ELI-ALPS Research Institute
TOWARDS THE SHARP END OF ATTOSCIENCE

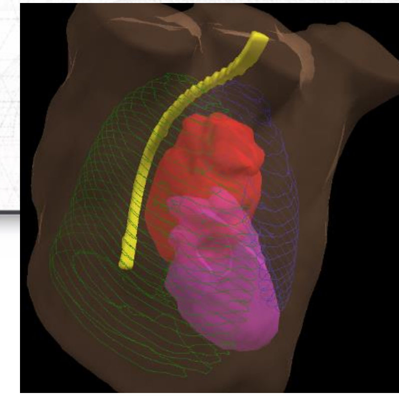
Perspectives of laser driven particle acceleration in radiation oncology

K. Hideghéty, ER. Szabó, R. Polanek, Sz. Brunner, T. Tőkés

SPIE-ALPA Workshop 03.04. 2019

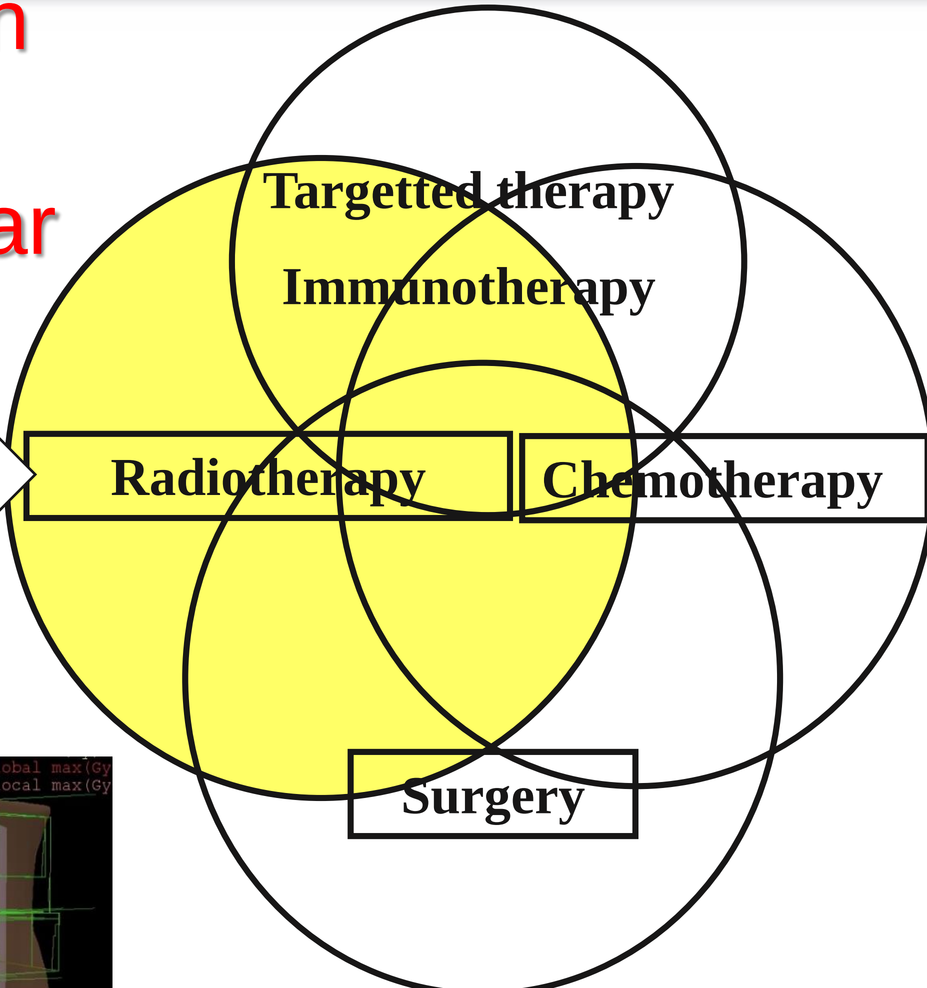
SZÉCHENYI 2020
Hungarian Government
European Union
European Regional Development Fund
INVESTING IN YOUR FUTURE

