JINR radiobiological research program with heavy ion beams of the NICA accelerator complex

A. N. Bugay

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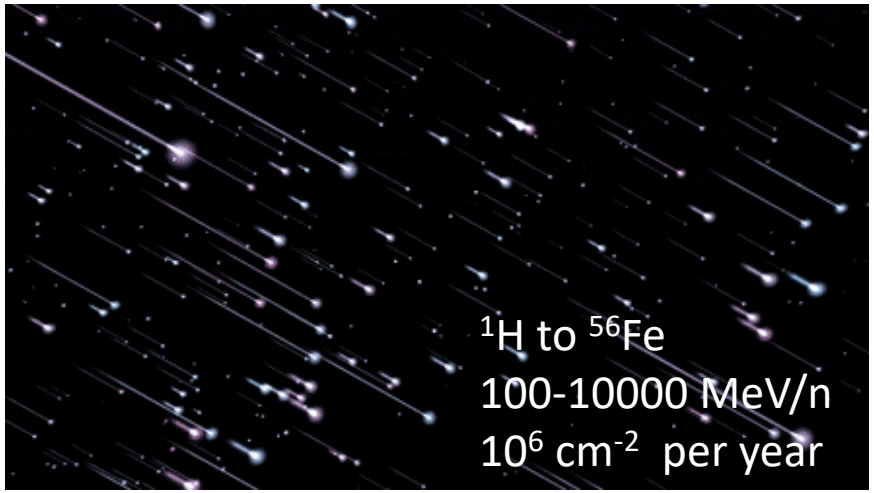
1959 - First radiobiological experiments at JINR

Relative biological effectiveness of charged particles
Radiation-induced mutagenesis

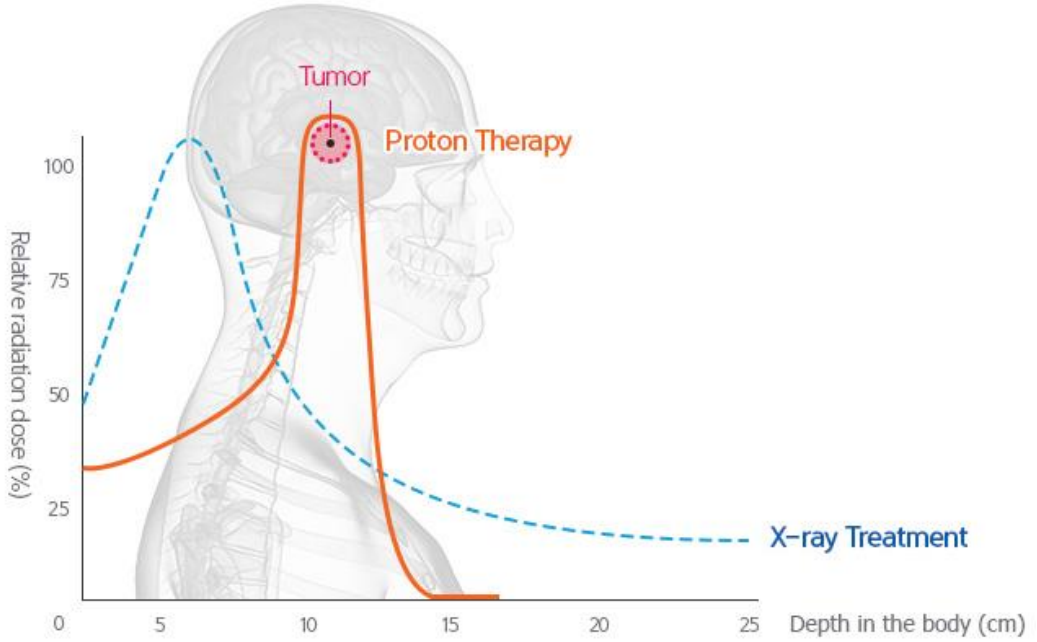
Radiation risk in space

1959 - Preparation of first manned space flight



Radiation therapy of cancer

1967 - start of proton therapy



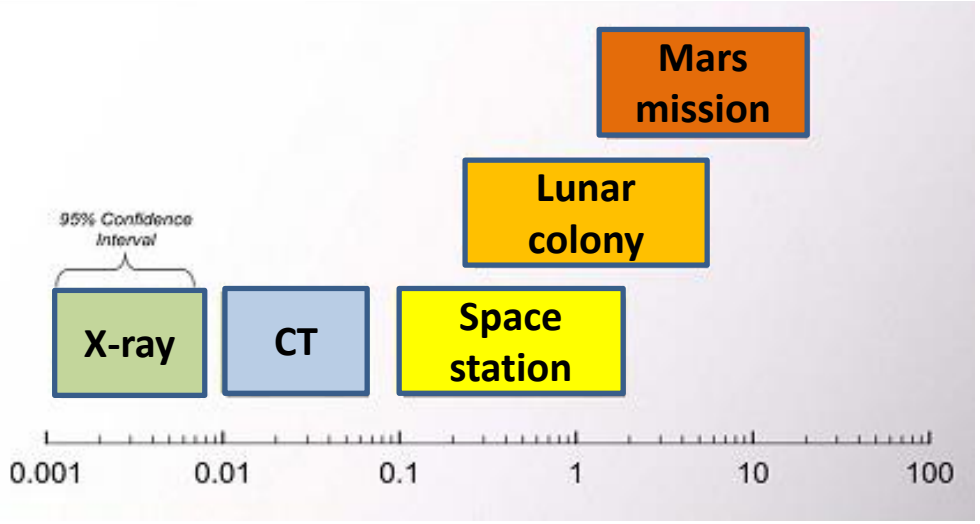
Milestones of heavy ion radiobiology at JINR

JINR, 1972.
C. Tobias (Biophysical Division, Lawrence Laboratory) with **E.A. Krasavin** during the visit to JINR heavy ion accelerators.

- **1969 - First radiobiological studies** on the beams of the U-300 accelerator, LNR, JINR (*Krasavin et al., 1970, Symp. on space biology and medicine, Budapest*)
- **1970 -** First **experimental confirmation of R. Katz's theory** on the role of radial energy distribution in radiation-induced radiation effects (accelerator U-300, LNR, JINR) (*Krasavin et al. Radiobiology, 1971*)
- **late 1970s - 80s -** Initial cytogenetic and **neuro-radiobiological** experiments at the synchrophasotron of the LHE JINR
- **1985 -** Monography *"**RBE problem and DNA repair**" Krasavin E.A.*
- **2017 - New concept of radiation risk** during manned deep space flights (*Grigoriev A.I., Krasavin E.A., Ostrovsky M.A., Bull. RAS 2017*)

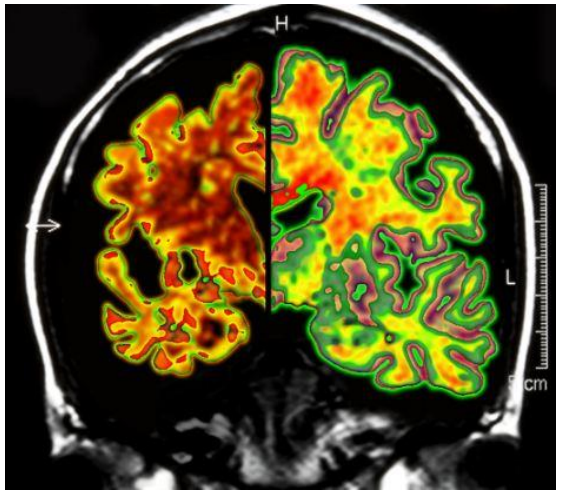
New concept of radiation risk for deep space flights: Damage to the central nervous system (CNS)

Grygoriev, Krasavin, Ostrovskii, Bulletin of RAS 2017



% Risk of cancer death

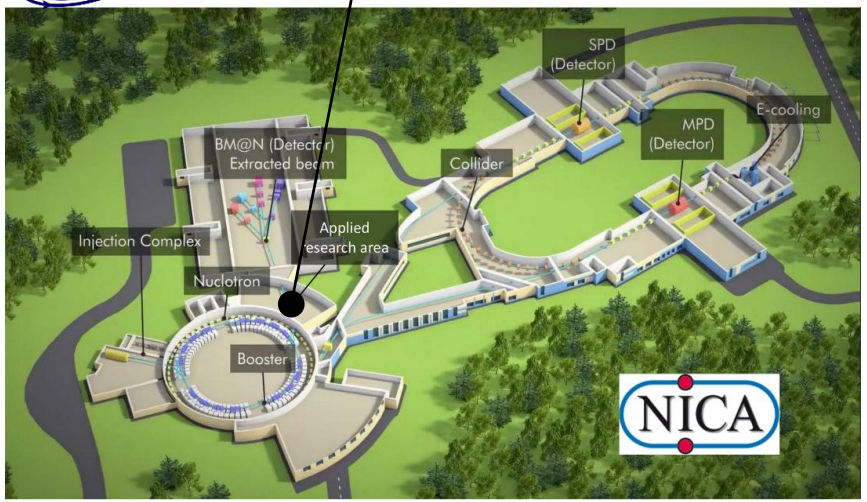
Paradigm shift

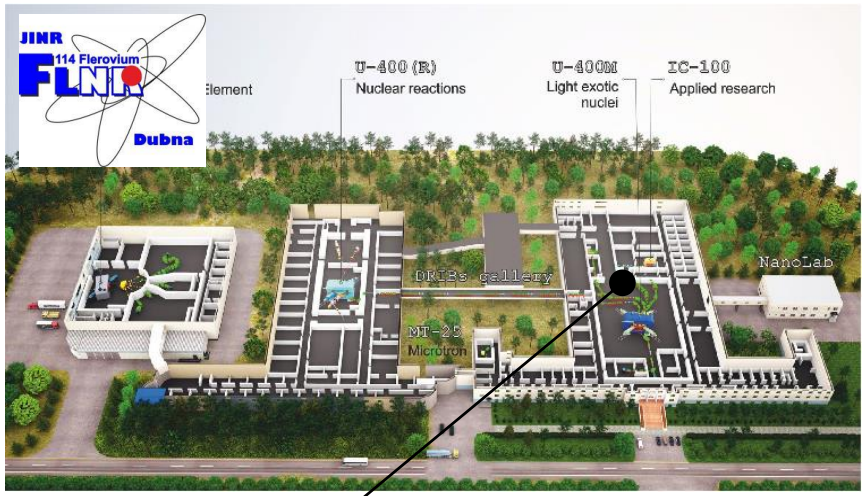


Radiation Neuroscience

JINR Research Network

NUCLOTRON (0.3 - 1 GeV/u, H - Au)

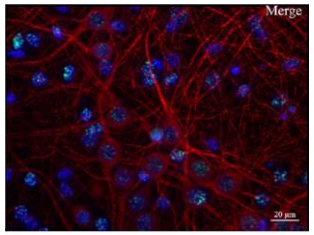


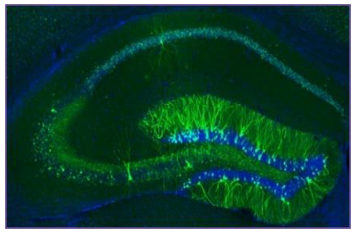


U 400M (50 MeV/u, Li – Ne)

Cell cultures

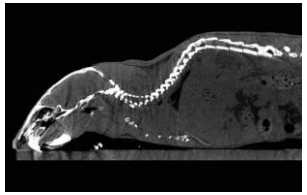
molecular damage, genetics, proteomics, neurodegeneration





