Radiation Biology
and its applications in space research and therapy of cancer

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JINR Life Science Program: Basic and Applied Research

Laboratory of Radiation Biology

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

Infrastructure for molecular, cellular and animal research

Dzhelepov Laboratory of Nuclear Problems

- Proton therapy of cancer
- Genetics
- Detectors and Tomography

Veksler and Baldin Laboratory of HEP

LHEP ЛФВЭ 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

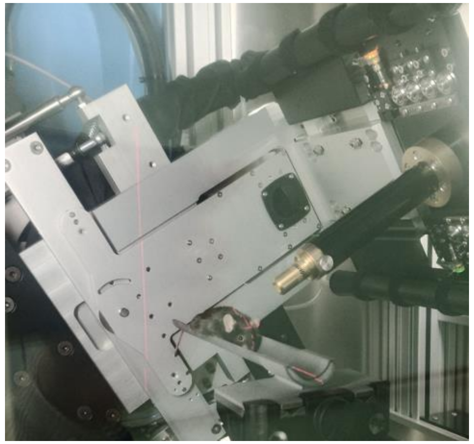
- High performance computing
- System for biological data storage and processing
- Bioinformatics, Machine Learning

Flerov Laboratory of Nuclear Reactions

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

Research Infrastructure for the Irradiation of Biological Samples

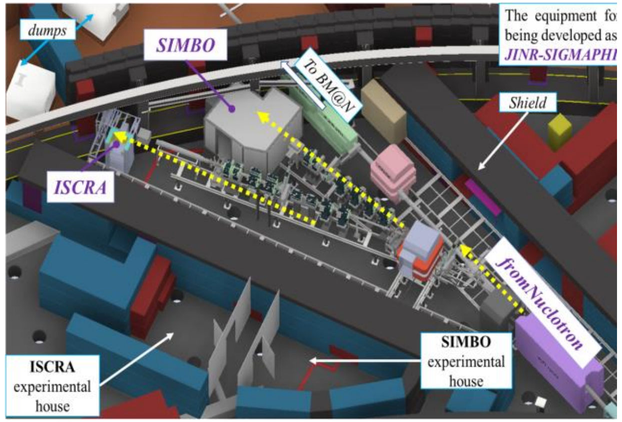
SARRP X-ray



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

Genom-3

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

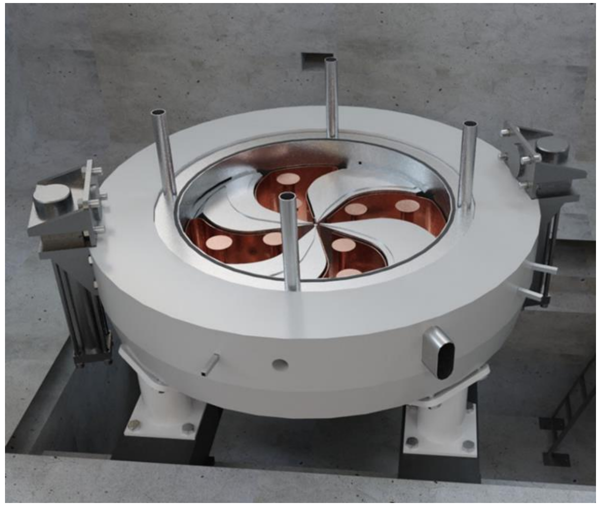


ARIADNA beamlines

SIMBO

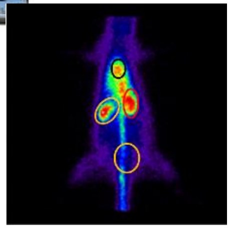
Linac200
electrons 20-200 MeV

new MSC230 medical cyclotron
protons 230 MeV



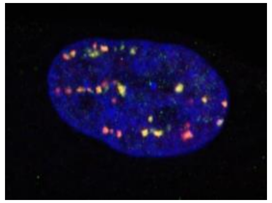
IBR-2, EG-5M neutrons

Radiopharmaceuticals

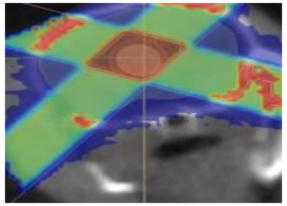


Laboratory of Radiation Biology

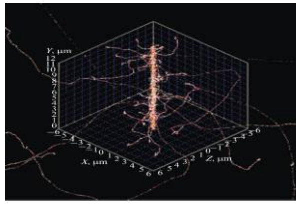
Molecular Radiobiology



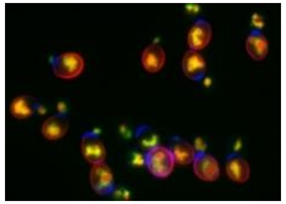
Clinical Radiobiology



Mathematical Modeling



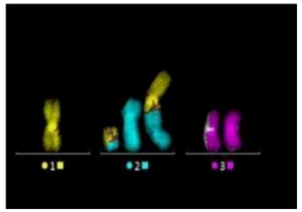
Radiation Genetics



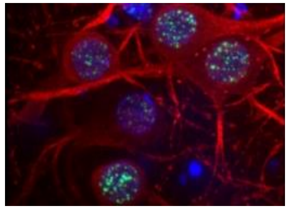
Radiation Physiology

Radiation Protection

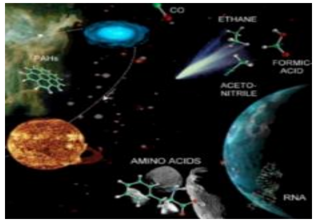
Radiation Cytogenetics



Radiation Neuroscience



Astrobiology



Contacts:

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JINR executive for cooperation with Mongolia

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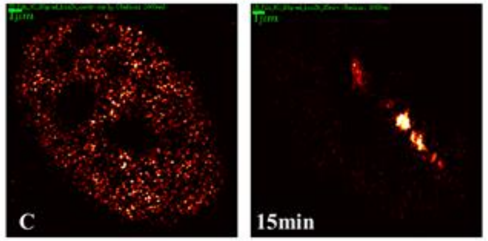
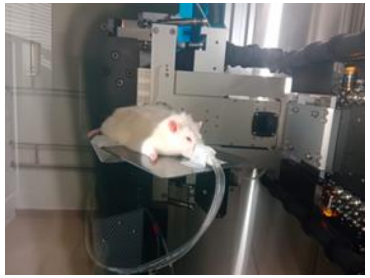
http://lrb.jinr.ru

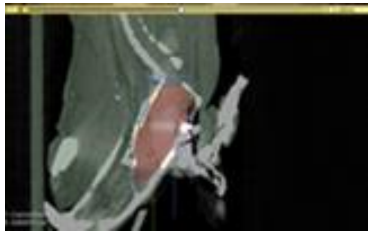
LRB Research Equipment

super-resolution microscope



CYTEK Aurora CS
Cell Sorter | Flow Cytometer

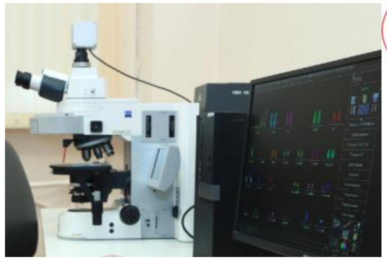


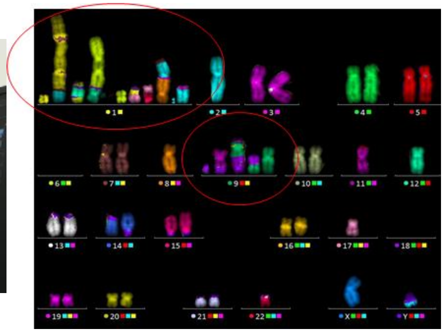


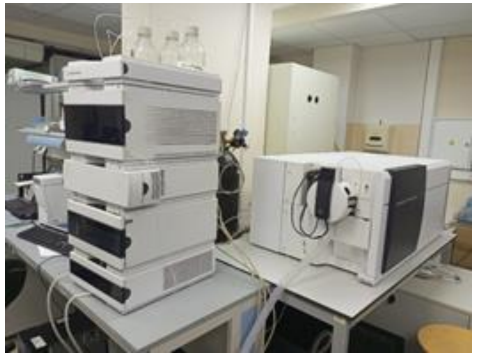
SARRP (Small Animal Radiation Research Platform)

Kubtec Xcell 320

METASYSTEMS
microscopy system for mFISH



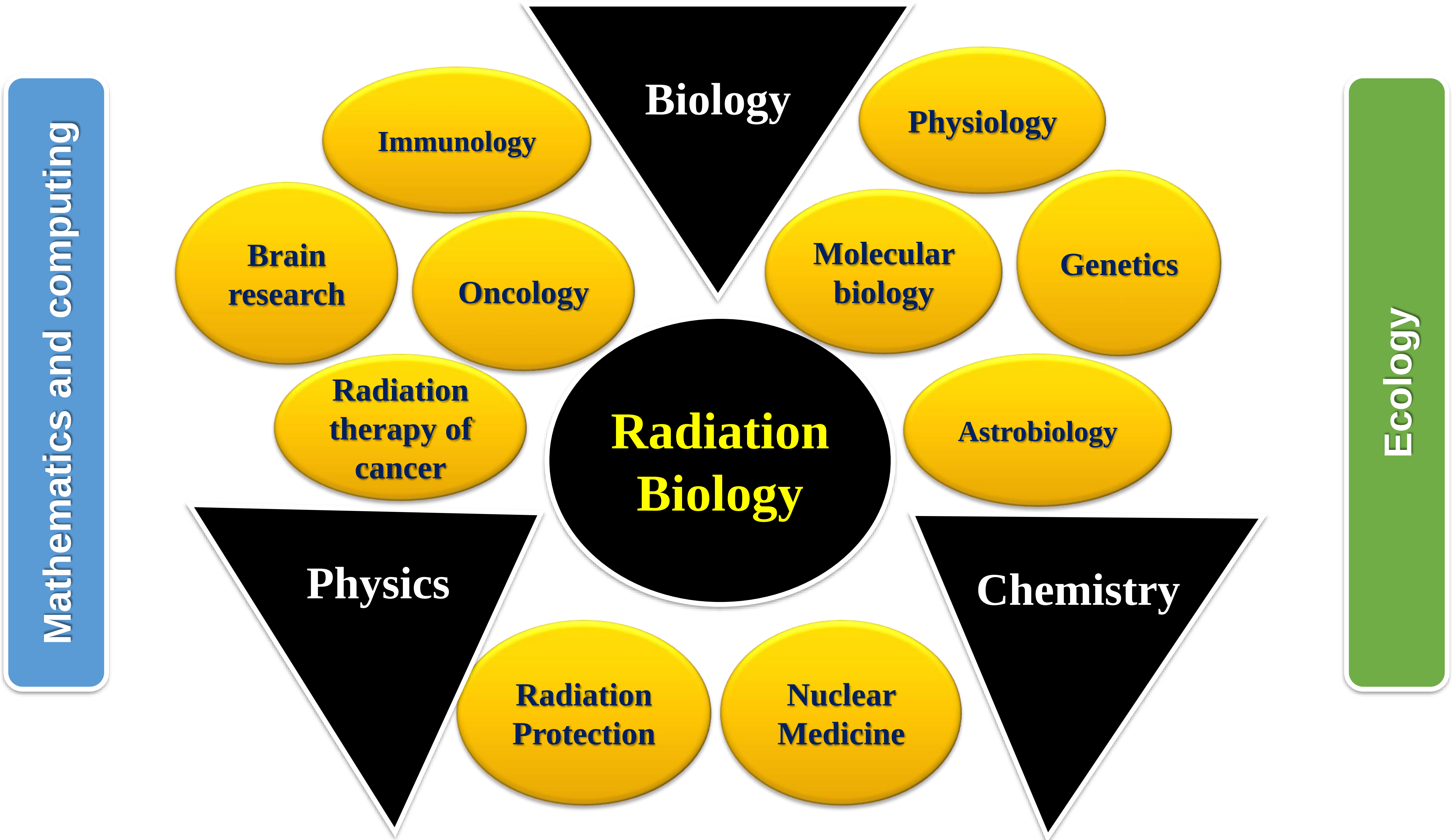




AGILENT
HPLC-MS
triple quadrupole

Scanning Electron Microscope

Vivarium (up to SPF grade cages)
Tomography Units



Mathematics and computing
Biology
Immunology
Physiology
Brain research
Oncology
Molecular biology
Genetics
Radiation therapy of cancer
Radiation Biology
Astrobiology
Physics
Chemistry
Radiation Protection
Nuclear Medicine
Ecology

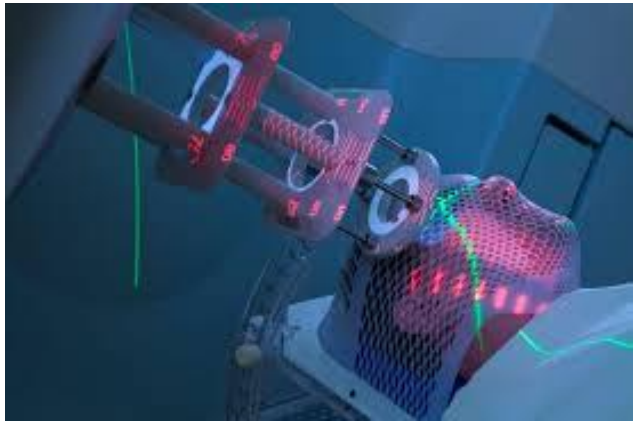
Main tasks of radiation biology:

Nuclear and Radiation Technologies

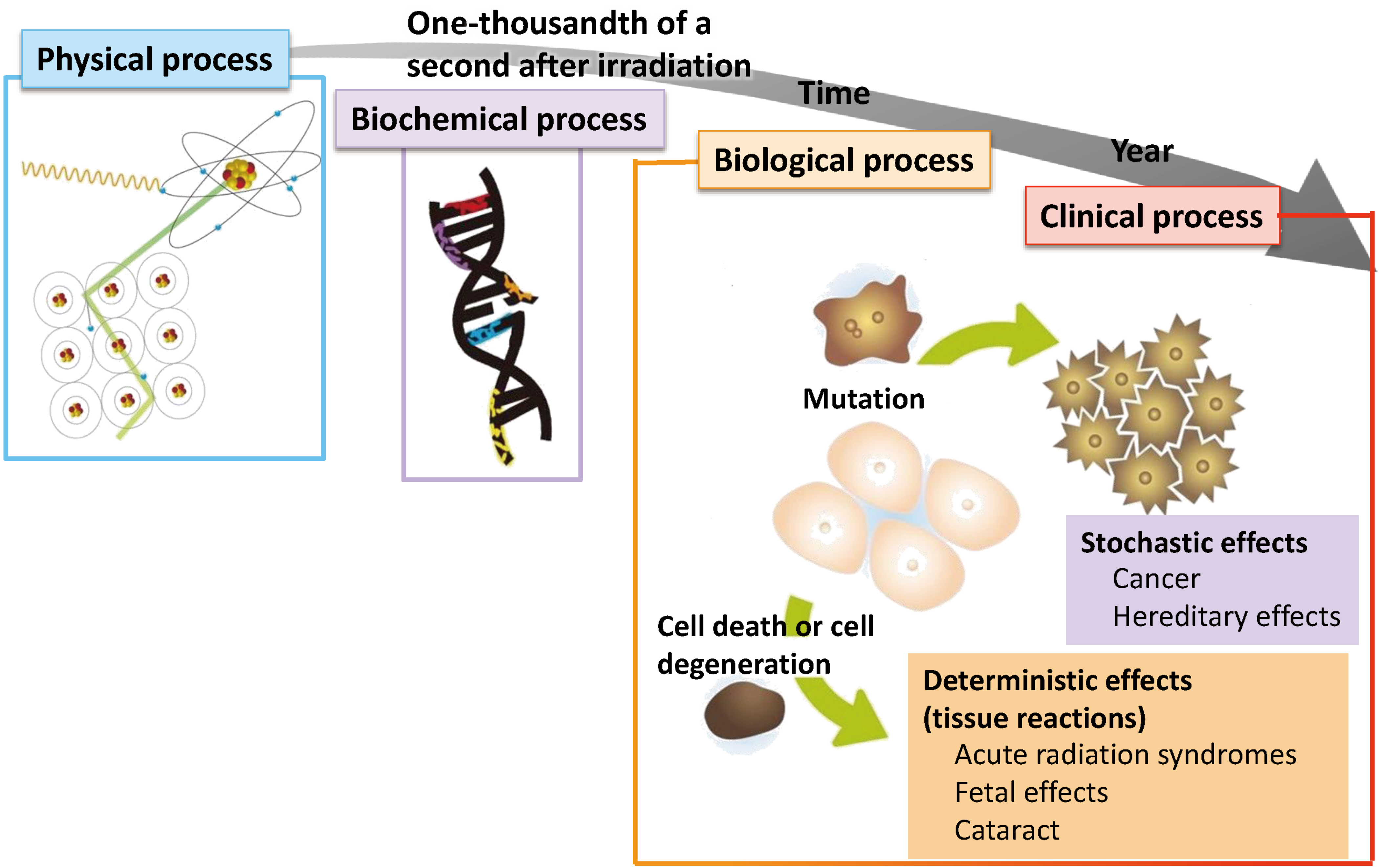
Nuclear Waste

- **Fundamental research**
- **Evaluation of radiation risks**
- **Application of radiations in medicine**

Diagnostics and Radiation therapy

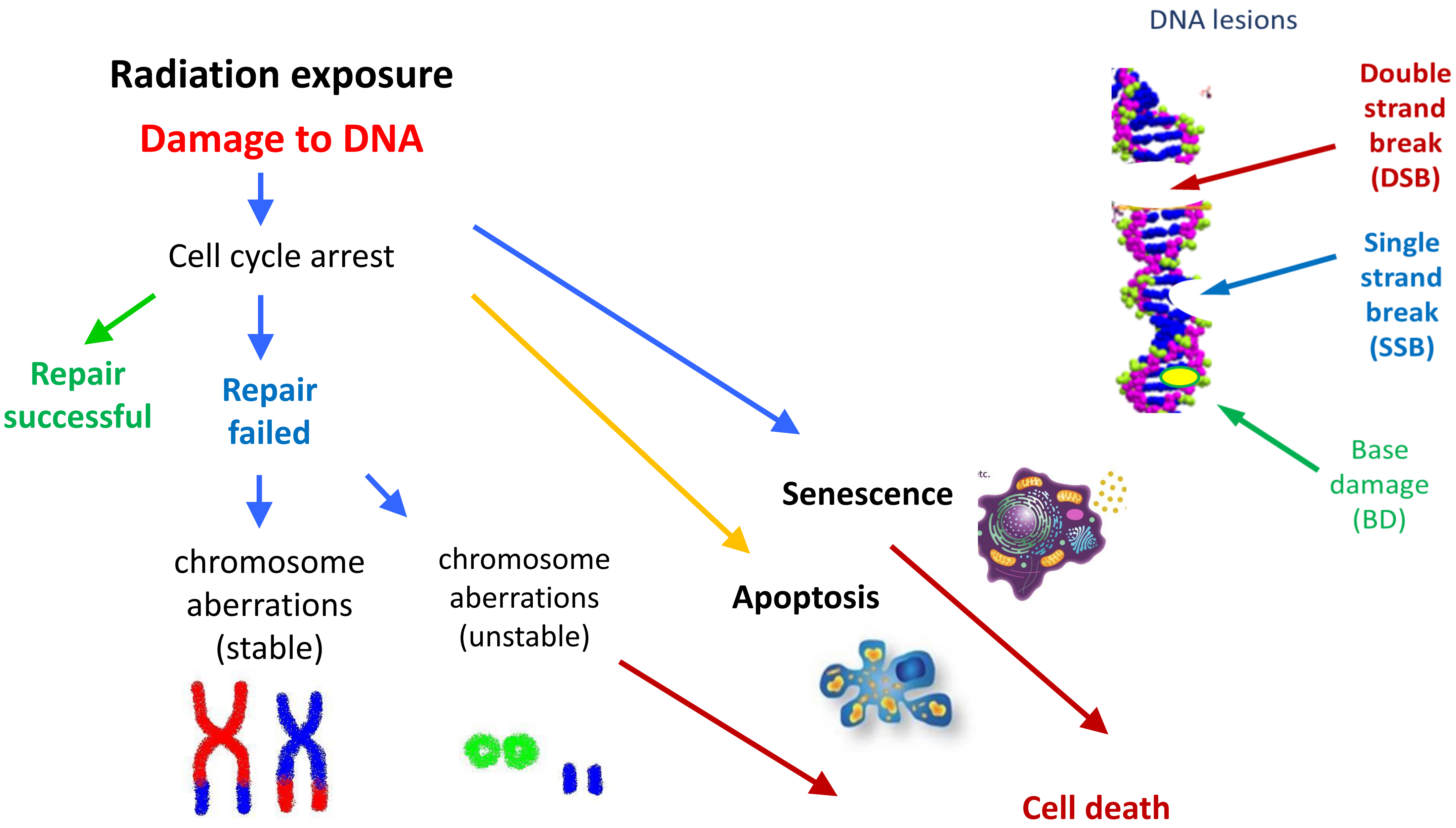


Space Exploration



One-thousandth of a second after irradiation
Time
Year
Physical process
Biochemical process
Biological process
Clinical process
Mutation
Cell death or cell degeneration
Stochastic effects
Cancer
Hereditary effects
Deterministic effects (tissue reactions)
Acute radiation syndromes
Fetal effects
Cataract

Cellular effects of radiation

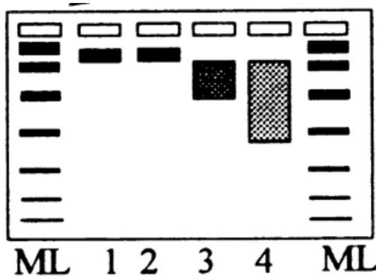


Experimental protocols *in vitro*

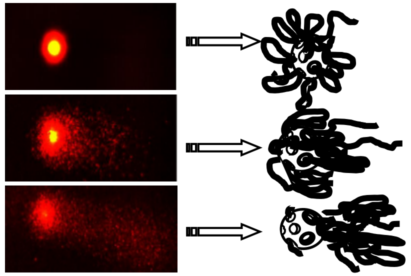
DNA lesions

Distribution of <u>DNA fragments</u> in electric field

Pulsed-field gel electrophoresis

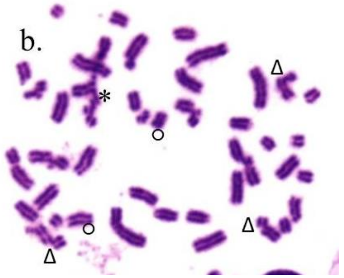


Comet assay



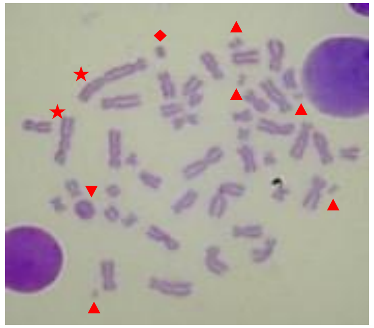
Chromatin breaks

Premature chromatin condensation PCC

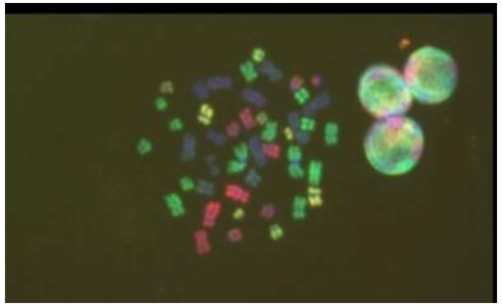


Chromosome aberrations

Metaphase assay

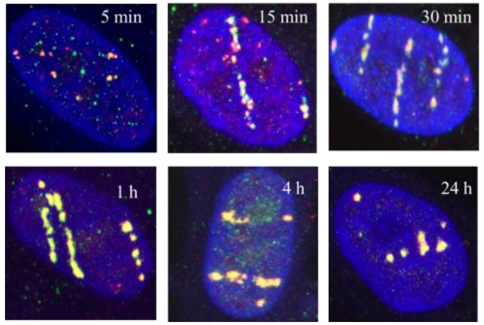


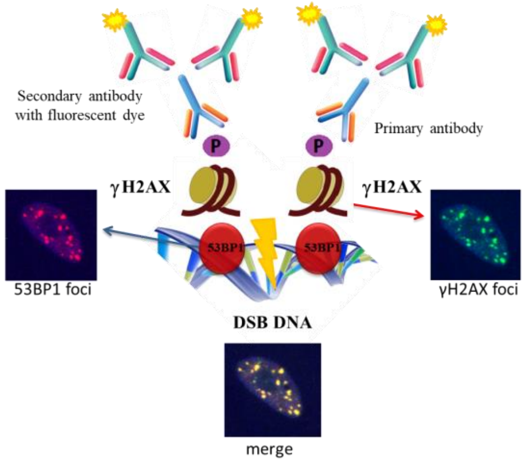
Multicolor fluorescence *in situ* hybridization mFISH



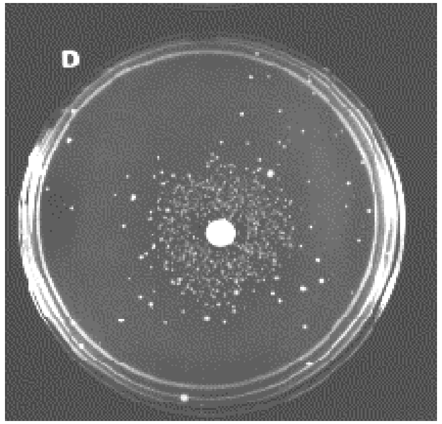
Fluorescent dyes + antibodies to DNA <u>repair proteins</u>

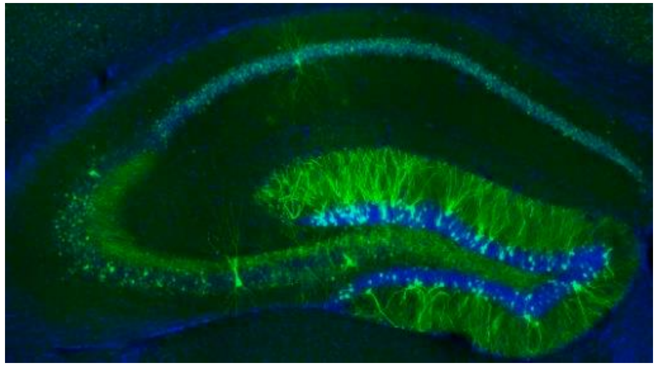
γH2AX foci



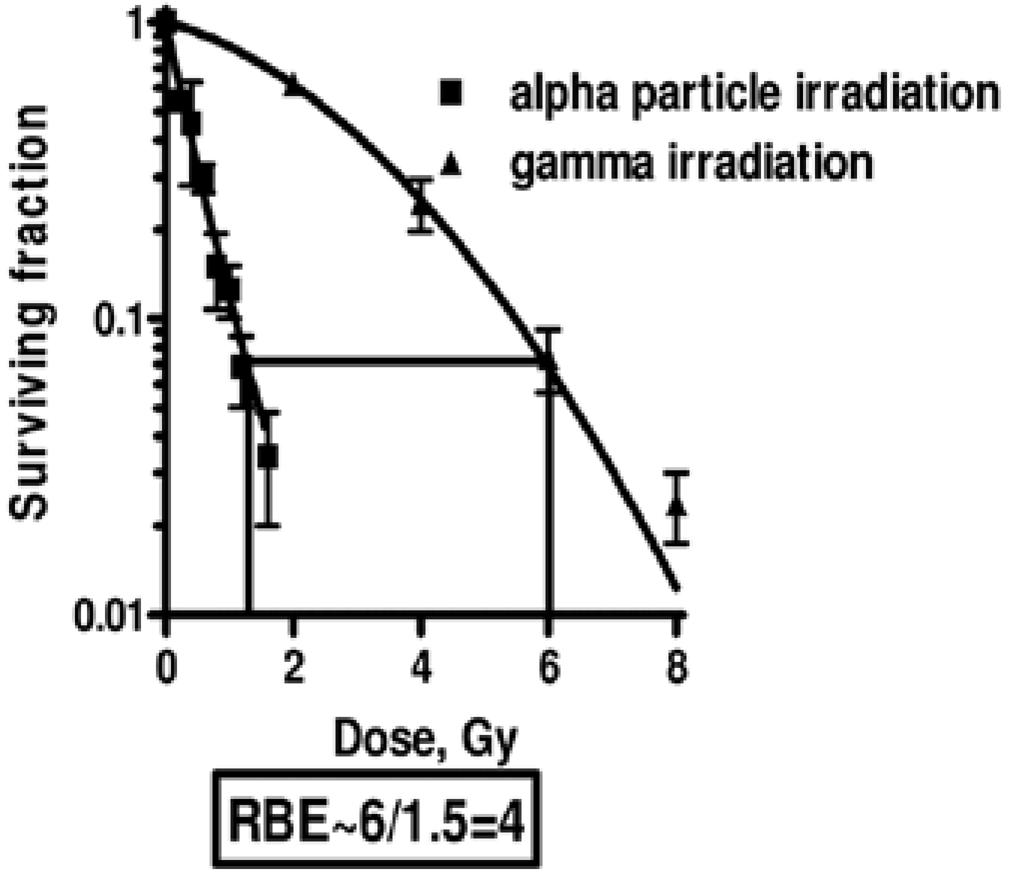


Cell survival





Relative biological effectiveness of ionizing radiations



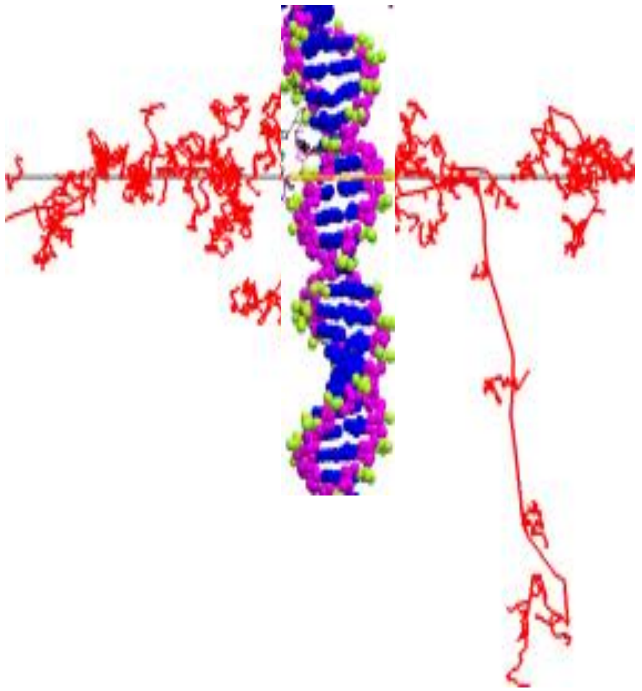
The RBE value is determined by two factors - physical and biological.

The biological factor is dependent on the physical one.

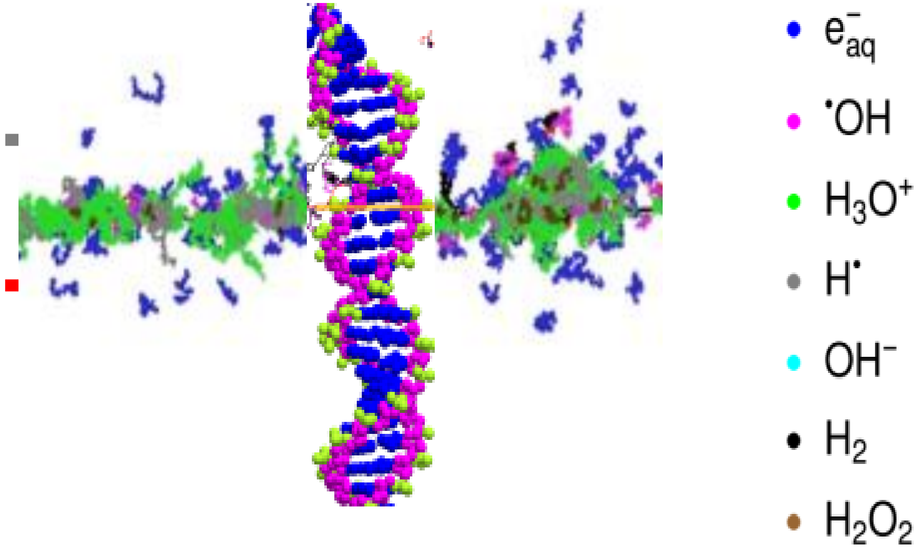
DNA damage caused by photon and hadron radiation is qualitatively different

Biological efficiency of ionizing radiations
Molecular basis

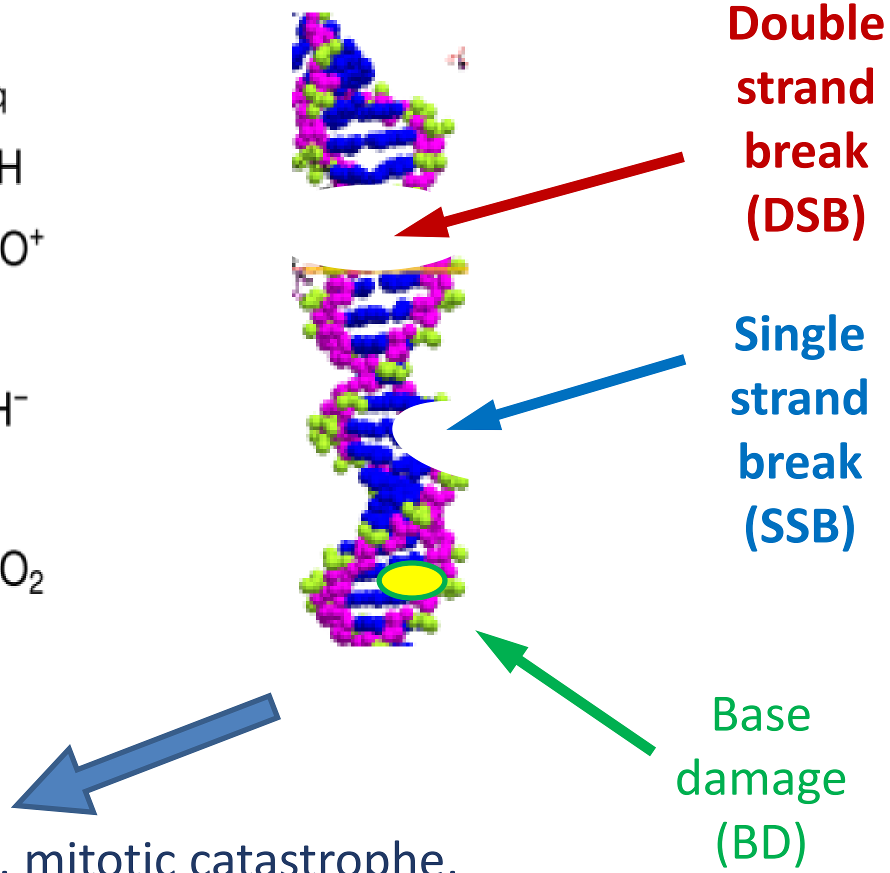
Ionization, bond breakage



Radical attack, indirect lesion



DNA lesions



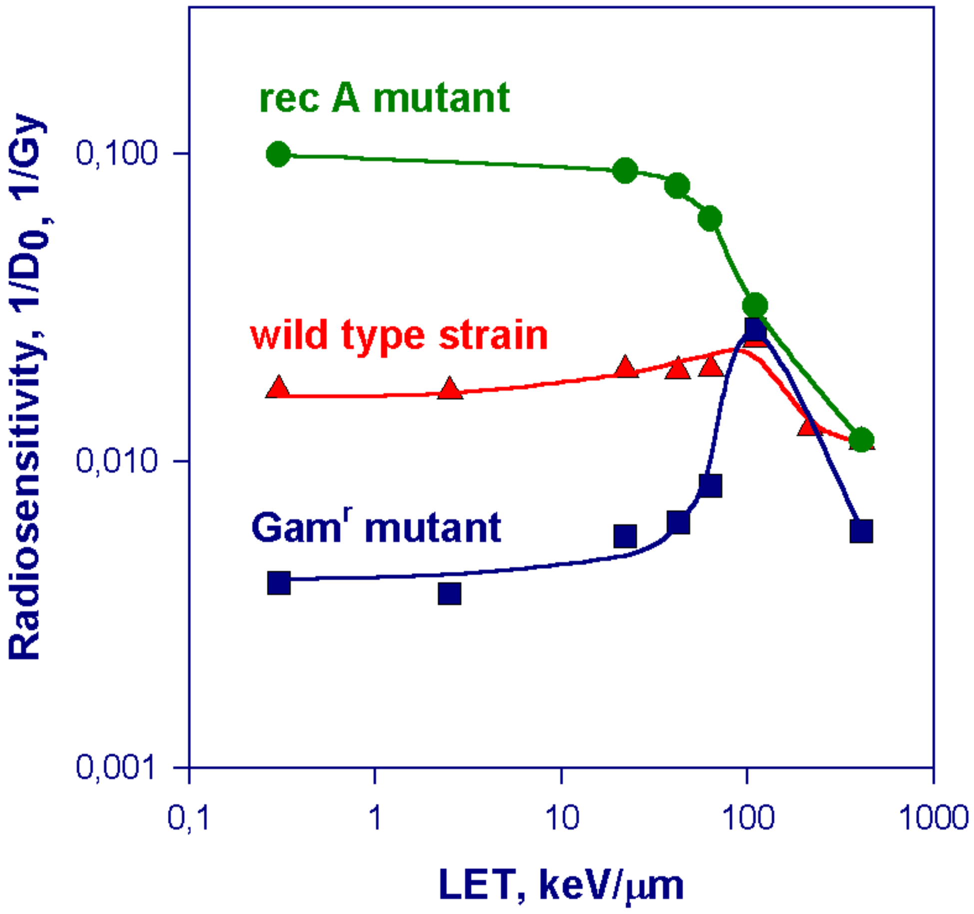
Apoptosis, chromosome aberrations, mitotic catastrophe, cell death

Important physical parameter – linear energy transfer (LET)

$$L = dE / dx$$

Radiation tye	LET (keV/µm)
^{60}Co γ-rays	0,2
200 MeV protons	0.45
290 MeV/u carbon ions	12.9
600 MeV/u iron ions	168
2,5 MeV α-particles	166
1 MeV electrons	0.25
10 keV electrons	2.3
1 keV electrons	12.3
^{235}U neutrons	48

E. Coli



Data source: LRB

LET of radionuclide decay products

Radionuclide	Type	Half-life	E_{max} (MeV)	Mean range (mm)	Imageable
^{90}Y	β	2.7 days	2.3	2.76	No
^{131}I	β, γ	8.0 days	0.81	0.40	Yes
^{177}Lu	β, γ	6.7 days	0.50	0.28	Yes
^{153}Sm	β, γ	2.0 days	0.80	0.53	Yes
^{186}Re	β, γ	3.8 days	1.1	0.92	Yes
^{188}Re	β, γ	17.0 h	2.1	2.43	Yes
^{67}Cu	β, γ	2.6 days	0.57	0.60	Yes
^{225}Ac	α, β	10 days	5.83	0.04–0.10	Yes
^{213}Bi	α	45.7 min	5.87	0.04–0.10	Yes
^{212}Bi	α	1.0 h	6.09	0.04–0.10	Yes
^{211}At	α	7.2 h	5.87	0.04–0.10	Yes
^{212}Pb	β	10.6 h	0.57	0.60	Yes
^{125}I	Auger	60.1 days	0.35	0.001–0.020	No
^{123}I	Auger	13.2 h	0.16	0.001–0.020	Yes
^{67}Ga	Auger, β, γ	3.3 days	0.18	0.001–0.020	Yes

LET ~ 0.1-1 keV/μm

LET ~ 50-200 keV/μm

LET ~ 5-25 keV/μm

Biological efficiency of ionizing radiations
Amount of DNA damage

Computer simulations

1) Base damage BD
2) Single strand breaks SSB
3) Clustered SSB
4) Double strand breaks DSB
5) Clustered DSB

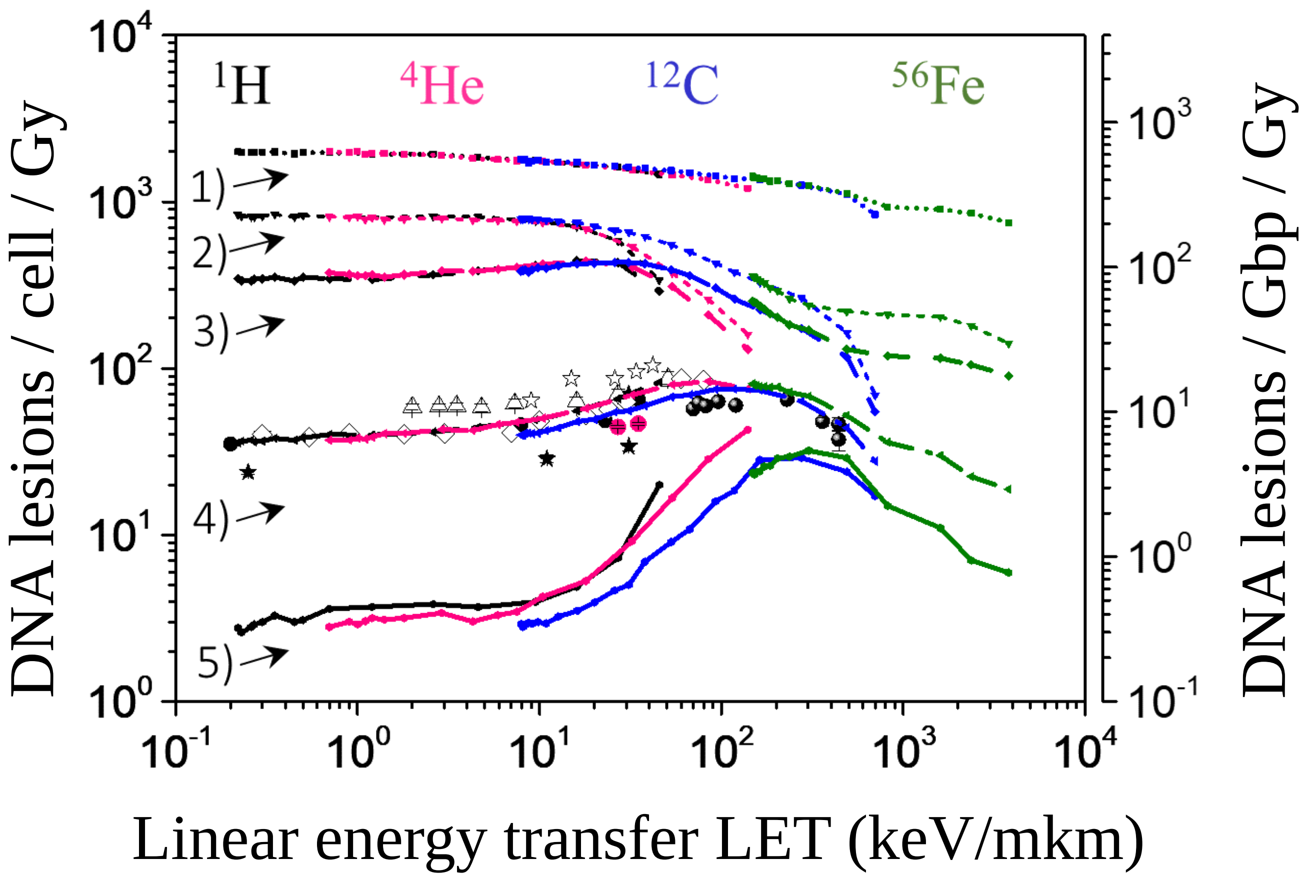
Expeiments (DSB)

- ● Frankenberg 1999
- ★ Belli 2001
- ● Belli 2006
- ■ Bulanova 2019

Calculations (DSB)