Complex tumor therapy

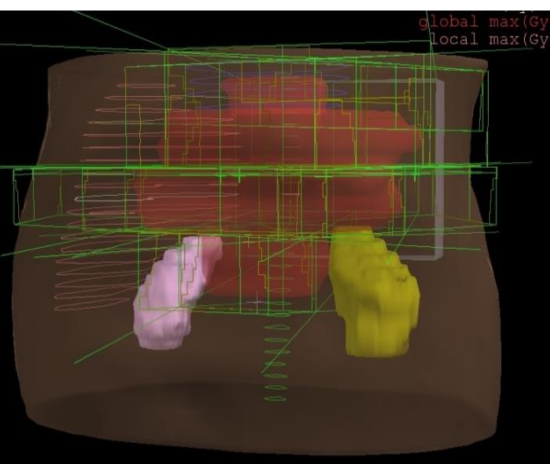


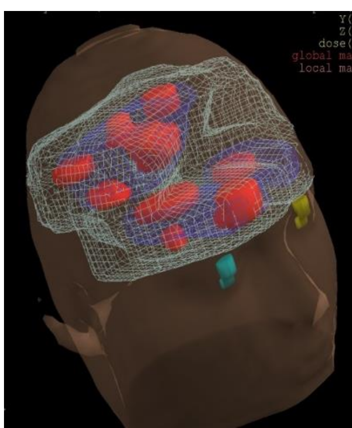
15 million cancer cases/year

Advanced diagnostics
imaging/histo/mol



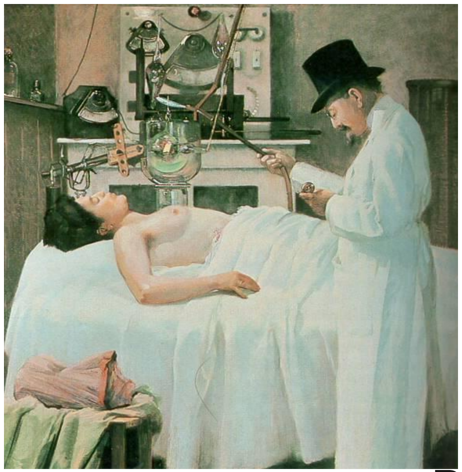
Improved outcome





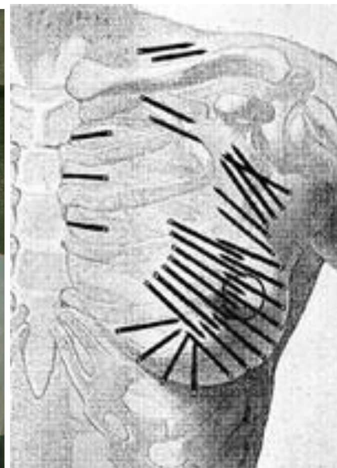
Historical view on radiotherapy

1896

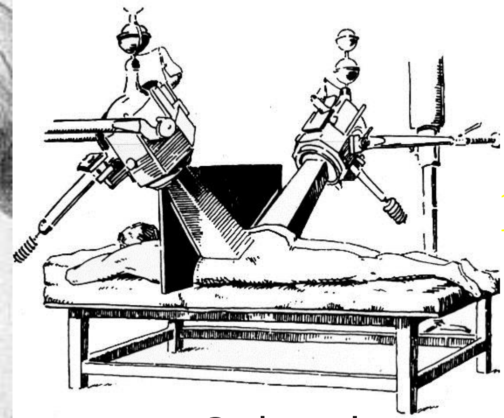


X-ray tube

1925



Radioactive needles



Orthovolt

1950

Synchrocyclotron

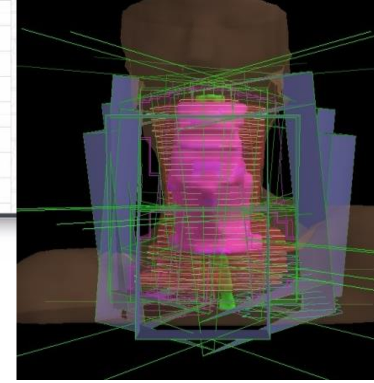
Simulator

1970

Cobalt beam

Afterloader

RT today

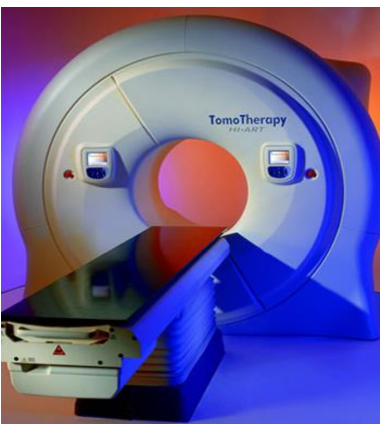


3DCRT IMRT/VMAT SRS/ SABR

Selectivity, effectivity, accuracy

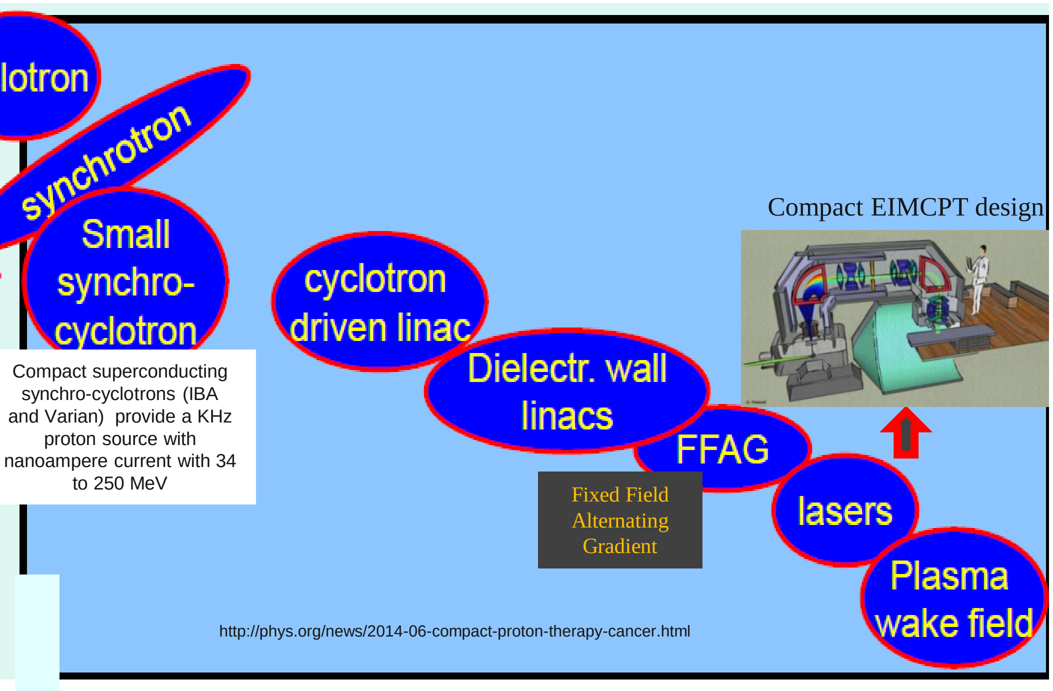
Hadron therapy