Animal research

cognitive tests, EEG, histology, tomography

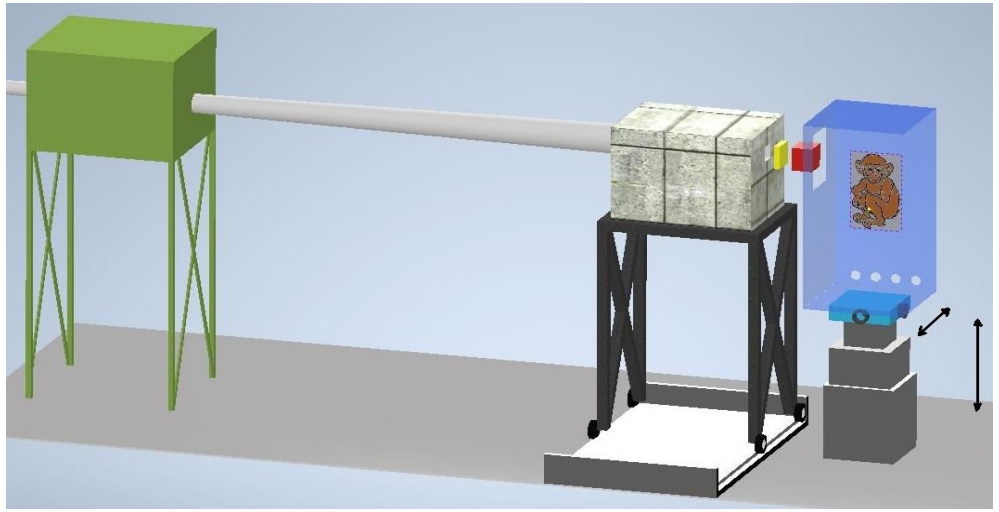


Medical proton beam

Supercomputing, data analysis

Neutron beams Structural analysis

SIMBA (СОДИБ) beamline for radiation biology



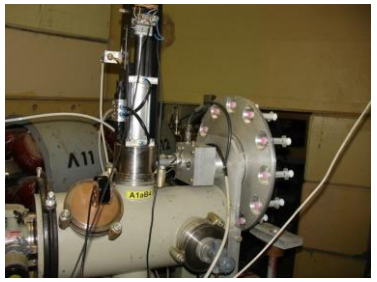
E = 500 - 1000 MeV/u

Ion, E (MeV/n)	LET (keV/μm)
^{12}C, 500	9,7
^{12}C, 800	8,2
^{20}Ne, 500	27,2
^{20}Ne, 800	23,1
^{40}Ar, 500	92,2
^{40}Ar, 800	78,3
^{56}Fe, 500	182,5
^{56}Fe, 800	155,0
^{84}Kr, 500	358,7
^{84}Kr, 800	305,1

Biological research infrastructure at the LRB, JINR and partners*

In vitro

automated sample exchange



In vivo

specially designed containers for rodents

anatomical chairs for monkeys

Cell cultures:

human and mammals

normal
cancer
neural

Animals:

Rats
Mice
Monkeys*

Xenograft tumor models*

Brain disease models*

Equipment and Methods:

laminars, incubators, auto cell counters
Immunohistochemistry & fluorescent microscopy
multicolor FISH
sequencing, PCR
flow cytometry*
mass spectrometry*
liquid chromatography*
electron microscopy
SANS, Raman spectroscopy

vivarium (IVC)
behavioral tests, video-tracking
EEG (wireless)
histology (classic, immunofluorescent)
X-ray tomography, bioluminescence option

Digital Data Storage

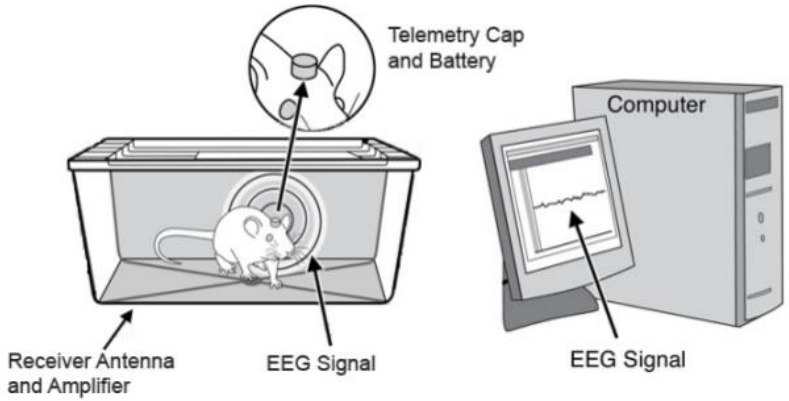
Machine learning based data processing
(in development)

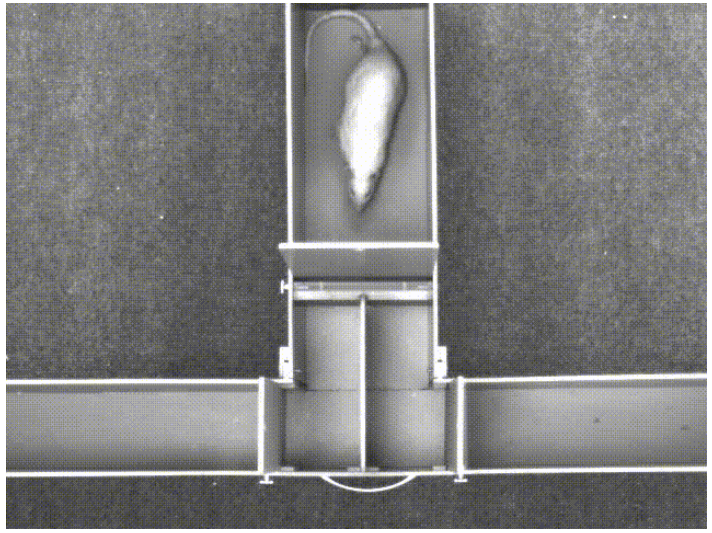
Set of equipment for the study of behavioral reactions and functional disorders of the central nervous system of animals

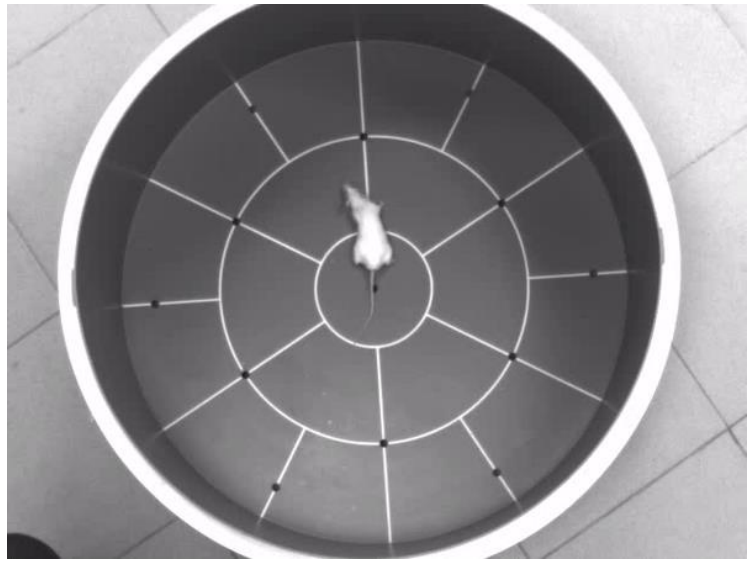
Behavior test systems

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

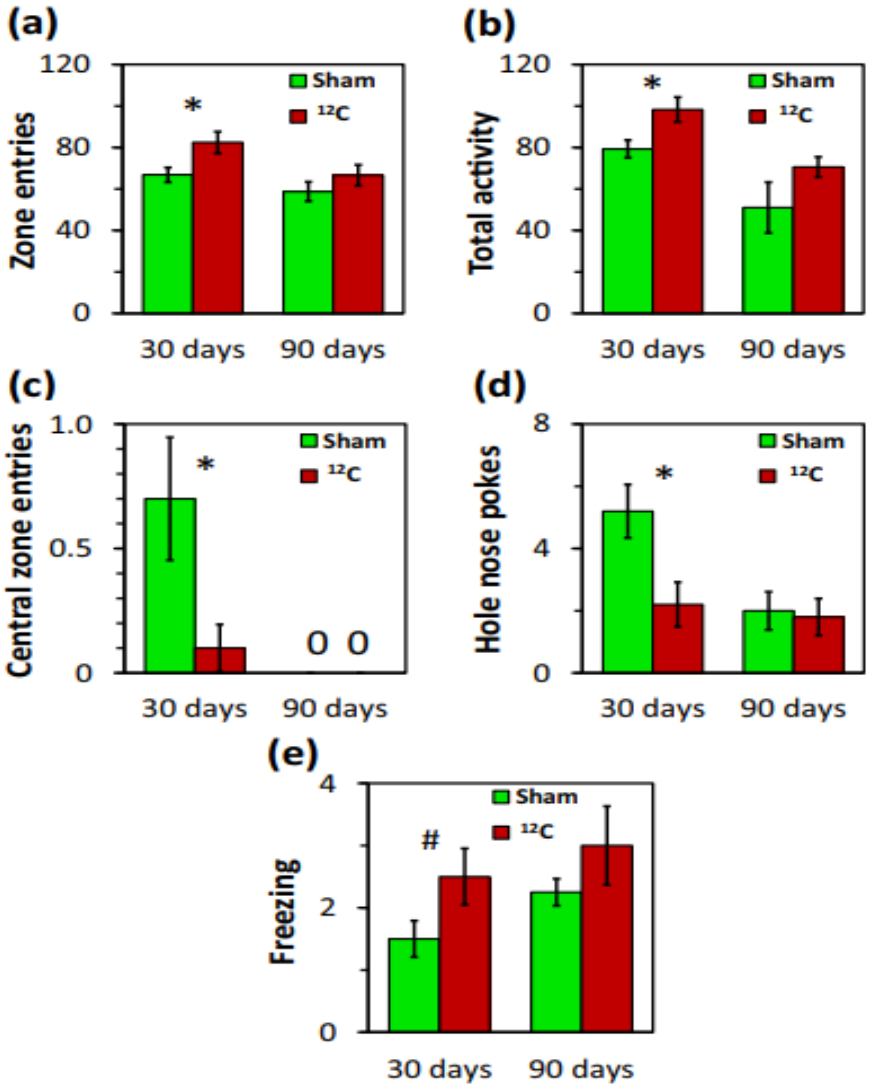
Electrophysiology studies

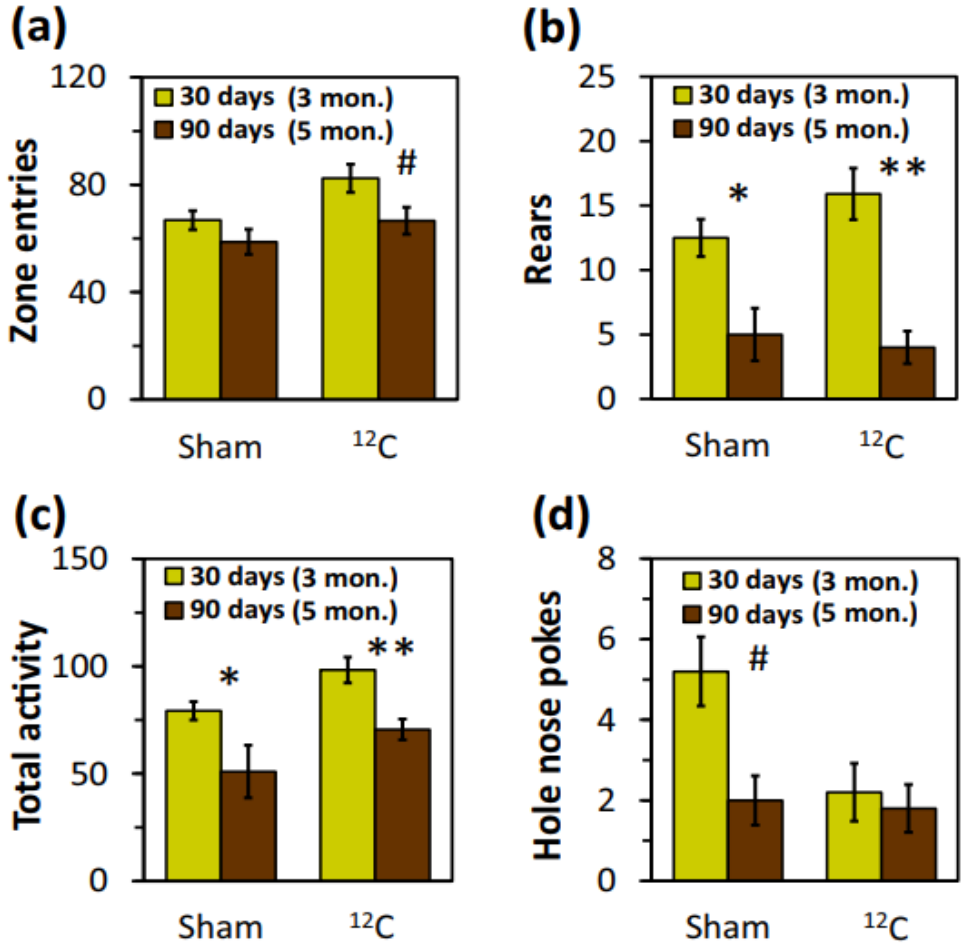






The effect of 1 Gy ^{12}C particle radiation exposure on rats
Behavior and emotional status



