ELI-ALPS Research Institute
TOWARDS THE SHARP END OF ATTOSCIENCE

Evaluation of the Various Aspects of the Progress in Clinical Applications of Laser Driven Ionizing Radiation

Katalin Hideghéty, Ákos Diósi, Máté Molnár, Róbert Polanek, Emilia Rita Szabó, Tünde Tőkés, Zoltán Szabó

3rd ELIMEDIC Workshop
CATANIA 2016.09. 7-9

SZÉCHENYI 2020
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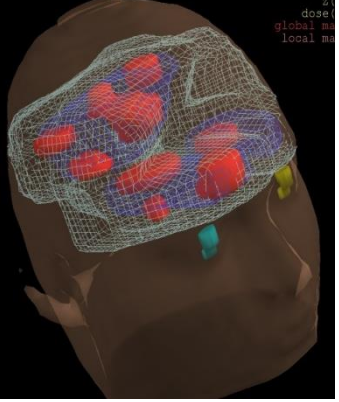
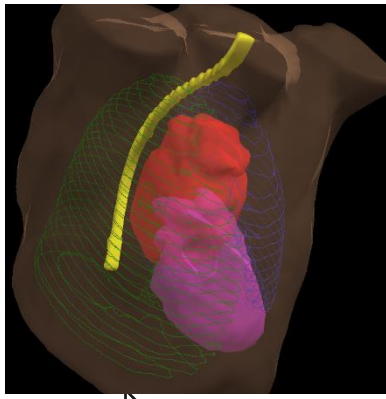
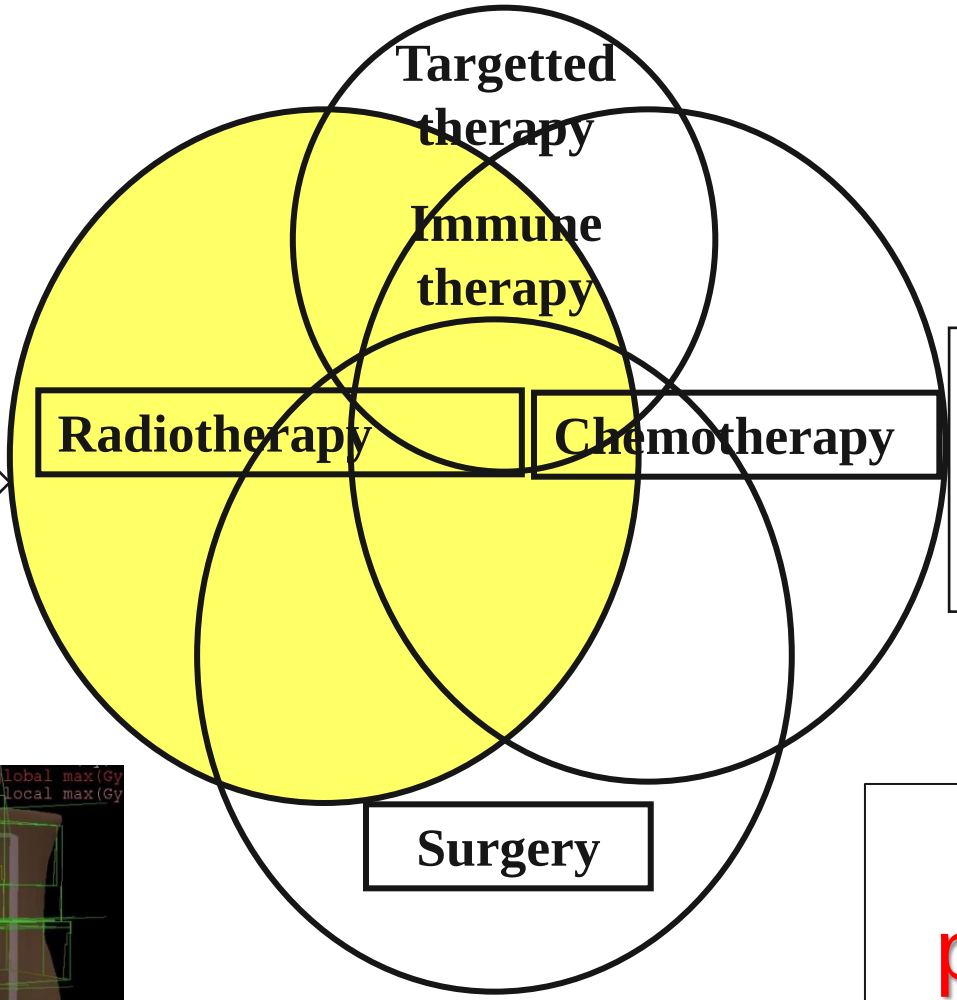
Complex tumor therapy

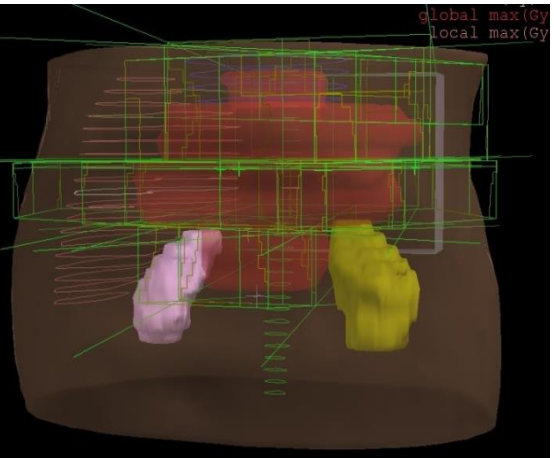




Advanced diagnostics

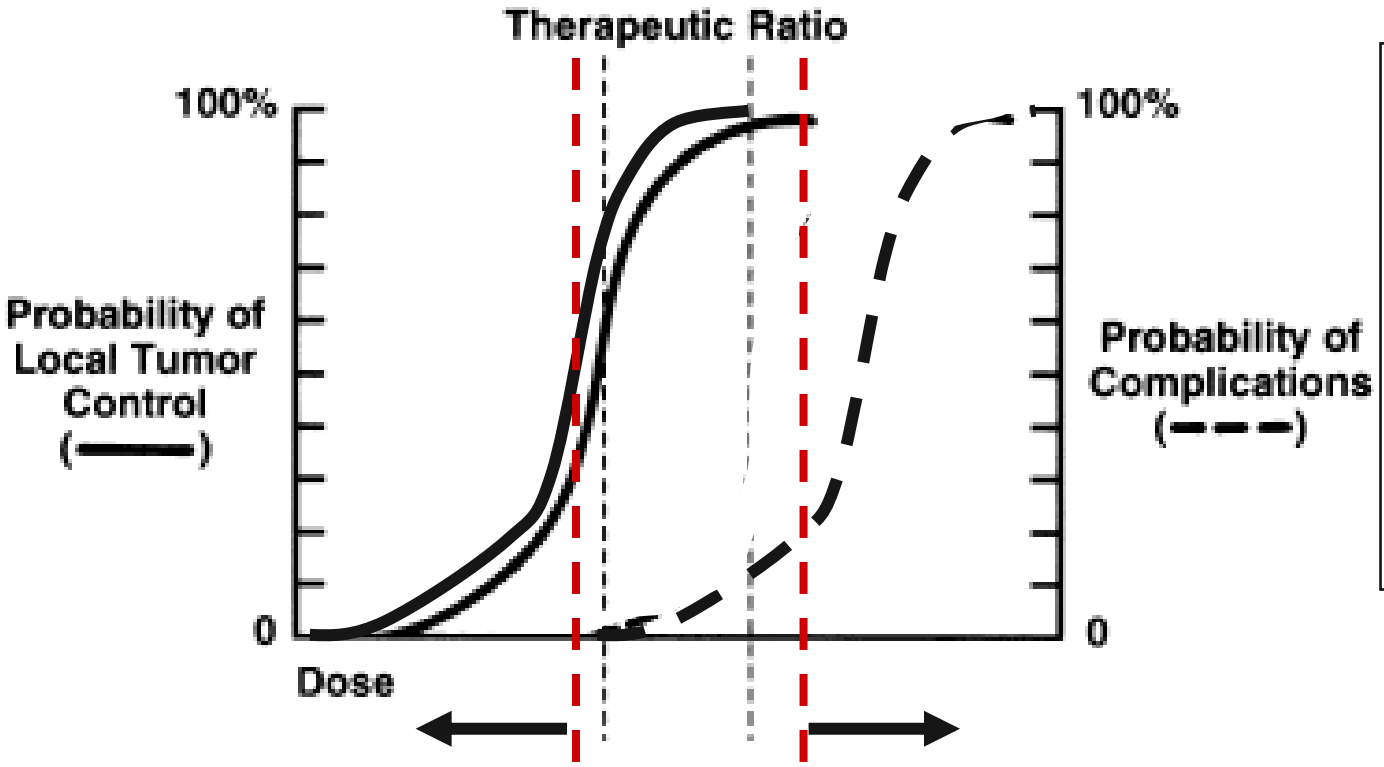


Improved outcome



10 million patients/year receive radiotherapy

Current approaches under clinical evaluation



Timing

Fractionation

Hypo-

Hyper-

Acceleration (CHART)

Prolongation

Combined treatment

sensitisation/protection

Chemo-, hormon, biol.m.,hypoxic sens.

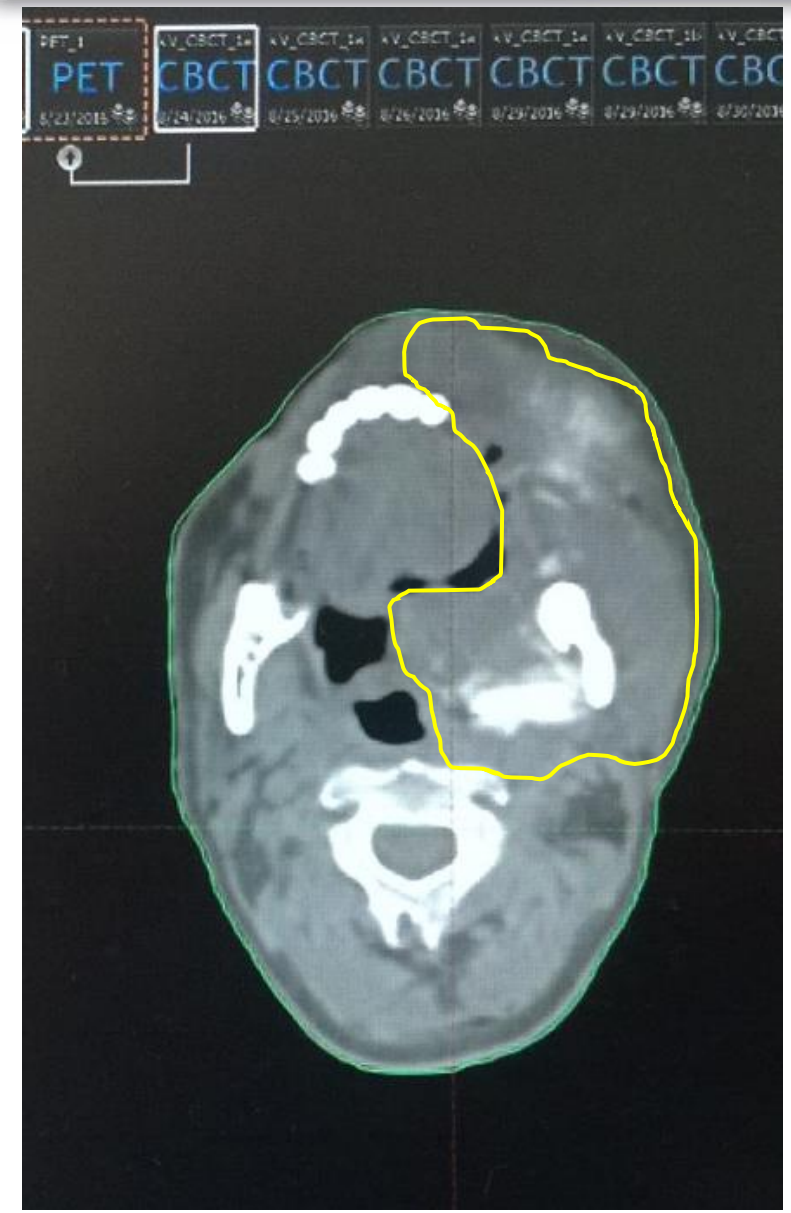
immuntherapy

Technical development

ConformalRT, IMRT, IGRT, dose painting

Hadron therapy, BNCT

Diagnosis: Tu maxillo-cerebrale l.s. /first removal on 16.09.2015
Histology: Osteosarcom

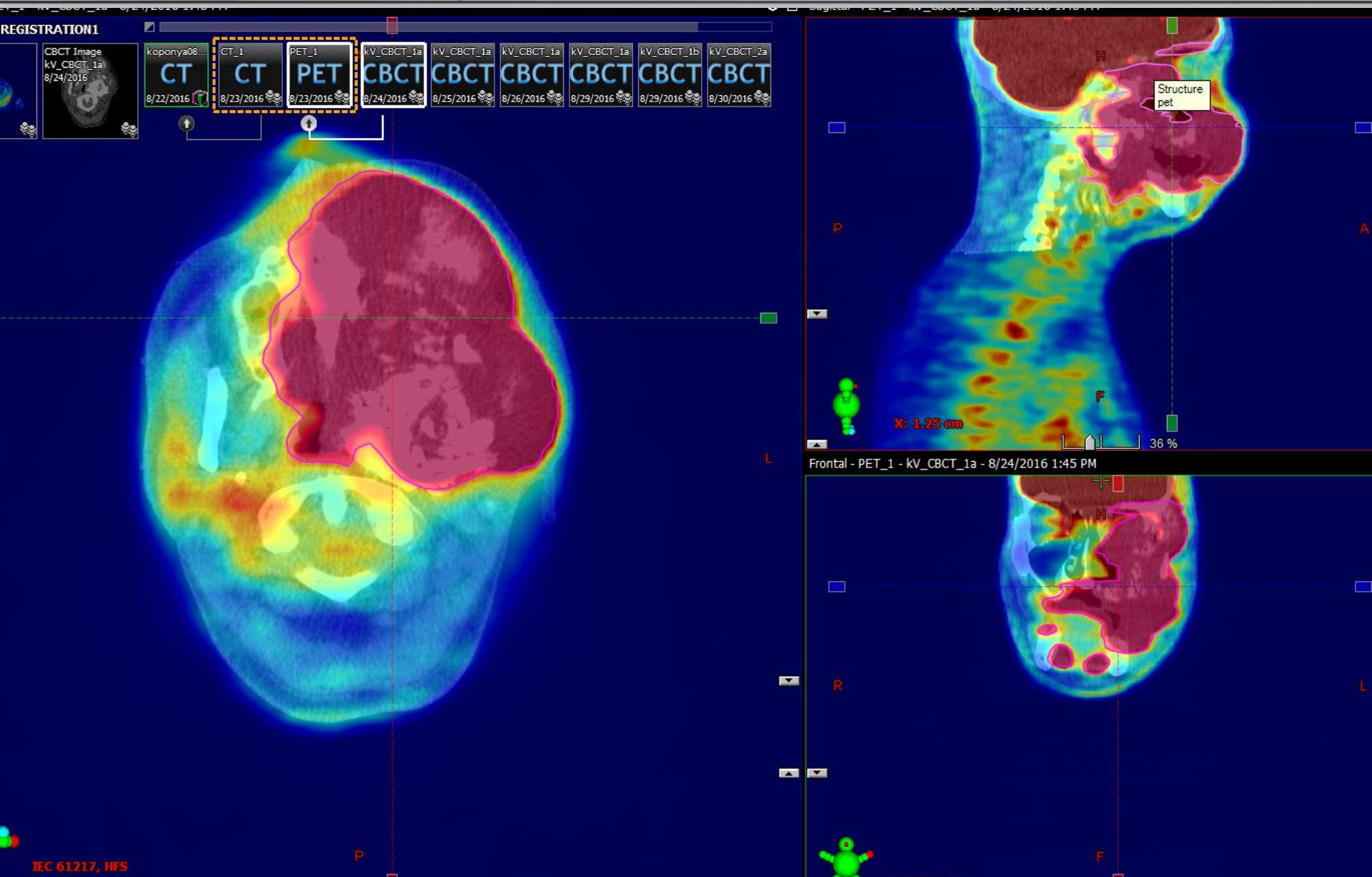


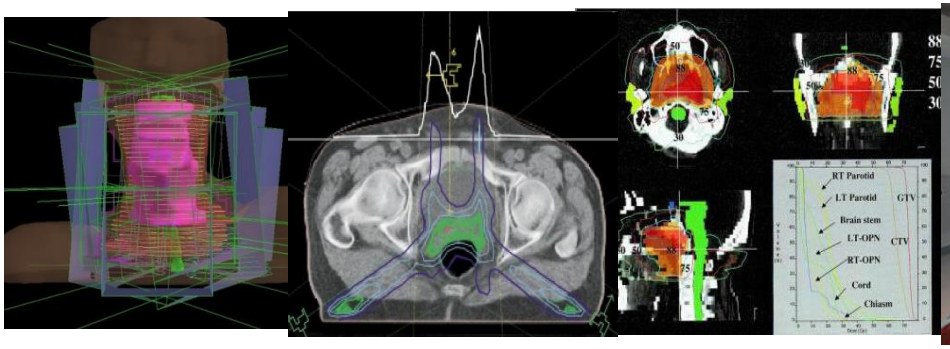
Adjuvant chemotherapy according to MAPIE protocol (6 cycles between 10. 2015- 04.2016)

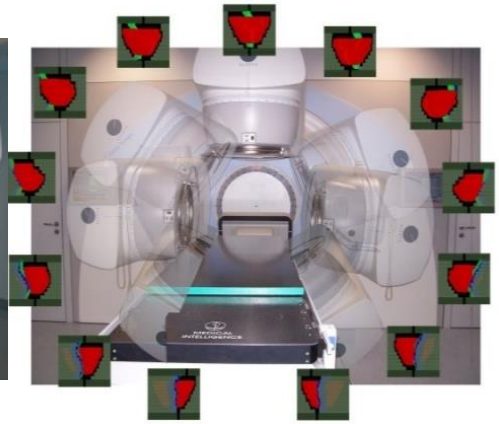
Reoperation because of progression (23.06.2016) R2

The second removal took place in common interdisciplinar (neurosurgeons-ENT experts) effort too. The majority of the high grade osteosarcom could be removed, but the postoperative MRI confirmed macroscopic residual tumor in critical location surrounded by radiosensitive structures.
Rapid clinical progression is detected

42 years old man with hypoxic inhomogeneous radioresistant tumor of the left maxilla



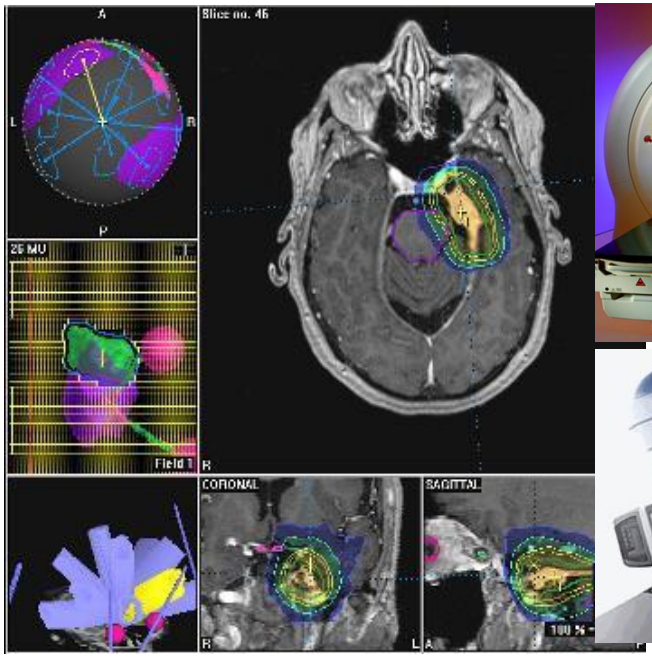




Photons 3-15 MeV, dose rate: 10 Gy/mi...

Selectivity, effectivity, accuracy

Hadron th.



Proton Therapy Scientific Milestones

1931 First cyclotron (E.O. Lawrence, LBNL)
1946 Biomedical advantages of Bragg-peak (R.R. Wilson, LBNL)
1947 184-Inch Synchrocyclotron (E.O. Lawrence, LBNL)
1948 First biology experiments using protons (C.A. Tobias, LBNL)
1955 Human therapeutic exposure (LBNL)
1993 Bevalac closed (LBNL)

Location, # pts treated by 12/2002	# pat treated by 2004
Bragg-peak treatment	
Hospital-Based	

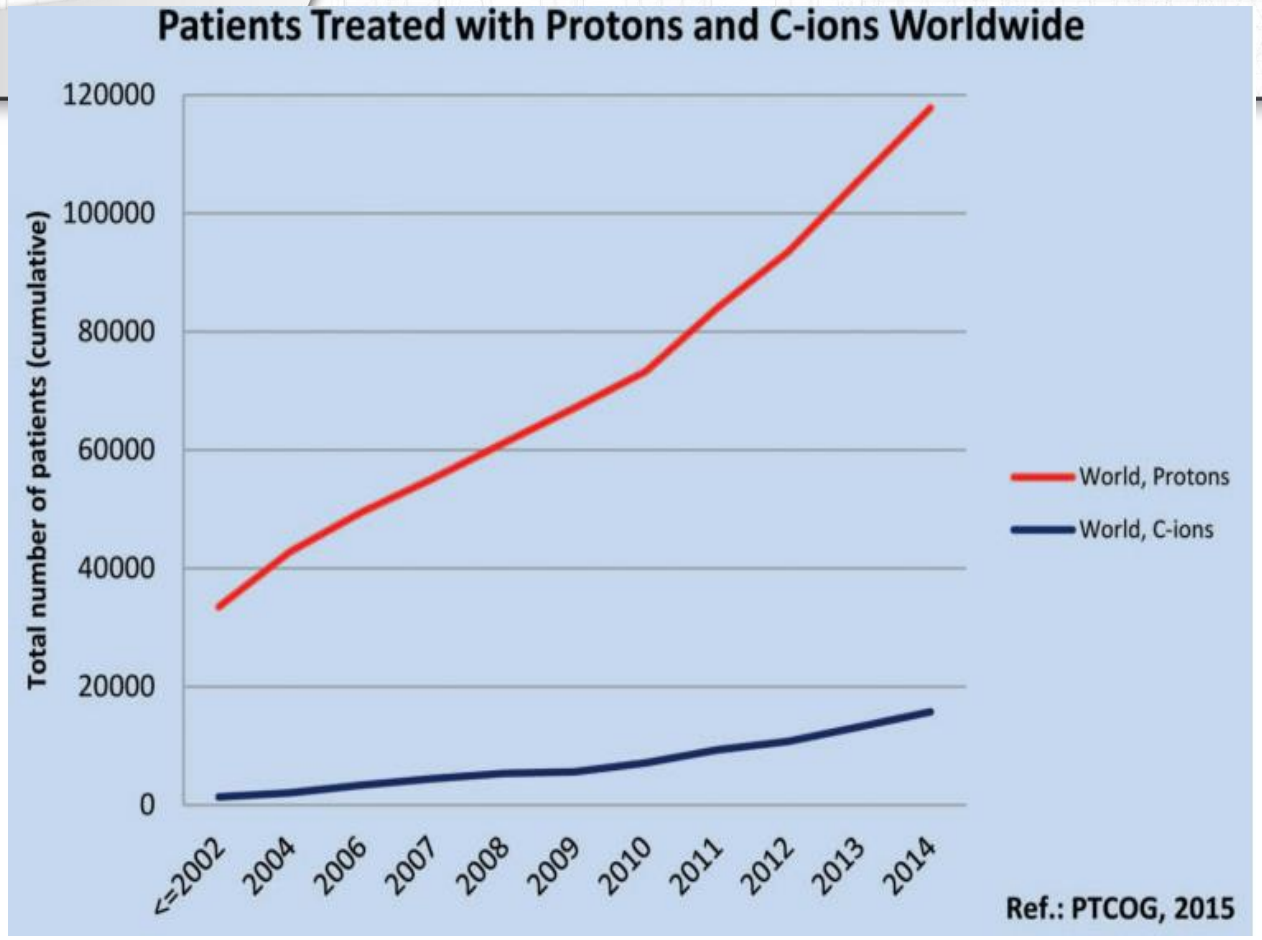
930 1940 1950 1960 1970 1980 1990 1995 2000

LBNL 30
LBNL (helium ion) 2054
Uppsala, Sweden 73 236
MGH,Cambridge, MA 9116
Moscow 3539
Dubna 84 154
St. Petersberg 1029
Chiba, Japan 133
Tsukuba, Japan 700
Villigen,Switzerland 3712 + 129
Clatterbridge,UK 1201
Loma Linda 7176
Louvain, Belgium 21
Nice, France 1951
Orsay, France 2157
Bloomington, IN 34
Faure, S Africa 398
Davis,CA 448
Vancouver 77
Berlin 317
Catania 24
Kashiwa 151
Hyogo 60
Wakasa 2
Boston 229
Tsukuba 145

1st Hospital based facility

CLINICAL TRIALS

56 years > 150000 patients

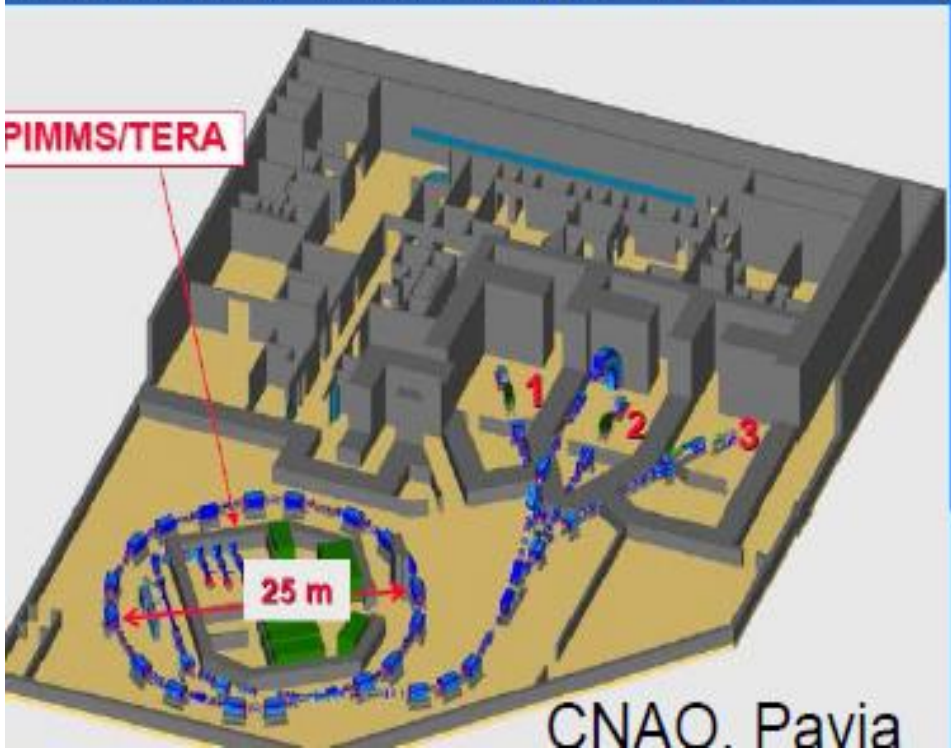


Total of all facilities (in and out of operation):		
He	2054	1957-1992
Pions	1100	1974-1994
C-ions	15736	1994-present
Other ions	433	1975-1992
Protons	118195	1954-present
Grand Total	137179	

