JINR Innovation Radiobiological Research Program

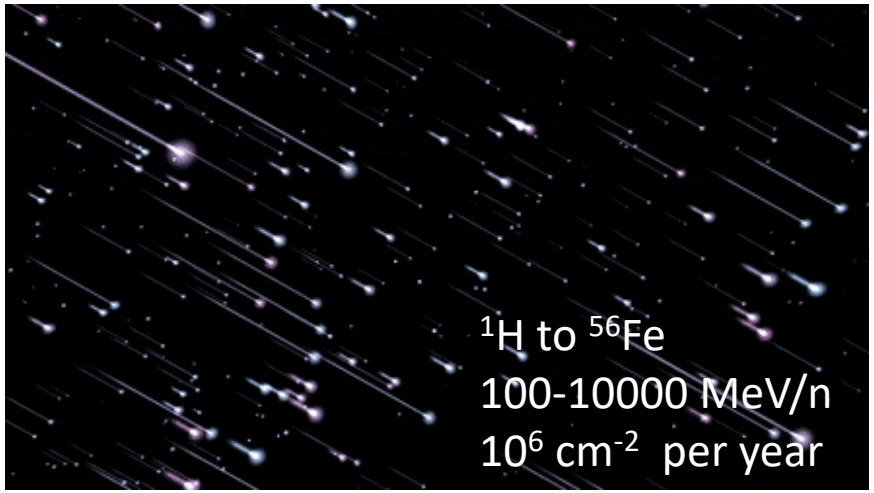
A. N. Bugay

Relative biological effectiveness of charged particles
Radiation-induced mutagenesis

JINR since 1959

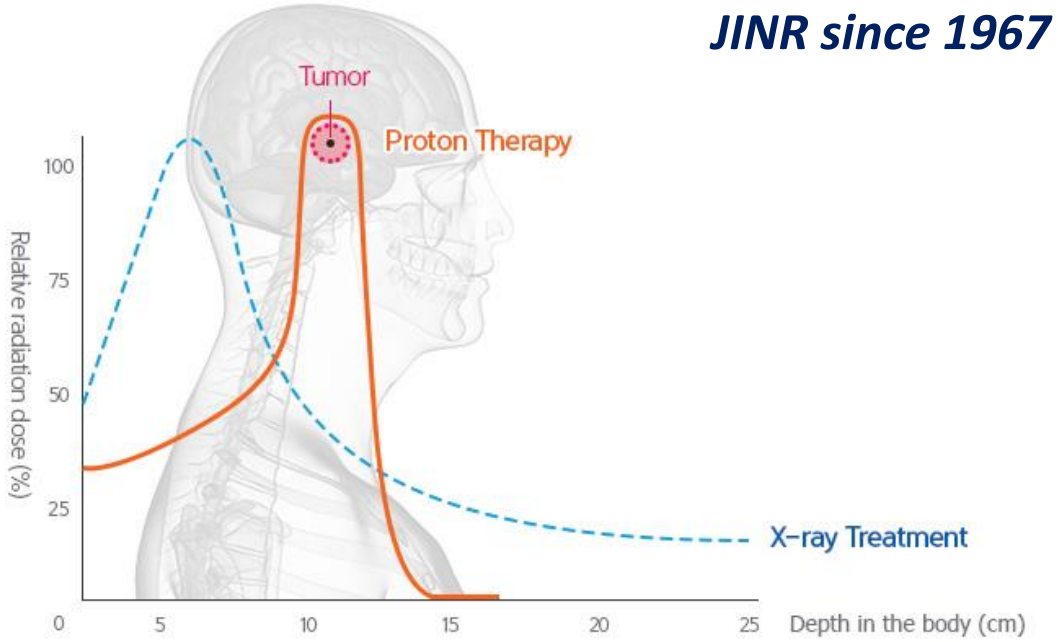
Radiation risk in deep space

JINR since 1959



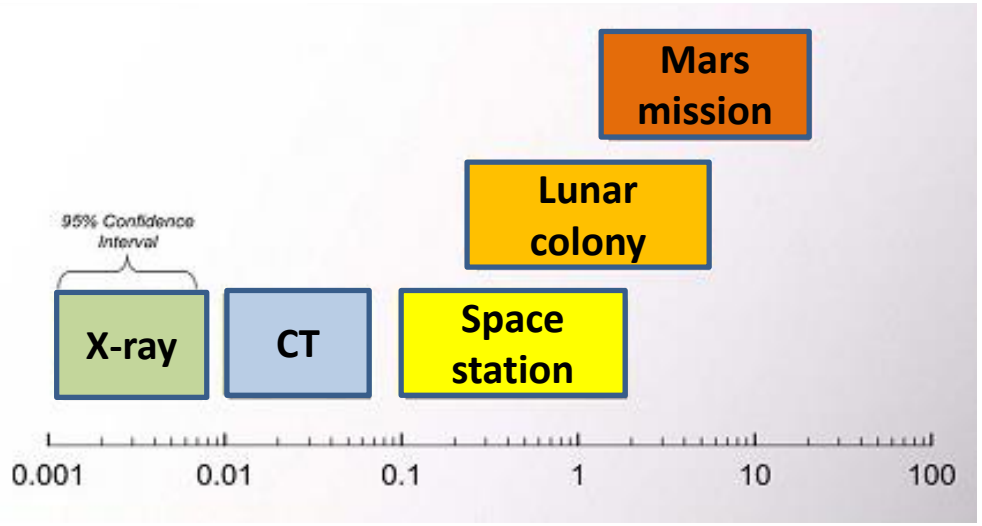
Radiation therapy of cancer

JINR since 1967



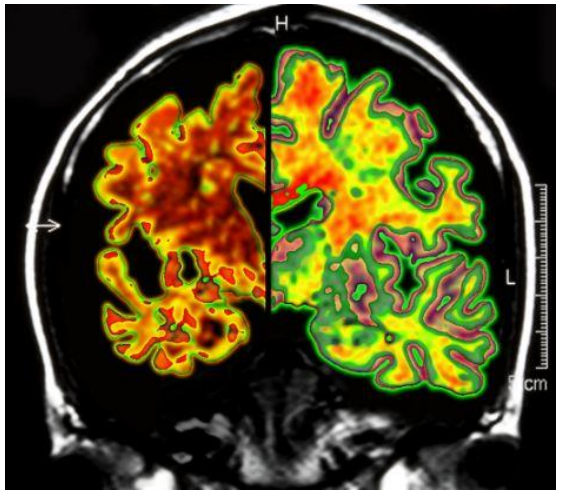
New concept of radiation risk for deep space flights: Damage to the central nervous system (CNS)

Grygoriev, Krasavin, Ostrovskii, Bulletin of RAS 2017



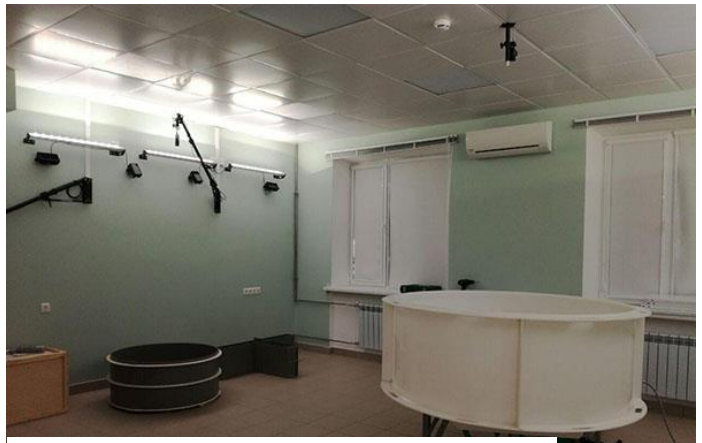
% Risk of cancer death

Paradigm shift

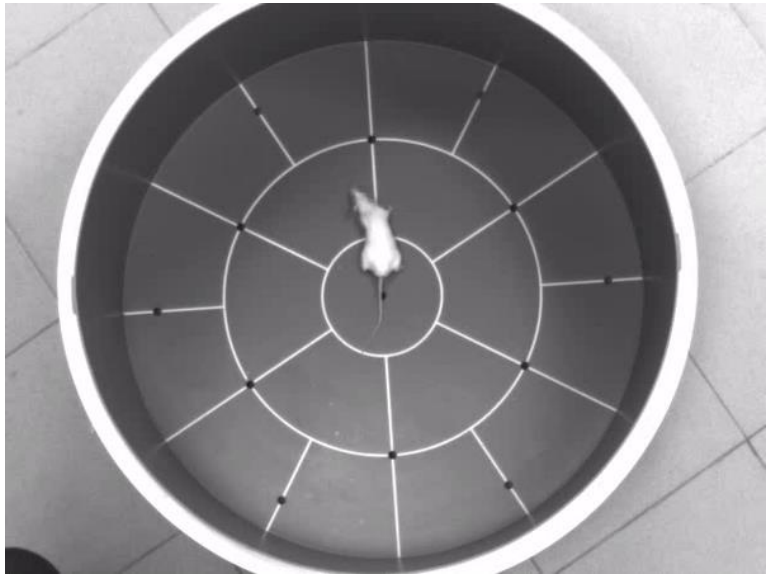


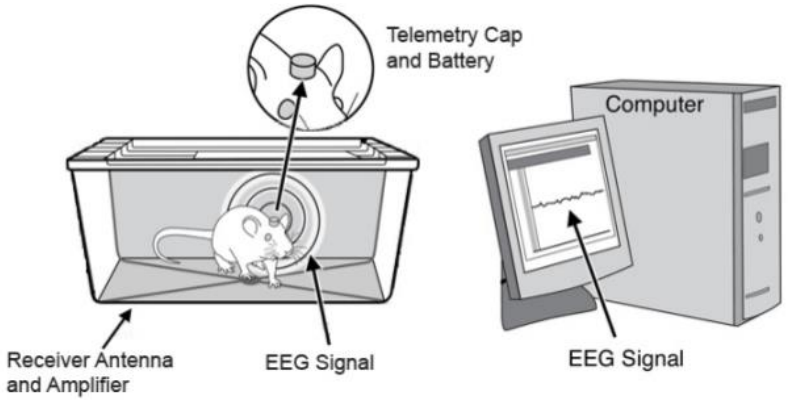
Radiation Neuroscience

Set of equipment for the study of behavioral reactions and functional disorders of the central nervous system of animals