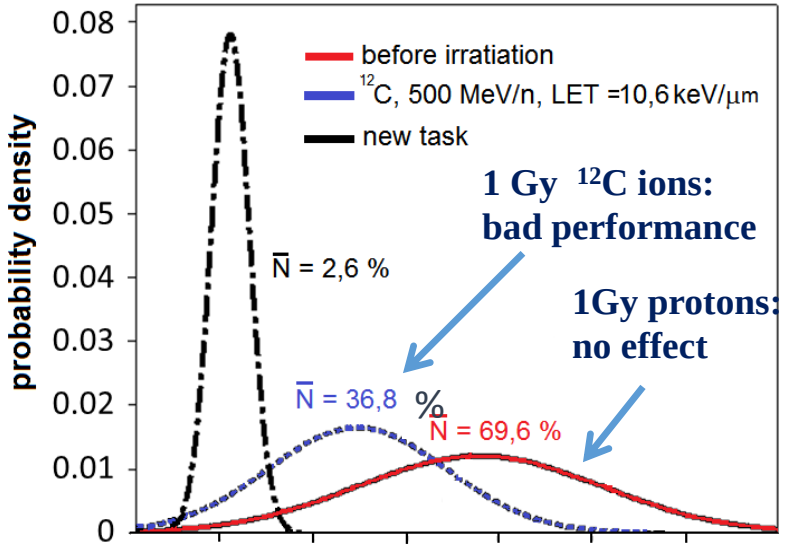


Unique experiments of the LRB with primates at Nuclotron

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

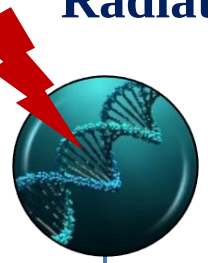
RAS Institute of Biomedical Problems,
RAS Institute of Medical Primatology,
RAS Institute of Higher Nervous Activity and Neurophysiology,
Moscow State University

The monkeys were preliminarily trained to solve logic 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.

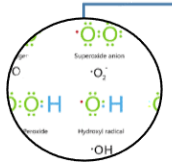


Towards the Mechanisms of Radiation Brain Injury

Radiation

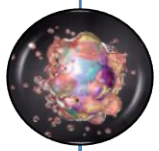


Damage to nuclear and mitochondrial DNA

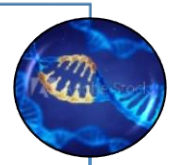


Oxidative stress

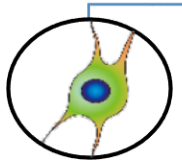
Microglia activation Neuroinflammation



Death of proliferating cells

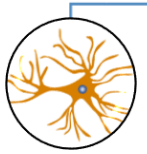


Accumulation of mutations

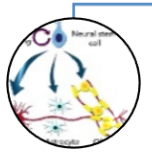


Oligodendrocyte death

Demyelination

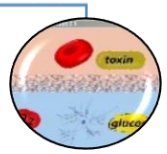


Astrocyte-mediated neurotoxicity



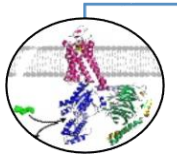
Progenitor cell death

Impaired neurogenesis



Endothelial cells death

Blood Brain Barrier disruption



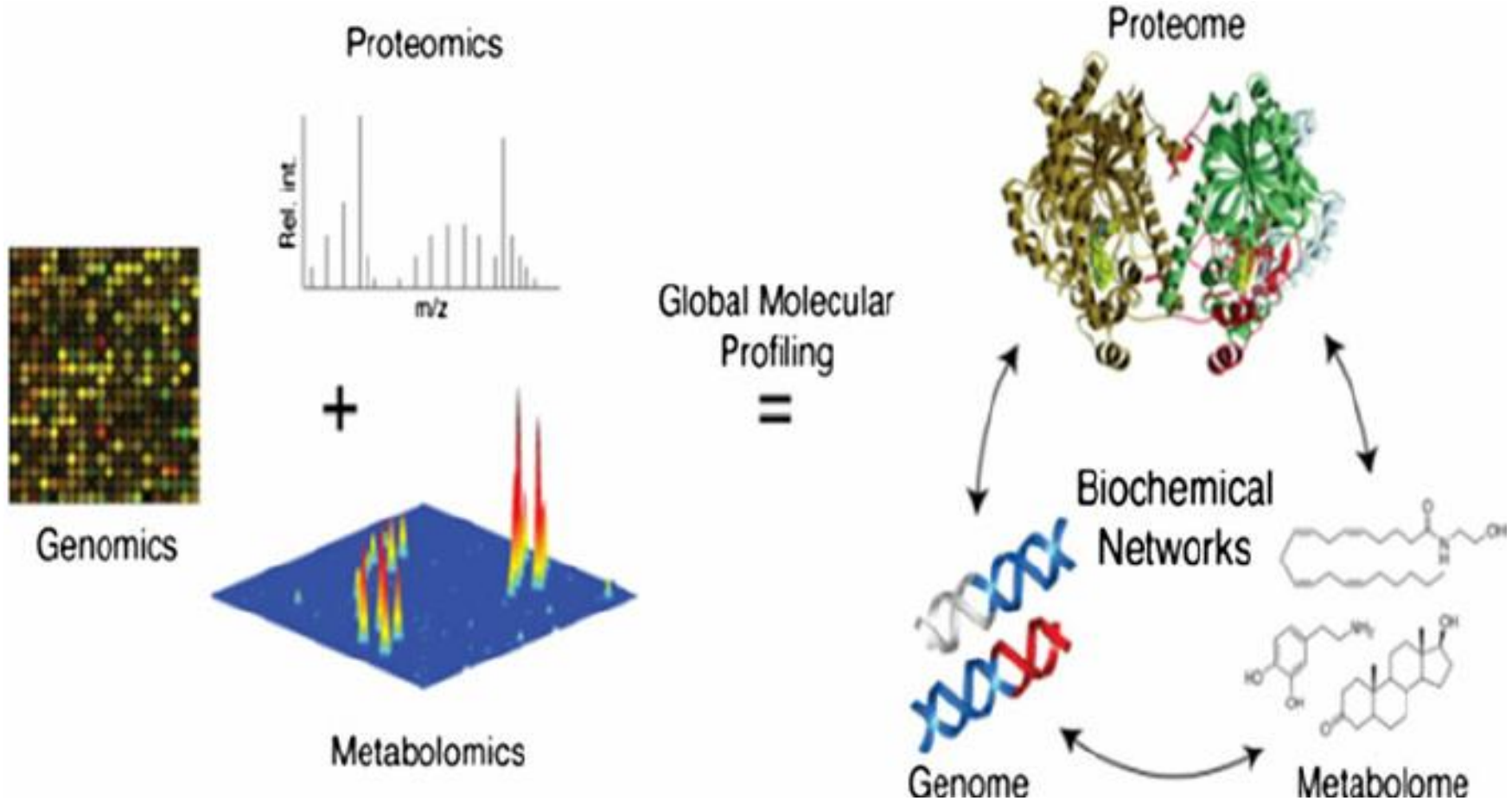
Impaired gene expression

Defect proteins

Carcinogenesis

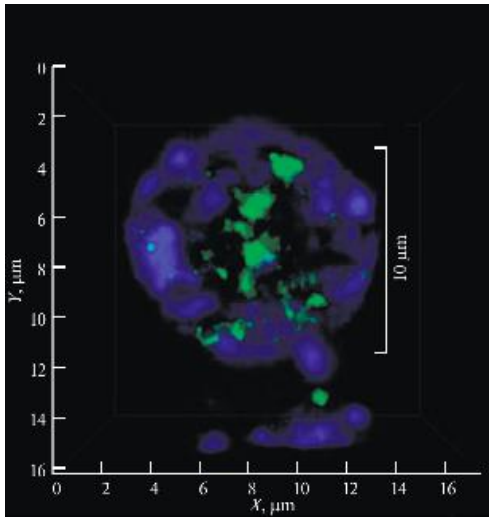
OMICs-technologies. Bioinformatics. Big data

Experiments 2020-21

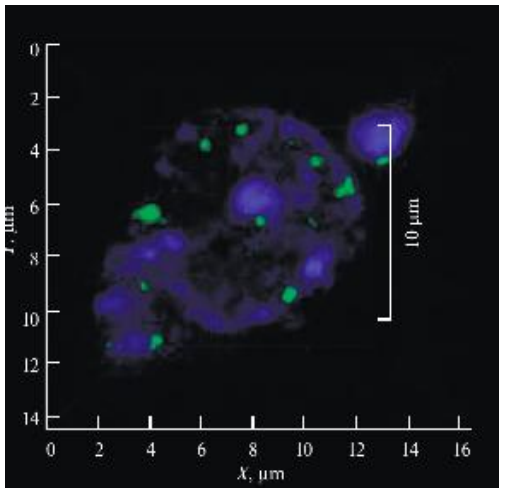


Molecular Radiobiology

DNA damage visualization in a dentate gyrus cell

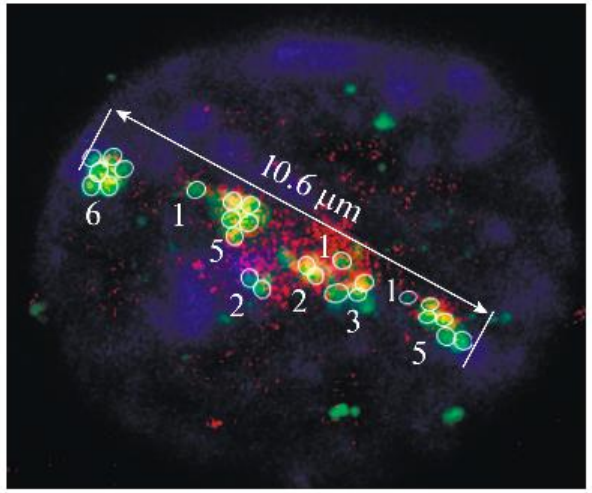


2GeV/u krypton ions

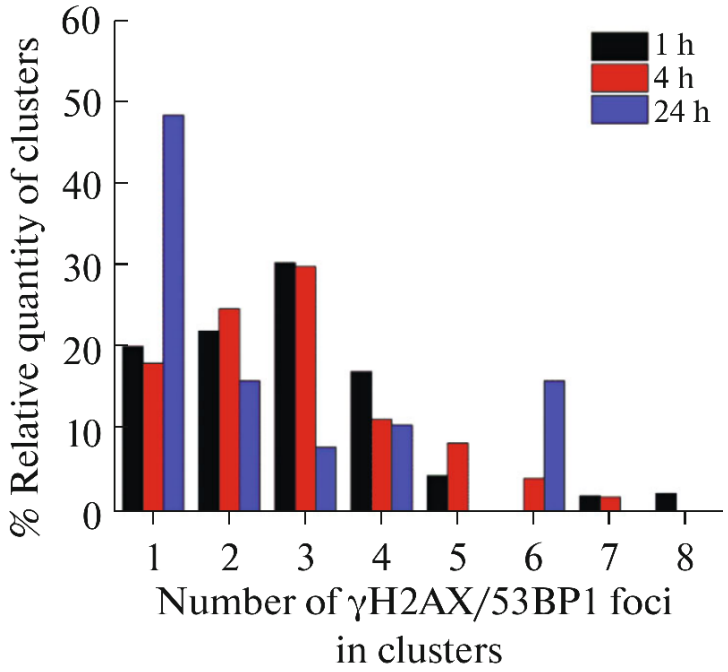


170 MeV protons

Formation of DNA double-strand breaks in rat brain neurons after irradiation of rats with Krypton ions



