Research on the Biological Effects of Ionizing Radiations with Different Physical Characteristics

Alexander Bugay

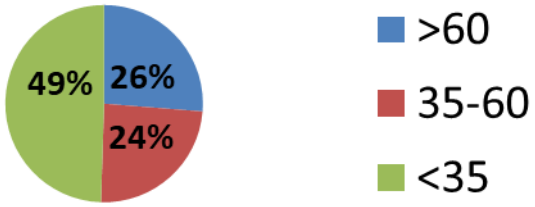
56th meeting of the PAC for Condensed Matter Physics

Laboratory of Radiation Biology

lrb.jinr.ru

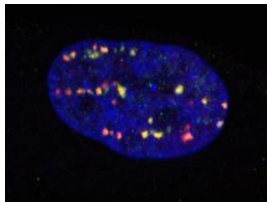
- 1959 - first radiobiological experiments (synchrocyclotron, LNP)
- 1978 - Biological Research Sector
- 1988 - Biological Division at DLNP
- 1995 - The Department of Radiation and Radiobiological Research
- **2005 - Laboratory of Radiation biology**

LRB personnel age distribution

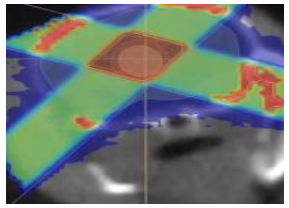


Main Research Fields:

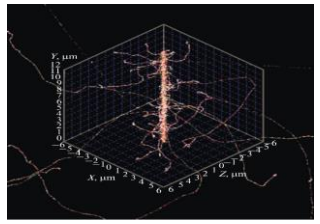
Molecular Radiobiology



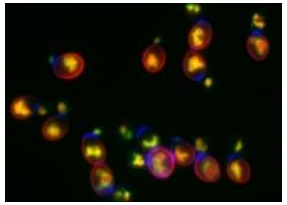
Clinical Radiobiology



Mathematical Modeling



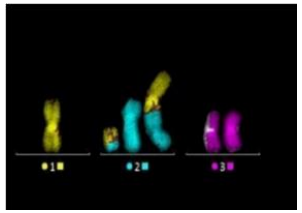
Radiation Genetics



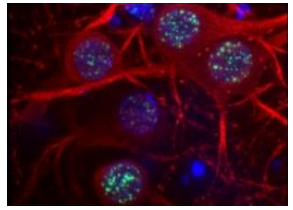
Radiation Physiology

Radiation Research

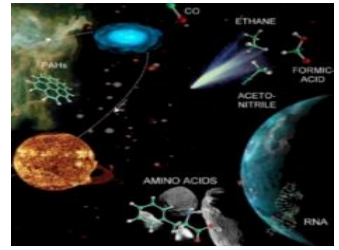
Radiation Cytogenetics



Radiation Neuroscience



Astrobiology

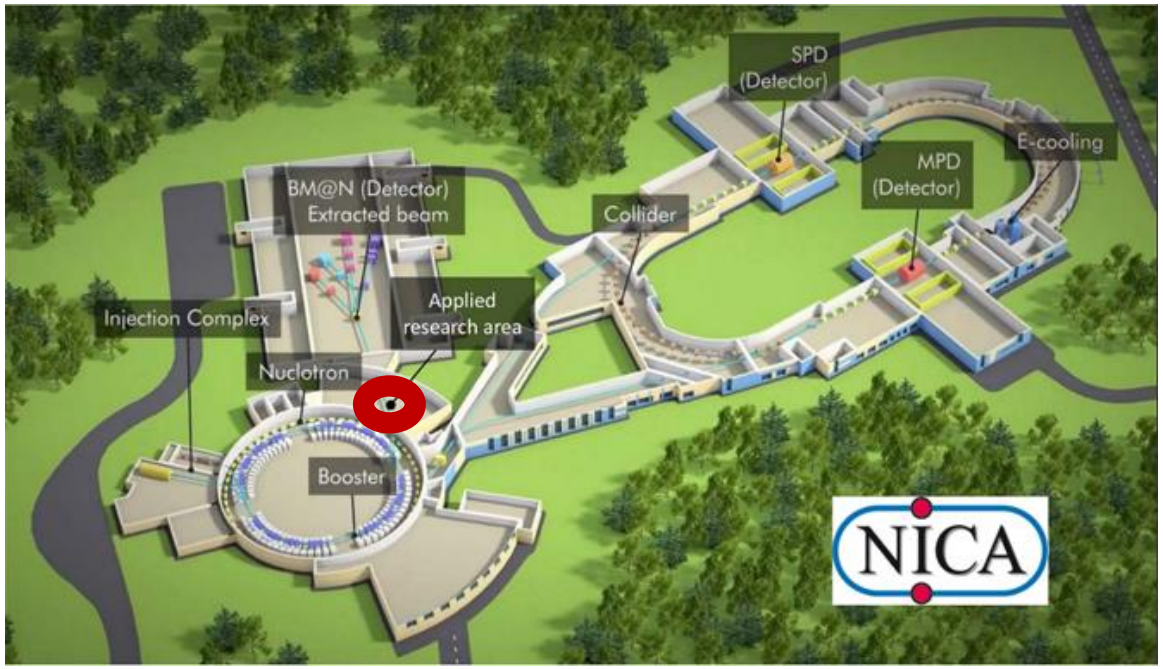


JINR's radiation sources for radiobiological studies

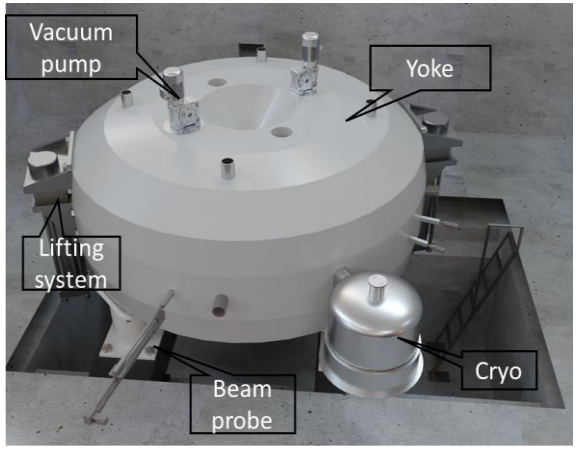
Phasotron:
protons 170 MeV

U-400M cyclotron:
heavy ions 50 MeV/u (Li-Ne)

Nuclotron: heavy ions 0.3-1 GeV/u (H – Kr)



cyclotron MSC230
(since 2024):
protons up to 230 MeV



IBR-2, IREN: neutrons

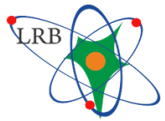
SARRP: X-ray

Linac200:
electrons 20-200 MeV

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

World landscape

World research trends in radiobiology:

Space radiation risks: brain damage, probability of cancer

Particle therapy and radiation medicine: FLASH effect, radioactive ion beams (RIB), mini-beam radiotherapy, combination with drugs and immune-therapy, theranostics, new radionuclides

JINR advantages

- Multiple radiation sources with applied channels (protons, neutrons, heavy ions, radionuclides)
- Specialized Laboratory and team of specialists
- Infrastructure for large scale animal research including primates
- Member of International Biophysics Collaboration

Leading accelerator centers with biomedical programs

in operation:

Germany:	GSI (protons, heavy ions)
France:	GANIL-SPIRAL2 (protons, heavy ions, neutrons, radionuclides)
Italy:	CNAO, LNS-INFN (protons, neutrons, heavy ions, radionuclides)
Japan:	HIMAC (protons, heavy ions)
South Africa:	iThemba (protons, neutrons, radionuclides)
USA:	NSRL at BNL (heavy ions +cosmic spectrum)

under construction:

FAIR (Germany), FRIB (USA), RAON (Korea), HIAF (China)
ELI (Europe), LhARA (UK)

Topical Plan for 2017-2023

04-9-1077-2015/2023

“Research on the Biological Effect of Heavy Charged Particles of Different Energies”

1 Project

04-9-1112-2013/2023

“Research on Cosmic Matter on the Earth and in Space; Research on the Biological and Geochemical Specifics of the Early Earth”

1 Project

Topical Plan for 2024-2030

New consolidated Theme

“Research on the Biological Effects of Ionizing Radiations with Different Physical Characteristics”

Theme Leaders: A.N. Bugay, E.A. Krasavin

2 Research Projects, 9 Subprojects

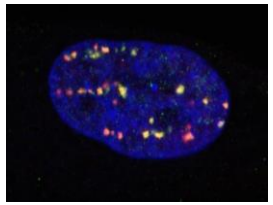
Theme

"Research on the Biological Effects of Ionizing Radiations with Different Physical Characteristics"

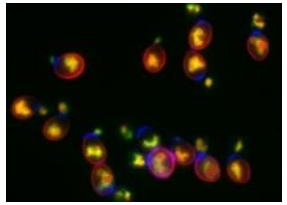
Project 1

6 subprojects

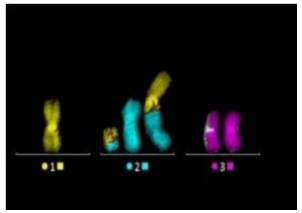
Molecular Radiobiology



Radiation OMICS

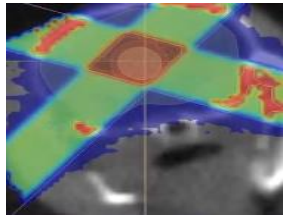


Radiation Genetics

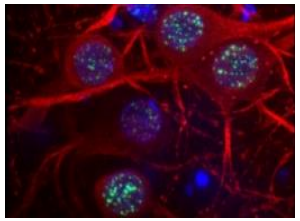


Radiation Physiology

Clinical Radiobiology



Radiation Neuroscience

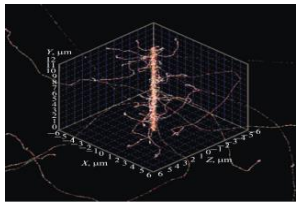


Project 2

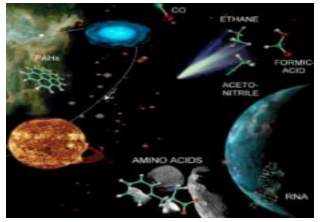
3 subprojects

Radiation Research

Mathematical Modeling



Astrobiology

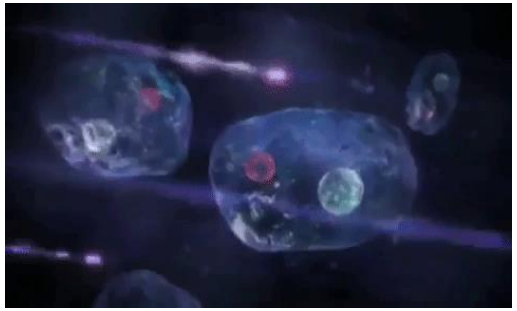


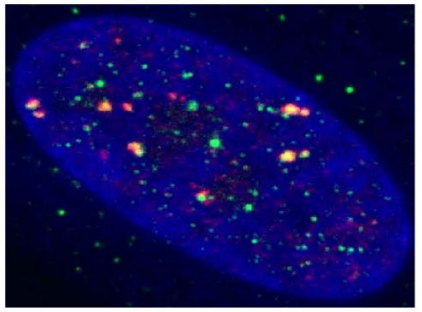
Activities

Molecular Radiobiology

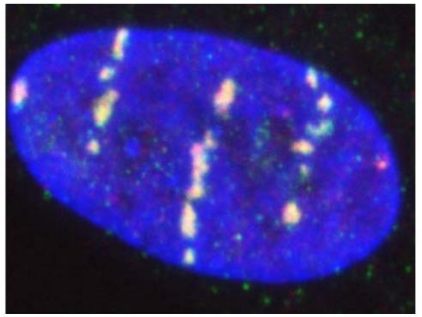
Studies of the patterns of formation and repair of cluster DNA damage after exposure of normal and tumor cells of mammals and humans to radiations of different quality.

