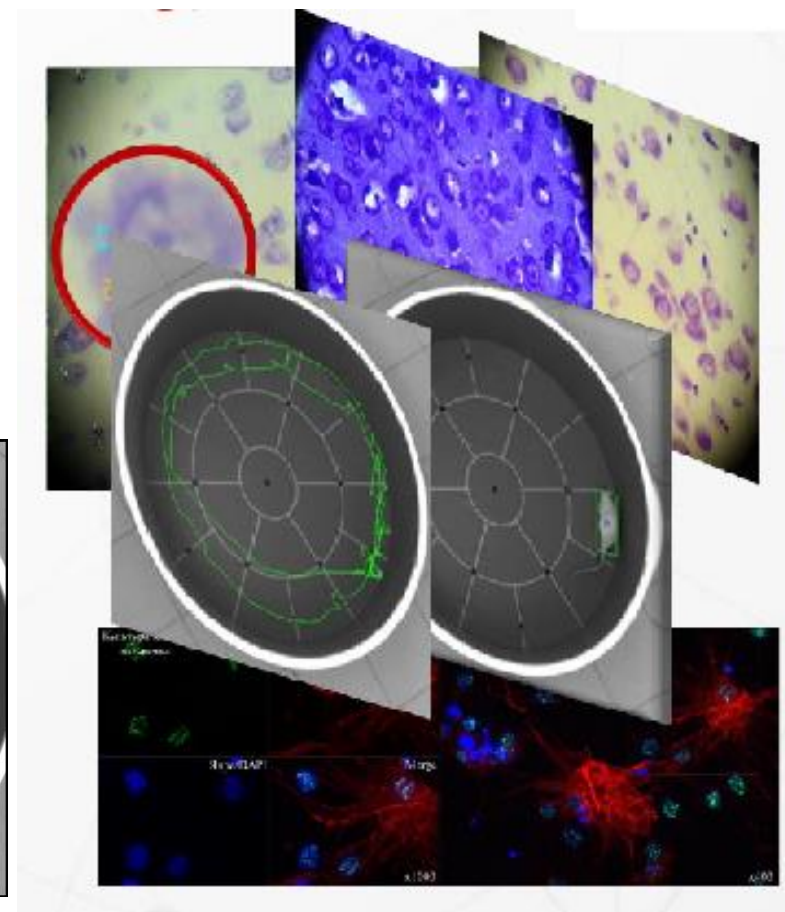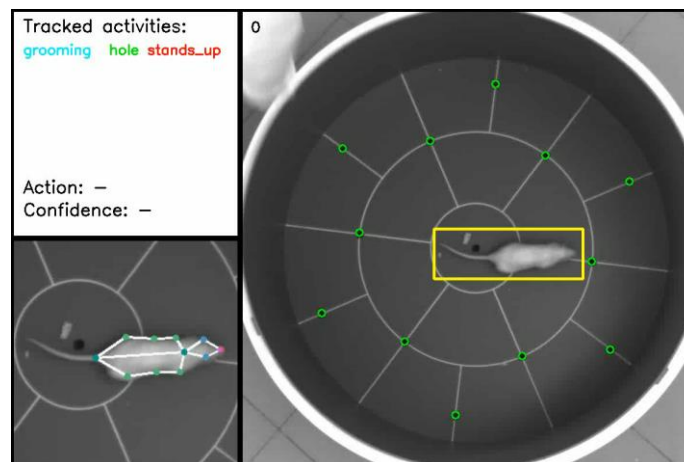
https://it4bio.jinr.ru

BIOHLIT information system

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

Data formats
- video recordings of animal behavior
- photo of histological sections
- confocal microscopy images

Radiation Protection

Radioprotectors:

regulatory mechanisms and pharmacological modulations of radiation effects
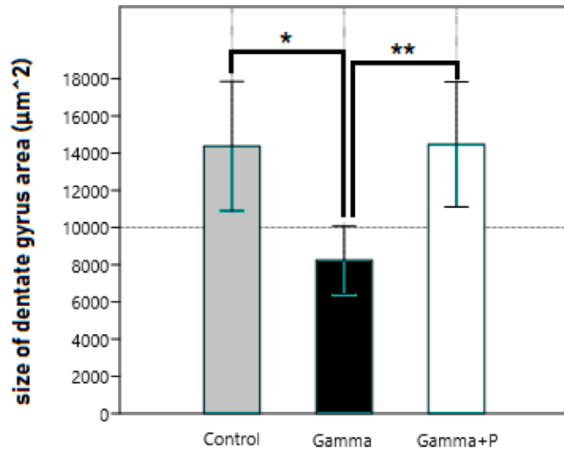
The effect of 2 week - piracetam injection after irradiation on size of DG area of hippocampus
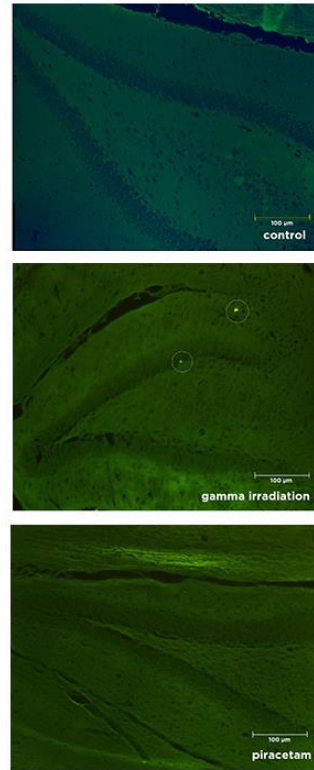
Radiation Research:

evaluation of radiation risks at nuclear objects, accelerator complexes, and spacecraft

A scheme of **Space Radiation Simulator** target to be installed at SIMBO station

^{56}Fe 1GeV/u

Comparison of space radiation charge spectra and simulator radiation field

Radiation Neuroscience

Main task

study of the mechanisms of radiation-induced disorders in the central nervous system

Space radiobiology

• Radiation physiological studies on mammals and primates, assessment of radiation risks for astronauts
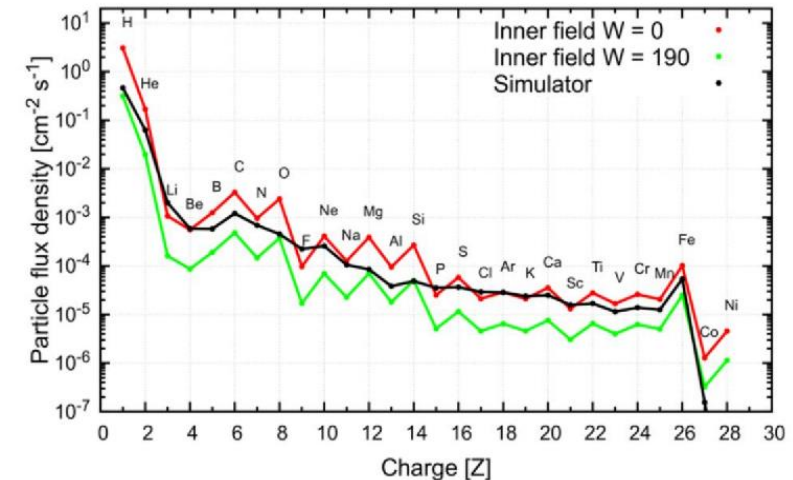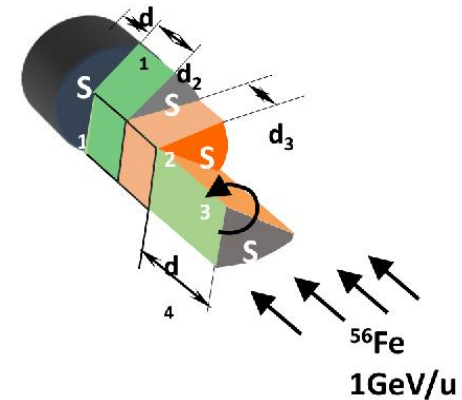
• Research of neuro-radioprotective properties of pharmaceuticals

Medicine

• Animal simulation studies of side effects of brain tumors radiation therapy
• Simulation on animals of the development of neurodegenerative diseases under the action of accelerated heavy ions
• Mathematical modeling of genetic and molecular mechanisms of neurodegenerative diseases