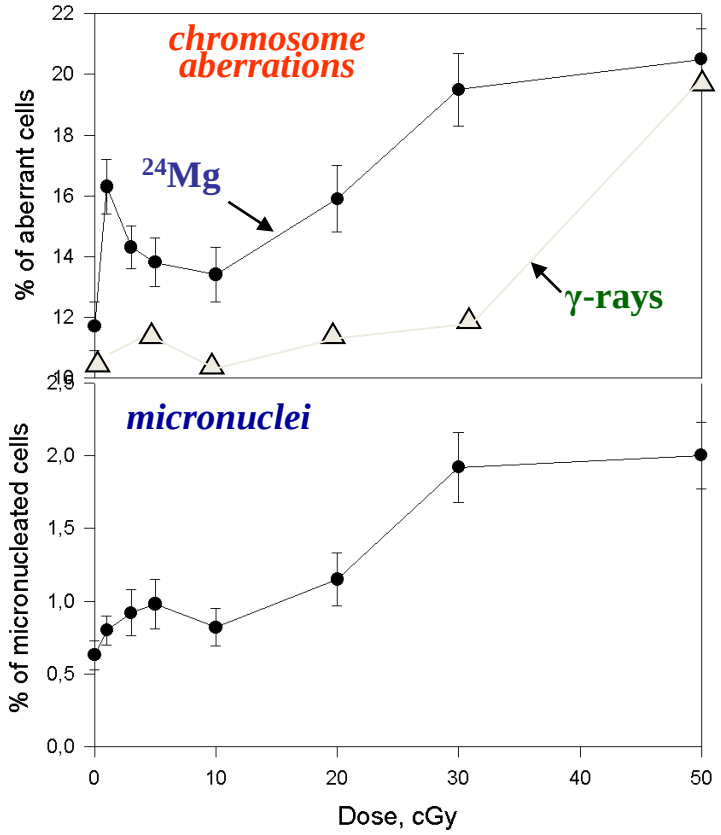
Clustered DNA DSB of high complexity in a hippocampal CA1 cell

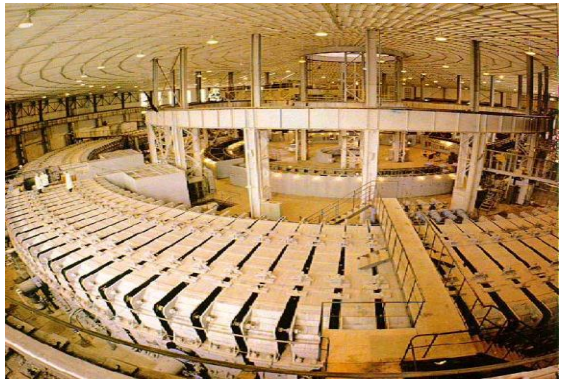


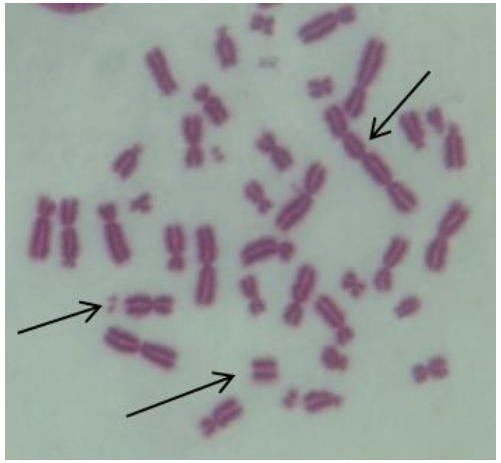
Bulanova, Boreyko, et al, Phys. Part. Nucl. Lett. 16 (2019) 336

Radiation Cytogenetics

Cytogenetic effect of low doses of ^{24}Mg ions at Synchrophasotron

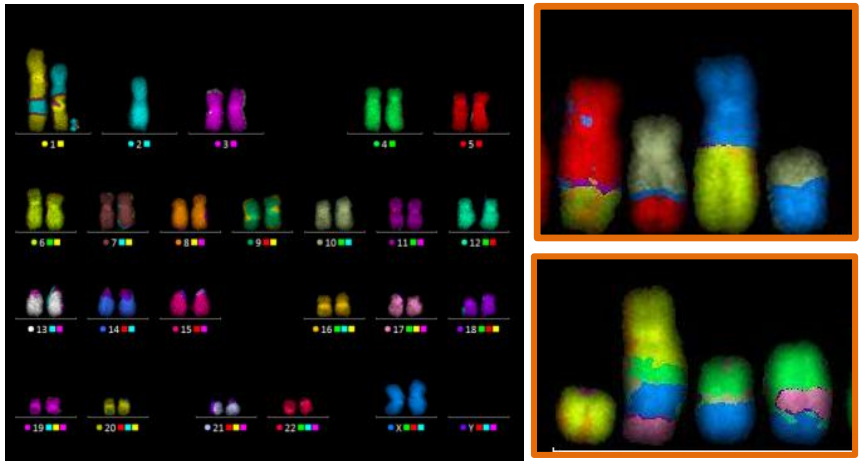






The frequency of cells with chromosome aberrations. Chinese hamster cells exposed to ^{24}Mg ions with energy 500 MeV/nucleon

- **Long-term consequences of radiation exposure**
- **Evaluation of complex chromosome aberrations induction**