Behavior test systems





Electrophysiology studies

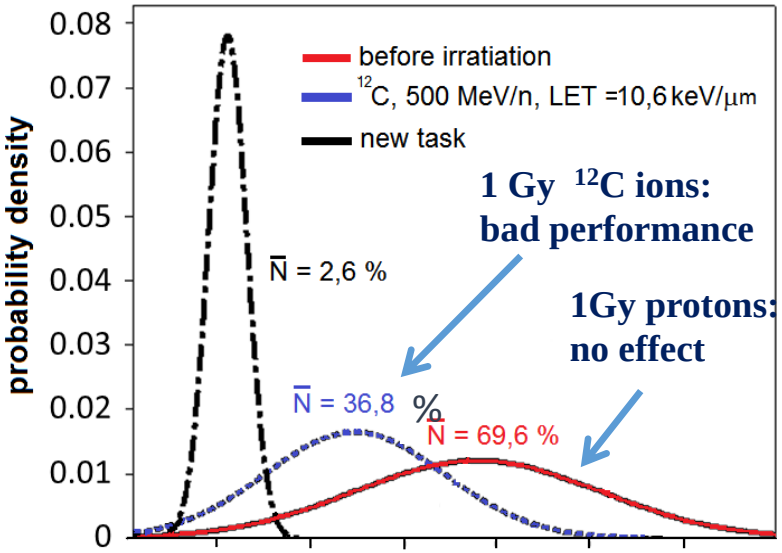
Study of neuro-radioprotective properties of pharmaceuticals

New visualization and tomography tools are foreseen

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.



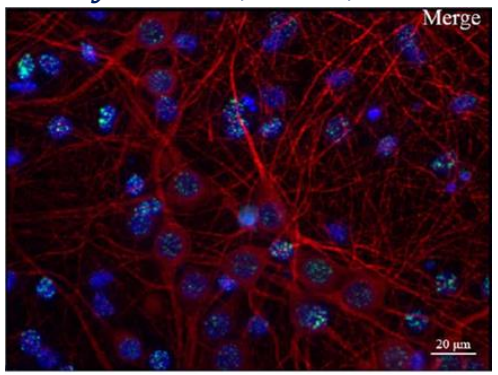
Automated computer system for the simulation of operator activity during the flight

Collaboration:

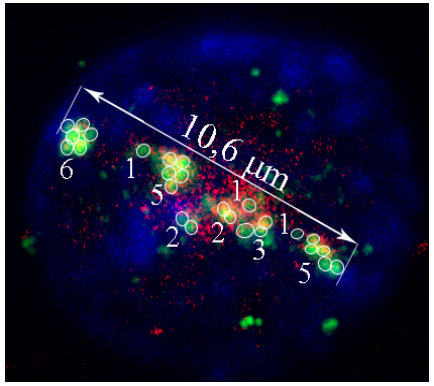
RAS Institute of Biomedical Problems,
RAS Institute of Medical Primatology,
RAS Institute of Higher Nervous Activity and Neurophysiology,
M.V. Lomonosov Moscow State University

Mechanisms of radiation damage at the molecular, cellular and tissue level

Boreyko et al, 2019,2020

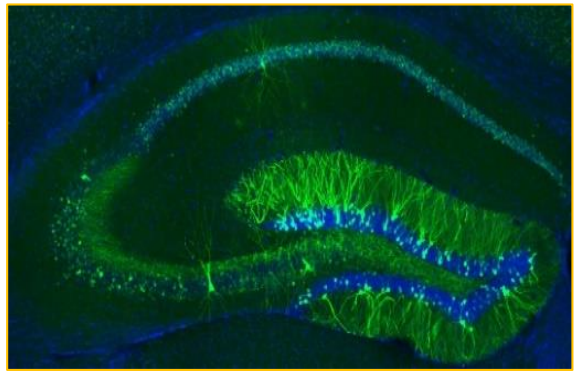


visualization of DNA damage in hippocampal cell culture

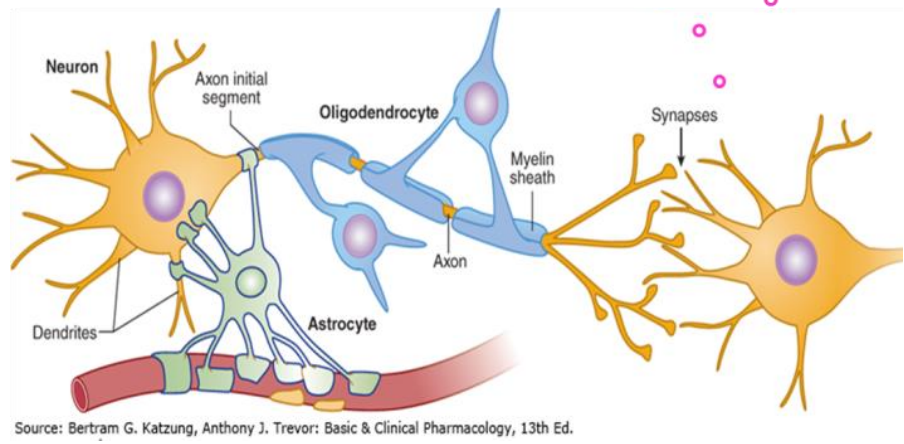


DNA damage in rat hippocampus cells 1 hour after exposure to ^{78}Kr ion tracks

- **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
- **Vascular disorders**



Visualization of different types of nerve cells in rat hippocampal slices



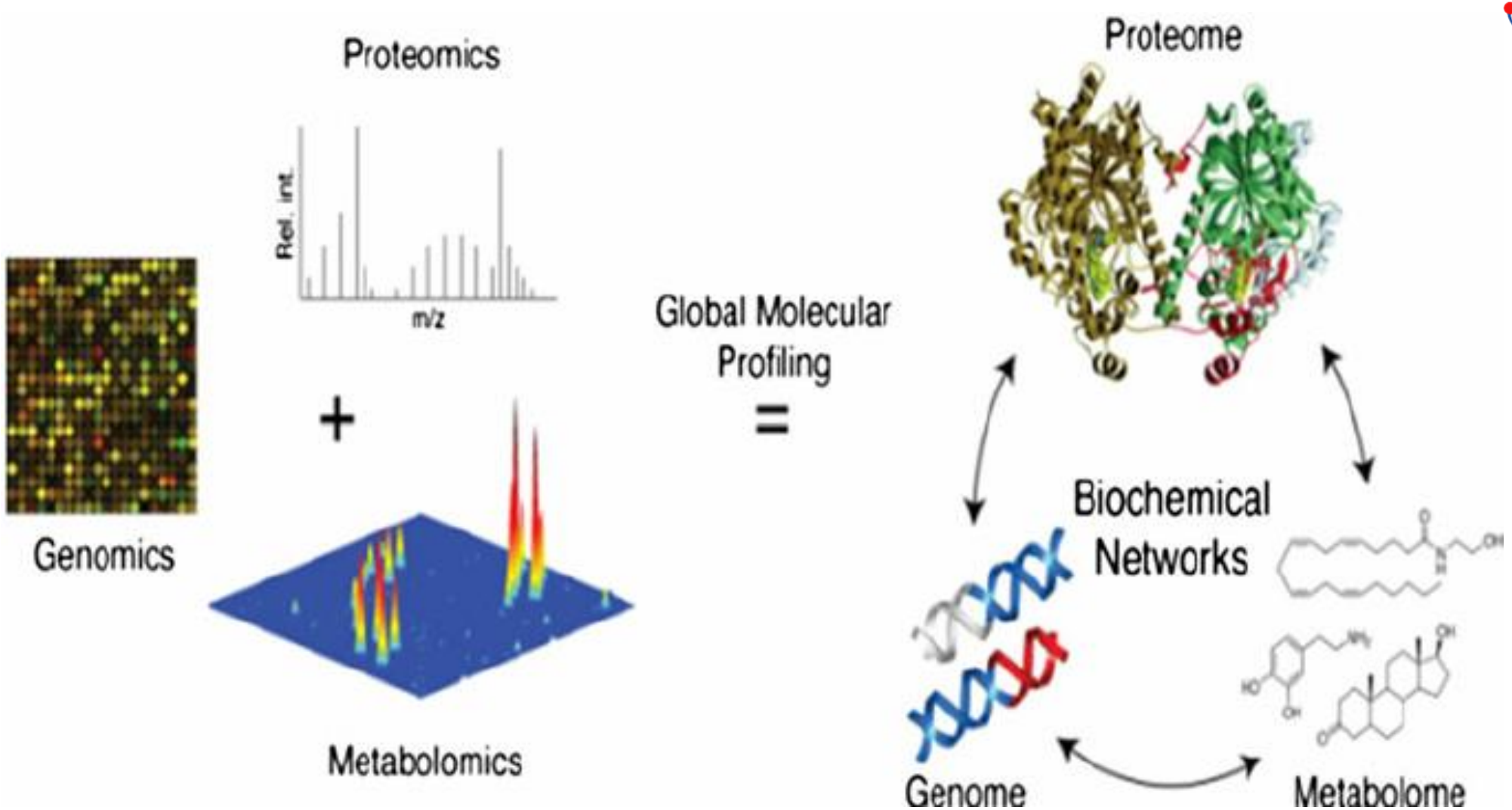
A link between irradiation and neurodegenerative diseases?

Alzheimer, Parkinson, Epilepsy …

The relationship between irradiation and aging?