Radiation Medicine

Novel method to improve the efficiency of radiation therapy of cancer
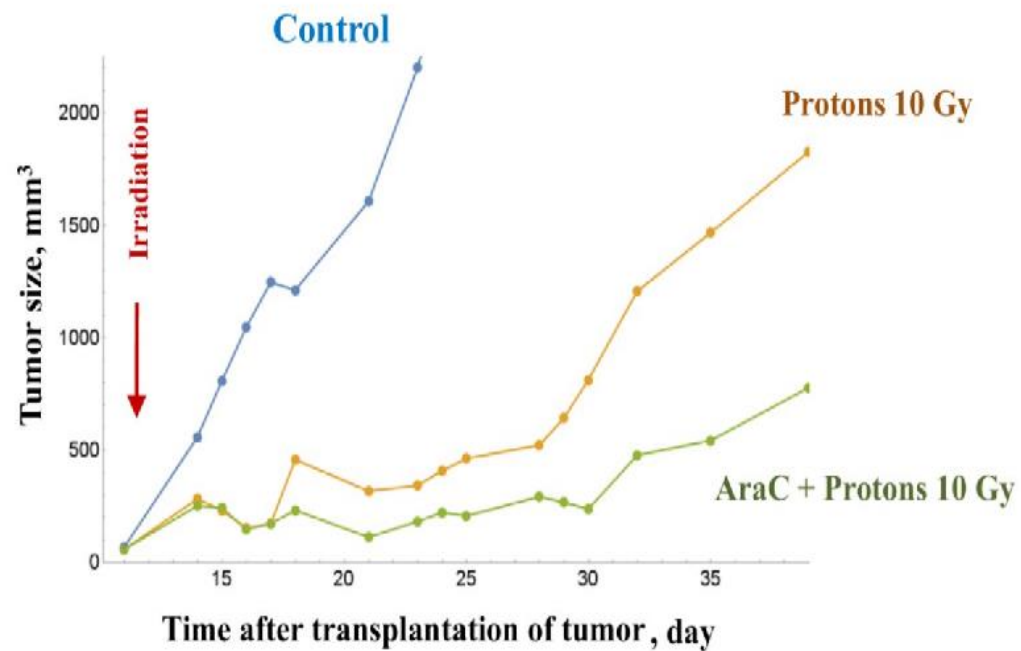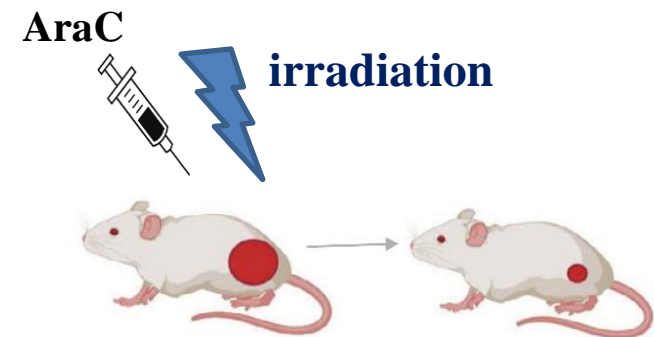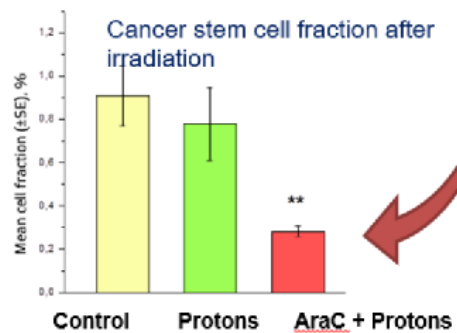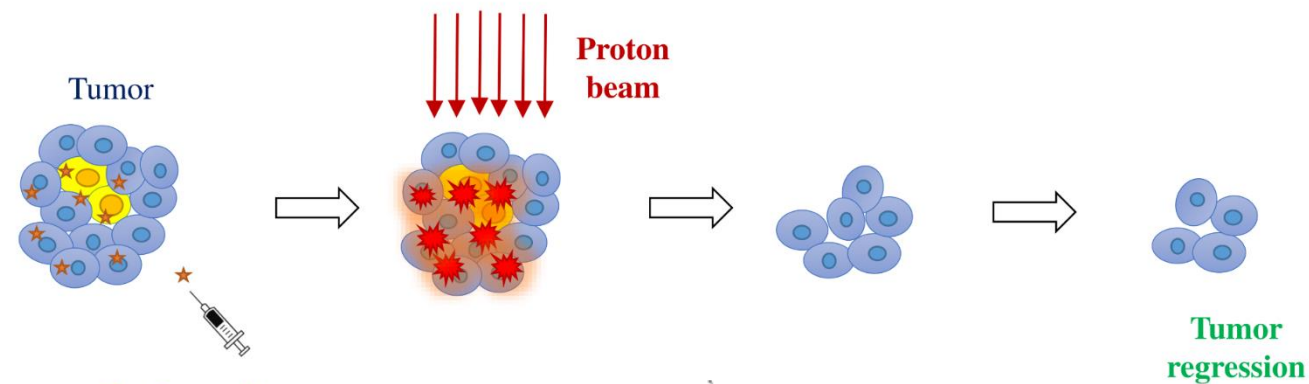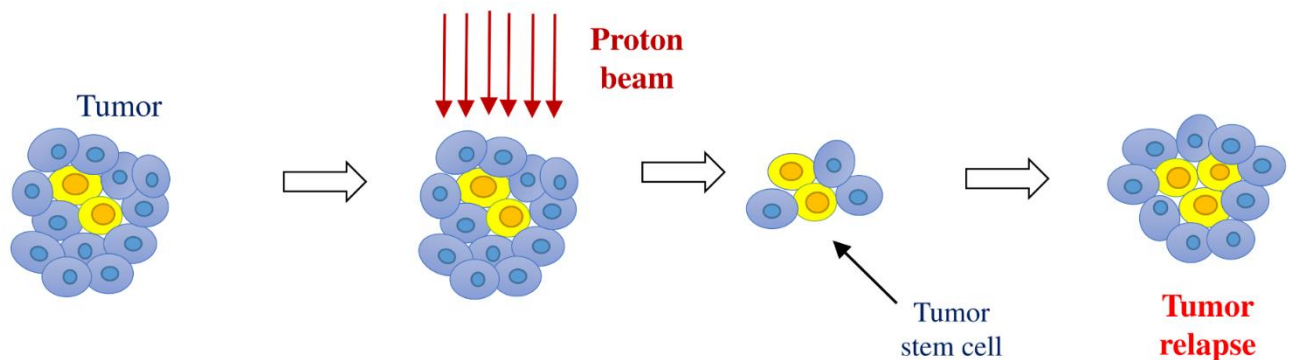
Radiation Medicine