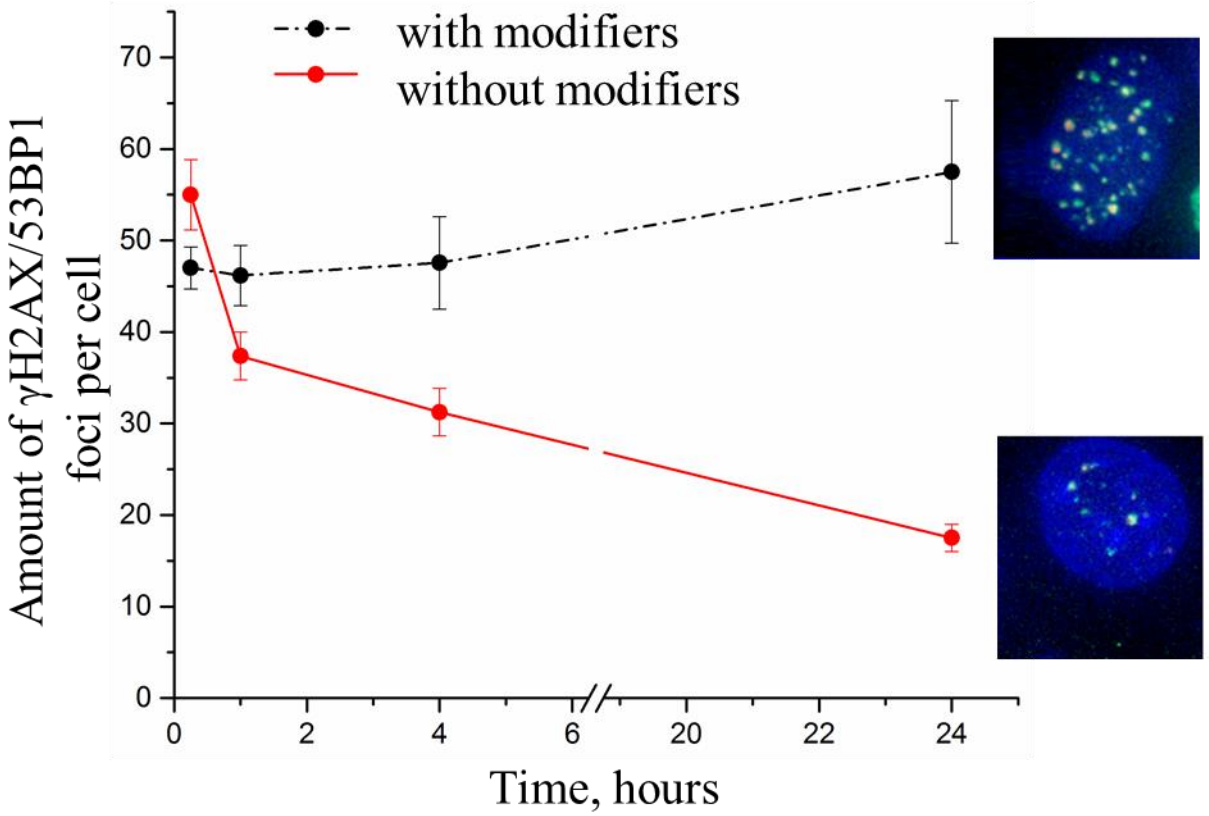


visualization of complex chromosome aberrations by mFISH method

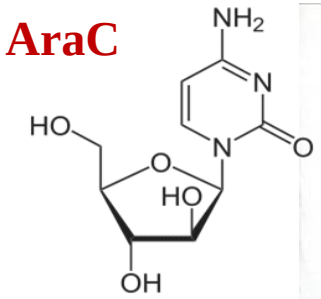
Clinical Radiobiology

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



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)*

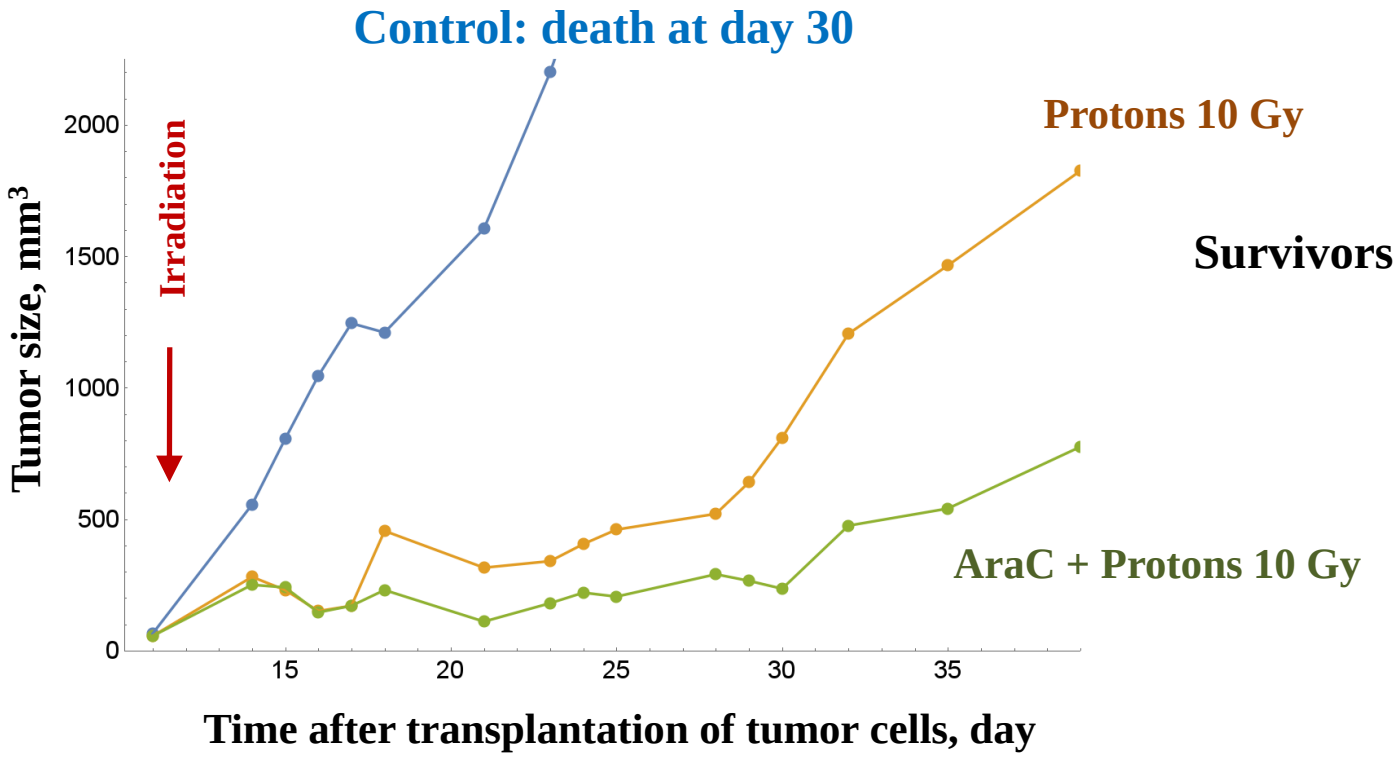
Заявка № 2018140538
Приоритет изобретения 16 ноября 2018 г.
Дата государственной регистрации в Государственном реестре изобретений Российской Федерации 09 сентября 2019 г.
Срок действия исключительного права на изобретение истекает 16 ноября 2038 г.

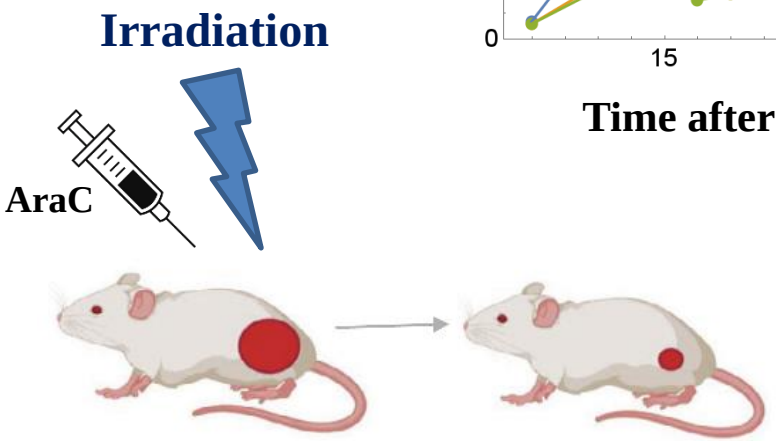
Руководитель Федеральной службы по интеллектуальной собственности

Г.П. Ивлиев

Clinical Radiobiology

- **Preclinical animal study** with transplanted **melanoma tumor cells** in mice (*in vivo* experiment)

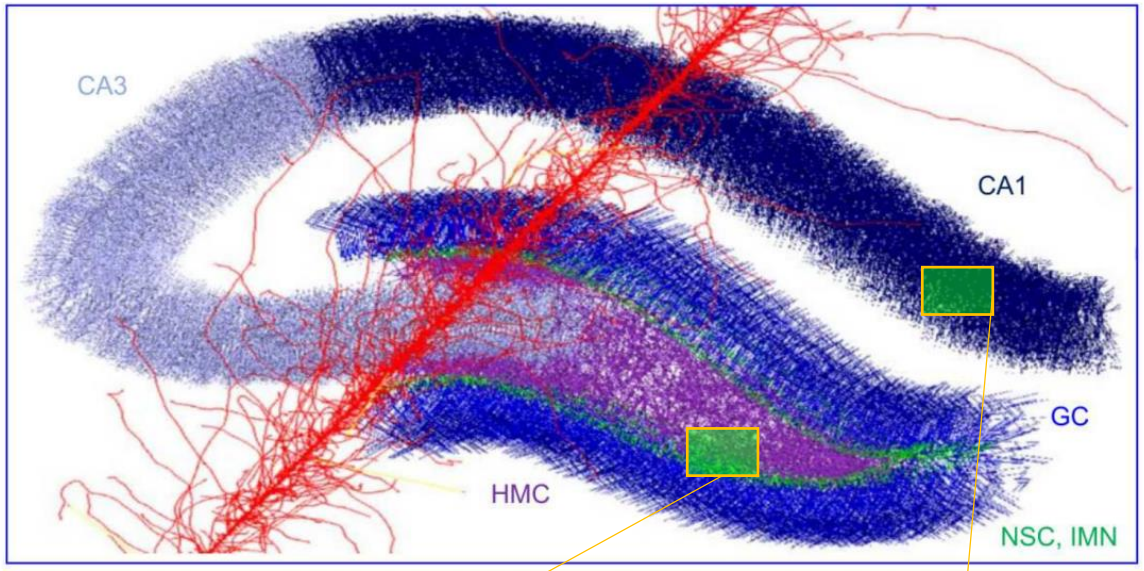




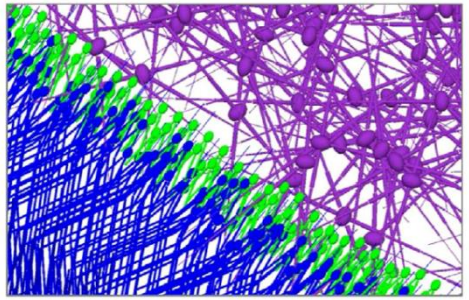
Melanoma tumor volume growth rate is 2.5 times lower with modifying agent !