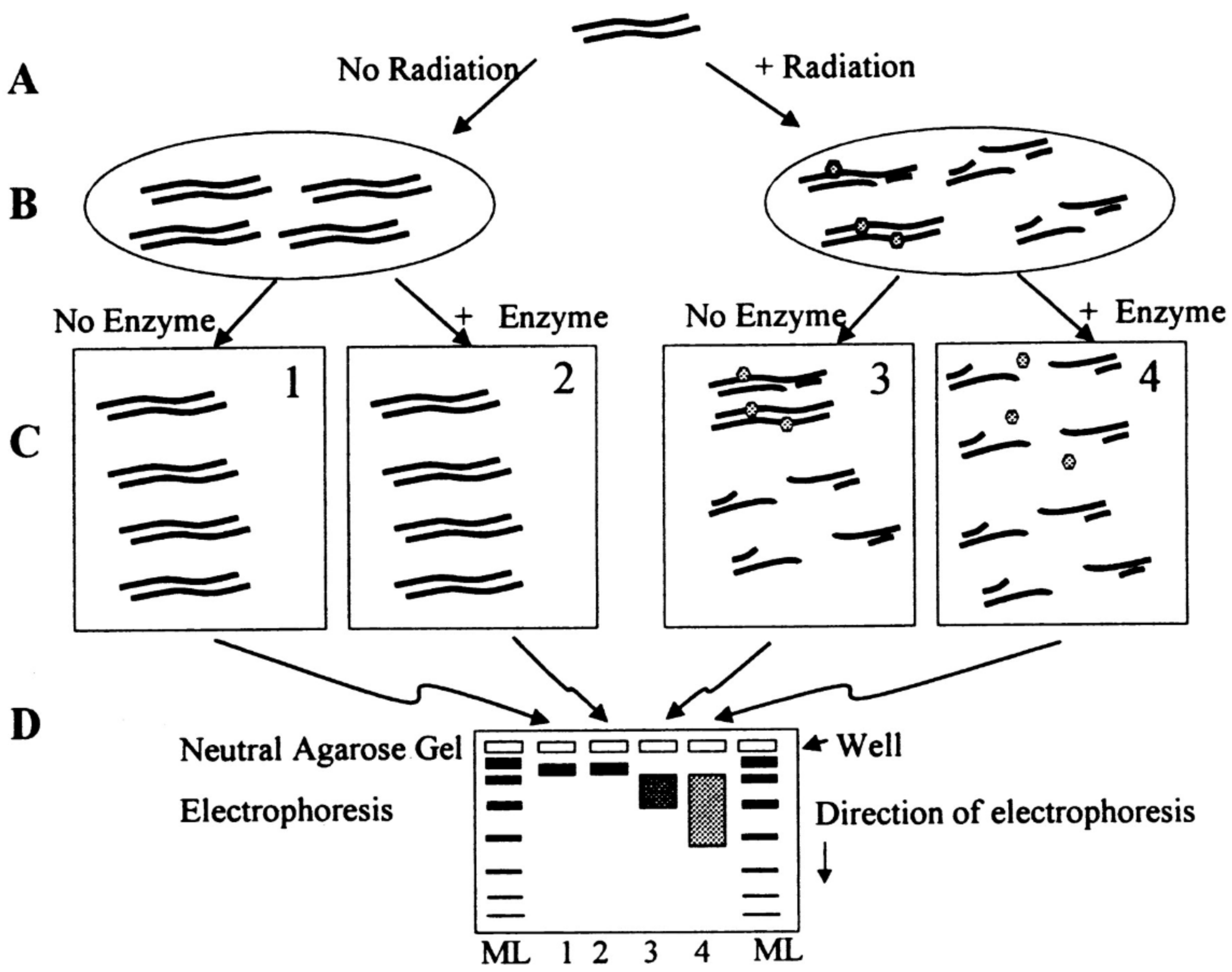
- -★- Nikjoo 2001
- -◇- Friedland 2011
- -△- Rosales 2018

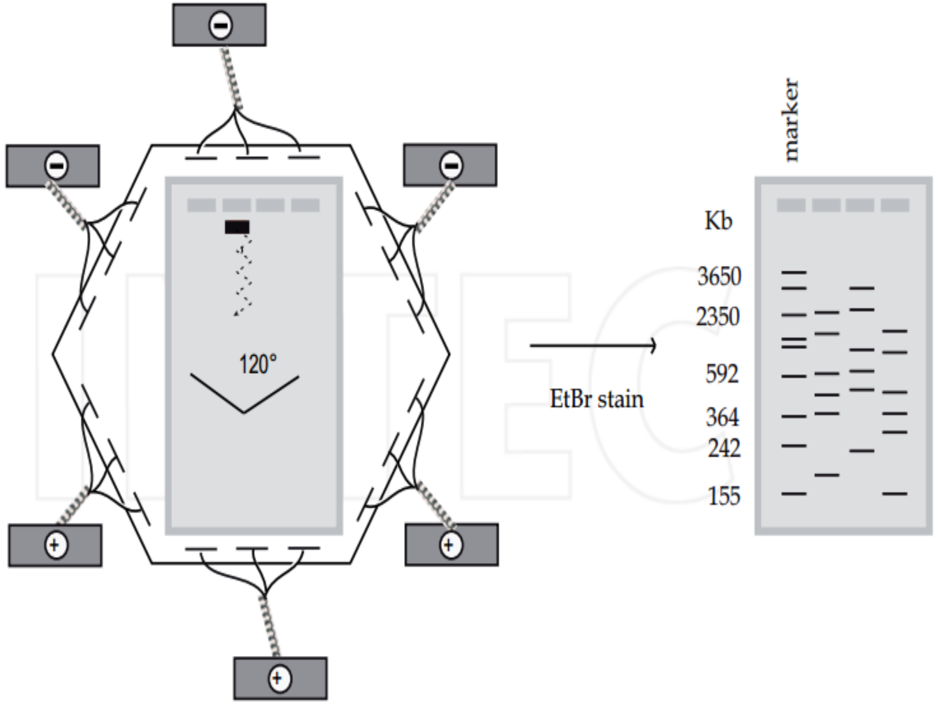
1 DSB
:
10 SSB
:
100 BD



Measurement of DNA lesions

1. Pulsed-field gel electrophoresis





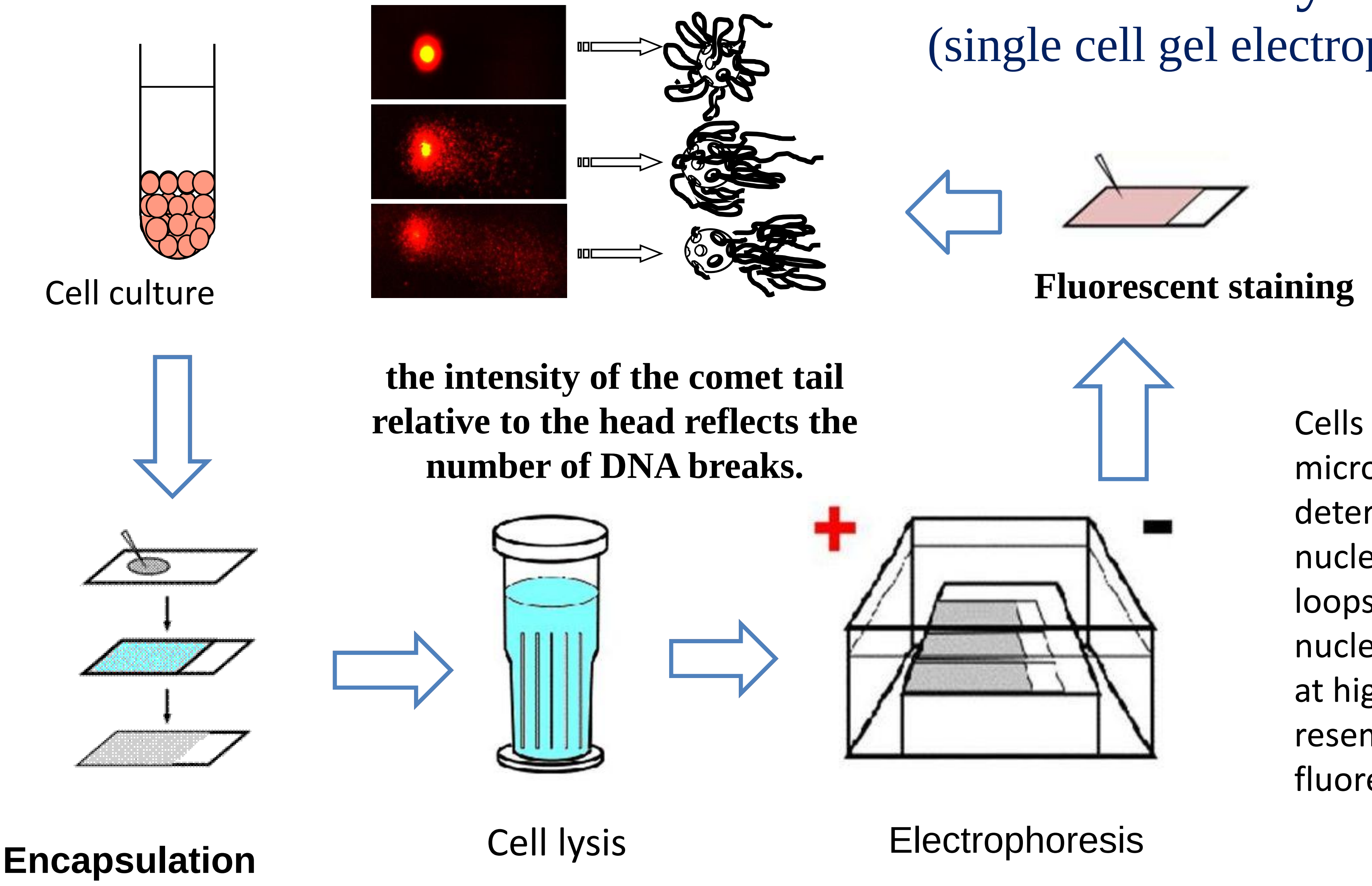
Electric field alternates 120° every
90 seconds for 18 to 24 hours at 14°C

Pulsed-field gel electrophoresis (PFGE) is a technique used for the separation of DNA fragments by applying to a gel matrix an electric field that periodically changes direction

Measurement of DNA lesions

2. Comet assay

(single cell gel electrophoresis assay)



Cells embedded in agarose on a microscope slide are lysed with detergent and high salt to form nucleoids containing supercoiled loops of DNA linked to the nuclear matrix. Electrophoresis at high pH results in structures resembling comets, observed by fluorescence microscopy;

Measurement of DNA lesions

3. Immunofluorescent microscopy

Irradiation

↓

Fixation of cells at different times post-irradiation (PI)

↓

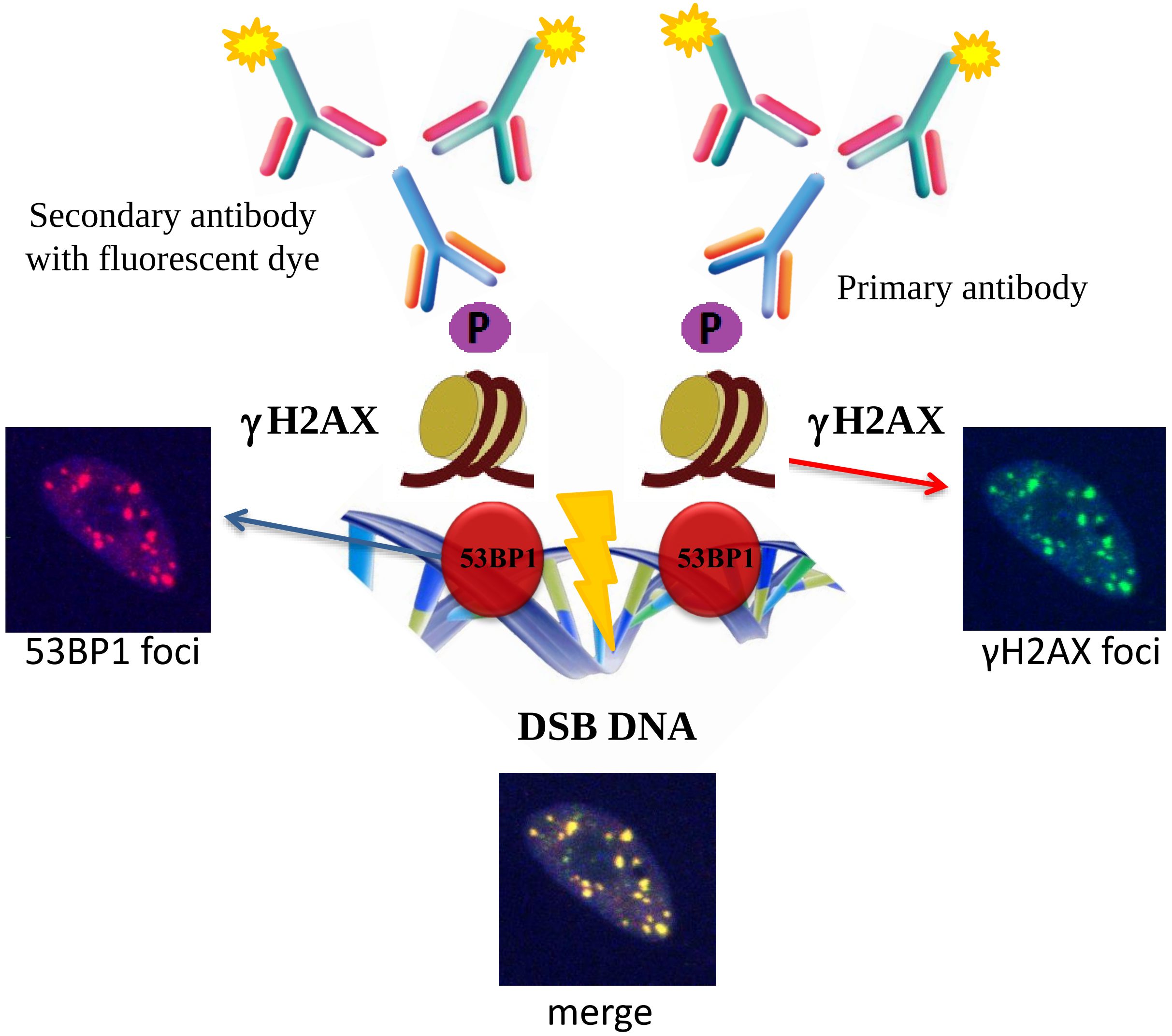
Visualisation of induced DSBs (γH2AX/53BP1 foci)

↓

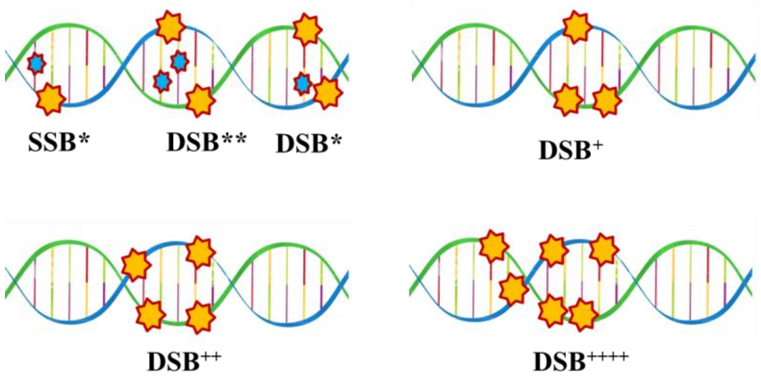
Acquisition of images

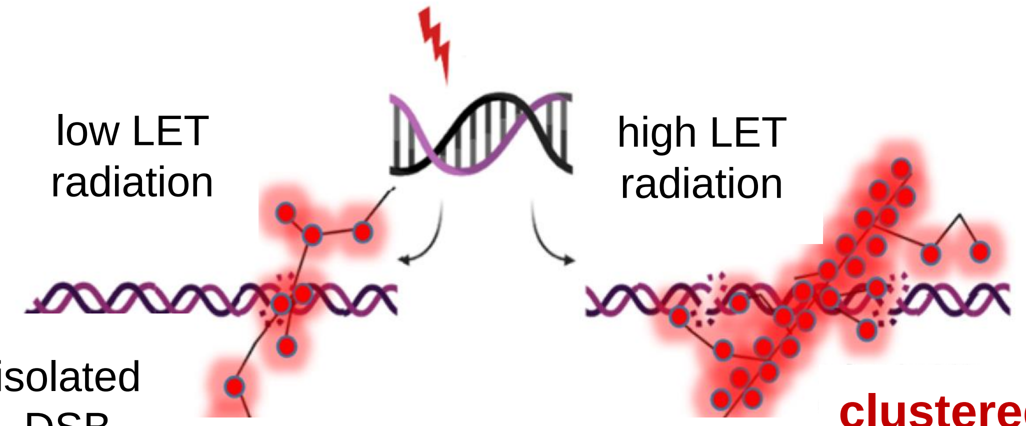
↓

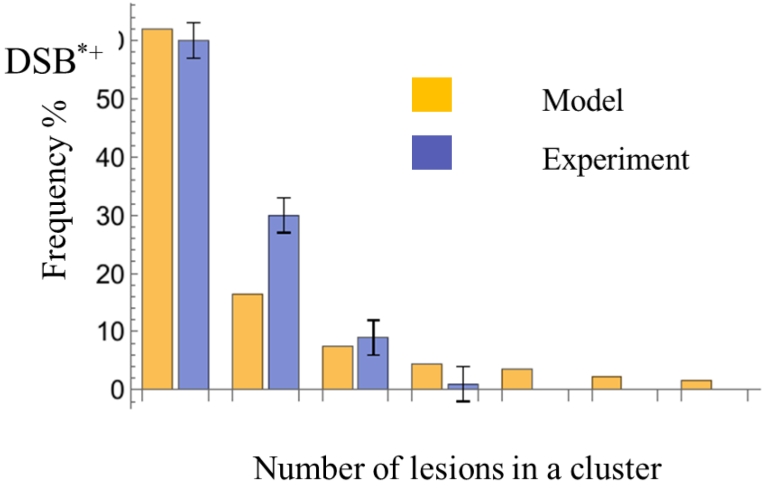
3D analysis of induced γH2AX/53BP1 foci - Acquiarium

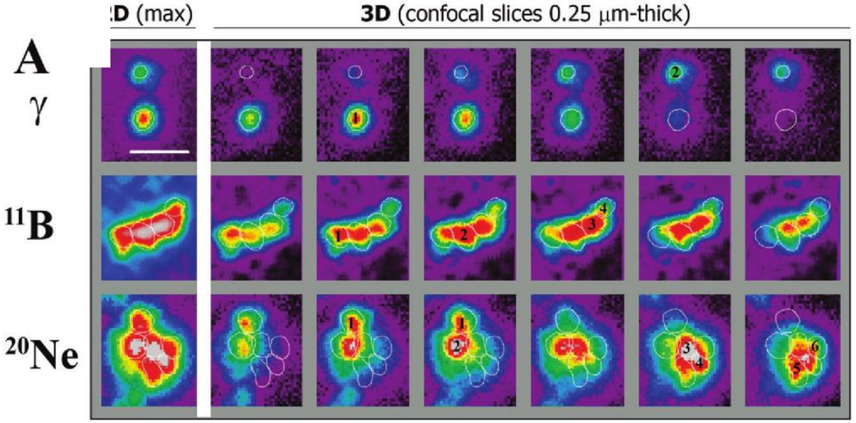


DNA damage complexity. Clustered DNA double strand breaks

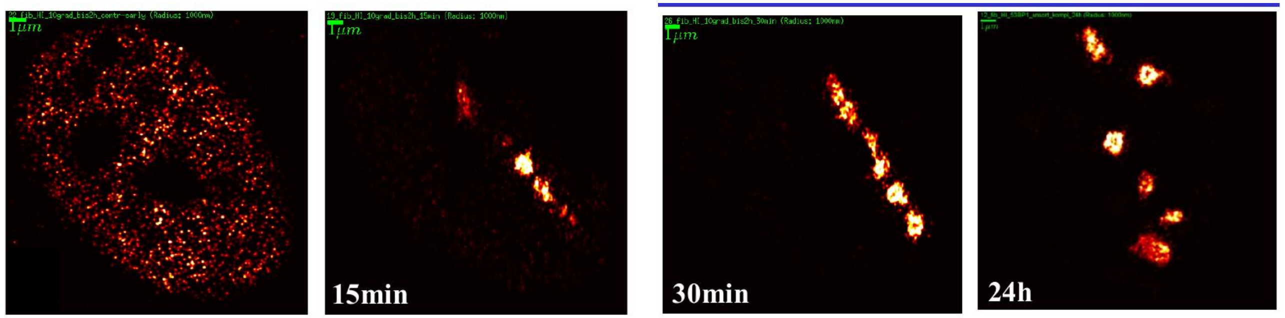




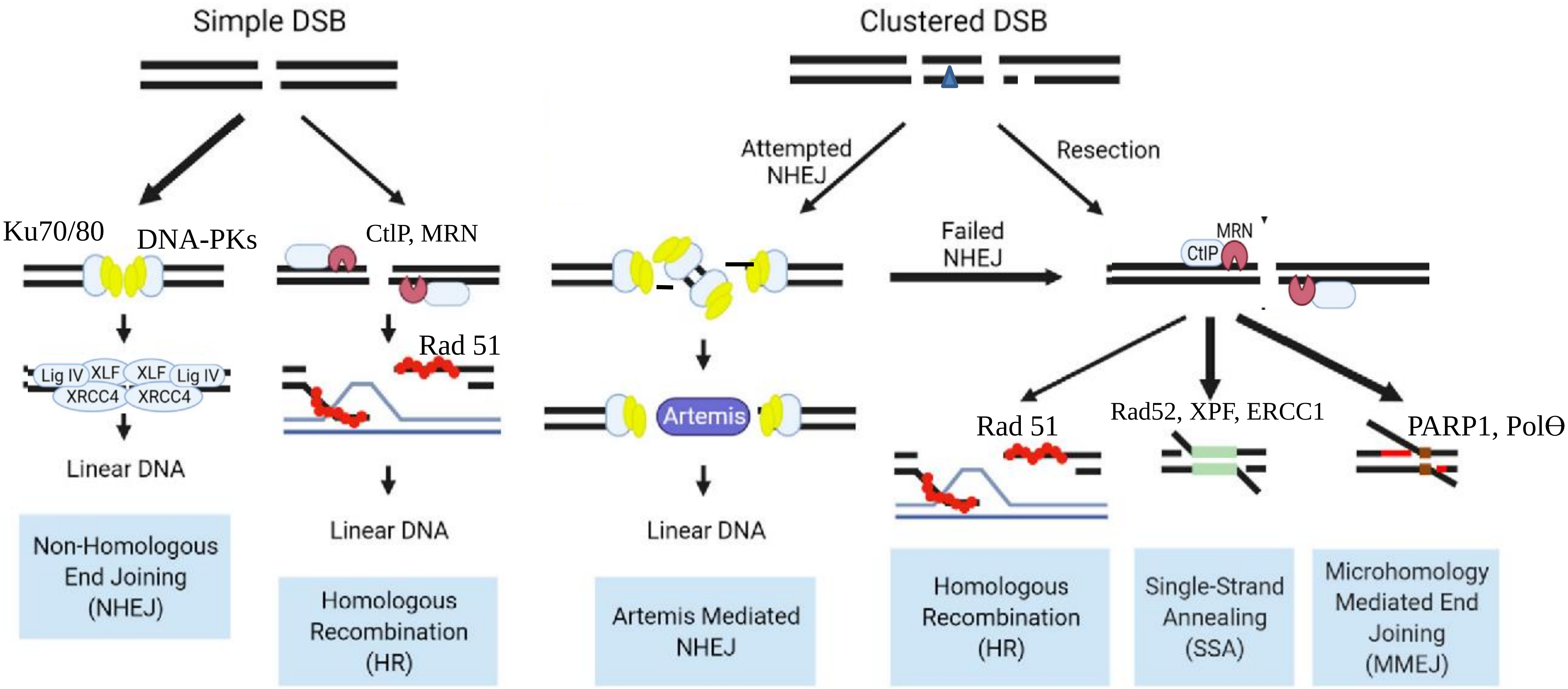




4Gy ^{15}N ions Glioblastoma U87 (superresolution)



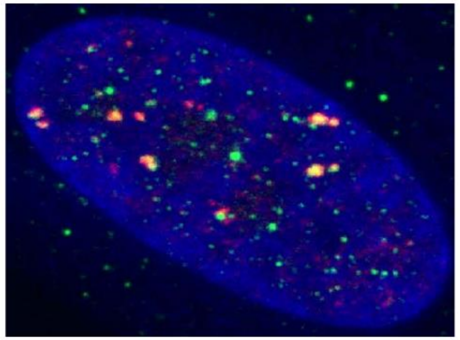
DNA repair. Pathways of DNA DSB reparation



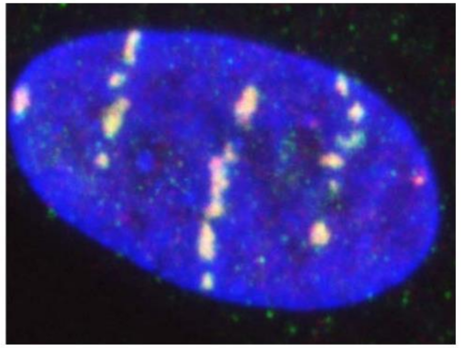
modified from Danforth et al(2022) Front. Cell Dev. Biol. 10:910440.

Research on DNA repair

a)

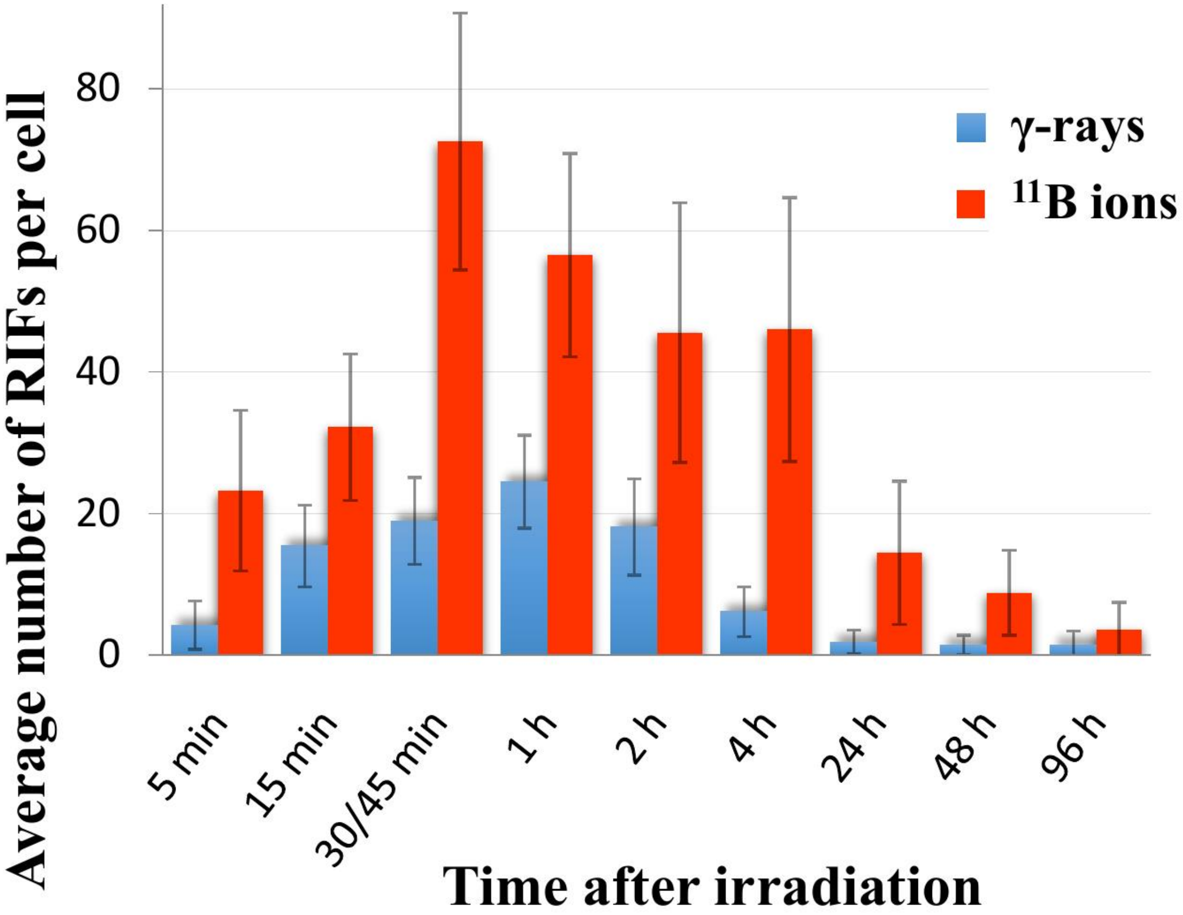


γ-rays

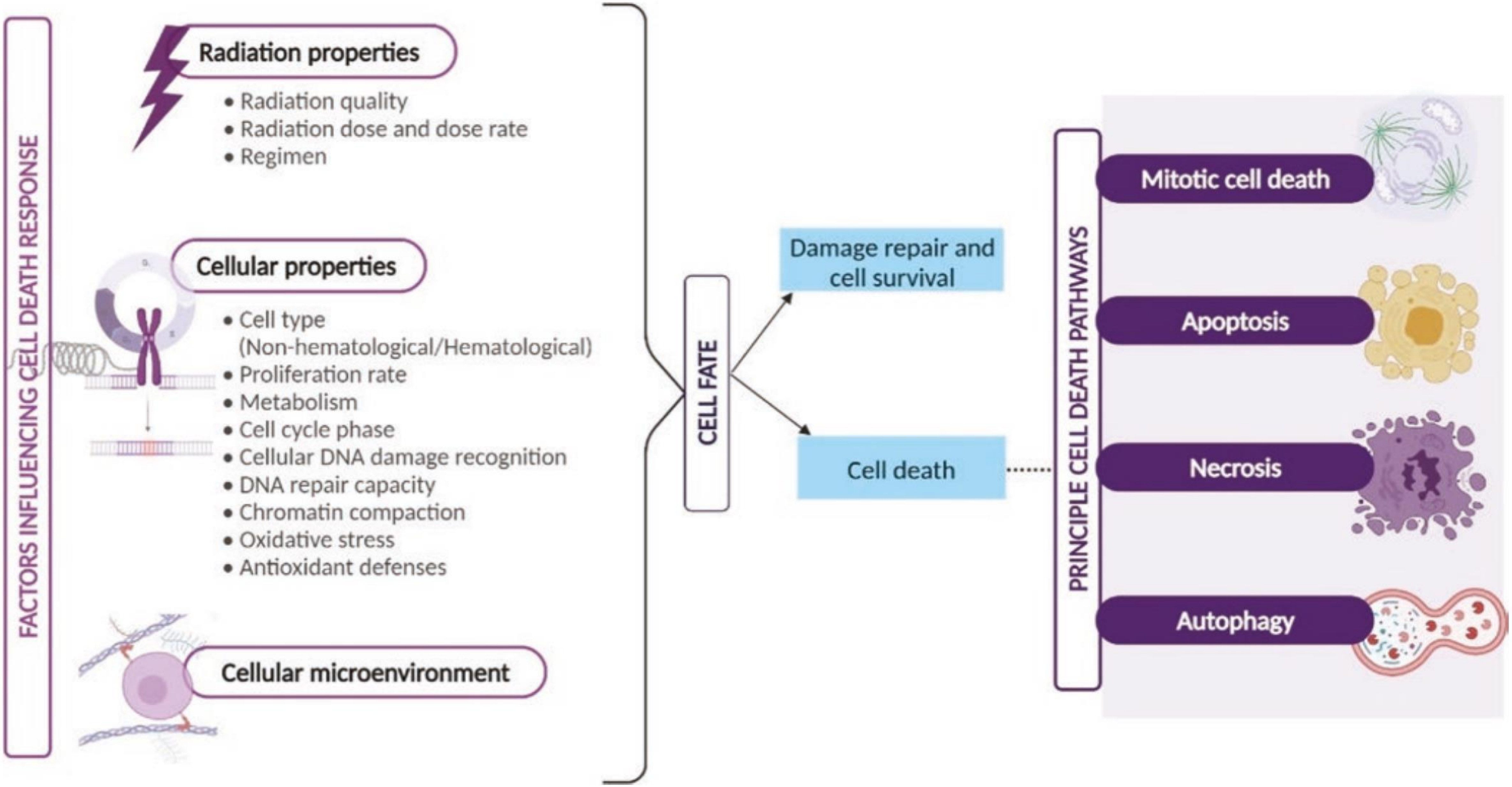


^{11}B ions

b)



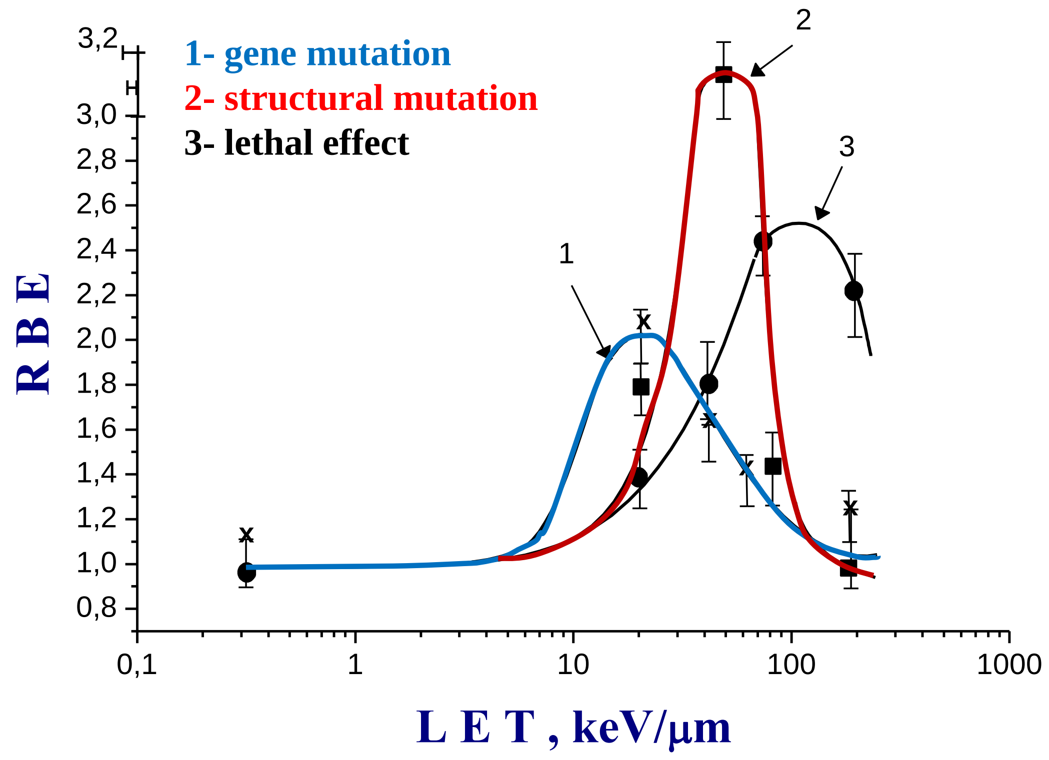
Pathways of cellular death

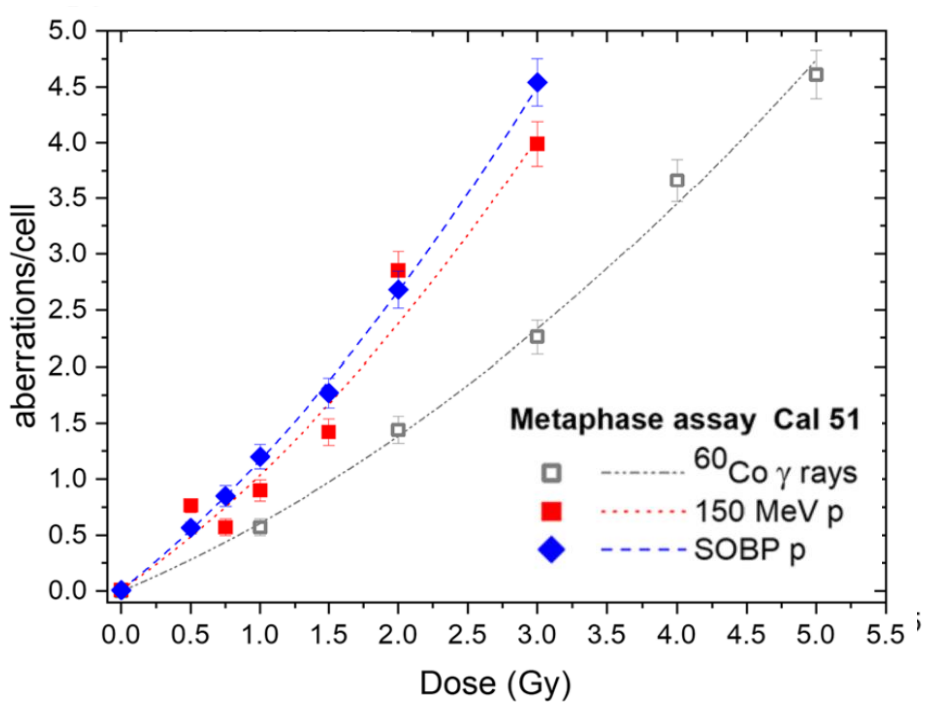


Mutagenic action of radiation

Genetic and cytogenetic effects of radiation:

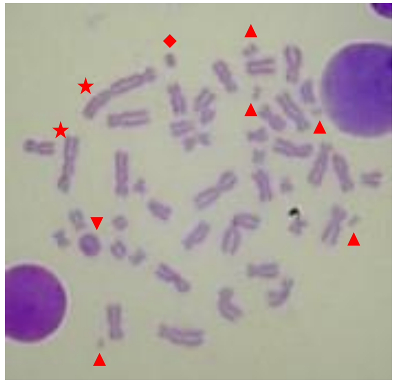
gene mutations, chromosome aberrations





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

(SOBP –spread out Bragg peak)



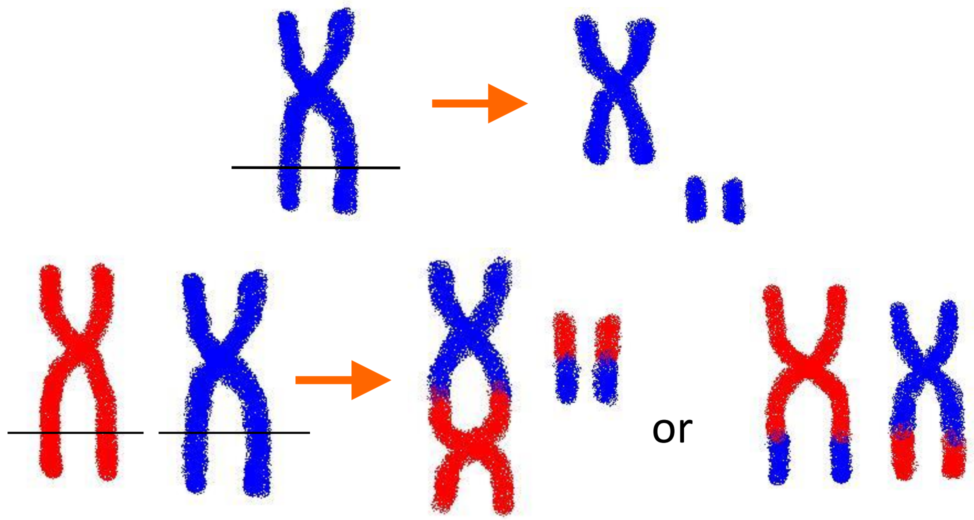
Radiation Cytogenetics

- Radiation exposure to cell
- (Damage to DNA)
- Cells try to repair

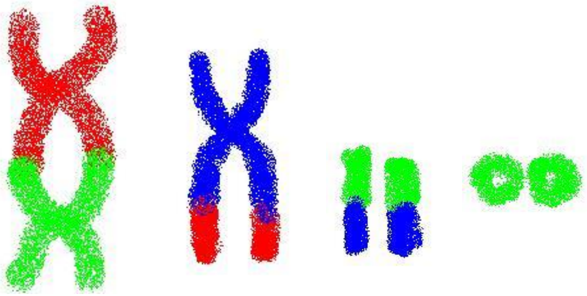
Repair successful | Repair failed | Cell death

eg chromosome aberrations

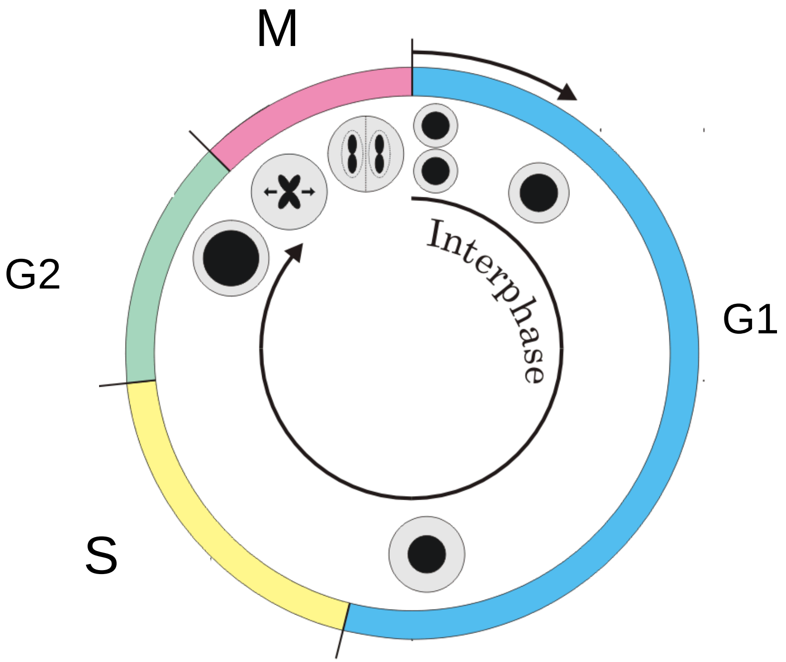
Examples of chromosome aberrations

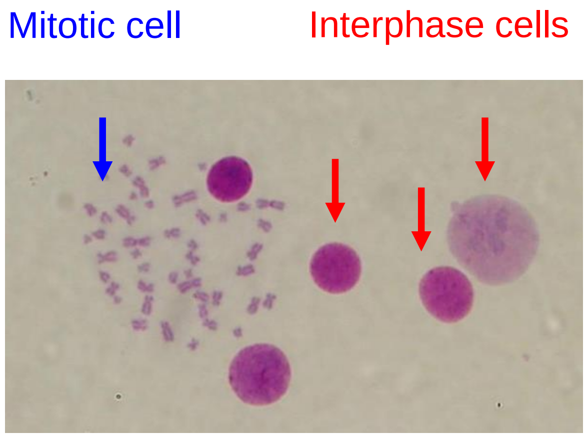


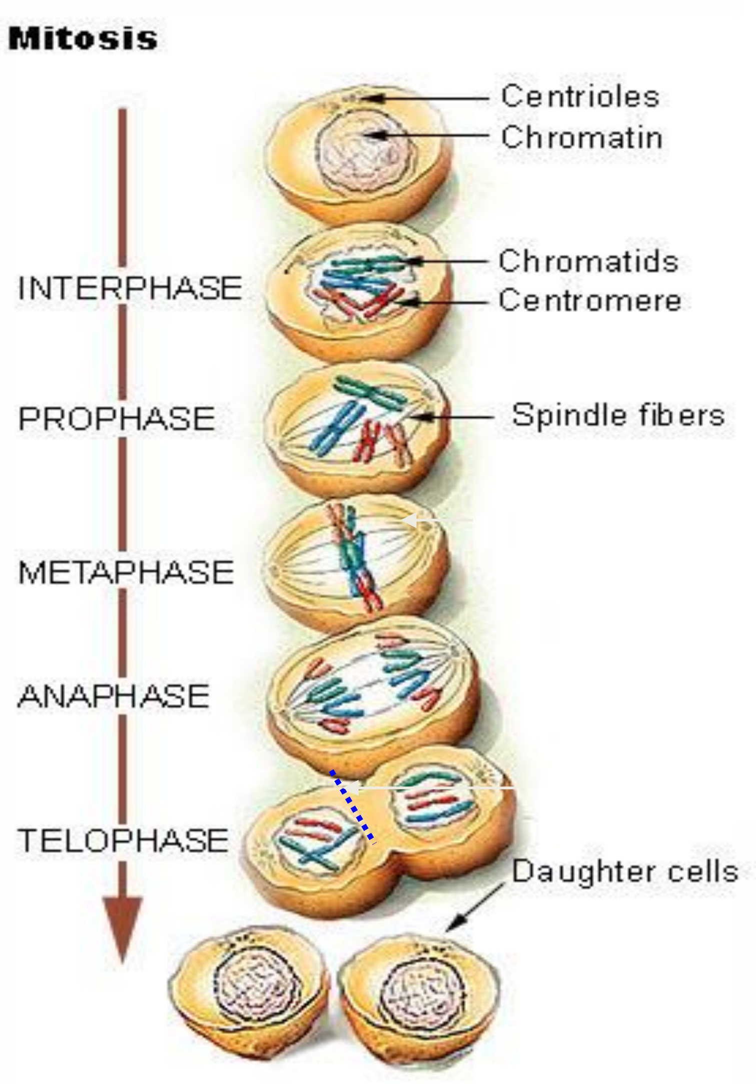
Following high LET exposure

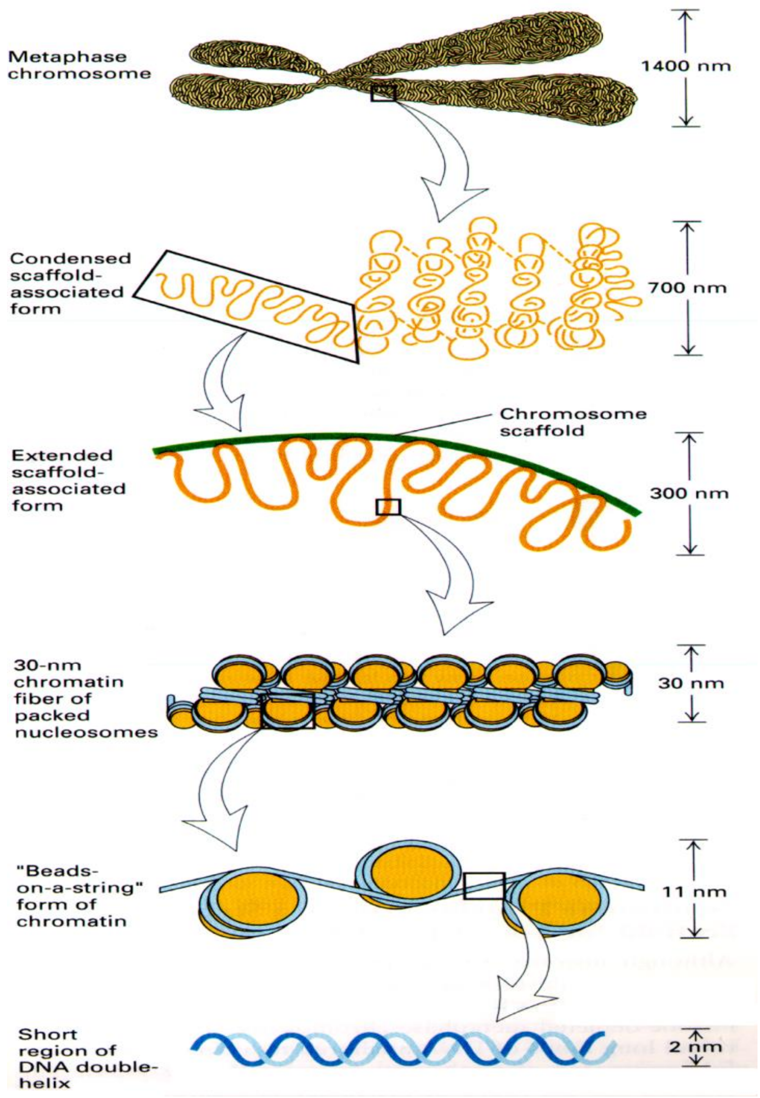


What is chromosome?