DNA double-strand breaks - the molecular basis of cell death

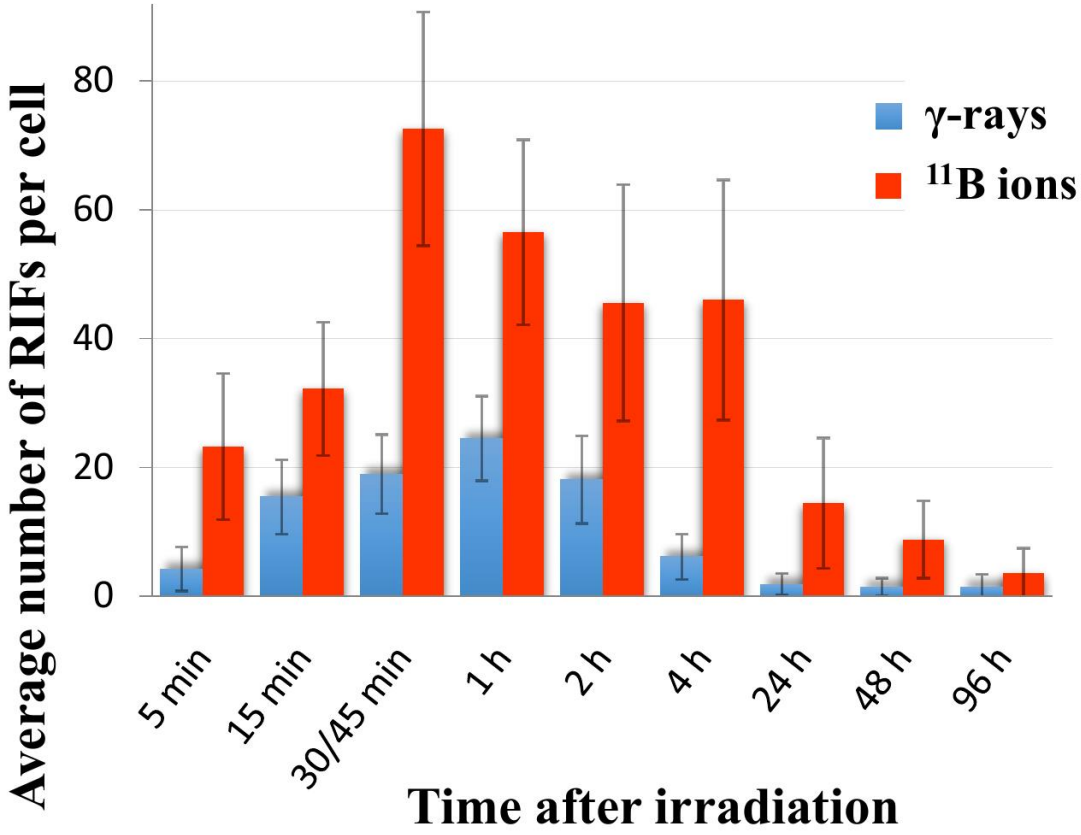




γ-rays

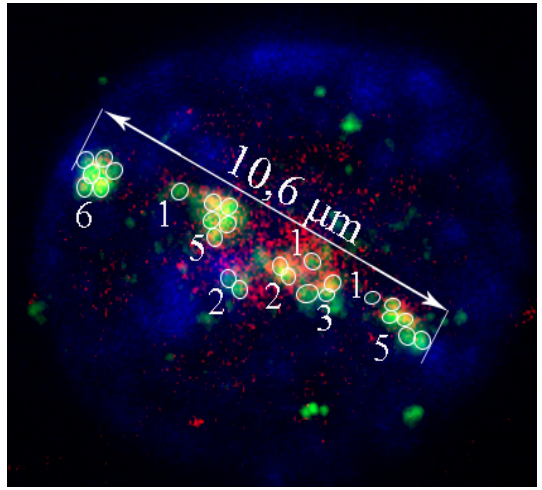


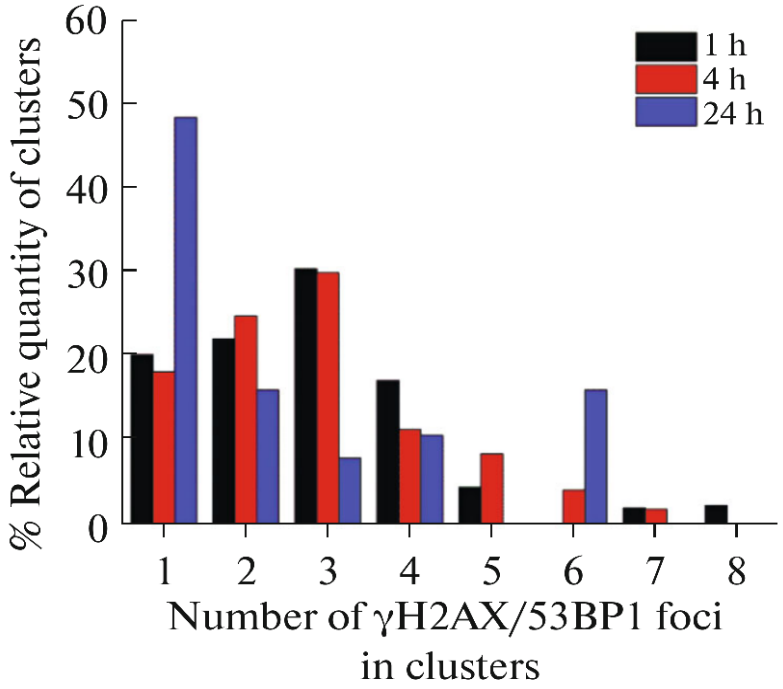
^{11}B ions

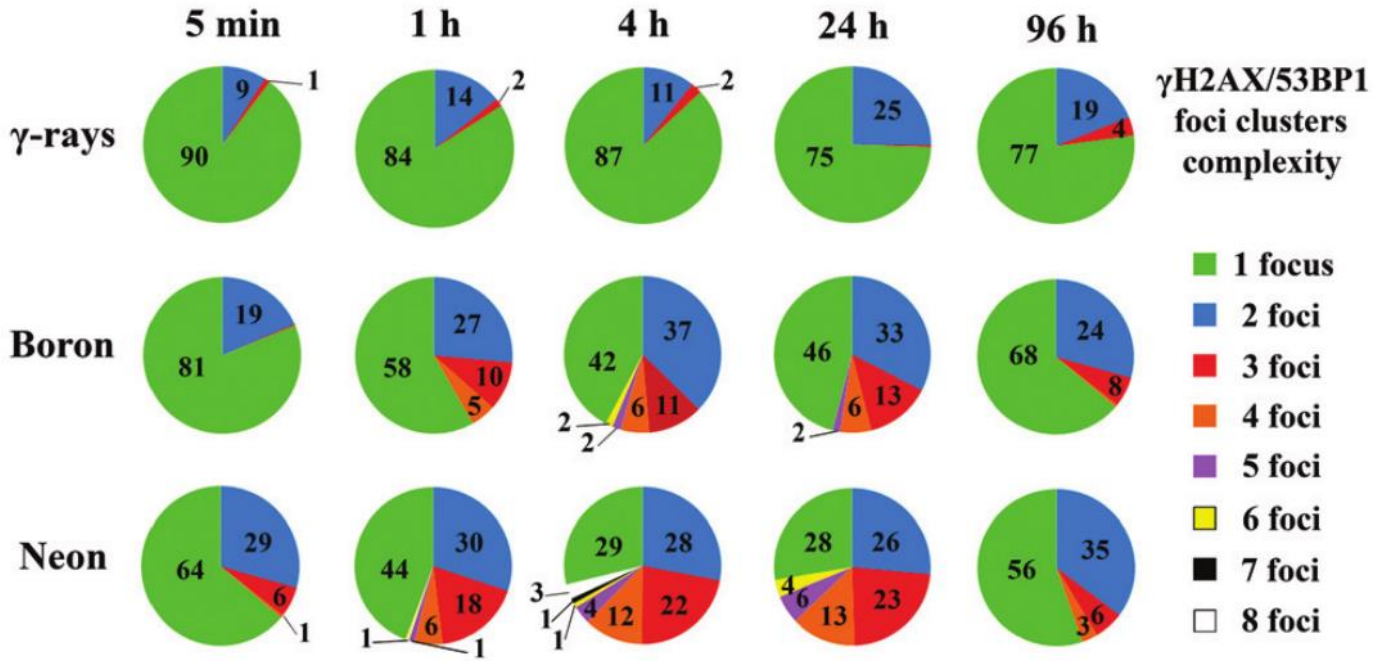


Molecular Radiobiology

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





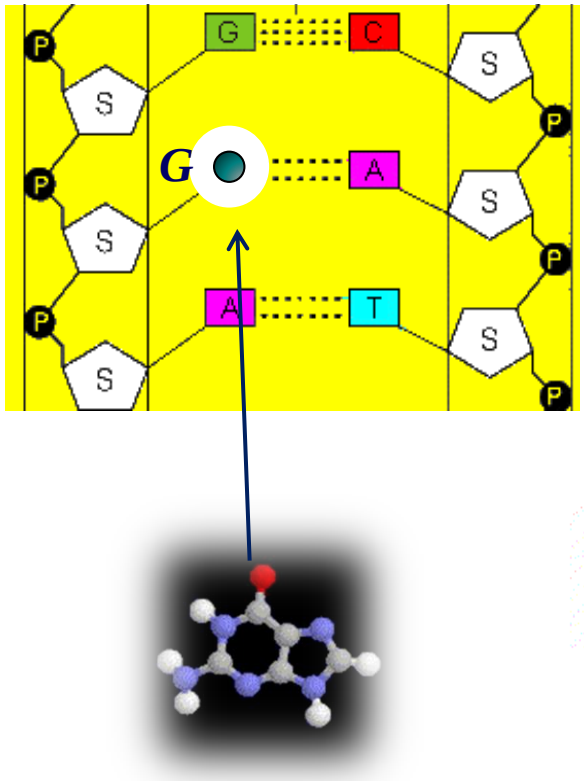


Ions with similar LET (~130 keV/mkm) generate foci clusters of different complexity

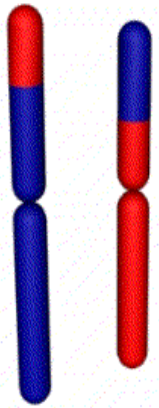
Radiation genetics

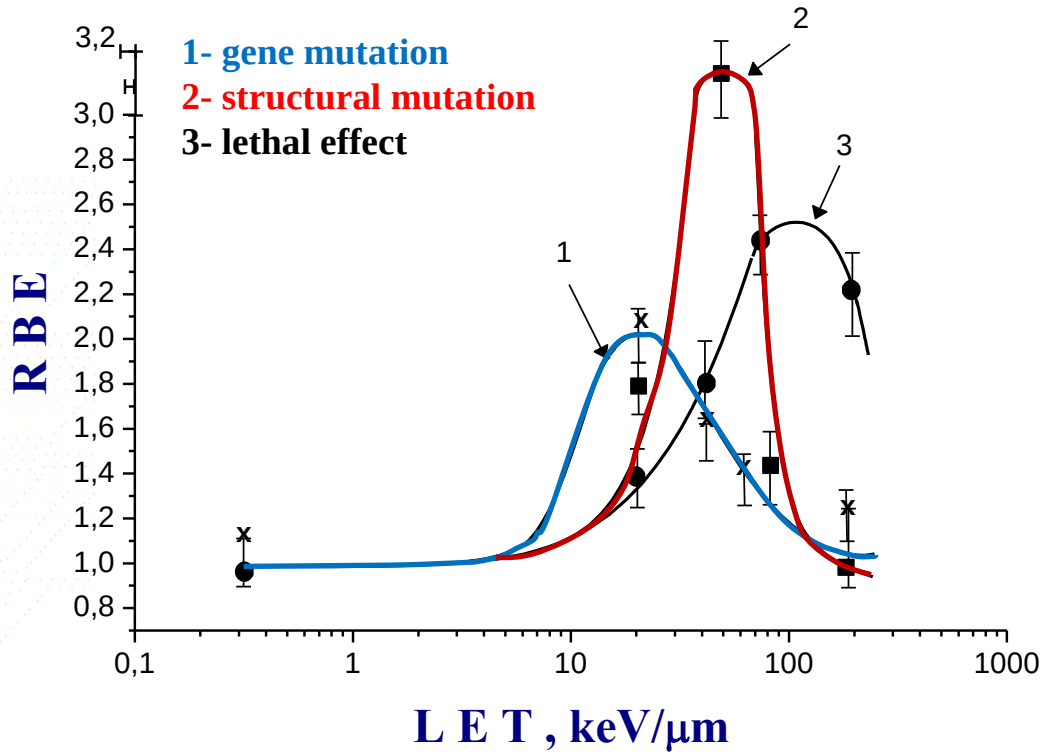
Mechanisms of induction of gene and structural mutations under the action of radiation of different quality on cells with different levels of genome organization had studied on microorganisms