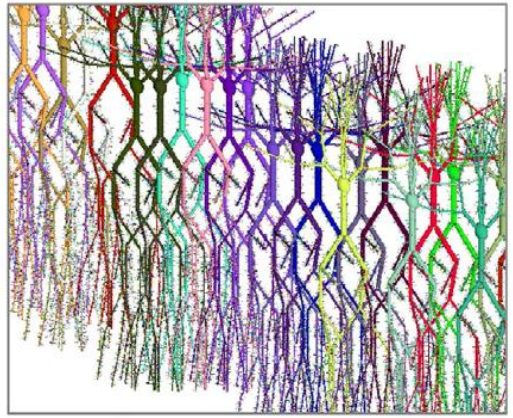
Monte Carlo Simulations

3D model of rat hippocampus traversed by 600 Mev/u ^{56}Fe ion track



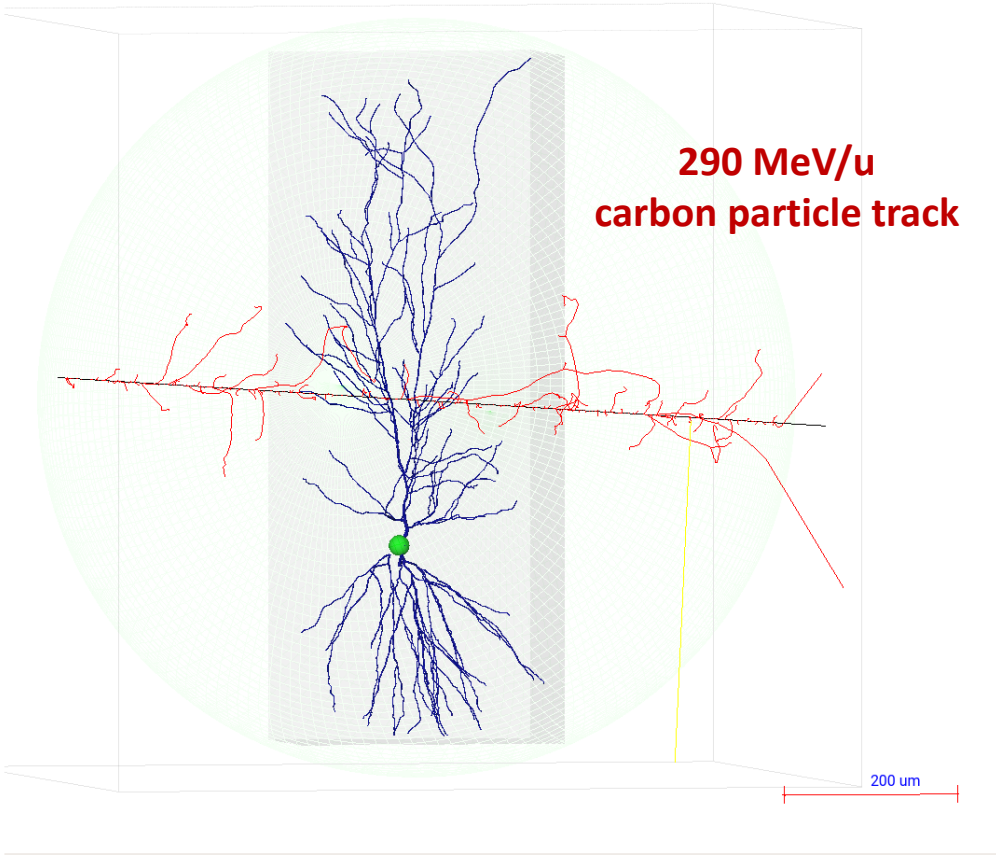
Element of subgranular zone





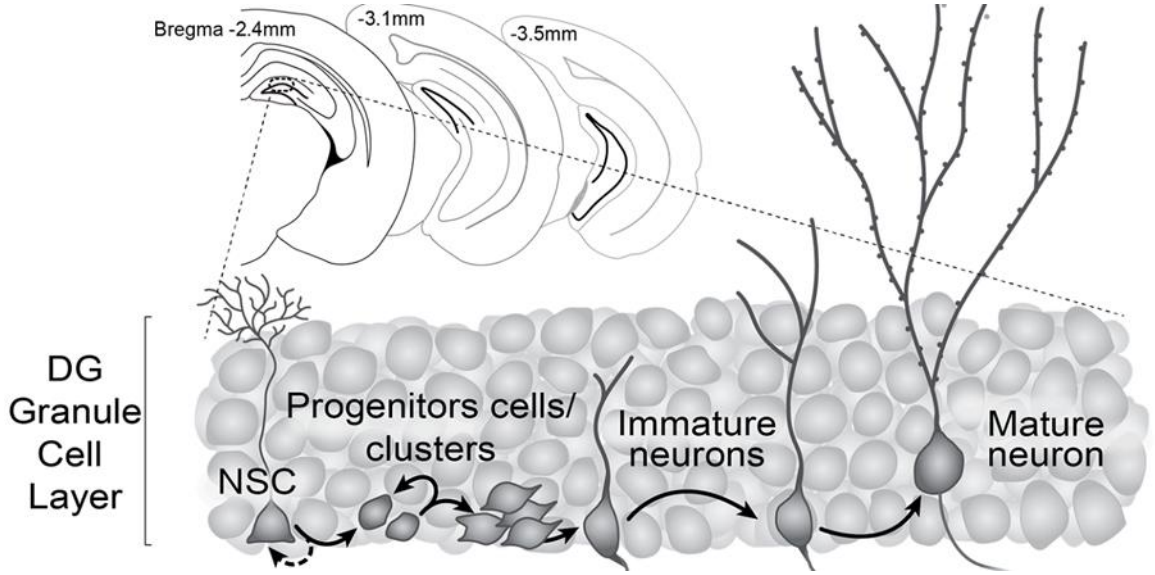
Layer of CA1 pyramidal neurons

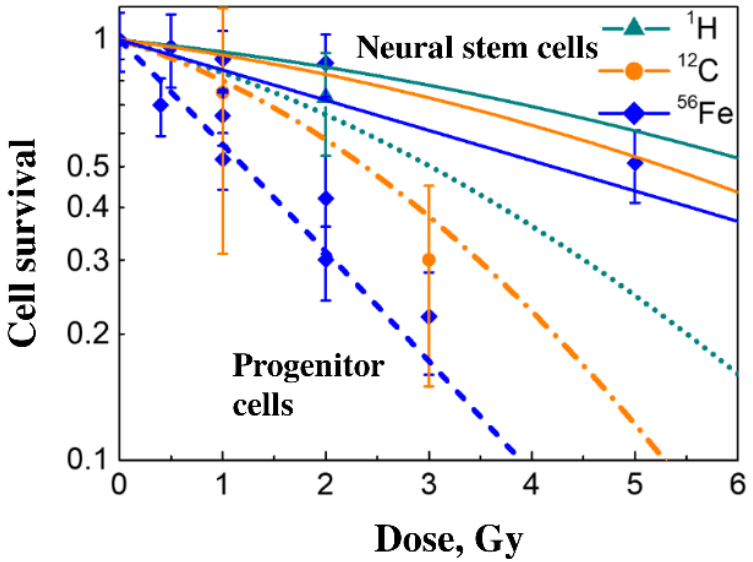
"neuron" - new radiobiology application of Geant4/Geant4-DNA

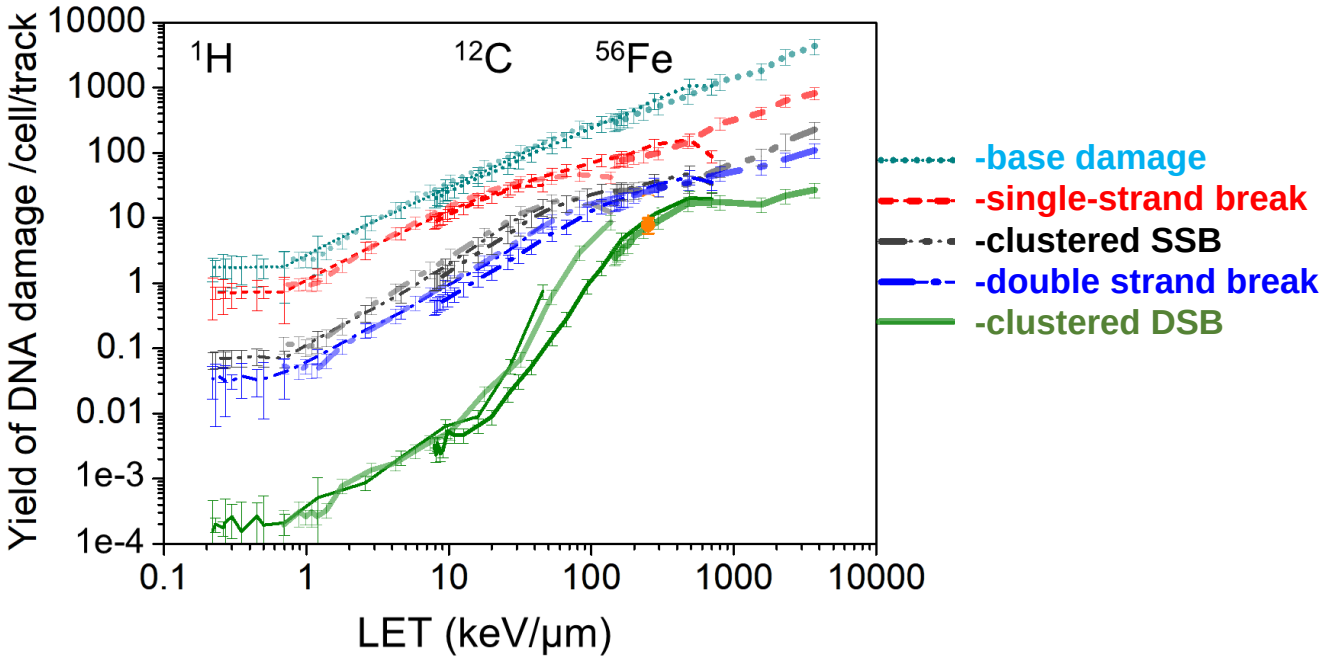


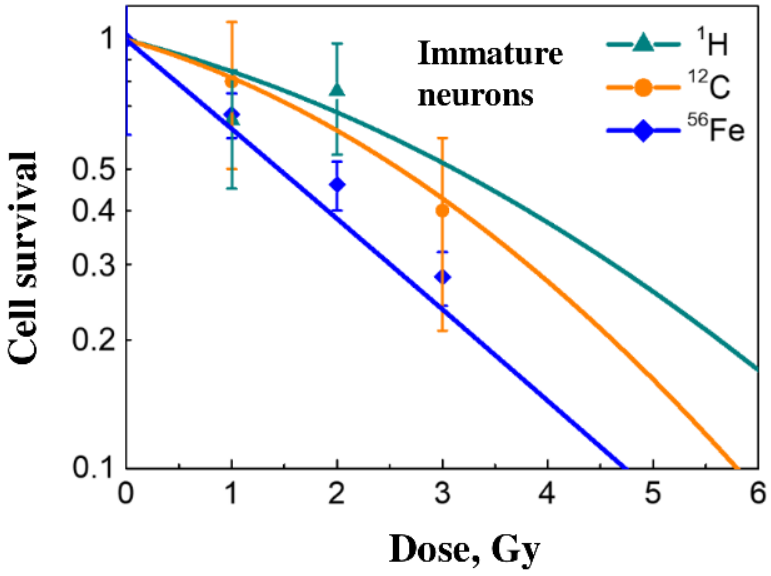
Batmunkh et al Phys. Med. 57 (2019) 88

Computation of DNA damage and survival of radiosensitive neural cells



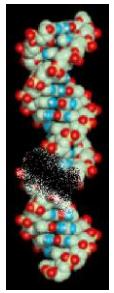




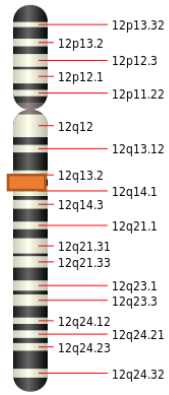


Batmunkh, Bugay, et al 2021

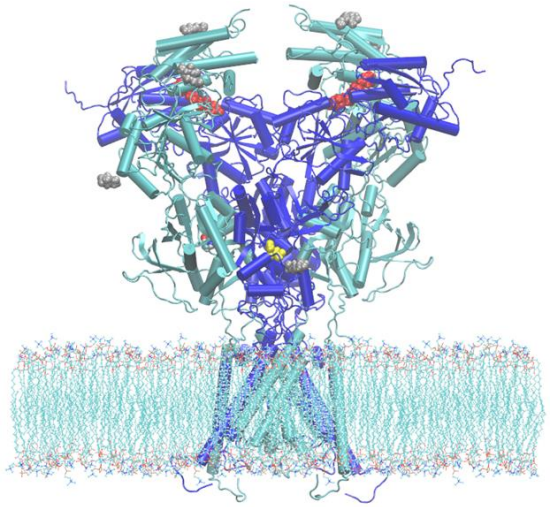
Genetic and molecular mechanisms of neurodegeneration



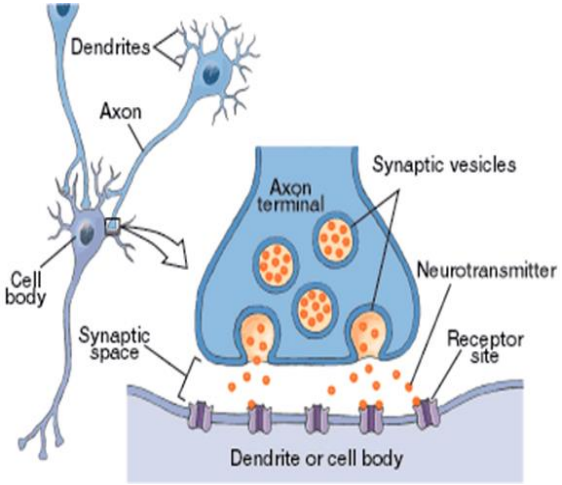
DNA damage



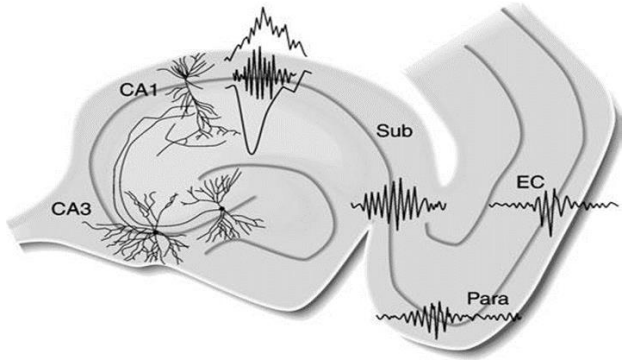
Chromosome 12
GRIN2B gene



NMDA synaptic receptor



Interconnections between neurons



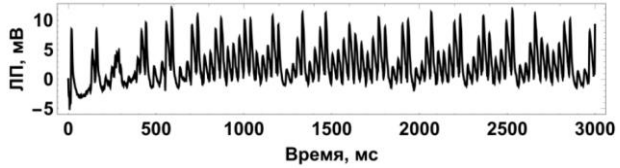
Brain neural networks

Multiscale simulation approach

- Molecular dynamics
- Biochemical kinetics
- Neural networks

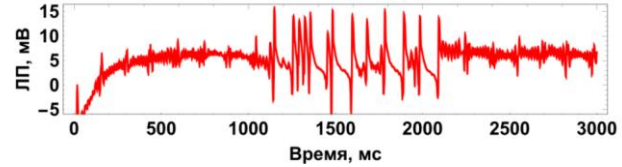
Mutation	Phenotype
p.Asn615Leu	West syndrome (epilepsy)
p.Val618Gly	West syndrome
p.Arg540His	ID, focal epilepsy
p.Phe671_Gln672del	Mild ID, Autism
p.Cys461Phe	Autistic features