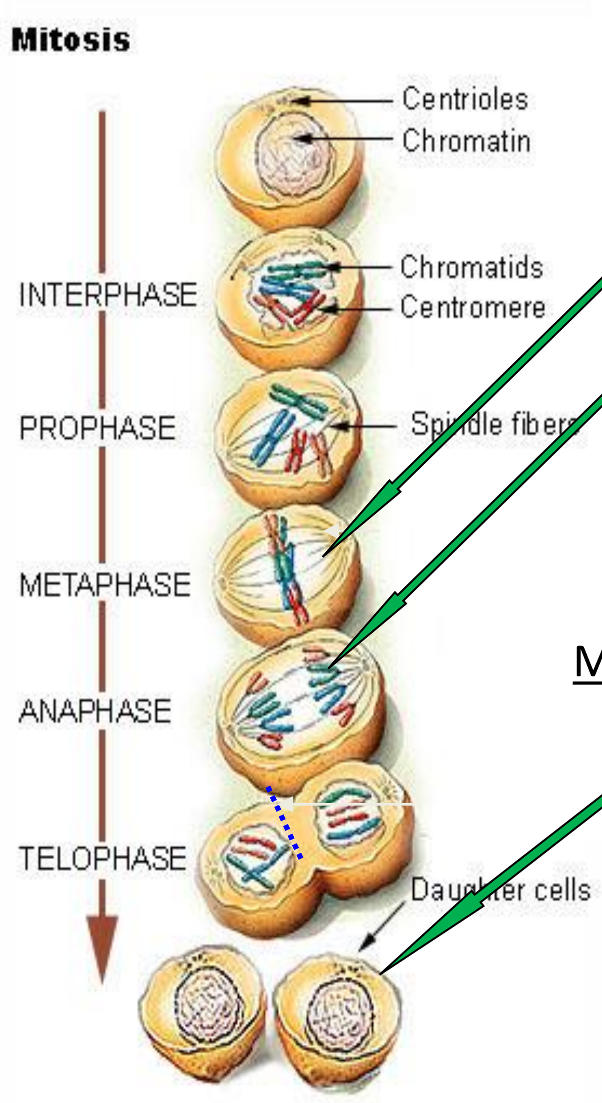


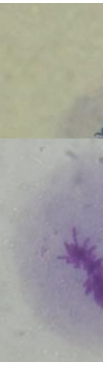




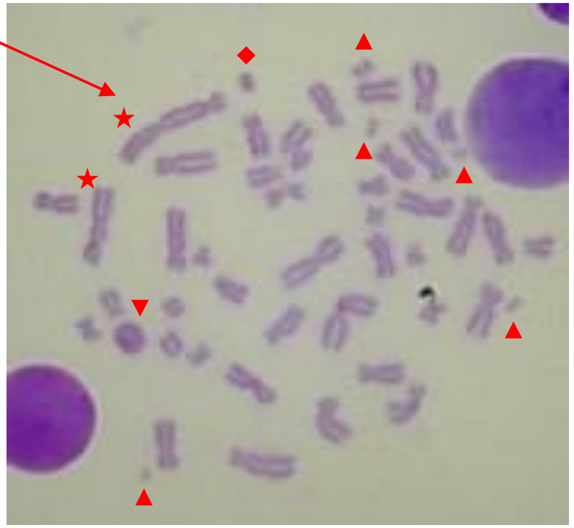


Cytogenetic methods





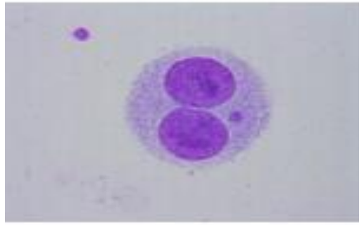
<u>Metaphase method:</u> cells are blocked in metaphase to analyze structural rearrangements – chromosome aberrations (marked with red symbols)

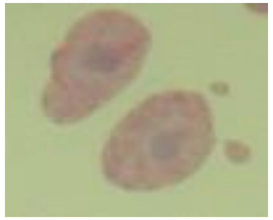


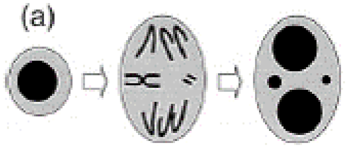
<u>Anaphase method:</u> cells are analyzed *in situ* on growing surface

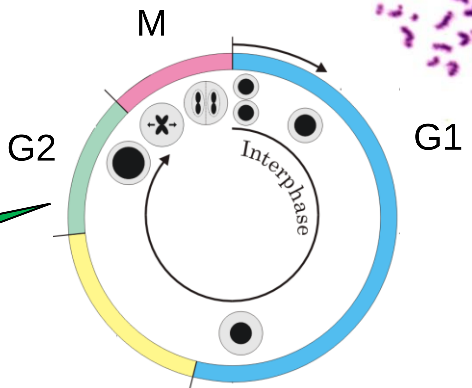
normal cell

<u>Micronucleus assay:</u> the damage is analyzed in daughter cells









<u>PCC - Premature chromosome condensation:</u> the damage is analyzed in interphase cells

G2- or G1 - cells

Multicolor fluorescence *in situ* hybridization (mFISH)

•5 types of probe DNA (≈150 - 400 bp long) labeled with 5 different fluorochromes **FITC SpO TR Cy5 DEAC**

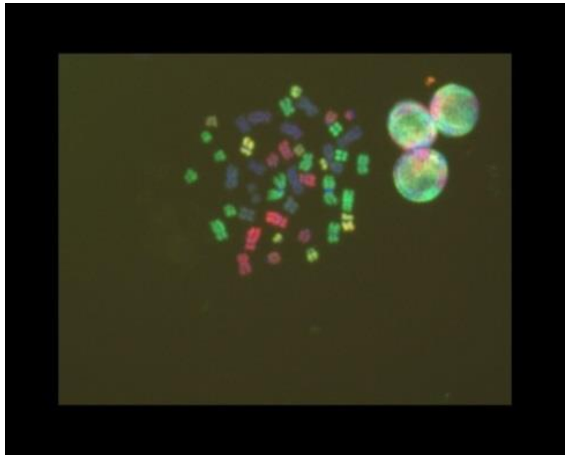
•Specific binding to chromosomes (1 – 3 differently labeled DNA probes bind to each chromosome ⇒ 25 fluorochrome combinations)

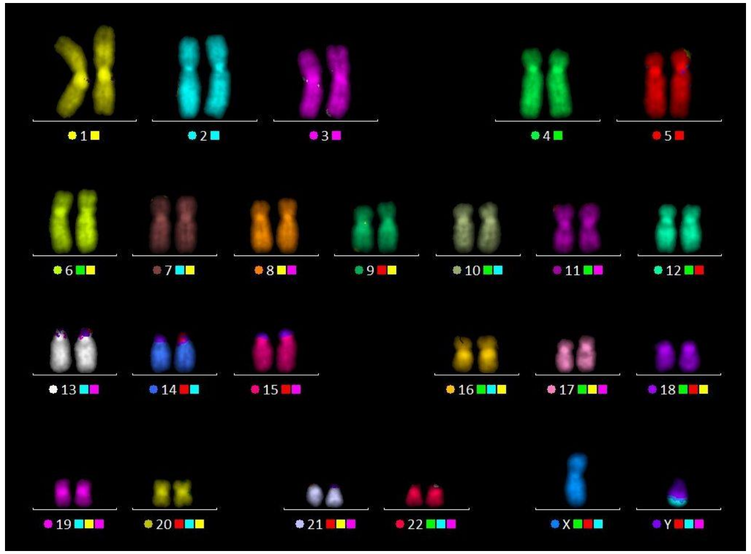
•DAPI-counterstaining

•Images are captured at fluorescence microscope using a filter set

•resolution: ≈ 2,6 Mbp, depending on fluorochrome composition involved and hybridization quality

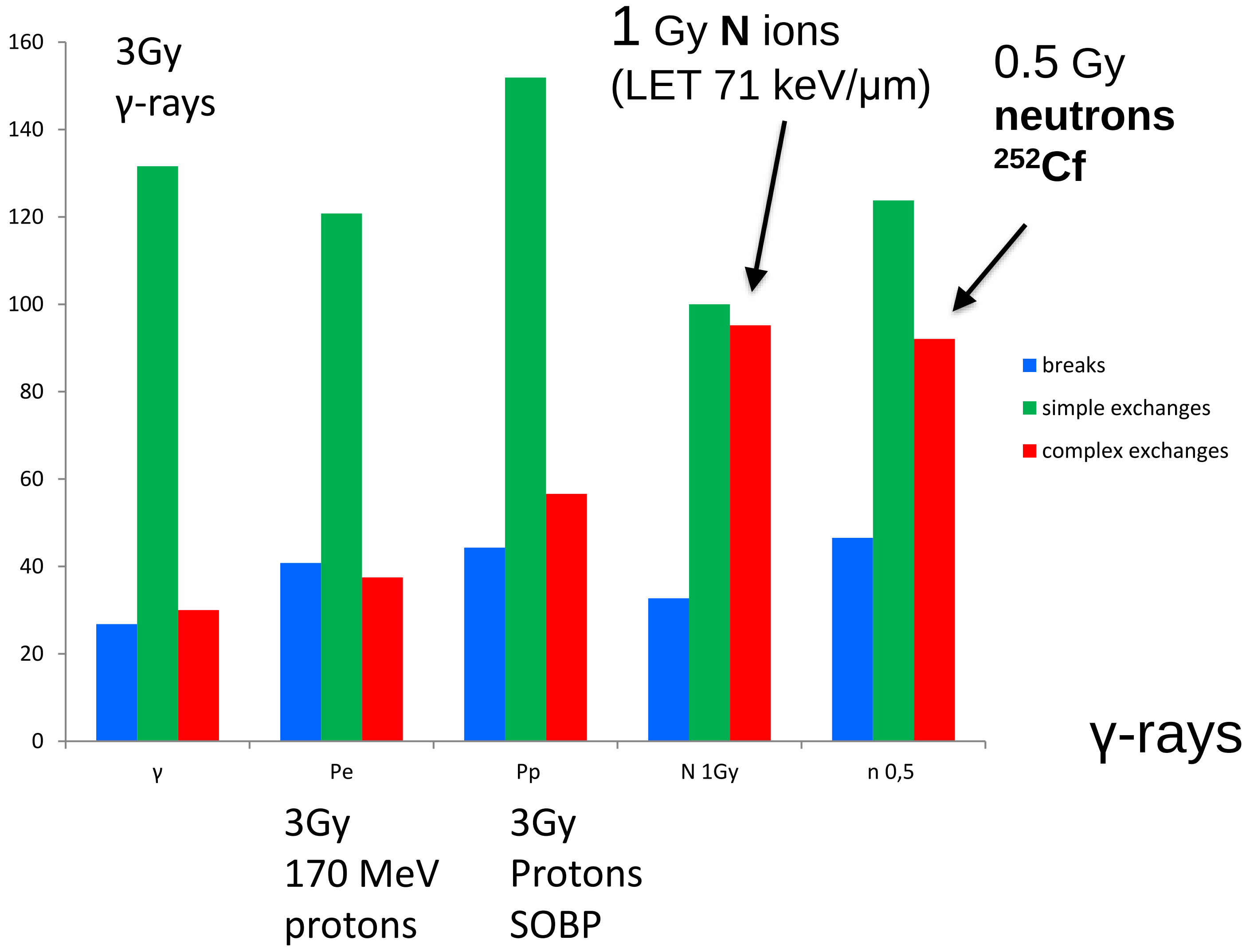
Probes and software of **MetaSystems, Germany**



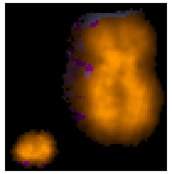


mFISH karyogram

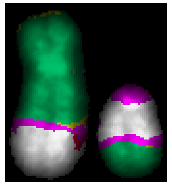
RBE evaluation by mFISH



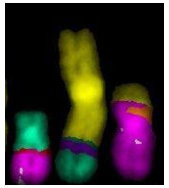
acentrics
(1 break)



simple exchanges
(2 breaks)



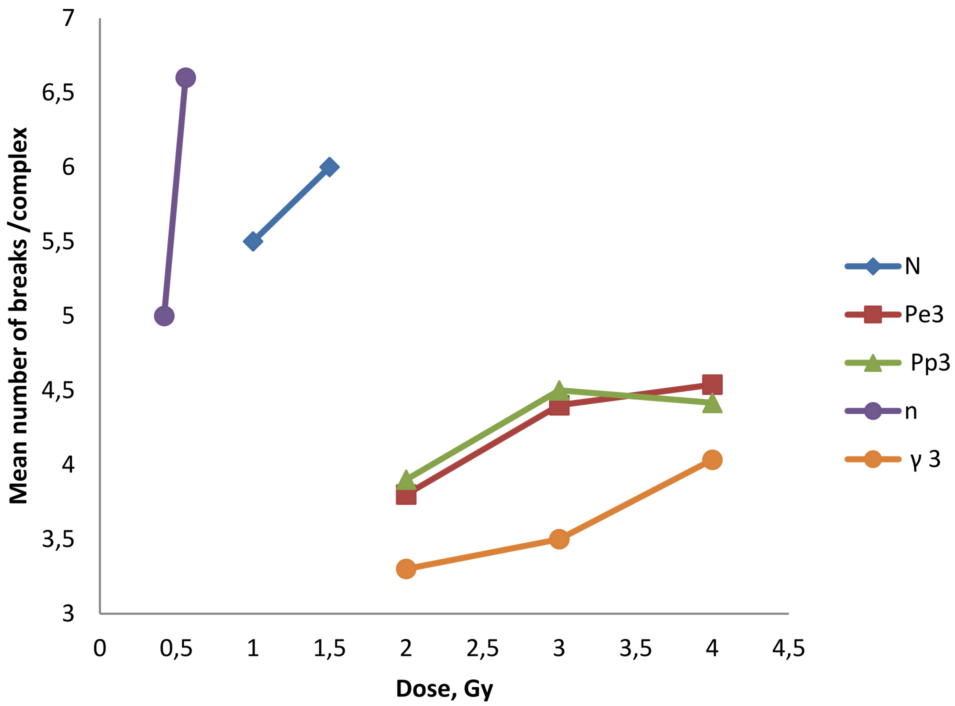
complex
aberrations
(≥3 breaks)



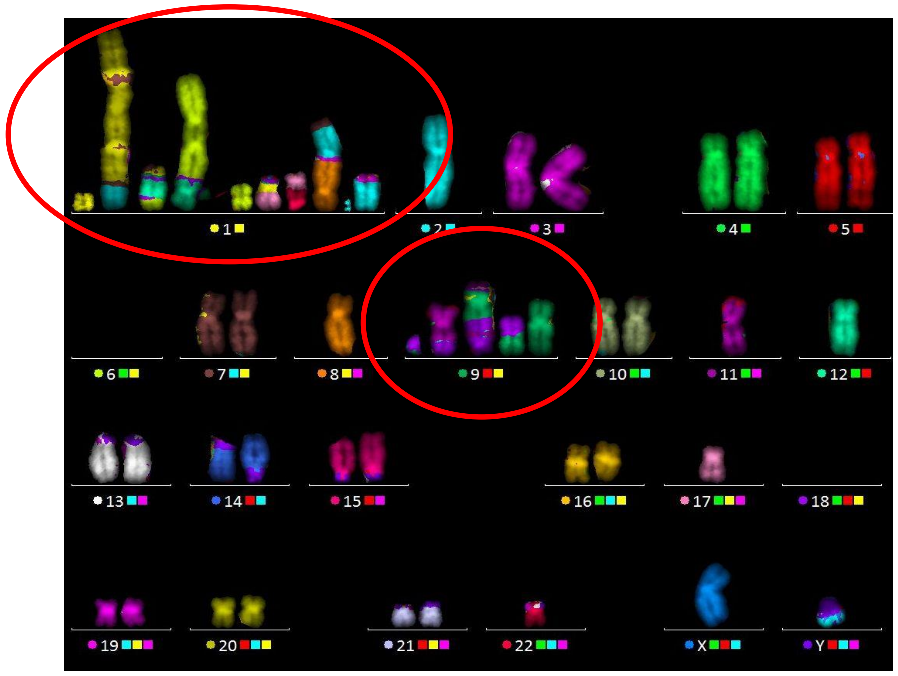
γ-rays and protons: 20 % / 60 % / 20 %

^{14}N ions: 14 % / 44 % / 42 %

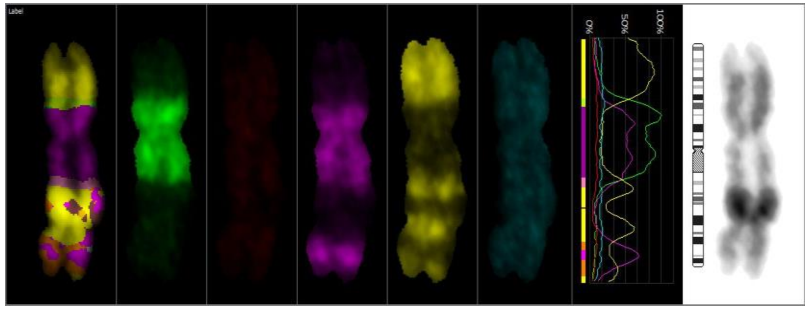
Complexity of complex aberrations



^{252}**Cf neutrons** (average energy of 2.12 MeV) 0.42-0.56 Gy induced 5-6.6 breaks/complex;
N ions 71 kev/μ 1-1.5 Gy – 5,5-6 breaks/complex



Cell with 2 complex aberrations 9/12/15 and 4/5/7 induced by neutron dose **0.28 Gy.** In total in the cell 22 breaks in 13 chromosomes were detected.



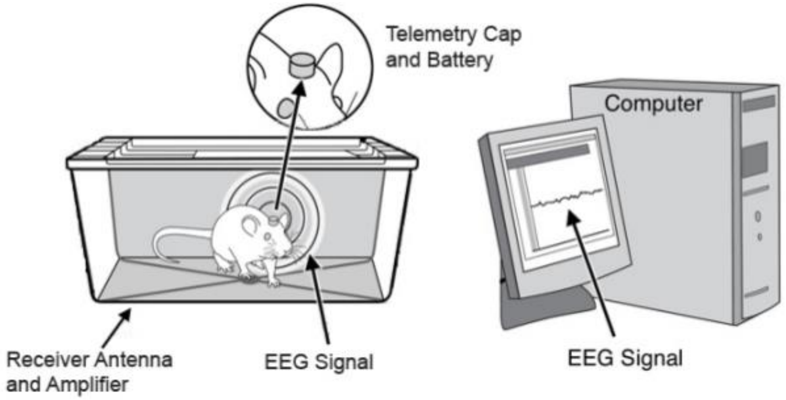
Dicentric chromosome 1-11’-1’-3-1 –
a part of complex aberration C/A/B 3/5/7
induced by neutron dose **0.28 Gy**.

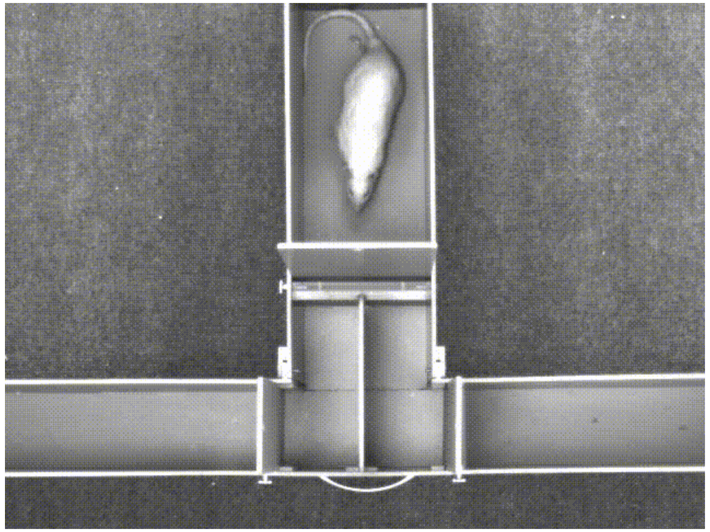
Set of equipment for the study of behavioral reactions and functional disorders of the central nervous system of animals

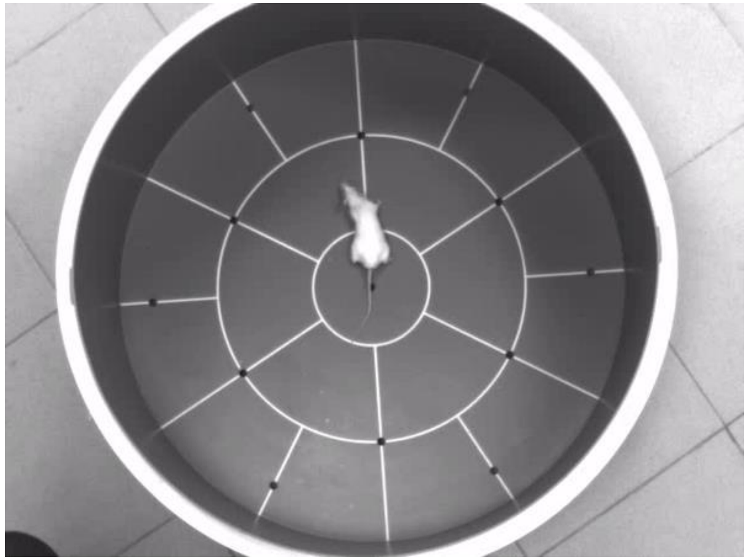
Behavior test systems

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

Electrophysiology studies

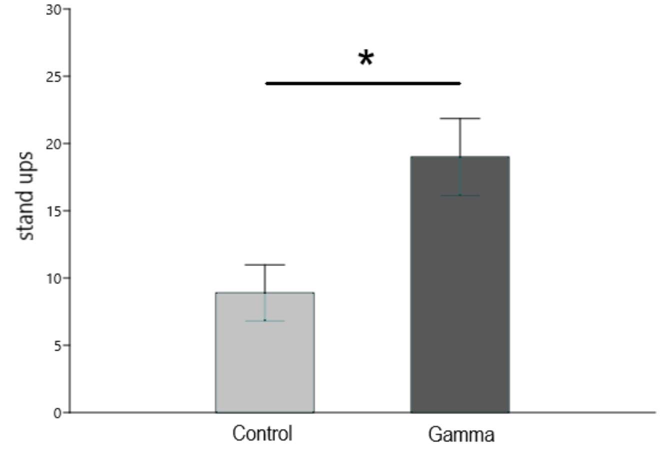


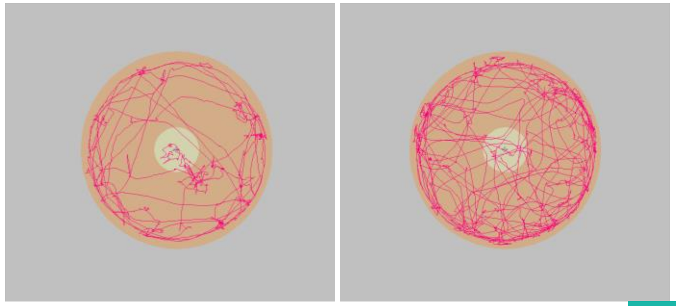




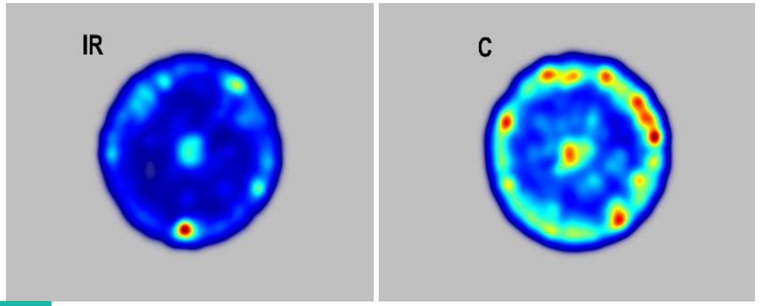
Behavioral analysis

3 min	*Grooming*	*Sectors crossings*	*Center entrance*	*Stand ups*	*Hole dipping*	*Freezing*	*Emotional status*	*Orientation-exploratory status*
Control	8		7		5			
Irradiated	5	4	6	3	4	0		
6 min								
control	5	1	4			1		
Irradiated	2	5	4	9	7	1		





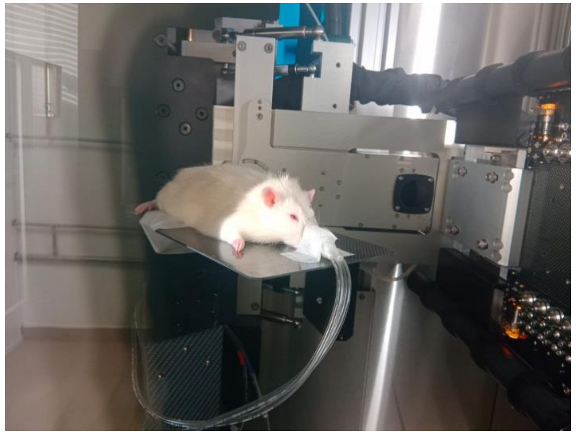
Tracking



Heatmap

EthoVision XT

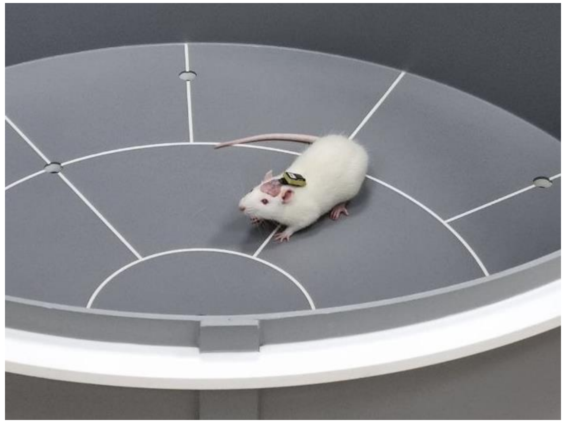
Analysis of the functional activity of the cerebral cortex of rats after exposure to ionizing radiation



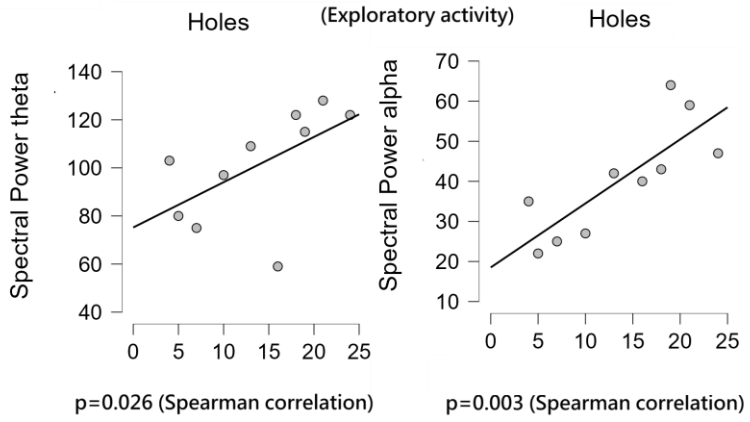
Animal irradiation

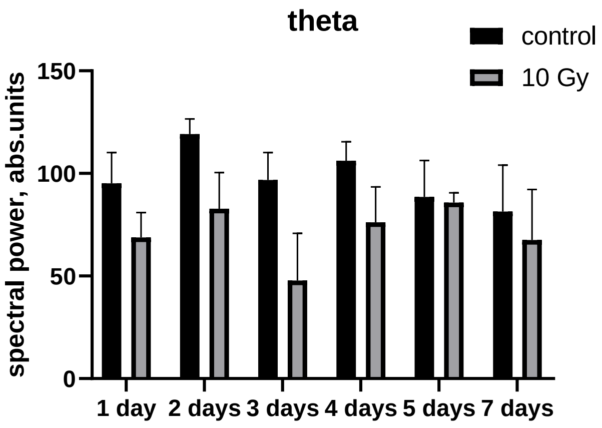
Treatment planning

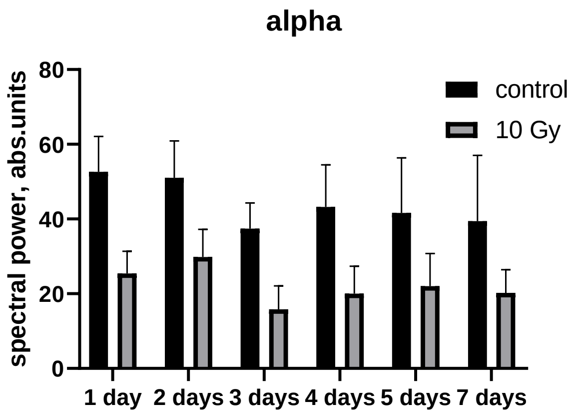
Electrode implantation



Behavior analysis

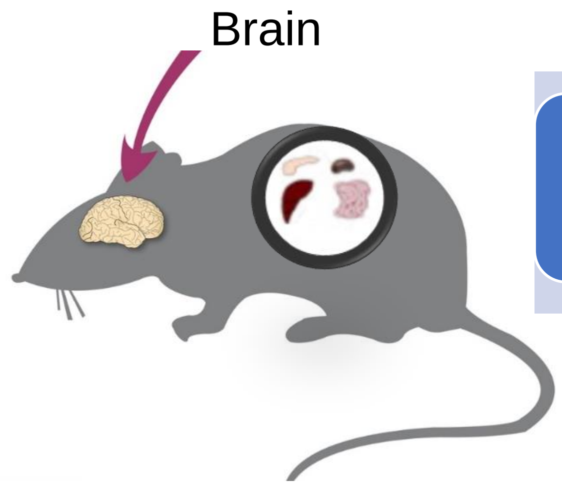






Correlation of behavioral disorders and electrical rhythms of the brain (EEG)

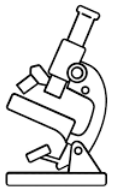
Autopsy of laboratory rodents



visual estimation → taking an organ → tissue fixation → embedding or blocking out → staining → microscopy

thymus, spleen, brain

liver, small intestine, kidney brain



blood

Histological methods

Paraffin block

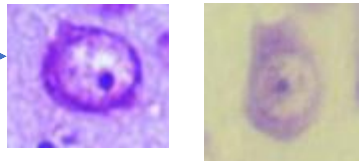
Histological slides

Staining

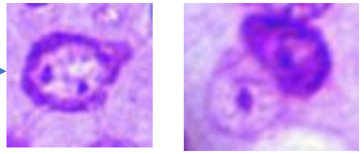
Histological analysis of brain tissue

Classification of brain cells:

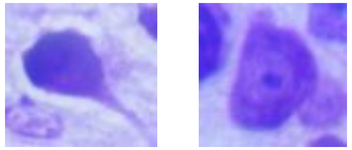
- normal



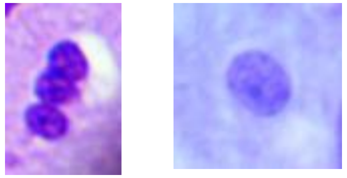
- altered



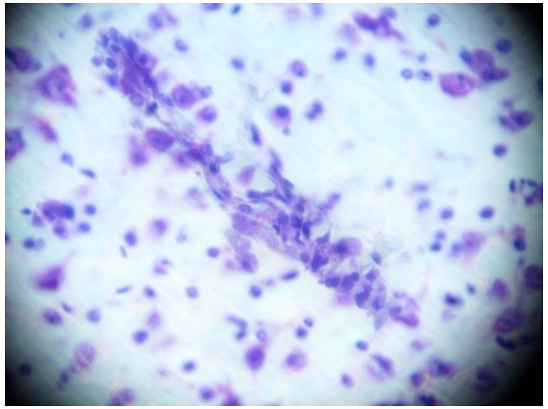
- degenerative

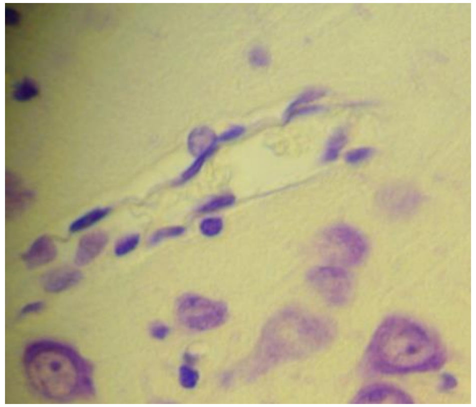


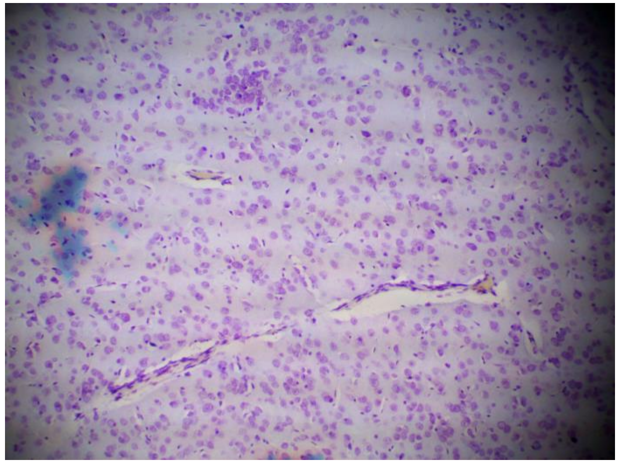
- glia



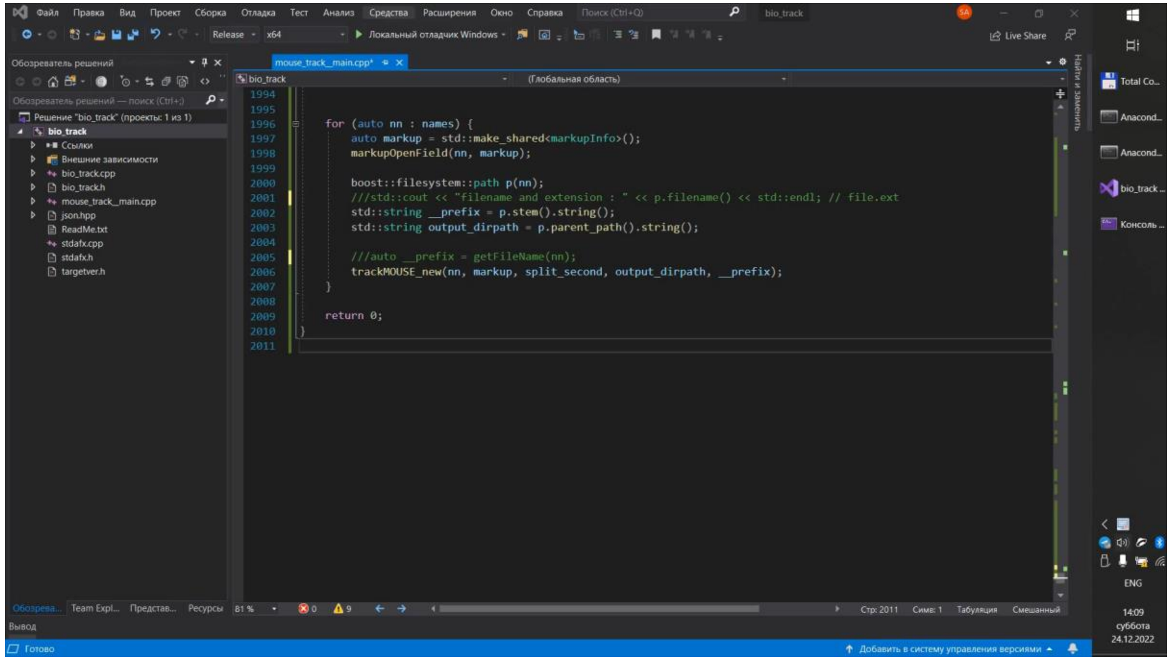
Vascular changes:

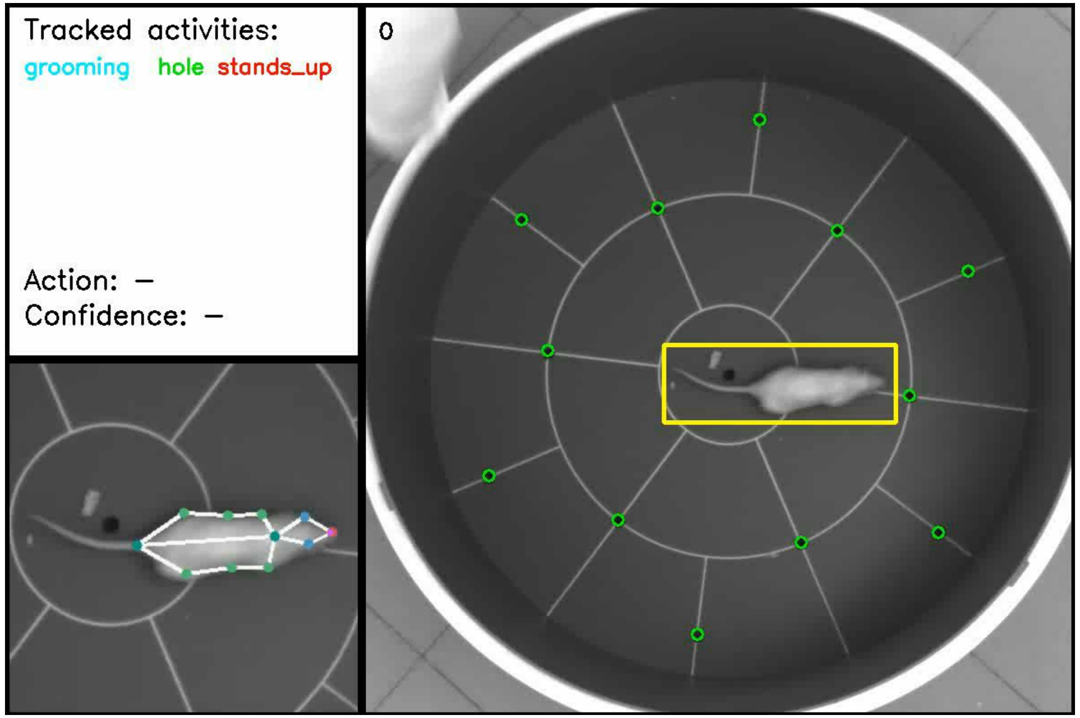




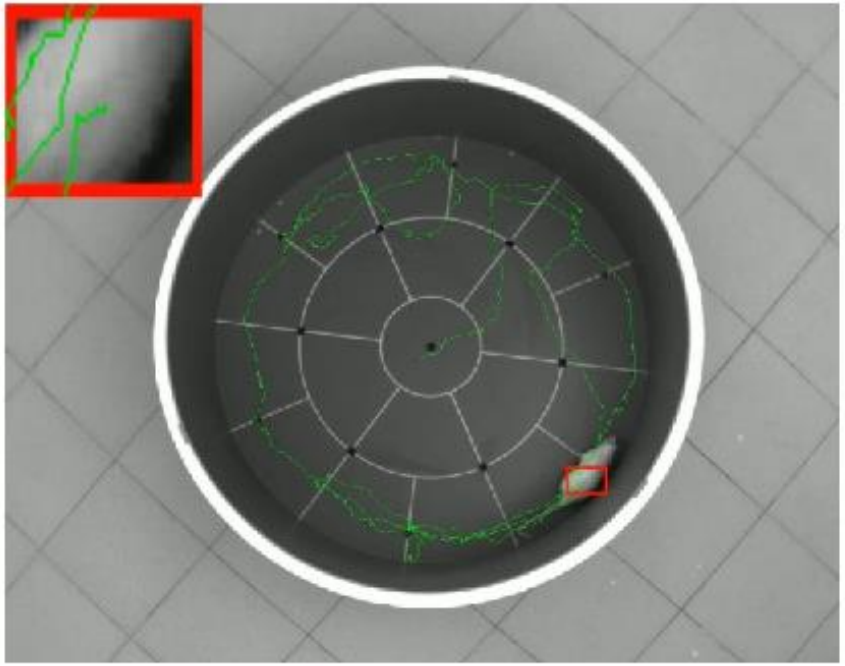


Examples of automated video data analysis

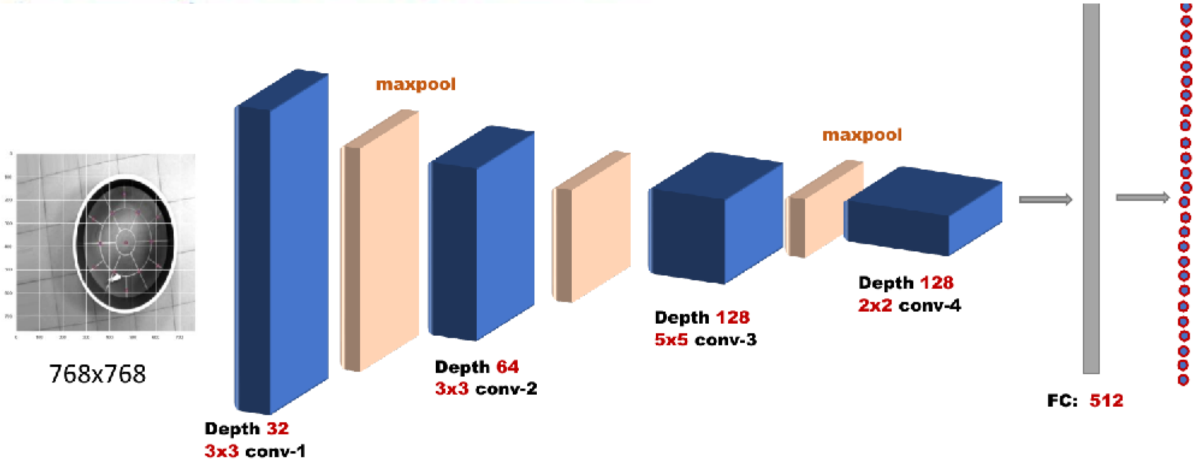


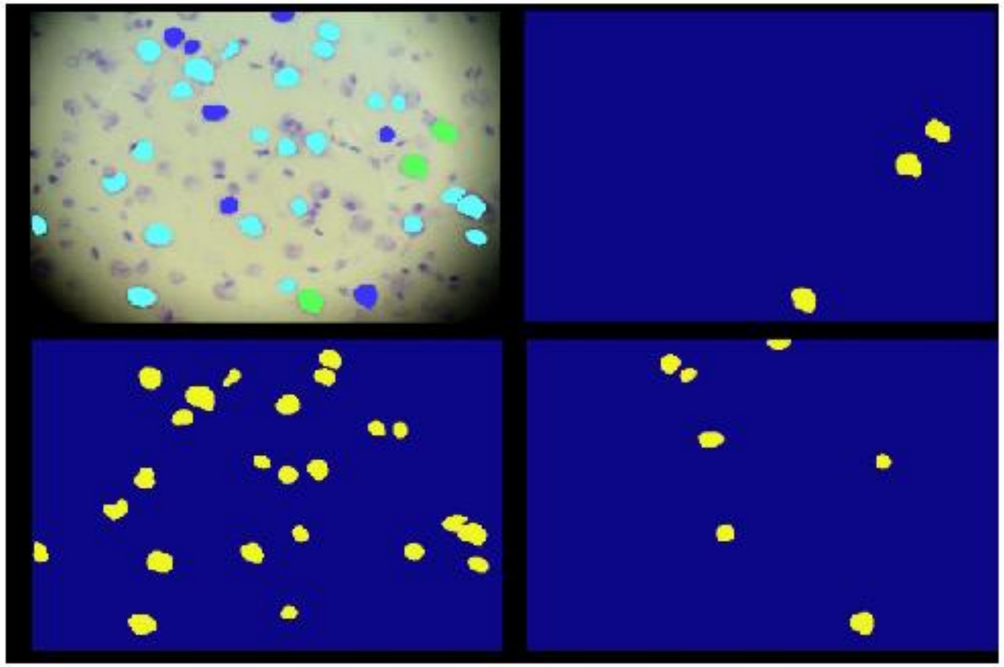


ML/DL/computer vision algorithms



Tracking a laboratory animal:

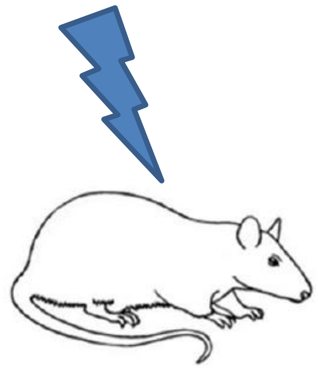




Neural networks for the task of neuron segmentation on brain slice images

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

Irradiation

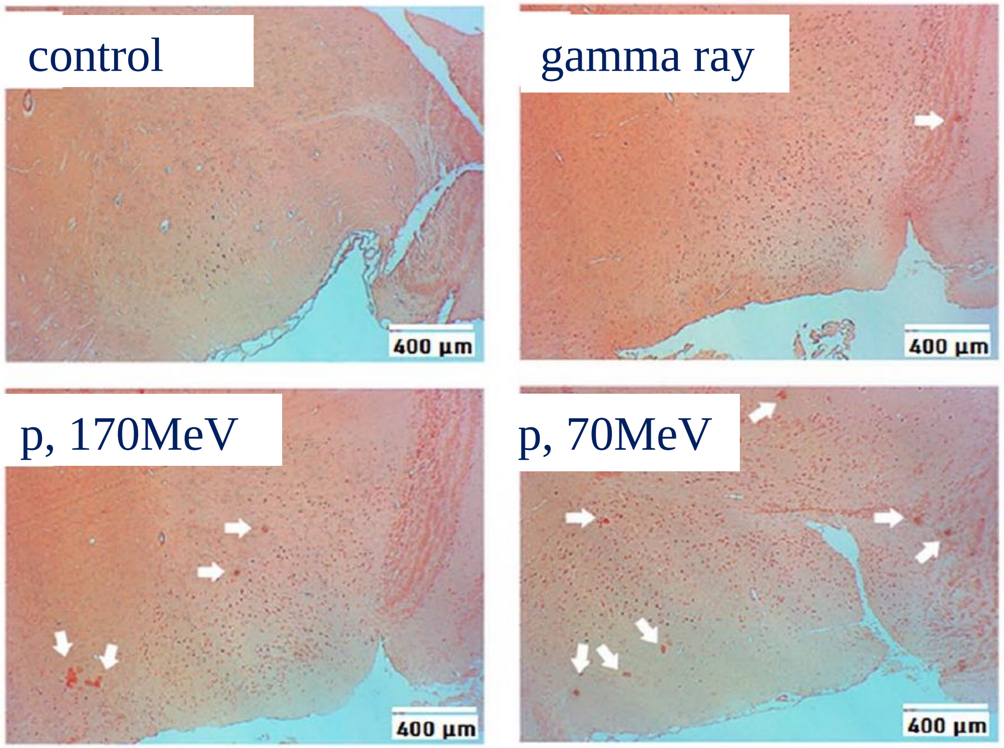


Dose:	1 Gy
LET:	0.2 keV/µm (gamma ray)
	0.5 keV/µm (170 MeV protons)
	1 keV/µm (70 MeV protons)

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

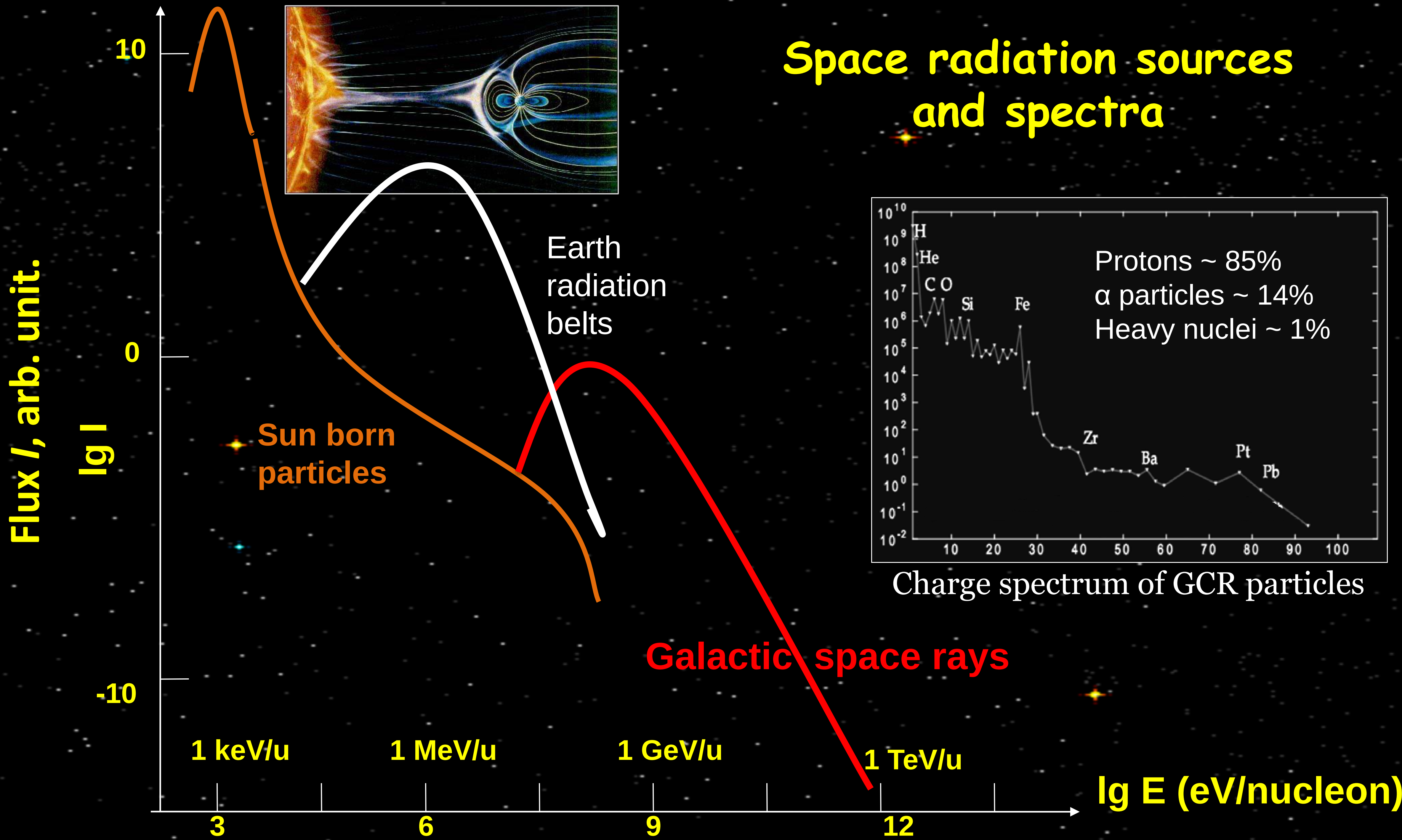


Amyloid plaques in the forebrain of rats (marked with white arrows)

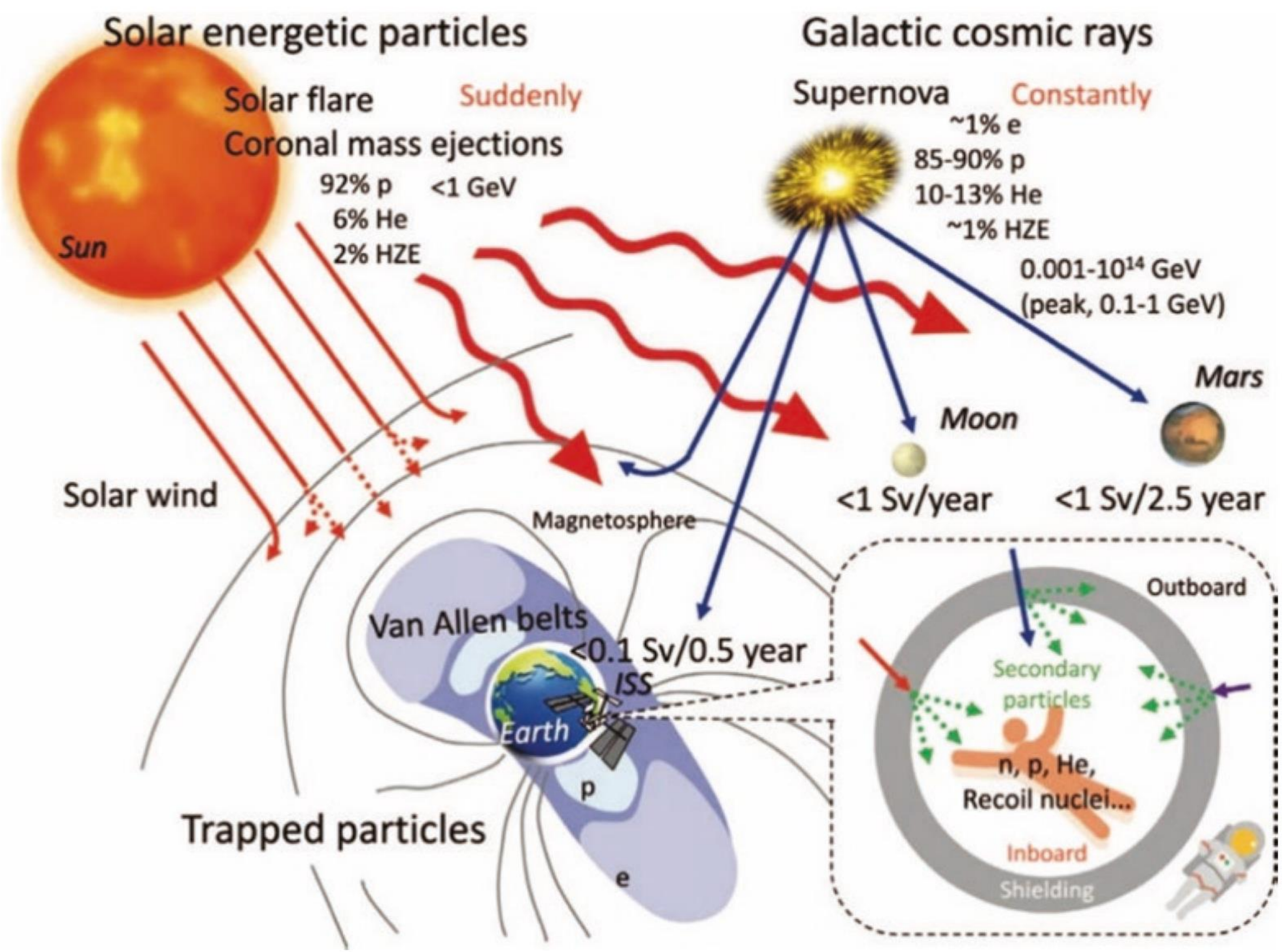
The neurodegeneration increases with LET of radiation

Space radiobiology

Space radiation sources and spectra



Charge spectrum of GCR particles



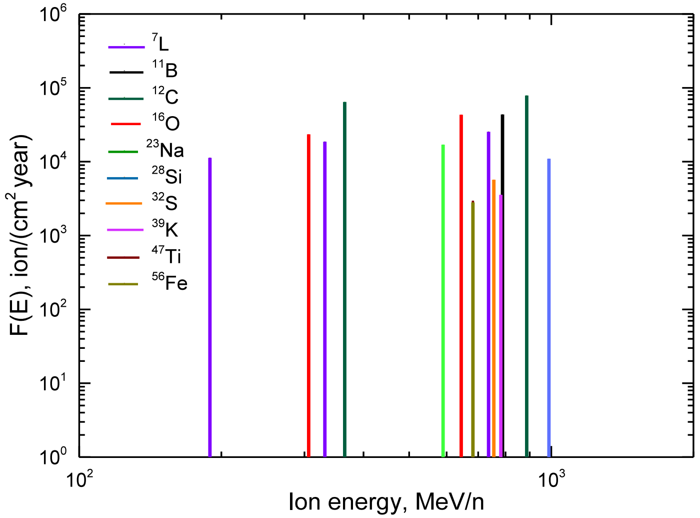
S. Baatout (ed.), Radiobiology Textbook,

Is it possible to reproduce cosmic ray spectra in ground experiments?

NASA's first ground-based Galactic Cosmic Ray Simulator: Enabling a new era in space radiobiology research

Lisa C. Simonsen[1]*, Tony C. Slaba[1], Peter Guida[2], Adam Rusek[2]

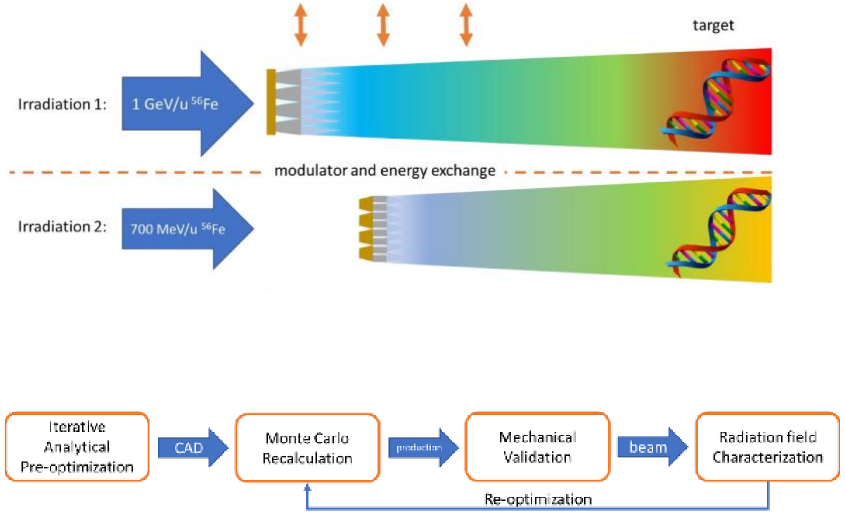
1 NASA Langley Research Center, Hampton, Virginia, United States of America, 2 Brookhaven National Laboratory, Brookhaven, New York, United States of America



Hybrid Active-Passive Space Radiation Simulation Concept for GSI and the Future FAIR Facility

*Christoph Schuy[1], Uli Weber[1] and Marco Durante[1,2]**

[1] GSI Helmholtzzentrum für Schwerionenforschung, Darmstadt, Germany, [2] Institut für Festkörperphysik, Technische Universität Darmstadt, Darmstadt, Germany

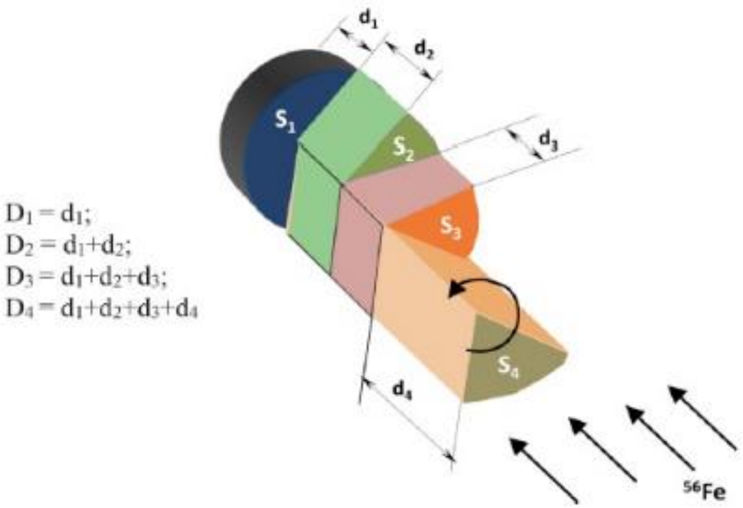


Front. Phys. 8:337.
doi: 10.3389/fphy.2020.00337

A new type of ground-based simulator of radiation field inside a spacecraft in deep space

I.S. Gordeev[a,b], G.N. Timoshenko[a,b,*]

[a] *Joint Institute for Nuclear Research, 141980, Dubna, Moscow region, Russia*
[b] *Dubna State University, 141980, Dubna, Moscow region, Russia*

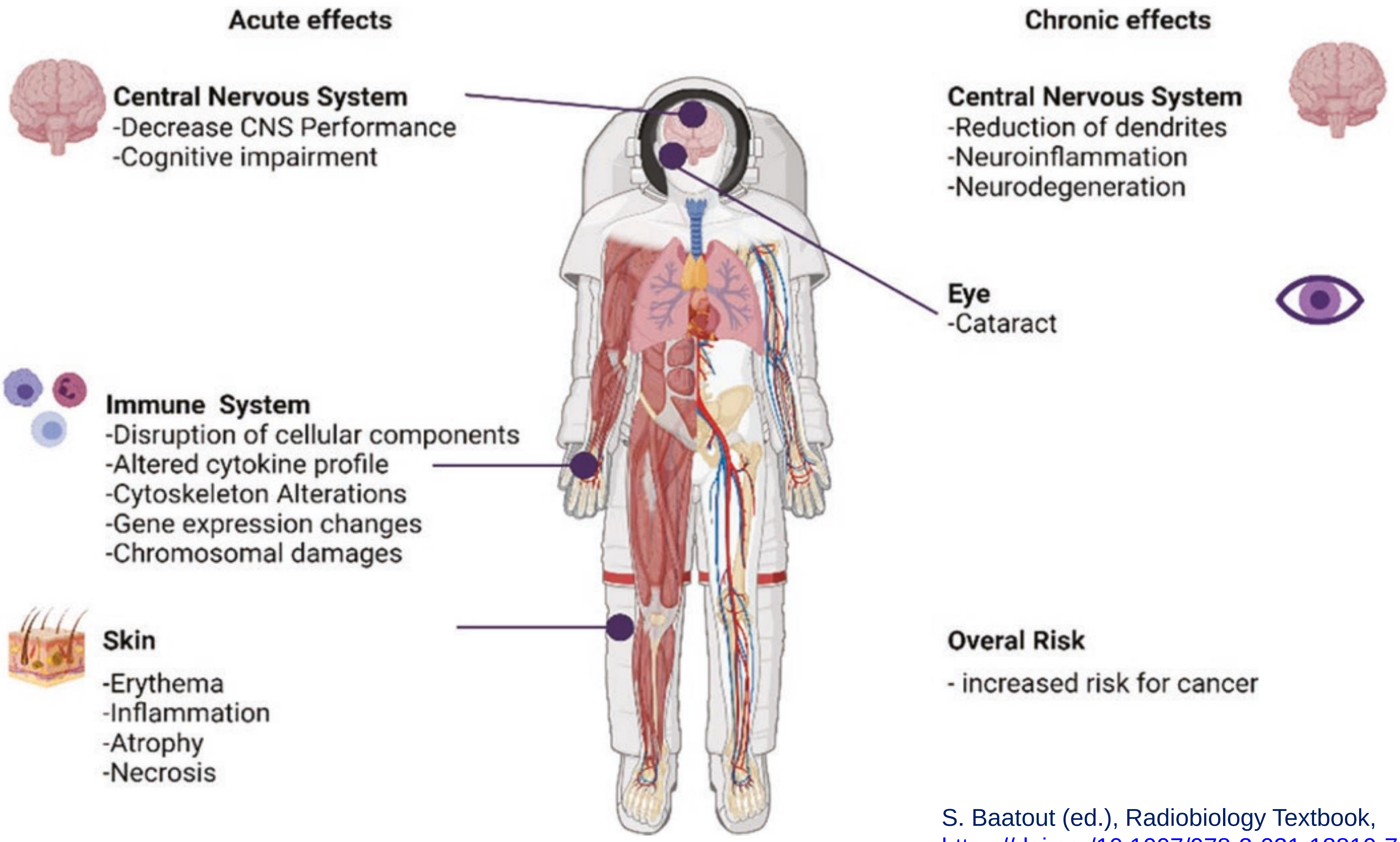


Life Sciences in Space Research, 30, (2021) 66

NSRL simulator

GSI/FAIR simulator

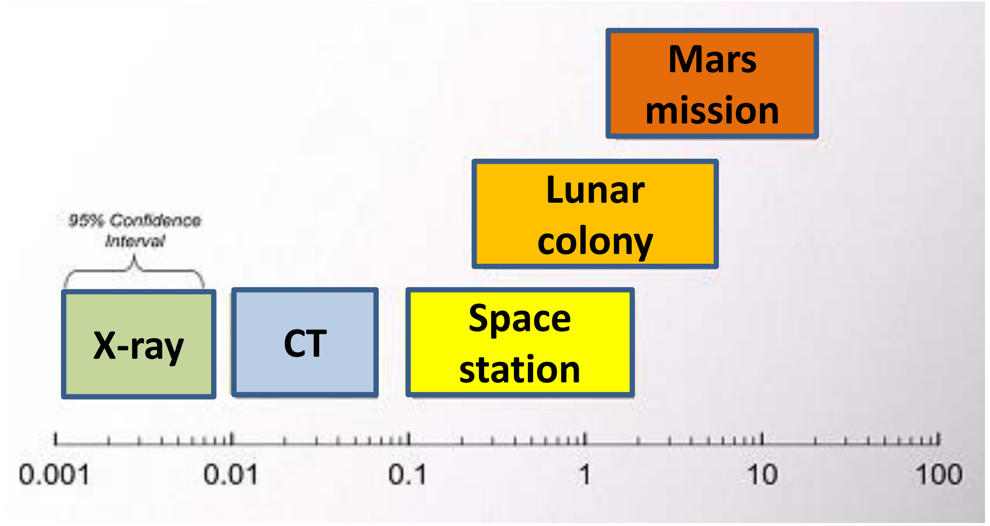
JINR simulator



S. Baatout (ed.), Radiobiology Textbook, https://doi.org/10.1007/978-3-031-18810-7_10

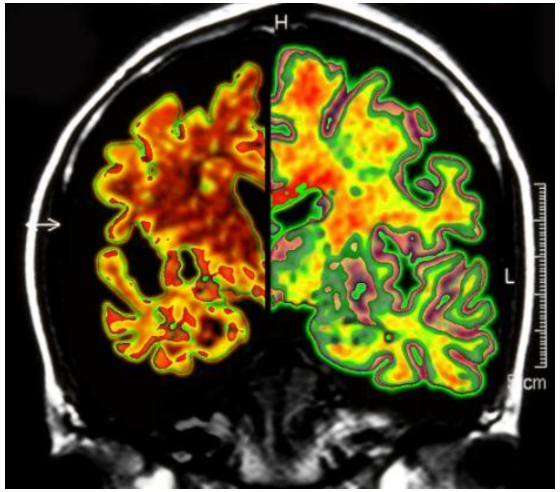
New concept of radiation risk for deep space flights:
Damage to the central nervous system

К ВОПРОСУ О РАДИАЦИОННОМ БАРЬЕРЕ ПРИ ПИЛОТИРУЕМЫХ МЕЖПЛАНЕТНЫХ ПОЛЁТАХ
А.И. Григорьев, Е.А. Красавин, М.А. Островский
Вестник Российской Академии Наук, 2017, том 87, № 1, с. 65–69



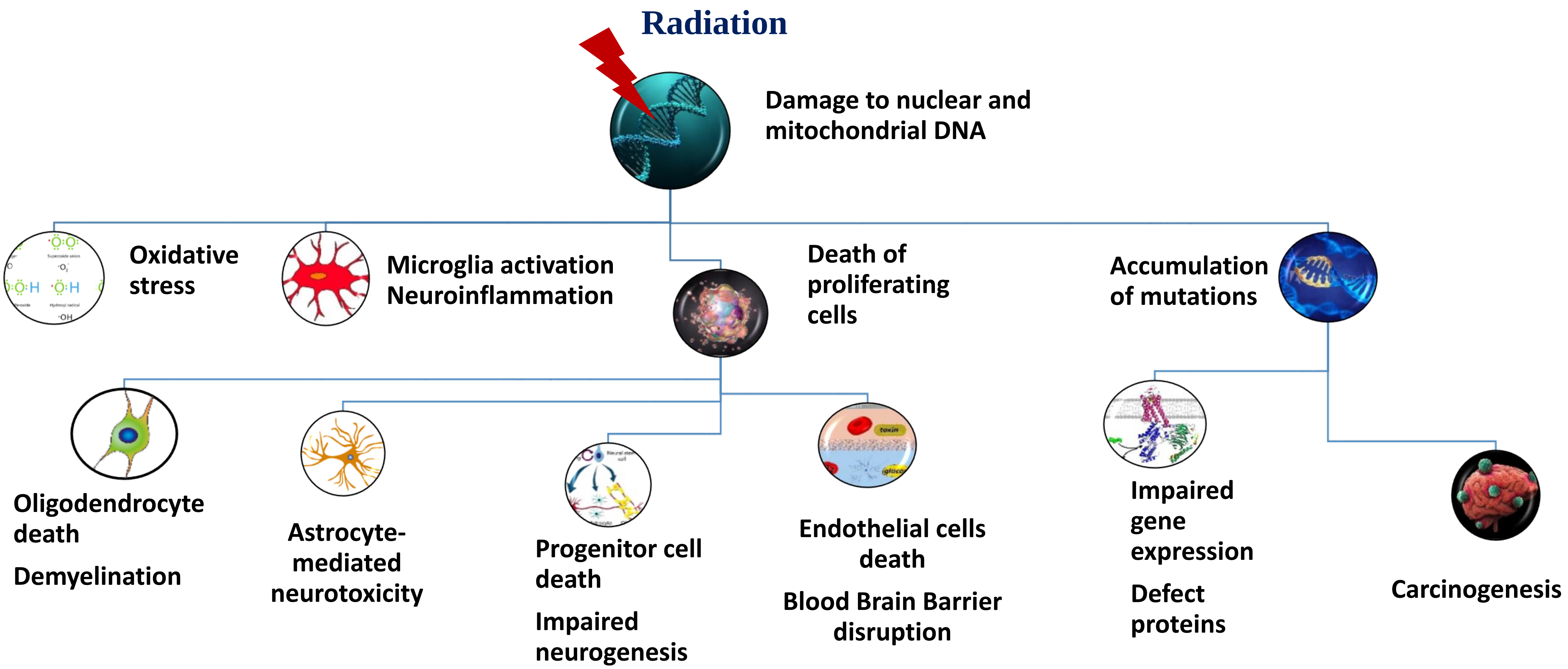
% Risk of cancer death

Paradigm shift



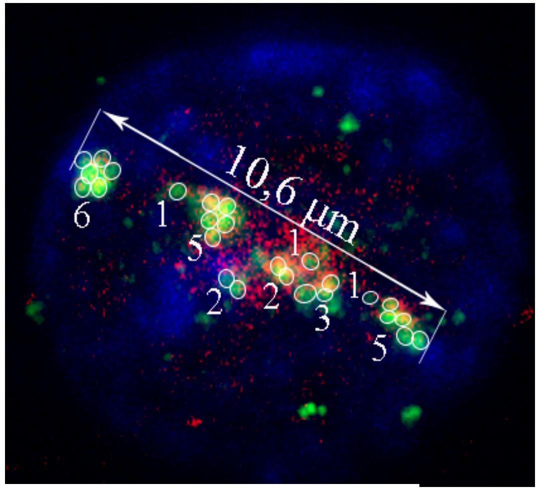
Radiation Neuroscience

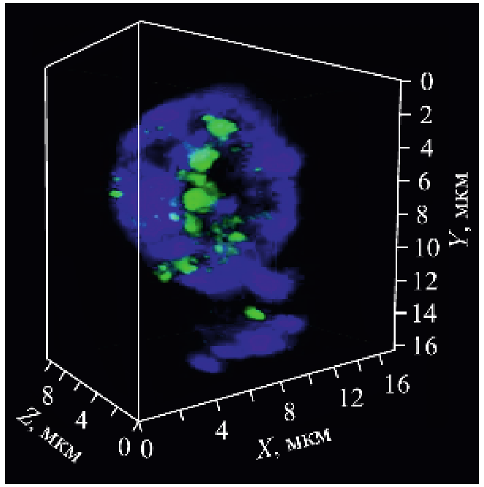
Mechanisms of Radiation Brain Injury

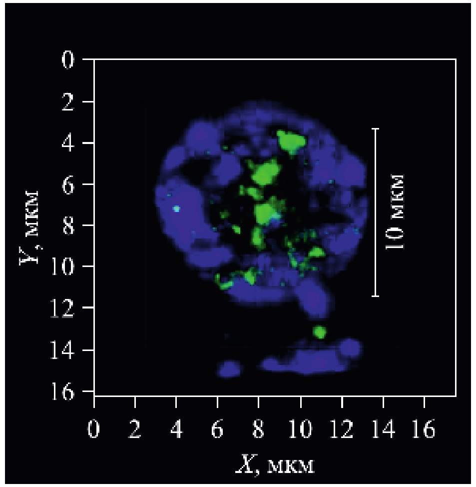


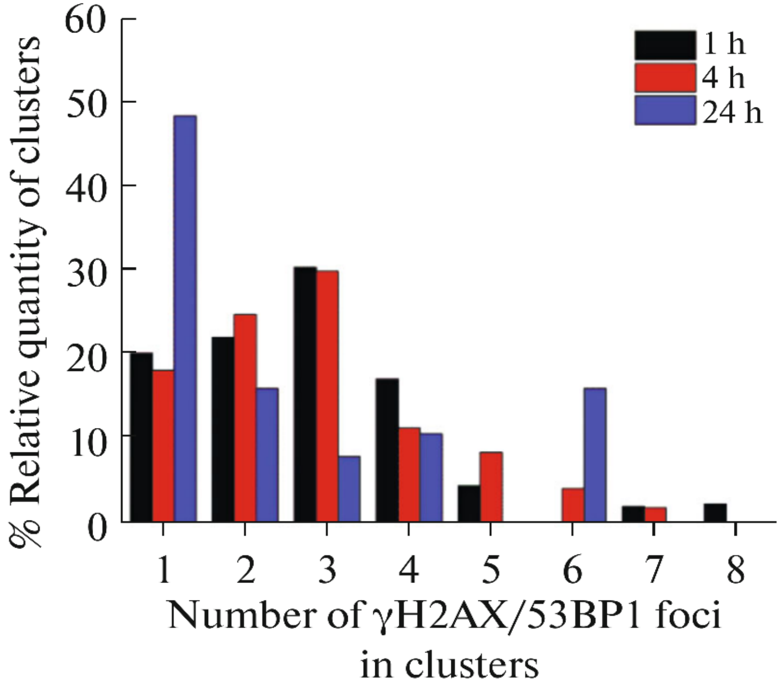
Clustered DNA double strand breaks in brain neurons

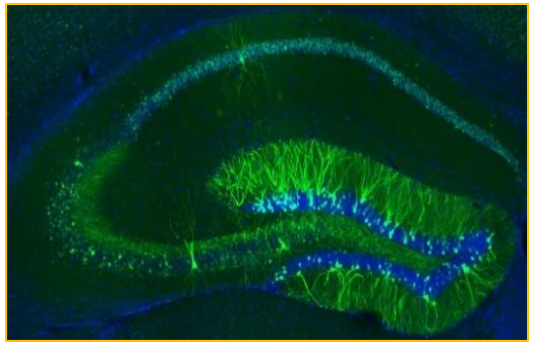
DNA damage in the rat hippocampus cells 1 hour after exposure to ^{78}Kr ion beam

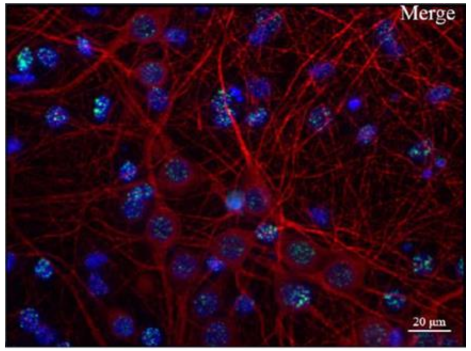










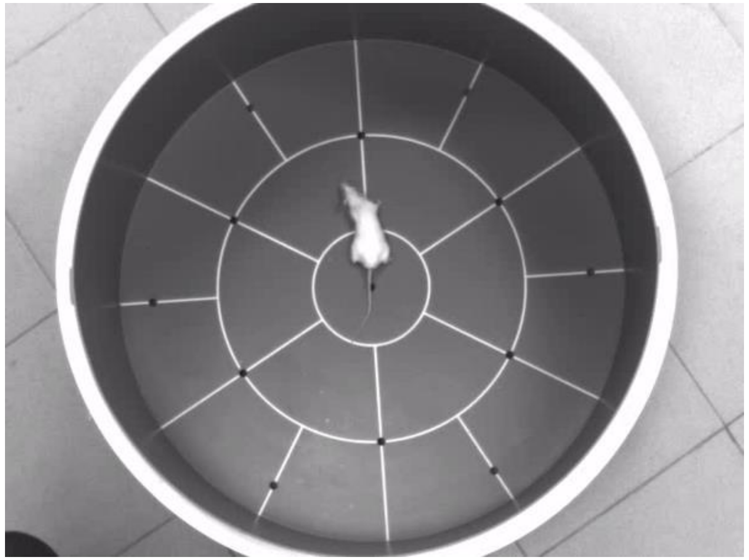


Visualization of cell viability in a hippocampal slice (right) and DNA damage in a hippocampal cell culture (left)

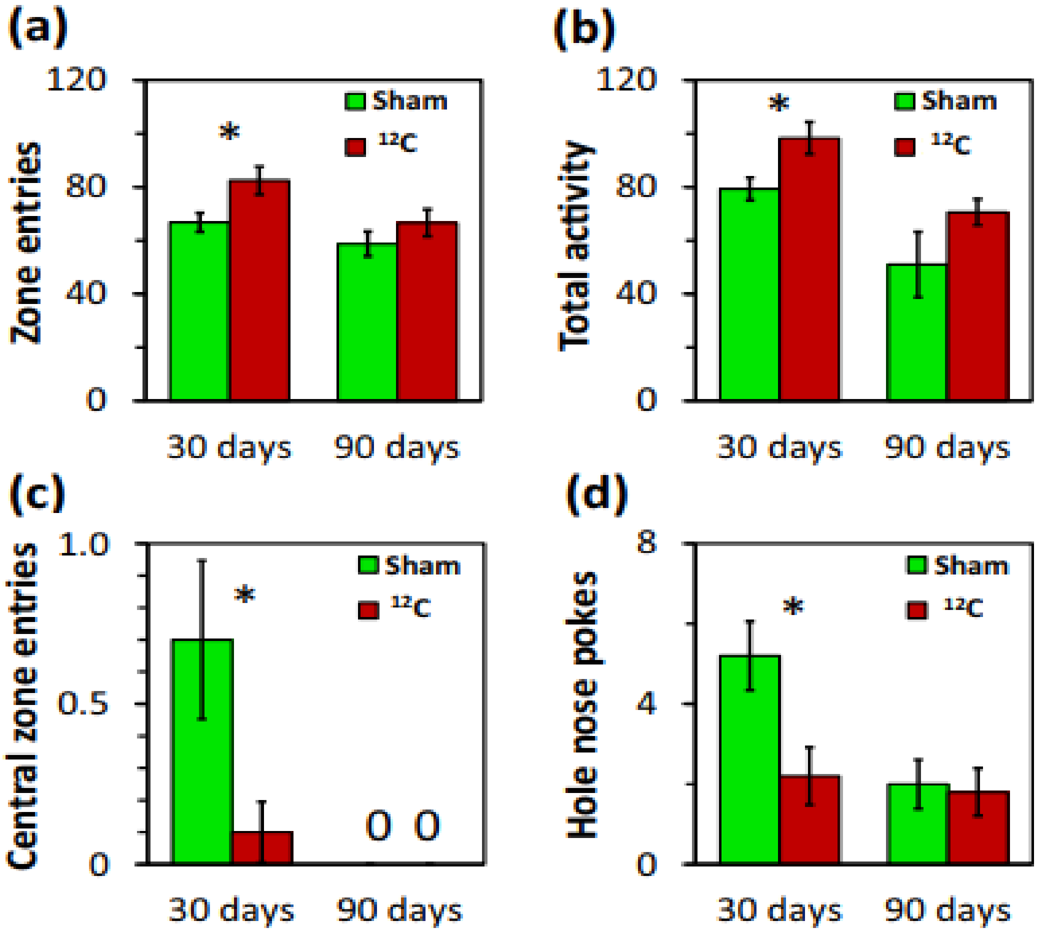
Evaluation of radiation risks for deep space missions

The effect of 1 Gy 500 MeV/u ^{12}C particle radiation exposure on rats

Behavior and emotional status

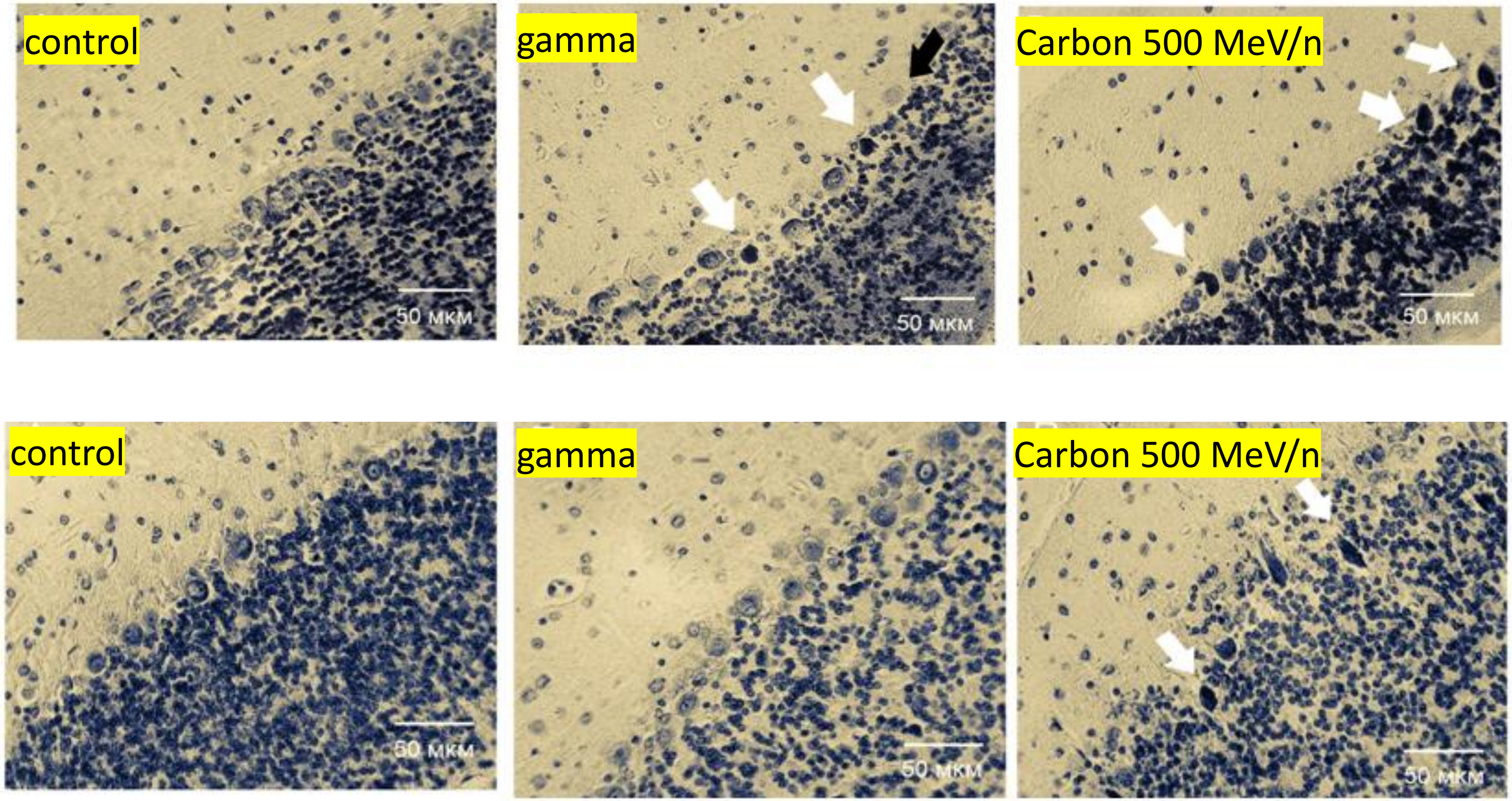


Open field test

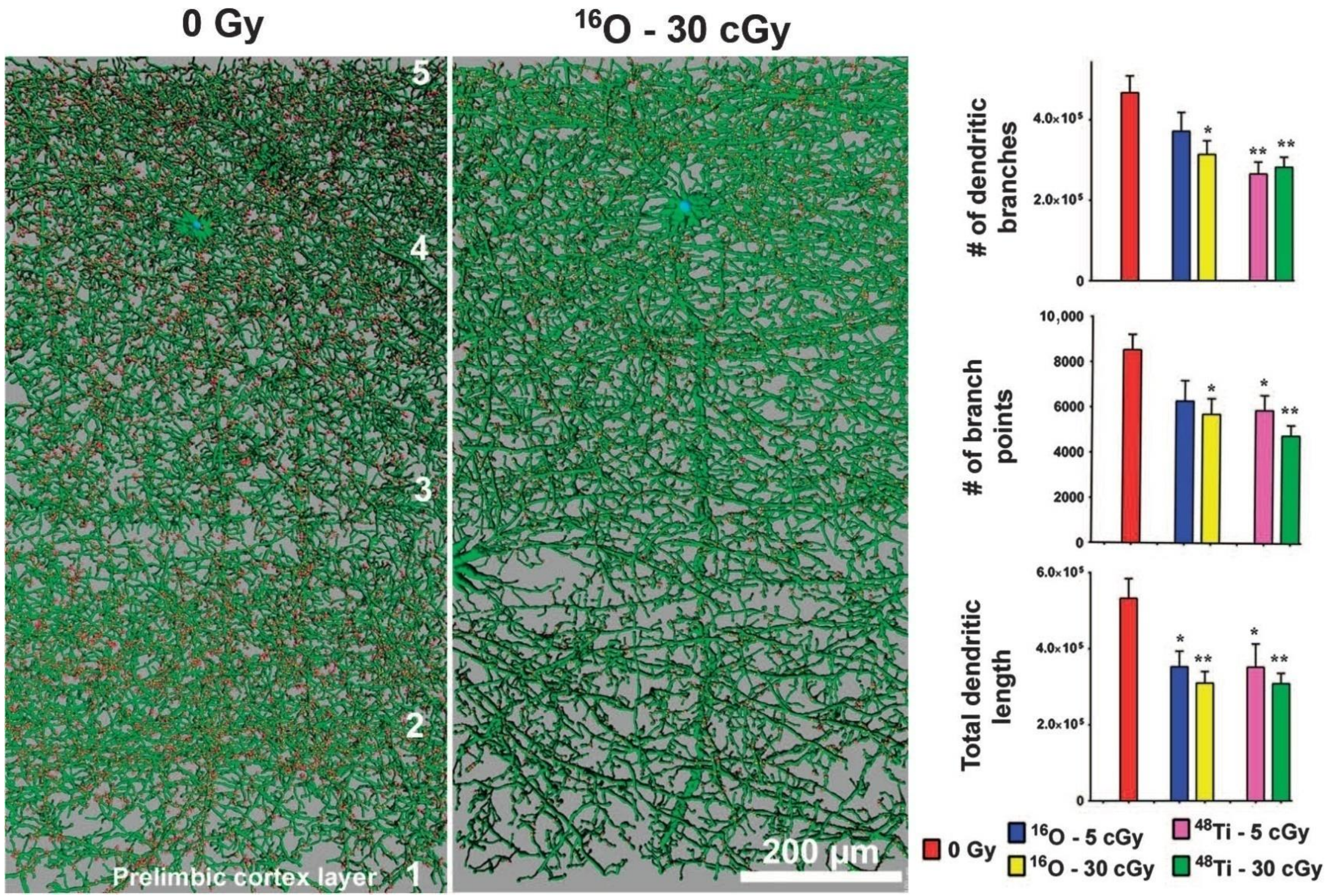


The effect of 1 Gy 500 MeV/u ^{12}C particle radiation exposure on rats

Morphological changes in Purkinje cells in the cerebellar cortex 90 days after irradiation