Novel methods to improve the efficiency of radiation therapy of cancer
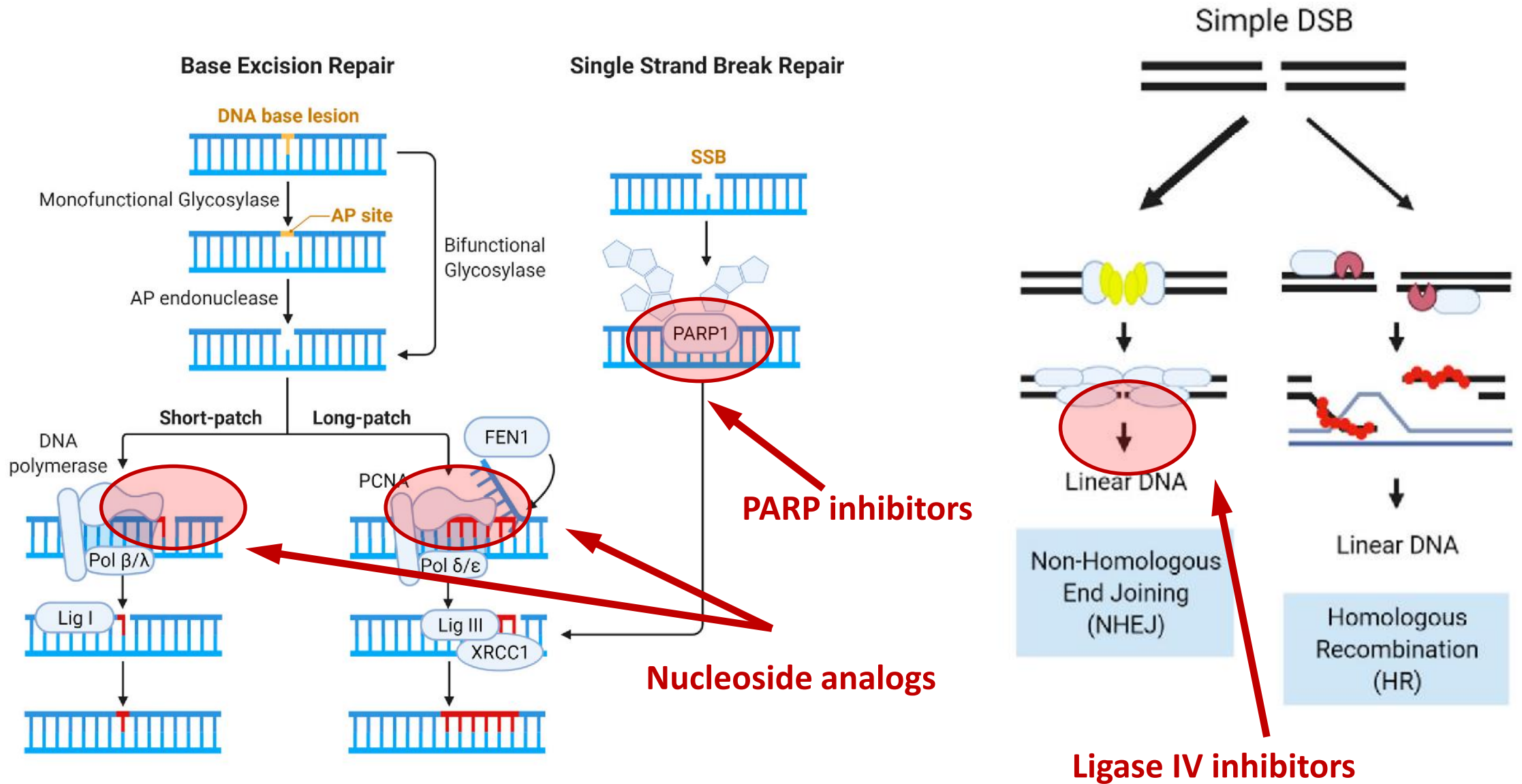
Radiation Medicine