Native



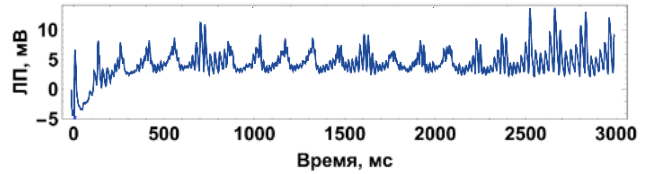
p.ASN615LEU

Epileptic seizure



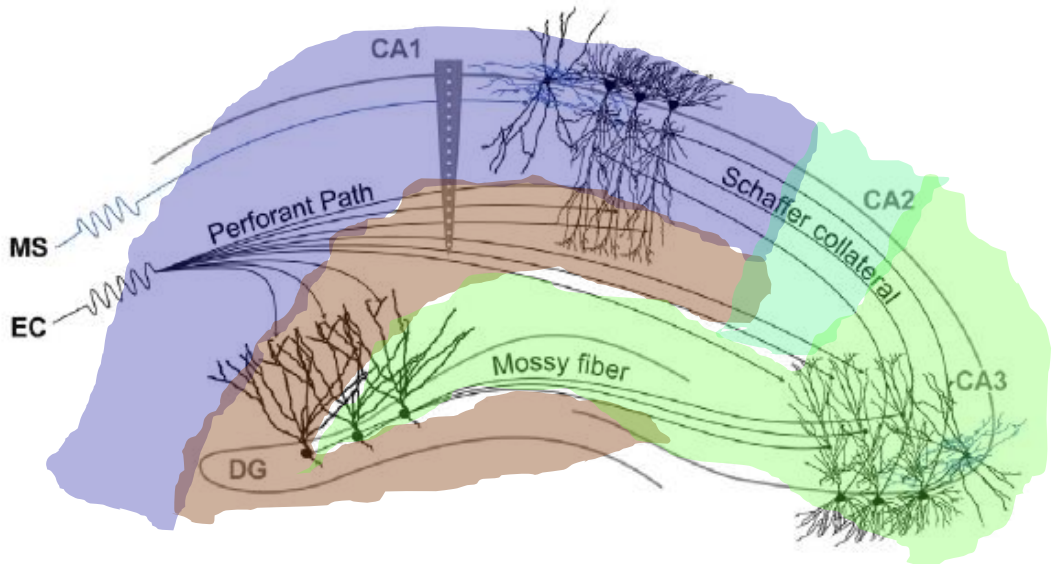
p.PHE671_GLN672del

Mild ID, autism

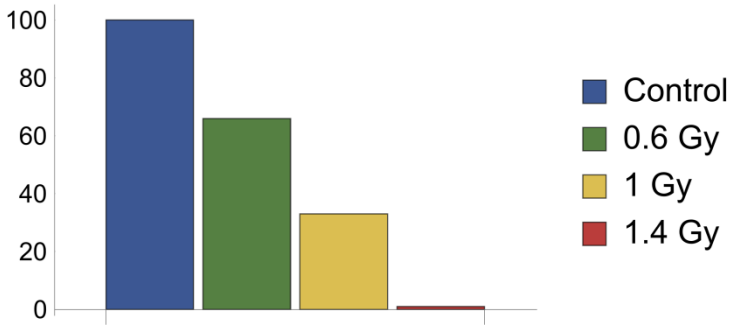


Batova, Bugay, Dushanov, et al, J. Bioinform. Comp. Biol. 2019

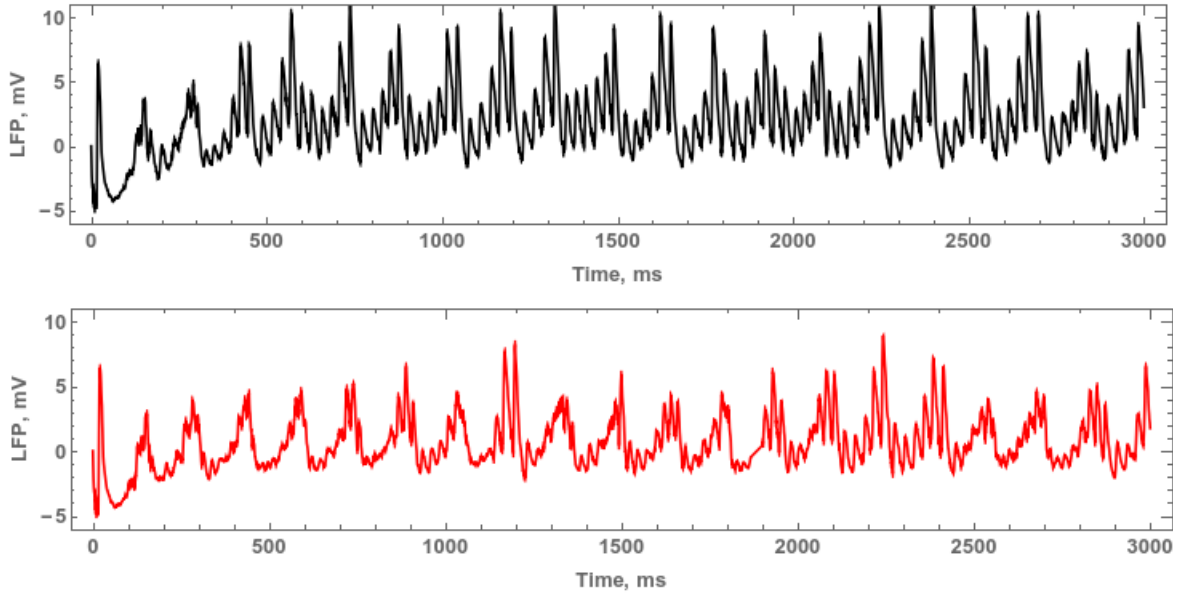
Brain neural network simulations after irradiation

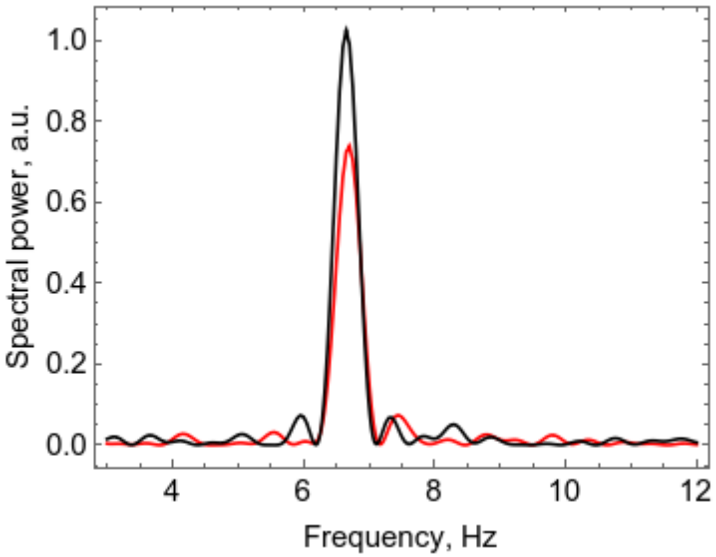


Encoding and retrieval success, %

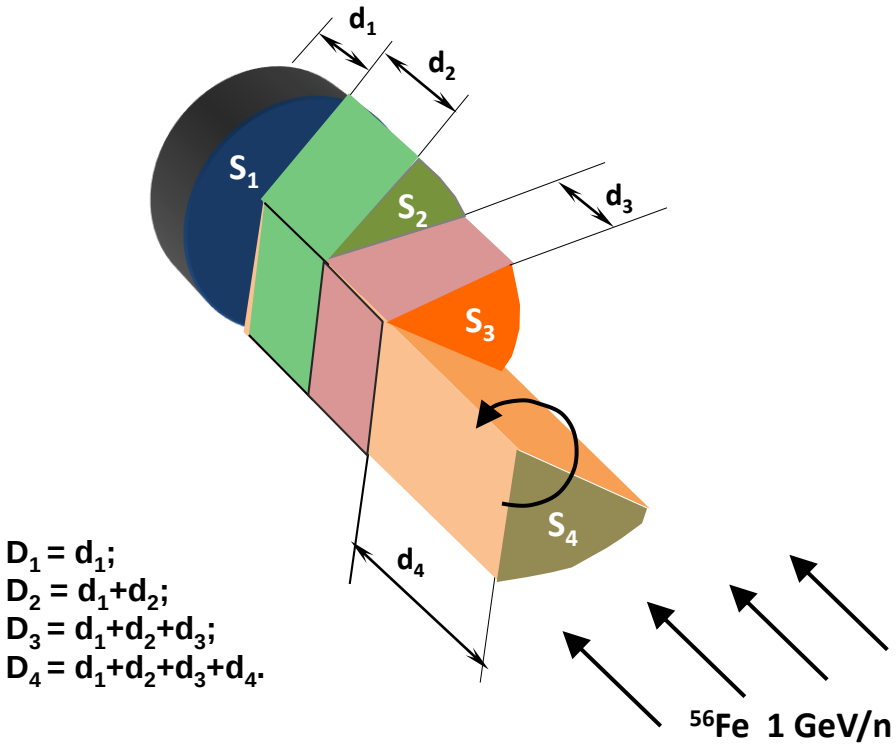


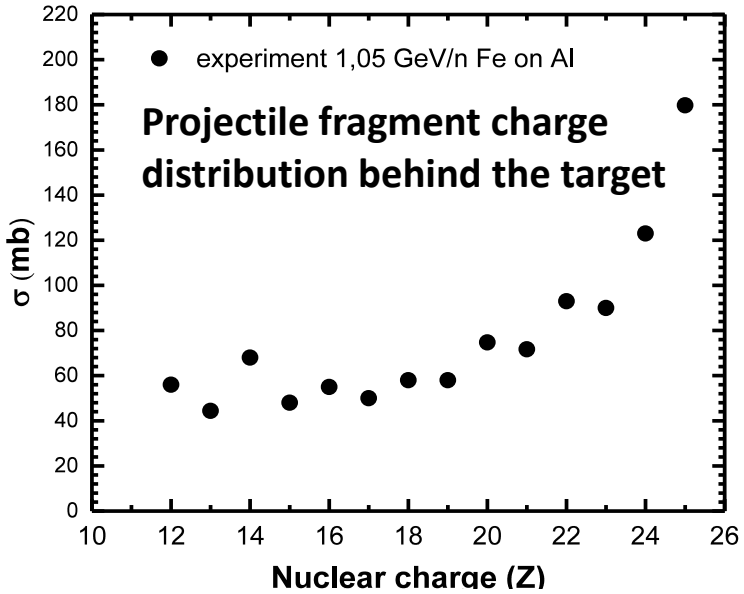
1.5 Gy 600 MeV/u ^{56}Fe

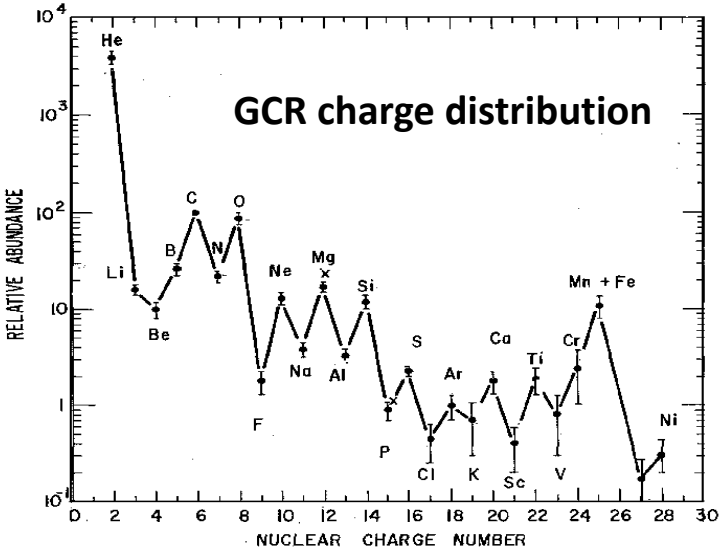




Proposal for a cosmic radiation field simulator at the SODIB







Different fragments of the projectile nucleus are born in various segment targets (polyethylene). The rotation of the targets ensures the fundamental uniformity of the radiation field behind the simulator. The contribution of each fragment is determined by the ratio of the area of the corresponding segment to the area of the circle.