Implementation of OMICs-technologies

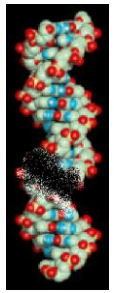
First experiments



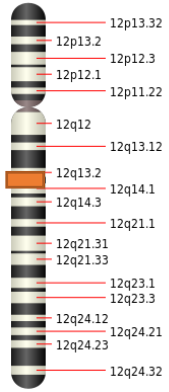
Bodrova et al 2012

Genetic and molecular mechanisms of neurodegenerative diseases

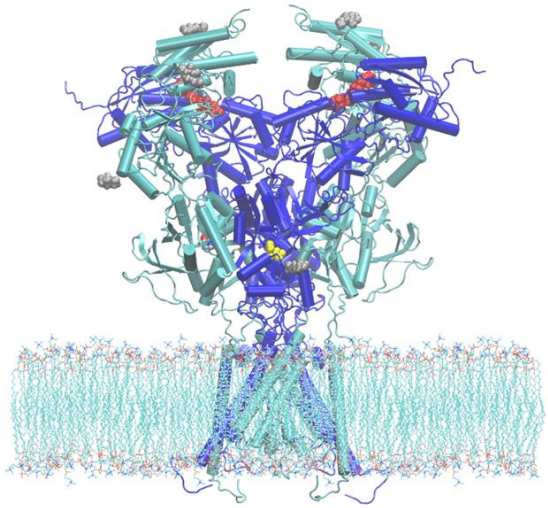
Bugay et al, 2019



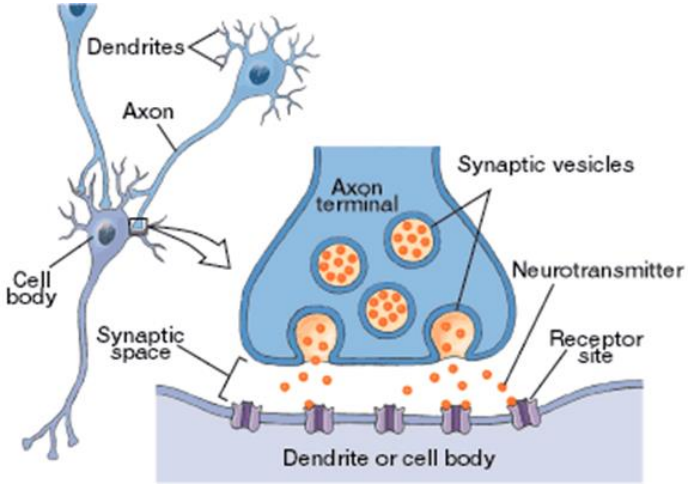
DNA damage



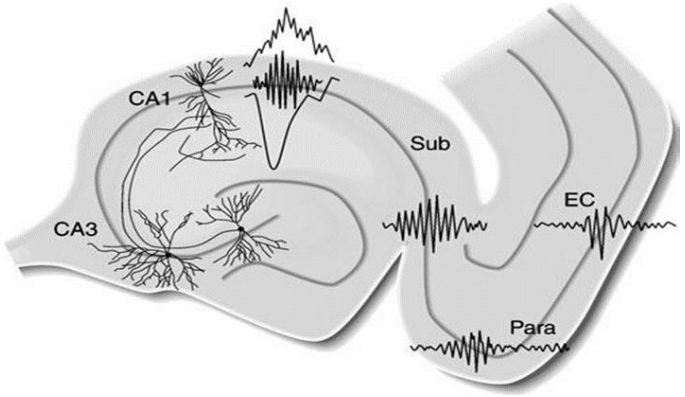
Chromosome 12
GRIN2B gene



NMDA synaptic receptor



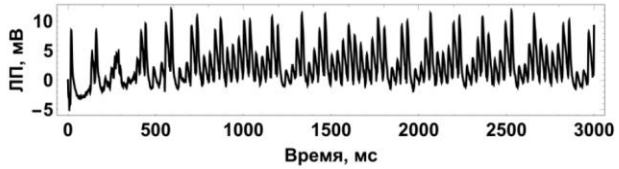
Interconnections between neurons,



Brain neural networks

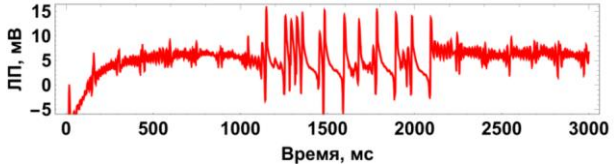
Mutation	Phenotype
p.Asn615Leu p.Phe671_Gln672del	West syndrome (epilepsy) Mild ID, Autism

Native

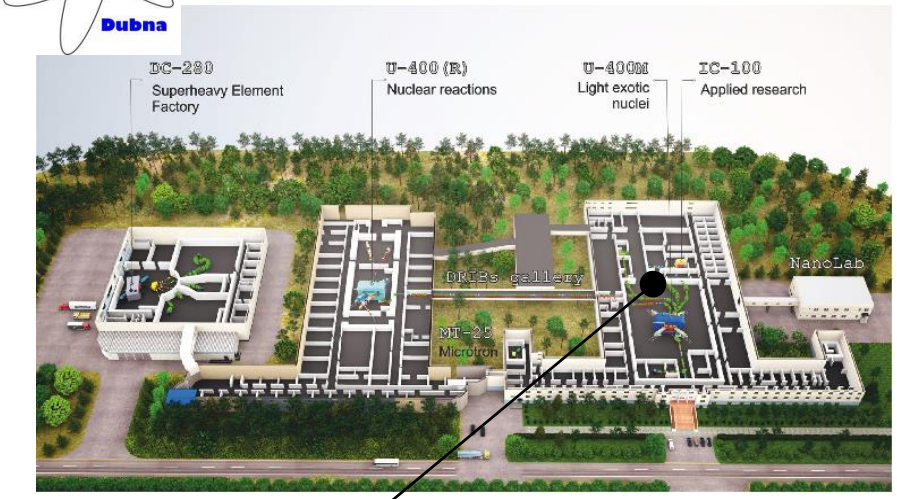


p.ASN615LEU

Epileptic seizure

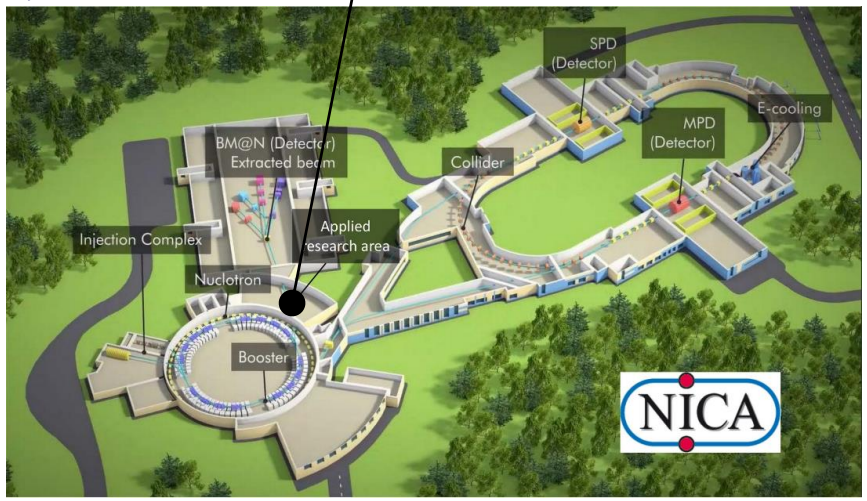


JINR Research Network



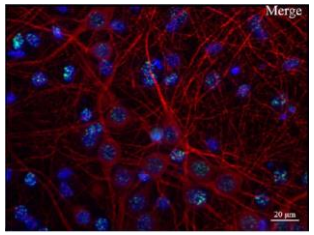
U400M (50 MeV/u, Li – Ne)

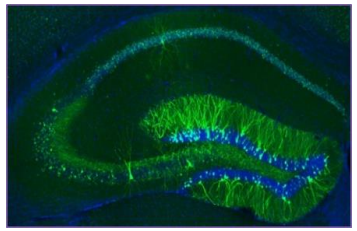
Nuclotron (0.3 - 1 GeV/u, H - Kr)



Cell cultures

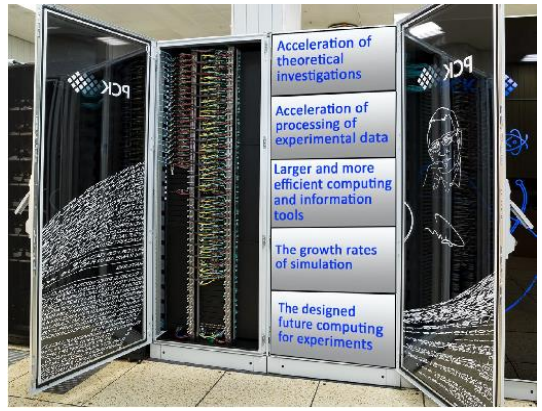
molecular damage, genetics, proteomics, imaging, neurochemistry