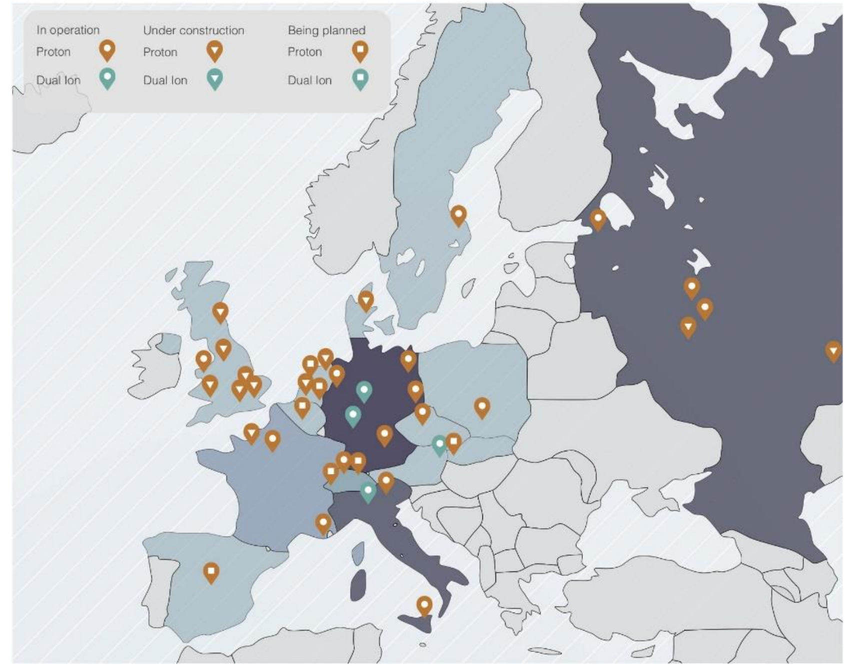
new gen. part. acc



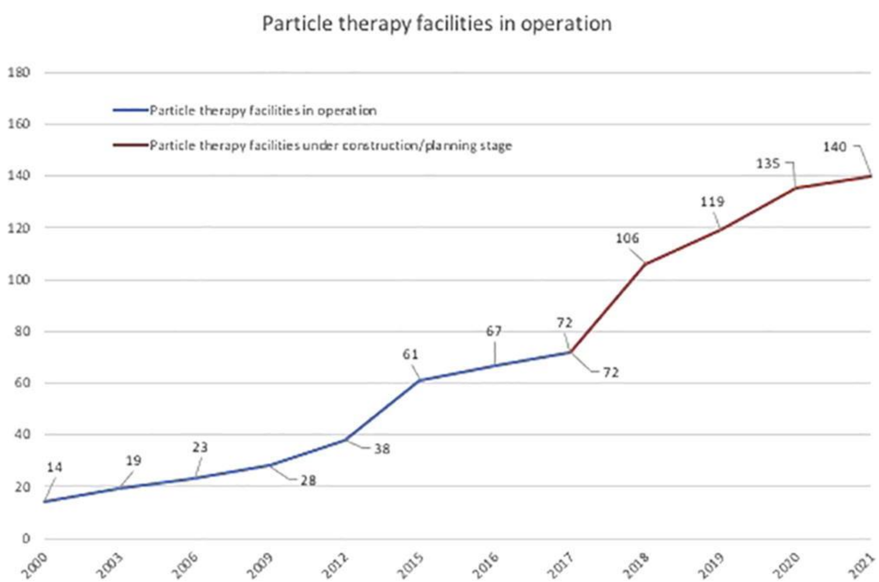
IGRT

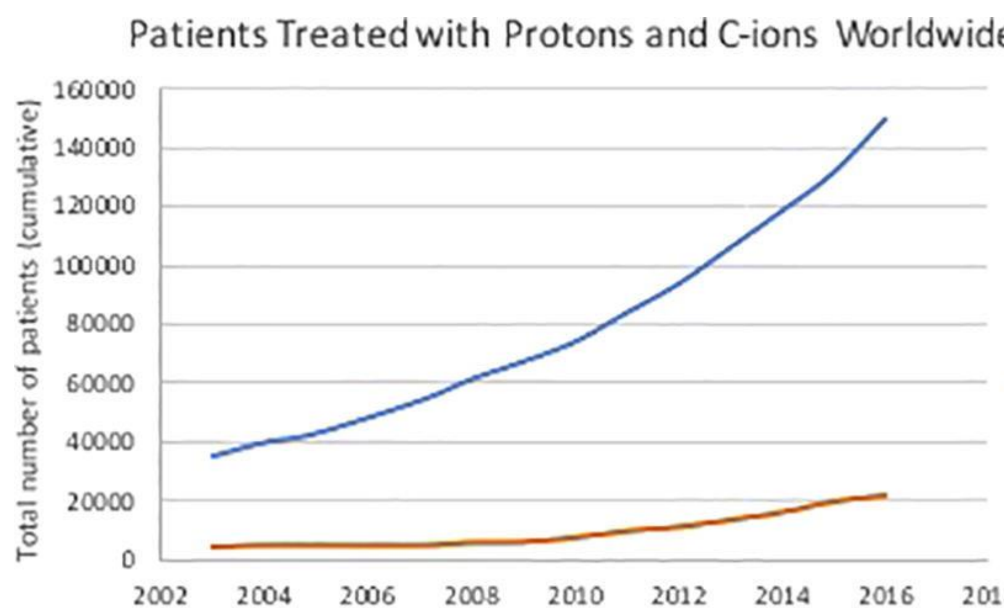
Motion control





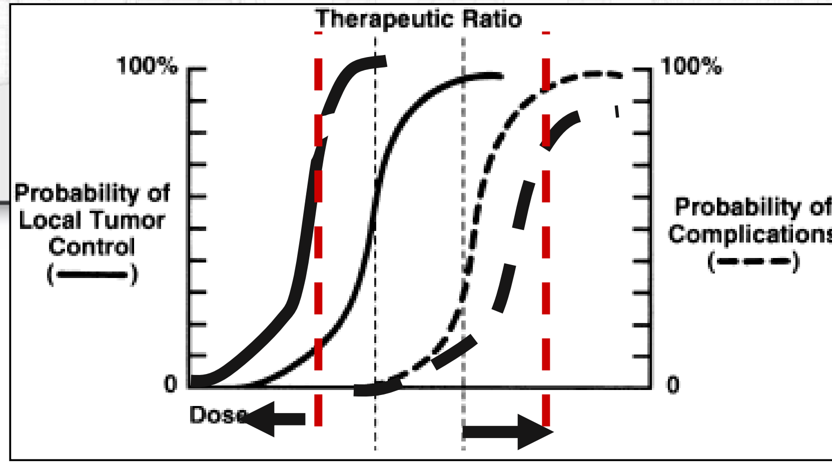
<2% of all RT





Radiotherapy and Oncology DOI: (10.1016/j.radonc.2018.03.014)

Future of RT

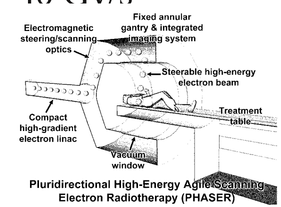


Novel approaches under clinical evaluation

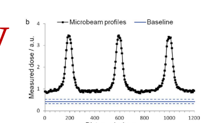
- **Fractionation:** hypofr./Acceler, Individ fr.
- **Technique:** Dose painting, **Hadron Th**
- Mixed energy RT
- **Combined treatment**
- sensitisation/protection
- Chemo-, hormon, biol.m., hypoxic sens.
- BNCT
- Immuno-Radiotherapy

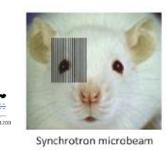