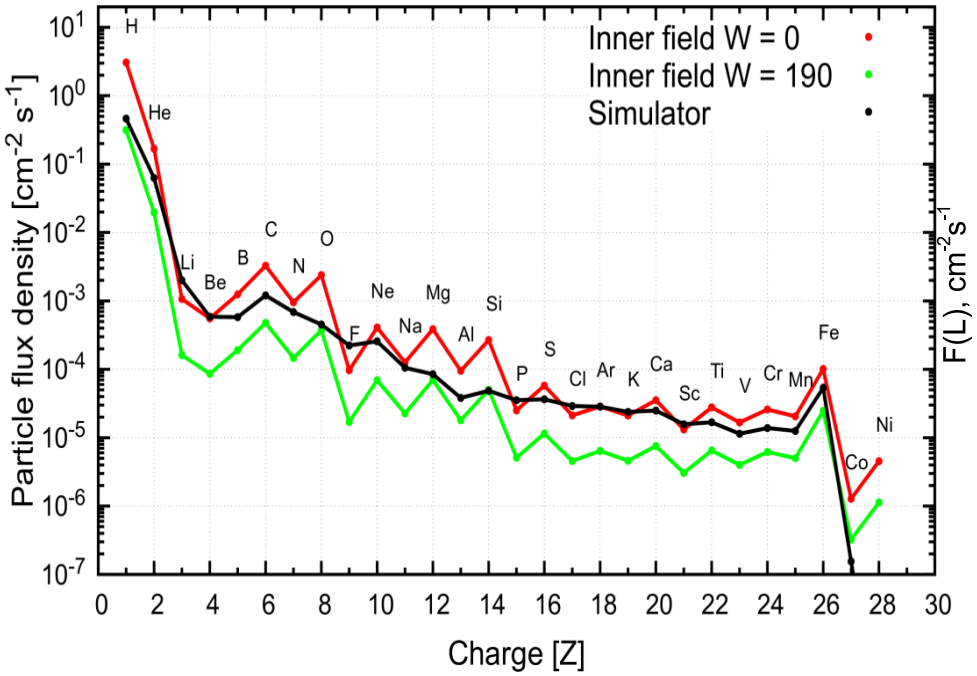
G.N. Timoshenko et al. Radiation Measurements 107 (2017) 27
I.S. Gordeev, G.N. Timoshenko. Life Sciences in Space Research, 30, (2021) 66

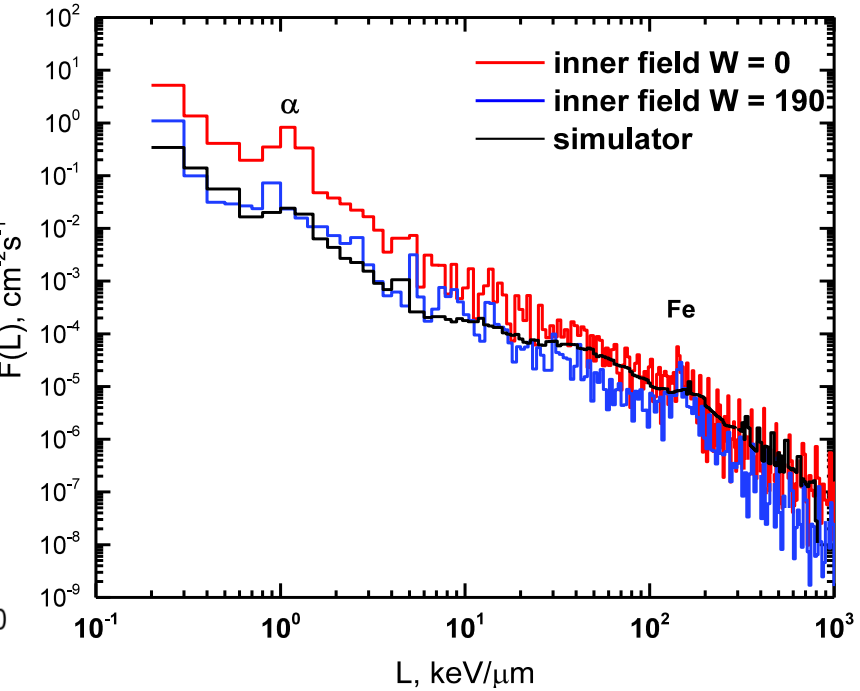
The simulator imitates the radiation field inside the habitable module of the spacecraft, generated by the GCR at minimum and maximum solar activity

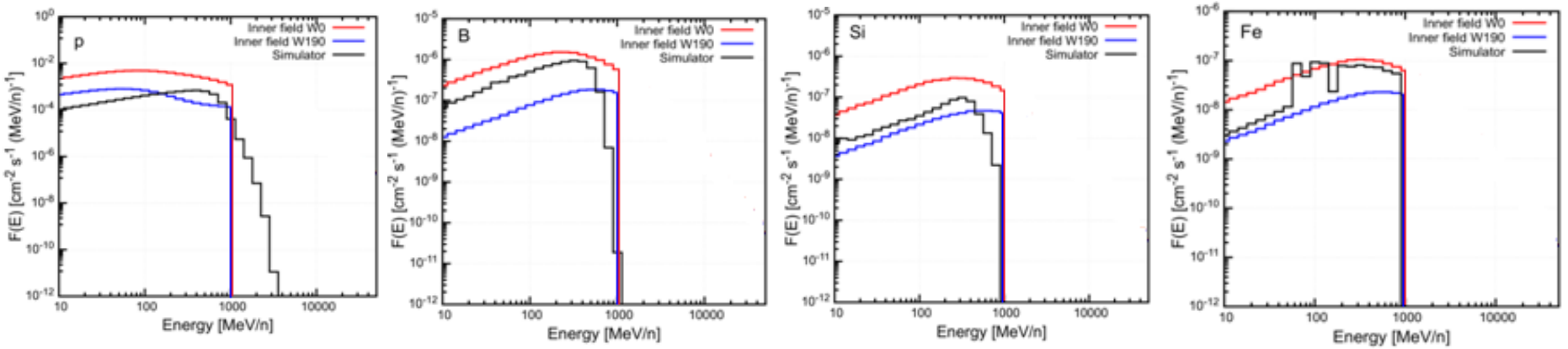
The internal radiation field was calculated in detail by FLUKA code for a module 12 m long and 6 m in diameter with an Al shell 15 g/cm^2 for mean Wolf numbers 0 and 190.

I.S. Gordeev, G.N. Timoshenko. Life Sciences in Space Research, 30, (2021) 66

G.N. Timoshenko I.S. Gordeev. J. Astrophys. Astr., 41 (2020) 5



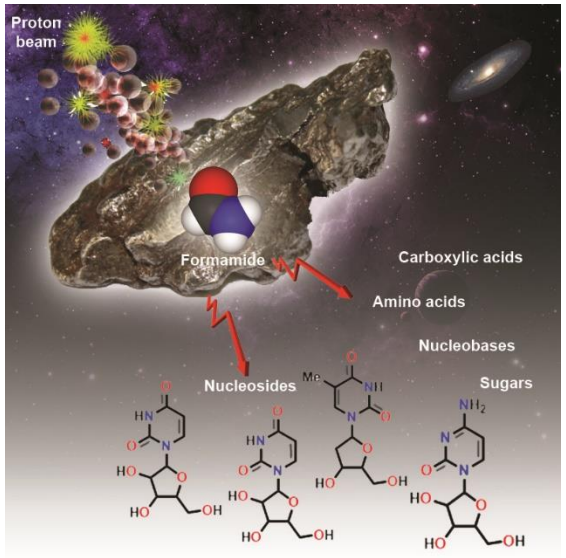




Astrobiology

QUEST FOR LIFE: biomolecules formation in space

Synthesis of prebiotic compounds from “formamide + meteorite matter” under particle exposure



SCIENTIFIC REPORTS

OPEN

Proton irradiation: a key to the challenge of N-glycosidic bond formation in a prebiotic context

Received: 5 June 2017
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Raffaele Saladino[1], Bruno M. Bizzarri[1], Lorenzo Botta[1], Jiří Šponer[2,3], Judit E. Šponer[2], Thomas Georgelin[4,5], Maguy Jaber[6], Baptiste Rigaud[7], Michail Kapralov[8], Gennady N. Timoshenko[8], Alexei Rozanov[8], Eugene Krasavin[8], Anna Maria Timperio[1] & Ernesto Di Mauro[1]

NATIONAL ACADEMY OF SCIENCES
PNAS SCIENCE SESSIONS

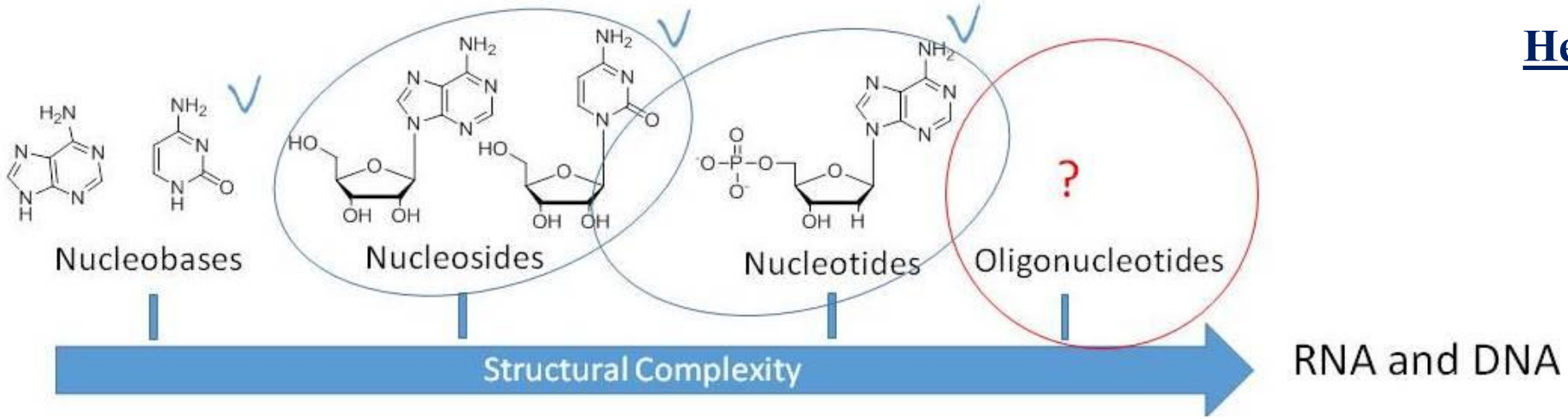
nature

Proton beam

Synthesis of biomolecules :

- aminoacids,
- sugars,
- phosphates
- nucleosides,
- nucleotides,
- oligo- and polymer molecules

Heavy ion beams…



Radiobiological Research @ NICA

Space radiobiology

- Simulation of cosmic ray spectra including chronic exposure regime
- Radiobiological studies on mammals and primates, assessment of radiation risks for astronauts
- Research on radioprotective properties of pharmaceuticals

Radiation neuroscience

- Animal simulation studies of side effects of brain tumors radiation therapy
- Simulation of neurodegenerative diseases development on animal models after the exposure to accelerated heavy ions
- Mathematical modeling of genetic and molecular mechanisms of neurodegenerative diseases

Astrobiology

- Synthesis of the prebiotic compounds under heavy charged particle irradiation

Clinical Radiobiology

- Increase of tumor radiosensitivity by interfering with the work of genetic regulatory networks
- Targeted delivery of radiomodifiers

Thank you for the attention!