Novel methods to improve the efficiency of radiation therapy of cancer

General strategy:
conversion of **simple**
DNA lesions **to complex**

Radiation

1 **DSB**
:
10 **SSB**
:
100 **BD**

Drug
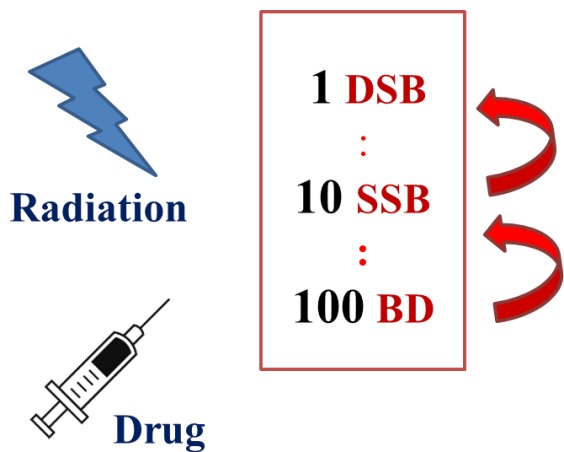
Patents No.
2798733 (2023)
2774032 (2022)
2699670 (2019)
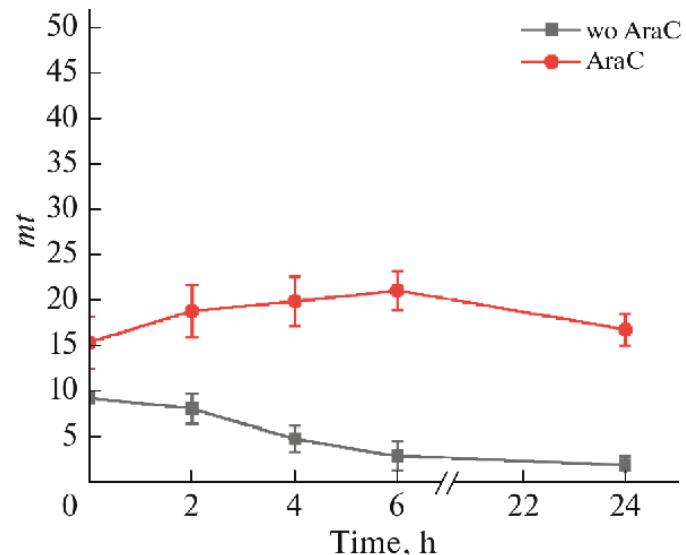
Melanoma B16