Animal research

cognitive tests, physiology, tomography



Supercomputing, data analysis, artificial intelligence

analysis of membrane proteins with SANS

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

Brain diseases

• 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 Neuroscience

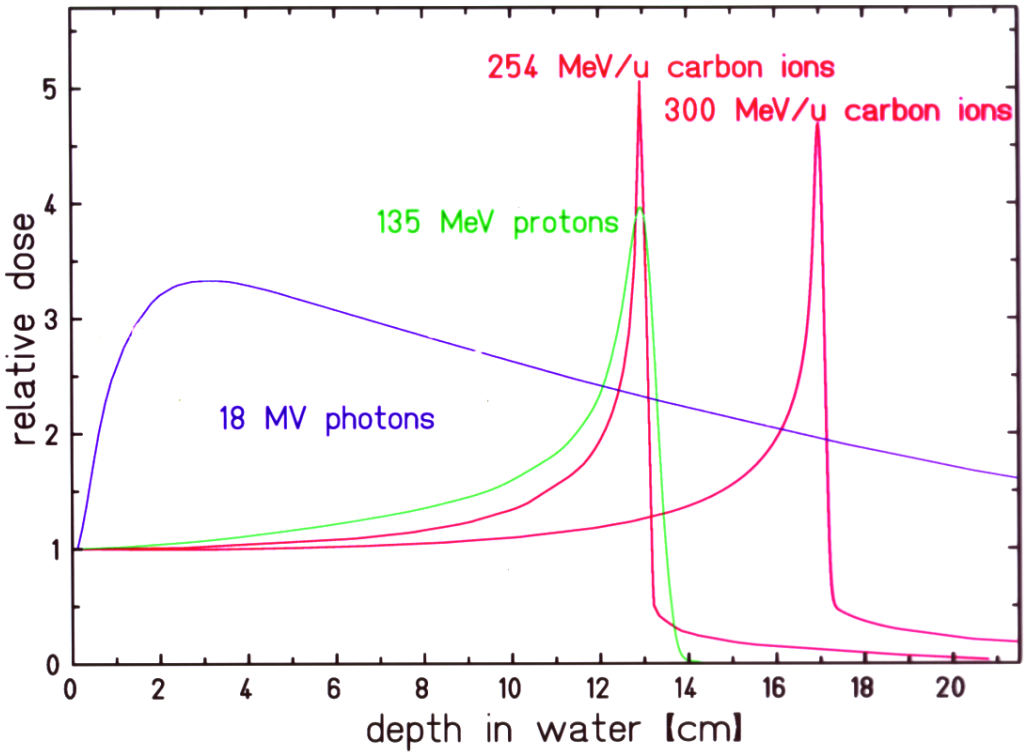
Expected results

- evaluate functional condition of animal CNS using: behavioral test systems; EEG analysis
- study formation and repair of **clustered DNA damage** induced by densely ionizing radiation in CNS cells and tissues
- study chromosome aberration induction in bone marrow and blood cells of animals to evaluate long-term consequences of irradiation
- identify neurodegenerative changes, neuroinflammation, apoptotic and necrotic changes, amyloid growths, and vascular pathologies
- study suppression of neurogenesis in the postnatal period
- study radiation-induced immune response in mouse brain homogenates and in glial cell culture
- study the viability of oligodendrocytes and their precursors and the axon myelination level
- study neurochemical mechanisms of CNS disorders
- test on rodents pharmacological drugs concerning the prevention CNS damage caused by radiation
- **map gene expression and proteomic changes** in main brain regions after irradiation
- map metabolome changes in animal brain after irradiation
- develop a hierarchy of mathematical models to **study the mechanisms of neurodegenerative disorders**

Clinical Radiobiology

Principles of radiation therapy of cancer

Conformal irradiation

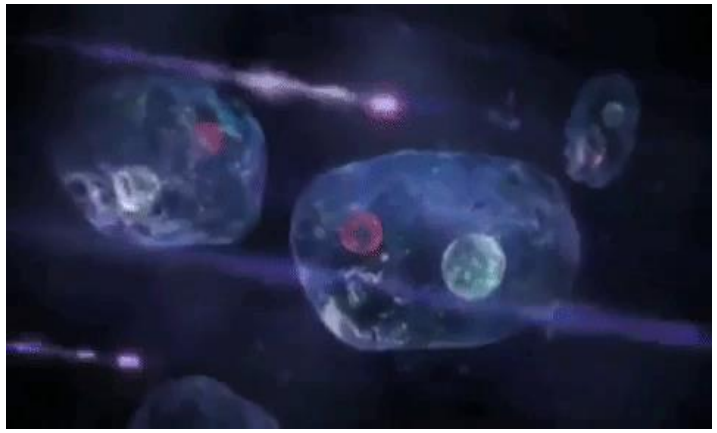


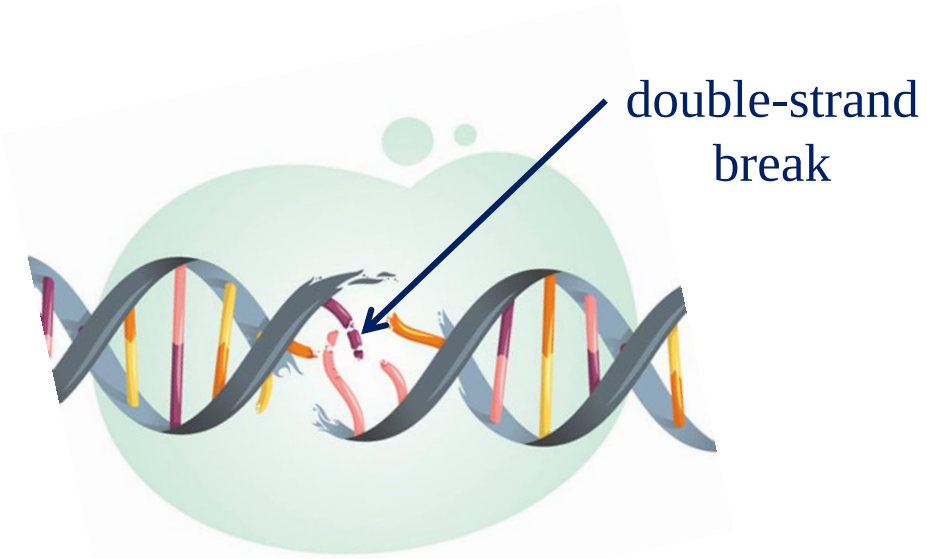
Formation of lethal DNA damage (double strand breaks) in tumor cells

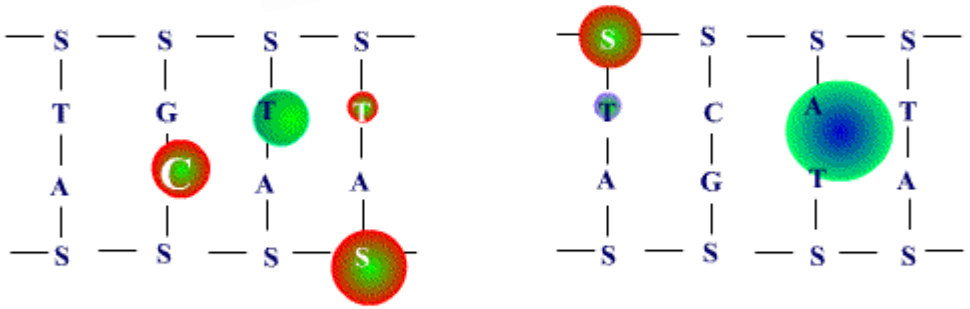
New strategy:

Interference in genetic regulatory networks of irradiated cells with modifiers

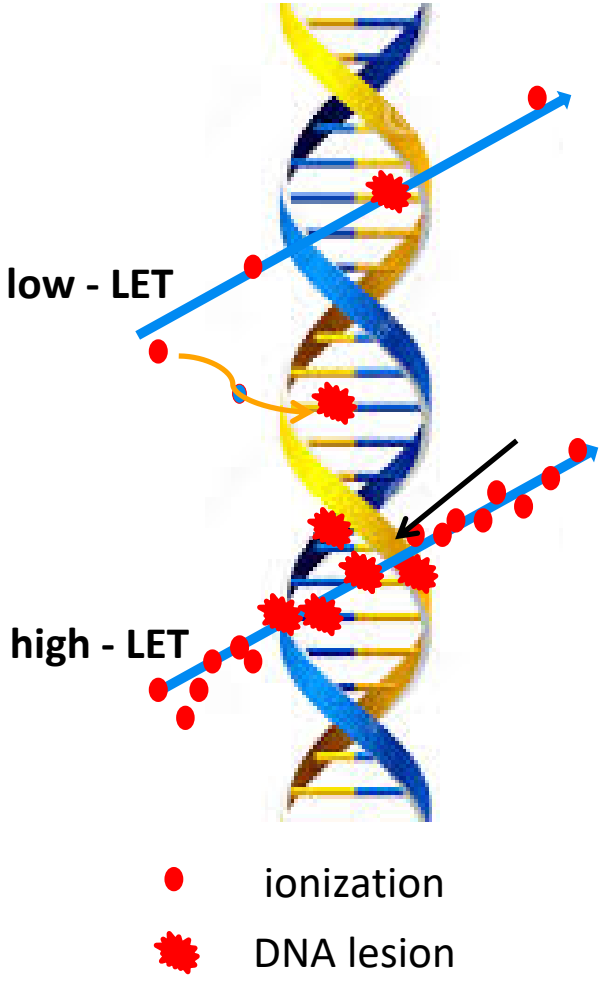
DNA double-strand breaks - the molecular basis of cell death





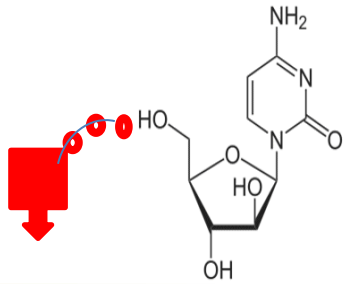


Clustered double-strand break

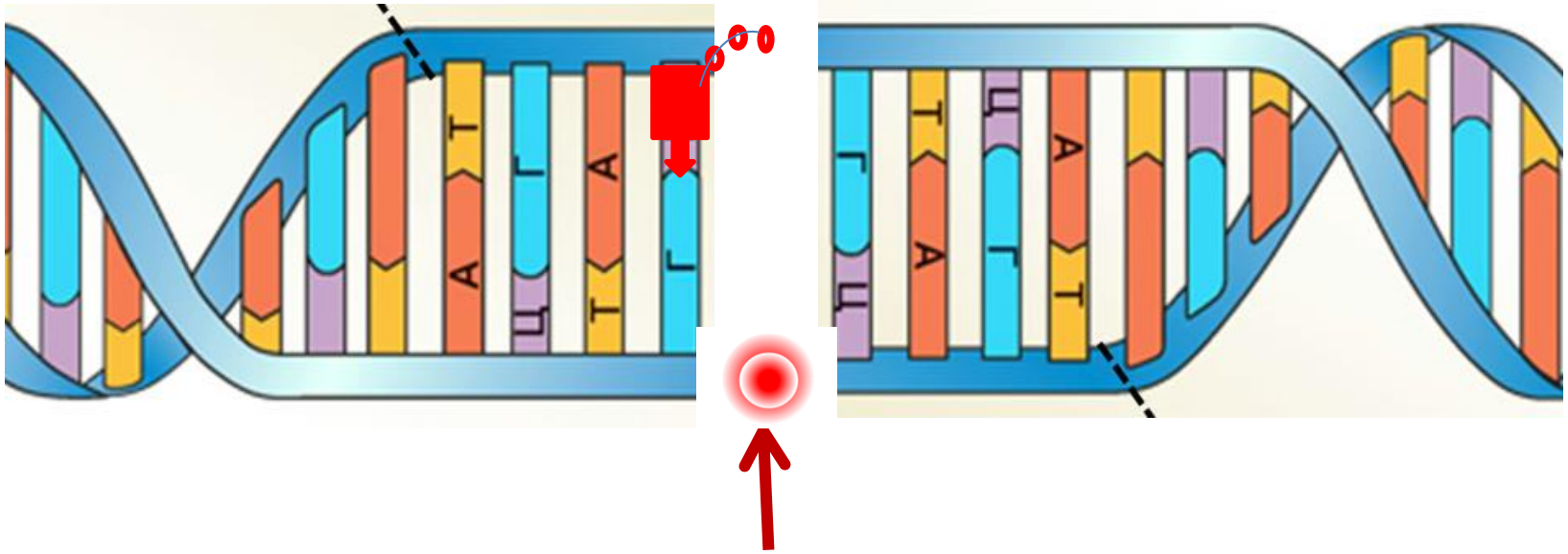


Interference in genetic regulatory networks of irradiated cells with pharmaceuticals