Gene mutation



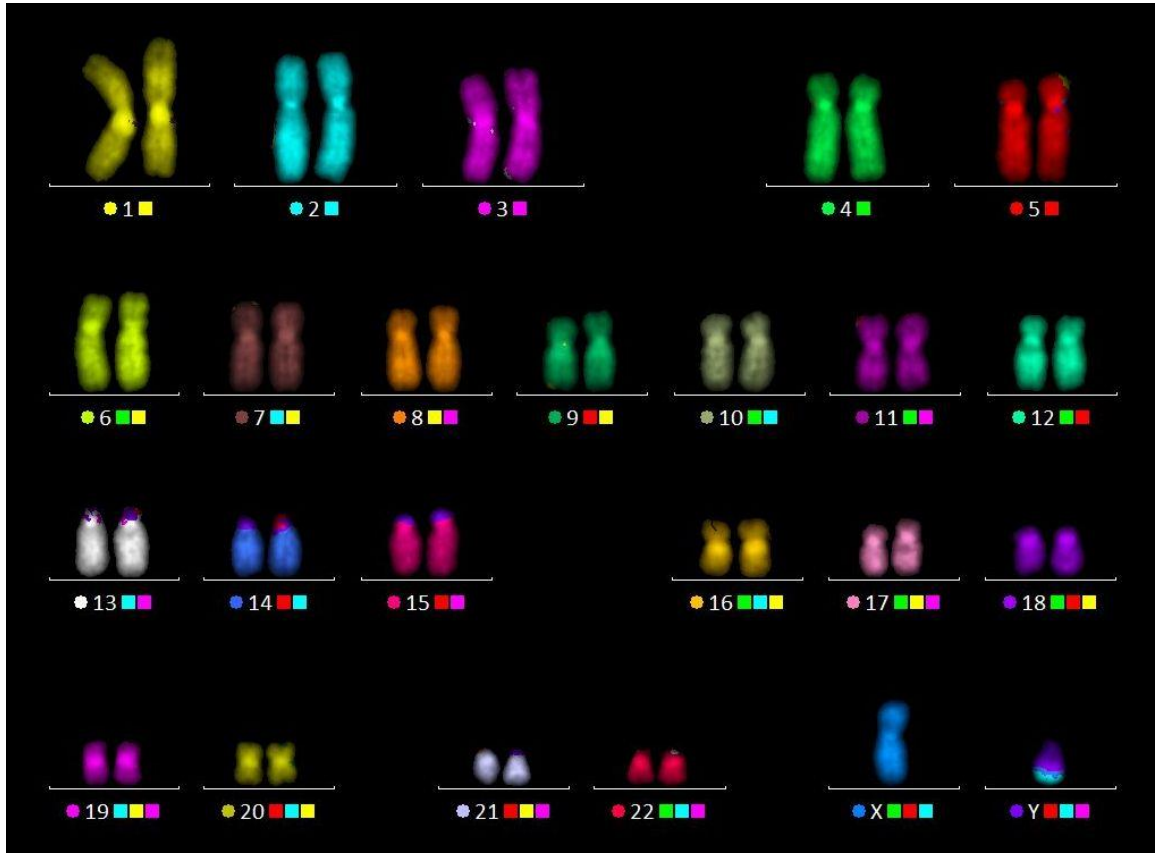
Structural mutation



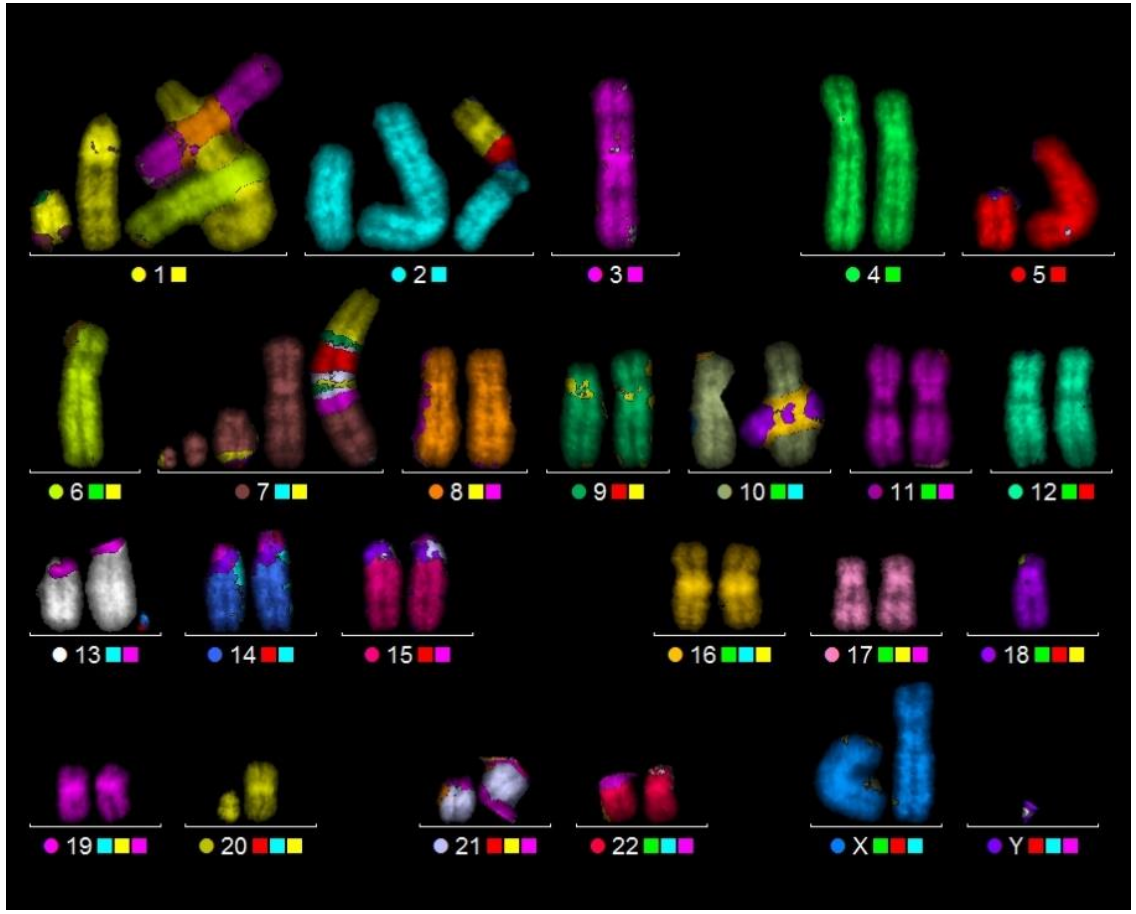


Radiation Genetics

Studies of patterns and mechanisms of formation of gene, structural and complex mutations in mammalian and human cells after exposure to radiations with different characteristics.

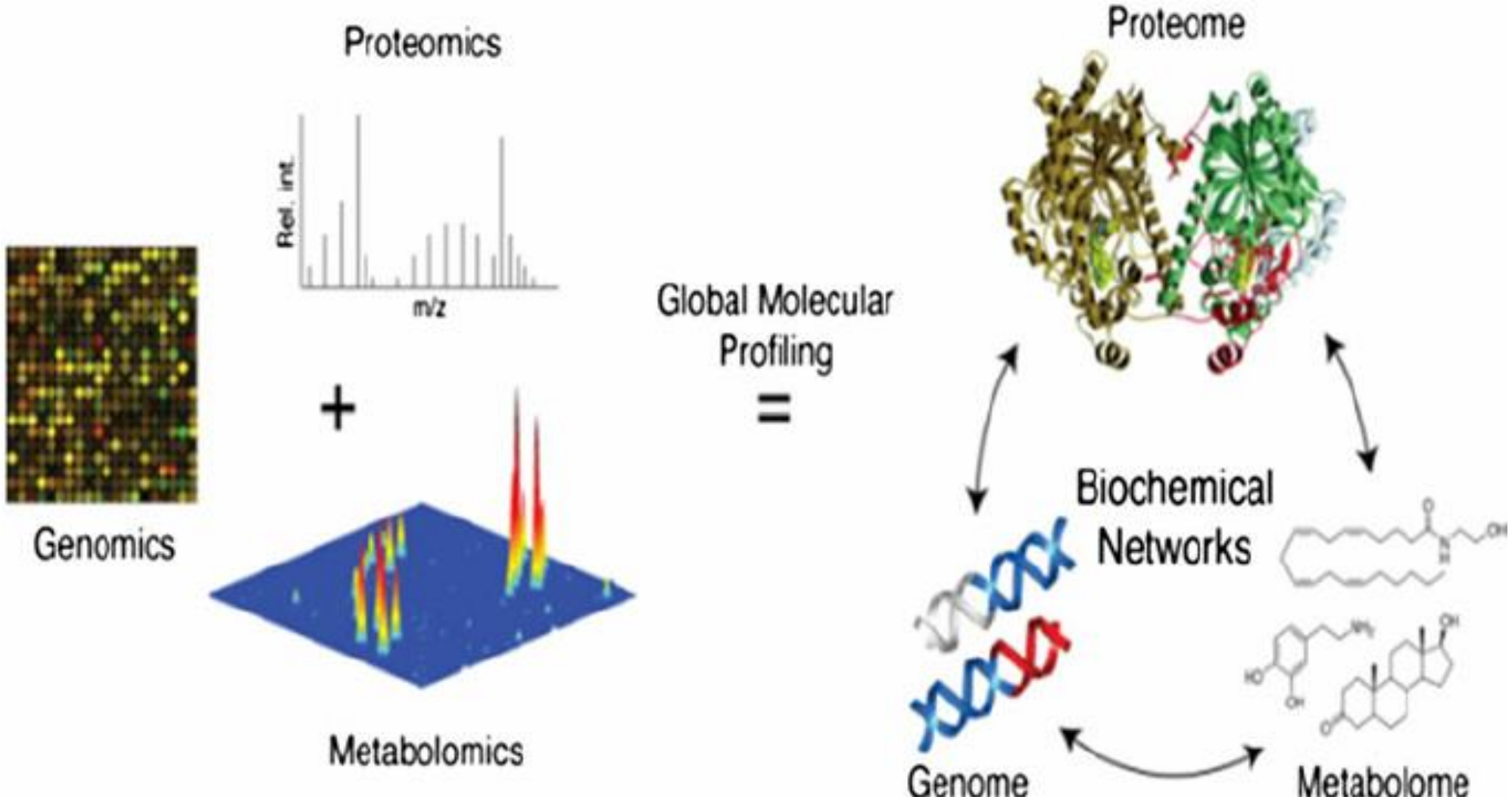


mFISH karyogram of normal human cells



Complex chromosome aberrations after irradiation with nitrogen ions

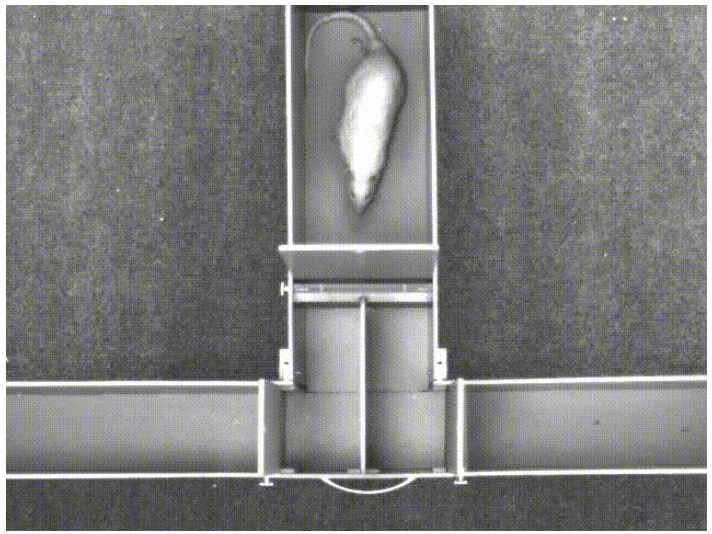
Implementation of OMICS-technologies



Bodrova et al 2012

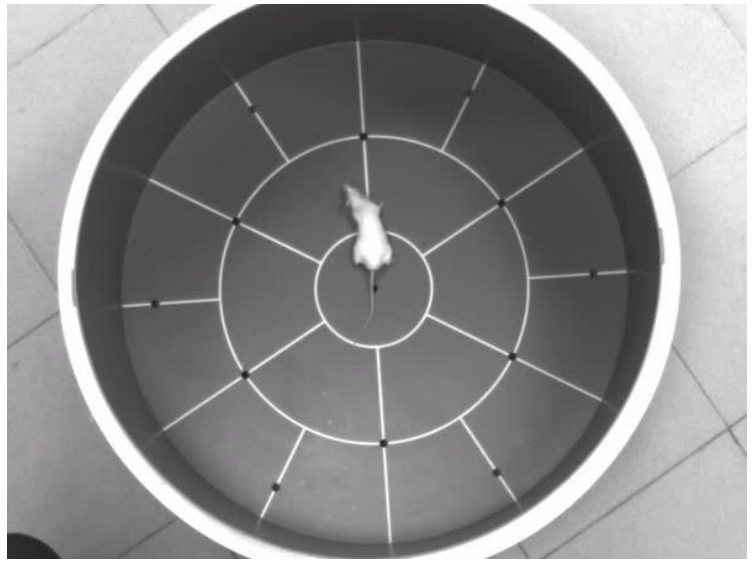
Radiation Physiology

Studies of violations of behavioral reactions and pathomorphological changes in various brain structures, critical organs and systems of irradiated animals under normal conditions and under the action of radioprotectors.