Degradation of the structure of neuronal dendrites in the prelimbic region 8 weeks after irradiation



Parihar et al. "What happens to your brain on the way to Mars" Sci. Adv. 2015; 1:e1400256

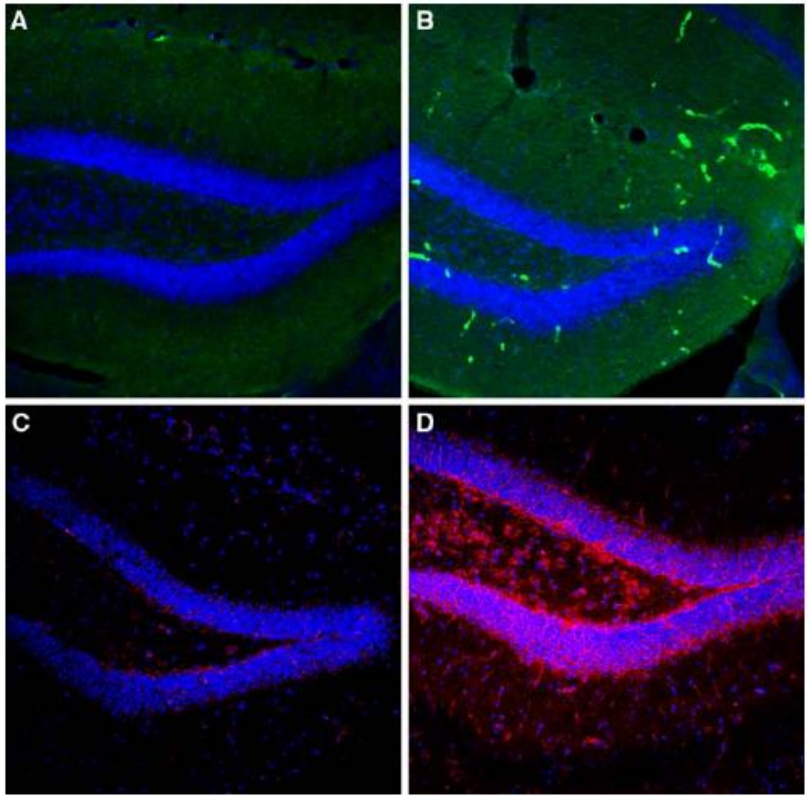
Oxidative stress and inflammation in the mouse hippocampus after ^{56}Fe ion irradiation

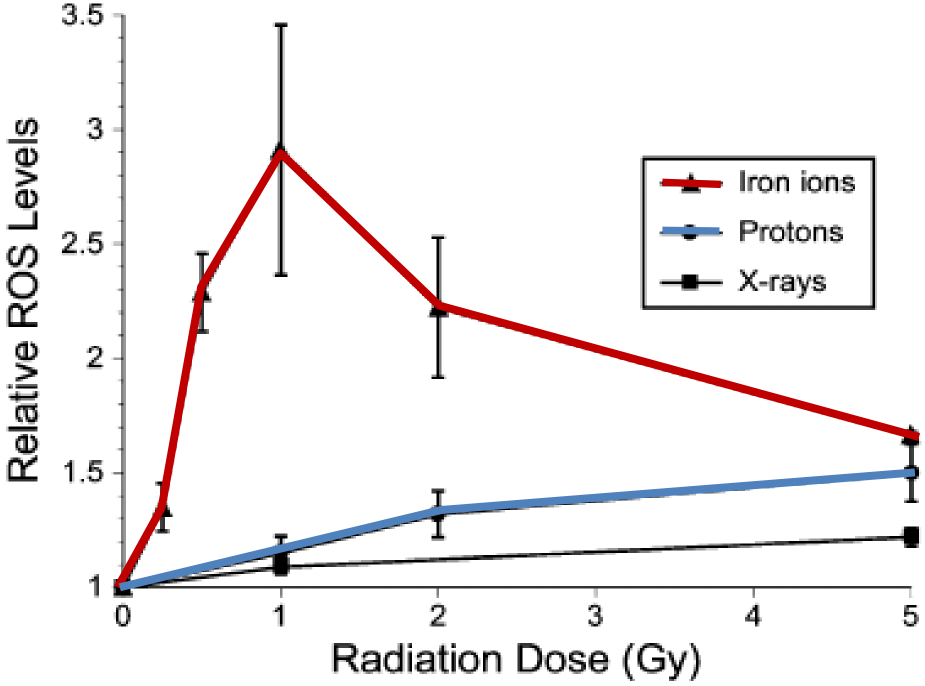
control

3Gy ^{56}Fe 1GeV/u

4-HNE

CCR2





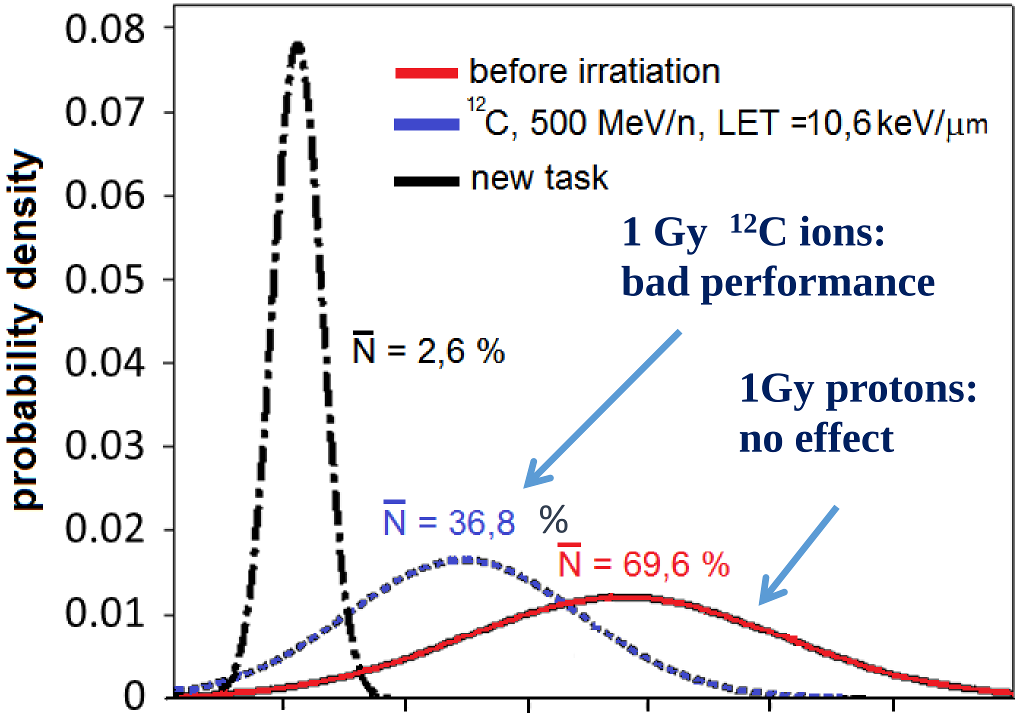
Limoli C.L. et al, Rad. Env. Biophys. 2007

Evaluation of radiation risks for deep space missions

Unique experiments on primates at LRB JINR

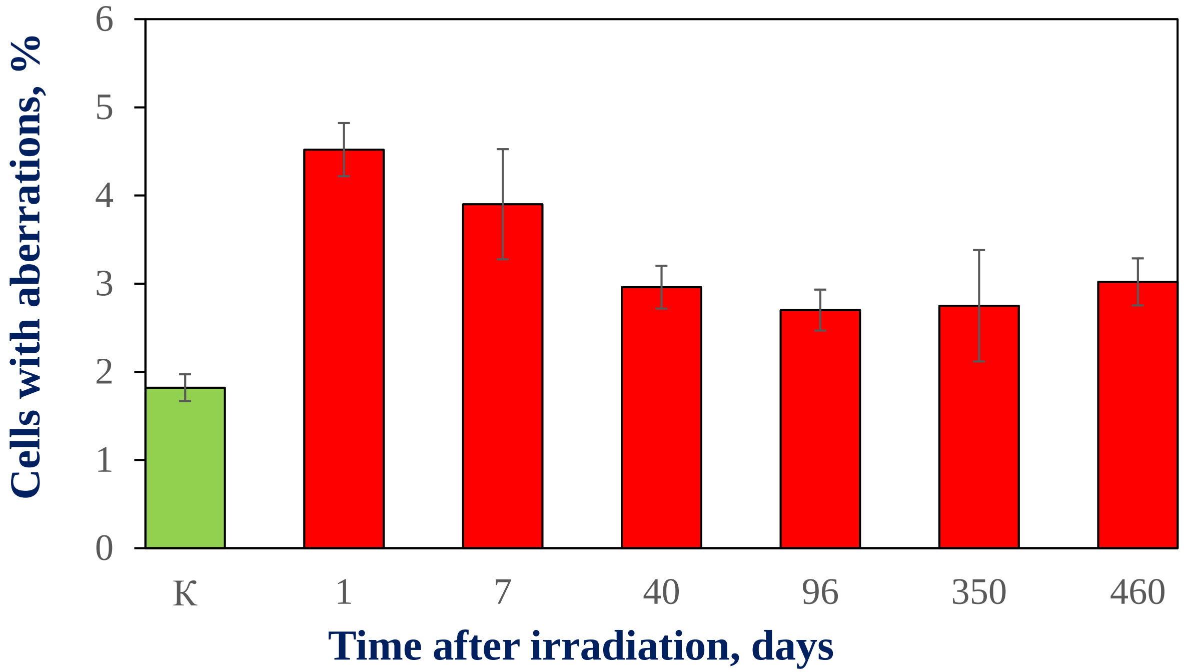
Automated computer system for the simulation of operator activity during the flight

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.



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

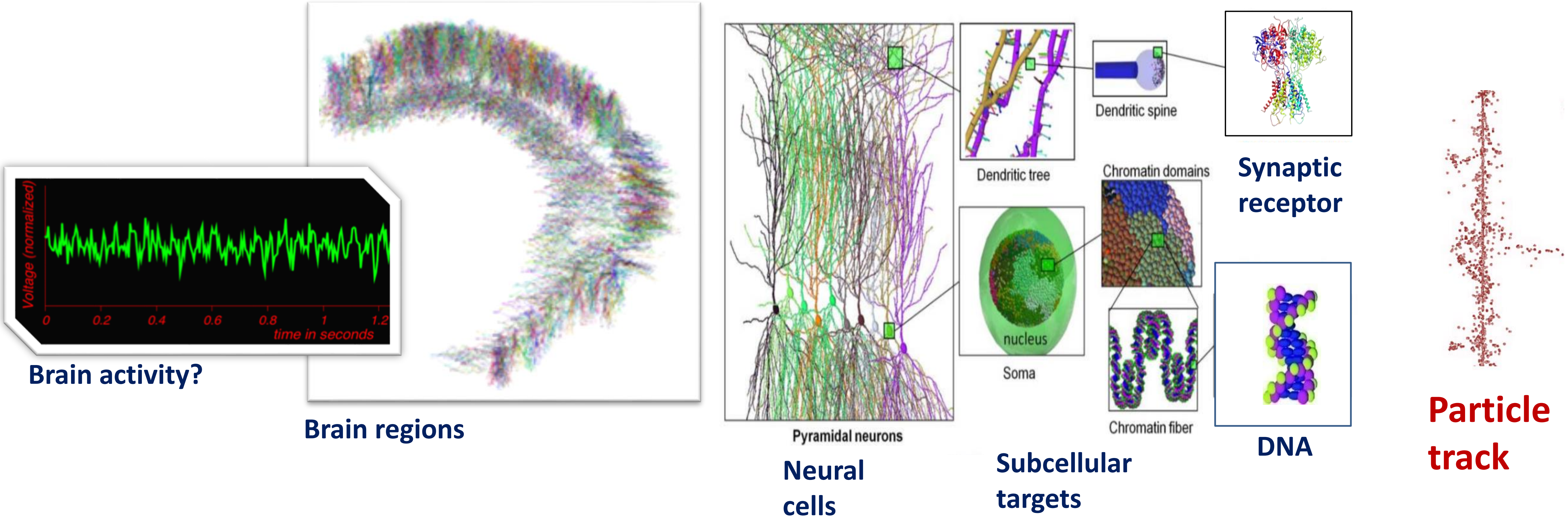
Long-term cytogenetic and behavioral disorders in monkeys after brain irradiation with accelerated heavy ions



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

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

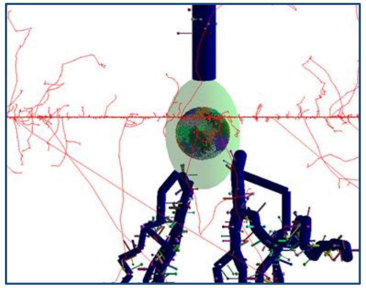
Multiple scale modeling of brain damage

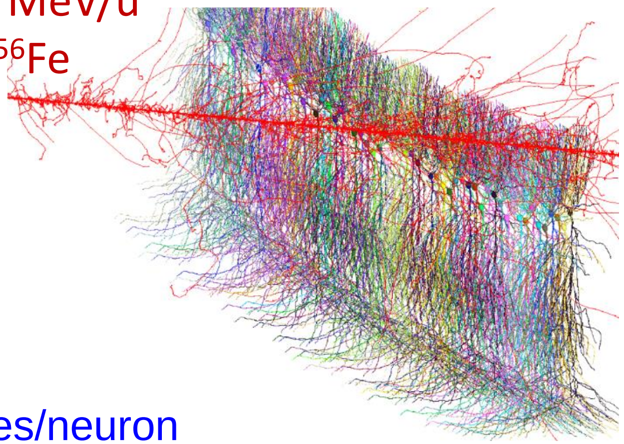


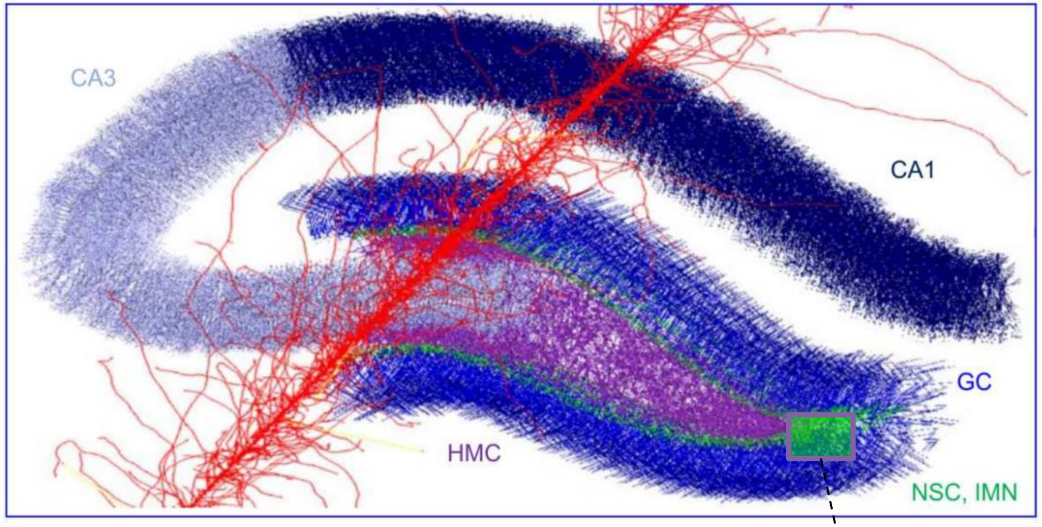
Information processing in brain neural networks ❮ Cell survival and cell population dynamics ❮ Biochemical processes (DNA repair etc) ❮ Molecular dynamics ❮ Physical and chemical events in particle tracks

Multiple scale modeling of brain damage

Simulation of damage to the central nervous system







http://geant4-dna.org/examples/neuron

Computation of neural stem cell survival in the sensitive region of brain - *hippocampus*

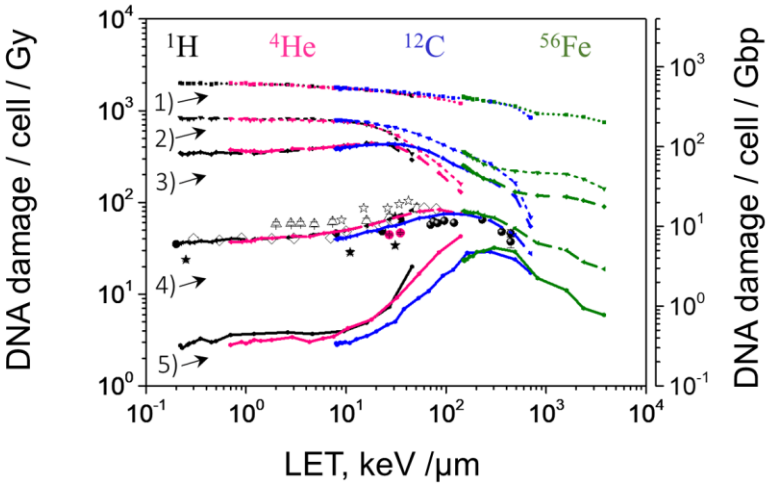
1) base damage (BD)

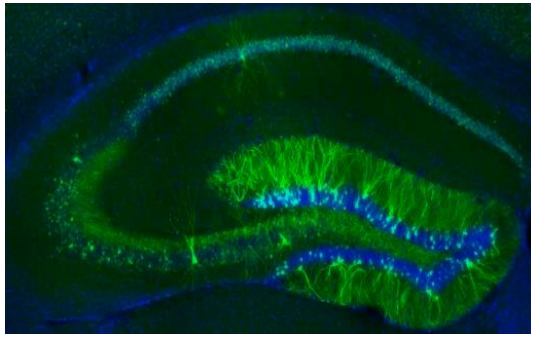
2) single strand breaks (SSB)

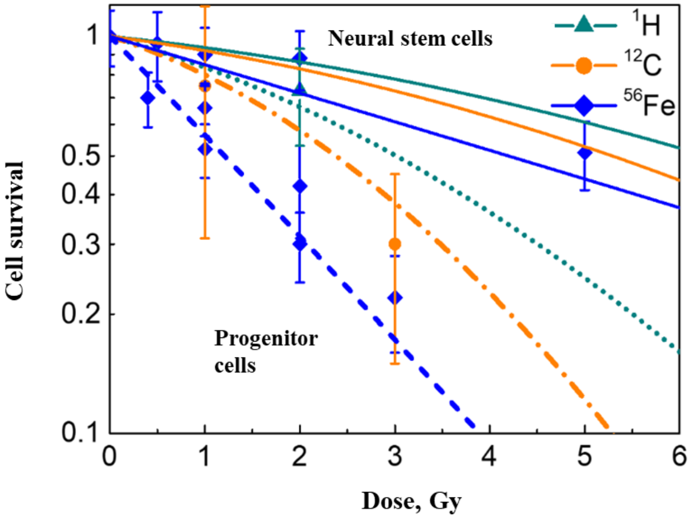
3) Clustered SSB

4) Double strand break (DSB)

5) Clustered DSB



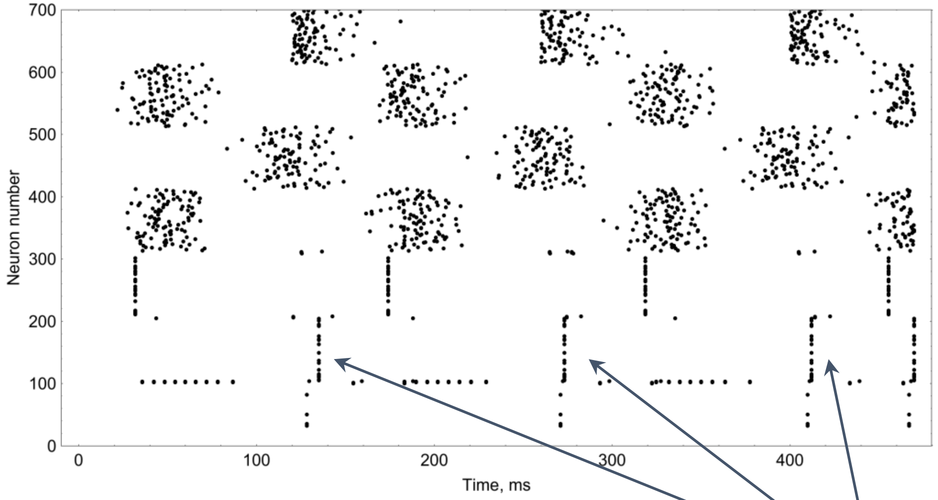




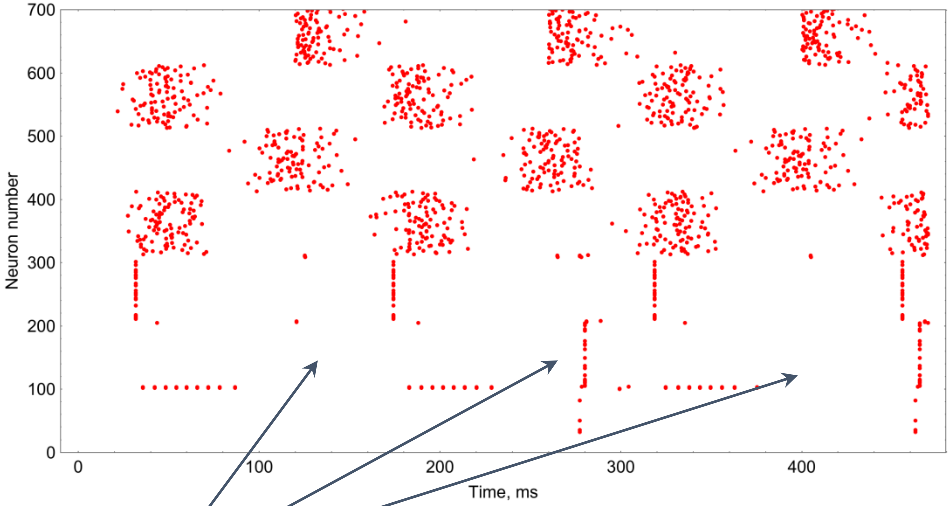
Multiple scale modeling of brain damage

Influence of immature cell loss on information processing

Control

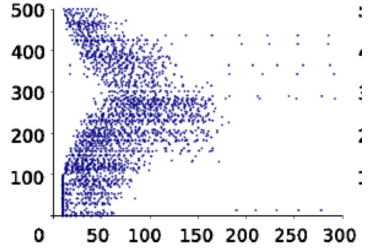


0.8 Gy 600 MeV/u ^{56}Fe

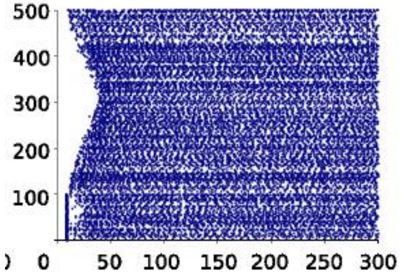


Encoded patterns

10% of newborn GC

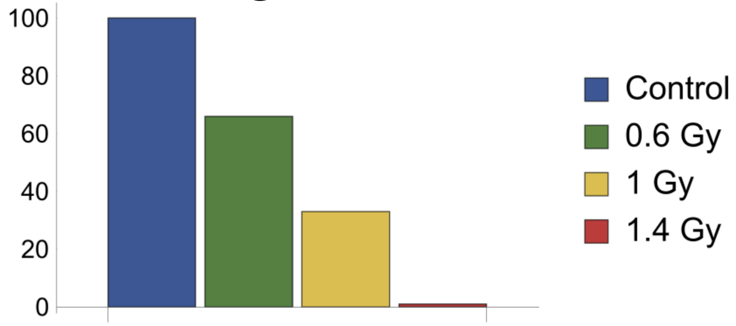


50% of newborn GC

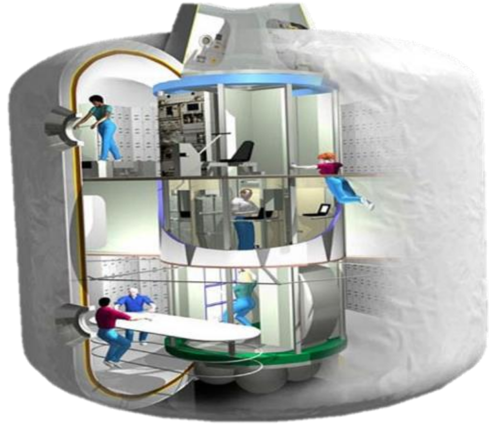


Local effect of immature neuron loss

Encoding and retrieval success, %



How to protect astronauts?!



- **Physical protection: magnetic field, water screen - technical barrier**

- **Radioprotective drugs - none for h charged particles**

- **Hibernation - myth or panacea?**

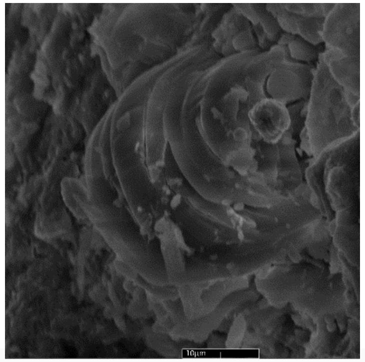
- **Radioresistant astronauts - professional selection or genetic modification?**

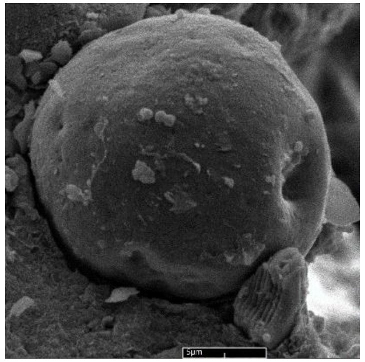
Nuclear planetology instruments and search of water

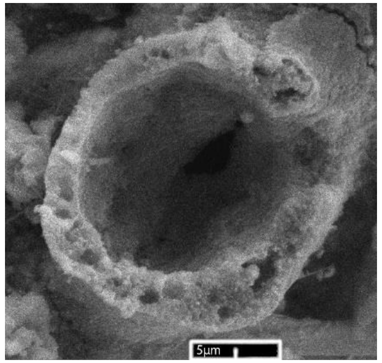
In cooperation with the FLNP and the Space Research Institute (Moscow), the LRB has been participating in the planetary surface research program for more than 15 years in accordance with the Implementation Agreements between the Roscosmos, NASA and ESA.

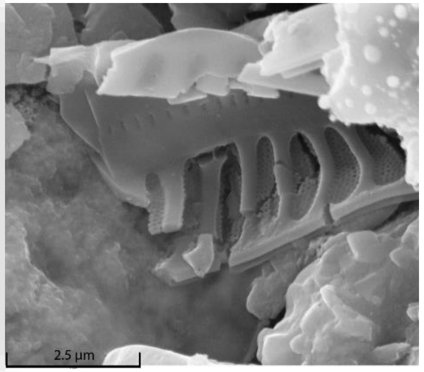
- The High Energy Neutron Detector (HEND) aboard NASA's 2001 Mars Odyssey spacecraft to study the elemental composition of the Martian surface and search for water in orbit. The spacecraft was launched in February 2001.
- The Lunar Exploration Neutron Detector (LEND) aboard NASA's Lunar Reconnaissance Orbiter (LRO) to search for water from low orbit. The spacecraft was launched in June 2009 and the mission was very successful;
- Spectrometer of gamma-rays and neutrons (NS-HEND) of the Russian mission "Phobos-Grunt" to study the distribution of elements on the surface of Phobos. The spacecraft was launched in October 2011, but its mission was not completed.
- BTN-M1, BTM-M2 are designed for the BTN-Neutron experiment to study fast and thermal neutrons aboard the service module within the Russian orbital segment of the International Space Station (ISS).
- The Albedo Neutron Dynamics (DAN) instrument with a pulsed neutron generator aboard NASA's Mars Science Laboratory (Curiosity) rover to search for water directly in the Martian earth (Gail Crater). The rover landed on Mars in the fall of 2012.
- The Gamma Ray and Neutron Spectrometer (MGNS), which will be deployed on board the ESA's BepiColombo mission to Mercury in 2015. The main task is the orbital search for water at the poles of Mercury.
- ADRON-LR is designed to measure the local elemental composition of the lunar surface using active neutron and gamma spectrometry. This is a joint Russian-Indian project "Chandrayan-2".
- Luna Globe, ExoMars (with ESA), NORD (with NASA)

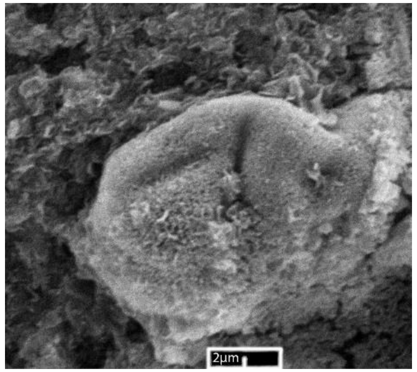
Search for remains of living organisms (microfossils) in meteorites





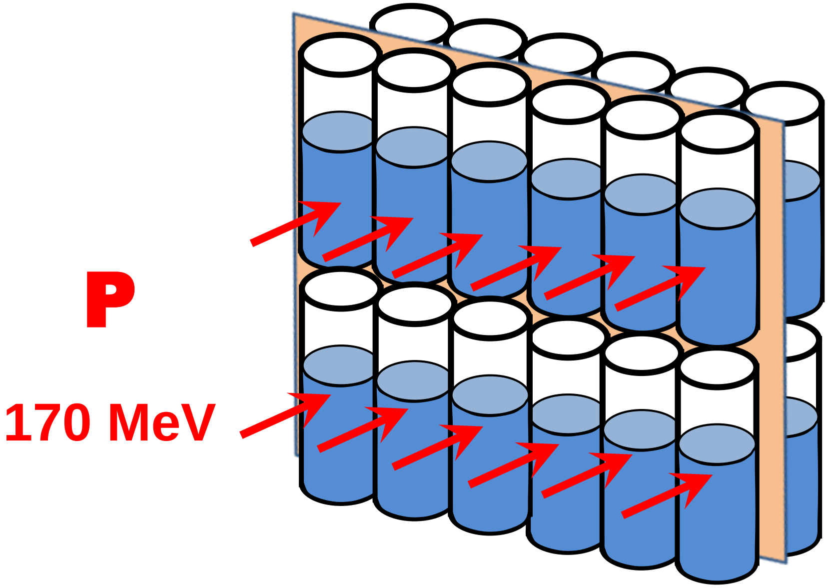


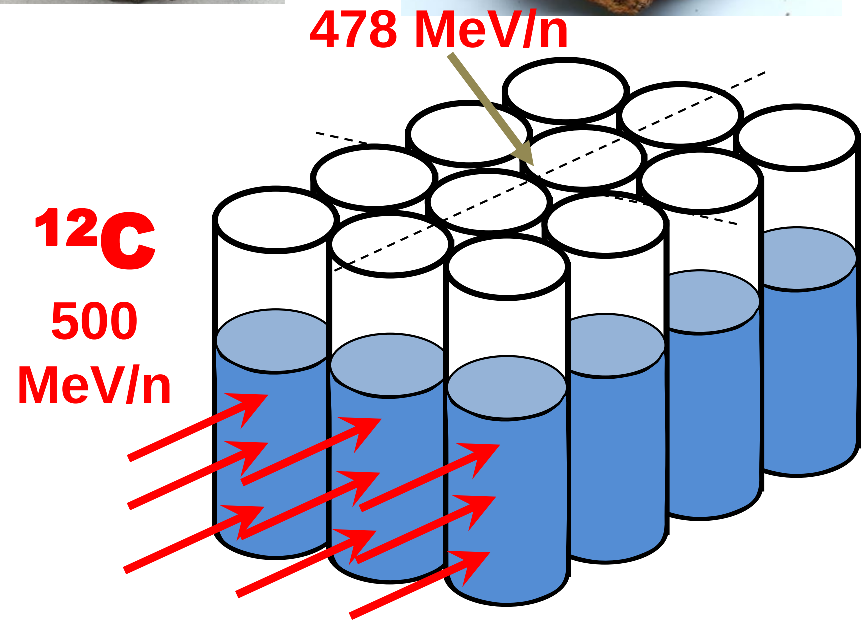




The Orgei meteorite is a unique phenomenon in the abundance and diversity of microfossils of prokaryotes and aquatic eukaryotes, including microalgae, protists, and even algae or fungal spores. The microfossils found are indigenous to the meteorite and not terrestrial biocontaminants. The consistency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

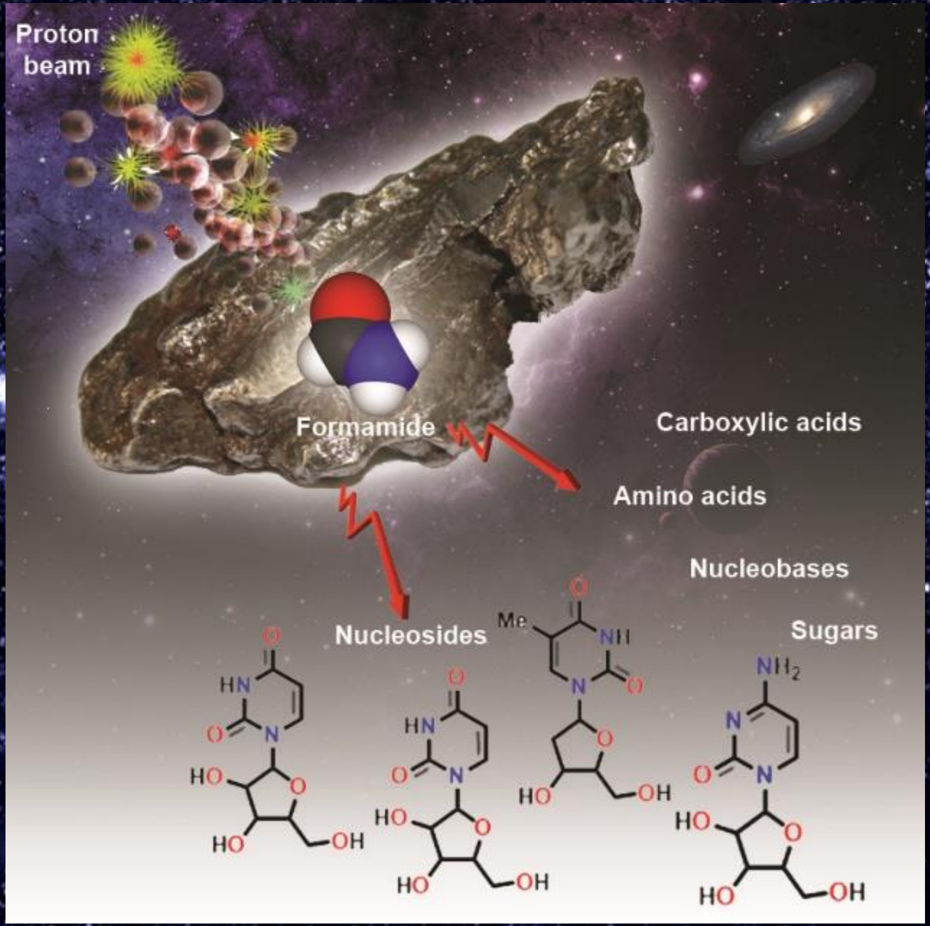
<u>Accelerator experiment</u>: irradiation of formamide in the presence of space matter under the influence of cosmic types of ionizing radiation





Prebiotic chemistry

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

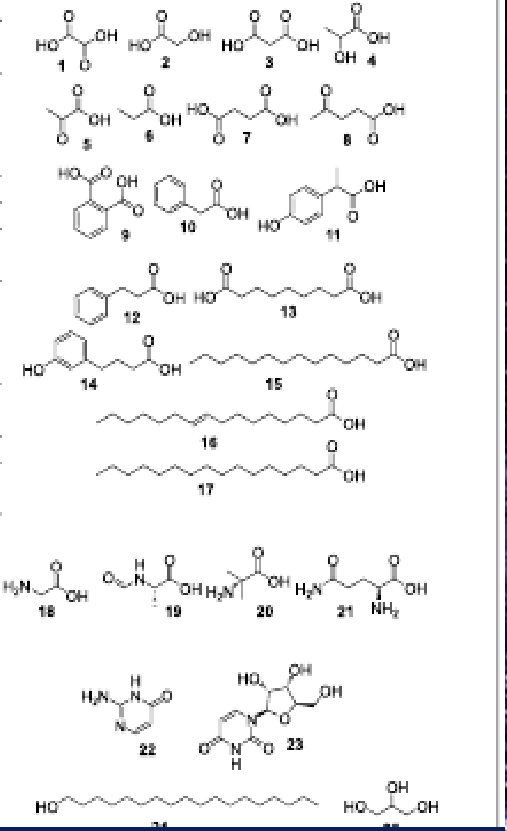
Acids (μg)

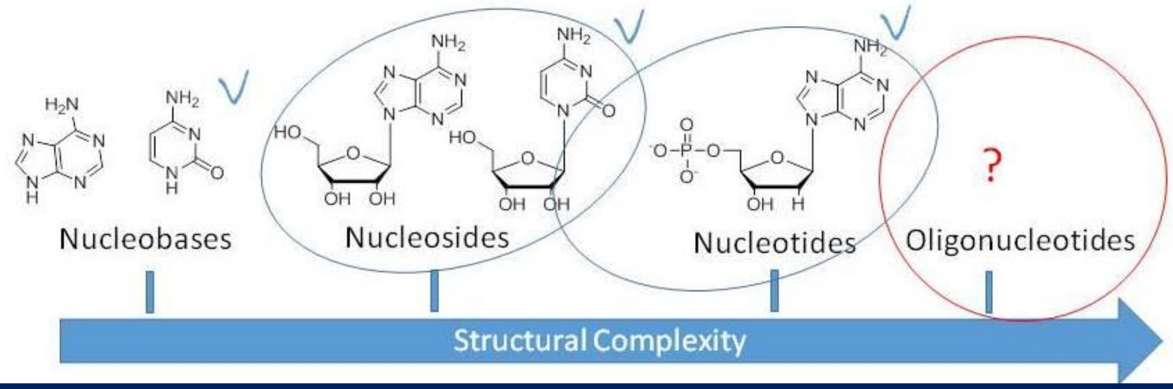
n° atoms C		
2	(1) Oxalic acid	1,93
	(2) Glycolic acid	0,51
3	(3) Malonic acid	3,23
	(4) Lactic acid	5,89
	(5) Pyruvic acid	0,33
	(6) Propionic acid	0,18
4	(7) Succinic acid	0,32
5	(8) 4-oxopentanoic acid	0,58
8	(9) Phthalic acid	2,45
	(10) Benzen acetic acid	121,81
9	(11) 4-hydroxyphenyl propionic acid	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

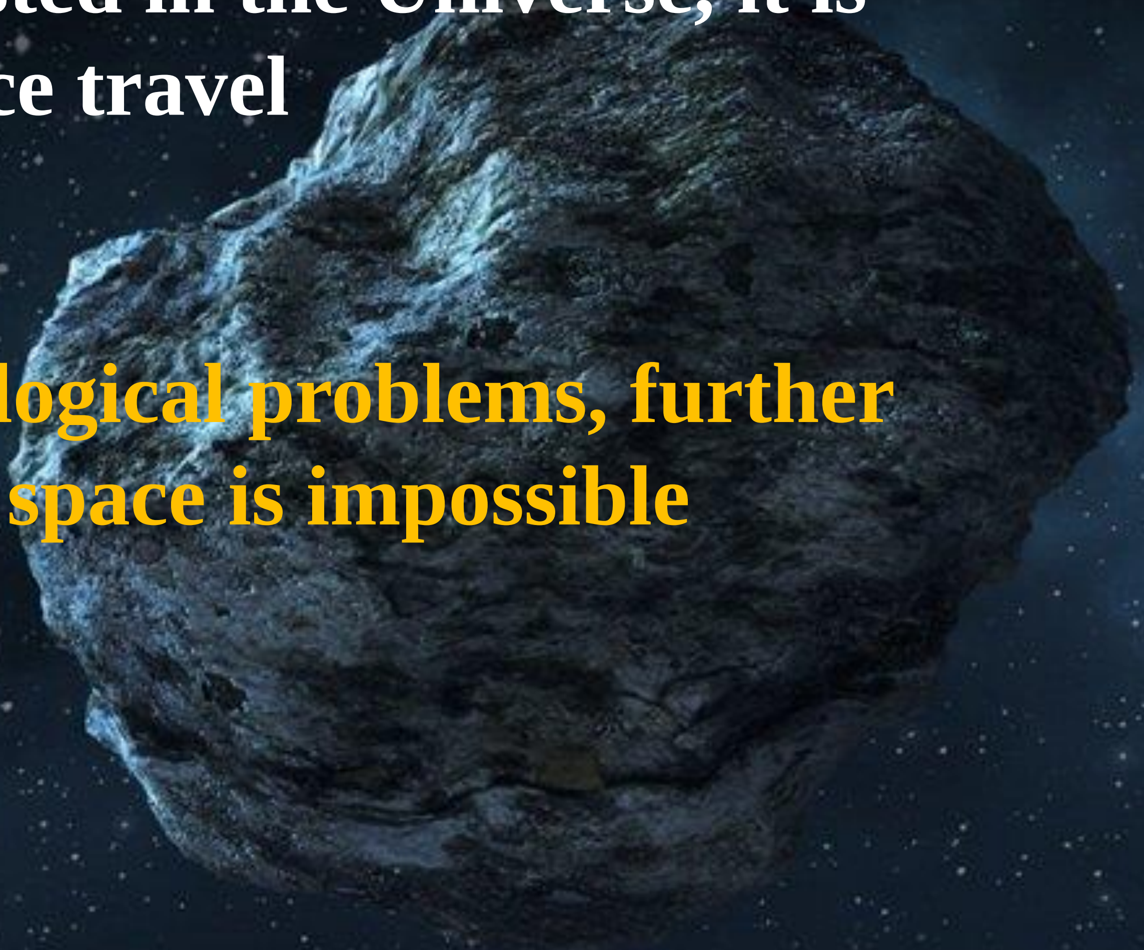
Miscellanea (μg)