1-β-D-arabinofuranosylcytosine (AraC, cytarabine)



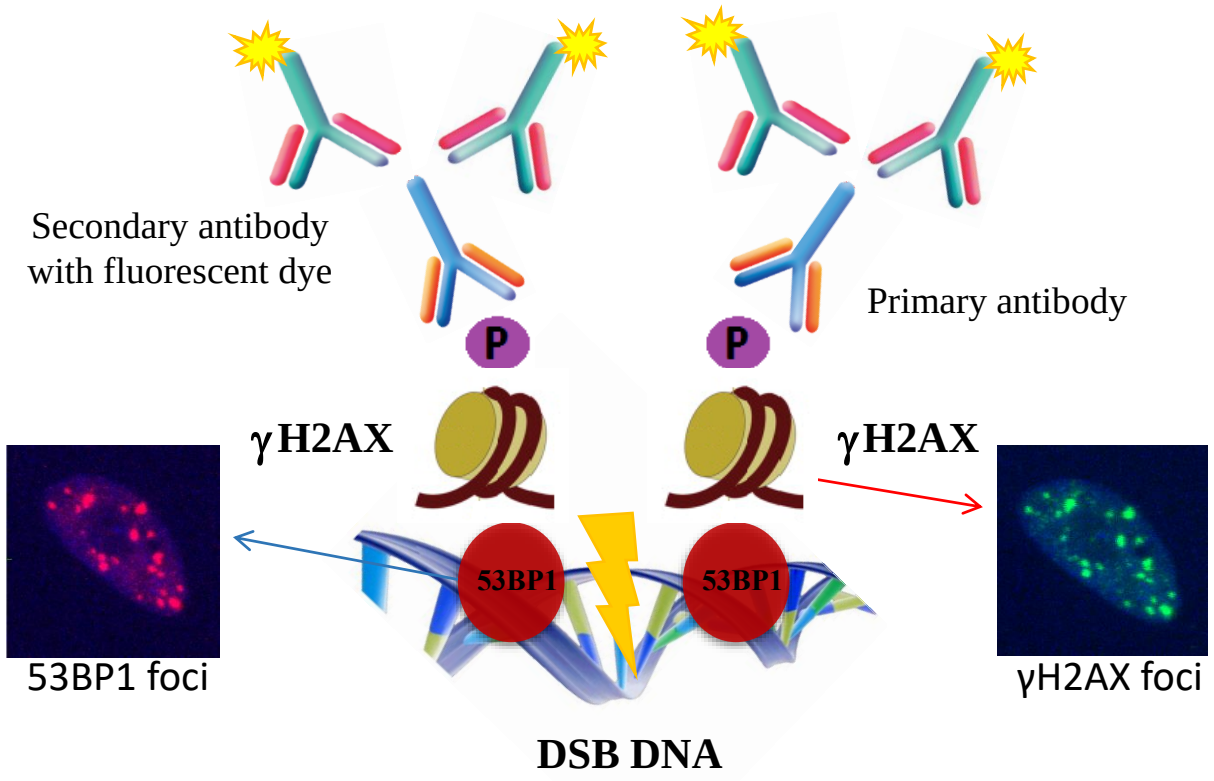
AraC- "The Trojan Horse"

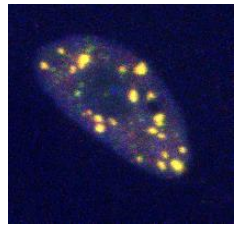


S1 endonuclease

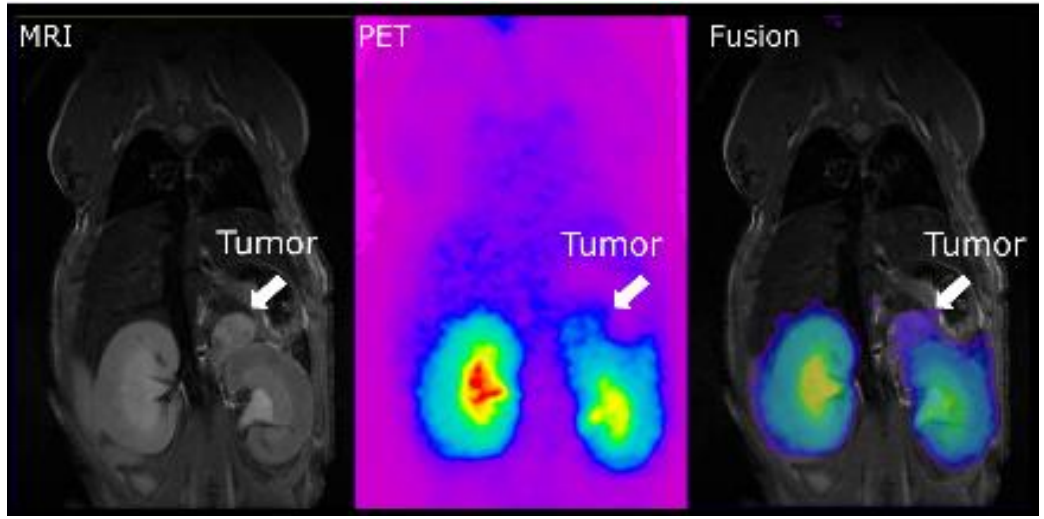
Stopping DNA synthesis and forming a double-strand break

Visualization of processes from molecular to organismal level




merge

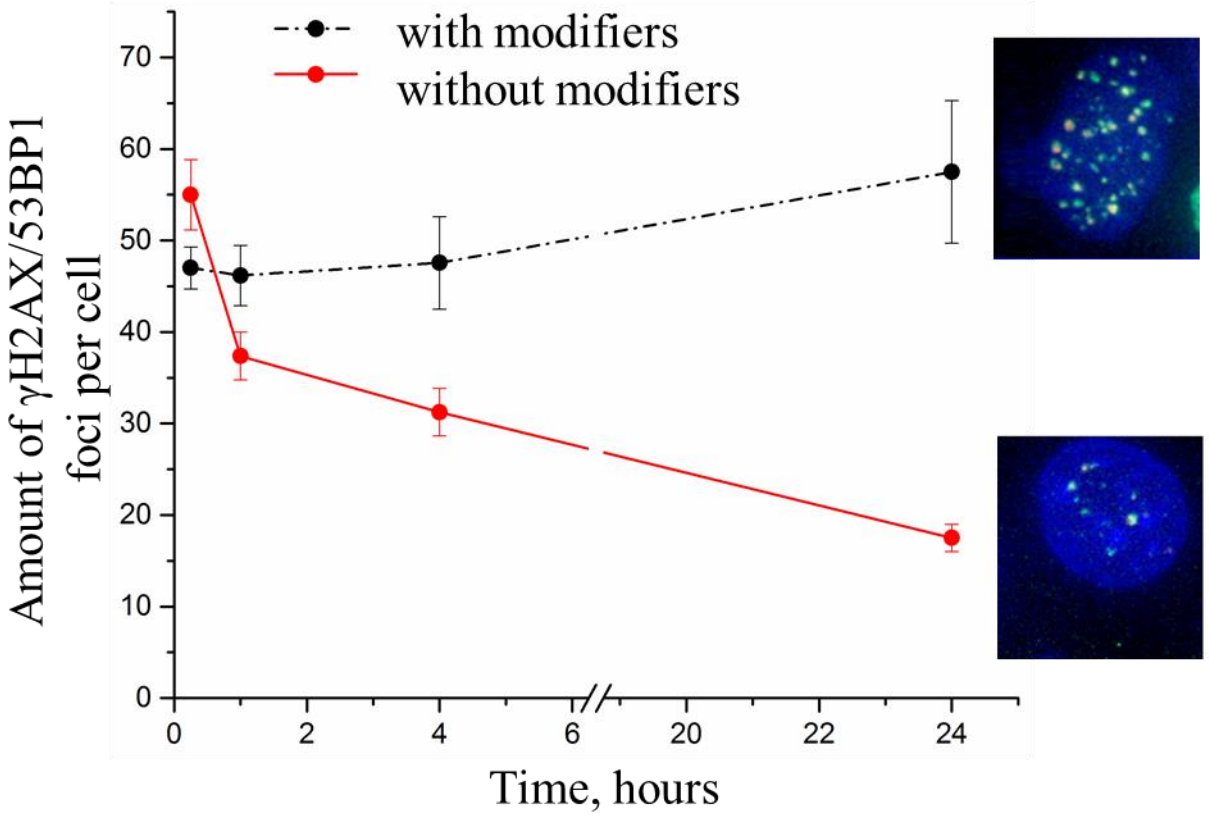
Pharmacokinetics



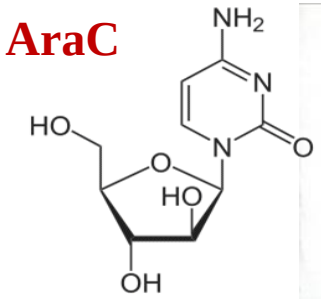
Fluorescence immunocytochemistry, single molecule microscopy