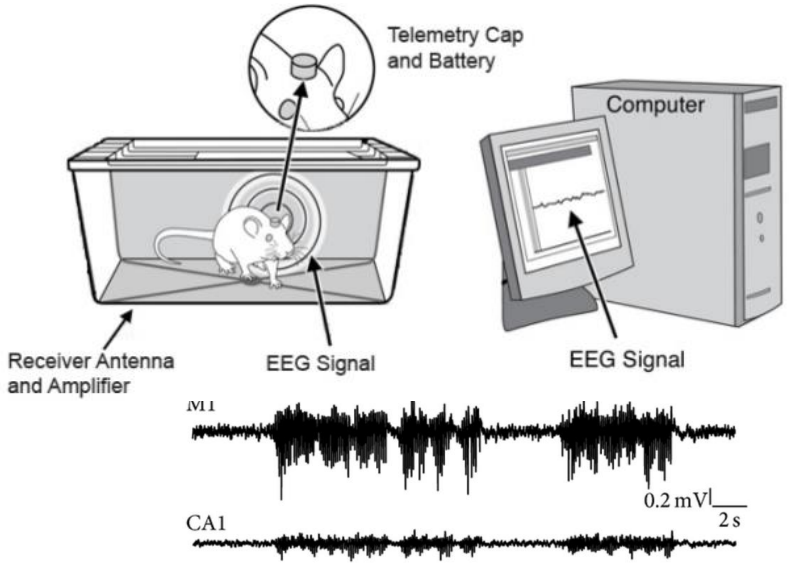


Behavior test systems

- Open field
- T - maze
- Morris water maze
- Barnes maze

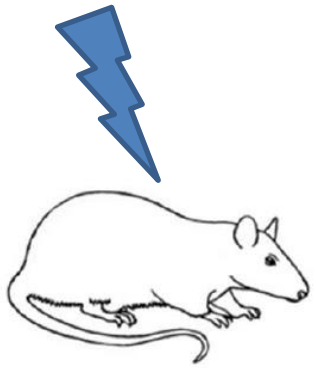


Electrophysiology studies



Comparative Analysis of Behavioral Reactions and Morphological Changes in the Rat Brain after Irradiation

Irradiation



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

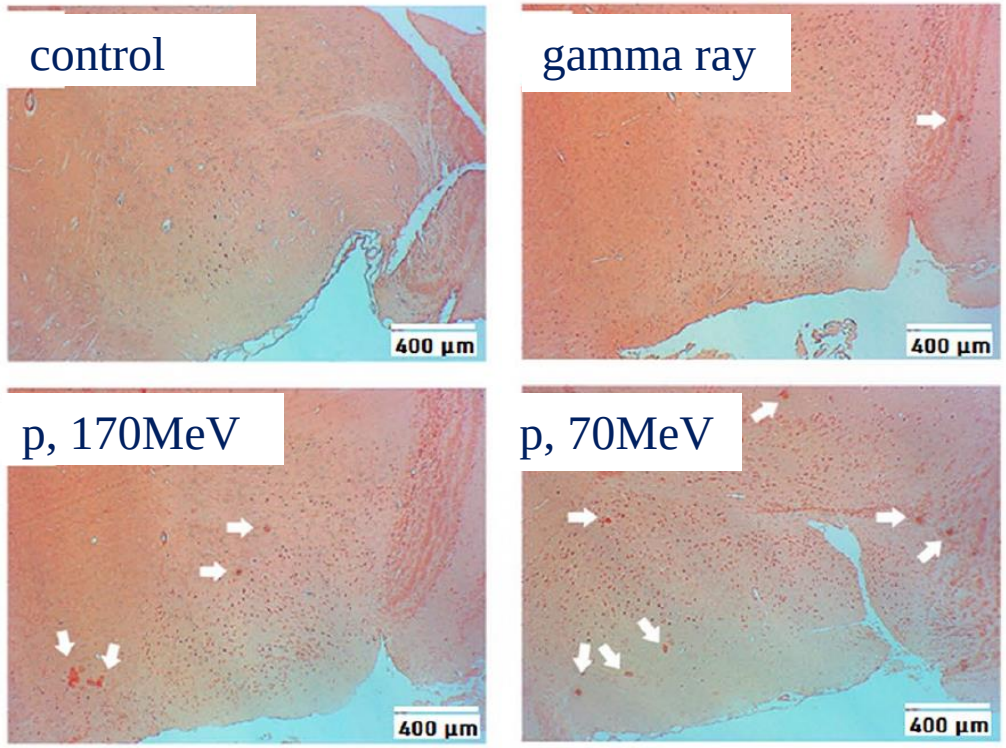
after 1 month

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



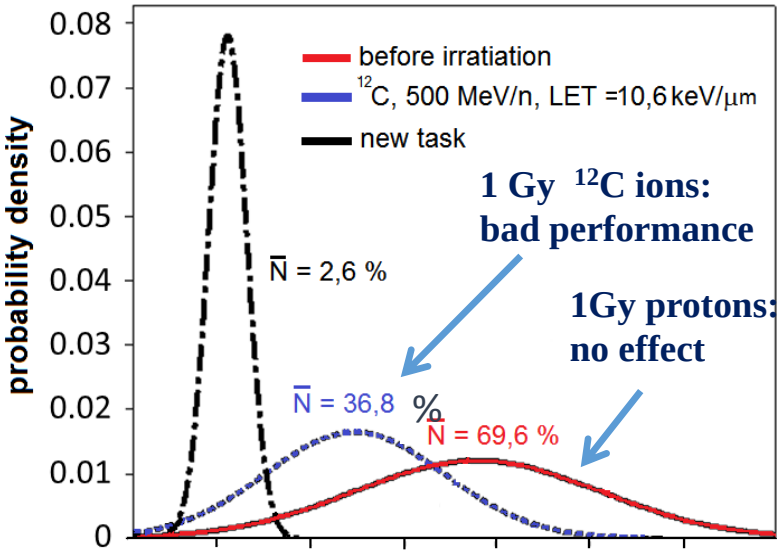
Amyloid plaques in the forebrain of rats (marked with white arrows)

The neurodegeneration increases with LET of radiation

Worldwide unique experiments with monkeys

The monkeys were preliminary trained to solve logical tasks with computer. The effect of exposure by 500 MeV/u ^{12}C ions at 1 Gy dose consisted in significant inhibiting cognitive activity of the monkeys.

Later on unique experiment was performed with irradiation of 2 GeV/u ^{78}Kr ions.

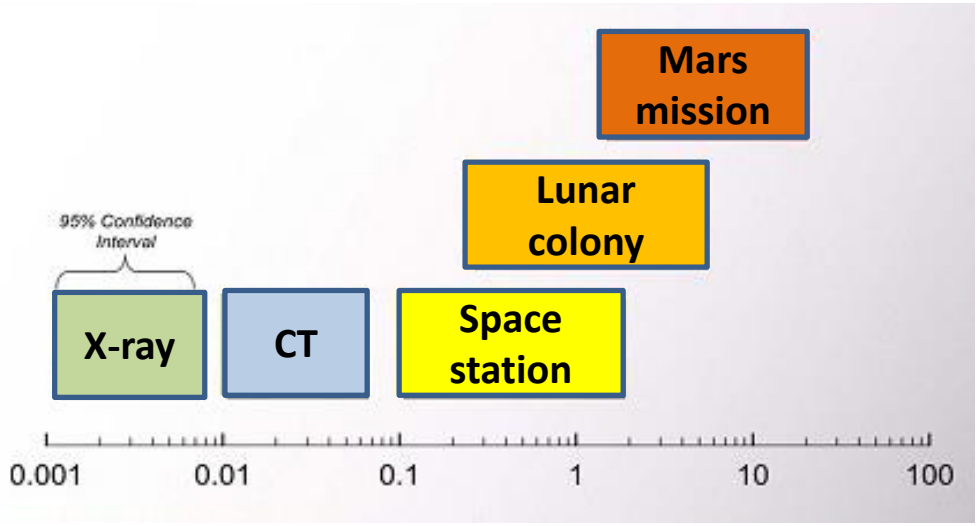


Automated computer system for the simulation of operator activity during the flight

Collaboration:

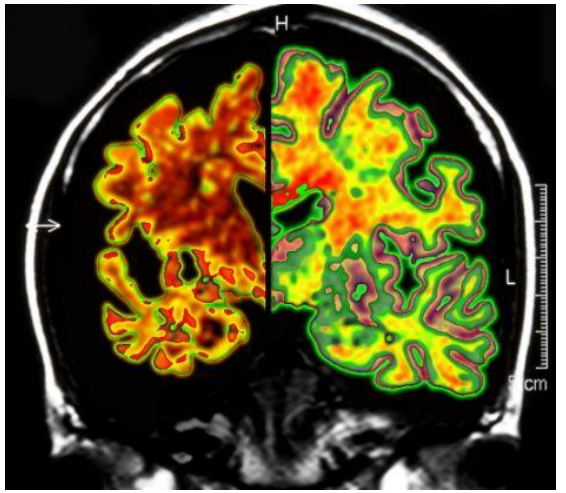
RAS Institute of Biomedical Problems,
RAS Institute of Medical Primatology,
RAS Institute of Higher Nervous Activity and Neurophysiology,
Moscow State University

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



% Risk of cancer death

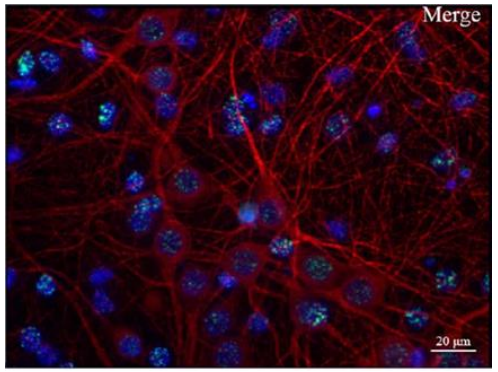
Paradigm shift



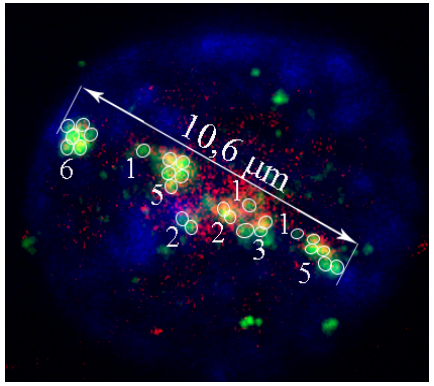
Radiation Neuroscience

Radiation Neuroscience

Studies of the mechanisms of neurodegeneration under the action of ionizing radiations of different quality