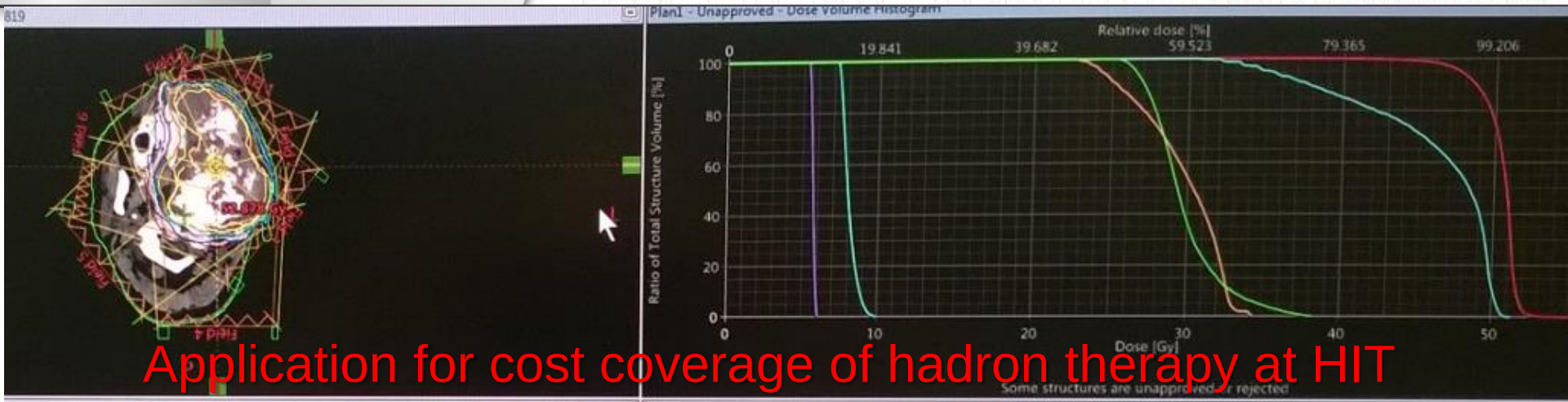
Hadron centers

54 centers are in operation and further 40 is planned

<2% of all RT



IGRT- IMRT

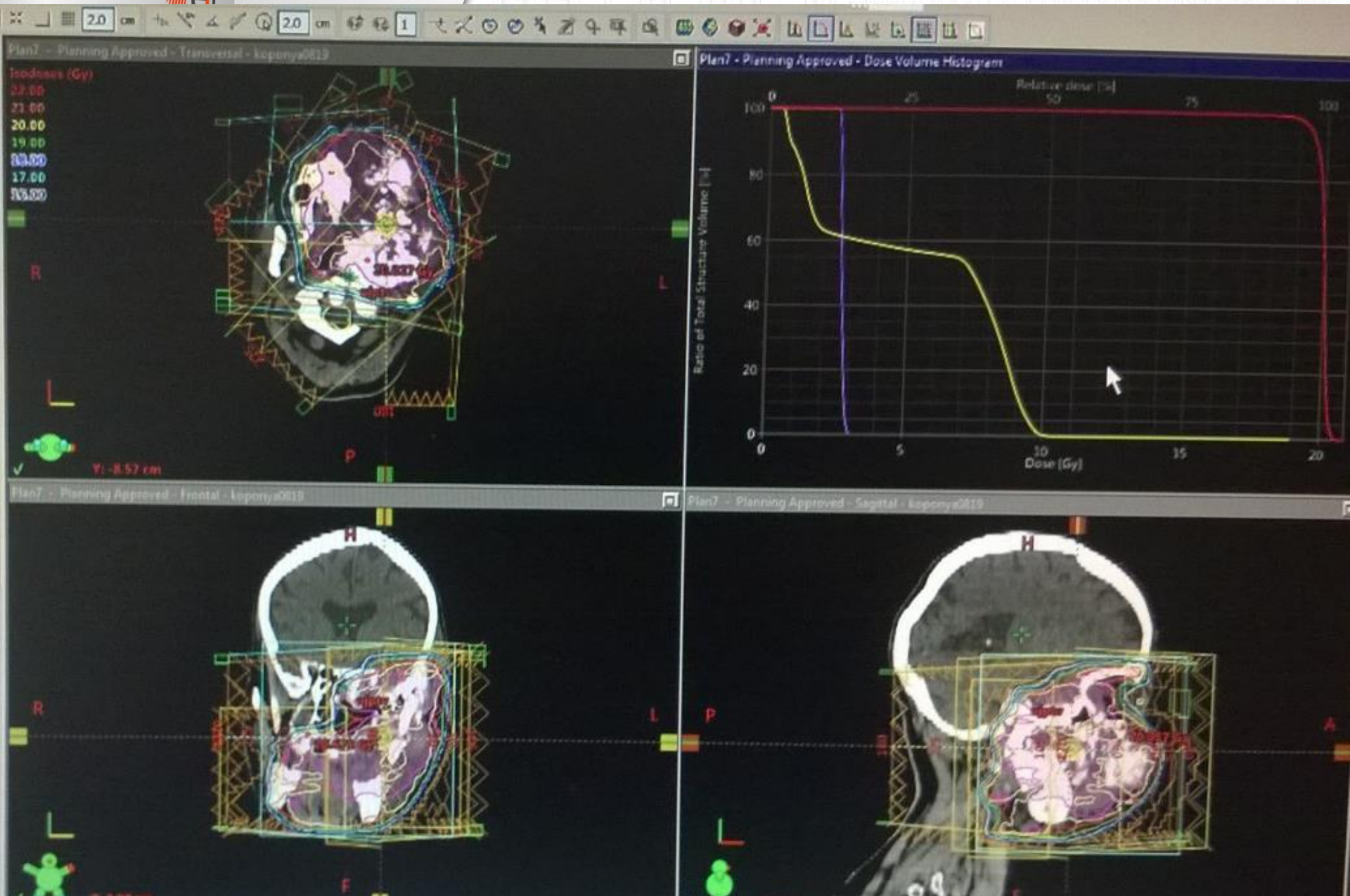


Application for cost coverage of hadron therapy at HIT

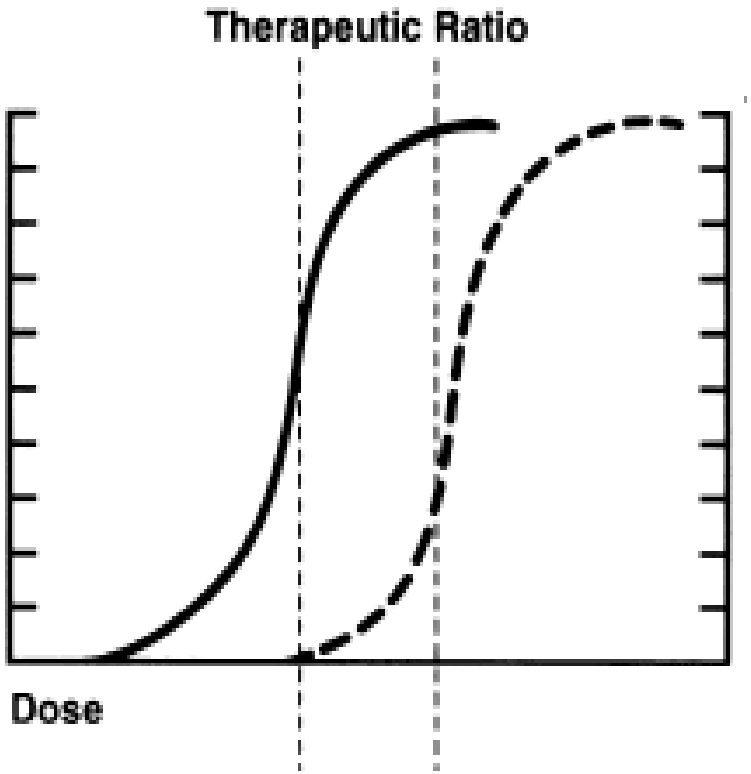
REFUSED

	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
	C1	1.0	100.0	100.0	25.138	38.436	29.740
	C1	0.9	100.0	99.4	30.503	51.306	46.070
	C1	0.4	100.0	100.0	22.110	34.399	29.706
	C1	0.2	100.0	98.6	7.241	10.073	8.078
	C1	0.2	100.0	99.4	5.316	6.144	5.704
	C1	751.7	100.0	100.0	34.753	55.309	50.400
	C1	6391.9	100.0	100.6	0.008	55.309	15.915

IMRT adaptive re-planing



Future approaches under preclinical evaluation



Increase of spatial resolution

- VHEE
- Mixed energy RT
- Mixed particle therapy
- Microbeam radiotherapy
- Dose and LET painting

Timing

Pulsed radiation

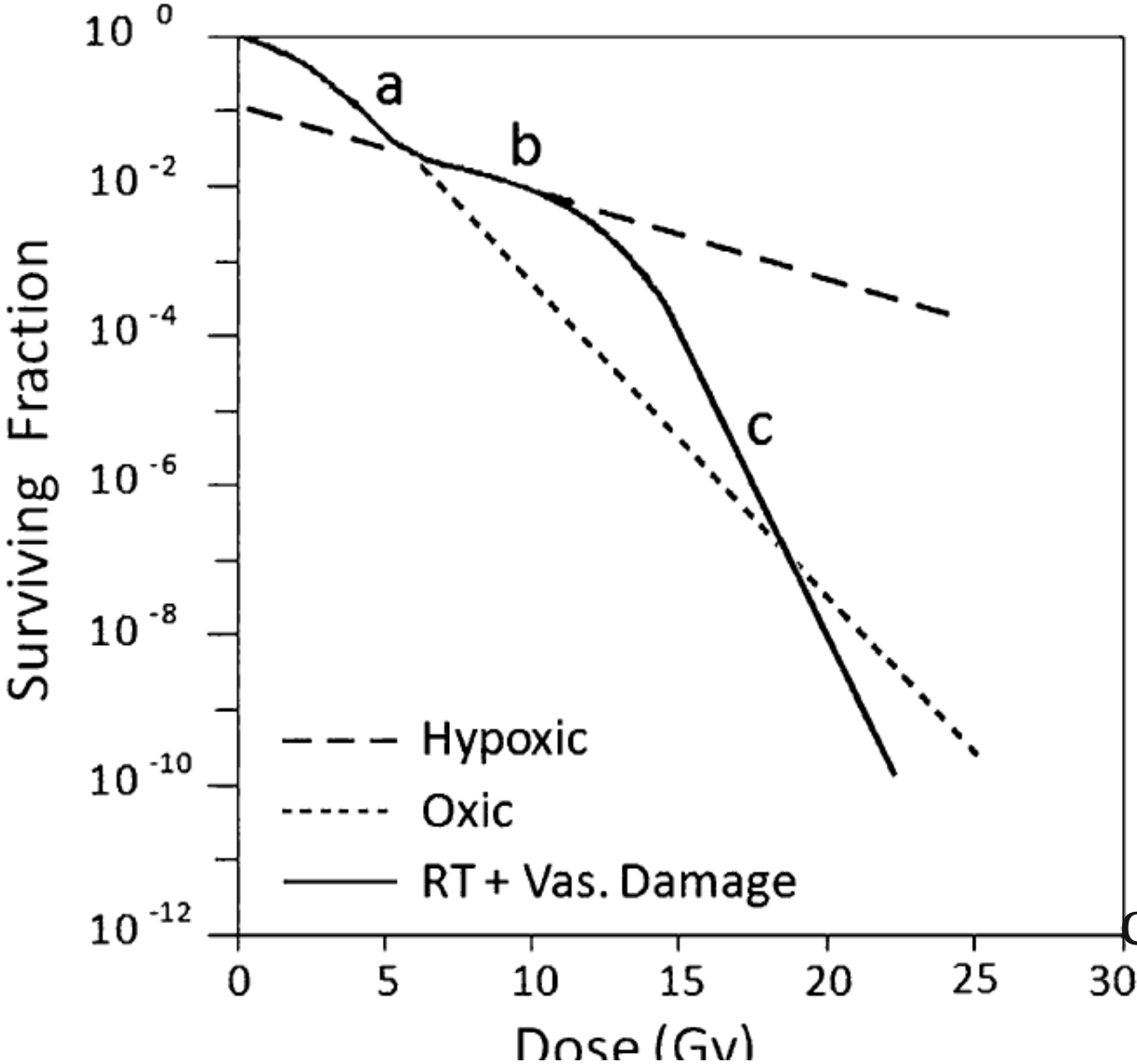
Flash irradiation

Combined treatment

Novel chemo-, hormon, molecular approaches (DBAIT) immunotherapy

Neutron capture/boron proton fusion

Large fraction dose – short time



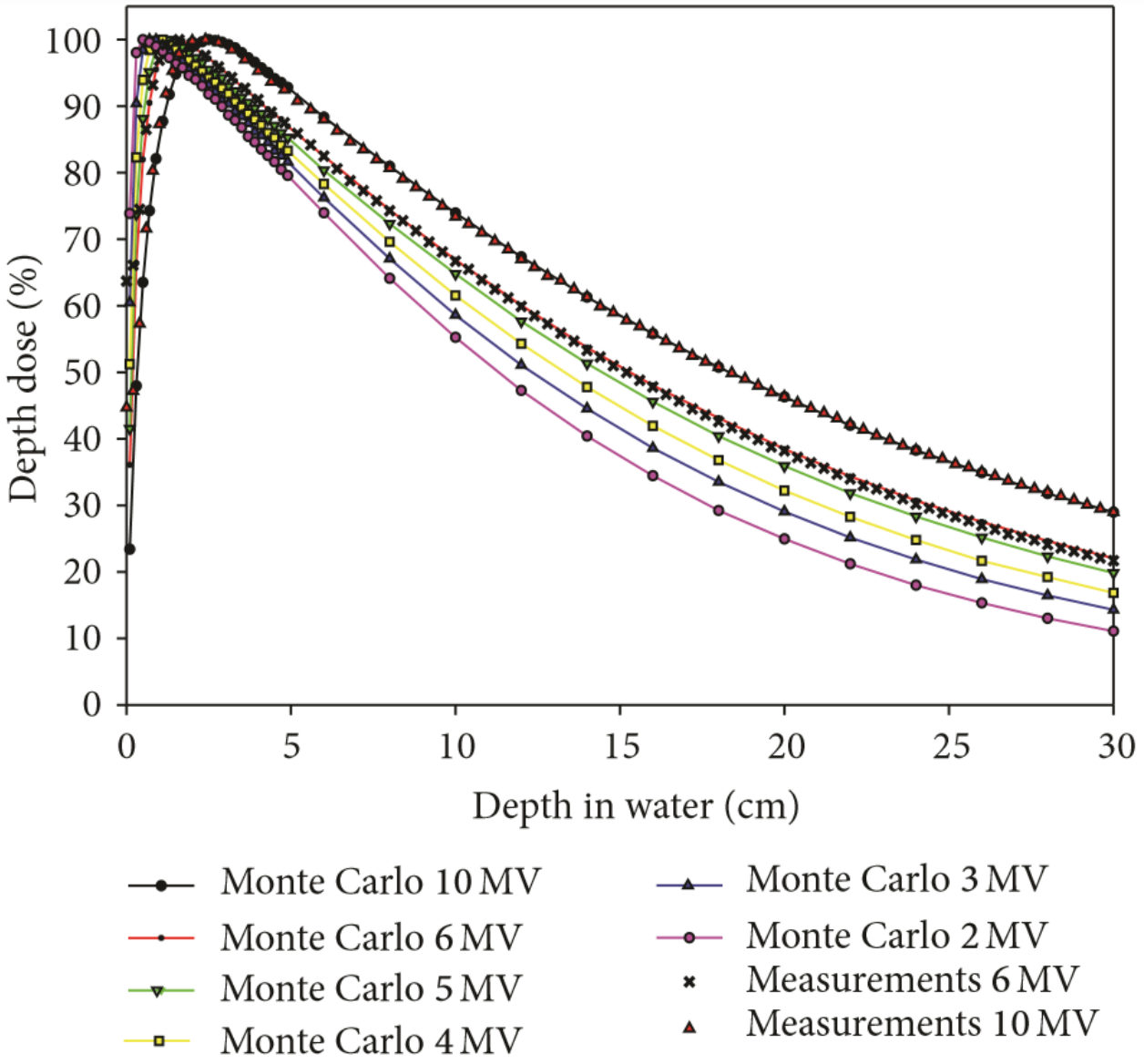
The functional vascularity in tumors decreases within several hours after irradiation with doses higher than 10–15 Gy.

Decrease of tumor stem cells, because tumor perivascular niche is the home of cancer stem cells state

attosecond

Energy Modulated Photon Radiotherapy: A Monte Carlo Feasibility Study

Y. Zhang, Y. Feng, XinMing, and J. Deng

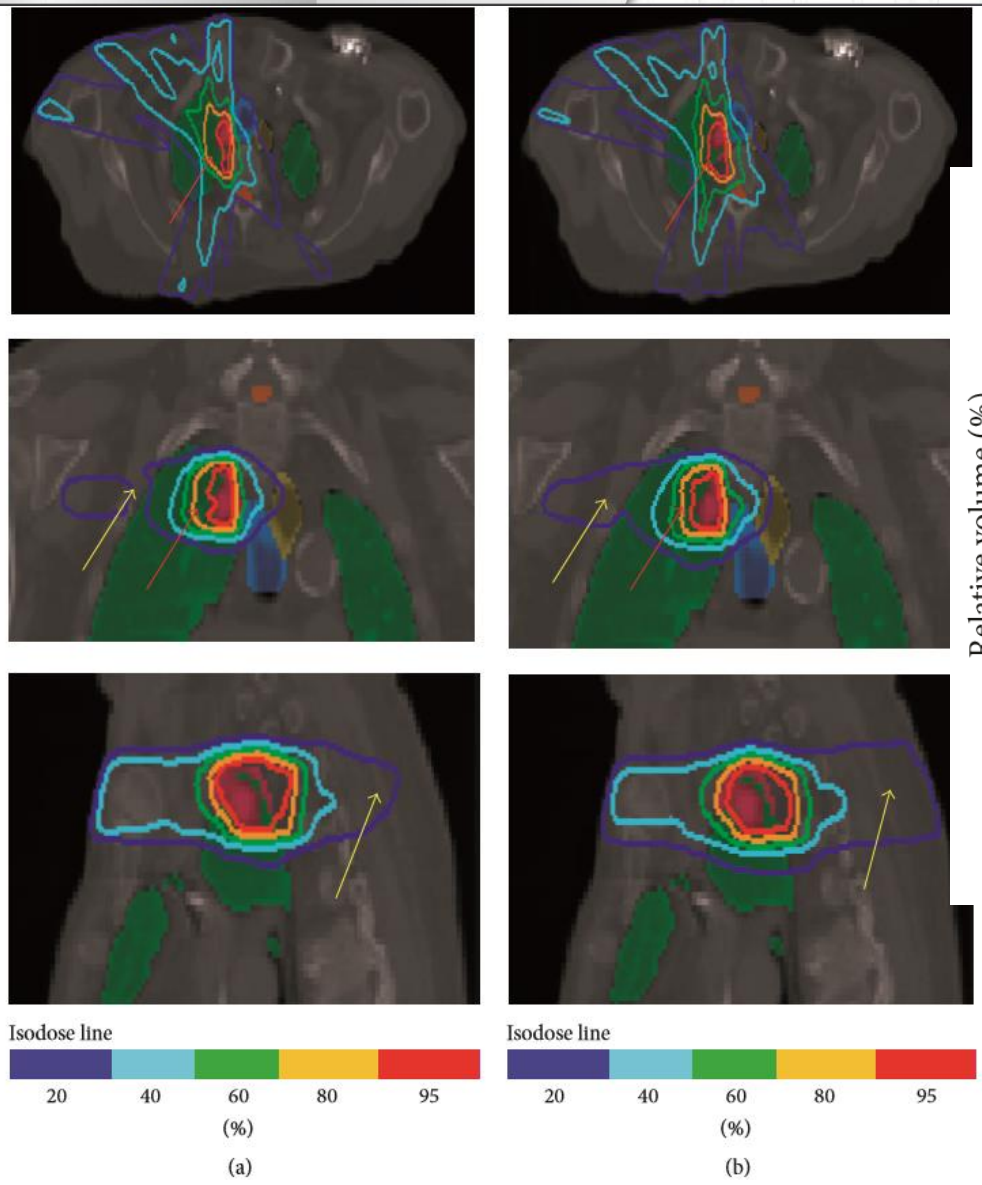


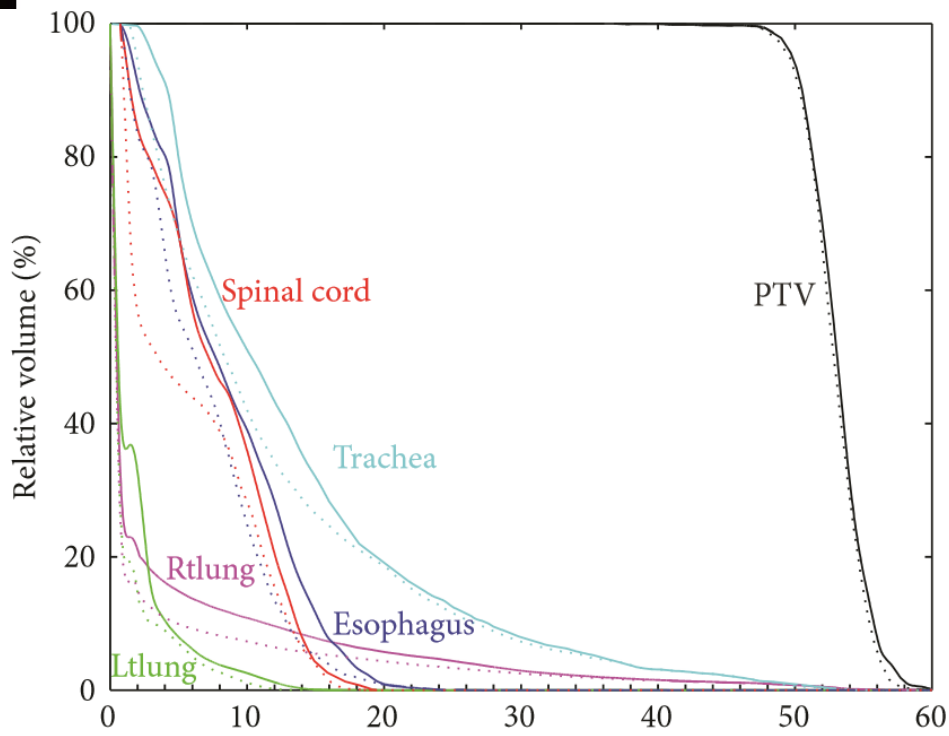
Comparison of EMXRT dose distribution to IMRT

Tumor site	OARs	Indices	IMRT/Gy	EMXRT/Gy	Relative difference*/%
Prostate	Rectum	D_{mean}	32.5	31.5	−3.1
		$D_{15\%}$	49.7	50.7	+2.1
	Bladder	D_{mean}	34.0	33.8	−0.6
		$D_{15\%}$	57.9	57.3	−1.0
	Femur head	D_{mean}	10.6	13.7	+29.2
		$D_{15\%}$	15.4	21.9	+42.2
Head and neck	Spinal cord	D_{mean}	14.3	13.9	−2.8
		D_{max}	44.7	45.2	+1.1
	Brainstem	D_{mean}	14.0	13.5	−3.6
		D_{max}	44.6	43.1	−3.4
	Mandible	D_{mean}	31.2	31.6	+1.3
		D_{max}	82.1	80.3	−2.2
	Left parotid	D_{mean}	13.4	14.9	+11.2
	Right parotid	D_{mean}	26.7	28.6	+7.1
Lung	Spinal cord	D_{mean}	7.7	6.3	−18.2
		D_{max}	19.4	17.2	−11.3
	Left lung	D_{mean}	3.5	2.6	−25.7
	Right lung	D_{mean}	1.7	1.1	−35.3
	Trachea	D_{mean}	13.1	12.9	−1.5
	Esophagus	D_{mean}	8.5	7.4	−12.9
Spine	Spinal cord	D_{mean}	4.9	4.7	−4.1
		D_{max}	15.9	14.6	−8.2
	Liver	D_{mean}	1.3	1.2	−7.7
	Kidneys	D_{mean}	0.3	0.3	0.0
Brain	Brainstem	D_{mean}	6.3	5.9	−6.3
		D_{max}	20.2	20.2	0.0
	Eyes	D_{max}	3.1	2.7	−12.9
	Chiasm	D_{max}	2.6	2.4	−7.7
Thyroid	Spinal cord	D_{mean}	17.6	16.0	−9.0
		D_{max}	41.6	40.6	−2.3
	Esophagus	D_{mean}	44	43.3	−1.7
	Trachea	D_{mean}	43.2	42.0	−2.7
	Pharynx	D_{mean}	8	9.7	+21.1

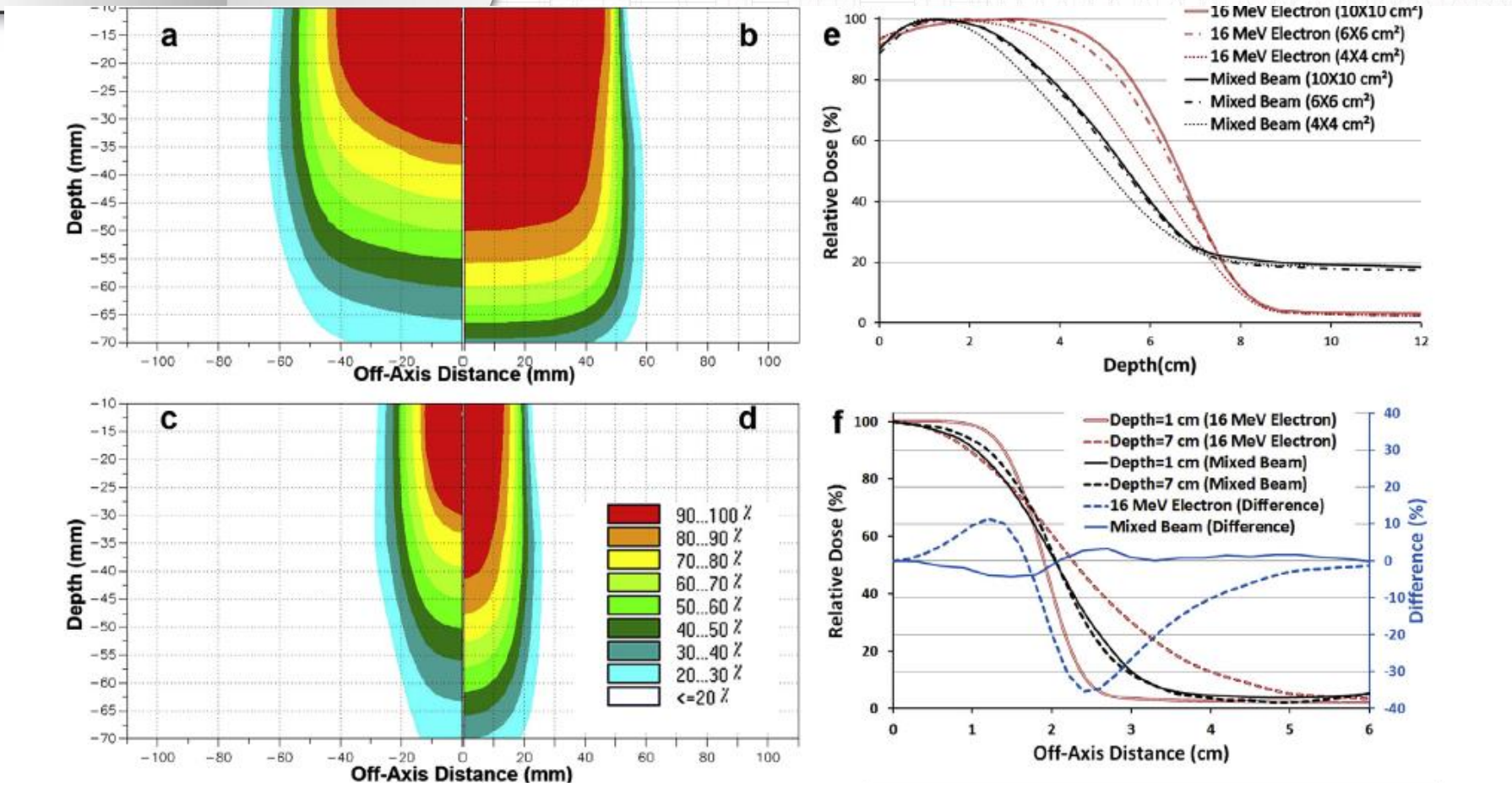
*Relative difference = 100% × ($Index_{EMXRT}$ − $Index_{IMRT}$)/$Index_{IMRT}$. The "+" and "−" indicate whether the dose index of the EMXRT plan is larger or smaller than that of IMRT plan. D_{mean} is the mean dose, and D_{max} is the maximum dose.