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



patent
LRB JINR, 2019

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
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Дата государственной регистрации в Государственном реестре изобретений Российской Федерации 09 сентября 2019 г.
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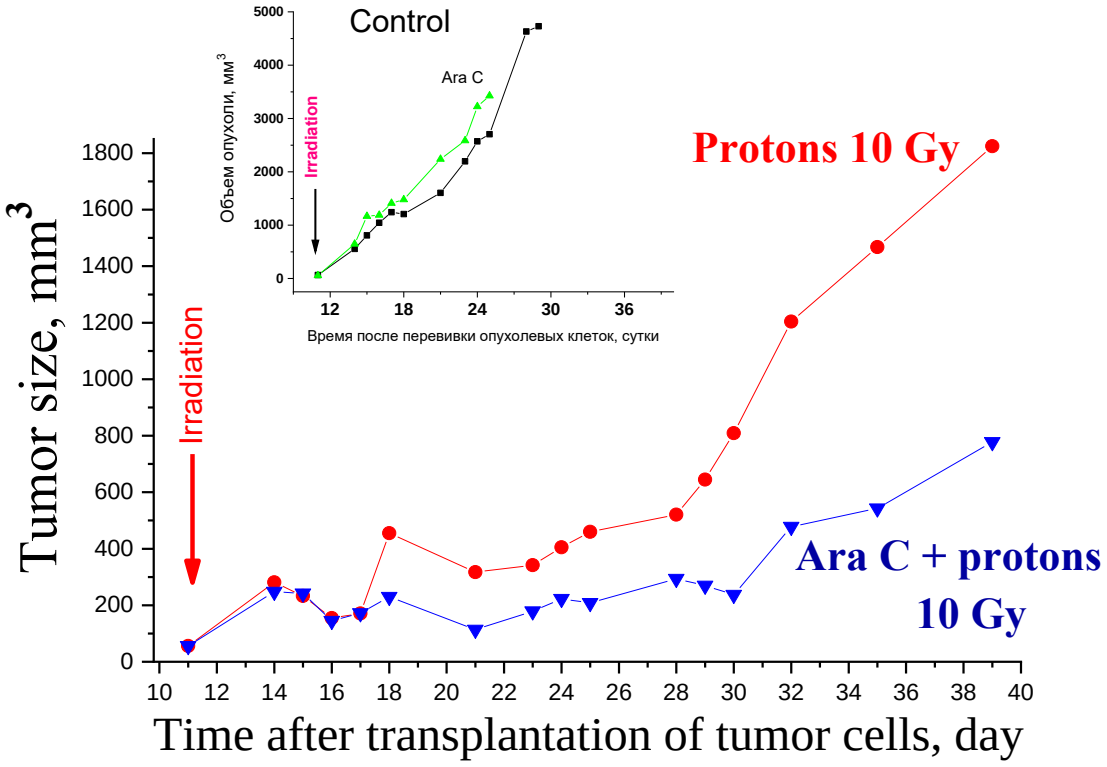
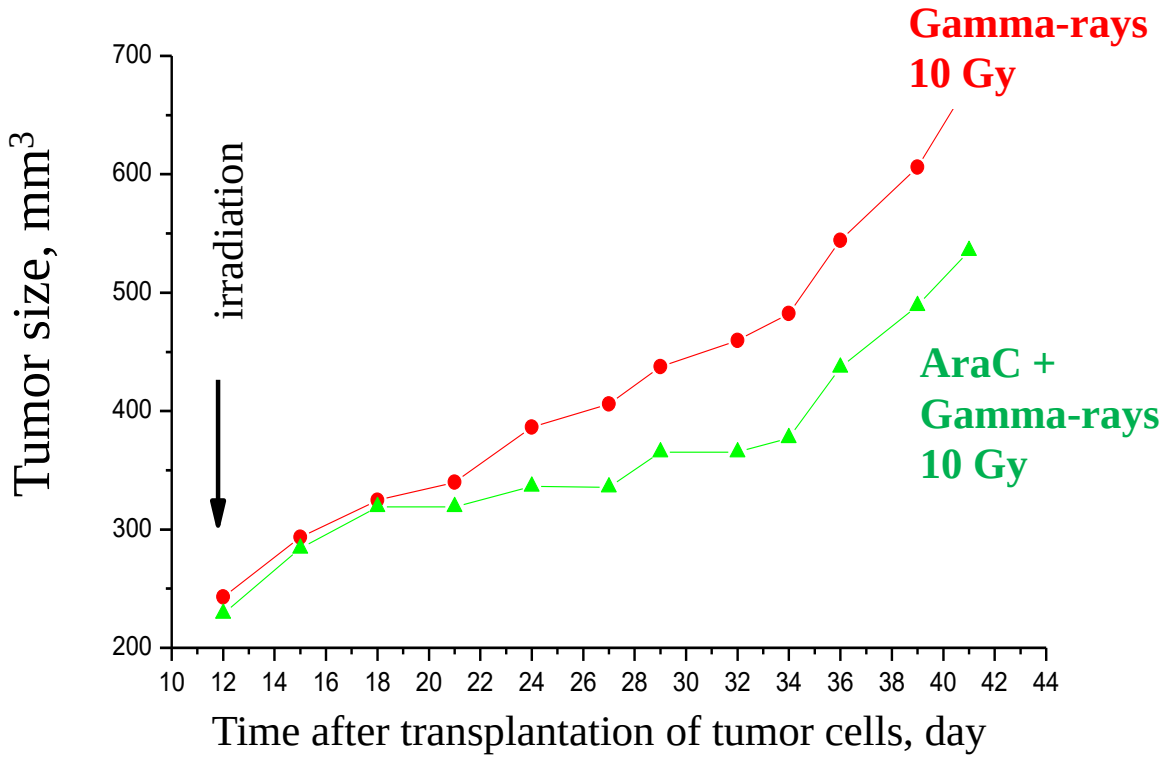
Руководитель Федеральной службы по интеллектуальной собственности

Г.П. Ивлиев

Preclinical studies on laboratory animals with transplanted melanoma tumor

Krasavin, Zamulaeva, Kaprin, 2019,2020





Methods of influence on the biochemical networks of cells

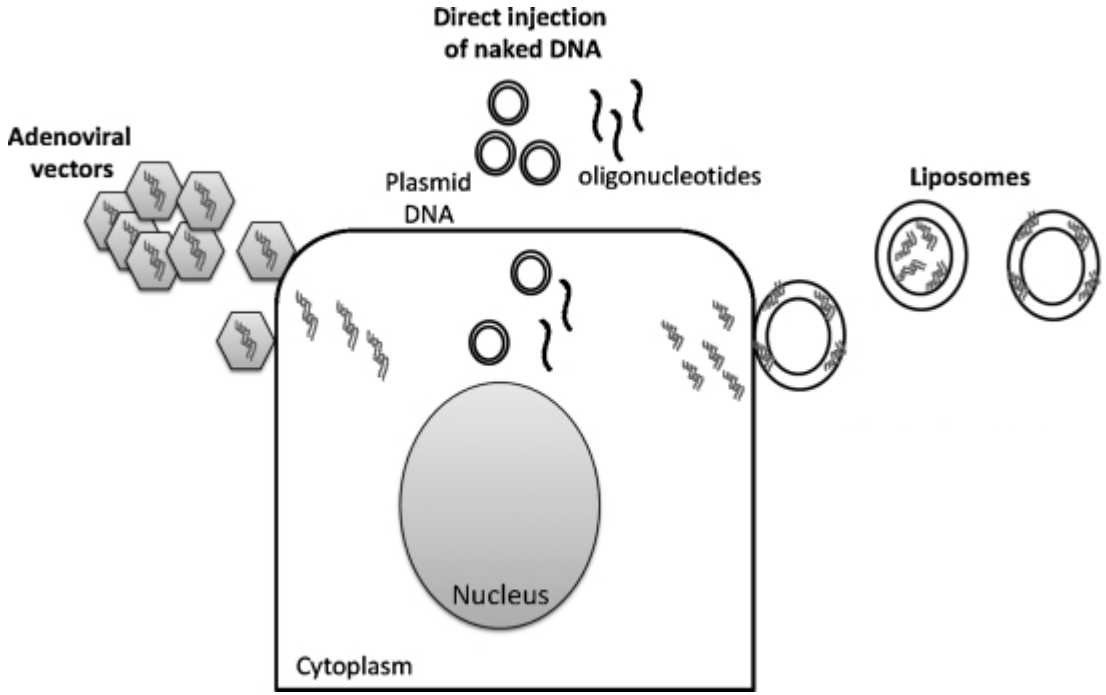
Pharmaceuticals

A big variety!
Registered for clinical use

DNA synthesis inhibitors, repair inhibitors, cell cycle blockers …

Transgene systems

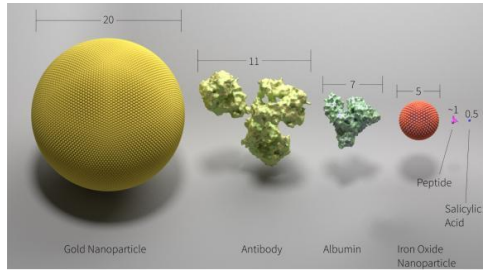
The latest biotechnology,
high selectivity,
targeted delivery is possible,
complexity in clinical registration



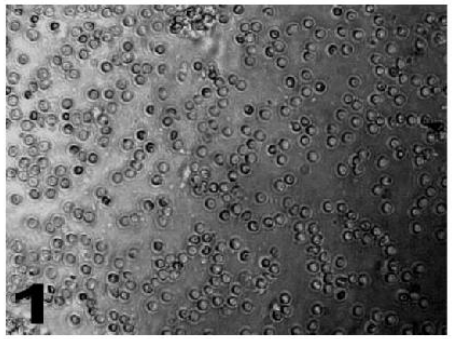
Artificial compounds

increase energy release when interacting with radiation

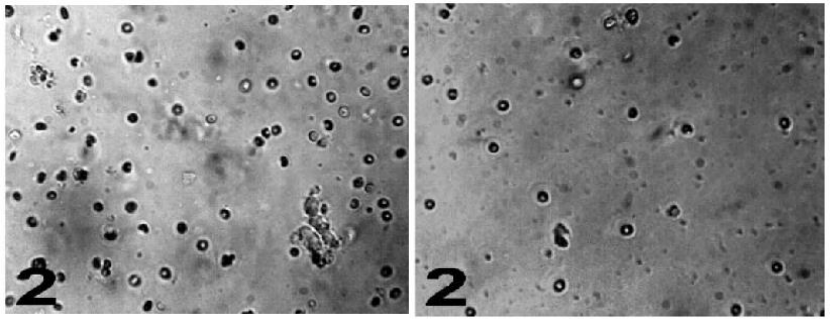
Metal nanoparticles, quantum dots, ...