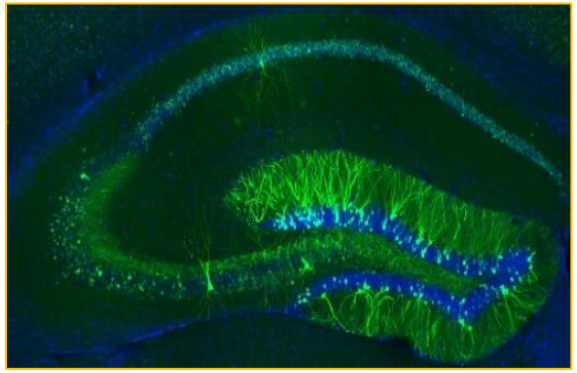


visualization of DNA damage in hippocampal cell culture

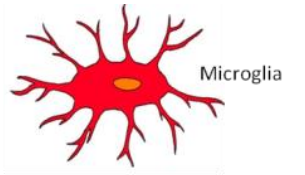


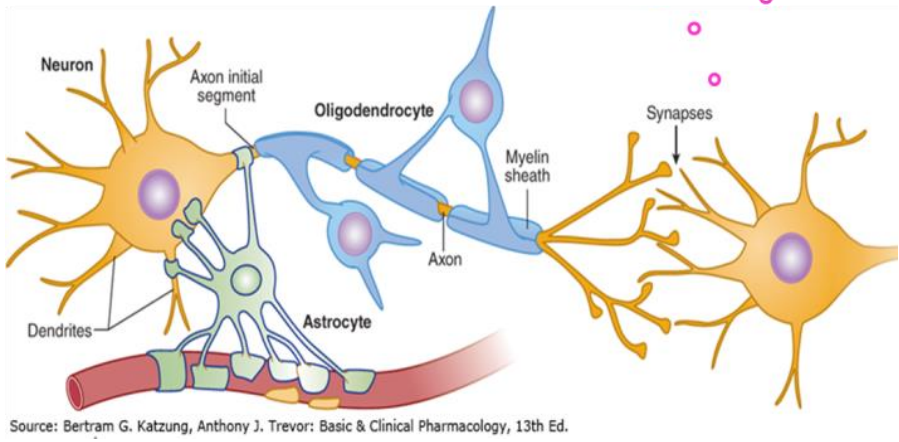
DNA damage in rat hippocampus cells 1 hour after exposure to ^{78}Kr ion tracks

- **Induction and repair of DNA damage:**
  - in neural cells (*in vitro*)
  - in brain structures (*in vivo*)
- **Suppression of neurogenesis**
- **The role of glial cells:**
  - demyelination
  - neuroinflammation
  - carcinogenesis



Visualization of different types of nerve cells in rat hippocampal slices





A link between radiation and neurodegenerative diseases?

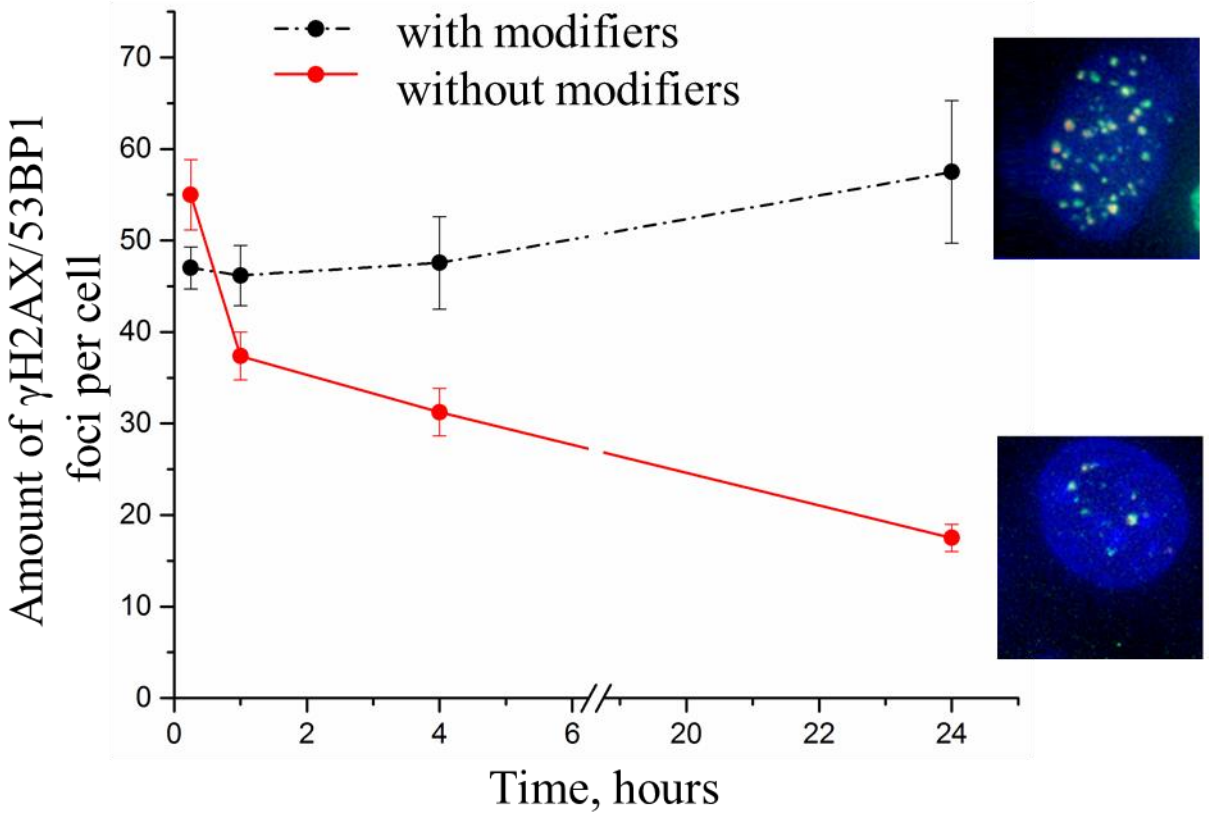
Alzheimer, Parkinson, Epilepsy …

The relationship between radiation and aging?

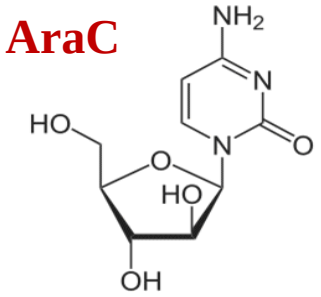
Clinical Radiobiology

A new method for increasing the biological efficiency of photon and proton beams

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



AraC



patents 2019, 2022

РОССИЙСКАЯ ФЕДЕРАЦИЯ

ПАТЕНТ

НА ИЗОБРЕТЕНИЕ

№ 2699670

СПОСОБ ПОВЫШЕНИЯ ЧАСТОТЫ ОБРАЗОВАНИЯ ДВУНИТЕВЫХ РАЗРЫВОВ ДНК В КЛЕТКАХ ЧЕЛОВЕКА ПРИ ДЕЙСТВИИ ИОНИЗИРУЮЩИХ ИЗЛУЧЕНИЙ В УСЛОВИЯХ ВЛИЯНИЯ РАДИОМОДИФИКАТОРОВ

Патентообладатель: *Объединенный институт ядерных исследований (ОИЯИ) (RU)*

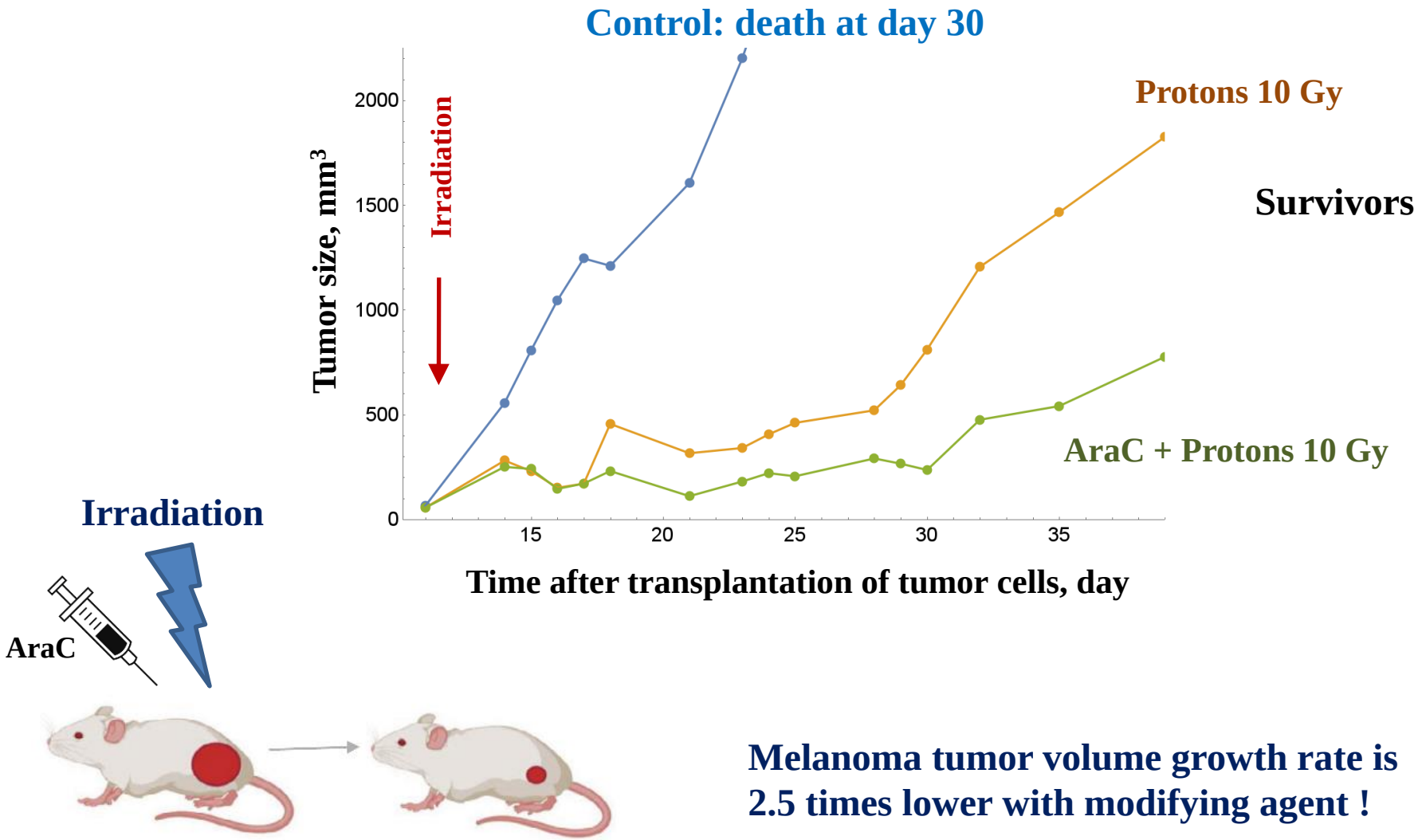
Авторы: *Красавин Евгений Александрович (RU), Борейко Алла Владимировна (RU), Куликова Елена Анатольевна (RU), Буланова Татьяна Сергеевна (RU), Тимошенко Геннадий Николаевич (RU), Чаусов Владимир Николаевич (RU)*

Заявка № 2018140538
Приоритет изобретения 16 ноября 2018 г.
Дата государственной регистрации в Государственном реестре изобретений Российской Федерации 09 сентября 2019 г.
Срок действия исключительного права на изобретение истекает 16 ноября 2038 г.