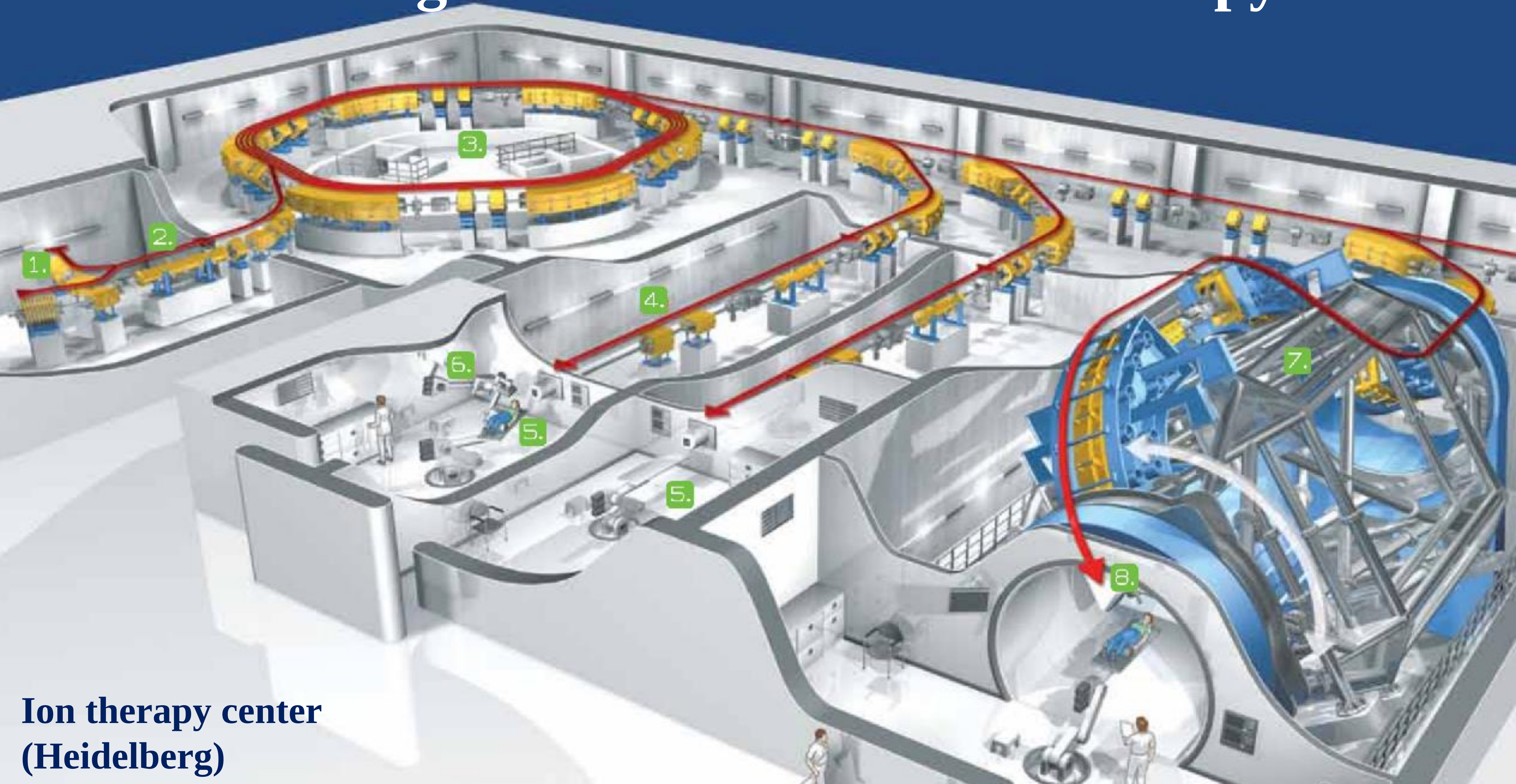


- **The simplest life exists or existed in the Universe, it is capable of enduring long space travel**

- **Without solving key radiobiological problems, further human penetration into deep space is impossible**



Ionizing Radiations in Cancer Therapy



Ion therapy center (Heidelberg)

Ionizing radiations used in radiation medicine

Distant radiation therapy and CT

Conventional RT and CT

- ^{60}Co gamma rays
- Electron linacs
- X-ray tubes

Hadron therapy

- Fast neutrons 6-50 MeV
- Proton therapy 70-250МэВ
- Neutron capture therapy 0.025-1eV
- Ion beam (He,C,O) 250-400 MeV/nucleon

Radionuclide therapy and diagnostics

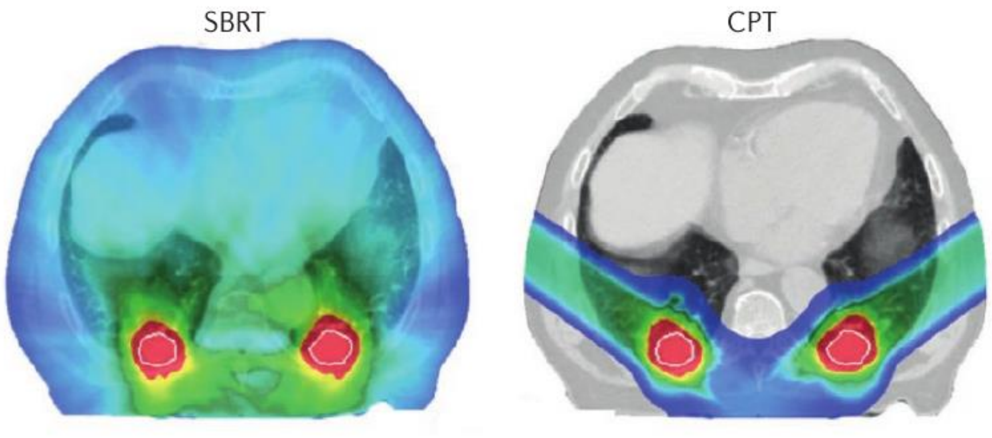
decay products:

- Gamma rays and electrons (beta-emitters)
- Auger electrons
- Alpha particles

Strategy of Radiation Therapy of Cancer

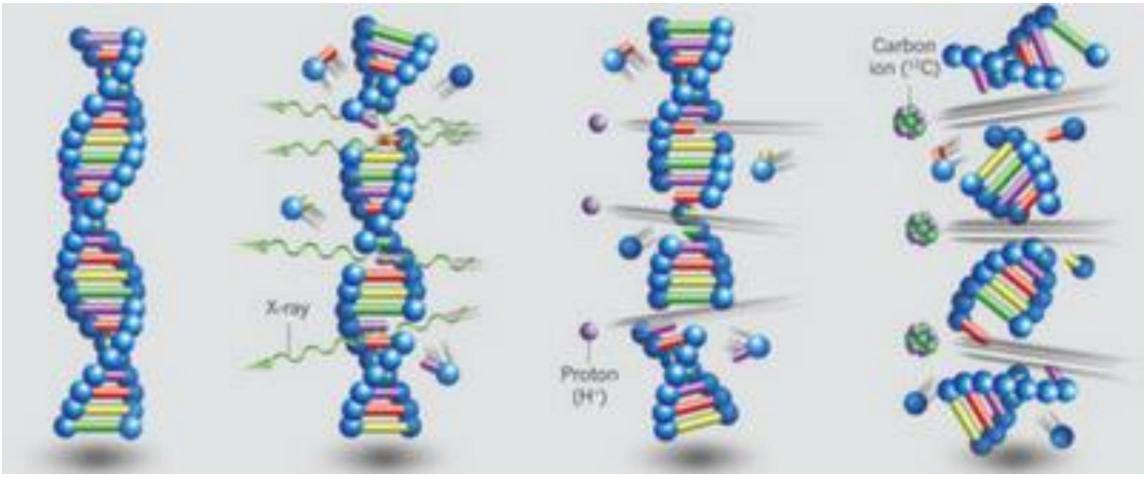
I. Conformal dose delivery

Minimize damage to healthy tissue



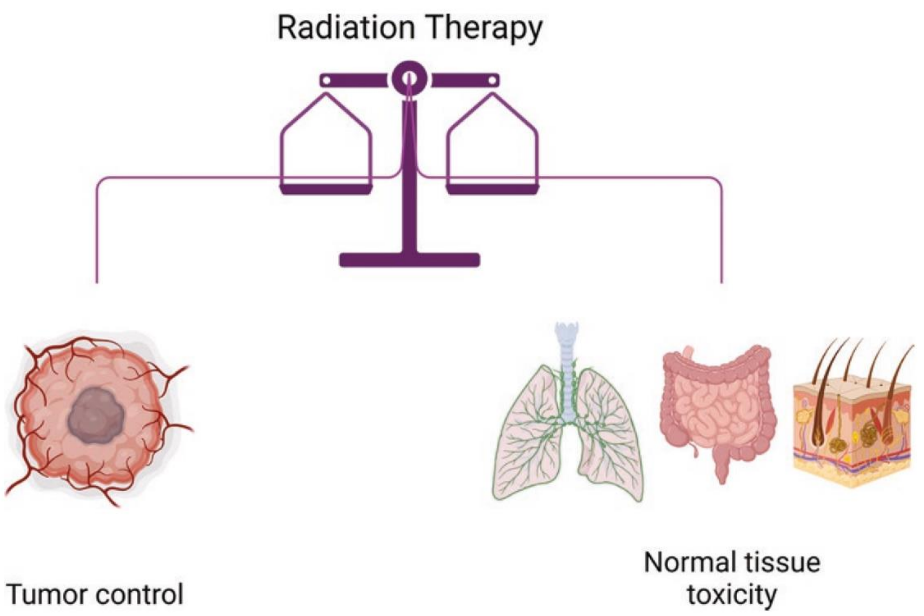
II. Biological efficiency of radiation

Maximize biological damage in tumor cells

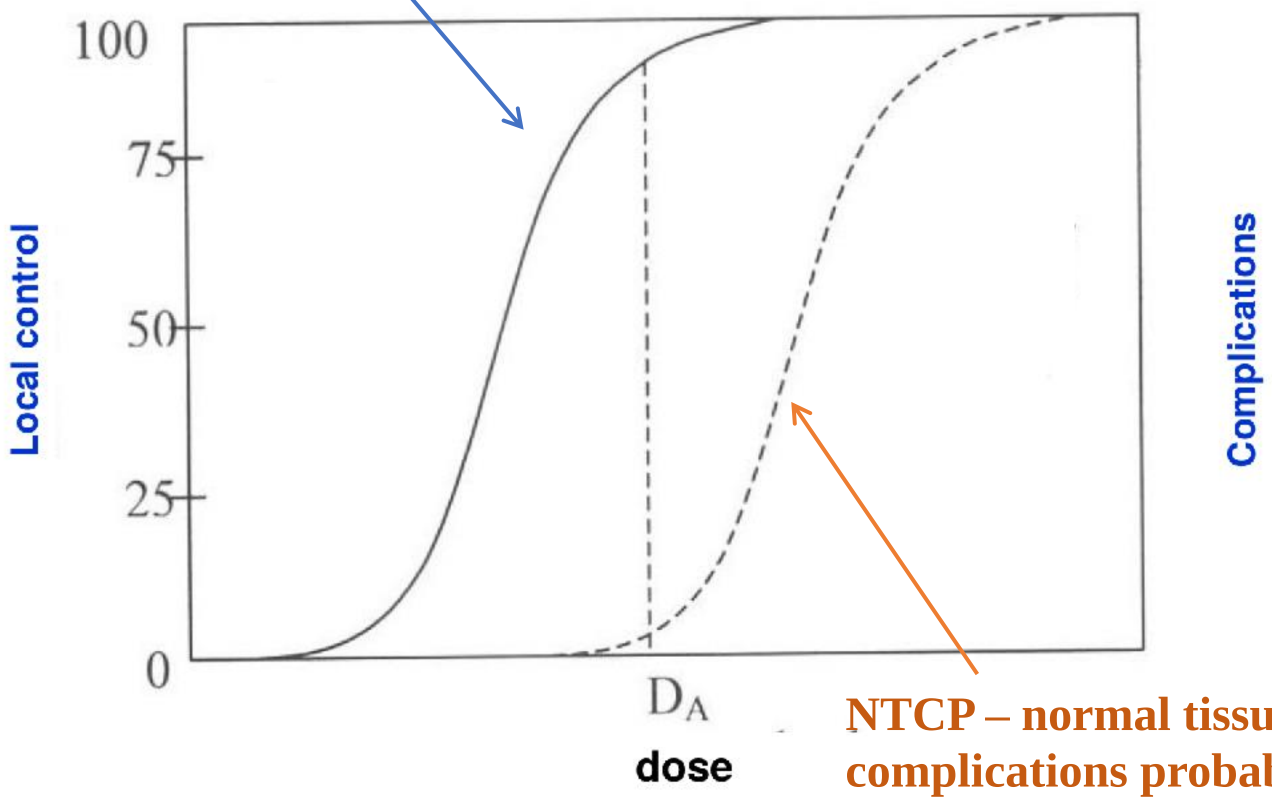


X-ray	protons	heavy ions
+	++	+++

Treatment planning



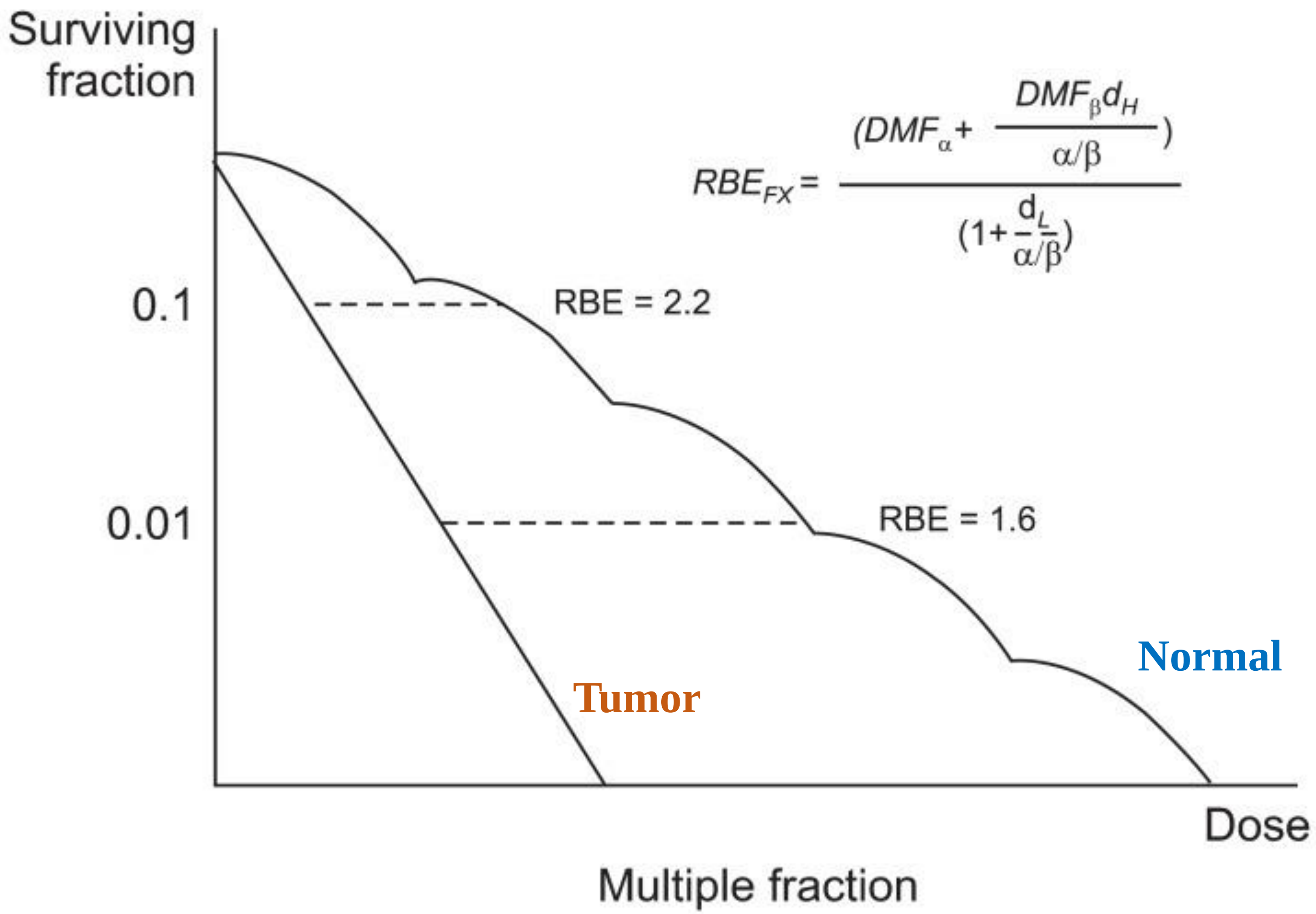
TCP – tumor control probability (%)



NTCP – normal tissue complications probability (%)

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

Treatment planning

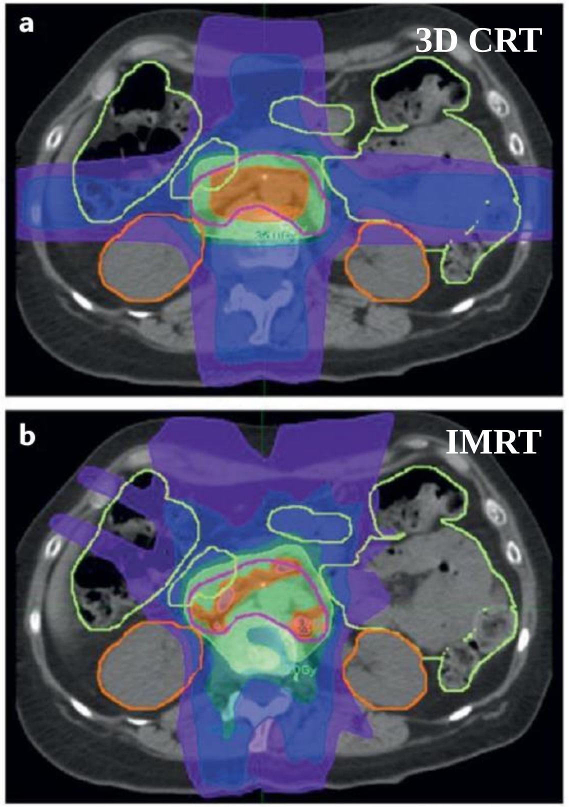


I. Dose delivery: Current status and new trends

1. Distant radiation therapy (X-rays and gamma-rays)

Modern technologies of photon radiation therapy:

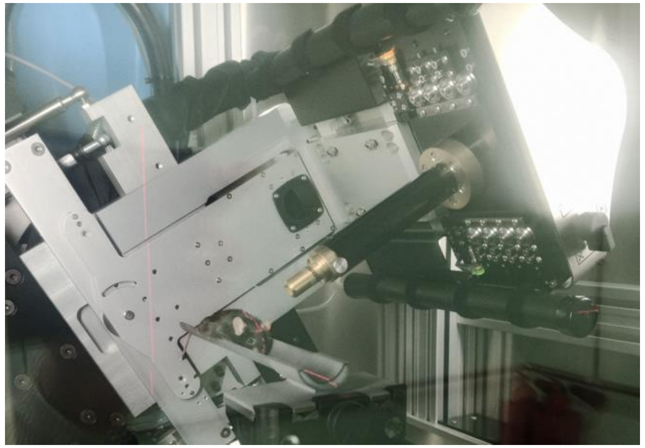
1) conventional radiation therapy (2D RT);
2) conformal radiotherapy (3D CRT) :
    a) stereotactic RT (SRT);
    b) stereotactic radiosurgery (SRS);
    c) intensity modulated RT (IMRT);
    d) RT with dynamic dose rate intensity modulation (RapidArc);
    e) image-guided RT (IGRT).



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

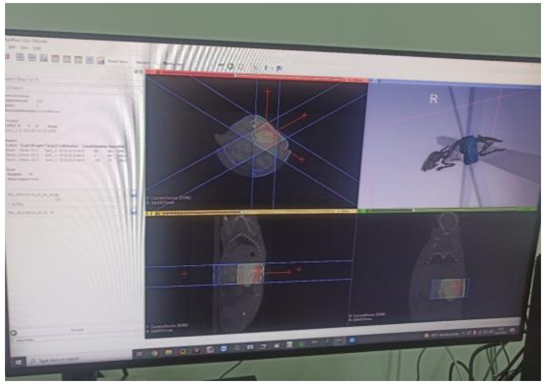
SARRP (Small Animal Radiation Research Platform)

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



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

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



Experiments on mice tumor irradiation at SARRP

I. Dose delivery: Current status and new trends

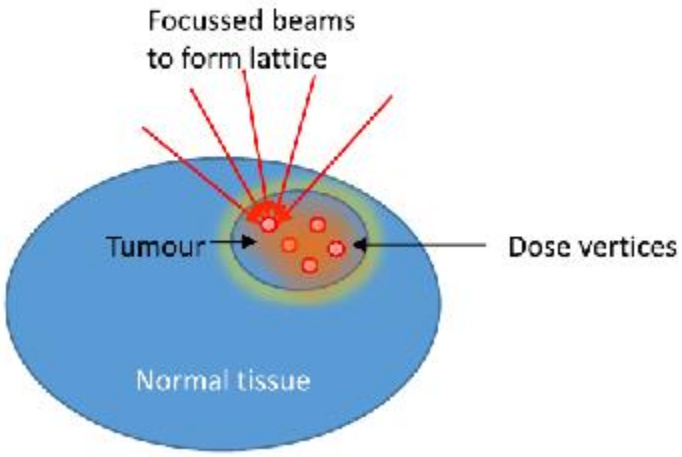
1. Distant radiation therapy (X-rays and gamma-rays)

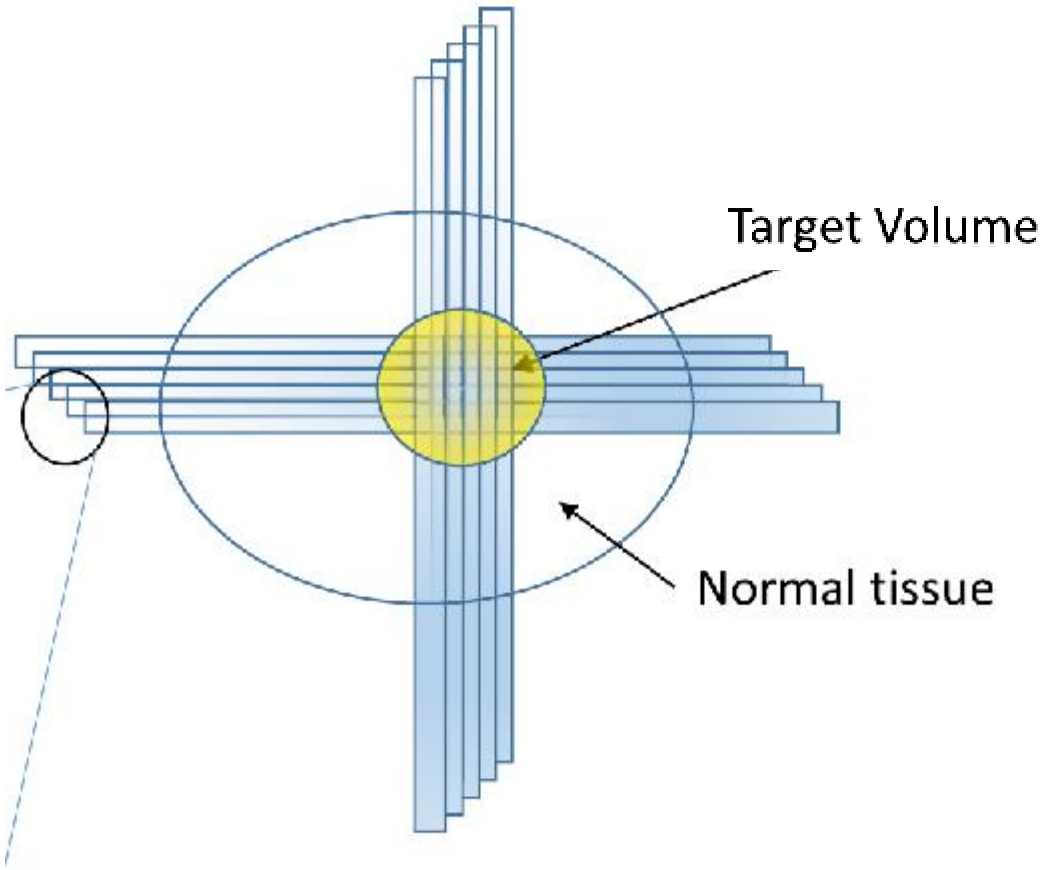
Modern technologies of photon radiation therapy:

3) GRID, mini-beam, micro-beam RT (MBRT)

Beam spot sizes:

0.5-2cm, 0.5-1 mm, 25-100 μm

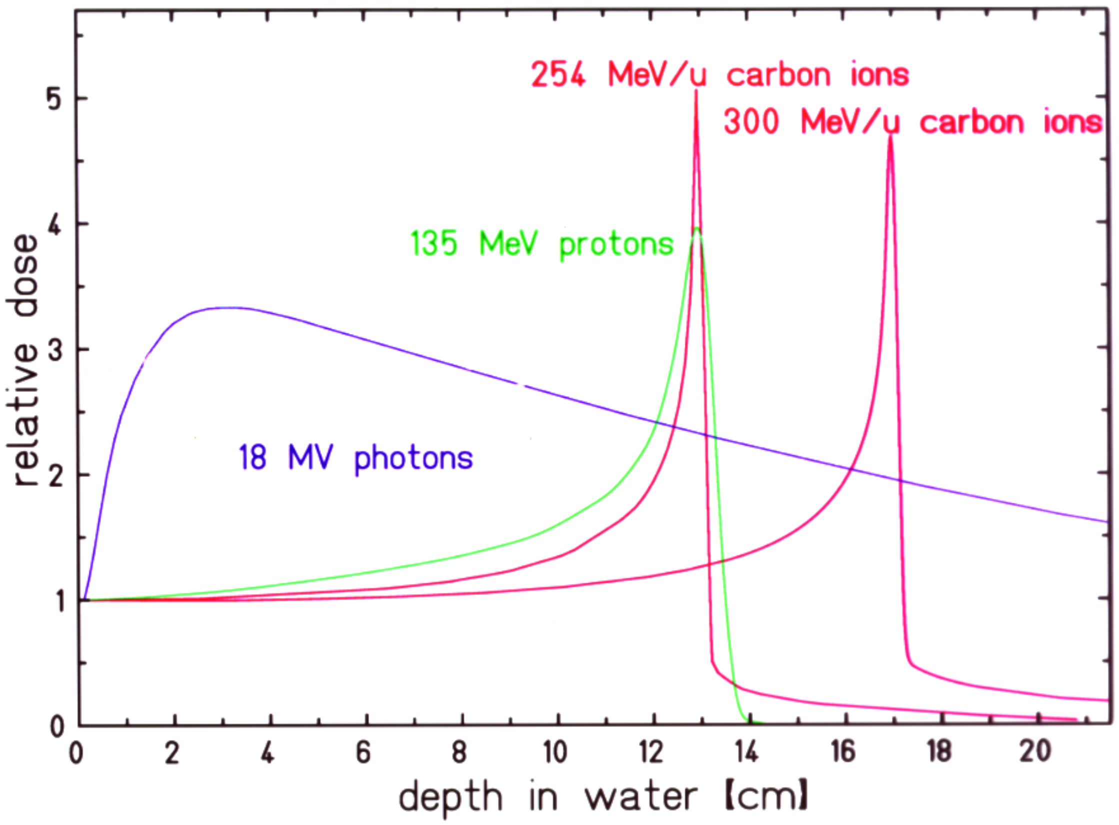




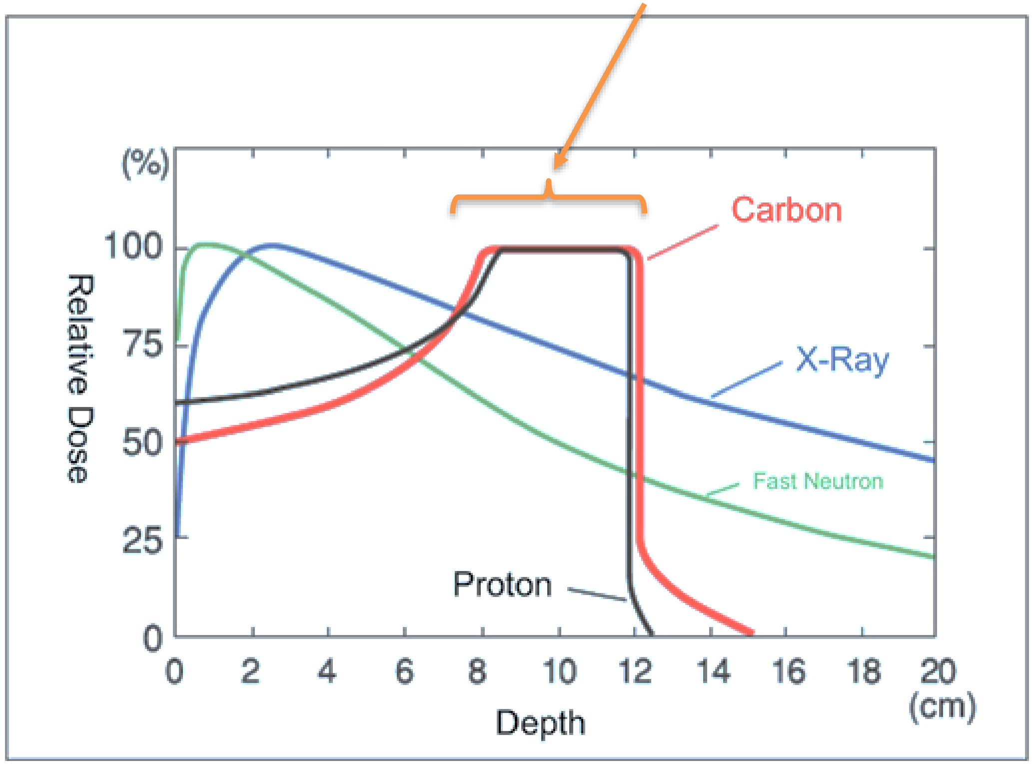
H Fukunaga et al, Clinical.Oncology 3 (2021) 705

I. Dose delivery: Current status and new trends

2. Protons and accelerated heavy ions



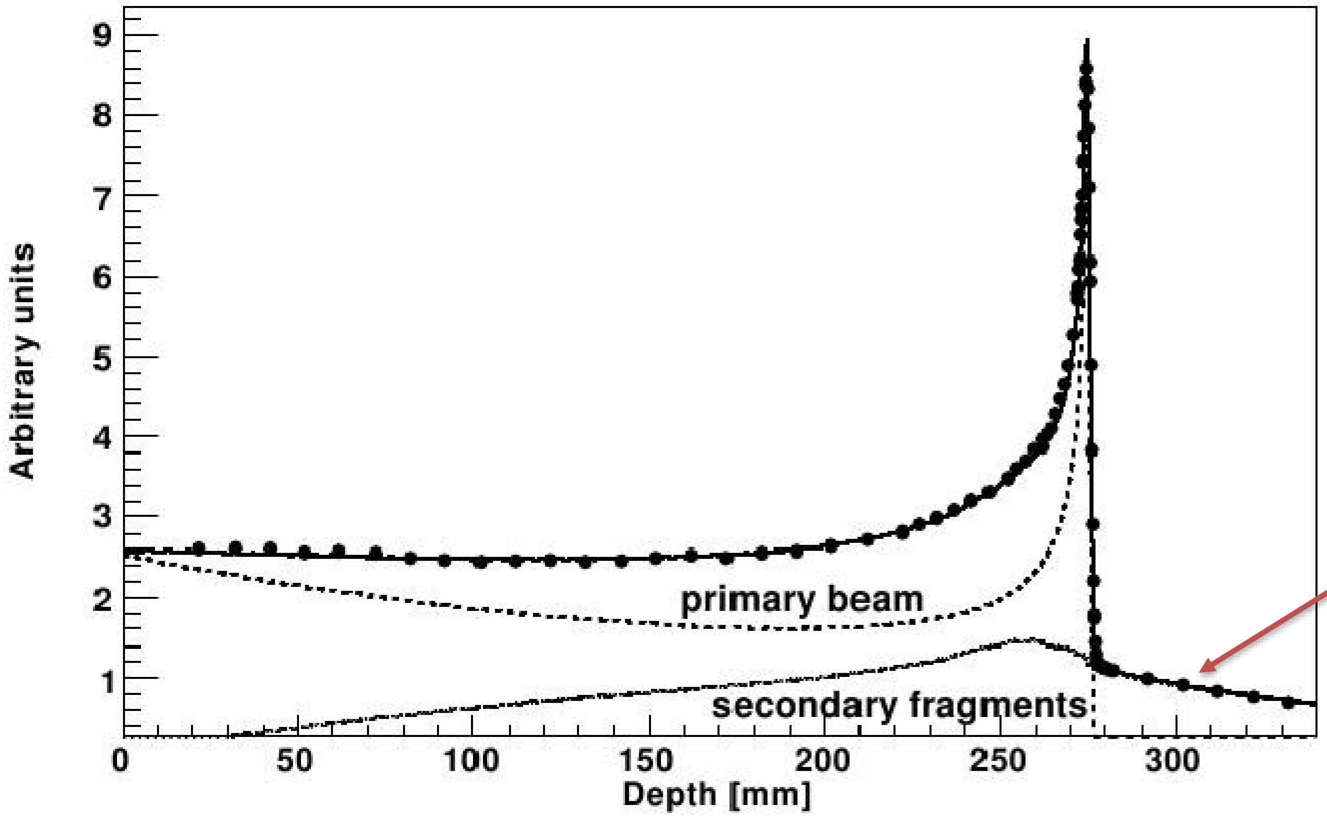
SOBP – spread our Bragg peak



I. Dose delivery: Current status and new trends

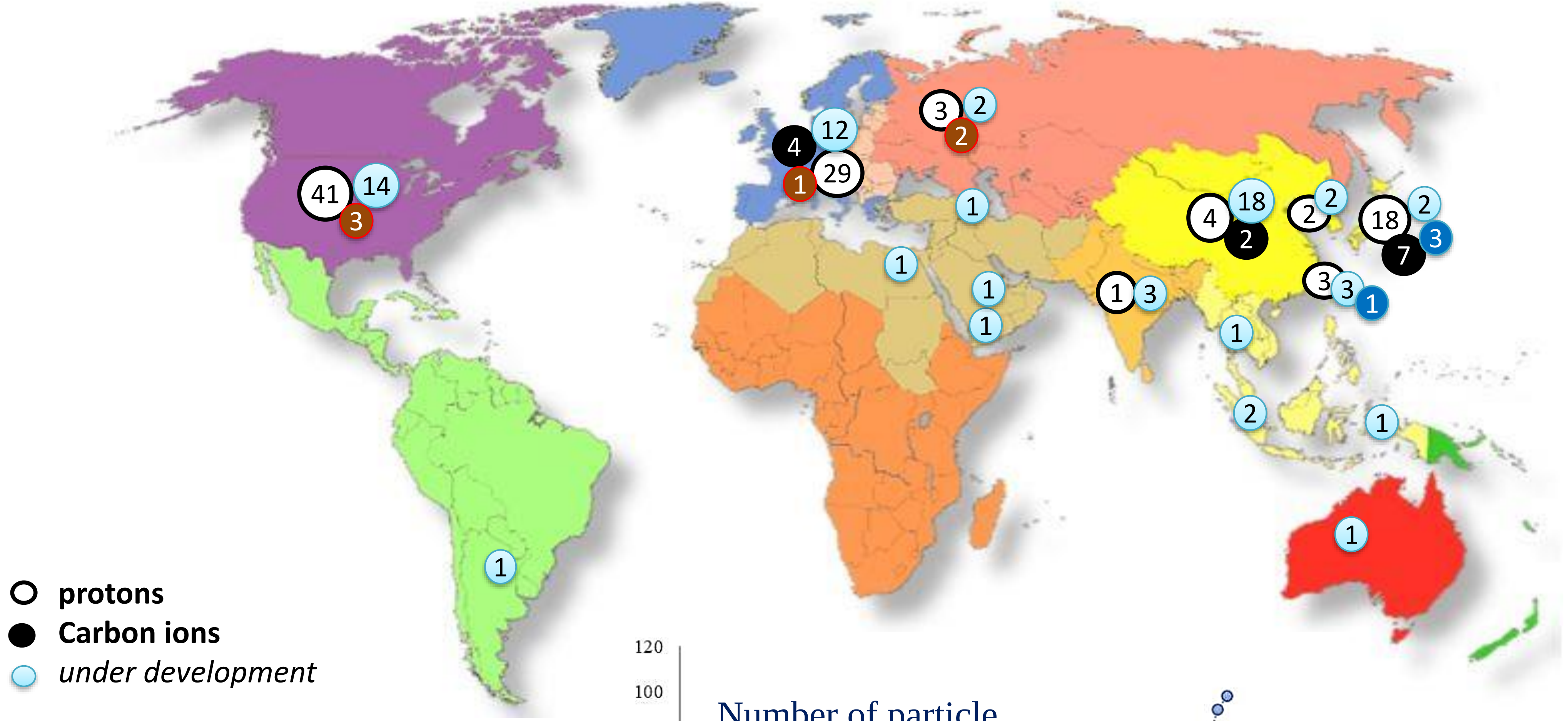
2. Protons and accelerated heavy ions

400 MeV/n C ion

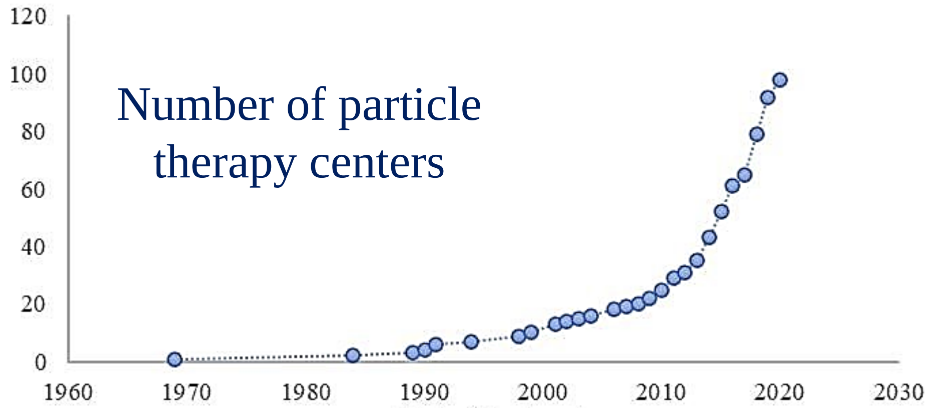


Very high LET and RBE

Development of particle therapy centers

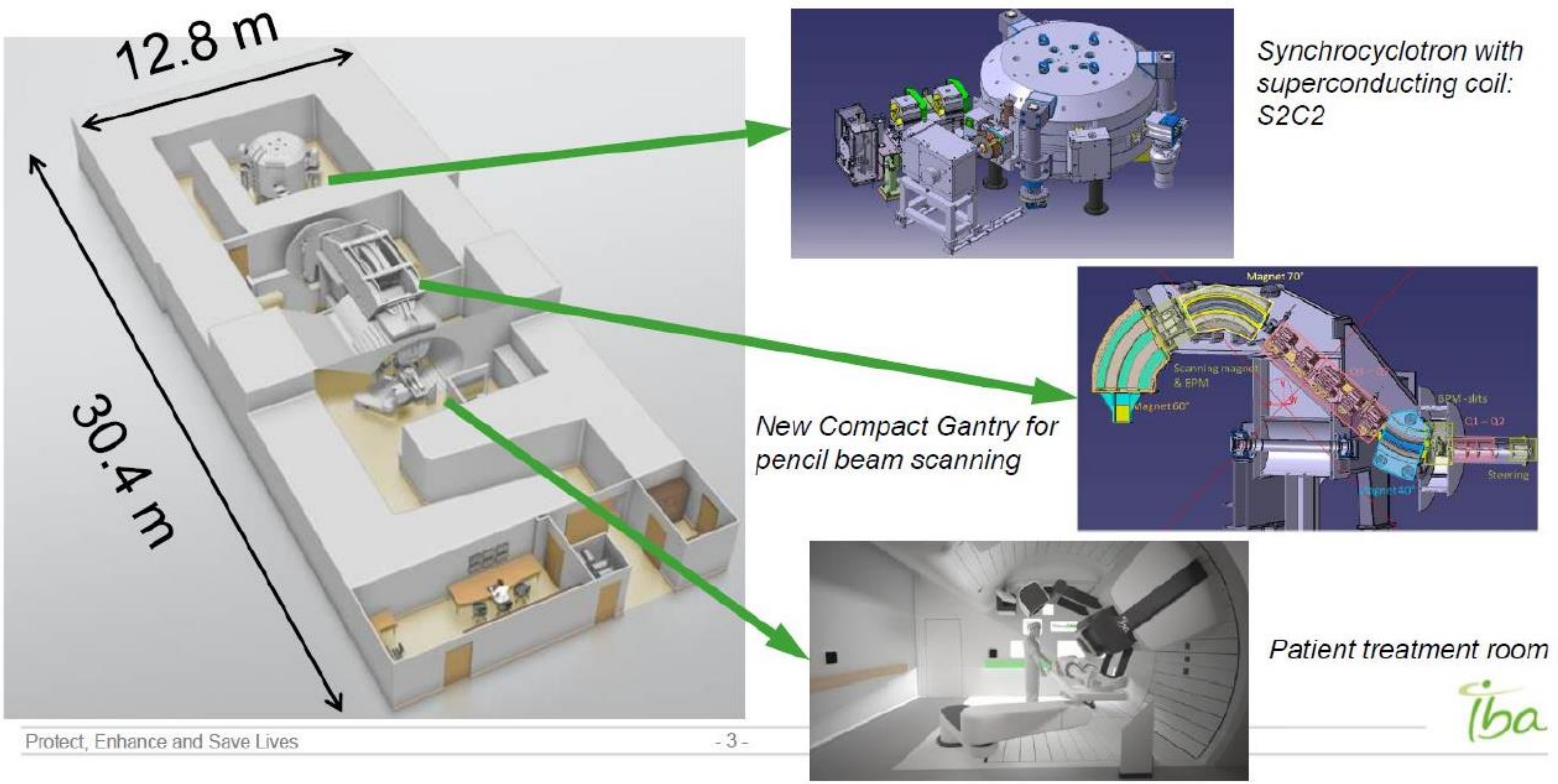


https://www.ptcog.ch/

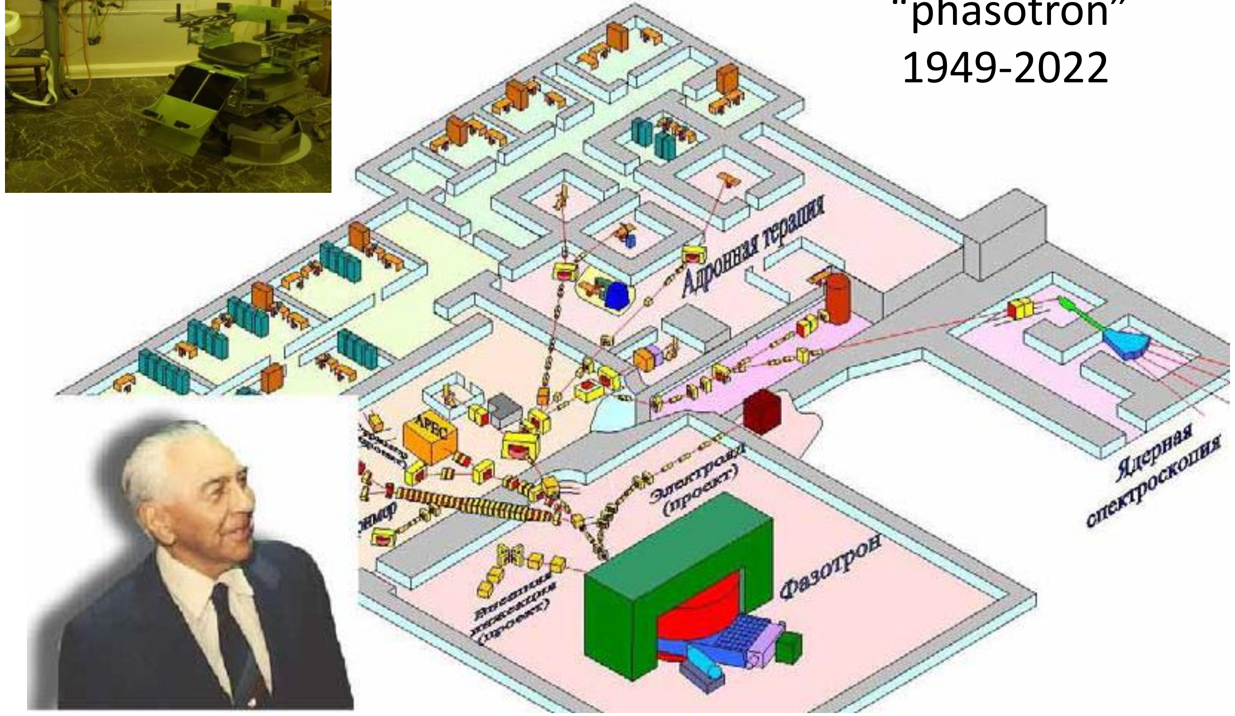


I. Dose delivery: Current status and new trends

S2C2 synchrocyclotron with single gantry room (Proteus One)