5 Gy 170 MeV protons
(spread out Bragg peak)

Glioblastoma U87

1.25 Gy 170 MeV protons
(spread out Bragg peak)
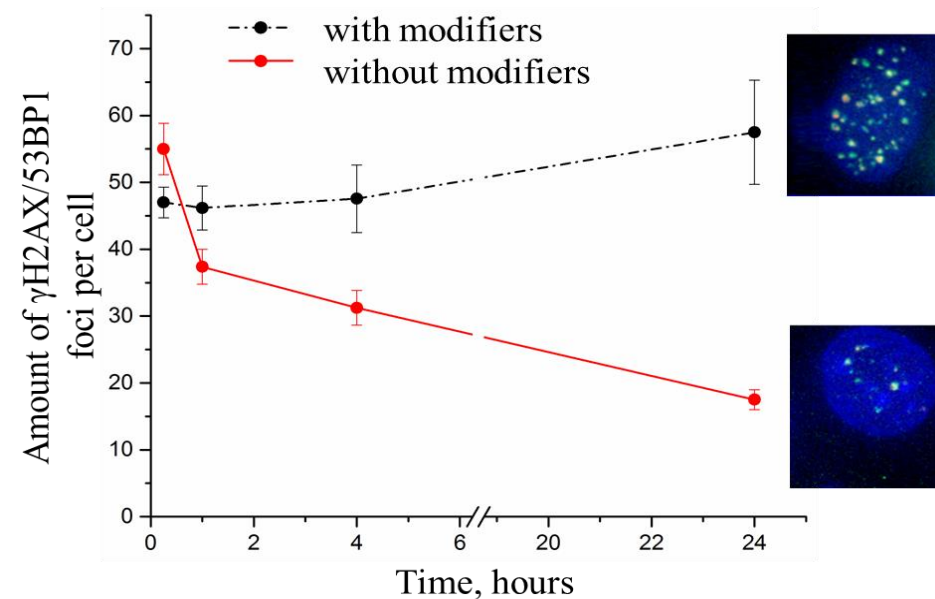
Radiation Medicine

Molecular vectors for theranostics

targeted therapy of melanoma with alpha-emitters

^{211}At

MB

^{211}At

^{211}At-MB

Melanoma cell survival

Volumetric activity of the isotope, kBq/mL

Accumulation, % /g

tumor
muscles
blood

Time, h

High affinity to melanoma cells

^{211}At-MTB melanoma Bro

^{211}At-MTB fibroblasts

Accumulated activity, Bq/10^5 cells

Time, hours

Methylene blue (MB)
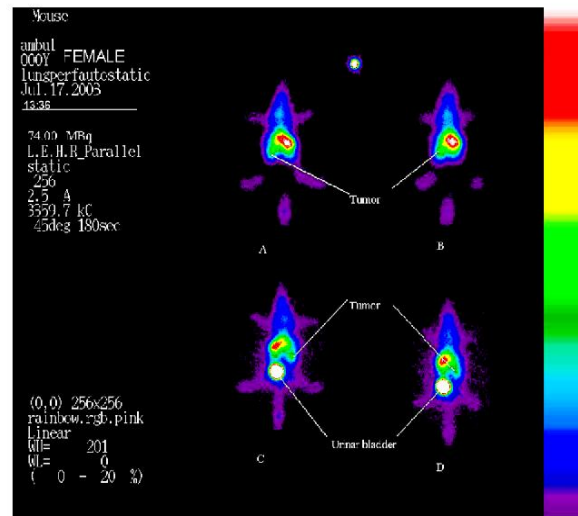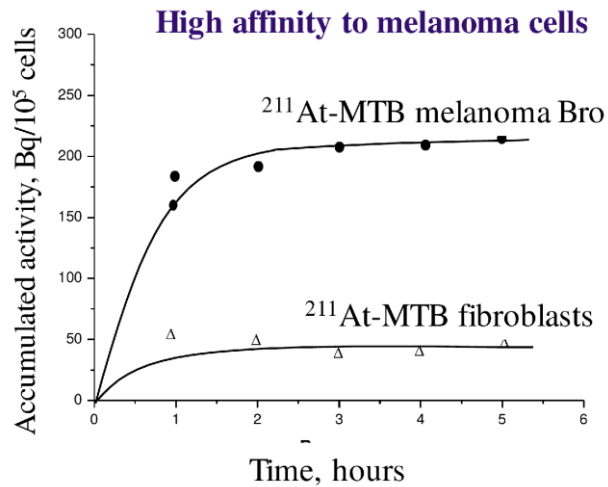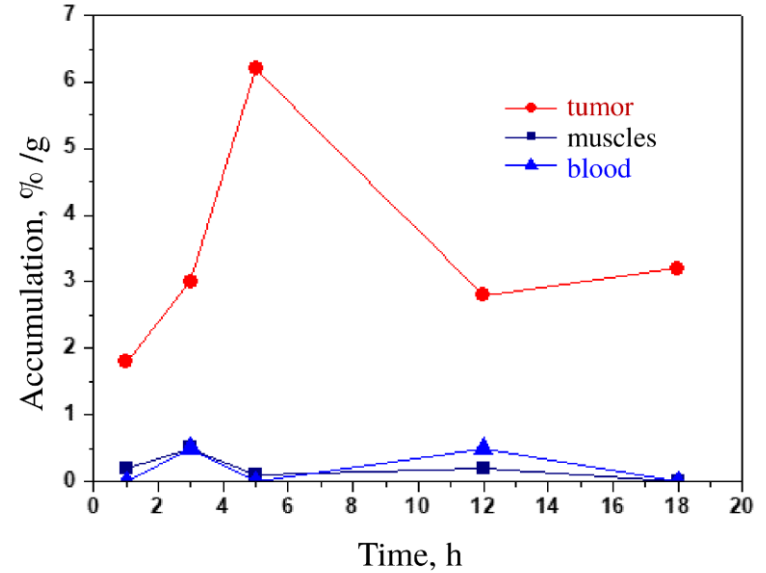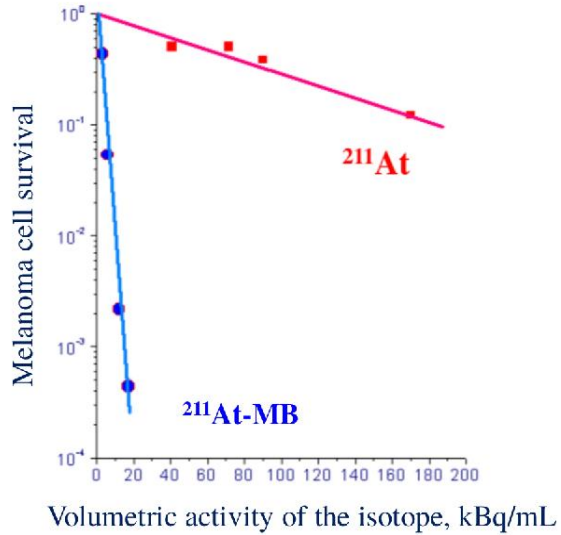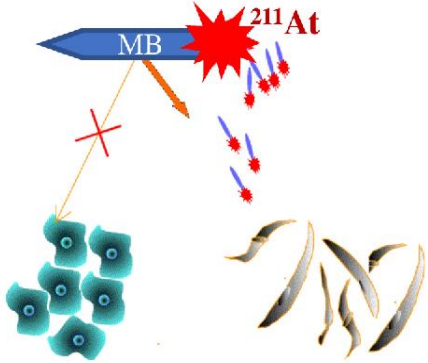
Visualization of ^{131}I-MB accumulation in of animals with inoculated melanoma