Руководитель Федеральной службы по интеллектуальной собственности

Г.П. Ивлиев

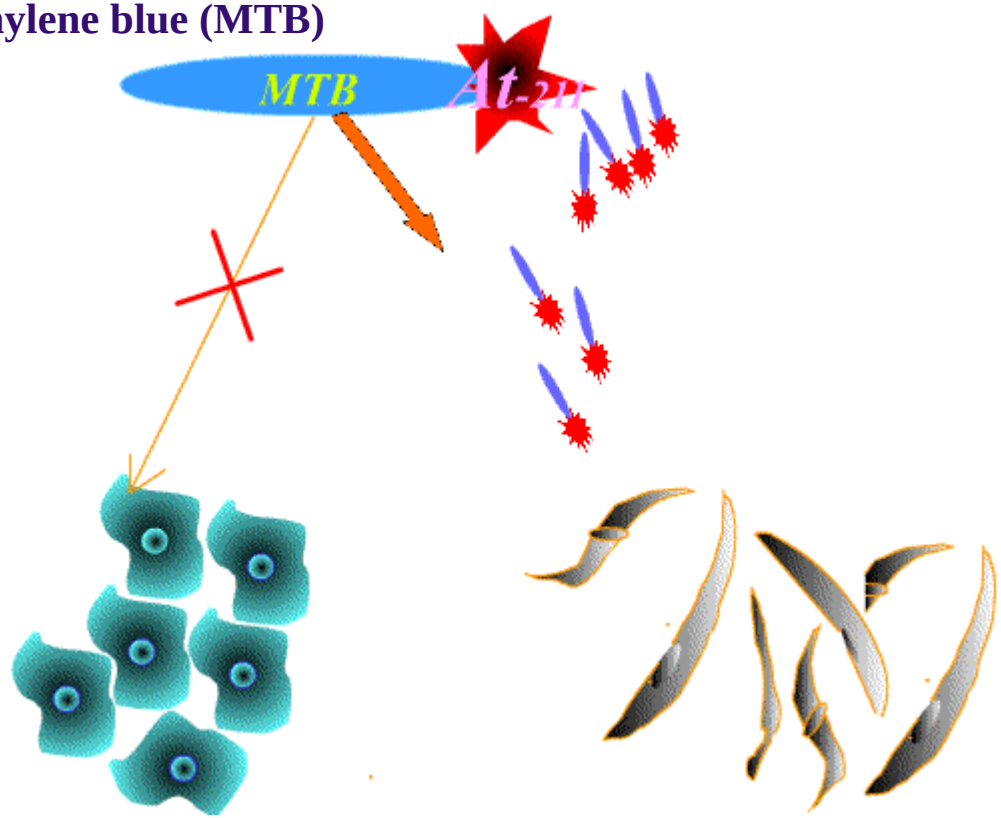
Preclinical animal studies with transplanted melanoma tumor cells in mice (*in vivo* experiments)



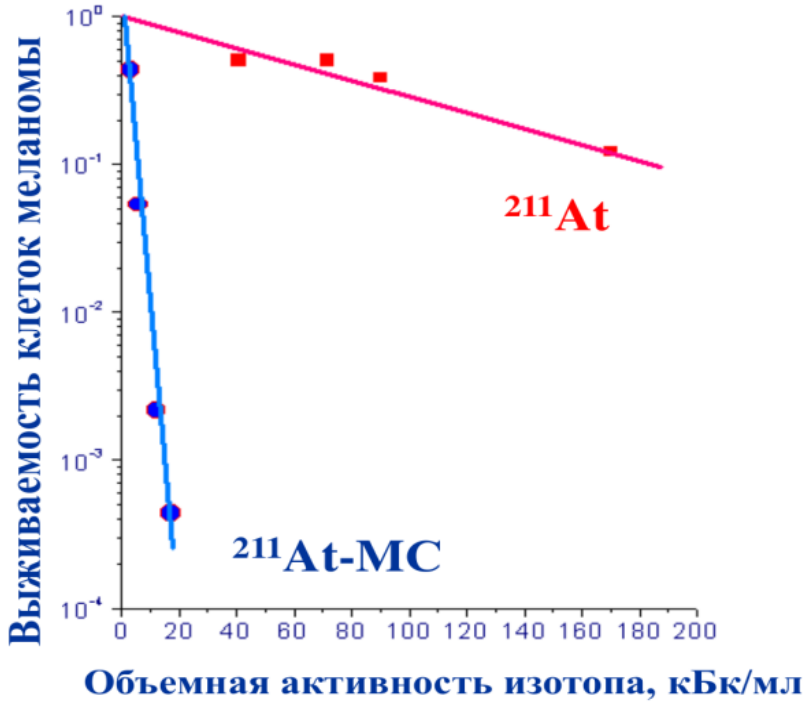
Melanoma tumor volume growth rate is 2.5 times lower with modifying agent !

Targeted delivery of radionuclides

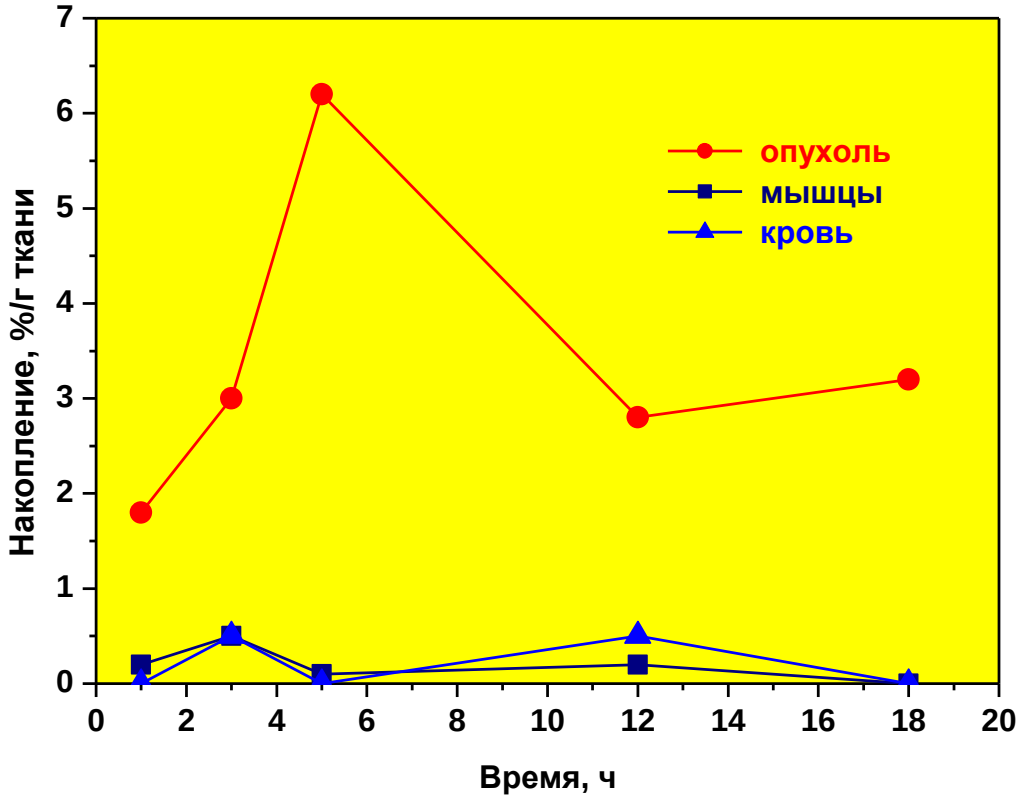
Methylene blue (MTB)



Melanoma tumor cell survival *in vitro*

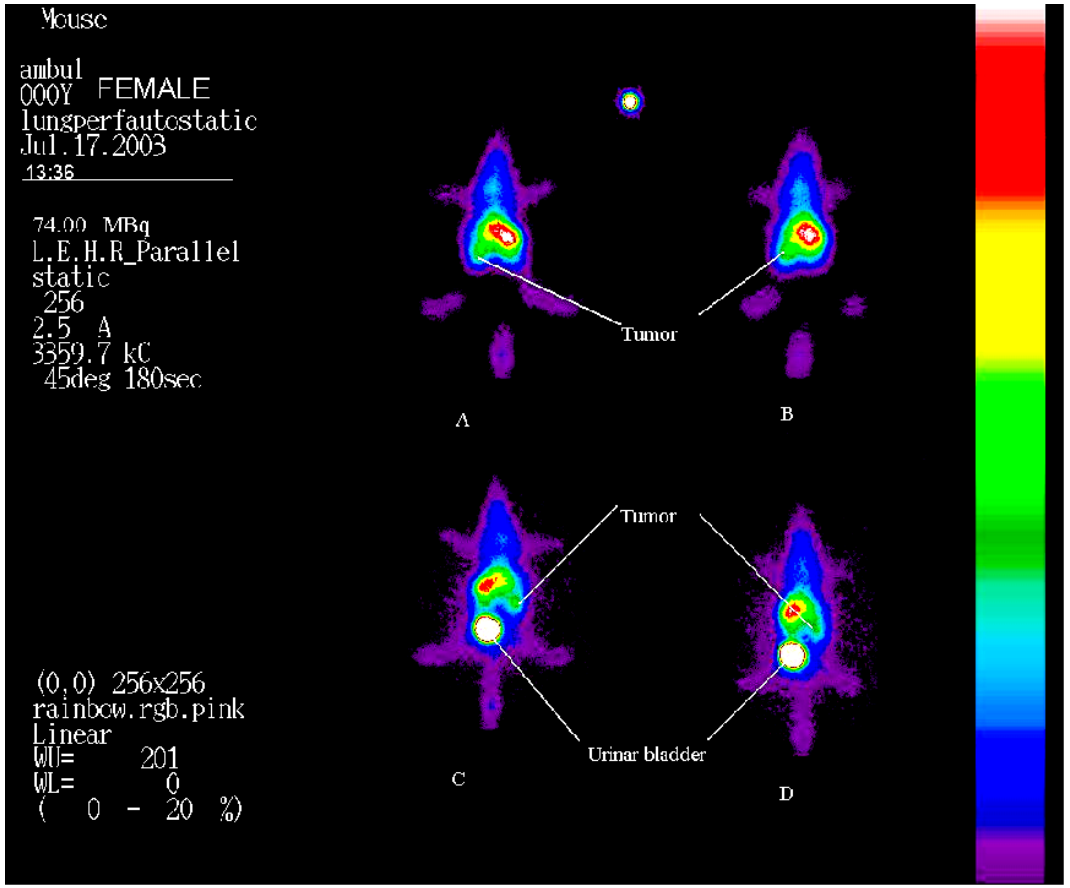


Targeted delivery of radionuclides



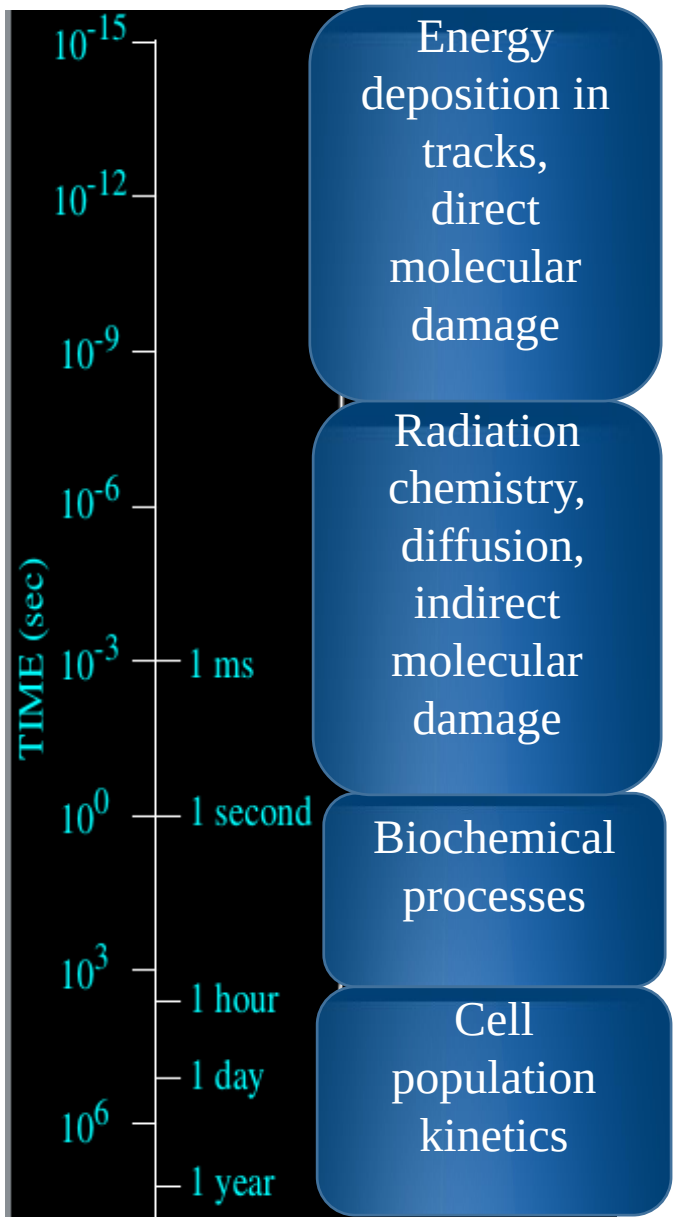
Accumulation of ^{211}At-MTB in various tissues of the body of animals with inoculated melanoma

Visualization of ^{131}I-MTB accumulation in tissues of animals with inoculated melanoma