Comparison of EMXRT dose distribution to IMRT for lung tumor irradiation





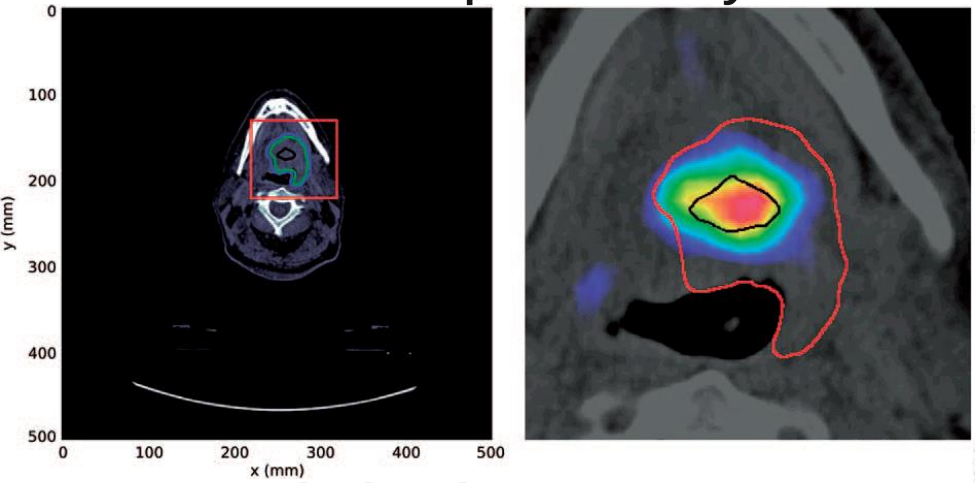
N. Khaledi et al. Simultaneous production of mixed electron-photon beam in a medical LINAC: A feasibility study *Physica Medica 31 (2015) 391-397*



The advantages of mixing the electron and photon beam is reduction of pure electron's penumbra dependency with the depth, especially for small fields, also decreasing of dramatic changes of PDD curve with irradiation field size.

Dose- and LET-painting with particle therapy. Bassler N, Jäkel O, et al. Acta Oncol. 2010 Oct;49(7):1170-6.

Simultaneous dose and LET optimisation has a potential to achieve higher tumour control and/or reduced normal tissue control probability.



LET-painting increases tumour control probability in hypoxic tumours

N. BASSLER J.TOFTEGAARD et al.
Acta Oncologica

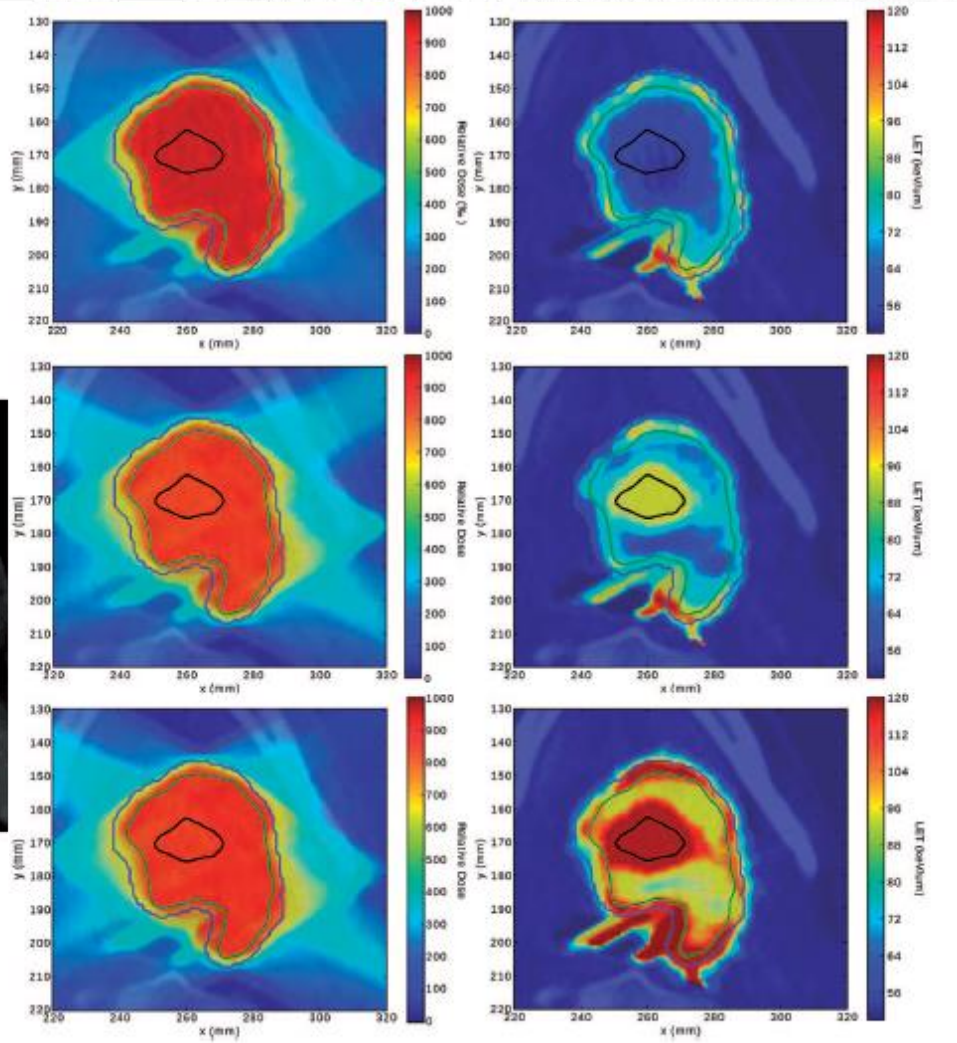


Figure 3. Dose and dose-averaged LET profiles shown in left and right column, respectively. First row is a carbon-12 ion plan using four conventional fields with homogeneous dose. The highest LET is then found at the rim of the SOBPs as seen in the upper right figure. LET-painting, as shown in the middle row, allows for redistributing LET to cover the assumed hypoxic structure, depicted as the black entity, with increased LET. The energy fluence budget for the amount of particles used is the same for both plans in the upper two rows. The last row shows LET-painting again, but now with oxygen-16 ions, resulting in a pronounced increase of LET in the HTV. HTV, hypoxic target volume; LET, linear energy transfer; SOBP, spread out Bragg peak.

Proton/ion acceleration techniqes

cyclotron

synchrotron

Small synchro-cyclotron

cyclotron driven linac

Dielectr. wall linacs

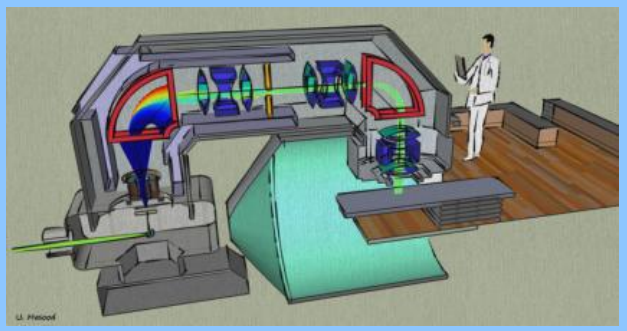
FFAG

Fixed Field Alternating Gradient

lasers

Plasma wake field

Compact EIMCPT design



http://phys.org/news/2014-06-compact-proton-therapy-cancer.html

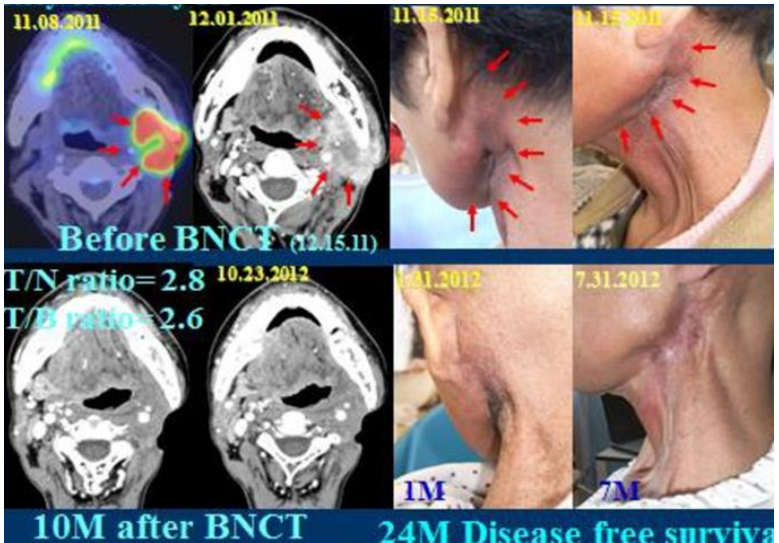
Boron Neutron Capture Therapy (BNCT) for GBM at the Petten facility- European phase I study

HFR Research reactor

<u>Boron carrier</u>

BSH

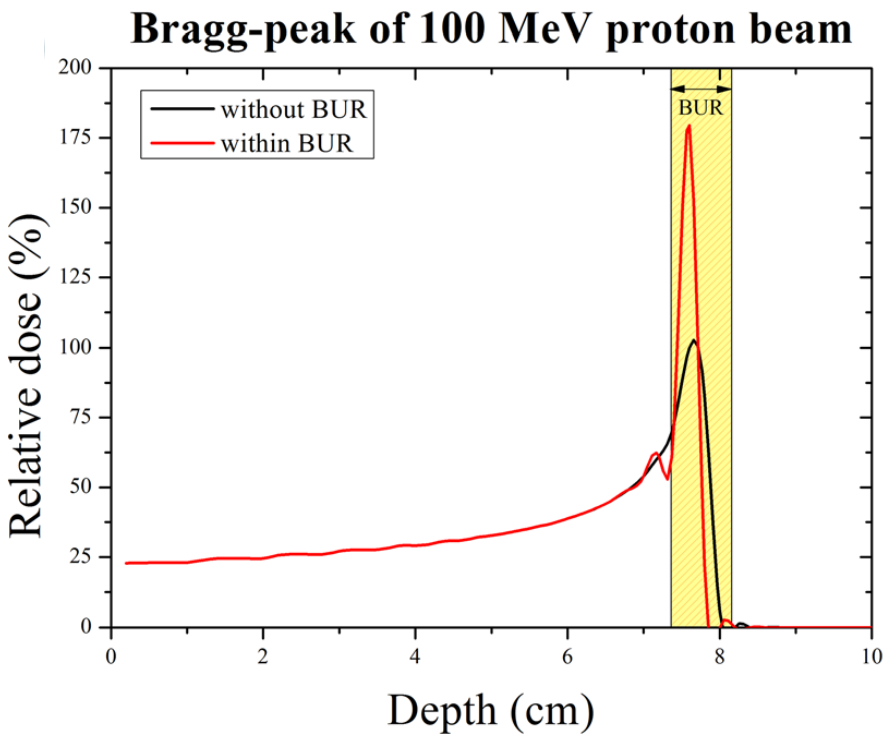
$Na_2B_{12}H_{11}SH$

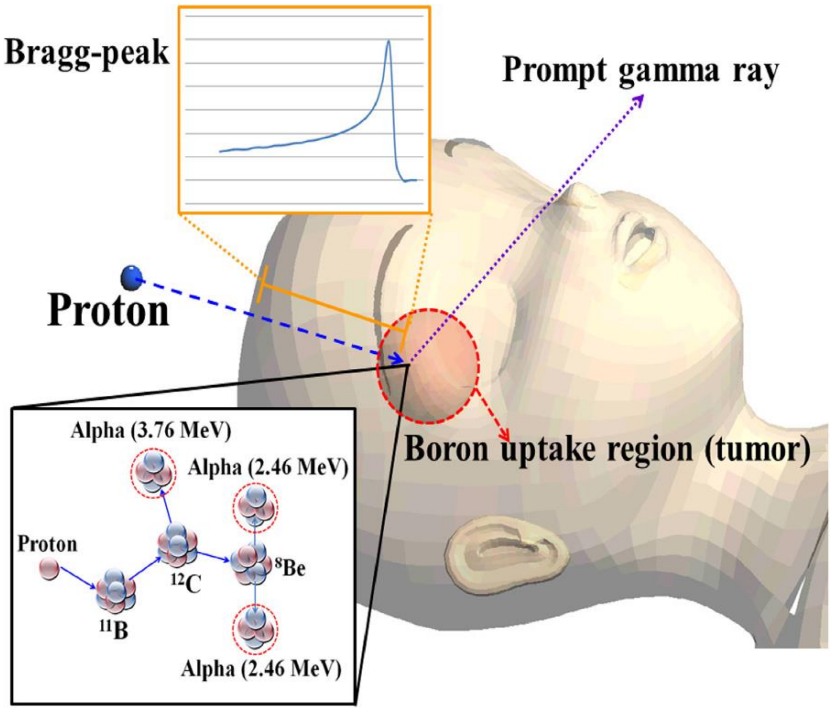


Recurrent H&N tumors

Boron carrier:
BPA

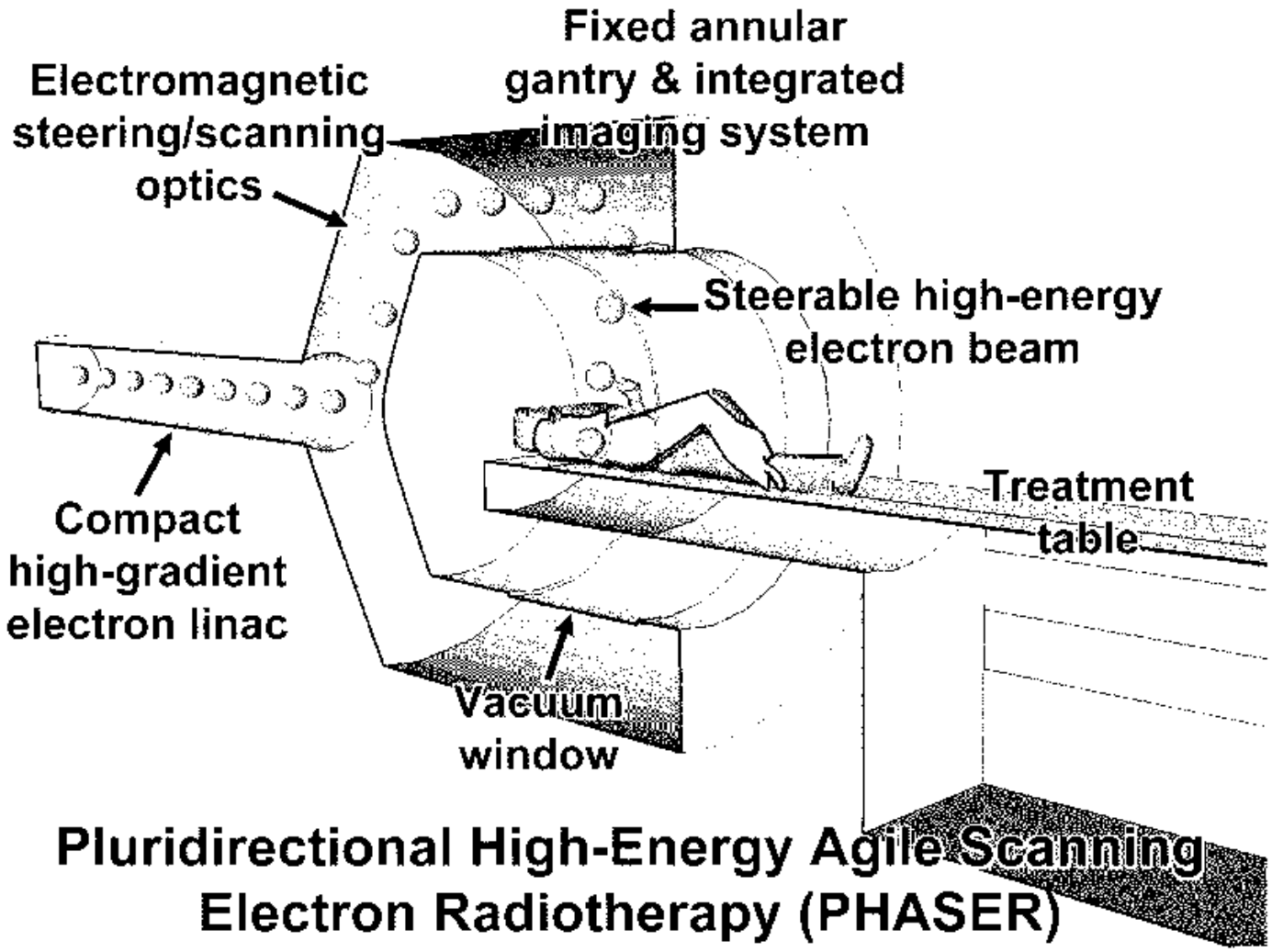
Yoon DK, Jung JY, Suh TS. **Application of proton boron fusion reaction to radiation therapy: a Monte Carlo simulation study**. Appl Phys Lett. 2014;105:223507.





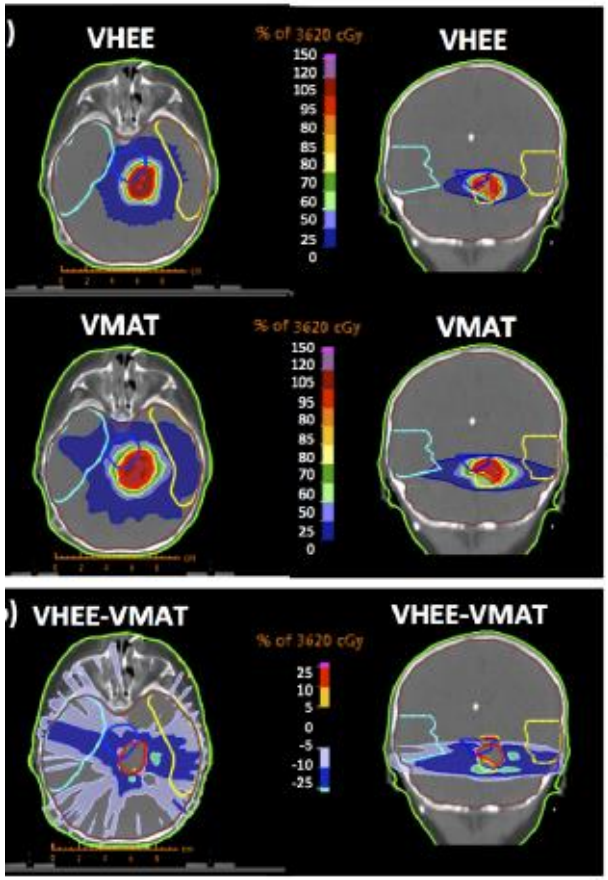
After the proton reacts with the boron (11B), the boron changes to carbon (12C) in an excited state. The excited carbon nucleus is split into alpha particle of 3.76 MeV and beryllium (8Be). Subsequently, the beryllium is divided into the two alpha particles of 2.74 MeV each. The maximum point of the Bragg-peak is increased by the boron at the BUR. In addition, the prompt gamma ray emitted by the reaction can provide information about the therapy region.

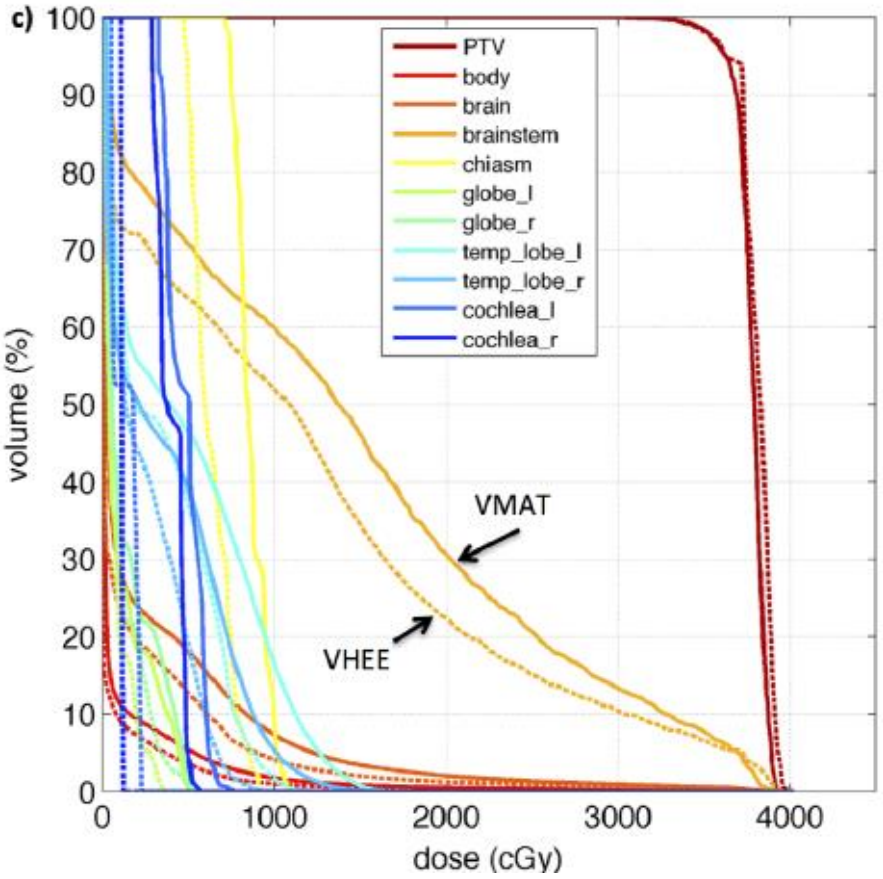
Multifield Very High Energy Electron accelerator



https://www.google.com/patents/US20130231516

The dosimetric advantage of VHEE radiotherapy over photon VMAT radiotherapy was demonstrated for different clinical cases (pediatric, lung, liver, esophage, prostate).





VHEE dose to allcritical organs was up to 70% lower than the clinical 6 MV VMAT dose for the same target and the integral dose was decreased by 33% compared to the VMAT plan.

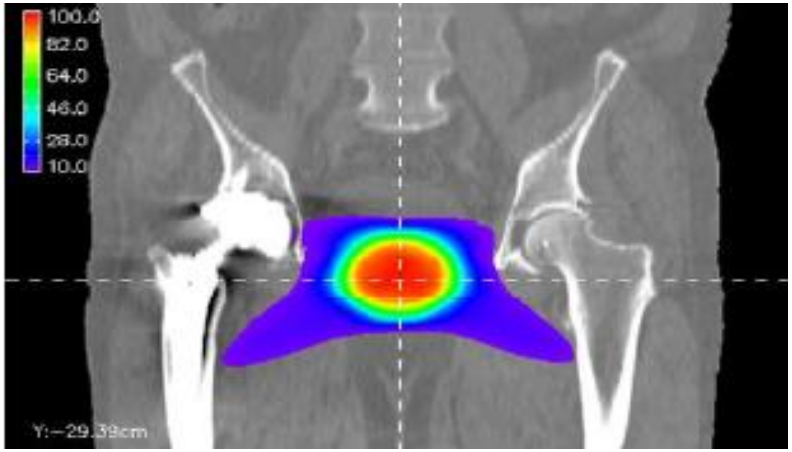
Palma B, et al Assessment of the quality of very high-energy electron radiotherapy planning Radiother Oncol. 2016 Apr;119(1):154-8.