Targeted drug delivery (molecular vectors)



Medulloblastoma tumor (IV stage)

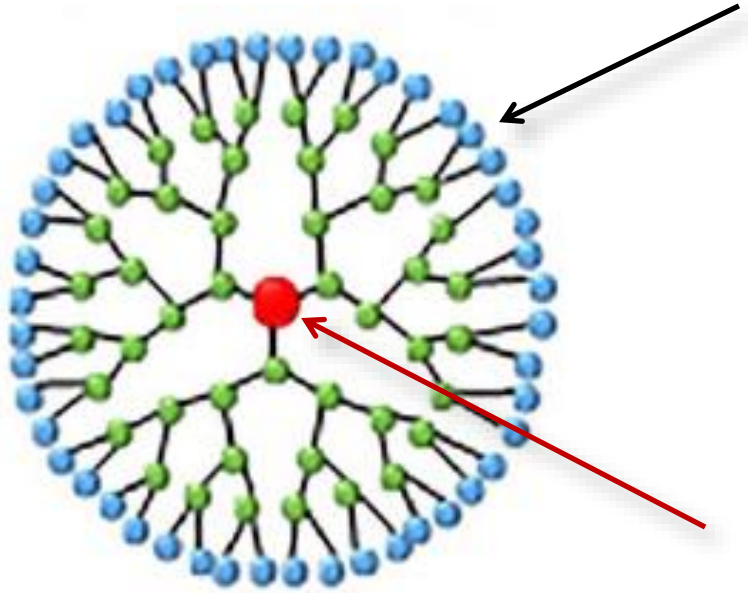


AraC 0.1 mg/ml

+ Ethyl (5 - (benzylthio)-4-chloroisothiazole-3 -yl) carbamate (10.0 mg / ml)

AraC 1 mg/ml

Organic NP (dendrimer)



Active drug (AraC)

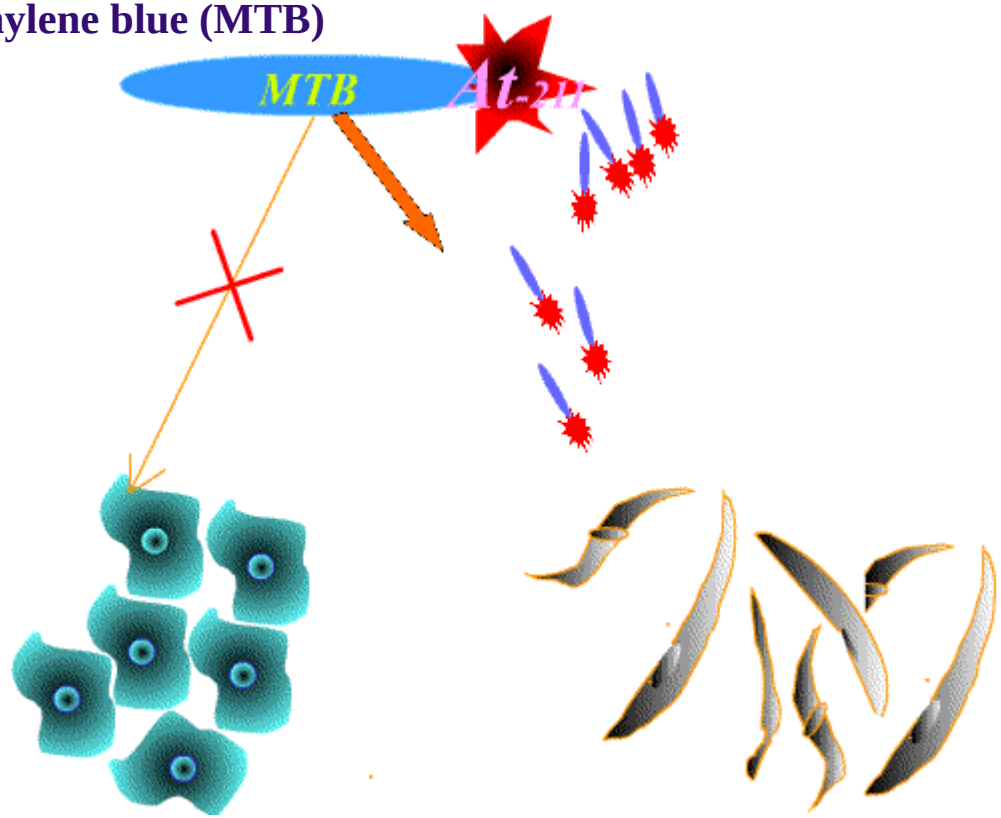
Kulchitsky et al. *2012*

Nuclear medicine:
targeted delivery of radionuclides

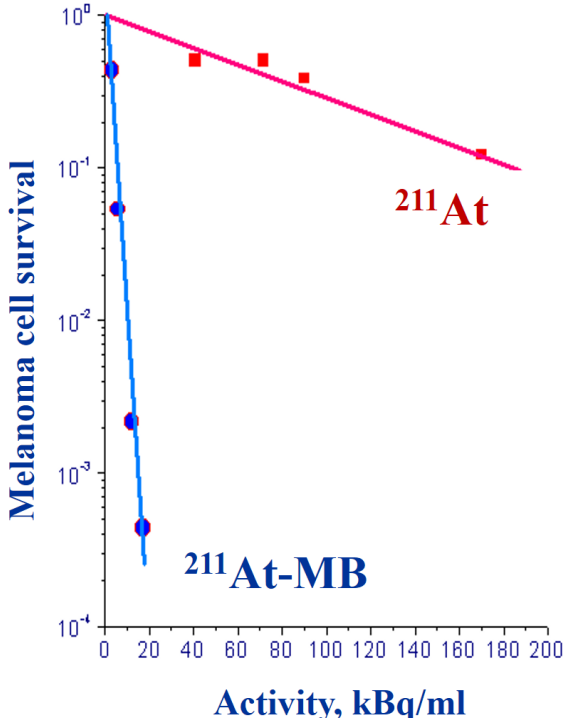
JOINT INSTITUTE FOR NUCLEAR RESEARCH

Shmakova, Norseev, Krasavin, Kodina et al, 2002

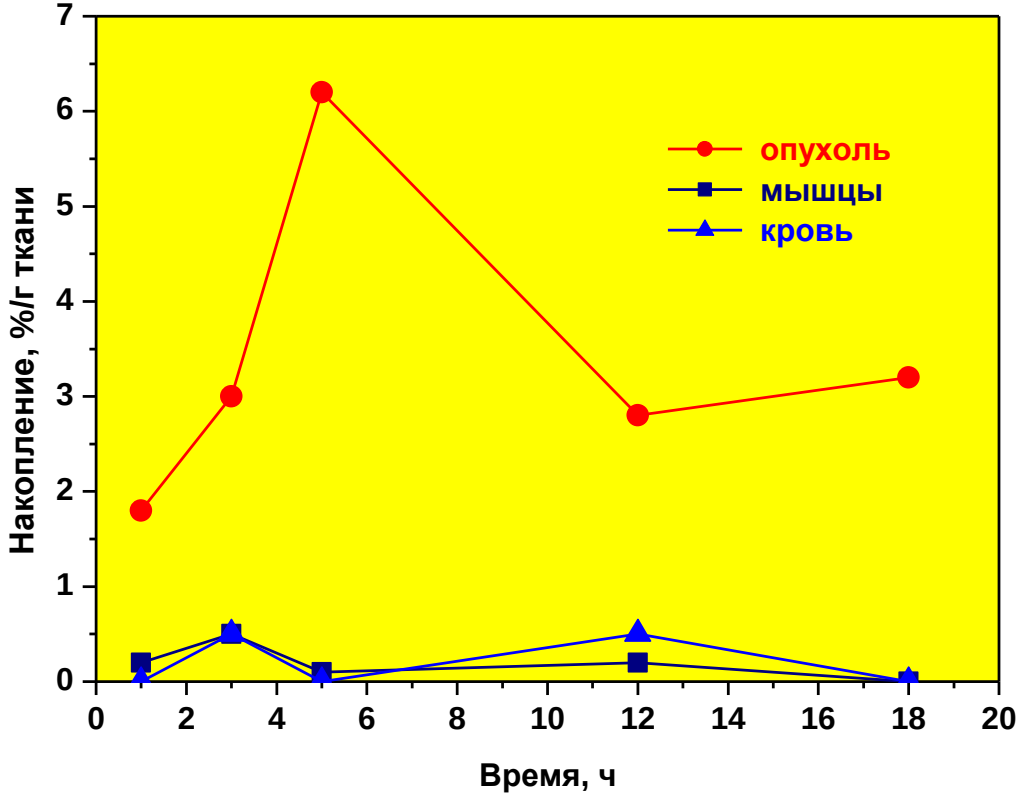
Methylene blue (MTB)