Mathematical Modeling

Development of a hierarchy of mathematical models



Monte Carlo radiation transport

GEANT4-DNA
A SIMULATION TOOLKIT

Molecular dynamics

NAMD
Scalable Molecular Dynamics

AMBER

Dynamical systems: ODE and PDE

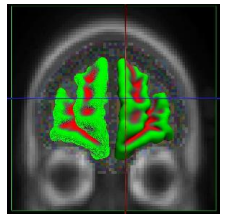
Wolfram Mathematica

MATLAB

Estimating final effect

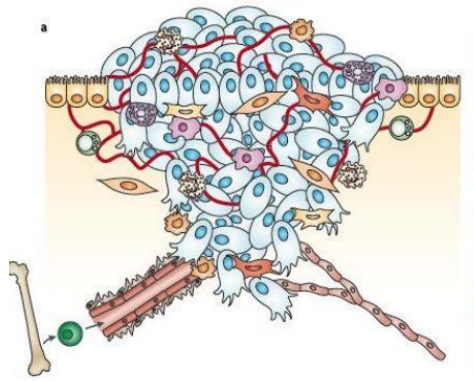
Radiation neuroscience:

Brain neural networks

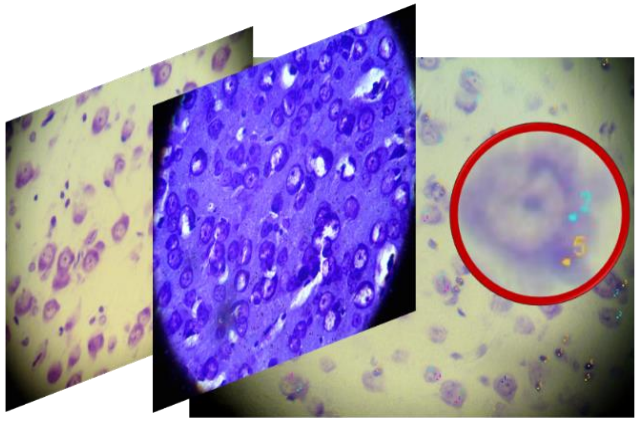


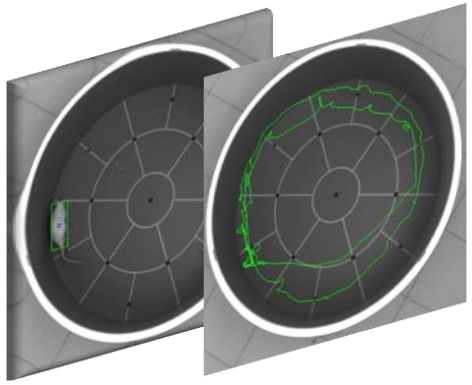
Clinical radiobiology:

Complex models of tumor growth



Information System for Radiation Biology





The joint project of LIT and LRB is aimed at creating an information system for storing and analyzing changes in the central nervous system of mammals based on **molecular**, **pathomorphological** and **behavioral** changes in the mammalian brain when exposed to ionizing radiation and other factors.

The information system is based on:

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

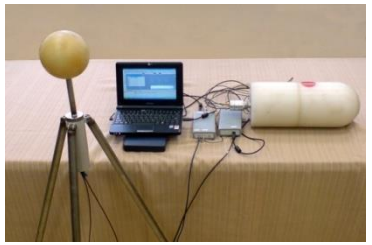
The information system will allow:

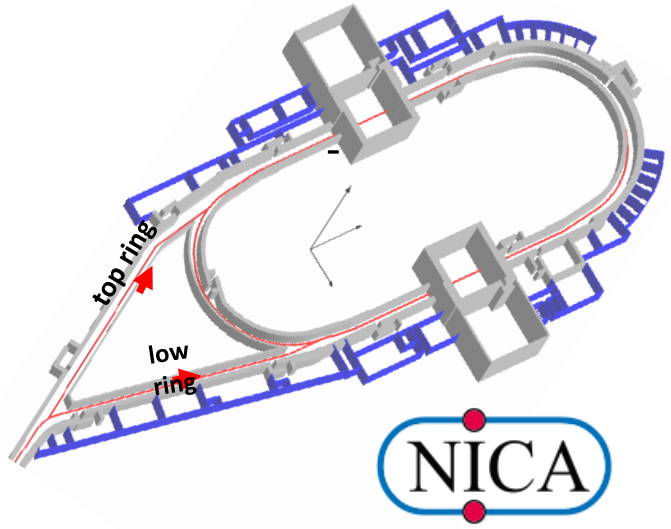
- to speed up and simplify the work with experimental data for various groups of researchers
- to simplify and accelerate the diagnosis of pathologies of the central nervous system, and in a particular case, the development of effective methods of prevention and protection from ionizing radiation.

Radiation Research

- **Radiation protection** management and shielding at new nuclear facilities
- Neutron spectrometry in wide energy range

Portable multisphere neutron spectrometer





- **NICA-based modeling of radiation fields with continuous particle energy spectra**
- Astronaut's risk assessment during long-term interplanetary flights

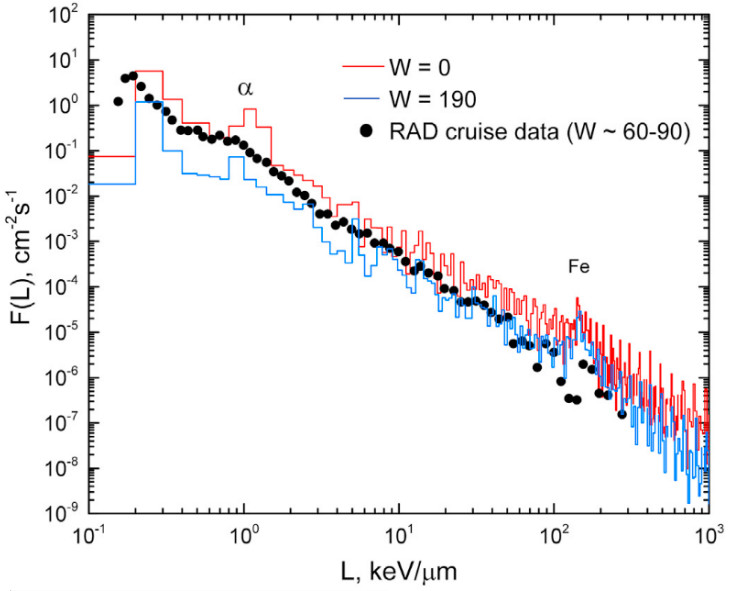
- **Nuclear planetary science instruments** (in collaboration with FLNP, ISR, Roskosmos, NASA, ESA)

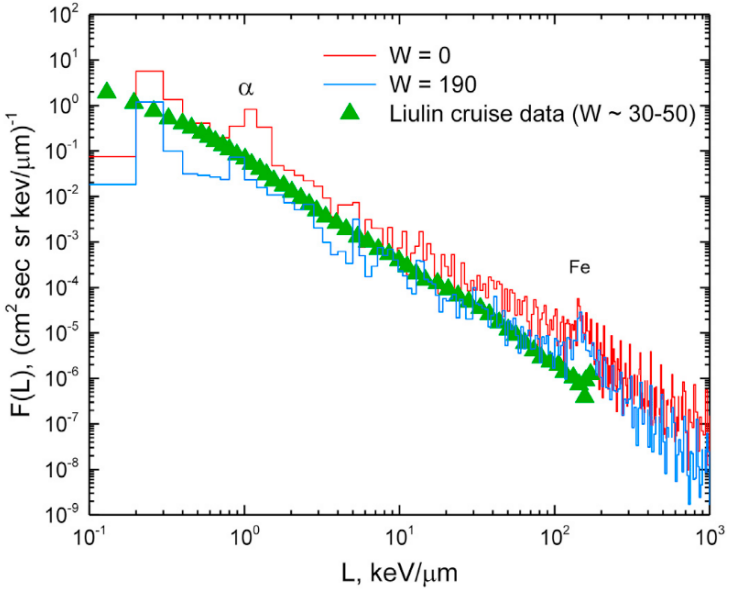
planetary ground facility for testing nuclear planetology instruments

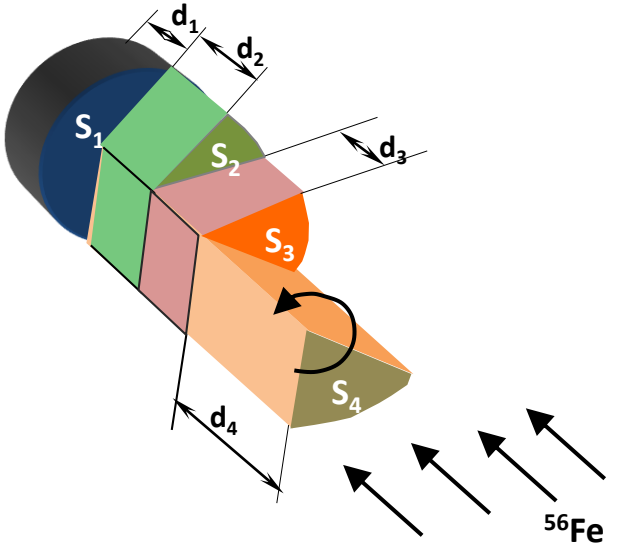
Our home-designed neutron and gamma-ray spectrometers onboard of ISS, Lunar, Martian, Mercury missions

New type of accelerator-based cosmic radiation field simulator

Comparison of simulated LET spectra with RAD and Liulin data








РОССИЙСКАЯ ФЕДЕРАЦИЯ

ПАТЕНТ

НА ИЗОБРЕТЕНИЕ

№ 2761376

Устройство моделирования на пучках тяжелых ионов высокой энергии полей смешанного излучения для целей экспериментальной радиобиологии

Патентообладатель: Объединенный институт ядерных исследований (ОИЯИ) (RU)

Авторы: Тимошенко Геннадий Николаевич (RU), Гордеев Иван Сергеевич (RU)

Заявка № 2021105845
Приоритет изобретения 05 марта 2021 г.
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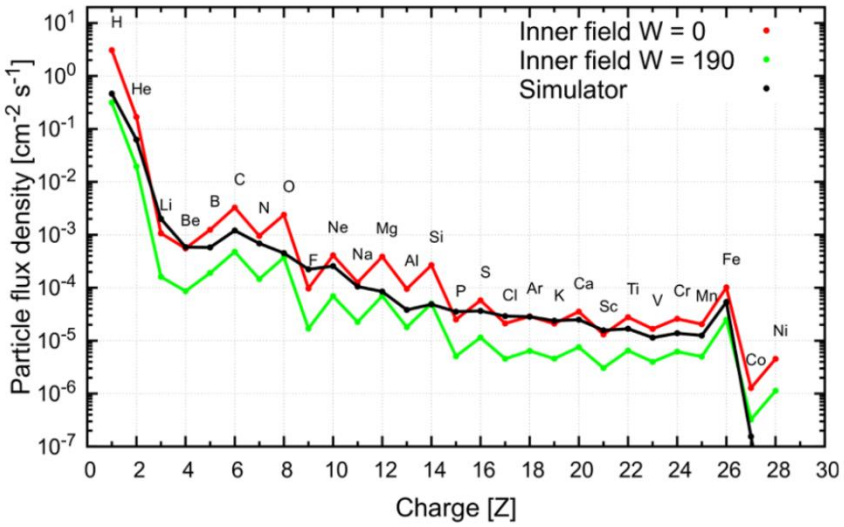
Руководитель Федеральной службы по интеллектуальной собственности

Г.П. Ивлиев

Timoshenko G. N. and Gordeev I. S. // Planetary and Space Science. 2021. V. 199. P. 105190.