Bazalova-Carter M.et al. Treatment planning for radiotherapy with very high-energy electron beams and comparison of **VHEE**and VMAT plan. Med Phys. 2015 May; 42 (5): 2615-2

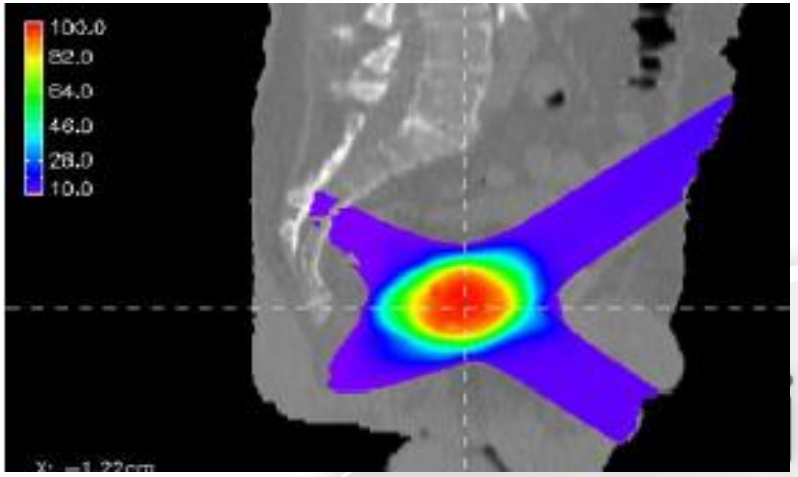
C, DesRosiers, V. Moskvina, M. Caoa, C. J. Joshib, M. Langera **Laser-plasma generated very high energy electrons in radiation therapy of the prostate**

Monte Carlo simulation of radiation treatment by laser accelerated very hig energy (200 MeV) electron VHEE.

Small diameter VHEE beamlets can be scanned, thereby producing a finer resolution intensity modulated treatment than photon beams.



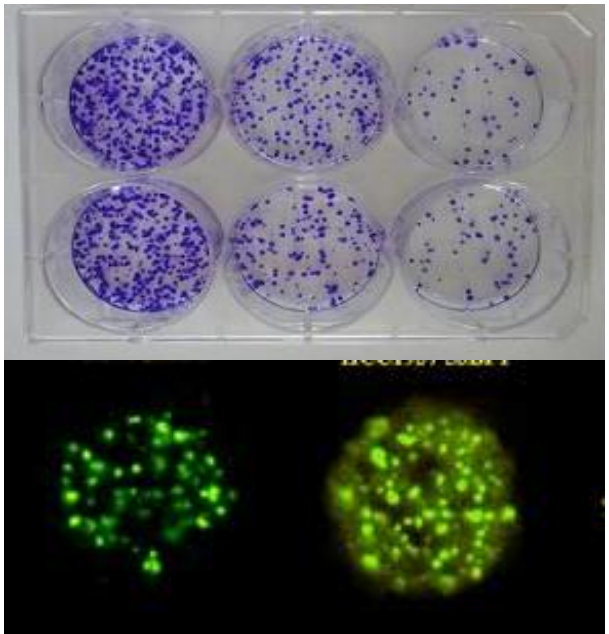
A VHEE accelerator may be optimally designed using laser-plasma technology



attosecond

Results on radiobiology experiments on laser driven ionizing RT sources

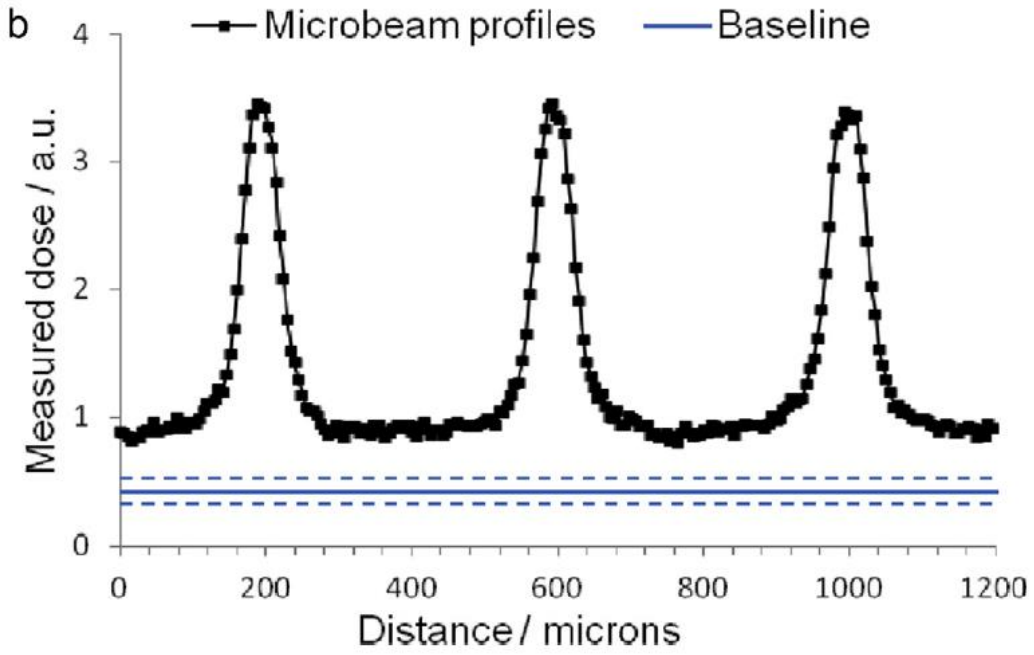
Up to now the results of both in vitro, and in vivo experimental data reveal no evidence for a substantially different radiobiology effect of **laser accelerated particles (electron/proton)** with ultra-high dose rate, pulsed or continous mode of operation.



Microbeam radiation therapy (MRT)

Synchrotron-based MRT composed of spatially fractionated, planar x-ray (50-600keV)
25-75 micron-wide beams, with a very sharp penumbra, separated by a distance several times of their beam width.
These microbeams create unique dose profiles of alternating peaks and valleys with high peak-to-valley-dose-ratios (PVDR)

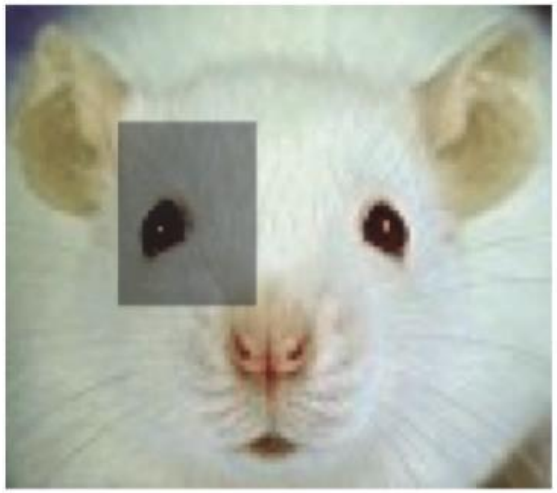
Zhang et al. *Expert Rev Anticancer Ther*. 2015 December



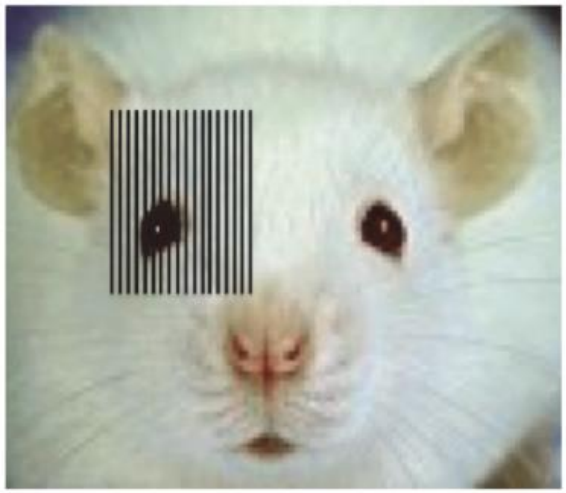
The highly brilliant Synchrotron sources have a very small beam divergence and an extremely high dose rate.

Peak entrance doses of several hundreds of Gy are extremely well tolerated by normal tissues and at the same time provide a higher therapeutic index for various tumor models in rodents.

E. Brauer-Krisch a, J-F.s Adam et al. Medical physics aspects of the synchrotron radiation therapies:Microbeam radiation therapy (MRT) and synchrotron stereotactic radiotherapy (SSRT) Physica Medica 31 (2015) 568e583



Synchrotron broad beam



Synchrotron microbeam

C. Fernandez-Palomo, C. Mothersill, E. Bräuer-Krisch, J. Laissue, C. Seymour, E. Schültke: γ-H2AX as a Marker for Dose Deposition in the Brain of Wistar Rats after Synchrotron Microbeam Radiation PLoS ONE 10(3): e0119924. 2015

Doses of 350 Gy can trigger the release of bystander signals that significantly amplify the DNA damage caused by radiation and that the γ-H2AX biomarker does not only represent DNA damage produced by radiation, but also damage caused by bystander effects.

Synchrotron-based MRT resulted in 10 fold prolonged survival of the treated animals with brain tumor xenograft

MRT

Donzelli *et al.*: Conformal image-guided MRT at the ESRF

With the implementation of conformal image-guided MRT,the treatment of deep-seated tumors in large animals will be possible for multiple port irradiations. The final workflow will consist of CT-imaging,subsequent individual treatment planning, including segmentation of target volume, organs at risk, and fiducial markers, and the definition of the treatment fields.

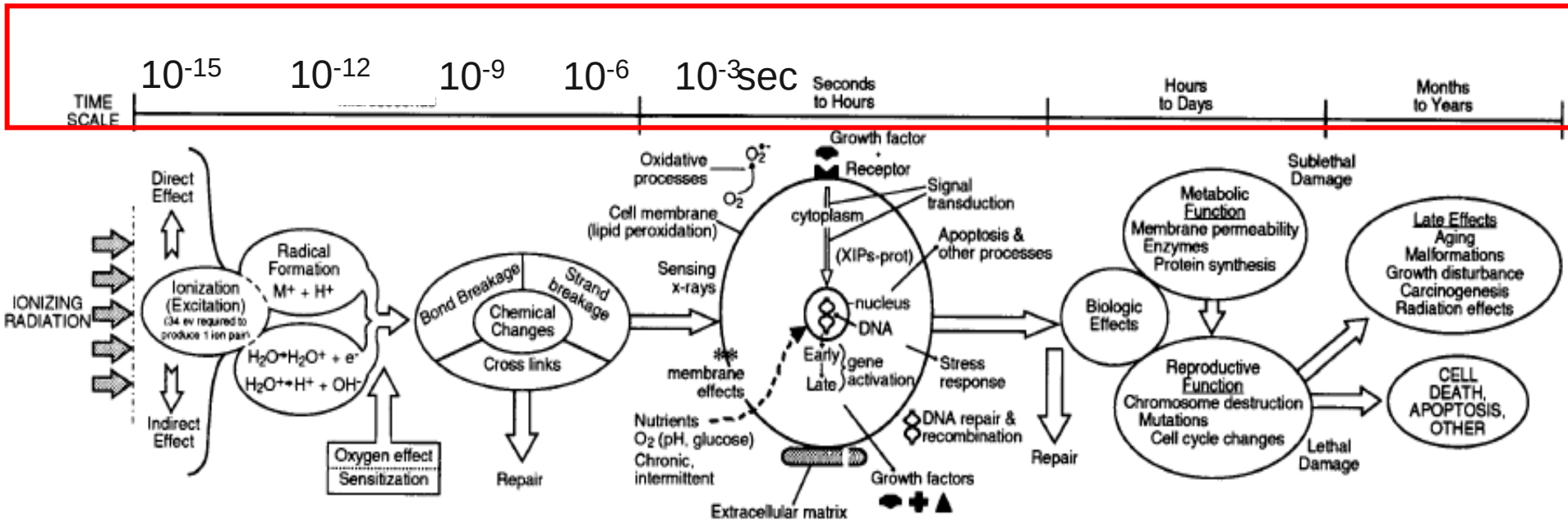
Physiologically gated microbeam radiation using a field emission x-ray source array

In the *in vivo* study, the histology result showed gating increased PVDR by a factor of 2.4 compared to the nongated case, similar to the result from the phantom study. The full width at tenth maximum of the microbeam decreased by 40% in gating *invivo* and close to 38% with phantom studies.

The CNT field emission x-ray source array can be synchronized to physiological signals for gated delivery of x-ray radiation to minimize motion-induced beam blurring. The technique allows for more precise MRT treatments and makes the CNT MRT device practical for extended treatment.

Cell culture and in vivo tumor model experiments on pulsed mode

Time scale of RT effects



Radiobiological influence of megavoltage electron pulses of ultra-high pulse dose rate on normal tissue cells L. Laschinsky
(10^{12} Gy/min, <80 mGy/ 1ps)

Oppelt M, et al. (2015) Comparison study of in vivo dose response to laser-driven versus conventional electron beam. Radiat Environ Biophys 54:155–166

FLASH irradiation: <500ms pulses of >40 Gy/s

A 17 Gy conventional irradiation induced pulmonary fibrosis and activation of the TGF-beta cascade in 100% of the animals 24-36 weeks post-treatment, as expected, whereas no animal developed complications below 23 Gy flash irradiation, and a

30 Gy flash irradiation was required to induce the same extent of fibrosis as 17 Gy conventional irradiation.

Favaudon V, Fouillade C, Vozenin MC ***Ultrahigh dose-rate, "flash" irradiation minimizes the side-effects of radiotherapy]*** *Cancer Radiother. 2015 Oct;19(6-7):526-31*

eli attosecond

Laser driven particle beams

X-UV, X-ray photons

Very high energy electron

Protons
ions
neutrons

Integrated facility with particle selection**?**

Ultra short pulses

Ultra high dose rate ($<1 Gy/s^{-10}$)

High repetition rate

Microbeams of photons (50-600 KeV) protons (20 MeV) **?**

Laser driven ionizing radiation beyond VHEE and proton acceleration

Ultraintense beam

-short treatment time without increased entrance (skin) dose

- high temporal resolution (adaptive response, FLASH RT

-Intensity modulation with higher resolution

-Microbeam RT

Ultrashort dose delivery

– no need for internal organ motion management

Potential for simultaneous multiple particle beams

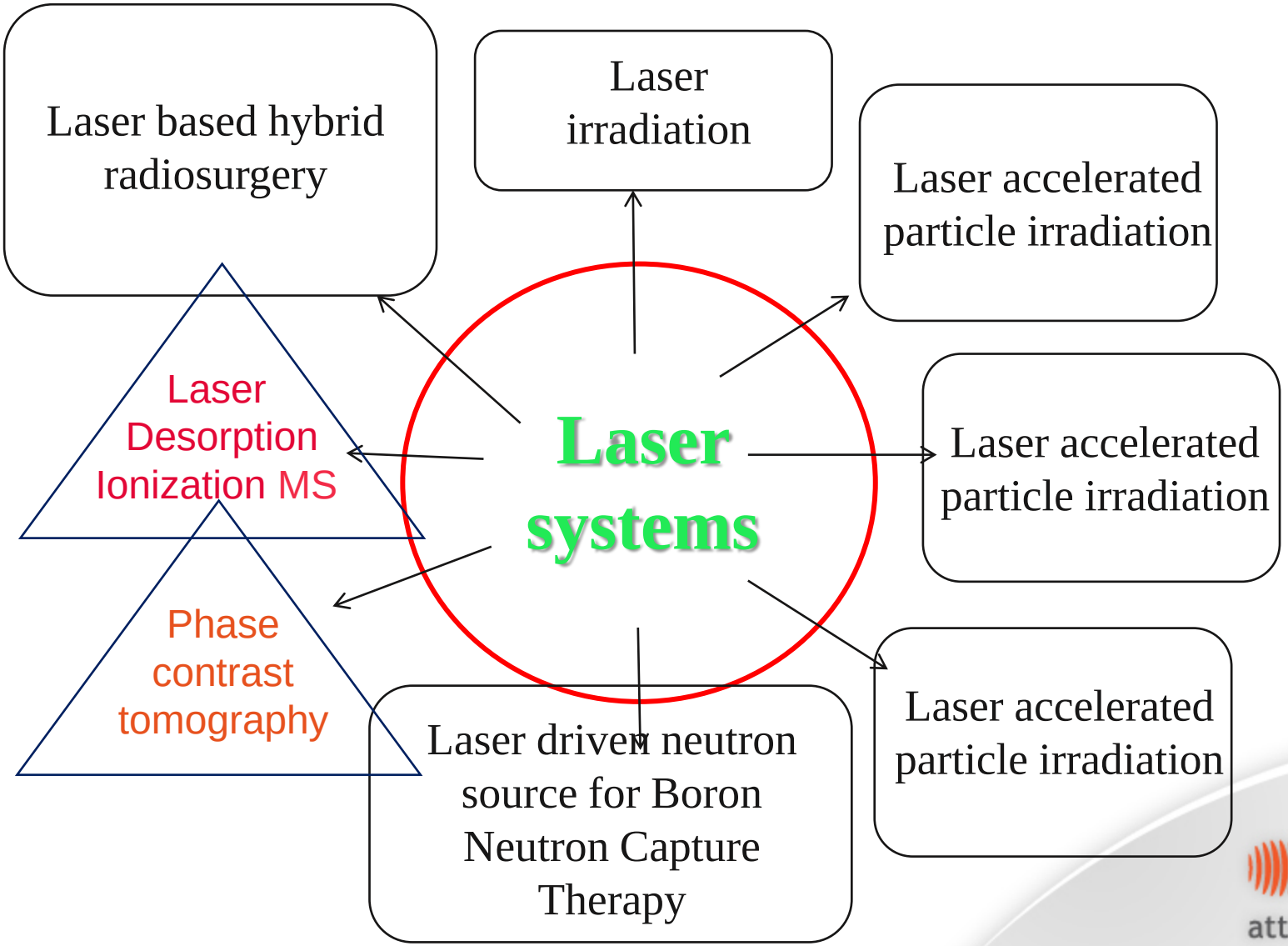
Epithermic neutron beam for BNCT

LET/RBE painting

Flexibility

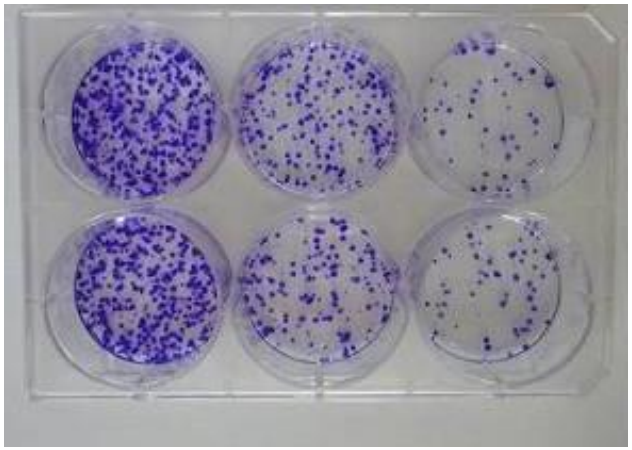
- intra operative radiotherapy – hybrid radio-surgery

Hospital based complex Laser Facility for cancer treament

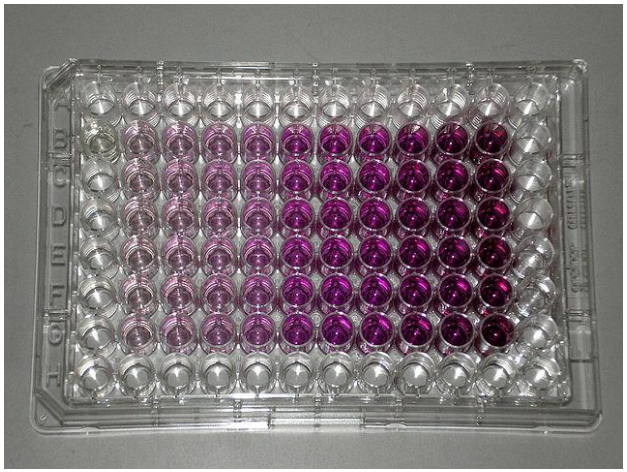


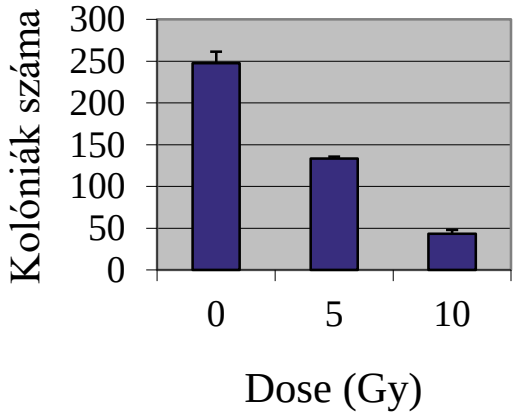
attosecond

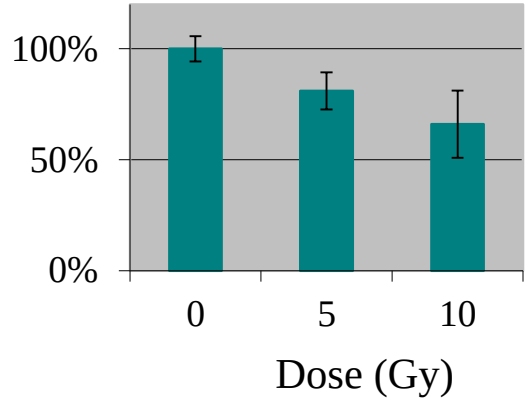
Colony forming assay



MTS assay

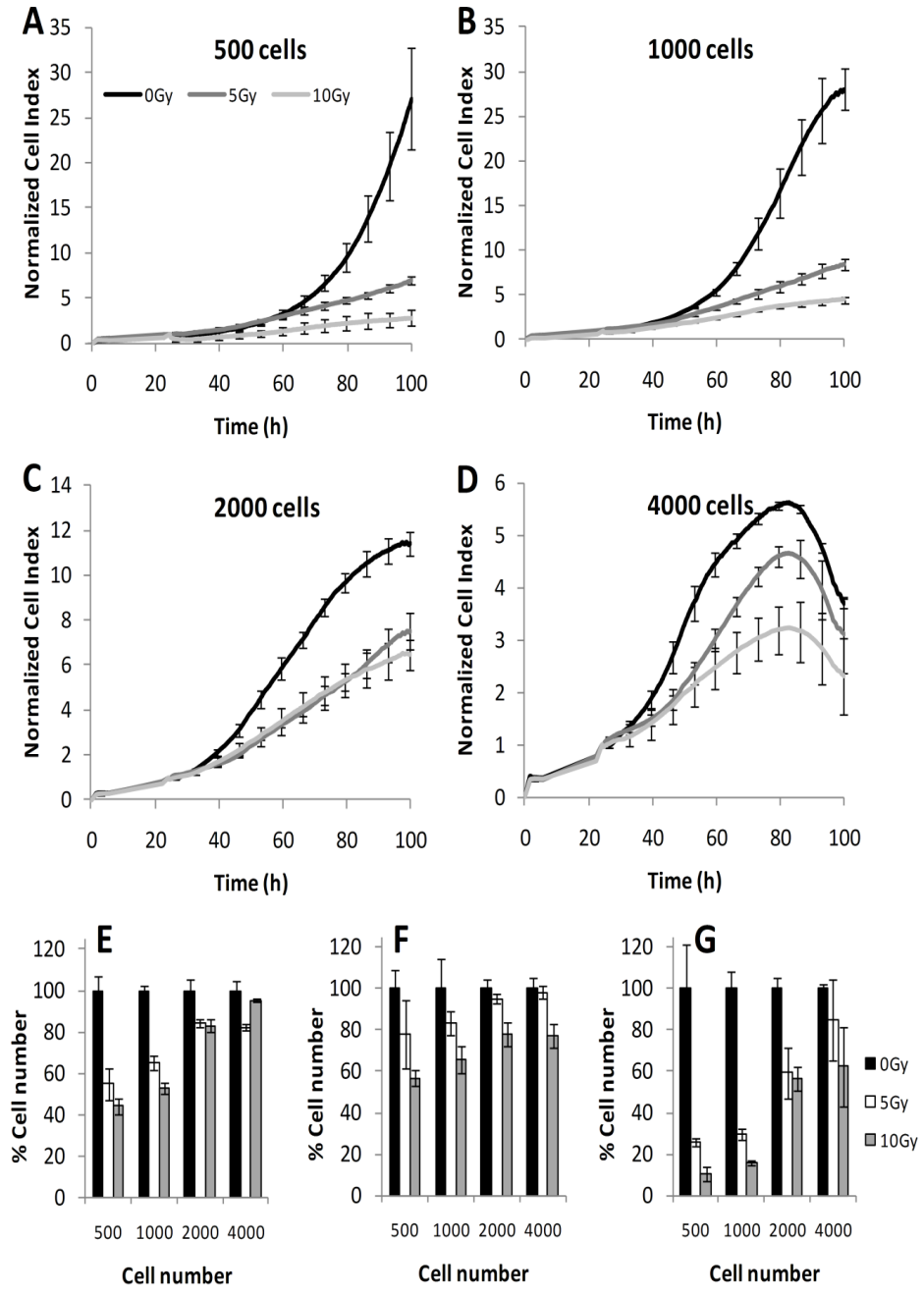


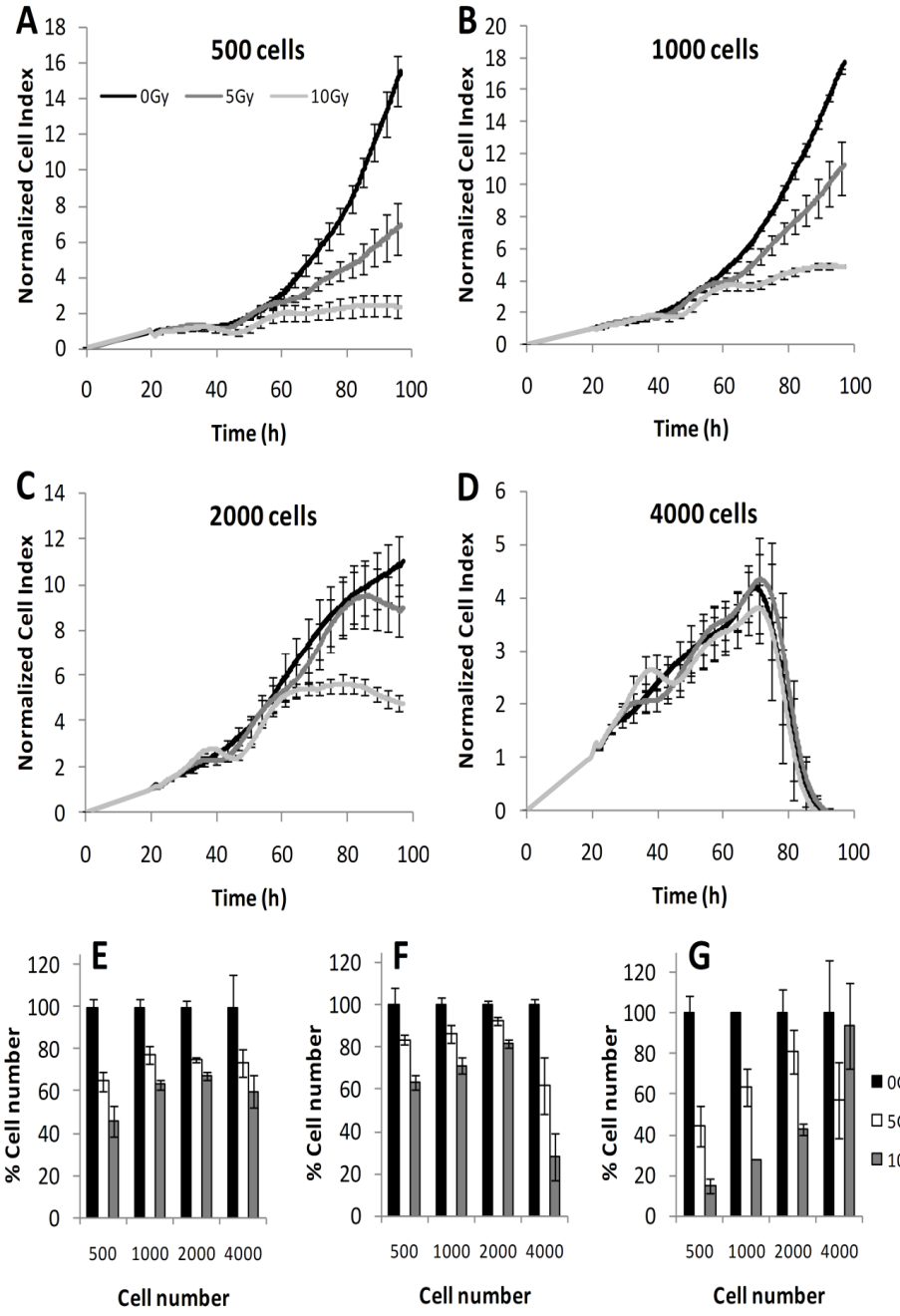




Dynamic monitoring of ionizing radiation effect using a Novel Real-Time Cell Analysis Platform