Radiation Medicine

Neutron beams

Fast neutrons

Epythermal neutrons:

neutron capture therapy:

$10^8 - 10^9$ n/cm²/s

Reactors
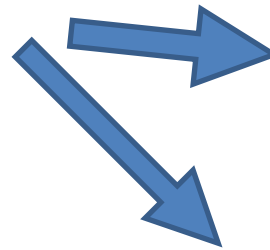
Neutron generators
e.g. 14 MeV n НГ12И

Proton accelerators

8 MeV p (Be target) 5mA

2.5 MeV p (Li target) 10-30mA

n → ^{10}B → ^{7}Li 0.84MeV
→ γ
0.48 MeV
→ α
1.47 MeV

n → ^{6}Li → ^{3}H 2.73 MeV
→ α 2.05 MeV

Taskaeva et al, Life 2023
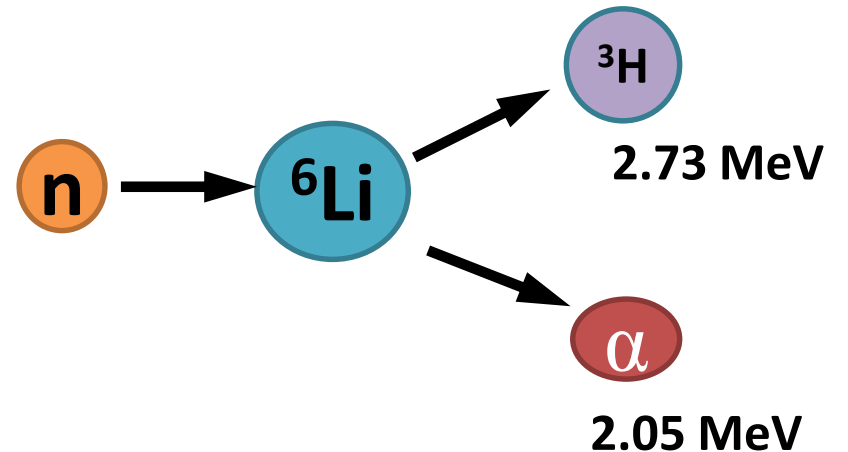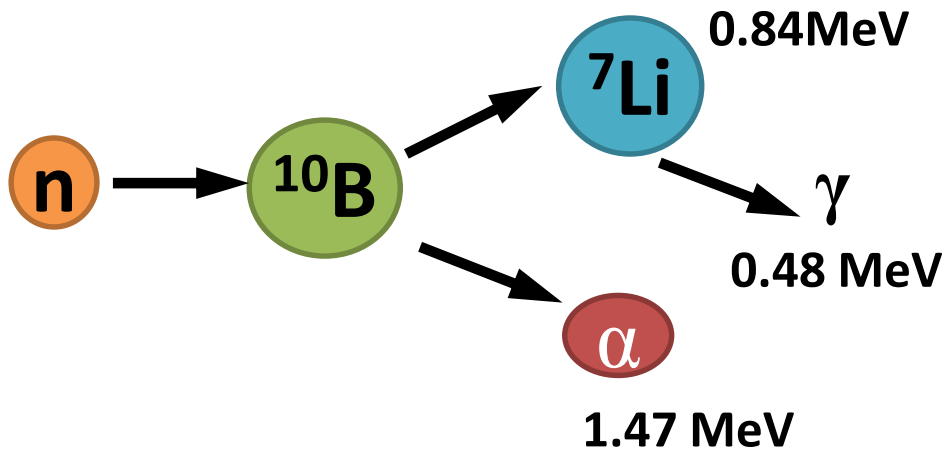
JINR Facilities for Research in Radiation Medicine

Conventional RT and CT

SARRP X-ray complex

2022 launched

Proton therapy

New superconducting cyclotron MSC230, FLASH regime

end of 2025

Heavy ion beams

U400M cyclotron
Genom-3 (in vitro)
Genom-4 (in vivo)