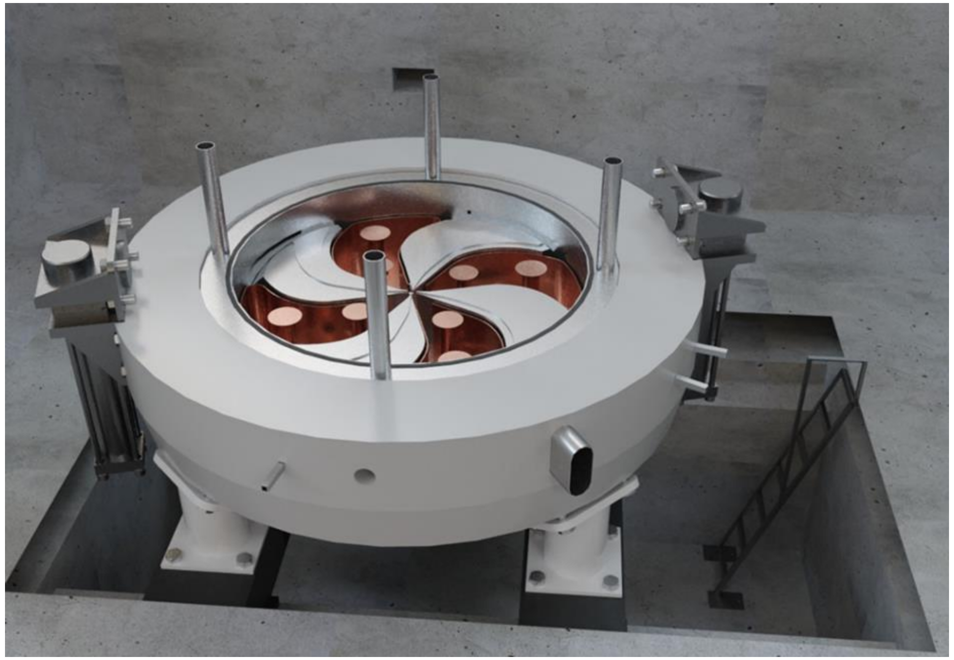


Proton therapy complex of JINR: past and future



JINR Proton therapy center at Dzhelepov Laboratory of Nuclear Problems

First proton center in USSR, 1967
First 3D conformal treatment technique
More than 1300 patients treated (tumors of head and neck)



New superconducting medical proton cyclotron MSC 230:

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

Proton therapy in Russia

МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ РОССИЙСКОЙ ФЕДЕРАЦИИ

ФГБУ «НМИЦ радиологии» Минздрава России

MRRC (Obninsk), Ministry of Health

“Prometeus” proton synchrotron

Fixed beam, chair for patient

МИБС МЕДИЦИНСКИЙ ИНСТИТУТ имени БЕРЕЗИНА СЕРГЕЯ

Commercial proton therapy center (S.Petersburg)

Varian ProBeam cyclotron, gantry cabin

ФМБА России

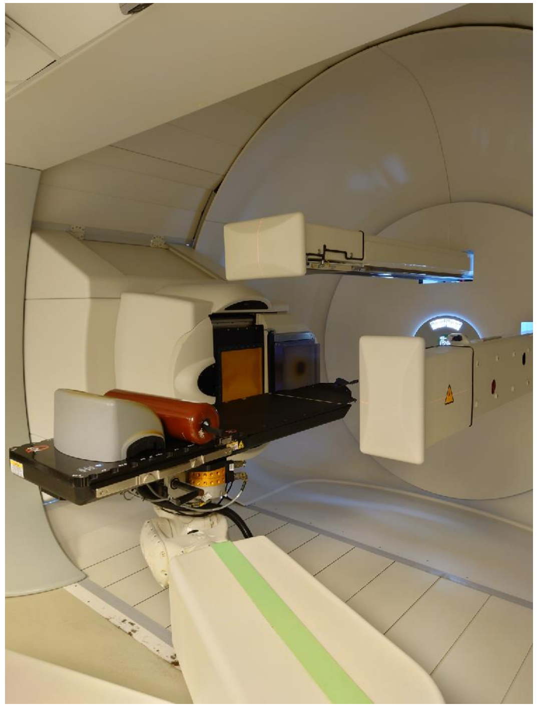
ФНКЦРиО

ФЕДЕРАЛЬНЫЙ НАУЧНО-КЛИНИЧЕСКИЙ ЦЕНТР МЕДИЦИНСКОЙ РАДИОЛОГИИ И ОНКОЛОГИИ

Federal Medical Biological Agency (Dimitrovgrad)

C235-V3 cyclotron (IBA + JINR)

2 gantry, 4 cabin

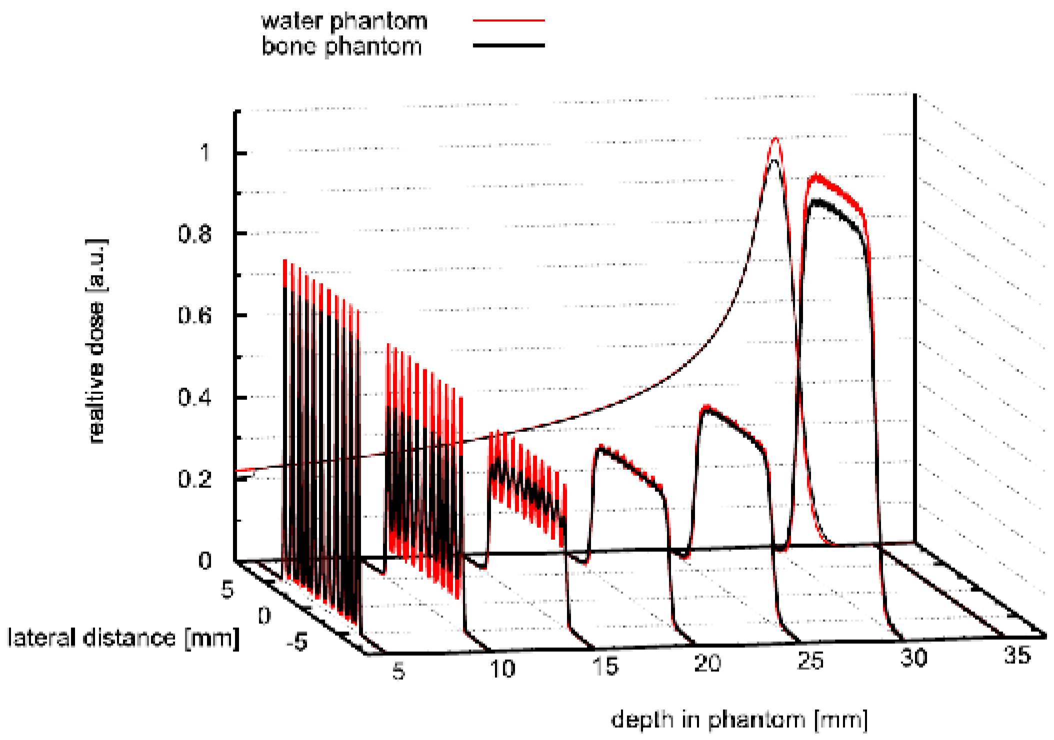


I. Dose delivery: Current status and new trends

2. Protons and accelerated heavy ions

Pencil beam technology

- More accurate formation of dose distribution
- Intensity modulated proton therapy available
- No collimator or compensator needed
- Reduced dose of secondary radiation



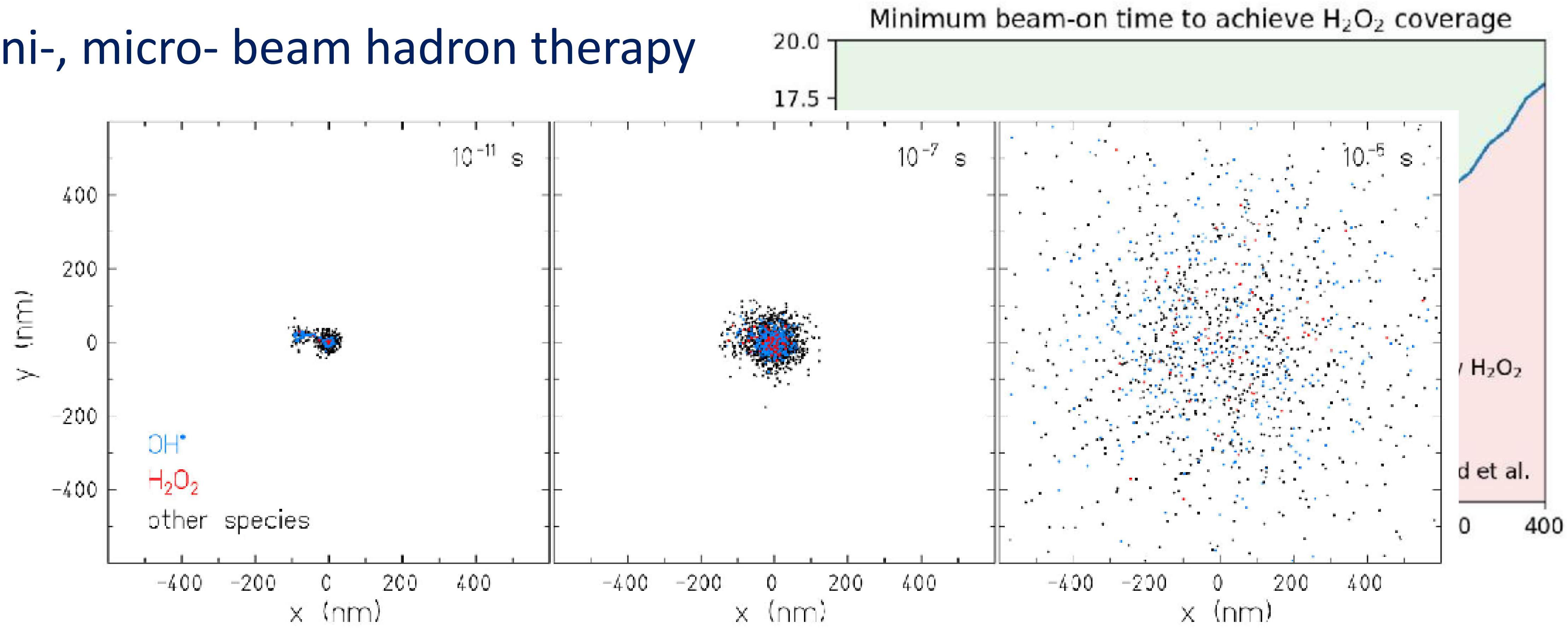
Mini-, micro- beam hadron therapy

+ Reduction of skin damage
  Reduction of neurotoxicity …
- Requires higher intensity of proton/ion beam

I. Dose delivery: Current status and new trends

2. Protons and accelerated heavy ions

Mini-, micro- beam hadron therapy

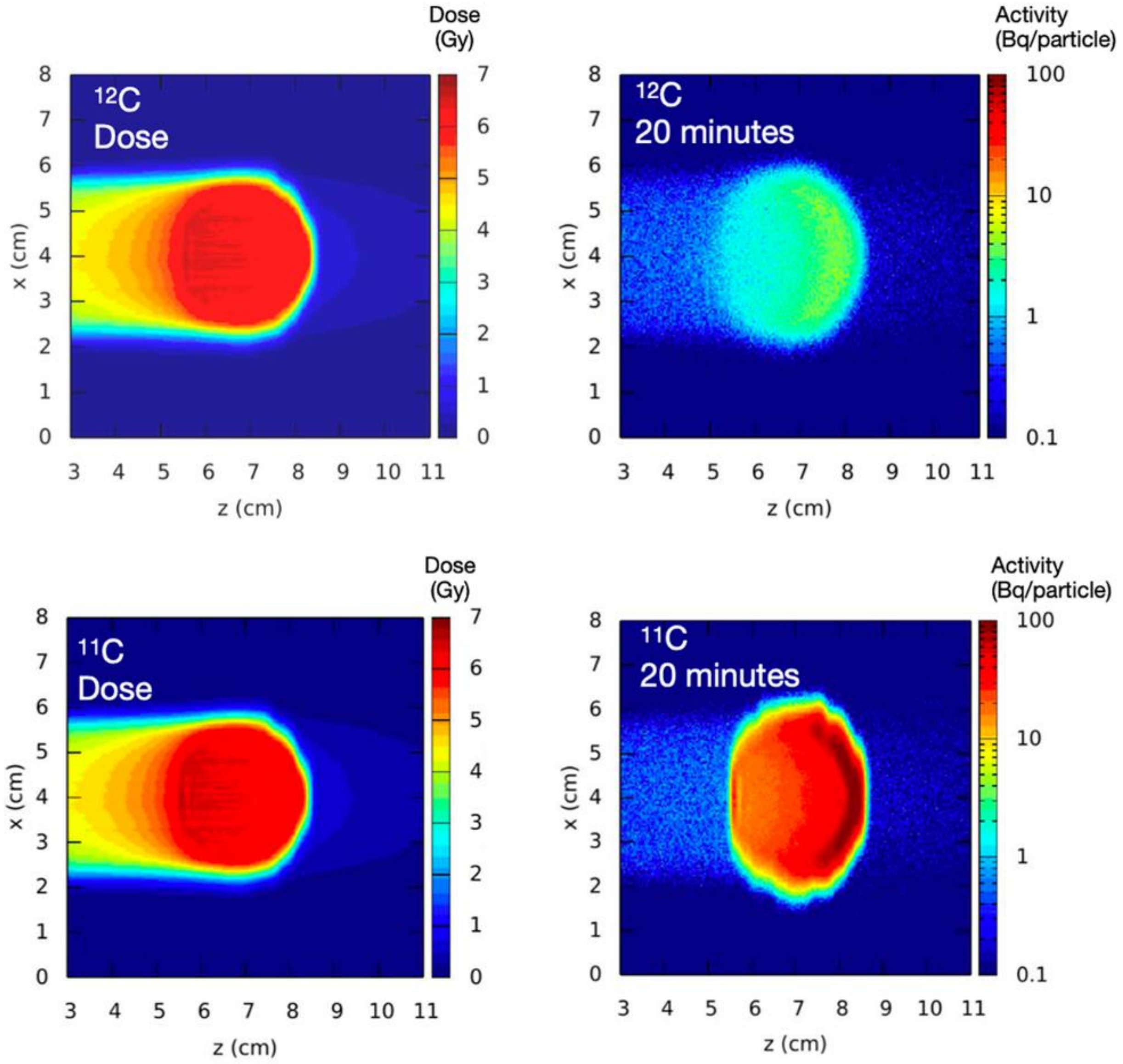


Dal Bello R, et alFront. Phys. 8 (2020) 564836.

I. Dose delivery: Current status and new trends

2. Protons and accelerated heavy ions

IGRT:
proton computed tomography,
radioactive ion beams



Boscolo et al. Front. Oncol. 11:737050 (2021).

I. Dose delivery: Current status and new trends

2. Protons and accelerated heavy ions

High dose rate beams (FLASH radiotherapy)

40 – 10^6 Gy/s

Minimum proton beam intensity ~10^{12}

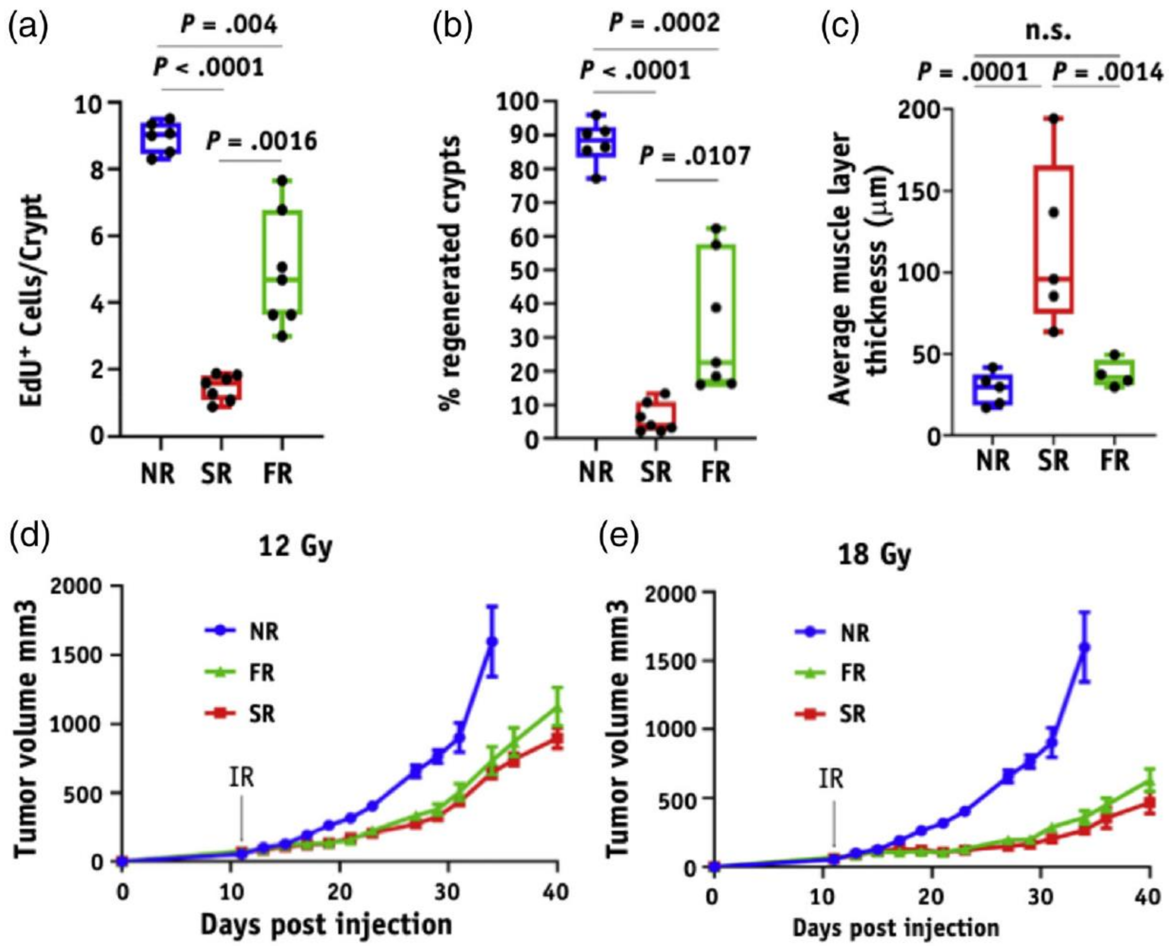
Sparing normal tissue with flash

control

conv

FLASH

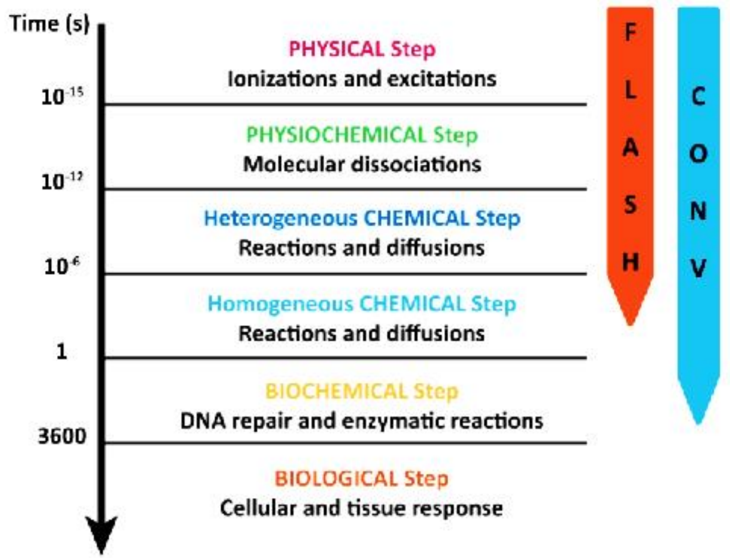
Comparable level of tumor control

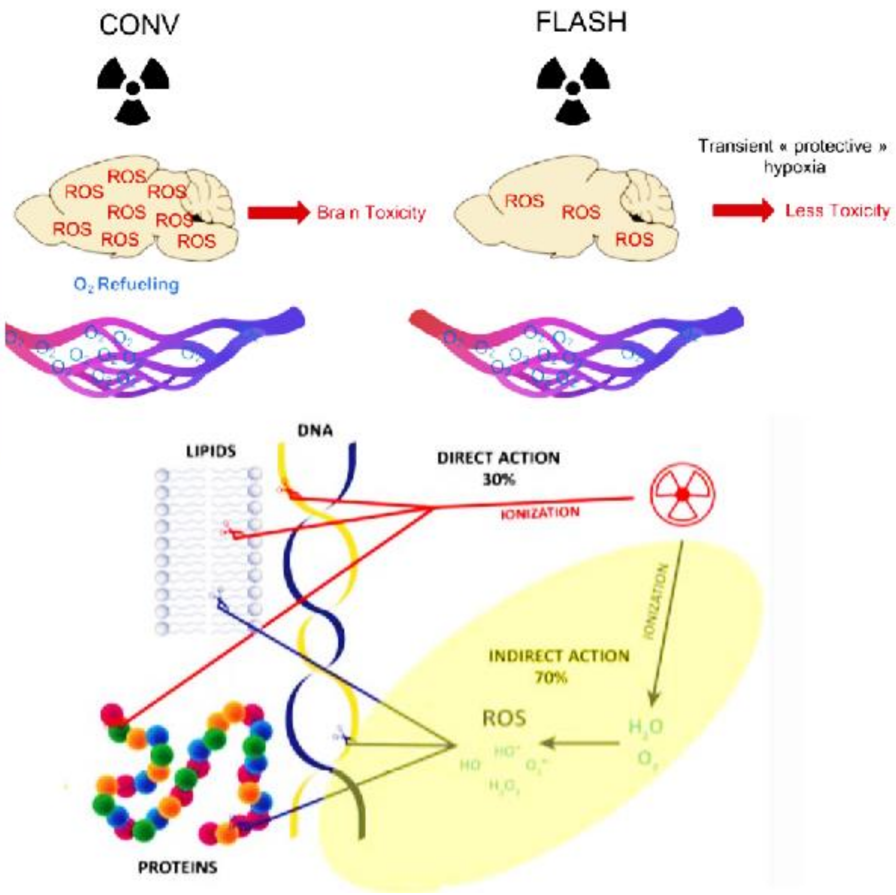


Diffenderfer ES, et al Int J Radiat Oncol. (2020) 106:440

I. Dose delivery: Current status and new trends

2. Protons and accelerated heavy ions





FLASH

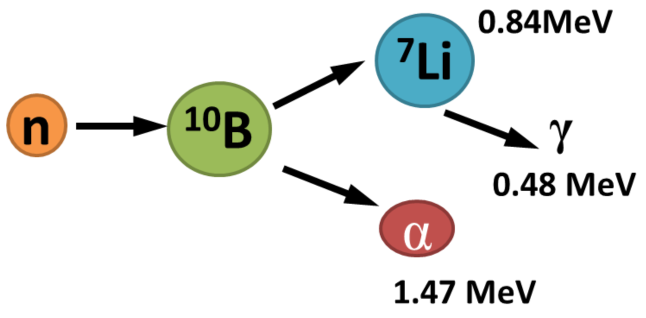
Oxygen depletion hypothesis

From Vozenin, Spitz, Limoli

I. Dose delivery: Current status and new trends

3. Neutrons

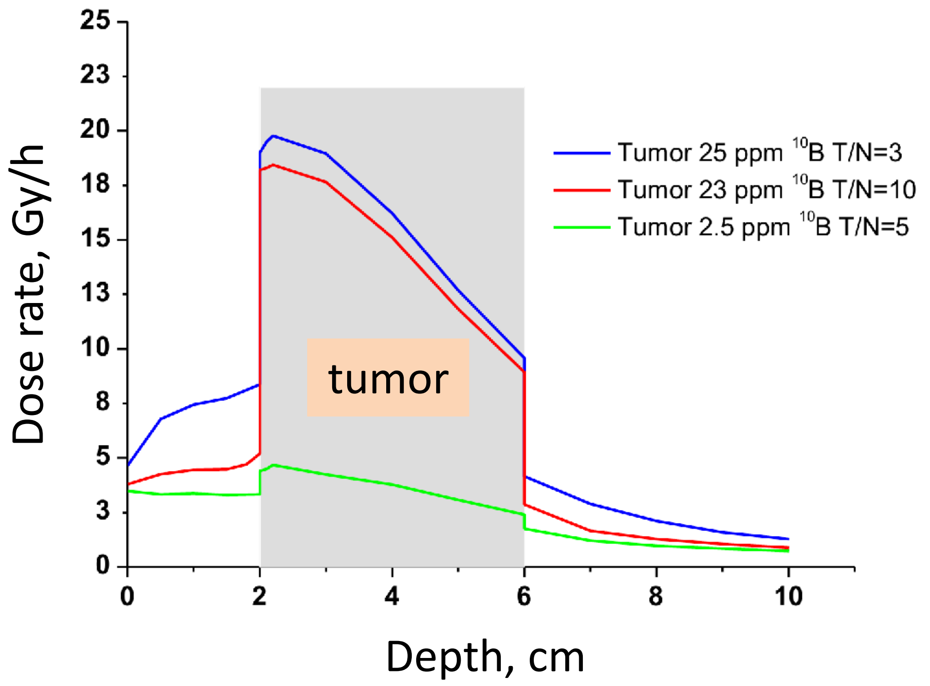
neutron capture therapy

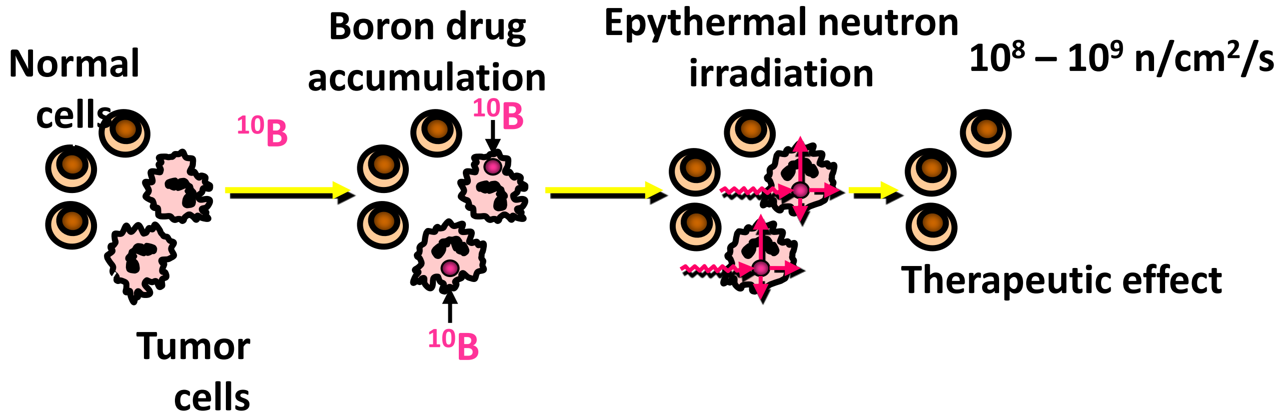


σ =3880 barn

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

Dose deposition





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

I. Dose delivery: Current status and new trends

I. Dose delivery: Current status and new trends

2,5 MeV 10 мА tandem accelerator VITA + Li target (Novosibirsk, INP, by S.Yu. Taskaev)

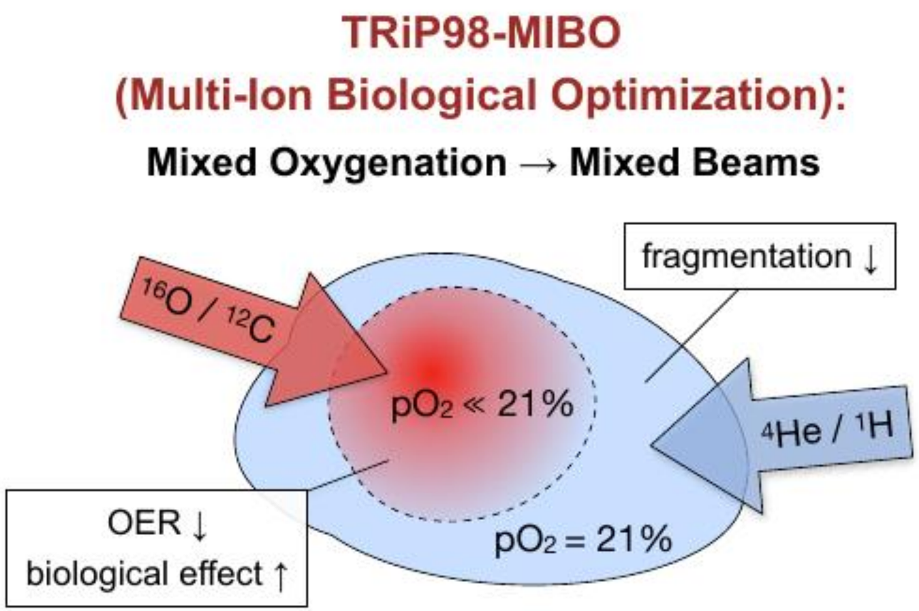
I. Dose delivery: Current status and new trends

4. Binary methods

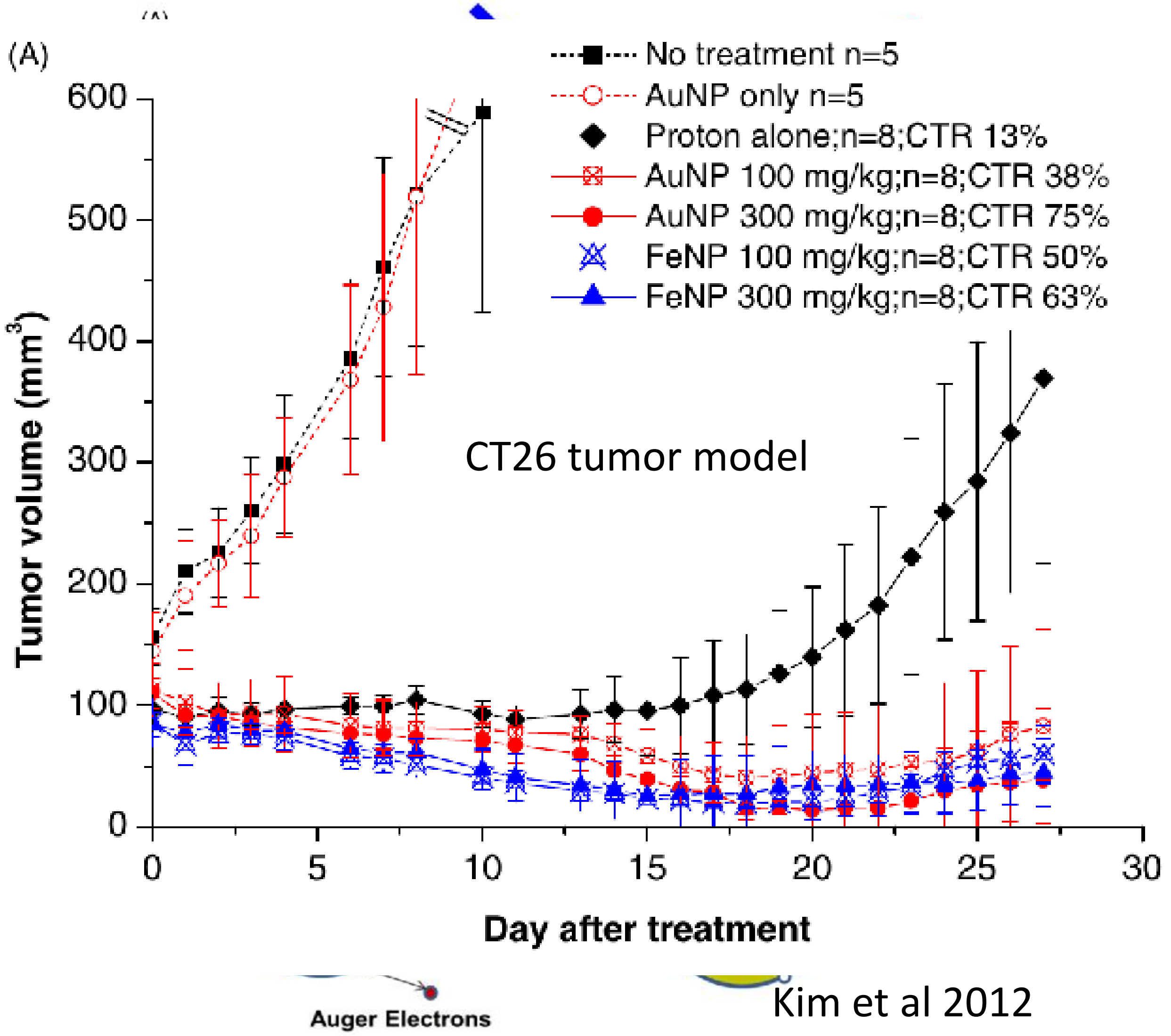
Dose enhancers: metal nanoparticles

Combinations of different particles:

neutrons + gamma
ions + gamma
multi-ion



by O.Sokol, M.Durante et al



Kim et al 2012
Phys. Med. Biol. 57 8309

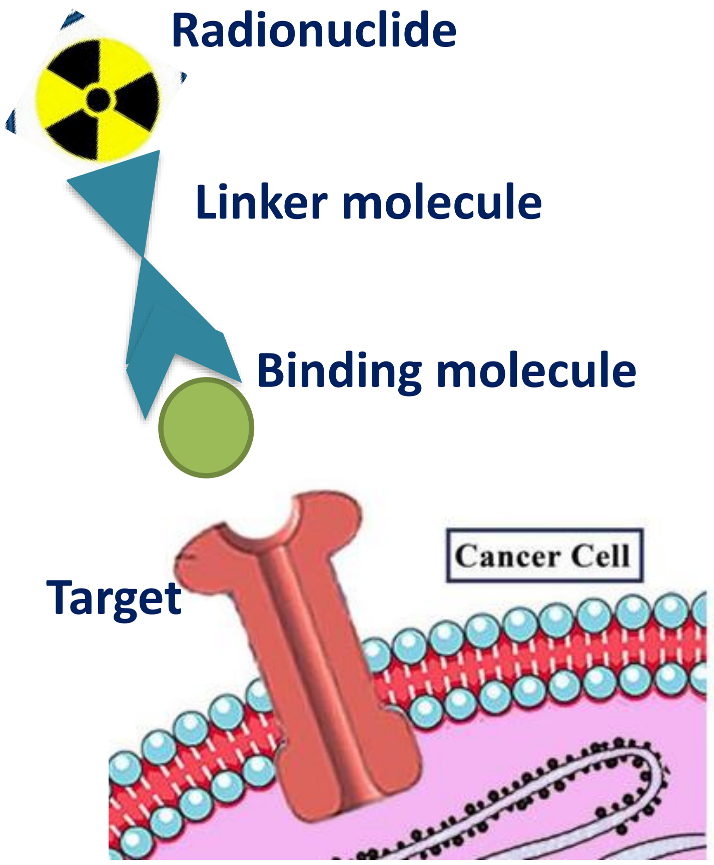
I. Dose delivery: Current status and new trends

5. Radionuclides

β-emitters +high variability, theranostic pairs
- low RBE, low precision (long tracks)

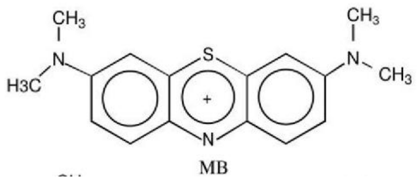
Auger-emitters + better RBE than β
high precision (short tracks)
- not implemented

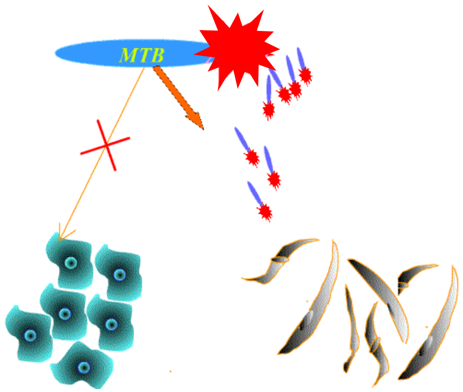
α-emitters + highest RBE, high precision
targeted therapy available
(^{223}RaCl, ^{225}Ac-pcma, ^{225}Ac-Dotatate)
- difficult to produce, difficult to visualize



5. Radionuclides

Radiobiology of alpha-emitter radionuclides

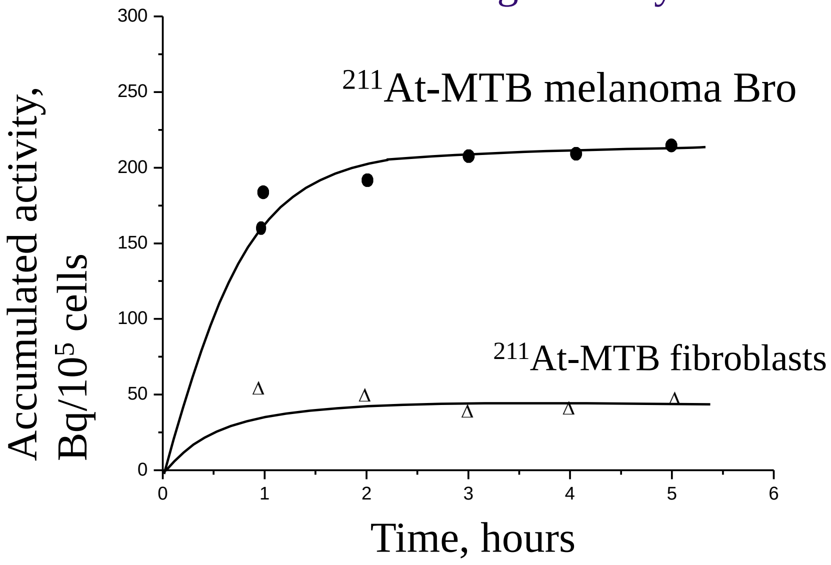


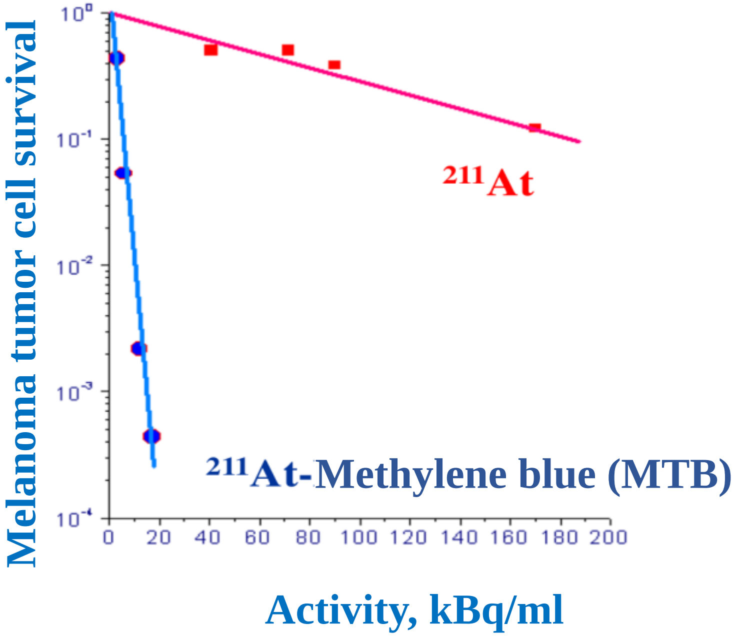


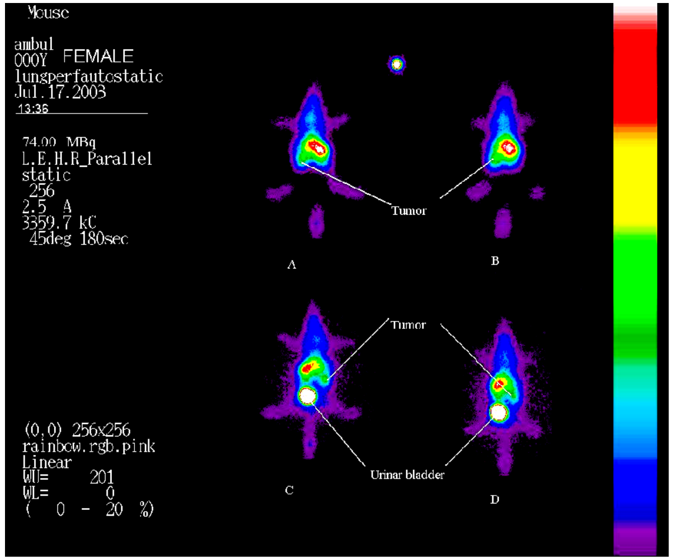
^{211}At–MB for therapy

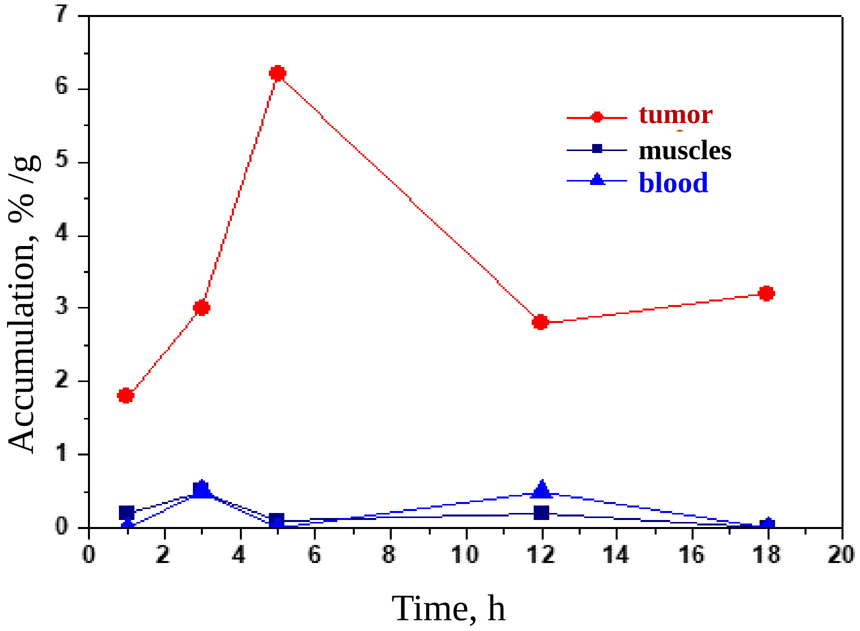
^{131}I, ^{123}I-MB for diagnostic

High affinity to melanoma cells







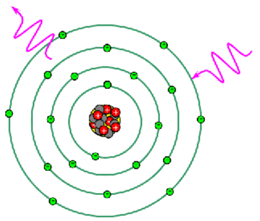


5. Radionuclides

Radiobiology of Auger-electron emitter radionuclides

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

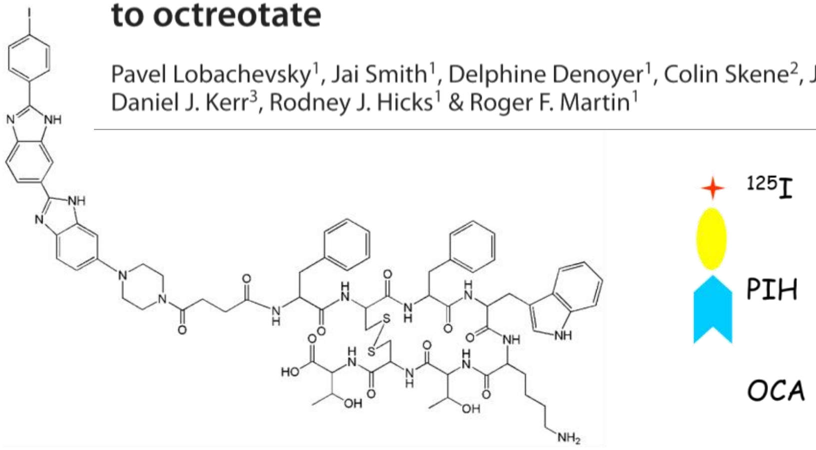
Auger- and conversion-electrons
+ *very high local dose*
- *Very low range*