Mán I, Plangár I, Szabó ER, Tőkés T, Szabó Z, Nagy Z, Fekete G, Mózes P, Puskás LG, Hideghéty K, Hackler L Jr


A
500 cells
0Gy
5Gy
10Gy
Normalized Cell Index
Time (h)
B
1000 cells
C
2000 cells
D
4000 cells
E
F
G
% Cell number
Cell number
500
1000
2000
4000
0Gy
5Gy
10Gy


A
500 cells
0Gy
5Gy
10Gy
Normalized Cell Index
Time (h)
B
1000 cells
C
2000 cells
D
4000 cells
E
F
G
% Cell number
Cell number
500
1000
2000
4000
0Gy
5Gy
10Gy

Acute project: Methods

„Peripheral inflammatory activation after hippocampus irradiation in the rat”

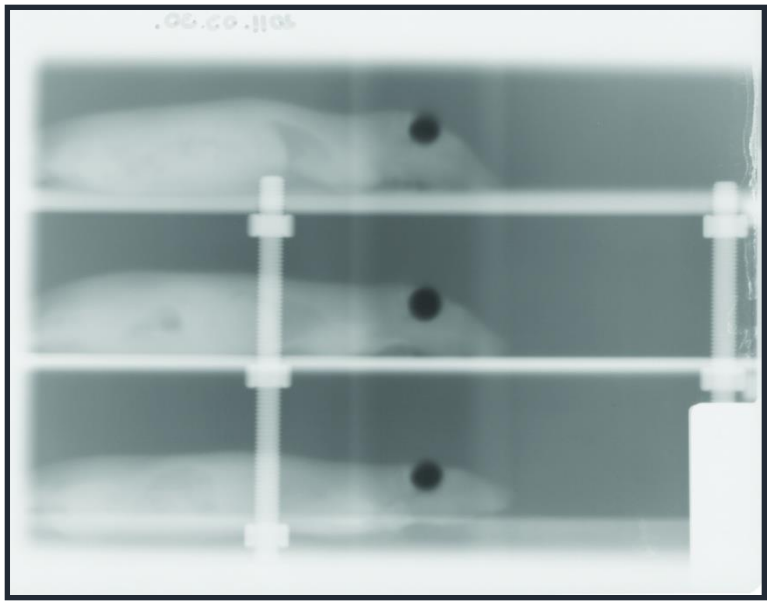
Anaesthesia: i.p. chloral-hydrate

Positioning: special bunk-bed

Source: 1,26 MeV energy Cobalt

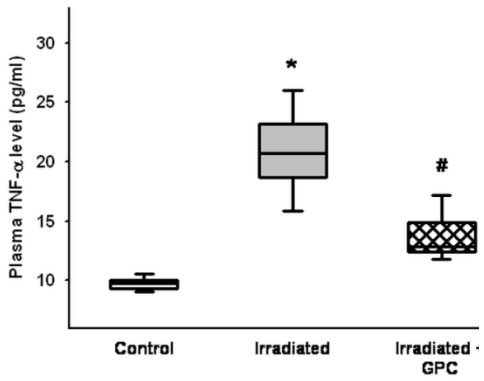
Dose: 40 Gy (2x20Gy)

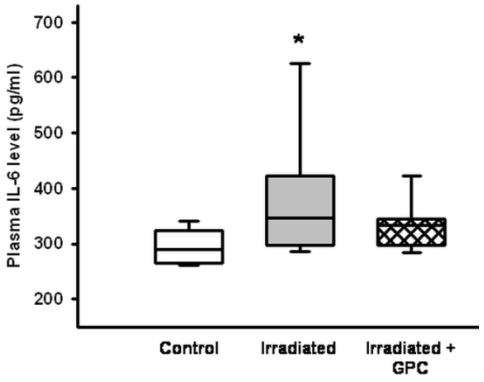
Irradiation: 10 mm diameter collimator, homogen irradiation of hippocampus (at both hemispheres)

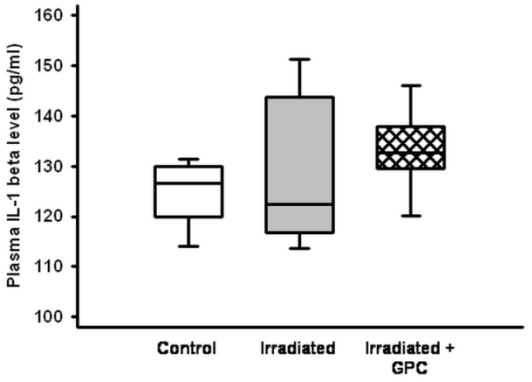


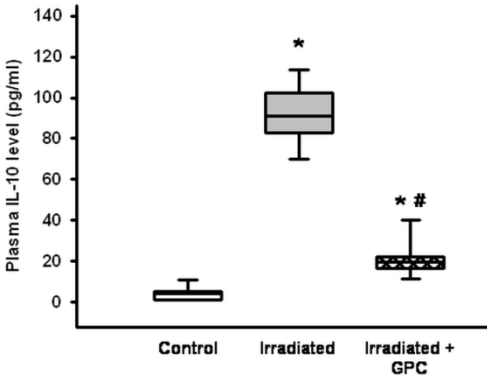
Acute project: Results

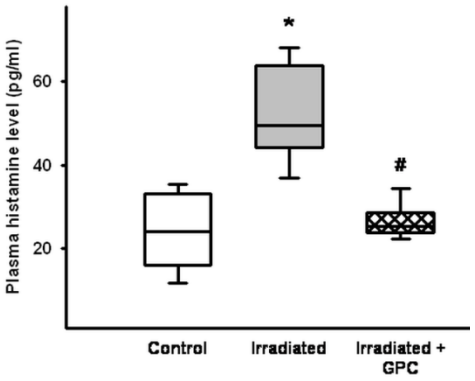
„Peripheral inflammatory activation after hippocampus irradiation in the rat"

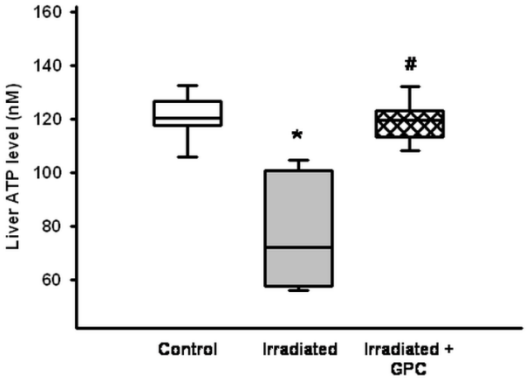












Statistics: Between groups: Kruskal-Wallis and Dunn-test
(Median, 25th and 75th percentiles) $^{*}p < 0.05$ *vs* Control group, $^{\#}p < 0.05$ *vs* Irradiated group.

Acute project: Summary

„Peripheral inflammatory activation after hippocampus irradiation in the rat”

*** There are significant production of pro- and anti-inflammatory cytokines (TNF-α, IL-6, IL-10) after 40 Gy hippocampal irradiation in the brain.**

*** Therefore the BBB opens and the inflammatory cytokines appear in the peripheral circulation.**

At the same time,

i.v. GPC treatment prevents:

- **the ATP depletion,**
- **the elevation of the histamine and the pro- inflammatory cytokine (TNF-α and IL-6) levels,**
- **increase the anti-inflammatory cytokine (IL-10) level**

The exogen GPC has anti-inflammatory effect and provide protection against the irradiation-induced brain inflammation caused biochemical consequences.

Chronic project: Methods

„Radio-neuroprotective effect of L-alpha-glycerylphosphorylcholine in experimental rat model”

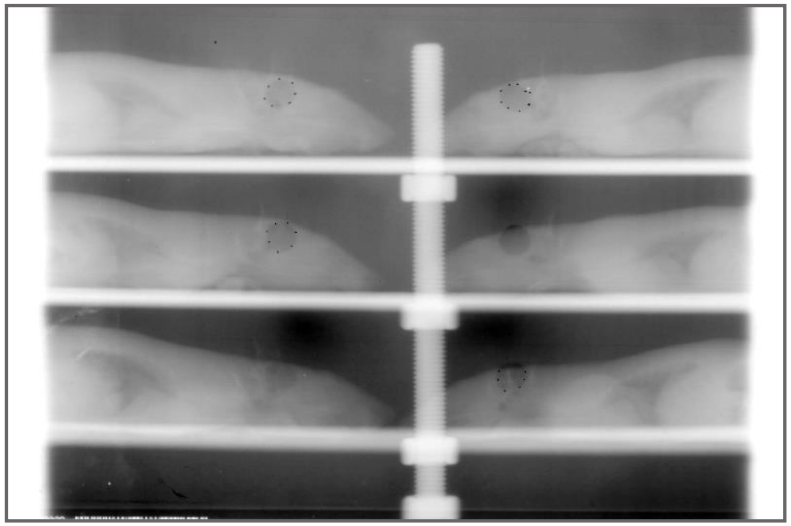
Anaesthesia: i.p. chloral-hydrate

Positioning: special bunk-bed

Source: 6 MeV energy Siemens linear accelerator

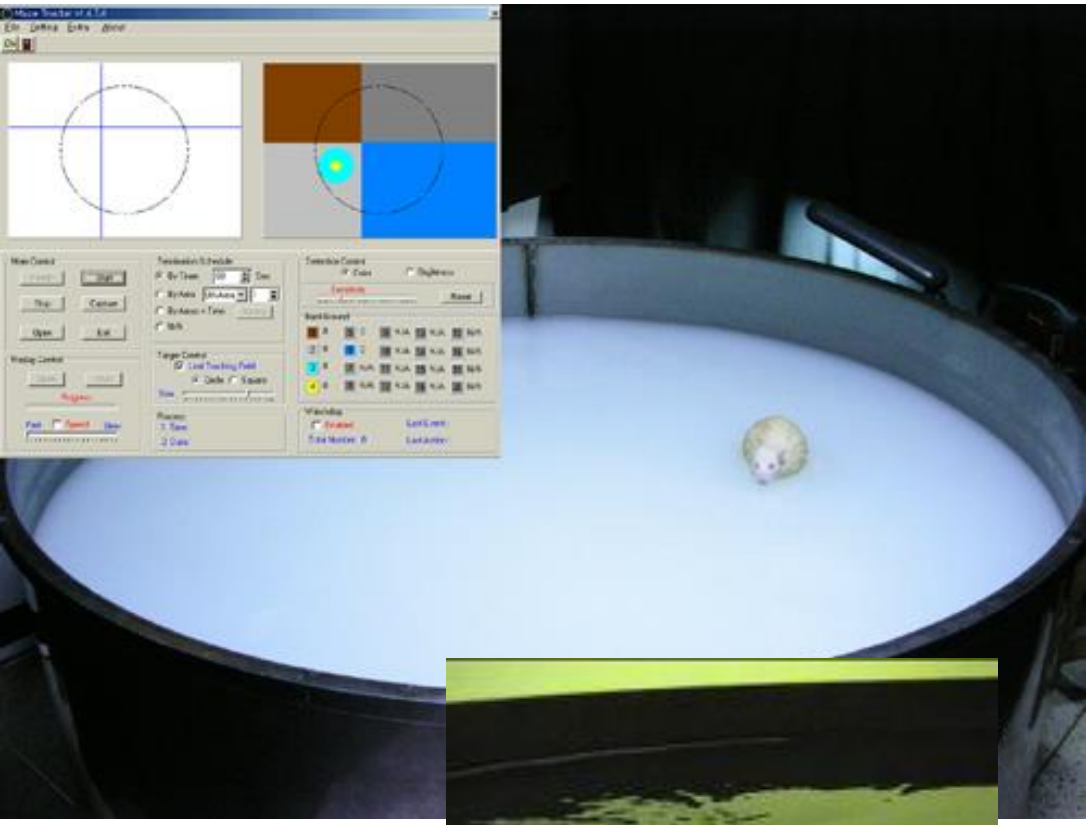
Dose: 40 Gy

Irradiation: 10 mm diameter collimator, homogen irradiation of hippocampus (at one hemisphere)

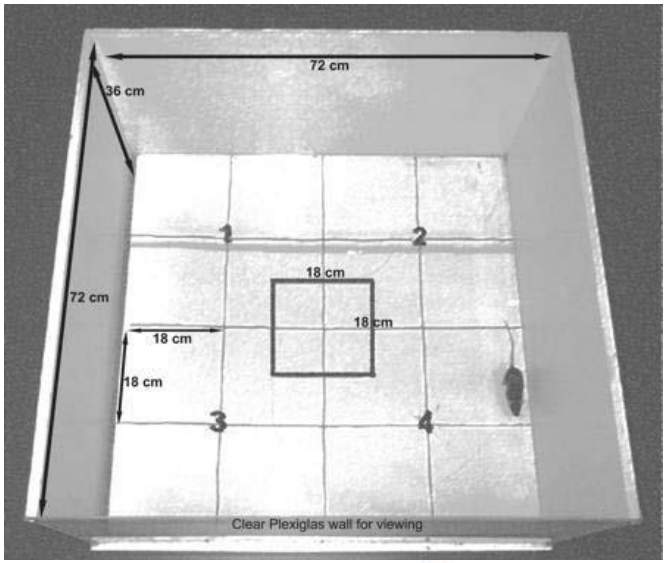


Neurofunctional tests

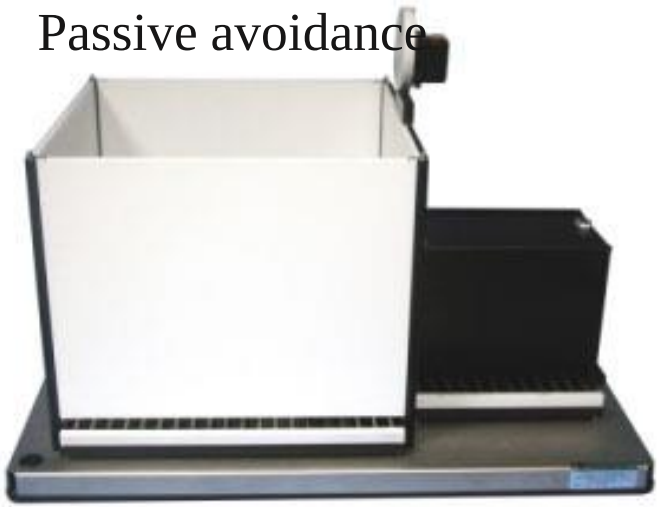
Morris Water maze



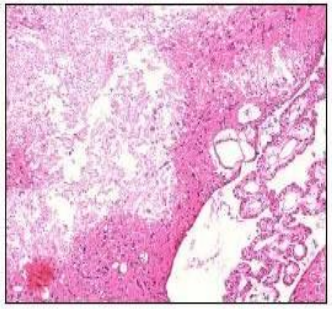
Open-field test



Passive avoidance

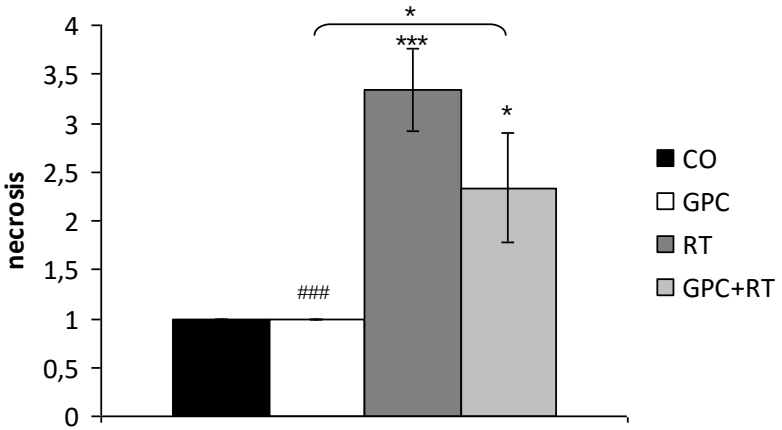


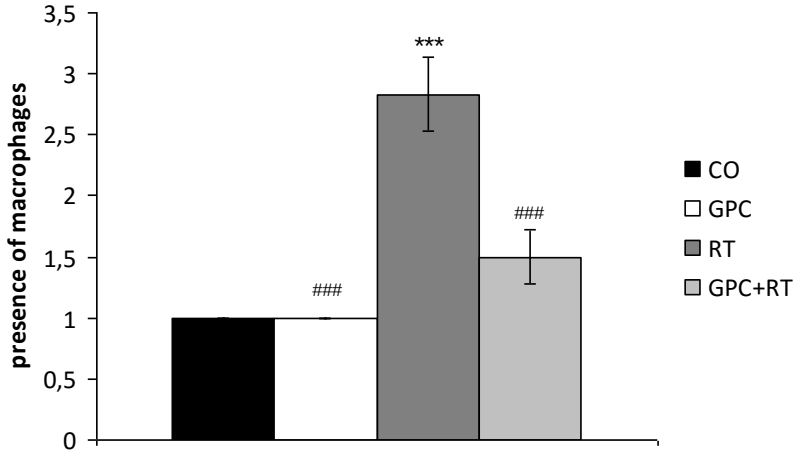
Late effects of focal brain irradiation

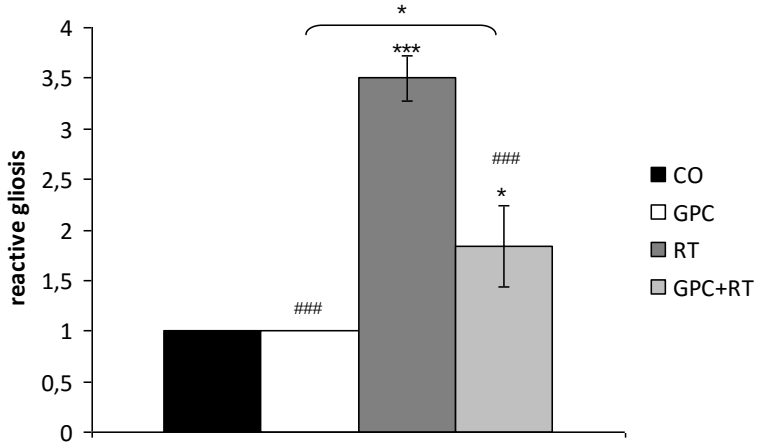


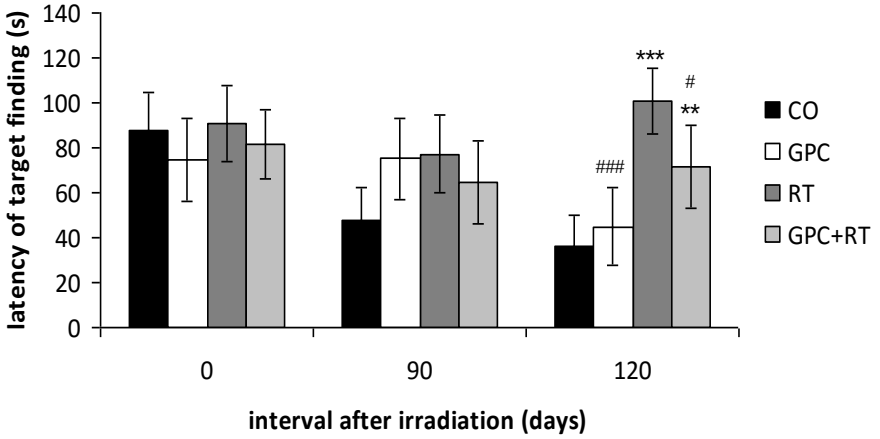
Chronic project: Results

„Radio-neuroprotective effect of L-alpha-glycerylphosphorylcholine in experimental rat model”







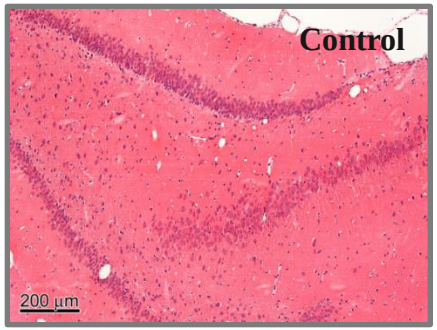


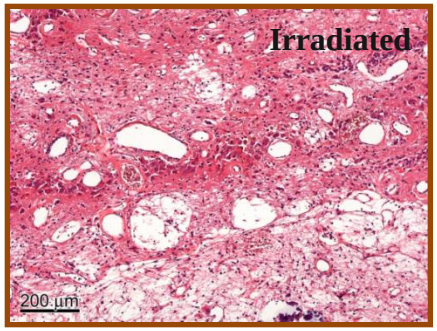
Statistics: Kruskal-Wallis, Fisher’s PLSD (mean ± S.E.M.) *p<0.05 *vs* Control group, #p<0.05 *vs* Irradiated group.

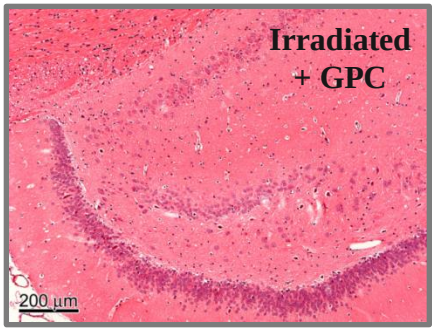
Chronic project: Summary

„Radio-neuroprotective effect of L-alpha-glycerylphosphorylcholine in experimental rat model”

The morphological changes in the irradiated brain tissue (significant macrophage accumulation, the levels of the reactive gliosis, calcification and demyelination) were reversed by the 4-month oral GPC treatment.







Significant functional and morphological changes were observed four months after 40 Gy single dose brain irradiation. GPC supplementation provided significant protection against cognitive disturbances and cellular damages.