Melanoma tumor cell survival
in vitro

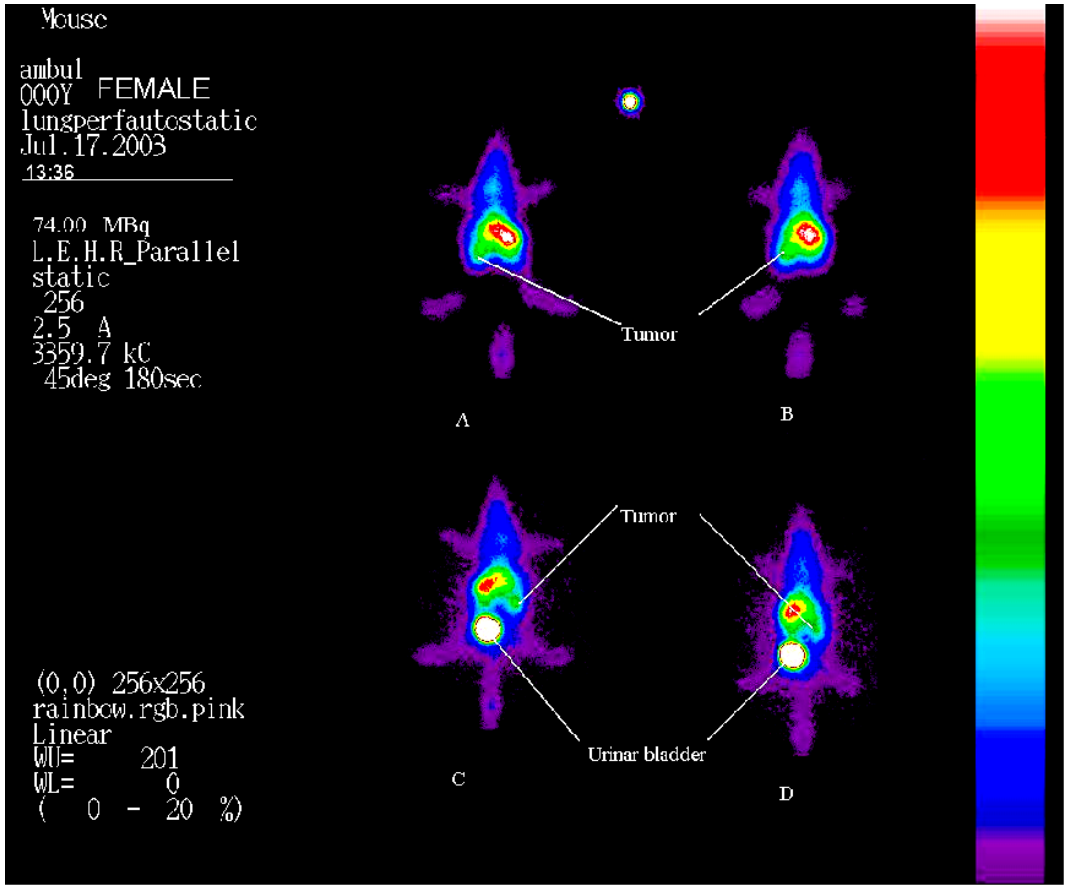


Nuclear medicine:
targeted delivery of radionuclides

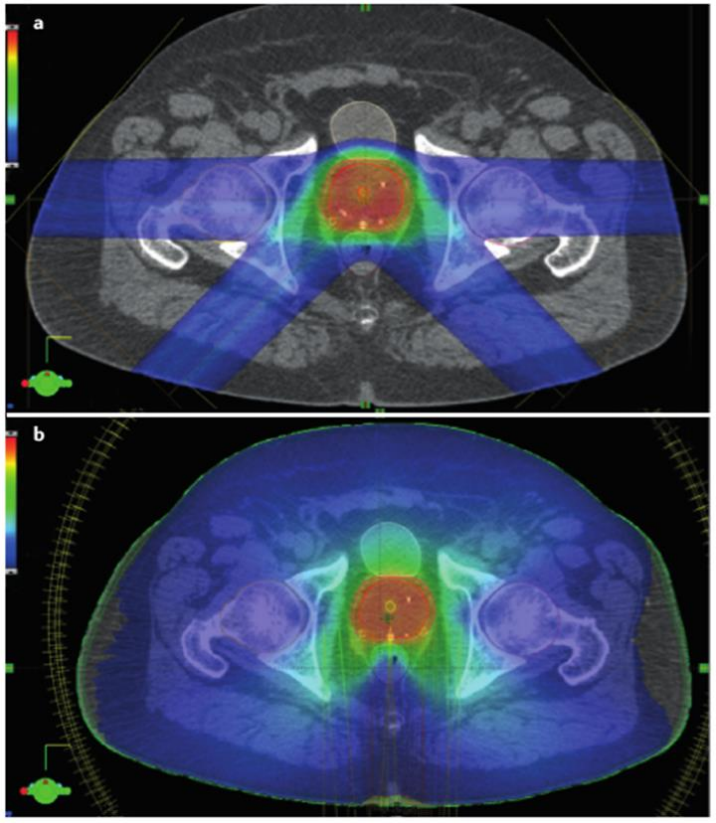


Accumulation of ^{211}At-MTB in various tissues of the body of animals with inoculated melanoma

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



New methods require the development of new therapy planning systems

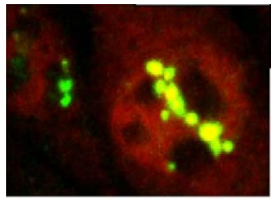


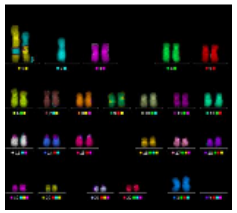
Monte Carlo simulation,
Pharmacokinetics,
Visualization
…

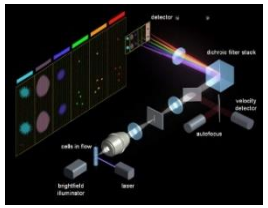
JINR Research Network

Cell cultures

Immunofluorescent imaging, single molecule microscopy, flow cytometry, radiation cytogenetics, genomics, proteomics, gene engineering, molecular vectors, drugs, radionuclides, microbeams





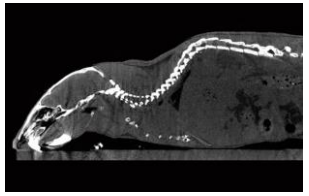


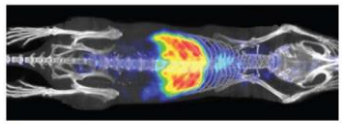
LRB

Animal research

physiology, tumor xenography, tomography

Preclinical research





Модель мыши; Радиофармацевтический препарат: ^{131}I. Активность введённого альбумина: 2,5 МБк; время визуализации: 1 час 45 минут

Proton & electron beams, detectors, collimators, treatment planning, development of new medical cyclotrons

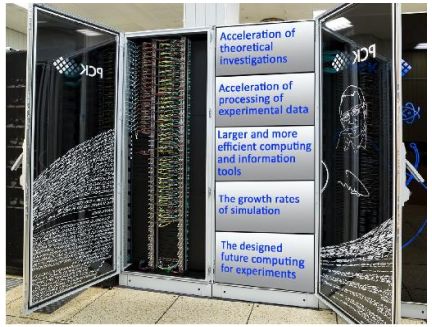
EG-5

Cf neutron source

FLNP

JINR University Centre

Education



Supercomputing, data analysis , artificial intelligence

JINR LIT

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

Clinical Radiobiology

Expected results

- molecular radiobiological studies of the **mechanisms modifying the cell regulatory networks** in response to radiation: DNA damage induction, DNA repair, apoptosis, bioinformatics analysis with omics-technologies
- investigation and testing of new **pharmaceuticals** and specially designed **transgene systems**
- development and testing of methods for **targeted delivery of drugs and radiopharmaceuticals**
- research of **new methods of radiation therapy** on laboratory animals with transplanted tumors
- investigation of autopsy material of tumor formations: the number of cancer stem cells (CSC), the proliferative activity of tumor cells, tumor vascularization, cell cycle control and proliferation, stem state, epithelial-mesenchymal transition, cell death, angiogenesis, and immune response
- development and application of cytogenetic methods for assessing long-term effects of radiation therapy
- assessment of the negative effects of radiation therapy on the CNS: simulation on animal models
- elaboration of new schemes for planning and verification of therapy
- **preclinical studies** and **transfer of innovation technologies** to clinical centers

Collaboration with JINR Member States and Associate Members

YSU,
CANDLE SRC
YerPhI
IMB NAS RA

Inst. Physiol. NASB
IBCE NASB
SPMRC NASB

IE BAS
NCRRP
Inst. Microbiol. BAS
Inst. Mol. Biol. BAS

INPC VAST
ITRRE VINATOM

CENTIS

NUM

INP PAS
INCT
SzU

IFIN-HH
UMF
UBB
IBR

CU
UPJS
IEP SAS

IBR ASCR
NRI

GSI/FAIR

INS “VINČA”

INFN
UNIUD

IBMP RAS
SINP MSU
ISR RAS
IMP RAS
IHNA RAS
SF IPh
I.P. Pavlov Inst. Physiol. RAS
M.V. Lomonosov MSU
IBMC
Skoltech
NMRRC (Obninsk)
FMBA FMBC
N.N. Blokhin NMRCO

Cooperation with International Research Centers

International biophysics collaboration, since 2019

Main members:

GSI FAIR

JOINT INSTITUTE FOR NUCLEAR RESEARCH

NICA

GANIL laboratoire commun CEA/DRF spiral2 CNRS/IN2P3

INFN Istituto Nazionale di Fisica Nucleare

INFN LNS Istituto Nazionale di Fisica Nucleare Laboratori Nazionali del Sud

SPES exotic beams for science

CNAO Centro Nazionale di Adroterapia Oncologica

TIFPA Trento Institute for Fundamental Physics and Applications

NRF National Research Foundation | iThemba LABS Laboratory for Accelerator Based Sciences

NIRS

eli beamlines

university of groningen

kvi - center for advanced radiation technology

umcg

frontiers in Physics

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Biomedical Research Programs at Present and Future High-Energy Particle Accelerators

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Thank you for your attention!