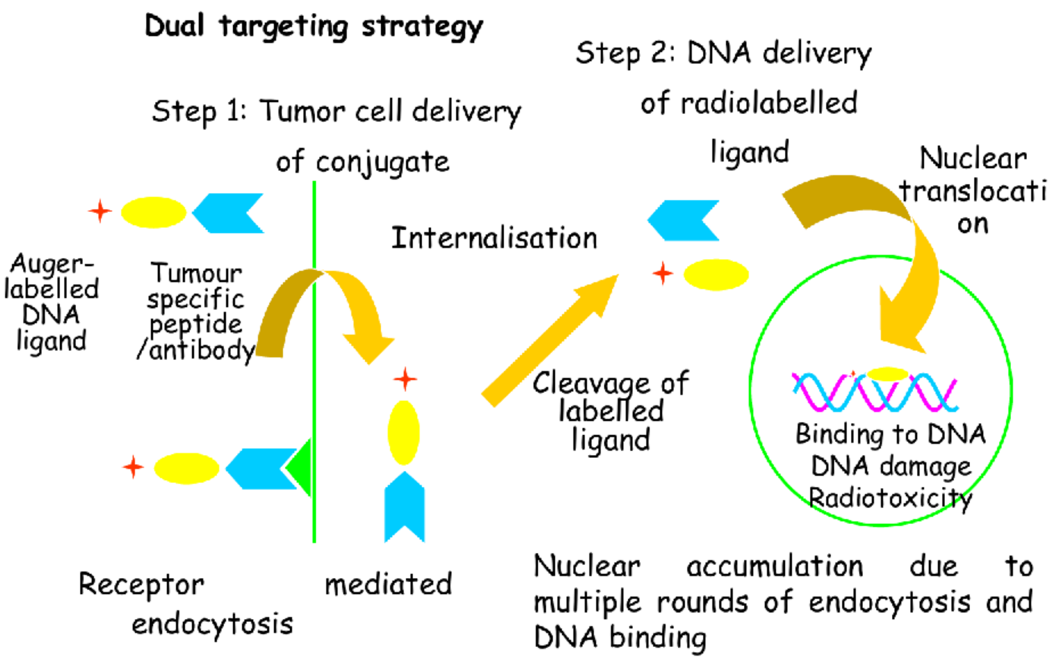
X-ray, γ
- *low RBE*
- *Long range*

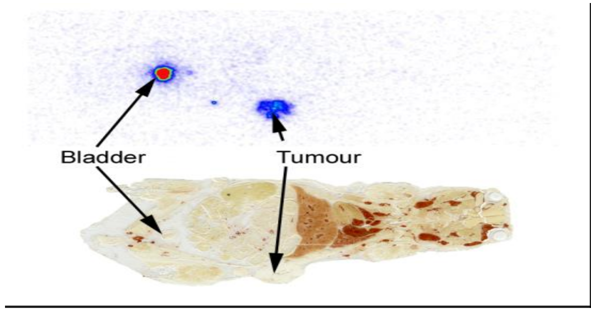
Tumour targeting of Auger emitters using DNA ligands conjugated to octreotate

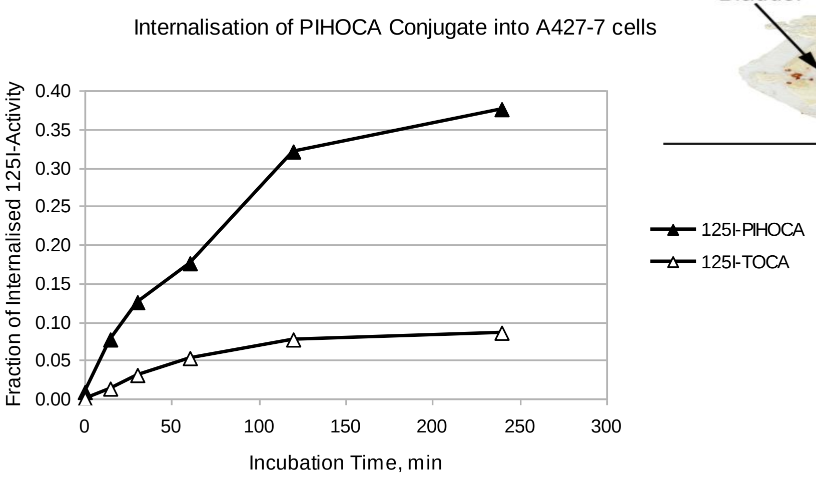
Pavel Lobachevsky[1], Jai Smith[1], Delphine Denoyer[1], Colin Skene[2], Jonathan White[2], Bernard L. Flynn[3], Daniel J. Kerr[3], Rodney J. Hicks[1] & Roger F. Martin[1]



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

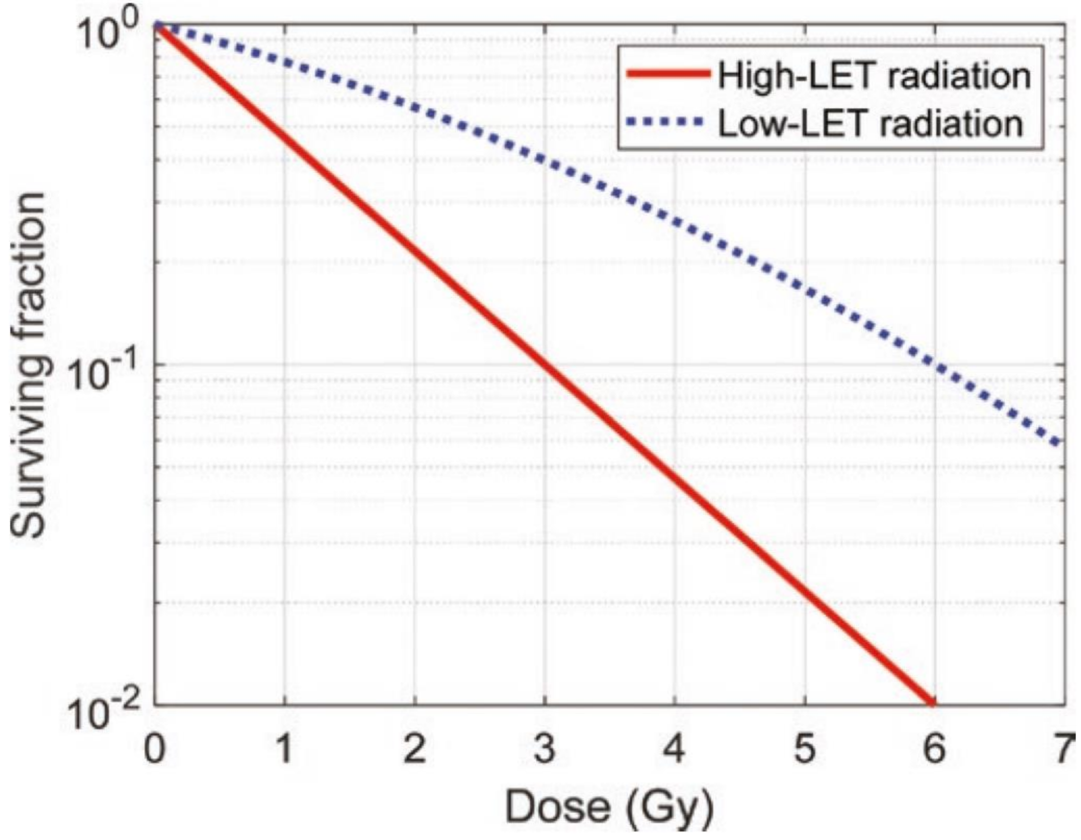




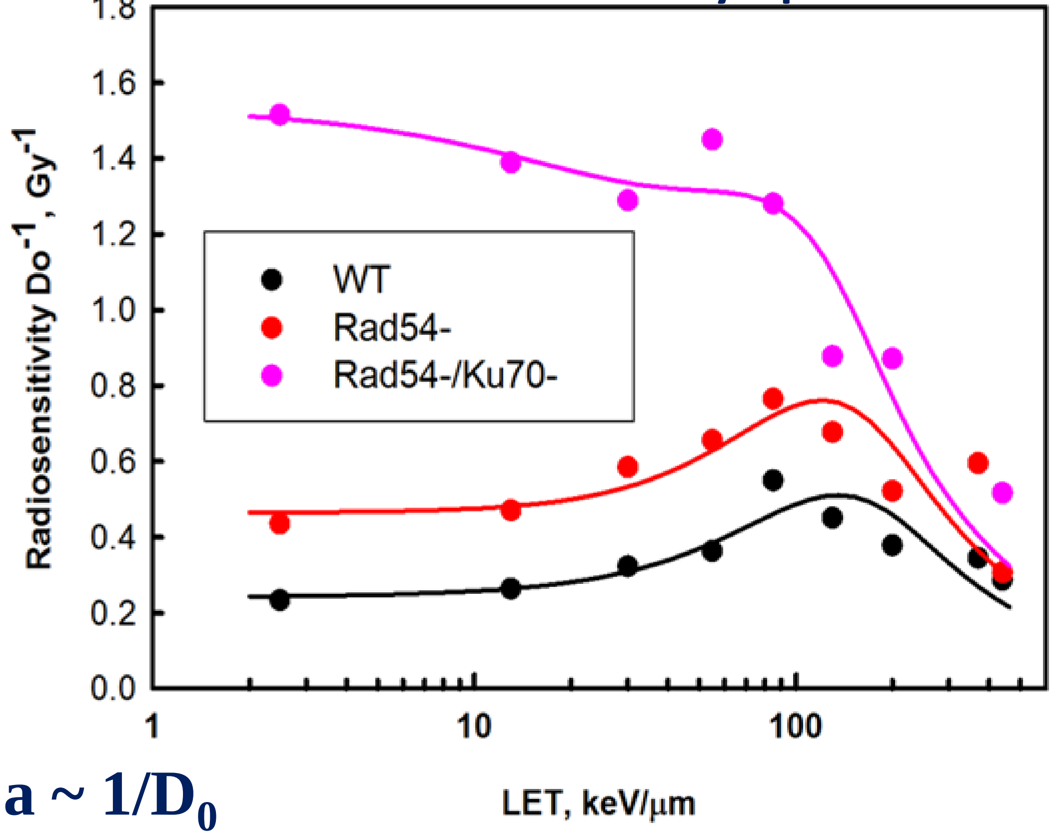


II. Biological efficiency of ionizing radiations

Radiobiological basis



B-lymphoma cells



$a \sim 1/D_0$

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

Data source: Furusawa 2013

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

Radiosensitivity of tumor cells can be modified

Biological efficiency of ionizing radiations
Amount of DNA damage

Computer simulations

1) Base damage BD
2) Single strand breaks SSB
3) Clustered SSB
4) Double strand breaks DSB
5) Clustered DSB

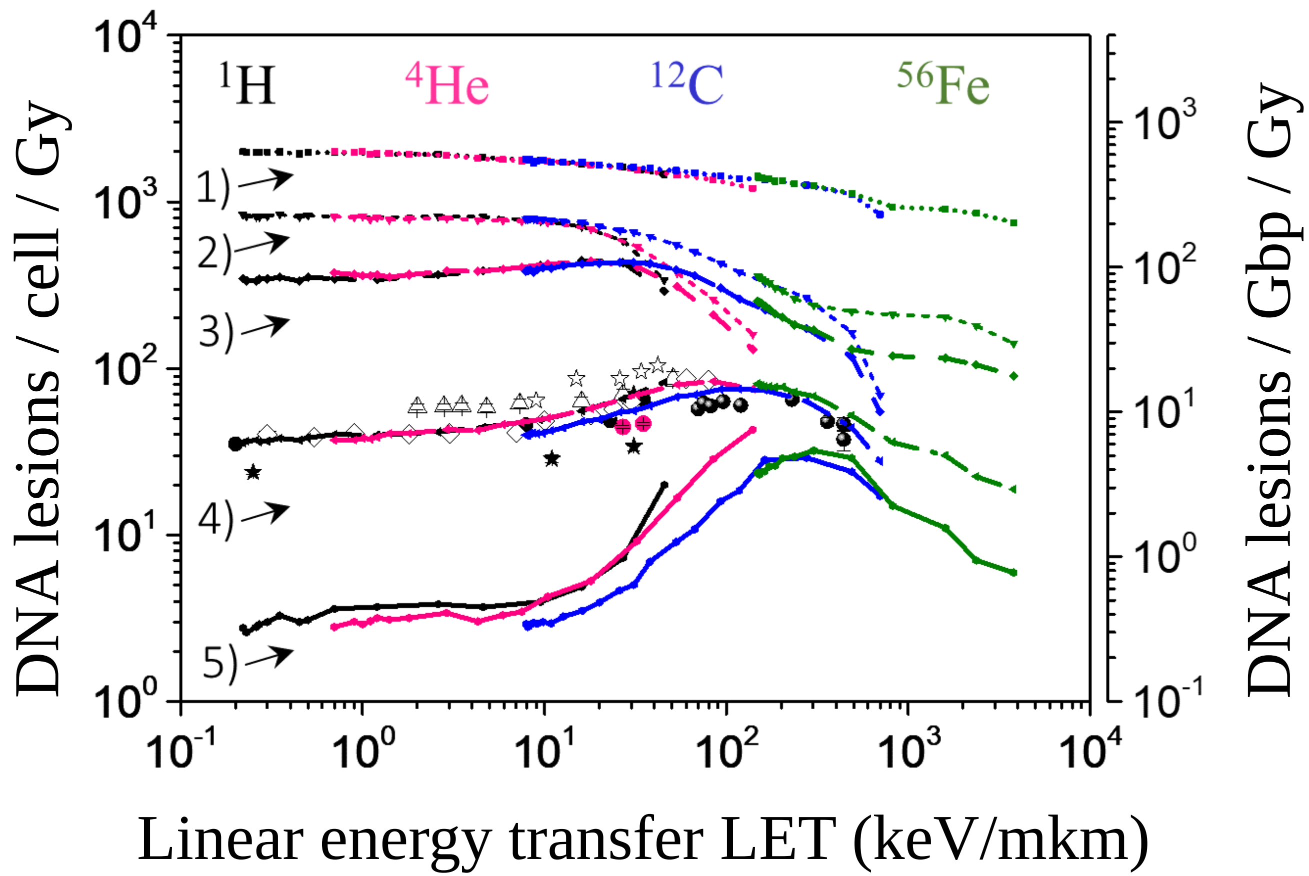
Expeiments (DSB)

- ● Frankenberg 1999
- ★ Belli 2001
- ● Belli 2006
- ■ Bulanova 2019

Calculations (DSB)

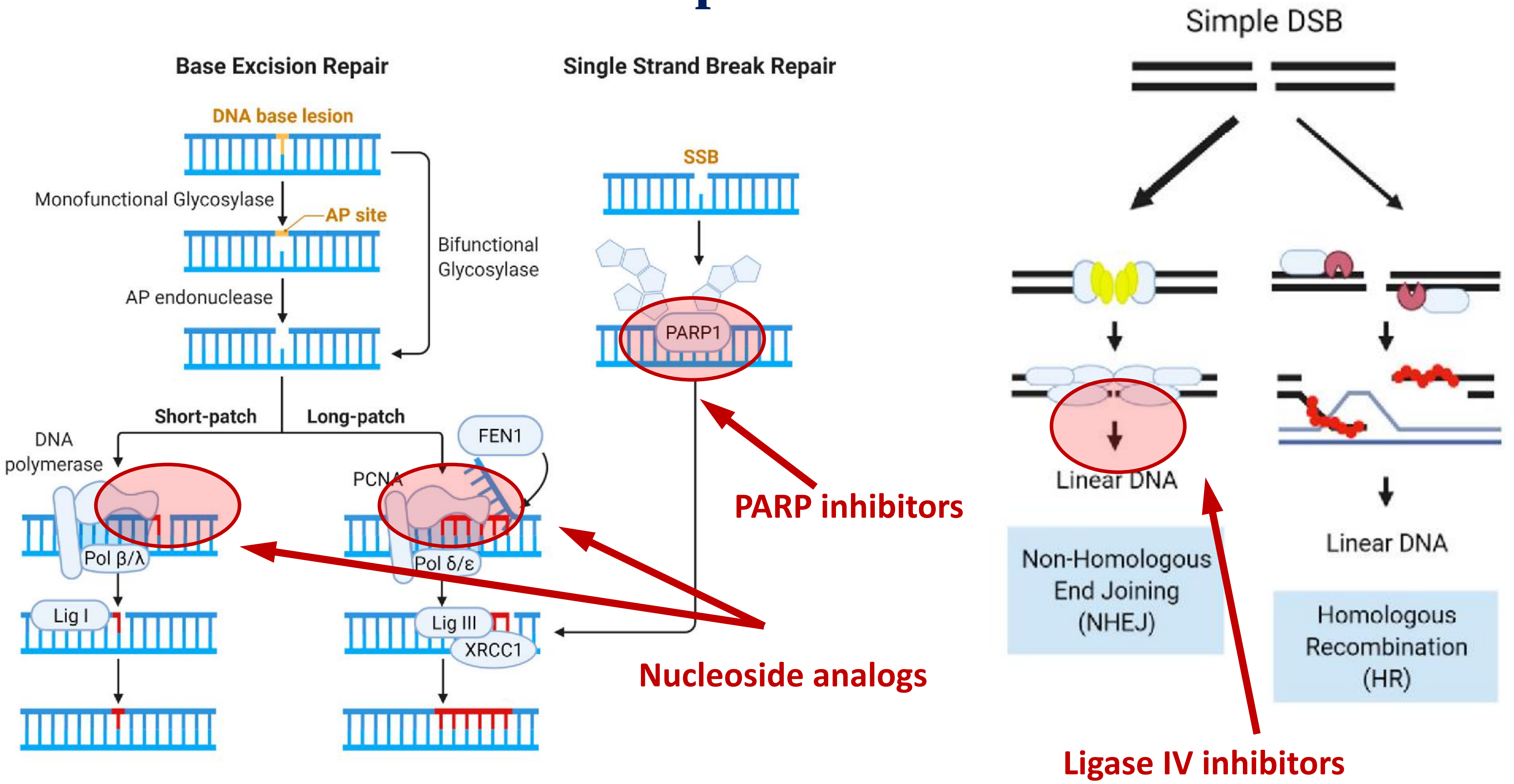
- -★- Nikjoo 2001
- -◇- Friedland 2011
- -△- Rosales 2018

1 DSB
:
10 SSB
:
100 BD



II. Biological efficiency of ionizing radiations

DNA repair inhibitors



II. Biological efficiency of ionizing radiations
DNA repair inhibitors

General strategy:

conversion of simple lesions to complex

Radiation

1 DSB

:

10 SSB

:

100 BD

Drug

Drug must be administered before the irradiation for this mechanism to work

Potential Drugs to apply:

PARP inhibitors

Veliparib, Olaparib….

Barcellini, A. et al Cancers 2021, 13, 5380

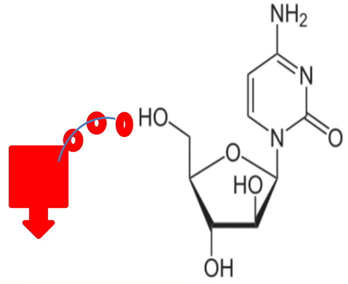
Nucleoside analogs

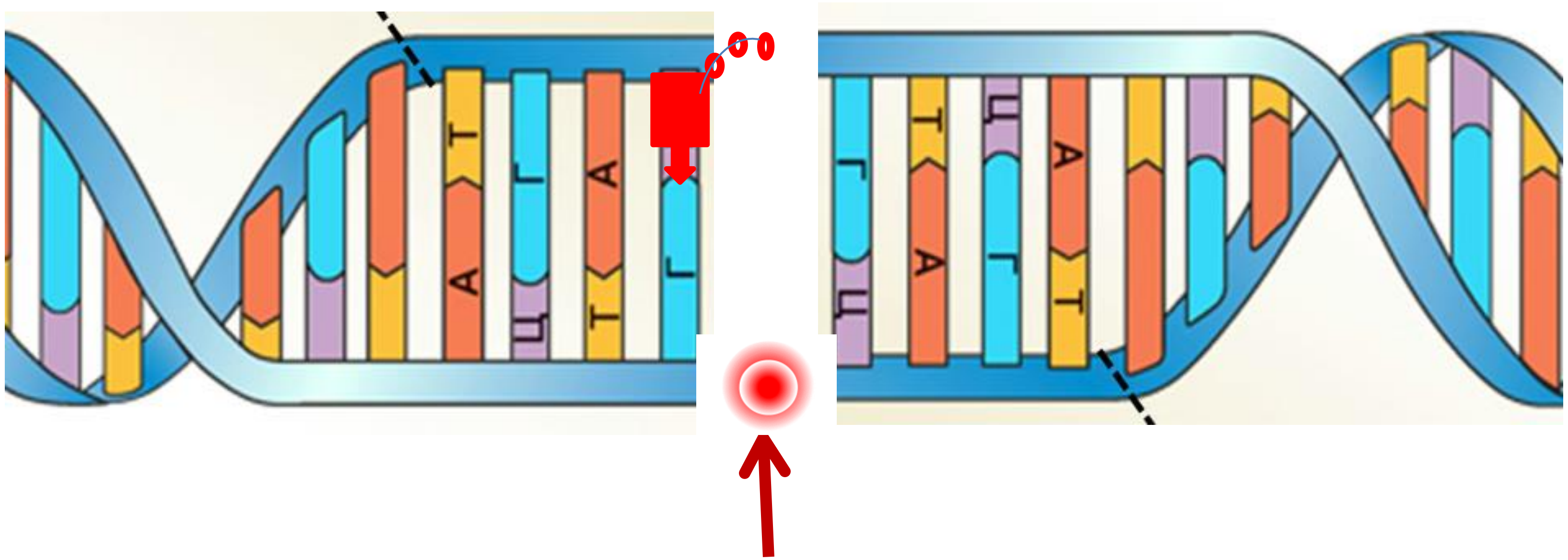
AraC, 5-FU, 2CdA, Ecyd ….

H Yasui. et al Nucleosides, Nucleotides and Nucleic Acids, 2019

1-β-D-arabinofuranosylcytosine (AraC)

An example of DNA synthesis inhibitor



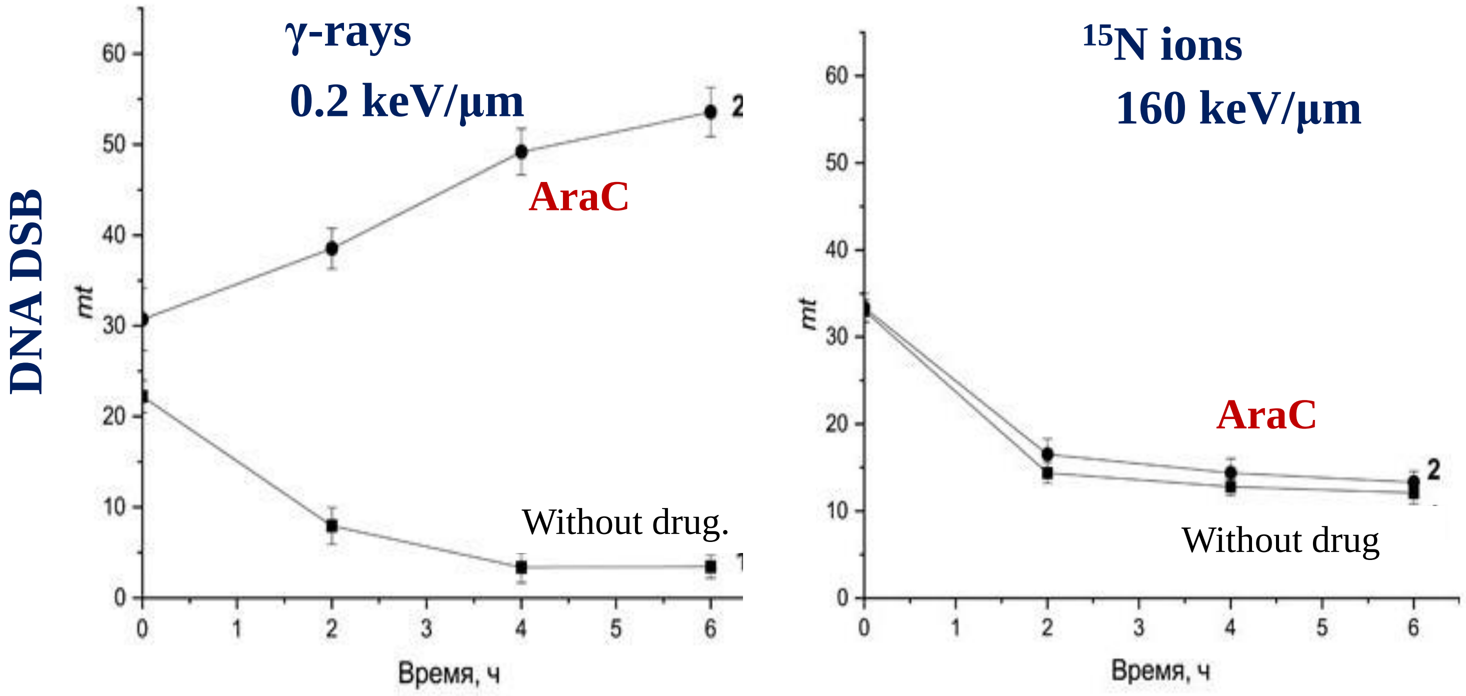


S1 endonuclease

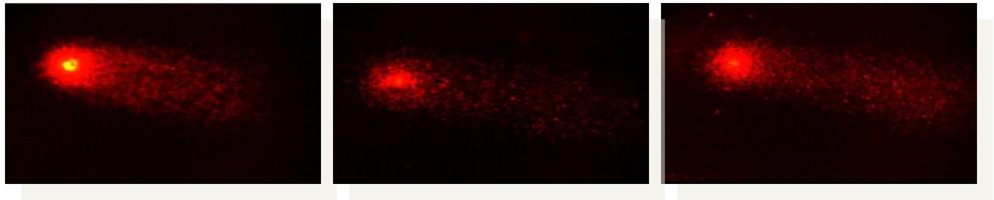
Stopping DNA synthesis and forming a double-strand break

In vitro experiments

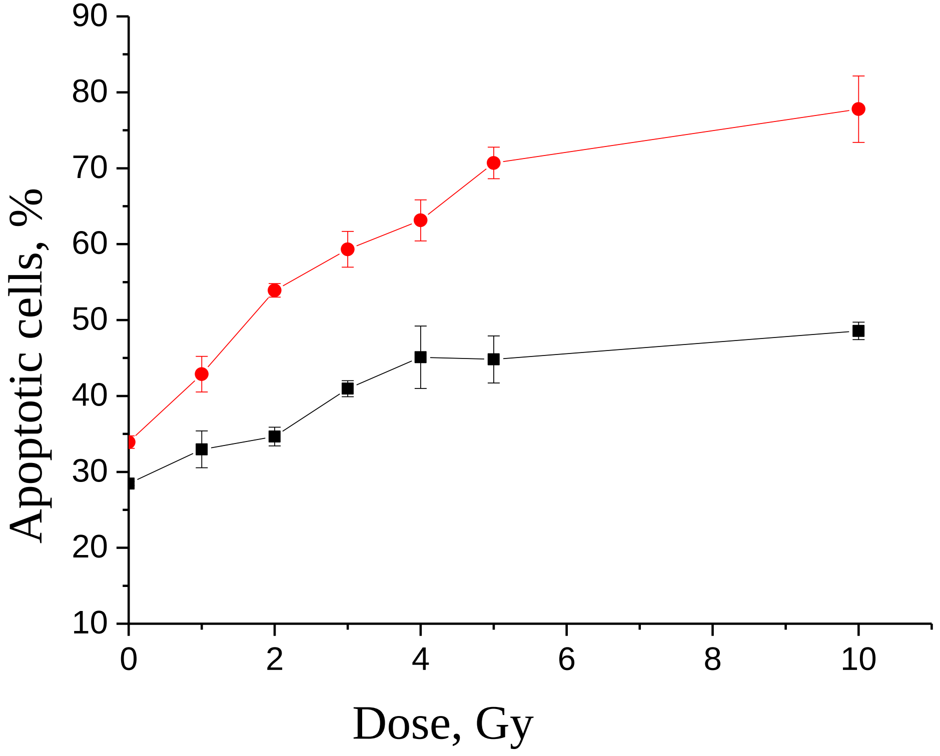
DNA damage in human fibroblasts (dose 20 Gy)



Comet assay



Level of apoptosis in human lymphocytes 48 h after irradiation with γ-quanta in the presence of AraC

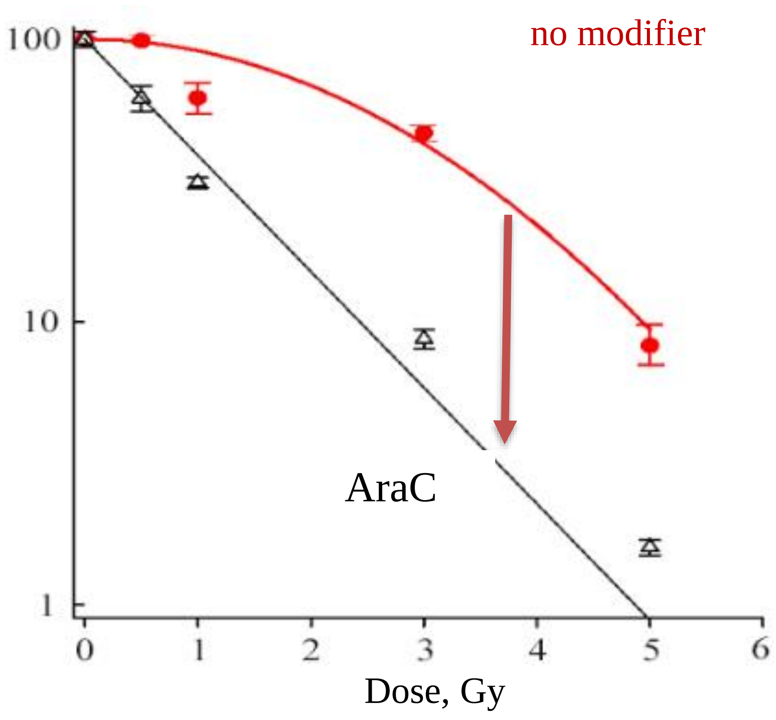


V. N. Chausov et al // Phys. Part. Nucl. Lett. (2018) 15: 700

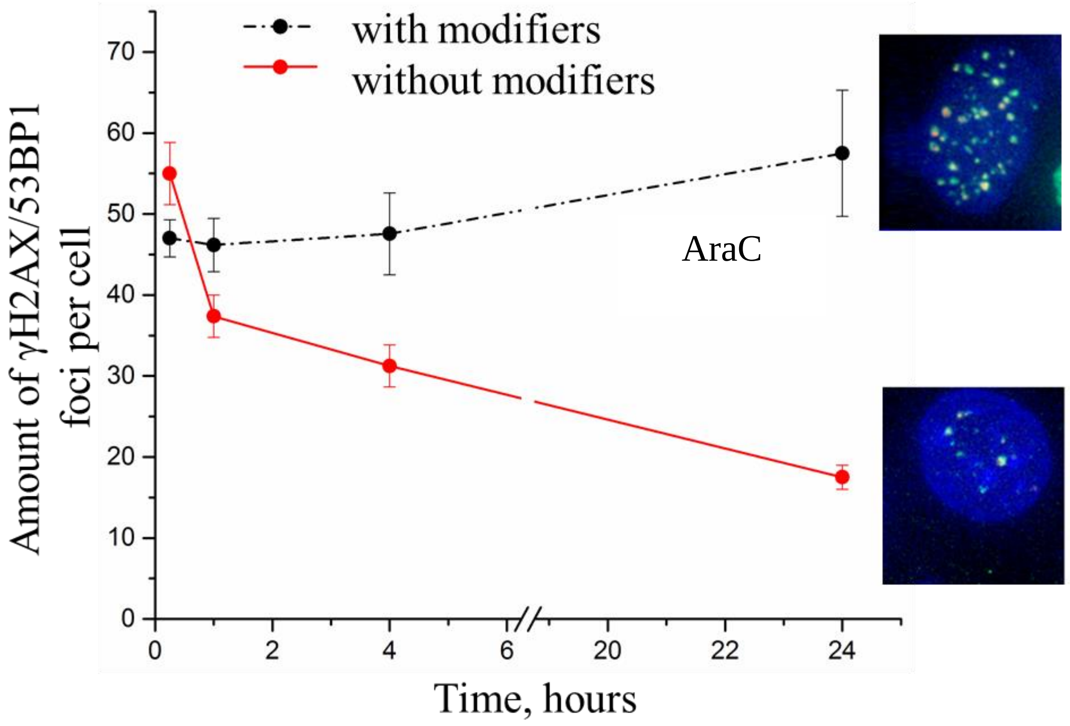
Effect of radiomodifier drugs on DNA damage and tumor cell survival

Glioblastoma U87

Tumor cell survival, %



DNA damage



1.25 Gy 170 MeV protons (spread out Bragg peak)

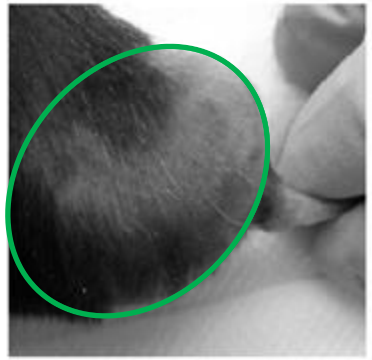
E. A. Krasavin et al // Phys. Part. Nucl. Lett. (2019) 16: 153

R. A. Kozhina et al // Phys. Part. Nucl. Lett. (2022) 19: 590

In vivo experiments with grafted melanoma B16 in mice

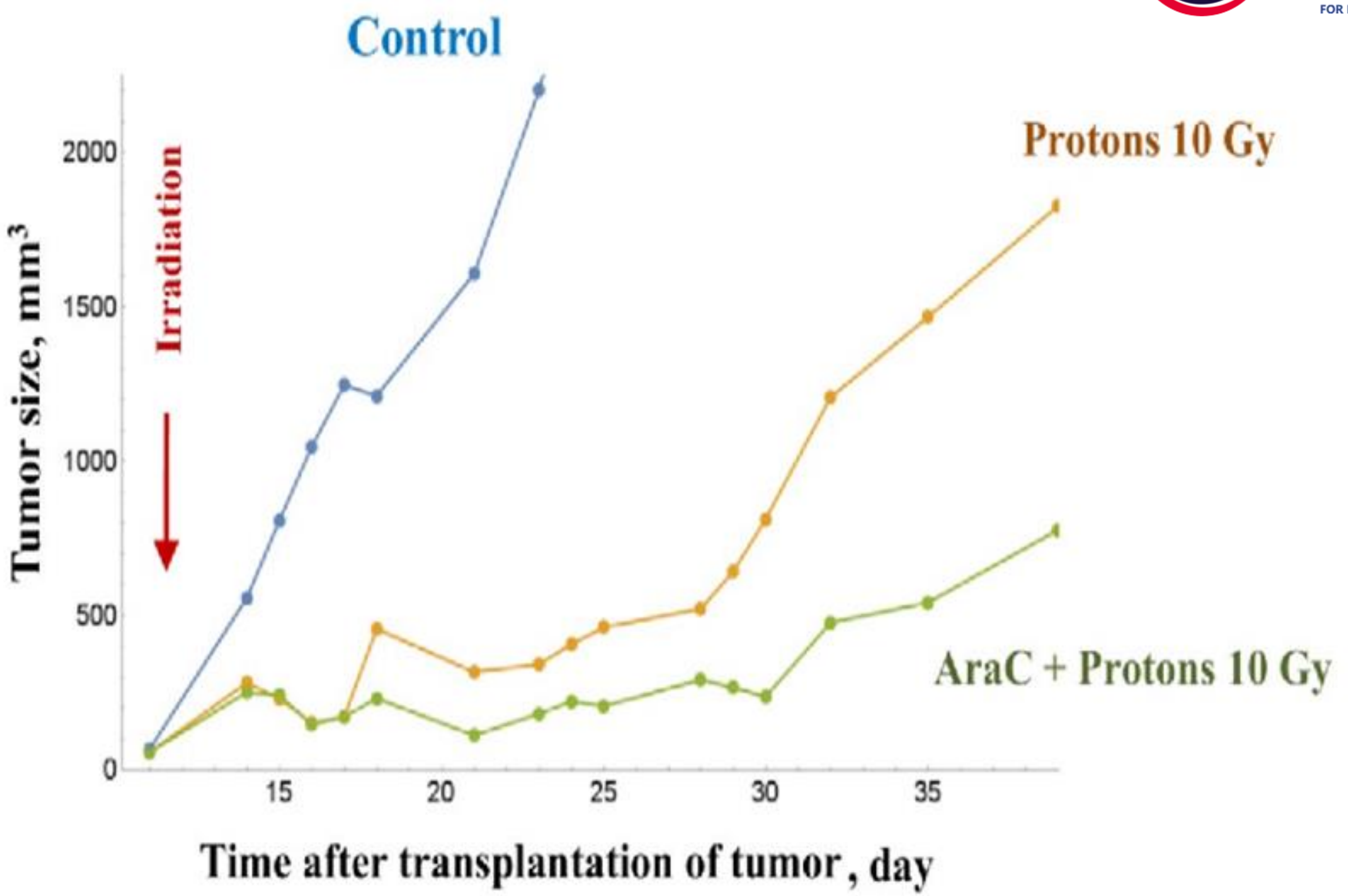
- Laboratory of Radiation Biology, JINR, Dubna
- National Medical Research Radiological Centre

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



Protons 10 Gy

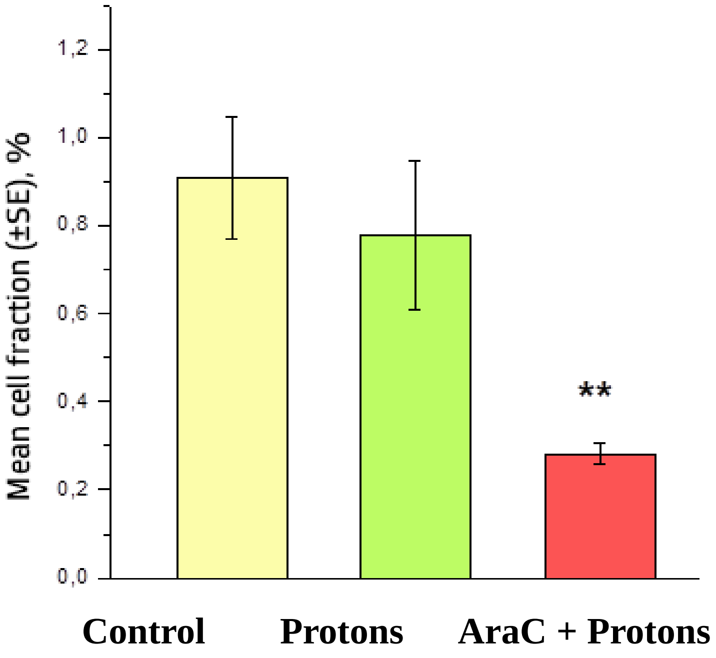
Protons 10 Gy + AraC



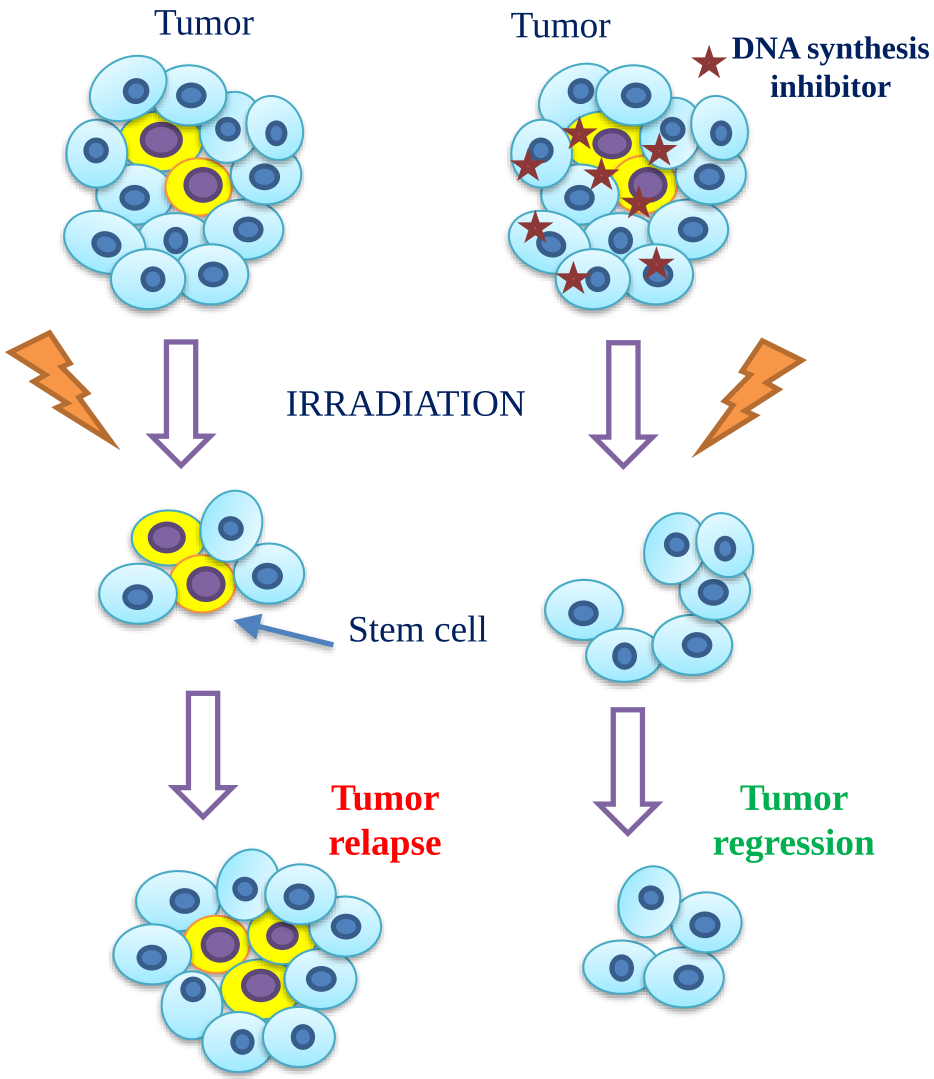
Suggested mechanism of tumor regression

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

Cancer stem cell fraction after the irradiation



Tumor regression due to stem cell death



Zamulaeva I.A. et al // Phys. Part. Nucl. Lett. 2023. V. 20(1).

Increasing the efficiency of radiation therapy

- Improving radiation conformity technologies
- Using the features of the physicochemical interaction of radiation with matter
- Modification of biological processes that occur in response to exposure

Thank you for the attention!