Ongoing mouse experiments

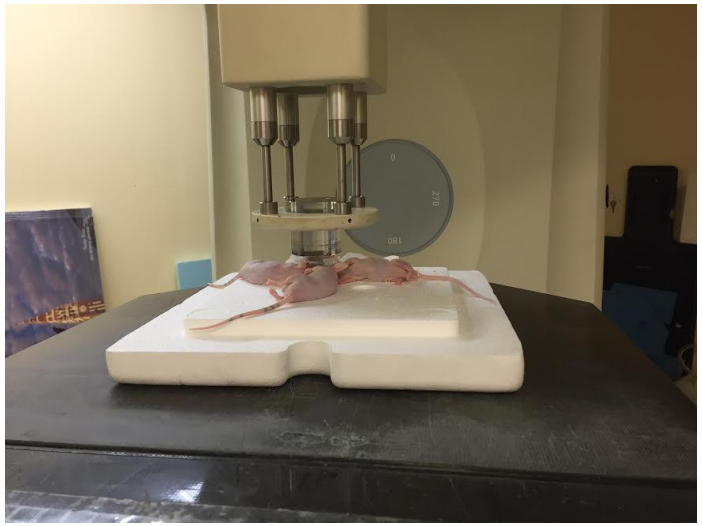
Anaesthesia: i.p. chloral-hydrate

Positioning: on one side

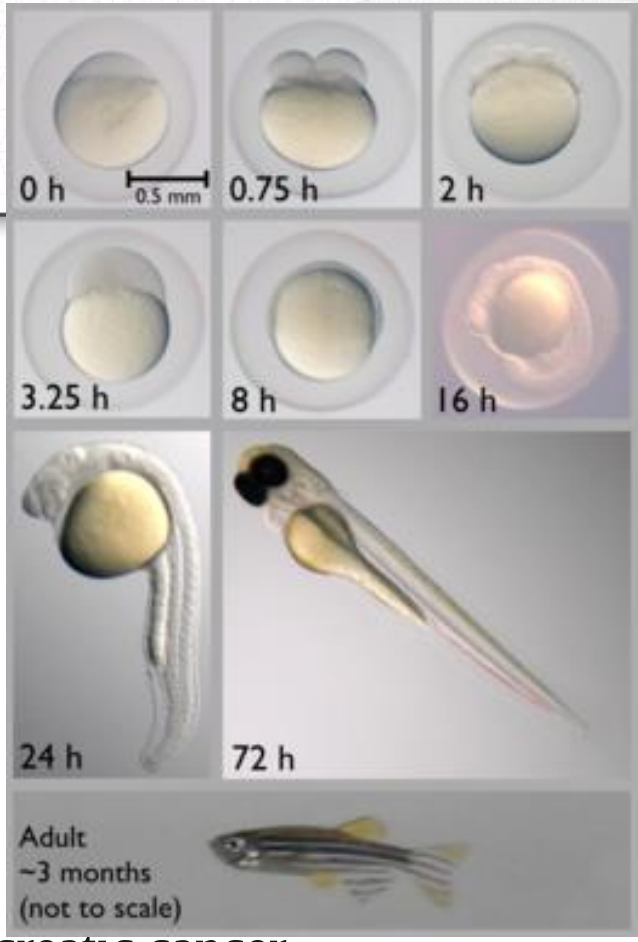
Source: 6 MeV energy Siemens linear accelerator

Dose: 40 Gy

Irradiation: 5 mm diameter collimator



Novel vertebrate model for radiobiology



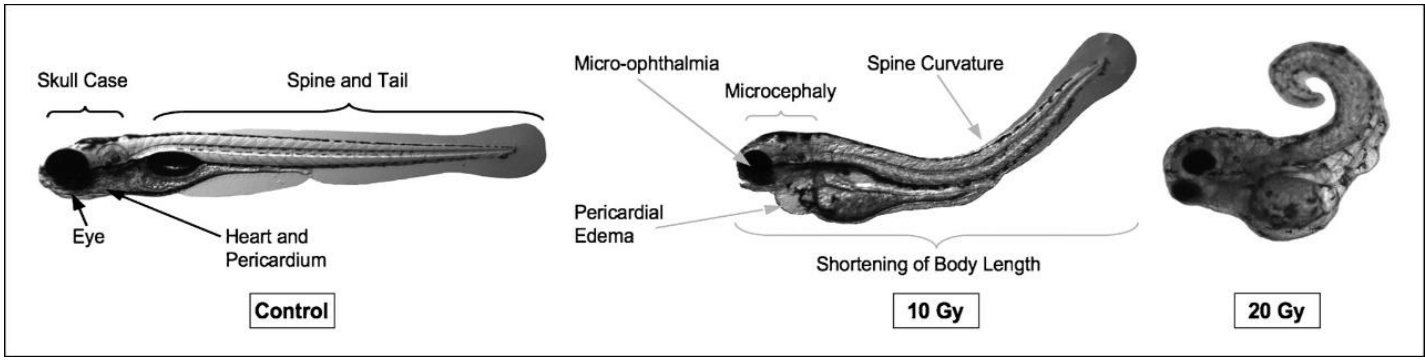
Zebrafish (*Danio rerio*):

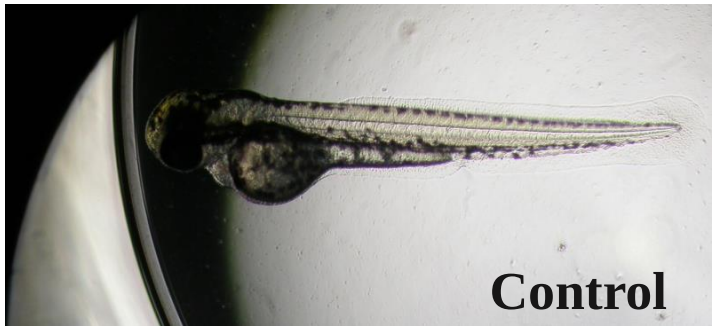
- Easy to handle, good reproduction captivity,
- transparent in larval stages
- external fertilization, rapid embryonic development,
- the complete genome sequence was published (2013)
- Availability of several transgenic lines

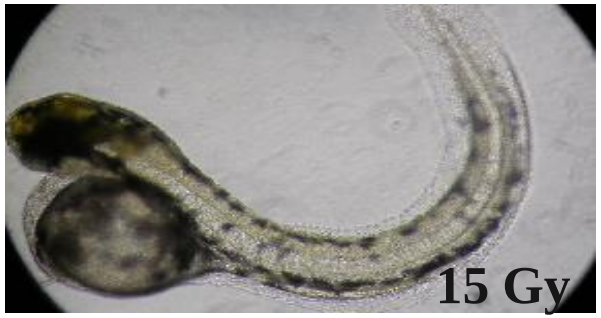
- **research fields:** radiobiology, melanoma, leukemia, pancreatic cancer, hepatocellular carcinoma, blood coagulation, heart failure, congenital heart and kidney defects, acute inflammation, retinal damage, teratology, biotechnological-, environmental protection-, toxicological- and pharmacological investigations.

End points of zebrafish embryo experiments

detection of malformation and survival

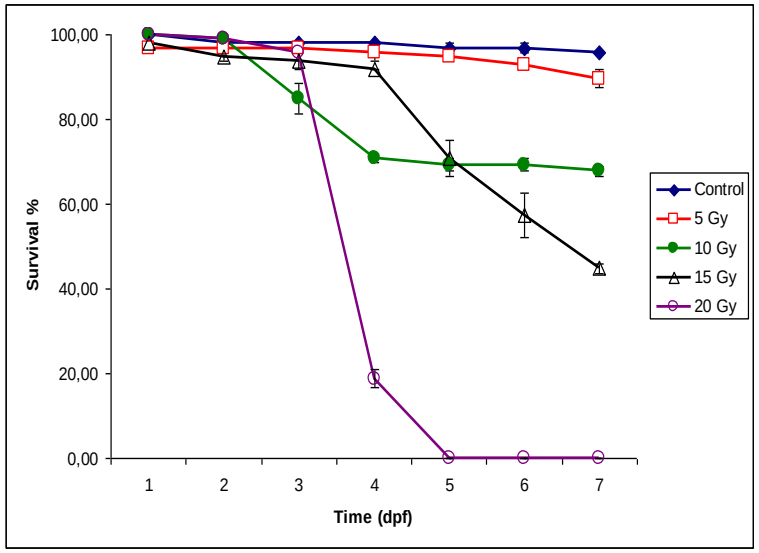


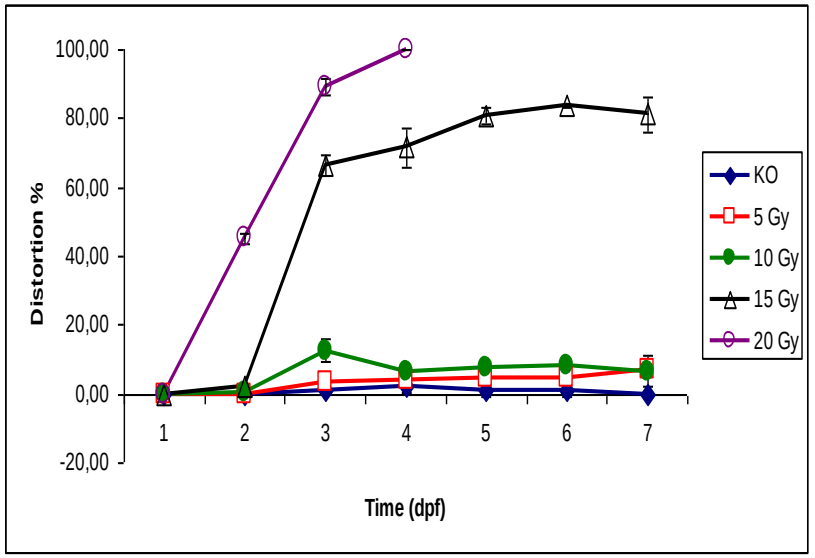




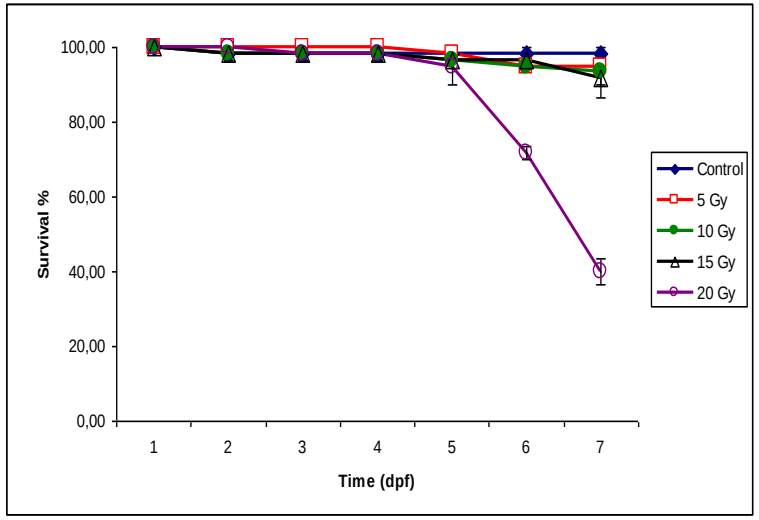
Results of the zebrafish embryos experiments

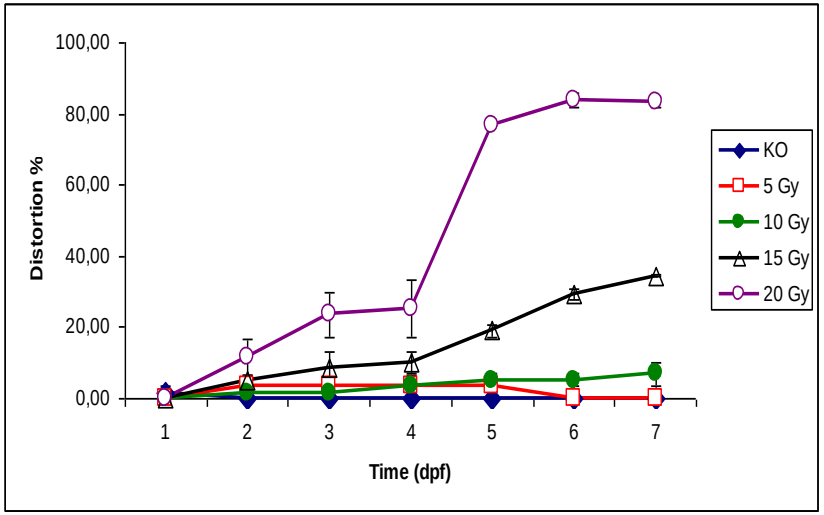
6 hpf



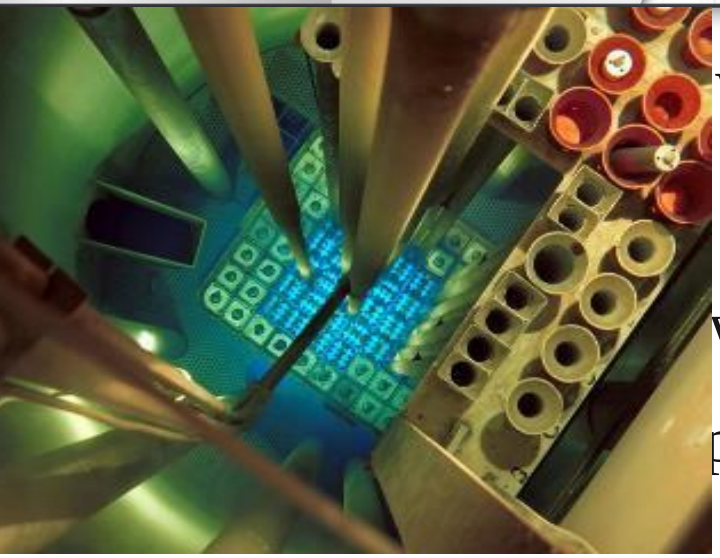


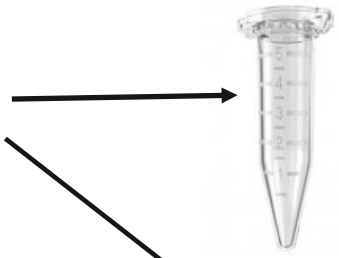
24 hpf



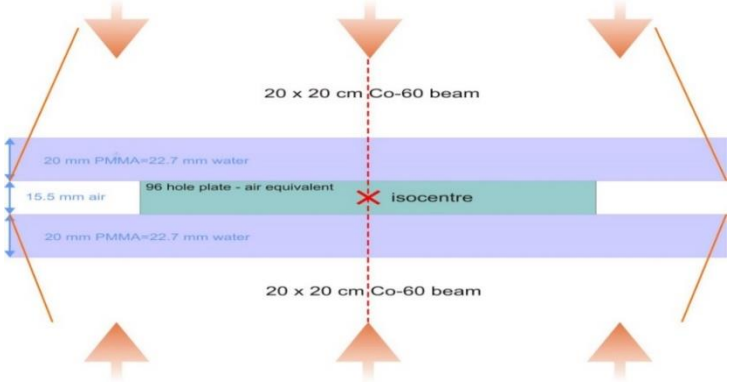


Irradiation of zebrafish embryos



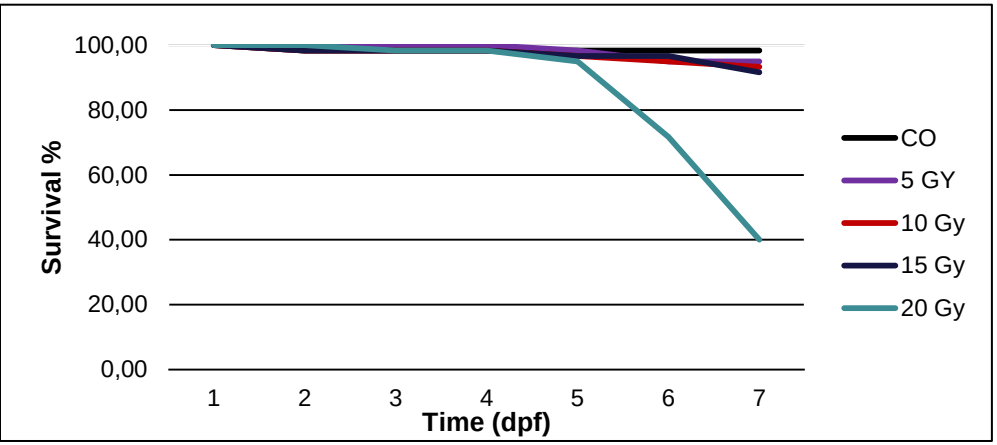


Wild type zebrafish embrios (24 hpf) were irradiated with photons at 5 - 20 Gy dose and reactor/cyclotron neutron-photon mixed beam at 1-8 Gy dose

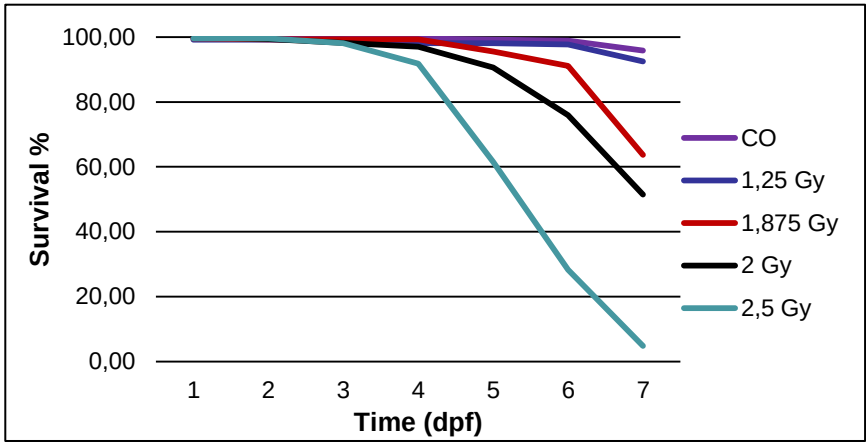


Results of the zebrafish embryos experiments

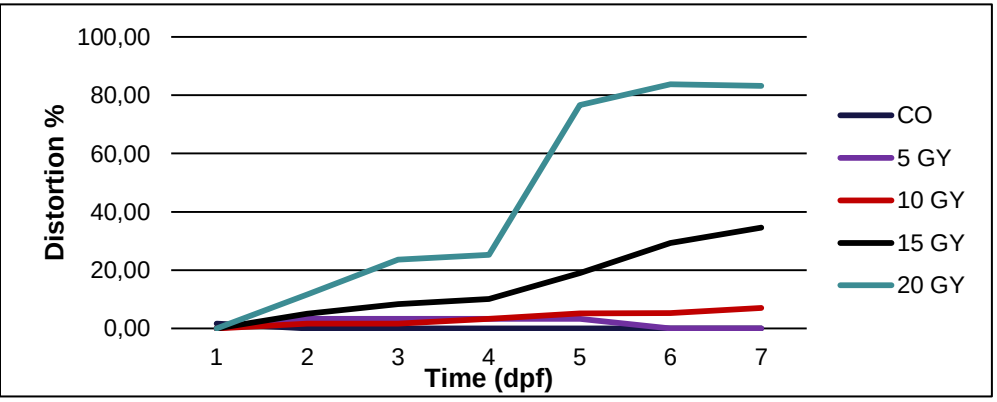
Photon

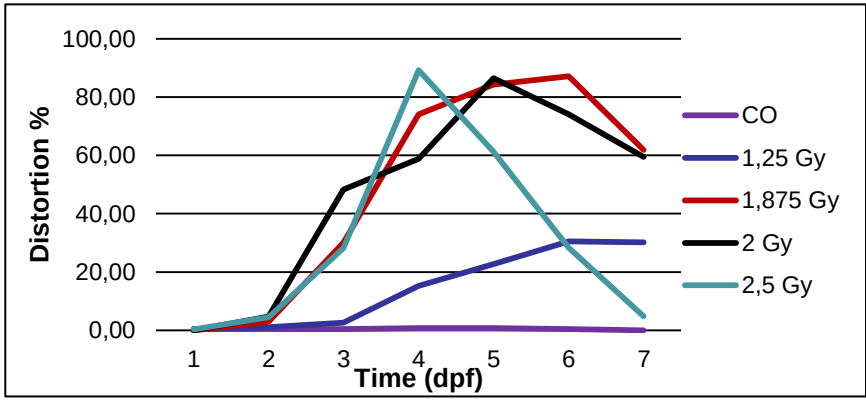


Neutron



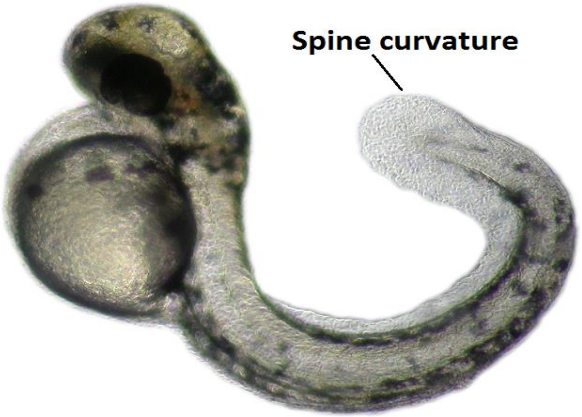
- RBE= $LD_{50}ph/LD_{50}n$= 20/2=10

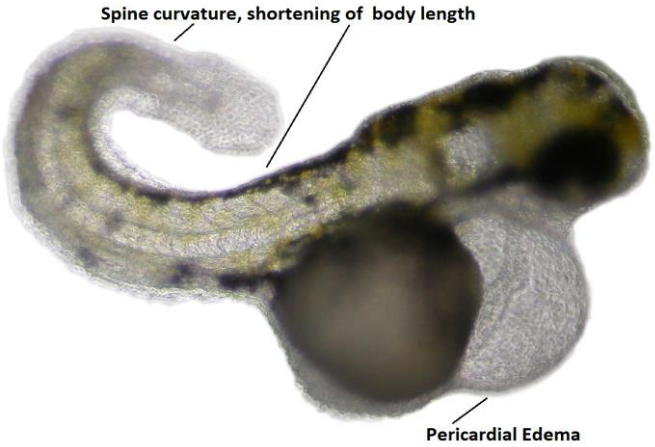


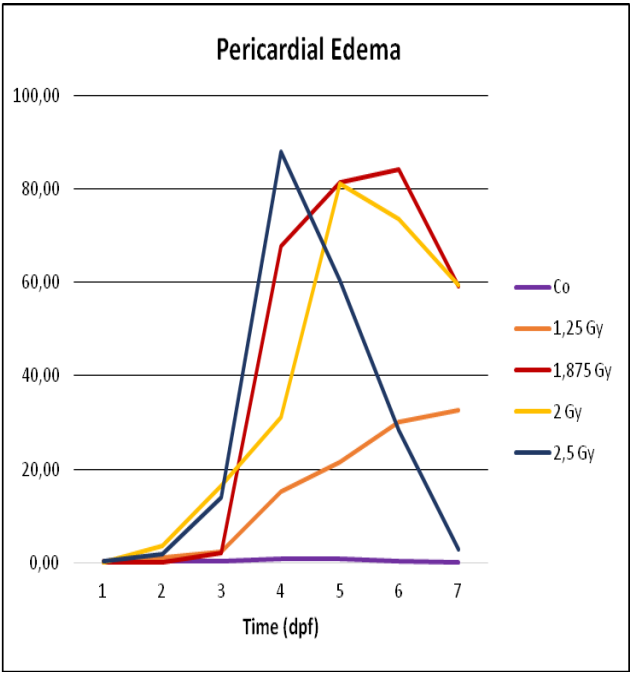


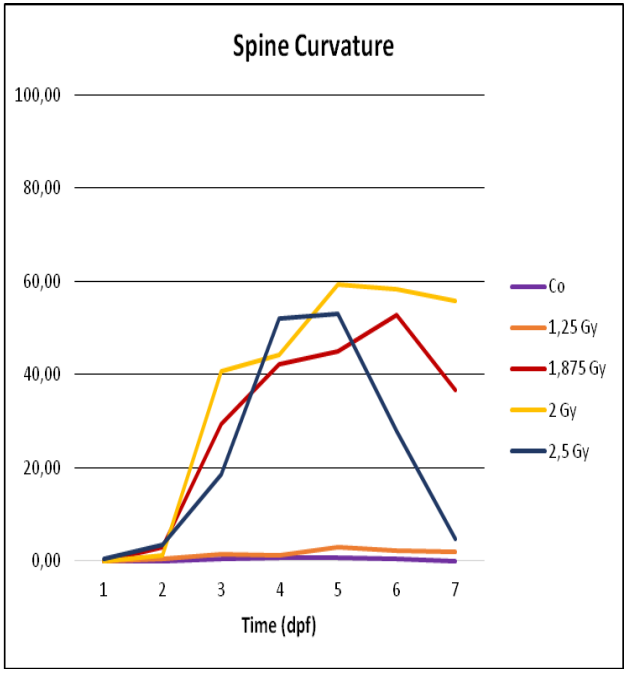
Macroscopic morphological abnormalities of the zebrafish embryos

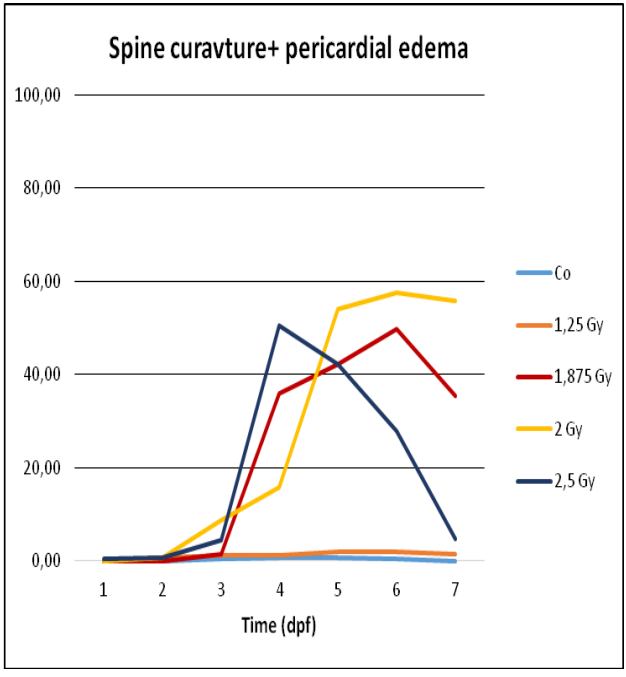
Control





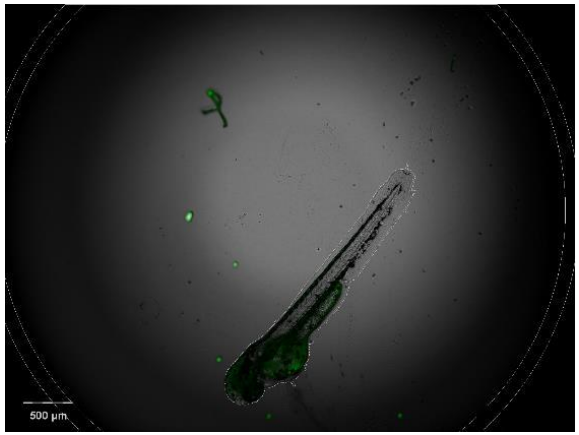


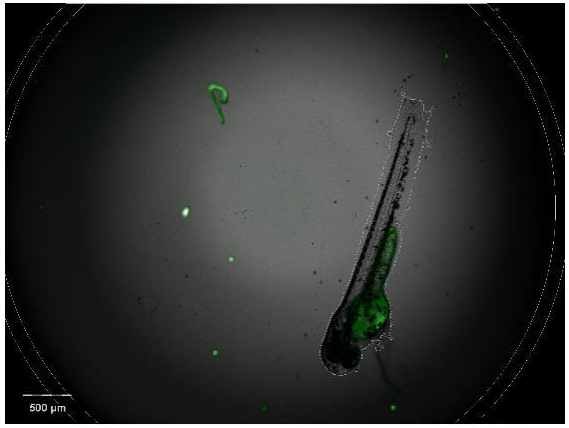




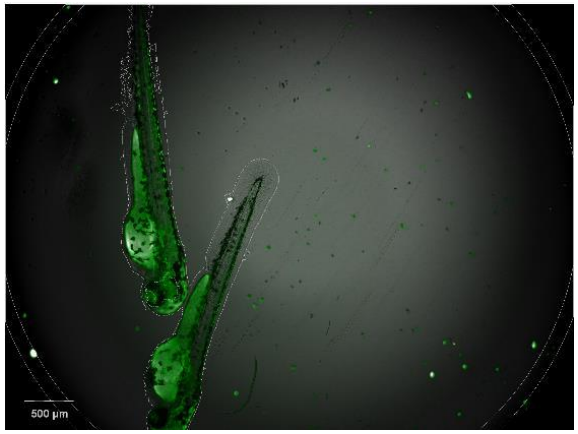
Imagig of neuron and blood vessel labeled transgenic zebrafish embryos

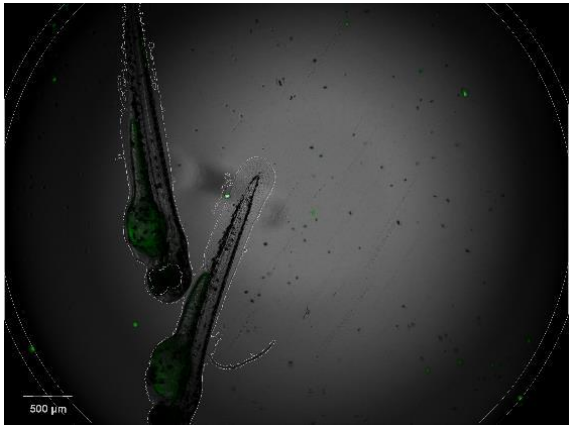
Confluency: 5.2
Signal GFP: 165
Signal dsRED: 65