Timoshenko G., Gordeev I. // Life Sciences in Space Research, 2021, V.30, P.66

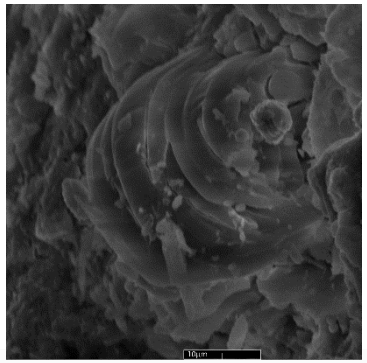
Patent No. 2761376

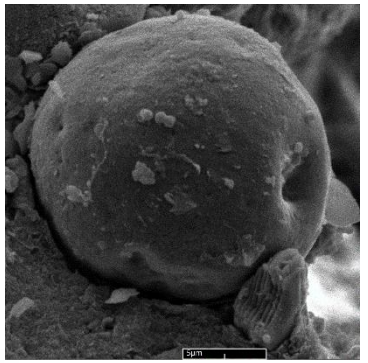


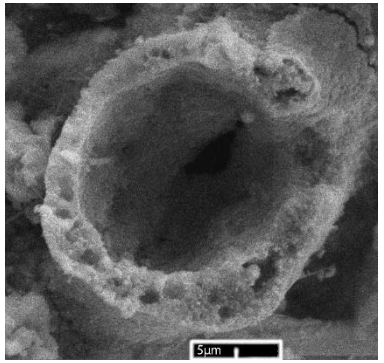
Comparison of simulator and space radiation charge spectra

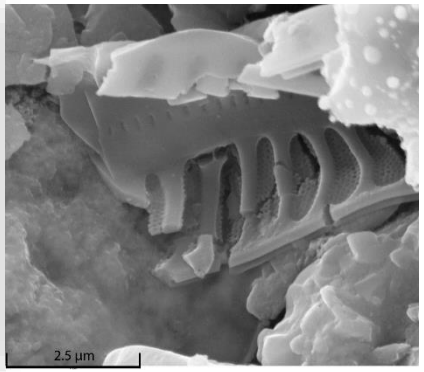
ASTROBIOLOGY

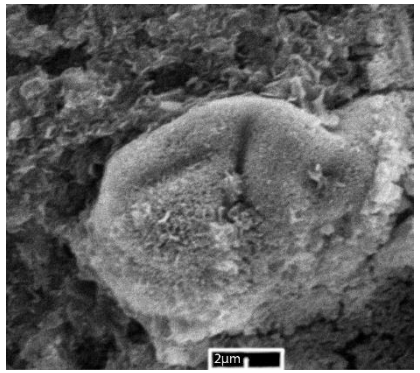
Search for microfossils in the meteorites







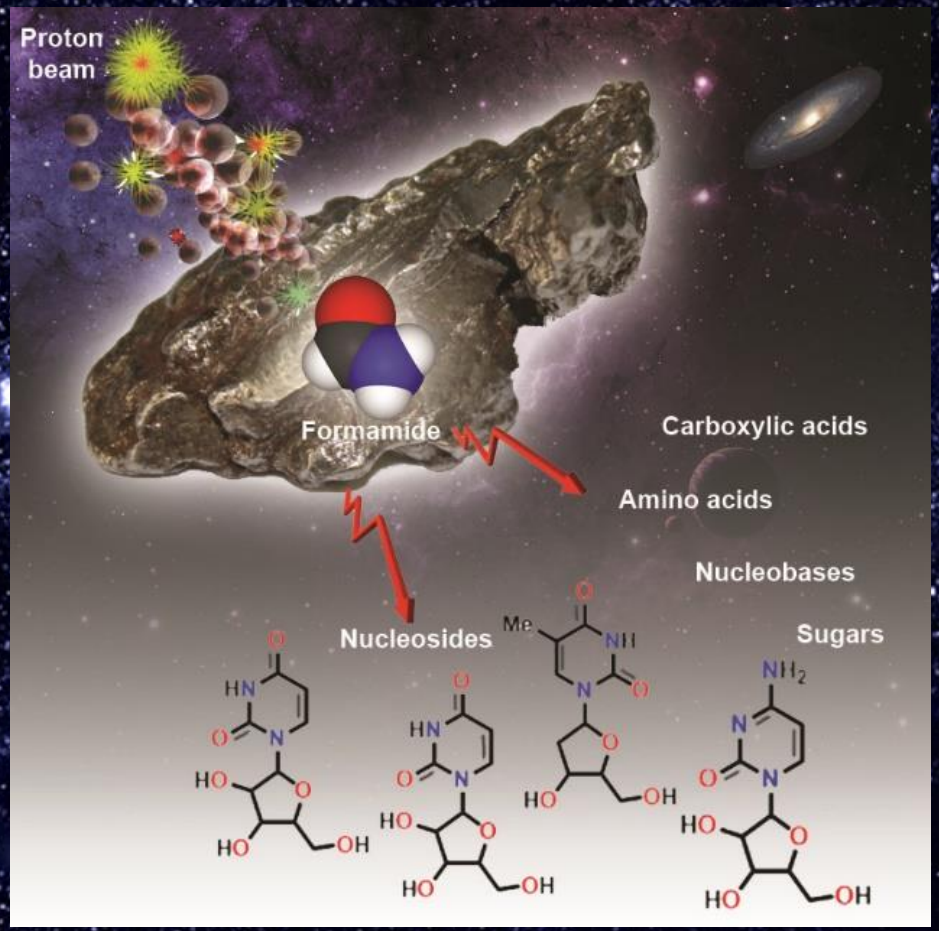


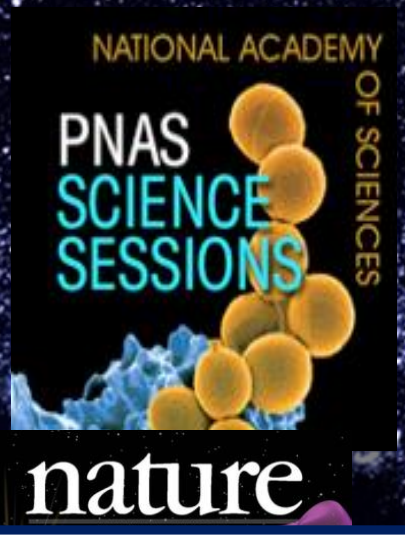


The Orgei meteorite is a unique phenomenon in the abundance and diversity of microfossils of prokaryotes and aquatic eukaryotes, including microalgae, protists, and even algae or fungal spores. The microfossils found are indigenous to the meteorite and not terrestrial biocontaminants. The consistency of the theory of panspermia is shown. The capabilities of SEM for the search and analysis of indigenous microfossils in meteorites are demonstrated.

ASTROBIOLOGY

Irradiation with protons with an energy of 170 MeV in the synthesis of formamide and meteoritic substances revealed precursors of nucleic acids, proteins, and metabolic cycles in appreciable amounts. In the absence of irradiation, prebiotic compounds are not formed.

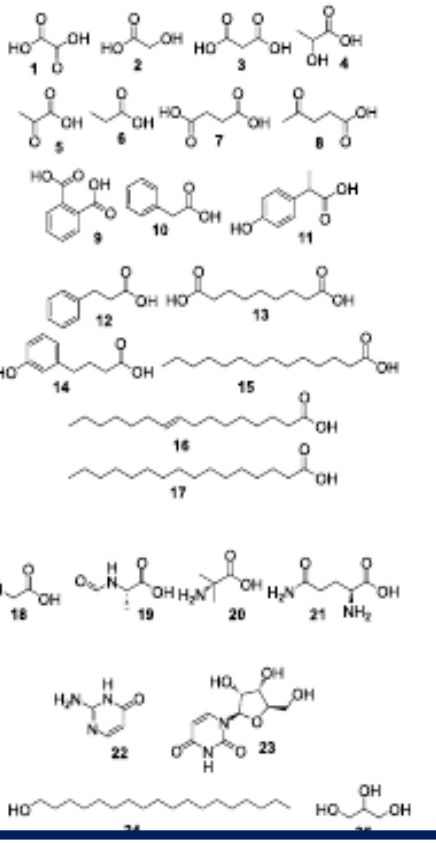


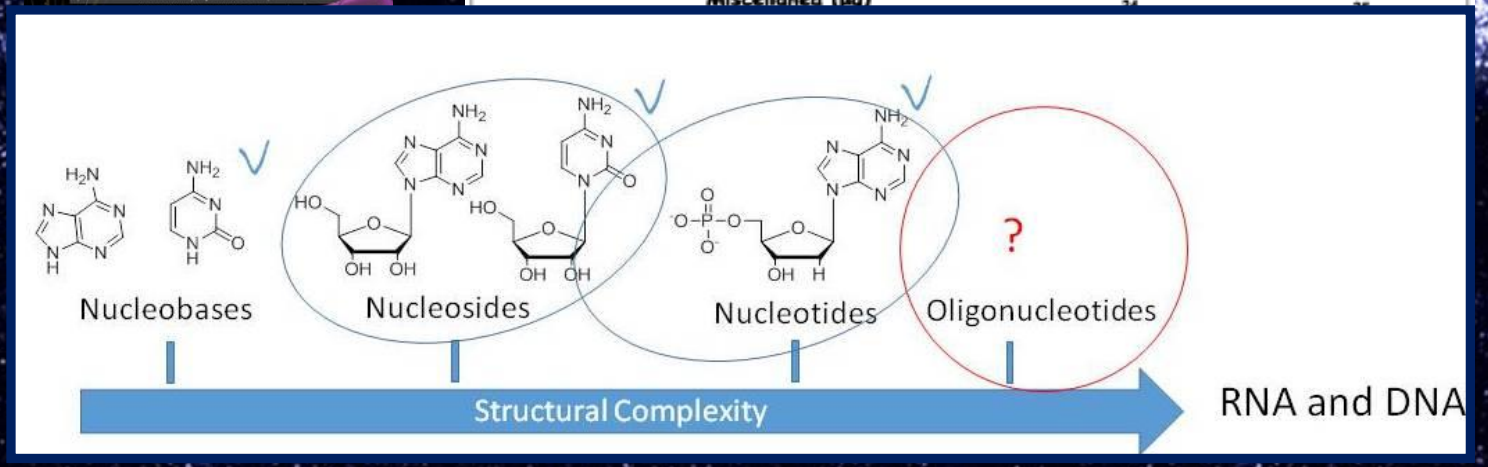


nature

Acids (μg)

n° atoms C		
2	(1) Oxalic acid	1,93
	(2) Glycolic acid	0,51
3	(3) Malonic acid	3,23
	(4) Lactic acid	5,89
	(5) Pyruvic acid	0,33
	(6) Propionic acid	0,18
4	(7) Succinic acid	0,32
5	(8) 4-oxopentanoic acid	0,58
8	(9) Phthalic acid	2,45
	(10) Benzen acetic acid	121,81
9	(11) 4-hydroxyphenyl propionic acid	1,13
	(12) Hydrocinnamic acid	0,4
	(13) Azelaic acid	0,58
10	(14) 3-Hydroxy phenyl butyric acid	1,16
14	(15) Tetradecanoic acid	1,43
16	(16) Palmitelaidic acid	0,64
	(17)Hexadecanoic acid	0,37
	Amino acids (μg)	
	(18) Glycine	0,86
	(19) Formyl-alanine	5,56
	(20) 2-methyl alanine	10,18
	(21) glutamine	0,71
	Heterocycles (μg)	
		75,6
	(22) Isocytosine	3
	(23) Uridine	0,54
	Miscellanea (μg)	





Main results 2017-2022

- A fundamentally new method to increase the efficiency of radiation therapy of cancer (JINR patent No. 2699670)
- Novel concept of cosmic radiation field simulator for ground-based accelerator experiments (JINR patent No. 2761376)
- Worldwide unique experiments with primates: cognitive tests and genetic damage after krypton ion irradiation
- New data on mechanisms of genetic damage formation and repair after heavy ion irradiation
- New approaches for computation of brain damage after irradiation
- Discovery of mechanisms responsible for prebiotic chemistry in meteorites under particle irradiation
- First monograph on biofossils in meteorites

Expected Results 2024-2030

- Establishment of **integrative interrelations of radiation-induced effects at different levels of biological organization**: molecular, cellular, tissue and organismal ones, under the action of radiation with different characteristics.
- Identification of the mechanisms of the **effect of ionizing radiations** of different quality on the higher integrative functions of the **central nervous system** and the development of **neurodegenerative diseases**.
- Assessment of **radiation risks** for various scenarios of manned space flights and mixed radiation fields of nuclear physics facilities.
- Development of new methods to improve the **effectiveness of particle and radionuclide therapy** of cancer.
- Development of **new mathematical models and computational approaches** for radiobiology, bioinformatics and radiation medicine.
- Identification of **mechanisms and pathways of catalytic synthesis of prebiotic compounds** under the action of radiation.
- **Development of new research protocols** in radiobiology, including: omics technologies, ultra-high resolution bio-imaging, new irradiation facilities, automated processing of biological data based on artificial intelligence technologies.