Novel approaches under preclinical evaluation

- FLASH-RT 500ms pulses of >40 Gy/s
- VHEE -PHASER patented US20130231516



- Nanoparticles for RT sensitisation
- Mixed particle therapy
- Microbeam radiotherapy
- Dose and LET painting
- BPCEPT





PERSONALISED RT
BASED ON RADIOMICS/GENOMIC

The implementation of precision medicine, such as genomics, radiomics, and mathematical modelling open the possibility to personalised RT adaptation and treatment.

Dose rate effectiveness factor DREF

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

A 17 Gy conventional irradiation induced pulmonary fibrosis in 100% of the animals 24-36 weeks post-treatment, whereas no animal developed complications below 23 Gy flash RT
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*

Large animal single dose FLASH-RT studies on SSC at a dose rate of 25-41Gy/s confirmed its advantage and shows promise as a new treatment option for the future

*M.-C. Vozenin, P. De Fornel, K. Petersson, V. Favaudon, et al **The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients** Clin Cancer Res 2018*

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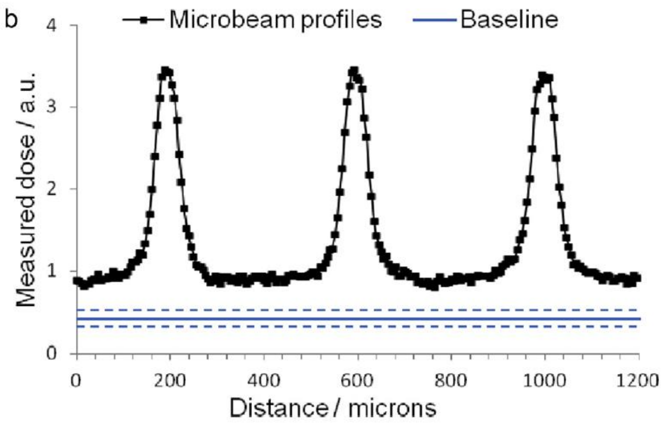
Microbeam radiation therapy (MRT)

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



Highly brilliant Synchrotron sources:

- very small beam divergence
- extremely high dose rate >100Gy/s.