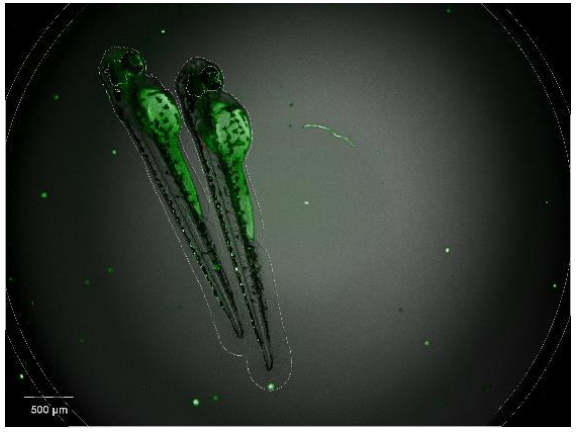


Confluency: 10.7%
Signal GFP: 164
Signal dsRED: 65

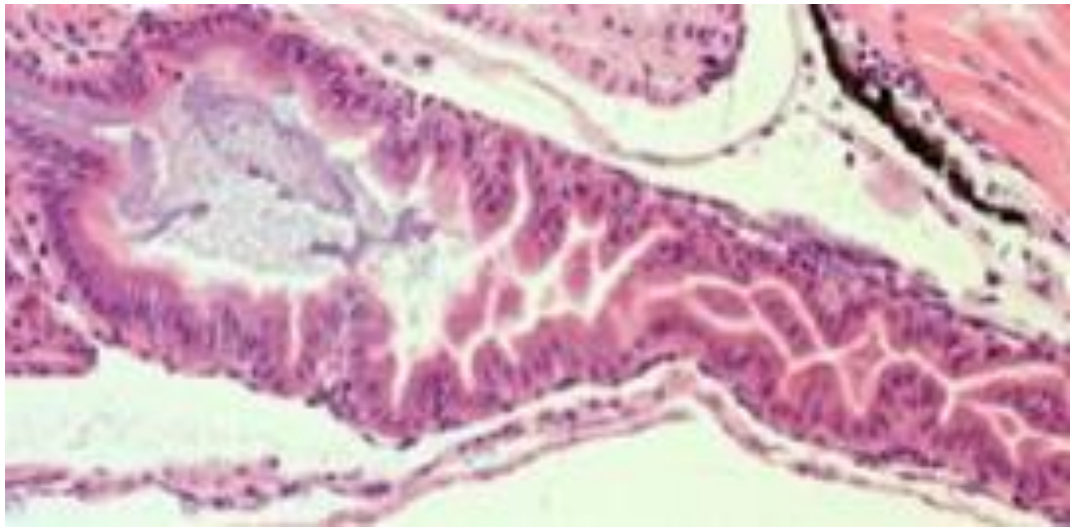




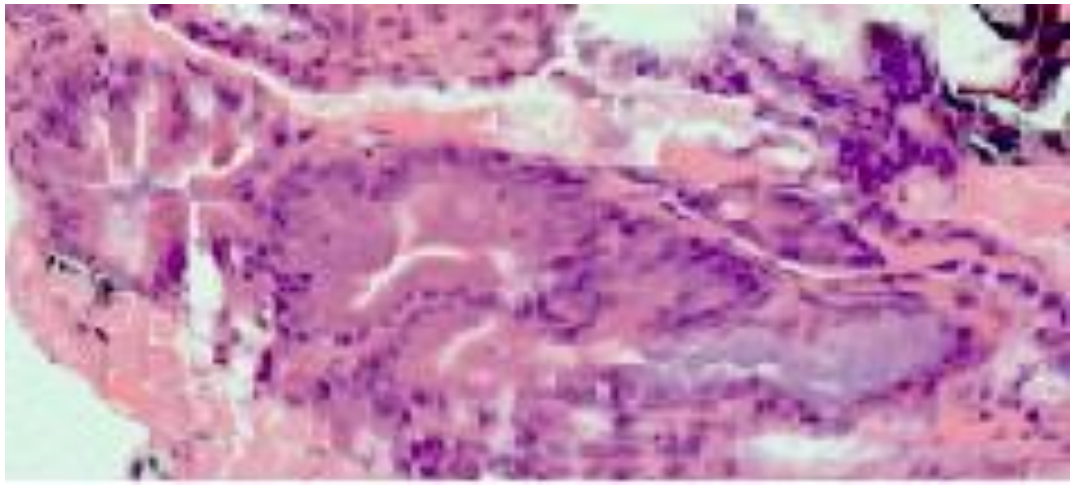
Confluency: 12.0
Signal GFP: 170
Signal dsRED: 65



Microscopic lesions of the zebrafish embryos



Control

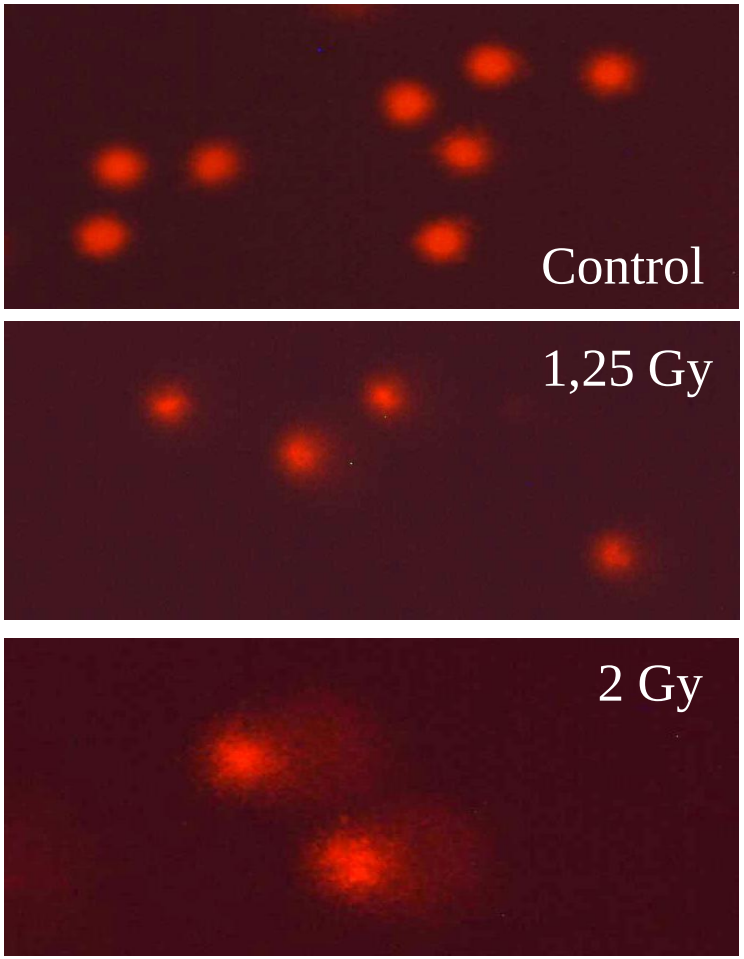


After 10 Gy

DNA-damage of the zebrafish embryos

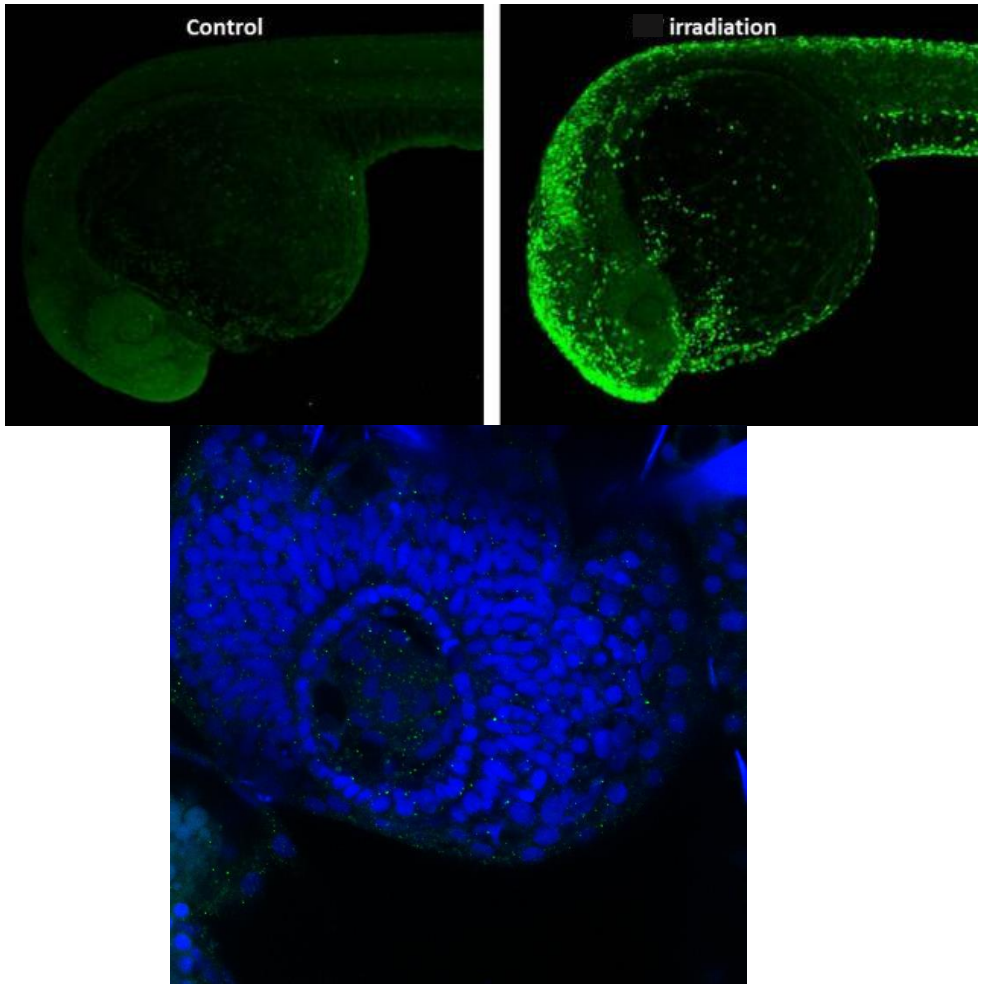
single strand breakes (SSD)

Comet assay



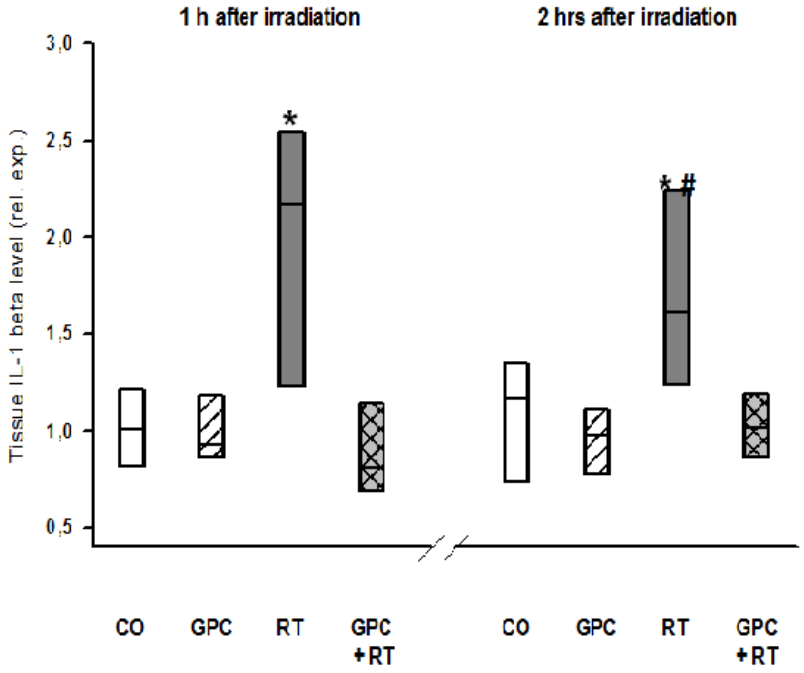
double strand breaks (DSB)

γH2AX



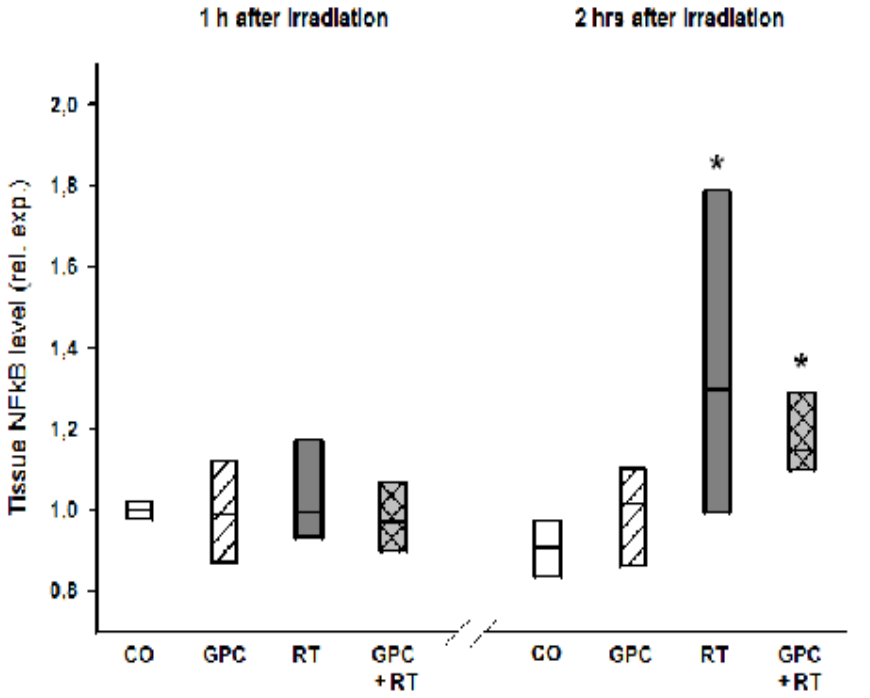
Inflammatory cytokines of the zebrafish embryos

Tissue interleukin-1β levels



*p<0,05 *vs* GPC + RT
#p<0,05 *vs* GPC

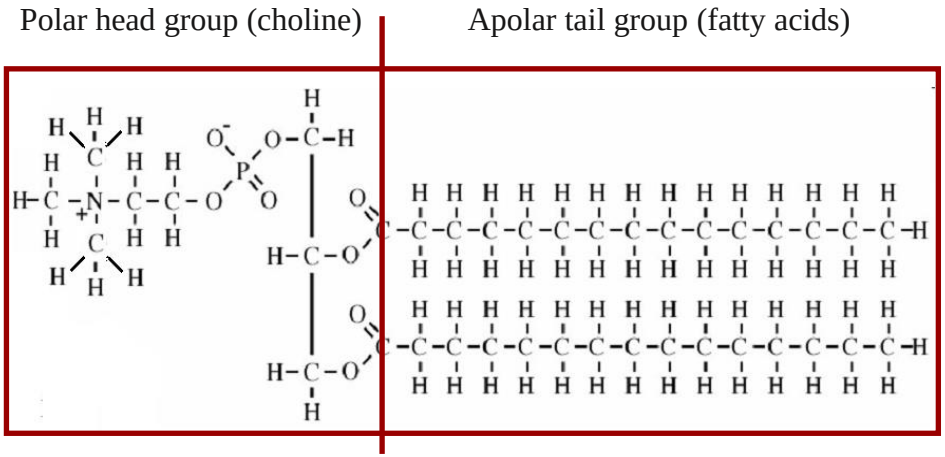
Tissue NFκB levels

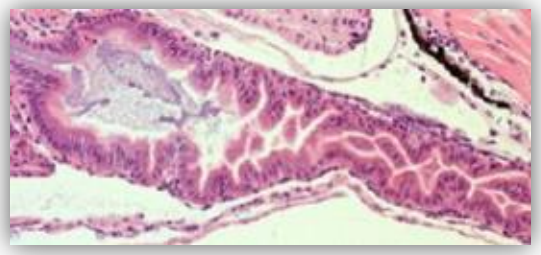


*p<0,05 *vs* Control

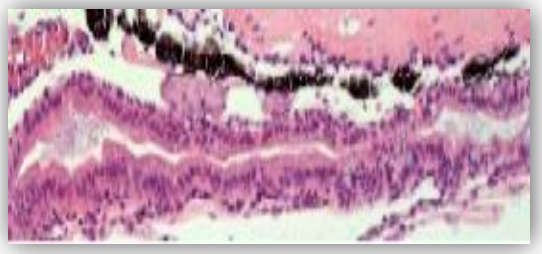
L-alpha glycerylphosphorylcholine (GPC)

- deacilated derivative of phosphatidylcholine,
- phospholipid precursor,
- water-soluble,
- protective in stroke and in transient ischemic attack,
- anti-inflammatory effects,
- ROS scavenger.

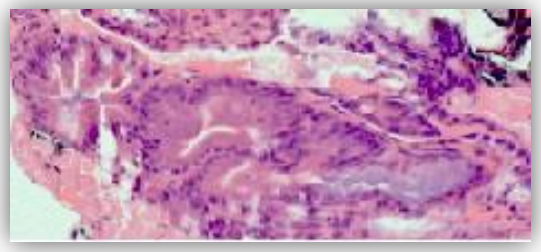




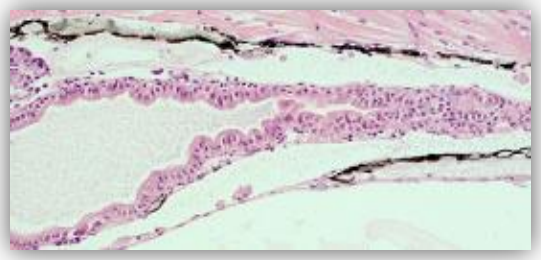
Control



GPC

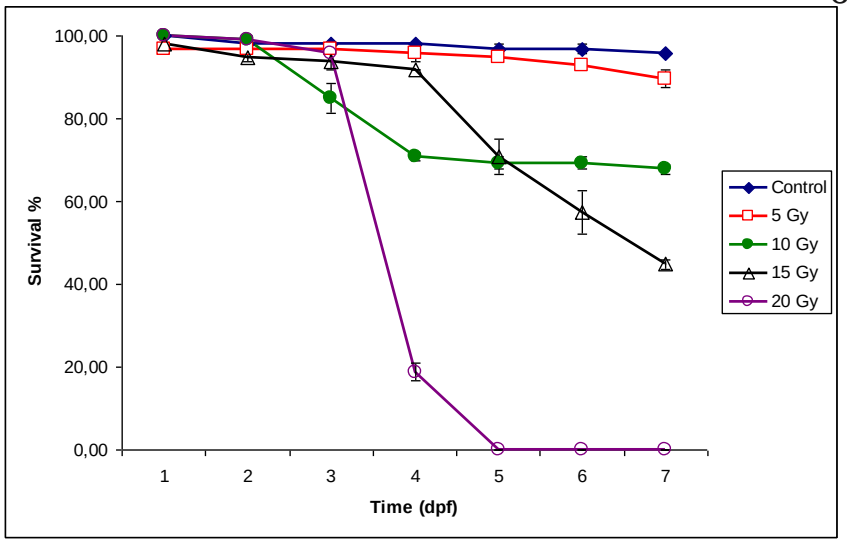


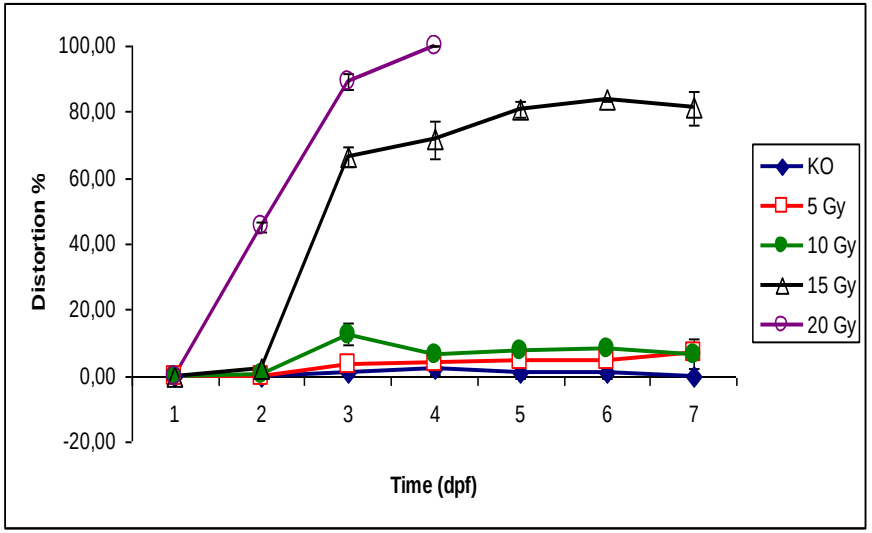
RT



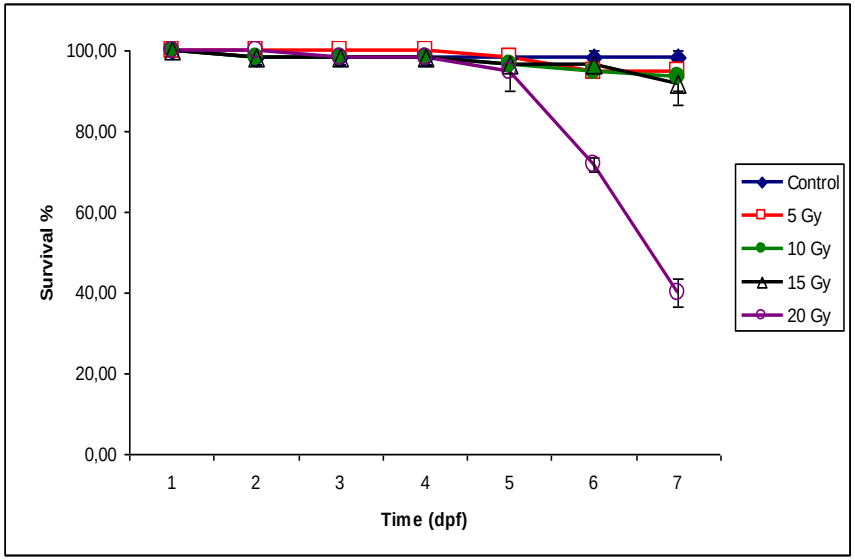
GPC + RT

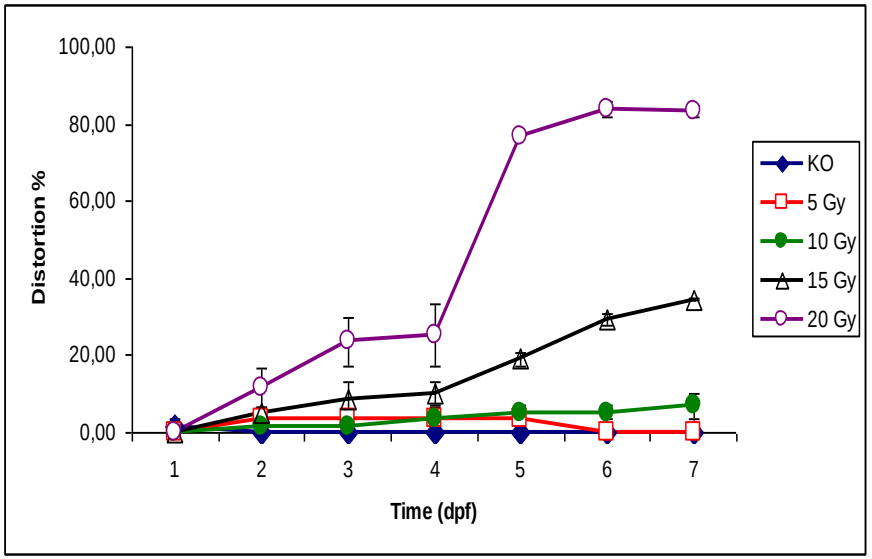
6 hpf





24 hpf





Testing of the potential radioprotective agent L-alpha glycerylphosphoryl-choline in a zebrafish embryo model Szabó ER, Plangár I, Mán I, Daróczi B, Tőkés T, Szabó Z, Fekete G, Kovács R, Baska F, Boros M, Hideghéty 2016 Zebrafish Res.

Study design

After valiadation of ZF model with standard *in vitro* and *in vivo* biologic systems wild, and tissue-specific fluorescent labelled, embryos will be irradiated at different centers for cross comparison of biological effect of laser accelerated ion beams.

1hpf embryos will be exposed to laser driven protons at 0, 2, 4, 8, 16 Gy dose level positioned in 1 mm-steps in 3 plastic bags from 0-3 mm at different laser driven proton facitity.

Endpoints:

- survival- definition of RBE, alpha/beta values
- organ devepolment deterioration
- tissues changes of different organs (eye, heart, bowel, liver)
- gammaH2AX staining 30 minutes after RT and 72 hours after
- frozen samples for further molbiol studies

Energy [MeV]	Proton range in water [mm]
5	0,36
8	0,8 ?
10	1,2

eli attosecond

THANK YOU FOR YOUR ATTENTION!