light ions
Li-Ar
50 MeV/u
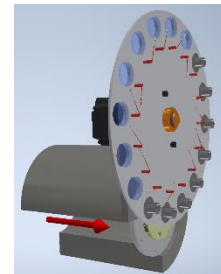
end of 2024
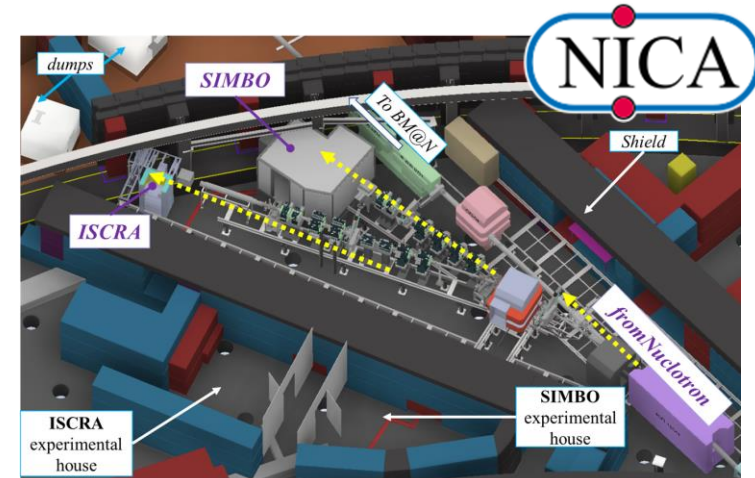
Nuclotron (ion synchrotron)

Station of **I**nvestigation of **M**edico-**B**iological **O**bjects (**SIMBO**)

$^{12}C^{6+}$, $^{40}Ar^{18+}$, $^{56}Fe^{26+}$, $^{84}Kr^{36+}$

Ion energy 400-1100 MeV/n

Flux density 10^3-10^5 particles/(cm^2.s)

Beam intensity, 10^6-3×10^9

particles per pulse

2025

JINR Facilities for Research in Radiation Medicine

Neutron capture therapy

1) IBR-2 reactor

2) EG-5m accelerator (p, Li target)

2025-2026

Nuclear medicine

Class I Radiochemical Lab

40MeV e-accelerator.

R&D in photonuclear reactions

for production of radioisotopes

^{99m}Tc, ^{177}Lu, ^{188}Re
^{225}Ac
^{47}Sc, ^{44}Sc, ^{67}Cu, ^{105}Rh
^{195m}Pt
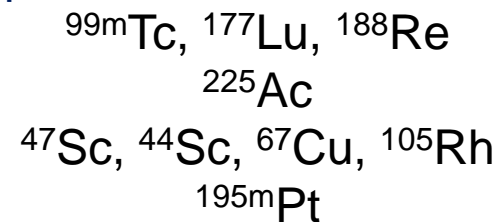
2026-2030

In vitro and *in vivo* biological research

Super-resolution
fluorescent microscopy
flow cytometry, NGS
LS-MS …

Automated
biological data
processing

SPF-grade vivarium
(w radiochemical block)
multimodal CT
(SPECT,PET,…)

2024-2028

SARRP (Small Animal Radiation Research Platform) Laboratory of Radiation Biology, 2022

SARRP imitates modern X-ray radiation therapy systems for animal research
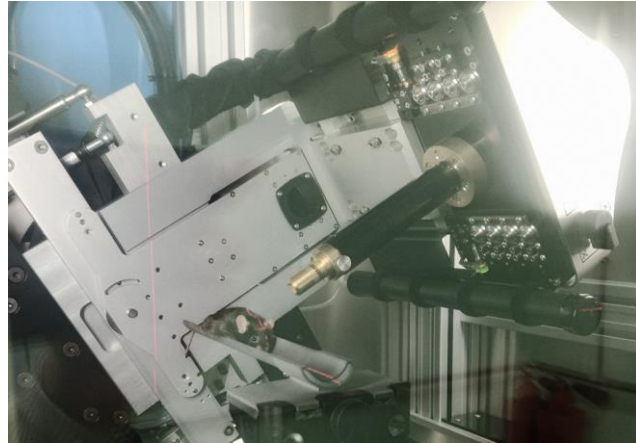
The 360° gantry and motorized stage allow for non-coplanar beam delivery from any angle.

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

Clinical Radiobiology

Main task:
Development of new breakthrough approaches to improve the effectiveness of radiation and radionuclide therapy of cancer

Radiation Therapy

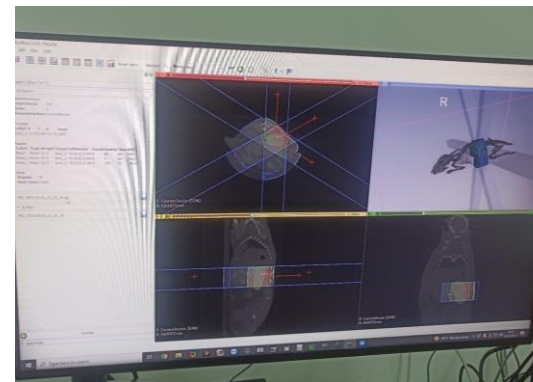*Development of approaches to increase radiosensitivity by interfering with the work of genetic regulatory networks of the cell :*

pharmaceuticals, transgene systems

targeted delivery (molecular vectors)

Nuclear medicine

Development of radionuclide targeted delivery

Preclinical animal research

Development of new treatment plans

International Research Program in Radiation Biology: Expected Results

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.

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