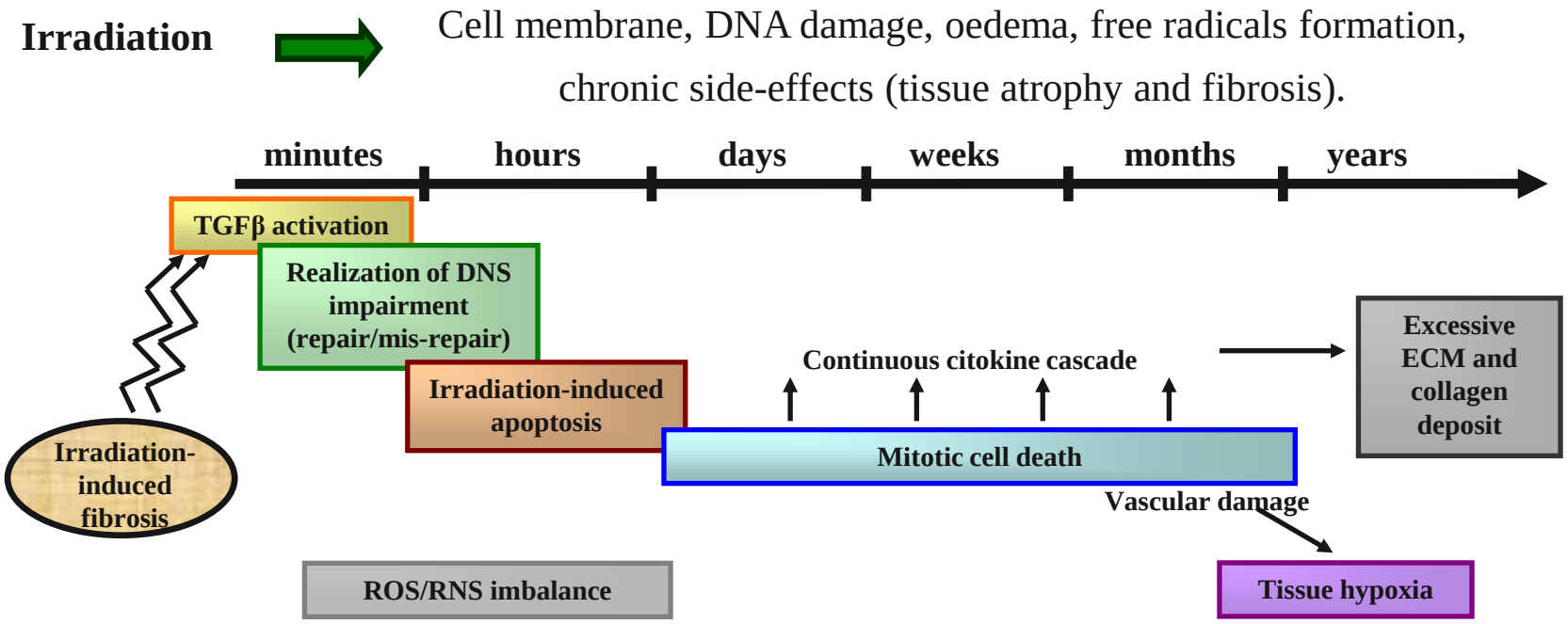
SZÉCHENYI 2020

HUNGARIAN GOVERNMENT

European Union
European Regional Development Fund

INVESTING IN YOUR FUTURE

Focal brain irradiation in rat models

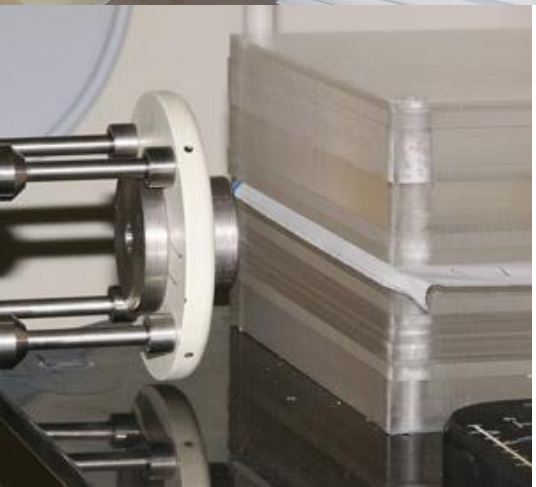


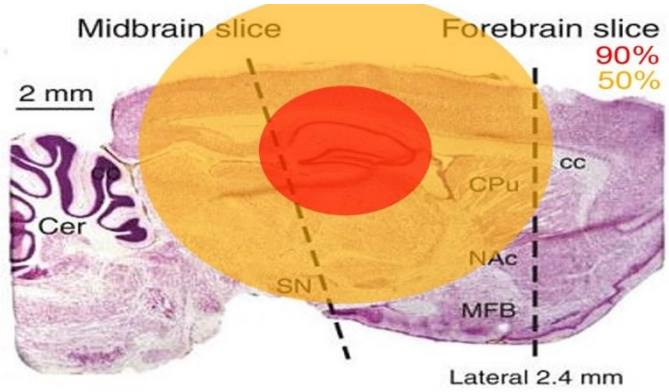
Acute project: Our aim was to examine the therapeutic effects of GPC after hippocampus irradiation-induced **acute peripheral inflammatory reactions**, *Chronic project:* and to characterize the **chronic histological and functional consequences** of partial rat brain irradiation and to determine the effects of GPC.

Dosimetry

Special collimators:

- Dose depth curve
- Field profile
- MU





A treatment planning study to assess the feasibility of laser-driven proton therapy using a compact gantry design

Select item 25979532.

Treatment planning for radiotherapy with very high-energy electron beams and comparison of **VHEE** and VMAT plans

Medical physics aspects of the synchrotron radiation therapies: Microbeam radiation therapy (MRT) and synchrotron stereotactic radiotherapy (SSRT)

Image-guided microbeam irradiation to brain tumour bearing mice using a carbon nanotube X-ray source array

Energy Modulated Photon Radiotherapy: A Monte Carlo Feasibility Study

Energy- and intensity-modulated electron beams for radiotherapy

LET-painting increases tumour control probability in hypoxic tumours

New challenges in high-energy particle radiobiology

Simultaneous production of mixed electron--photon beam in a medical LINAC: A feasibility study.

Radiobiology network

DERMATOLOGY
Cellculture and genetic lab

BRC
Xcelligence, Tumor xenograft DNA repair..

PATHOLOGY
Histology, immunohistochem

ONCOTHERAPY
Dosimetry
RT planning, linac
foton, electron radiation

NEUROLOGY
RTPCR

TeWaTi
IR Fs laser filamentation

Univ.Gödöllő
Fish laboratory

KFKI/BME/
ATOMKI

RADIOLOGY
small animal MRI

Proton/ion
MedAustron

Laser driven proton
HZDR
OncoRay

PHYSIOLOGY
neurovascular function

EXPERIMENTAL SURGERY
Oroboros, protein level..

APPLIED AND ENVIRONMENTAL CHEMISTRY
Polymer gel preparation

Development of ionizing radiation

What is beyond the laser driven particle generation, acceleration?

Why is it worth to work on LD secondary sources for medicine?

Where we stand actually in laser based particle acceleration?

Where to go?

What is needed?

Why do we need laser driven ionizing radiation sources?

To enlarge the availability of charged particle beams: cost effective hadrontherapy

economic aspect

Provide special particle beams epithermic neutron, VHEE, microbeams, combined particle beams

physical aspect

To use the potential biological advantages of pulsed mode operation and ultra high dose rate- ultra high spatial and temporal resolution differential tumor- normal cell effect

biological aspect

eli attosecond

Biomedical Application group at ELI-ALPS

Head of the Scientific Application Division Péter Dombi (physicist)

Group leader: Katalin Hideghéty (radiation oncologist)

and the group:

Róbert Polanek (medical physicist, physical background)

Emilia Rita Szabó (biologist, zebrafish experiments)

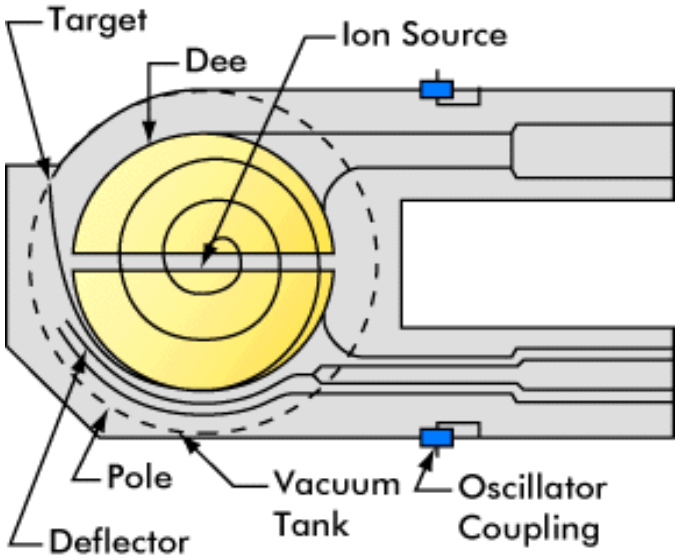
Bettina Ughy (chemist, cell culture experiments)

Zoltán Szabó (biologist, molecular examinations)

Tünde Tőkés (biologist, rodent experiments)

Cyclotron development

1929	Lawrence, inspired by Wideröe and Ising, conceives the cyclotron.
1931	Livingston demonstrates the cyclotron by accelerating hydrogen ions to 80 keV.
1932	Lawrence's cyclotron produces 1.25 MeV protons and he also splits the atom just a few weeks after Cockcroft and Walton (Lawrence received the Nobel Prize in 1939).



Aims of our group/ongoing projects

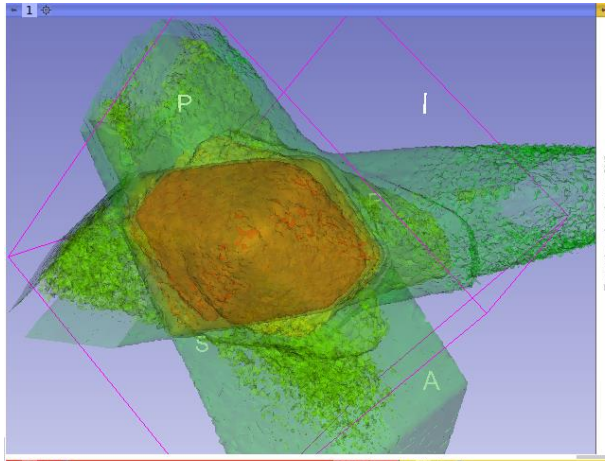
Conventional X-ray beam	Femtosecond IR laser filamentation	Laser-electron beam	Laser-proton/ion beam

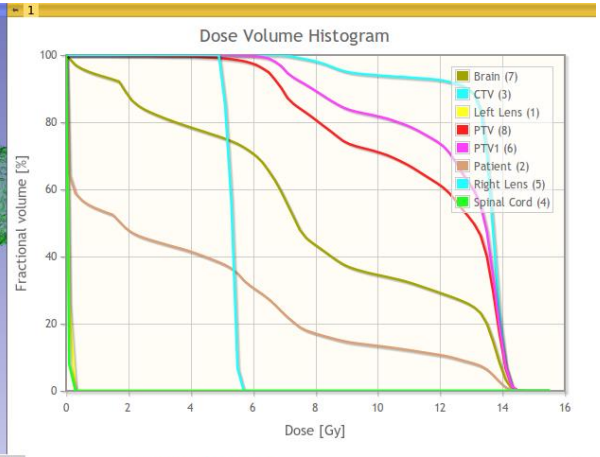
FACILITY DESIGN, RADIATION PROTECTION TRANSPORT AND POSITIONING OF THE BIOLOGICAL OBJECTS, DOSIMETRY, DOSE CALCULATION,

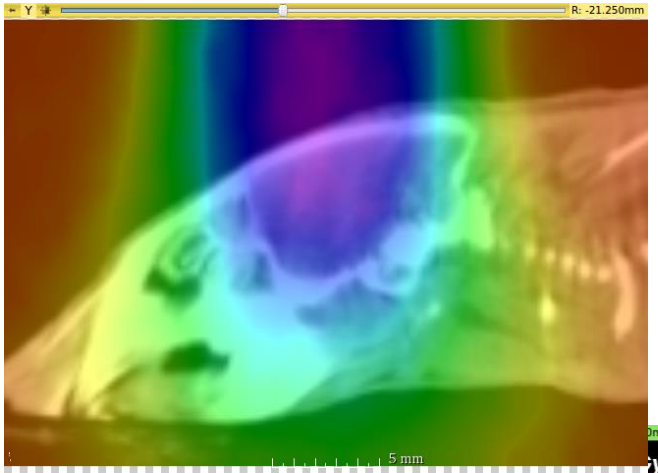
Development of *In vitro* and *in vivo* biological systems	Use of traditional *In vitro* and *in vivo* biological systems	Use of validated *In vitro* and *in vivo* biological systems	Use of validated *In vitro* and *in vivo* biological systems

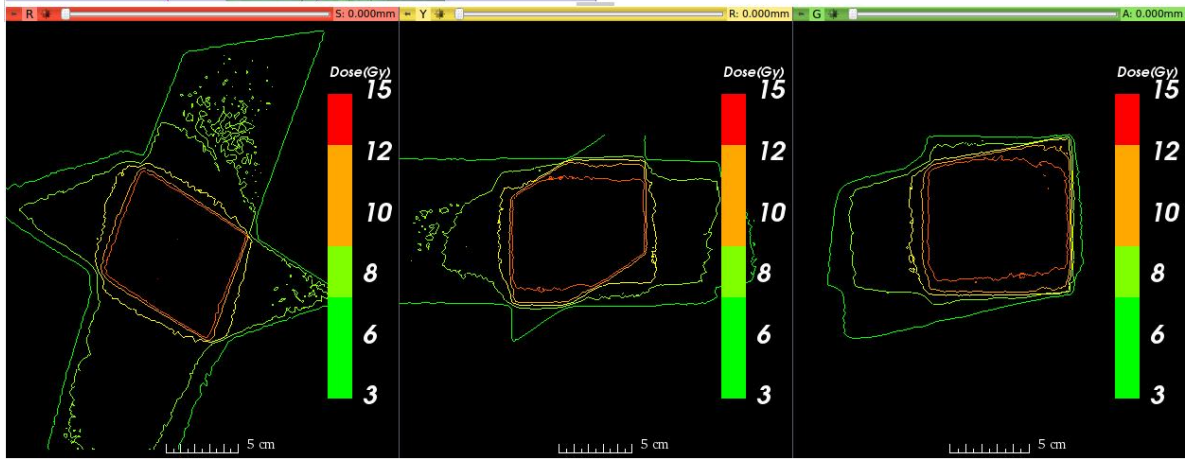
Evaluation of morphologic, functional, cellular, molecular changes, and comparison of these biological effects

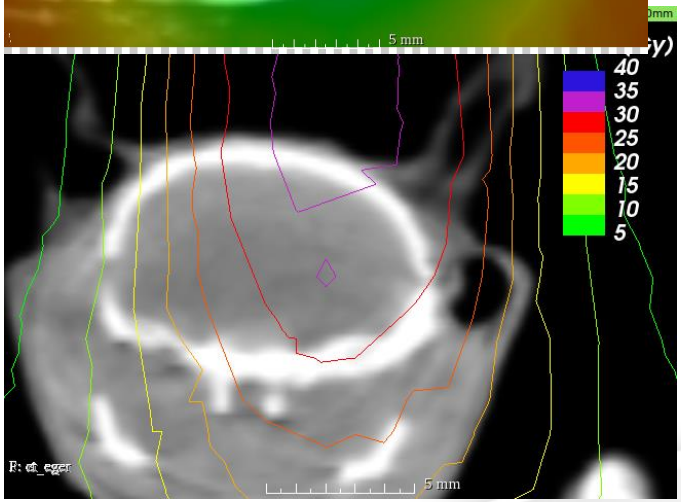
Very High Energy Electron Beam VHEE





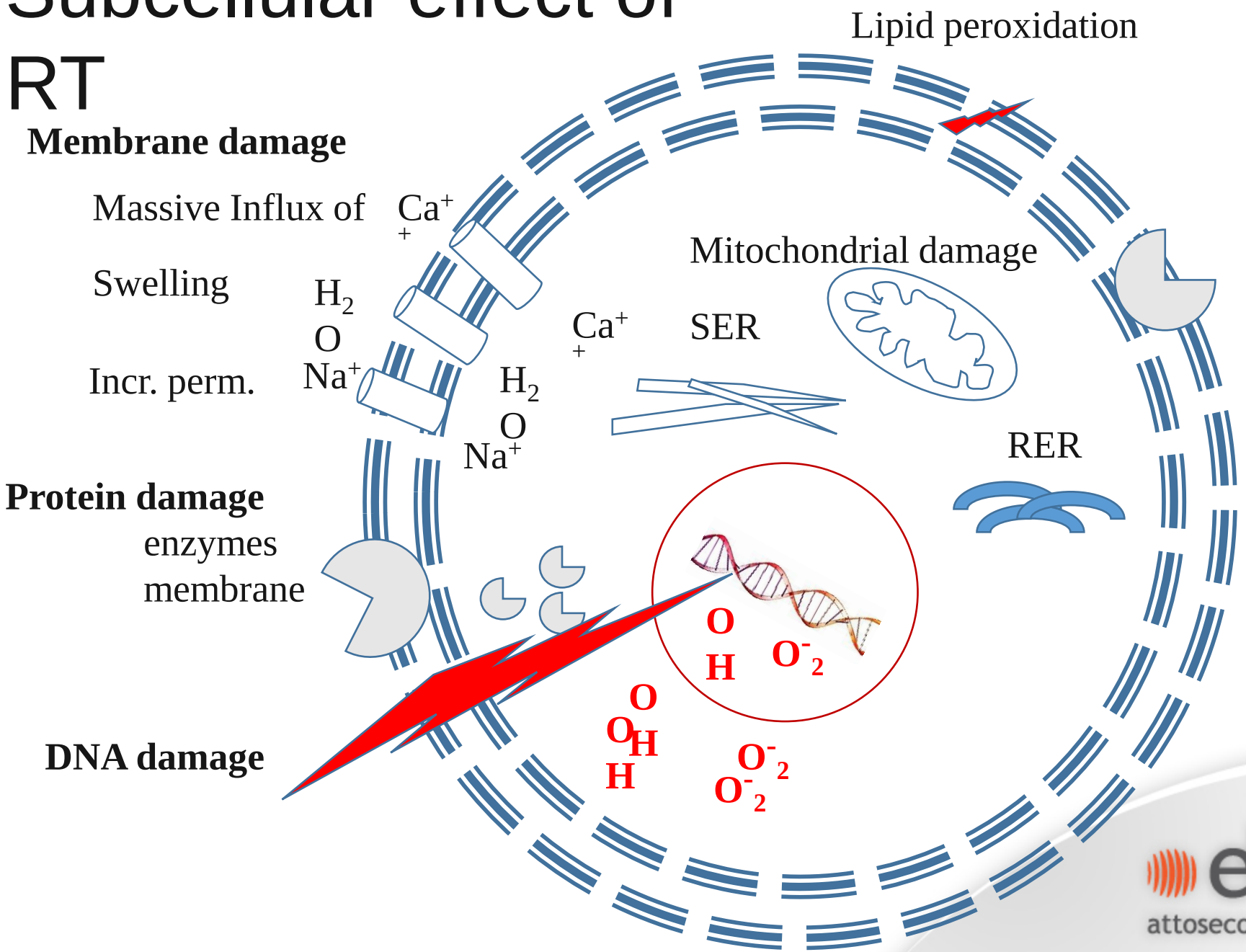




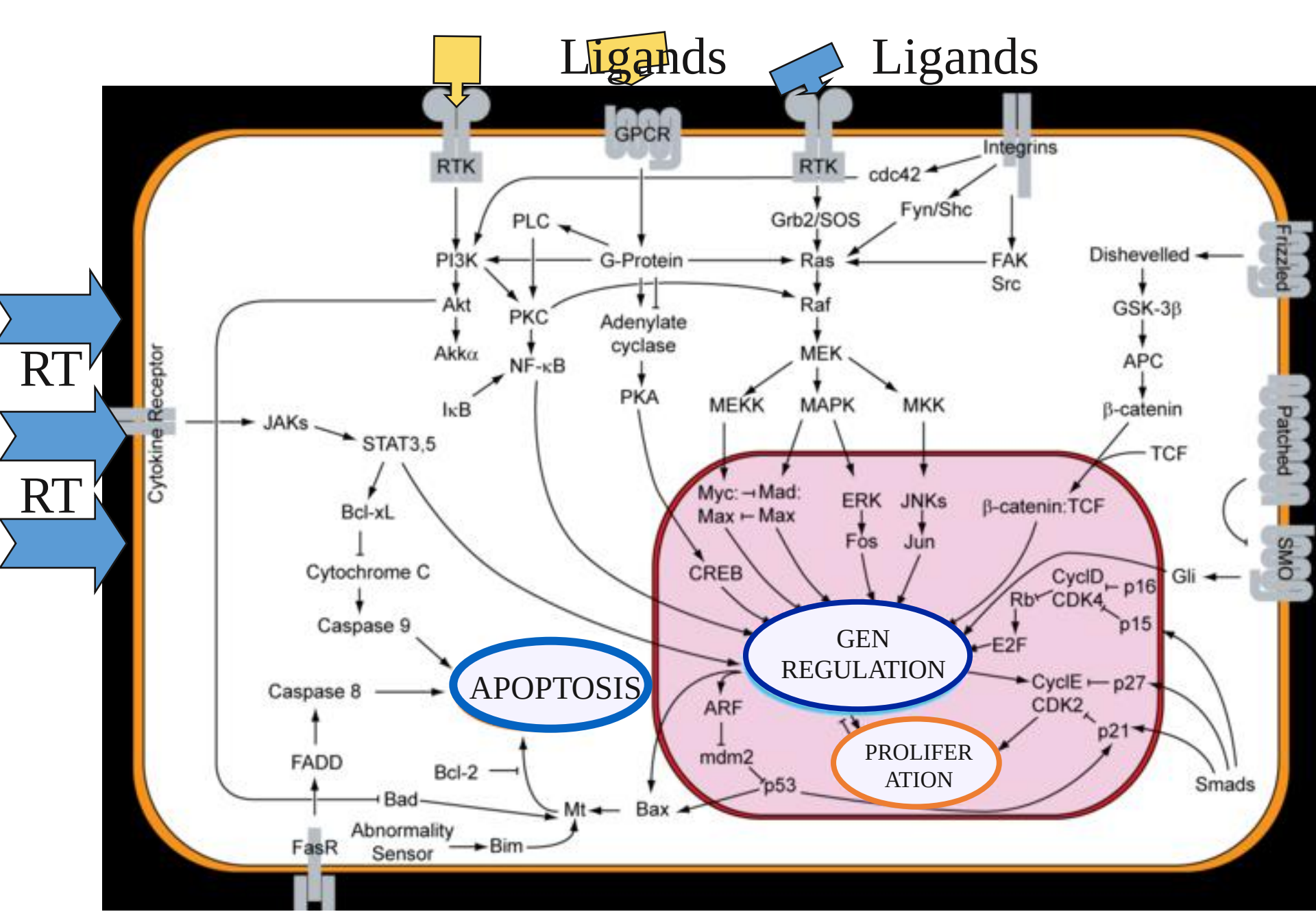


eli attosecond

Subcellular effect of RT

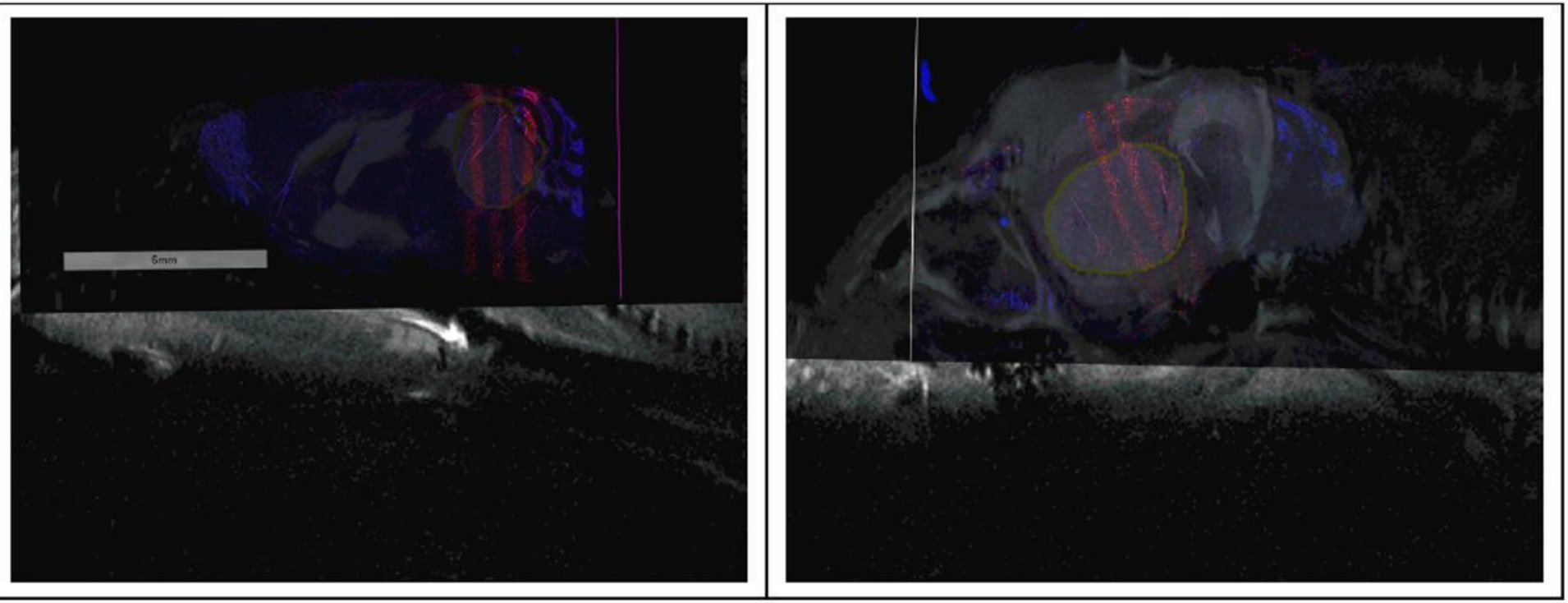


attosecond


Ligands
Ligands
RT
RT
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Dishevelled
Frizzled
Akt
PKC
Adenylate
cyclase
Raf
GSK-3β
Akkα
NF-κB
MEK
APC
IκB
PKA
MEKK
MAPK
MKK
β-catenin
Cytokine Receptor
JAKs
STAT3,5
TCF
Patched
Myc: Mad:
Max Max
ERK
JNKs
β-catenin:TCF
Bcl-xL
Fos
Jun
CREB
Gli
SMO
Cytochrome C
CyclD
p16
Rb
CDK4
p15
Caspase 9
GEN
REGULATION
E2F
APOPTOSIS
Caspase 8
CyclE
p27
ARF
CDK2
p21
PROLIFER
ATION
mdm2
FADD
Bcl-2
p53
Smads
Bad
Mt
Bax
FasR
Abnormality
Sensor
Bim

Ongoing research on laser driven radiation

- Development of cost effective, compact, intensity and energy modulated, hospital based hadron therapy source
- Very high energy electron beam
- Radiation biology experiments to explore the potential biological advantages of
  - **pulsed mode operation**
  - **ultra high dose rate**
  - **ultra high spatial and temporal resolution** potentially resulting in differential tumor - normal cell effects



γ-H2AX stained, sagittal image registered with MR projection for the same slice of tissue, from two animals irradiated with three microbeams of 48 Gy/beam

Aims of our group

Our aims are to develop appropriate dosimetry system and preclinical models for Relative Biological Effectivity (RBE) investigation on laser driven particle beams.

* **Frike liquid/gel chemical systems**
* **Cancer and normal cell lines**
* **Zebrafish embyos**
* **Rodents (different organs/tumor)**

will be exposed to escalated doses of accelerator based photons, electrons, protons, carbon ions, photon-neutron mixed beam of a nuclear research reactor and laser driven very high energy electron-, and hadron beam.

Ongoing and planned research

Conventional RT sources

Laser-electron beam

Laser-photon beam

Laser-proton/ion beam

SETUP DESIGN, DOSIMETRY, DOSE CALCULATION,

Healthy tissue reaction

RBE/tissue reaction cross comparison

MRT Flash

Classic *In vitro* and *in vivo* biological systems

Development of novel vertebrate model

Assessment of morphologic, functional, cellular, molecular changes of different normal tissue and tumor models