GRID therapy (field size of mm), monoplanar beam arrays, Compton sources, pencil beam, Carbon nanotube X-rays, Proton MBT

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..

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

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

E. Schültke, J. Balosso et al. . :Microbeam radiation therapy (MRT) – GRID therapy and beyond. Clinical perspectives- BJR 2017 90

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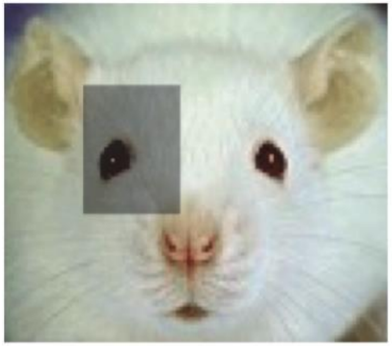
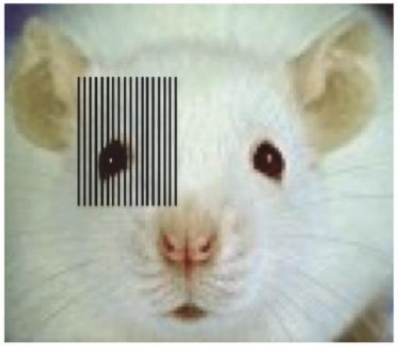


Synchrotron broad beam



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

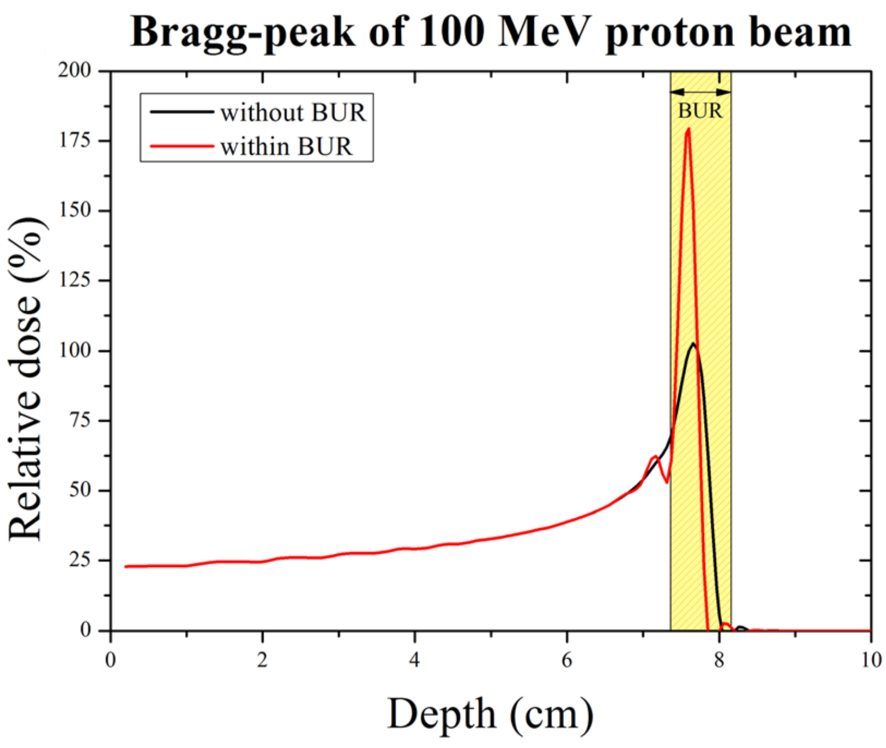
Synchrotron-based MRT resulted in 10 fold prolonged survival of the treated animals with brain tumor xenograft, larger animal studies are ongoing

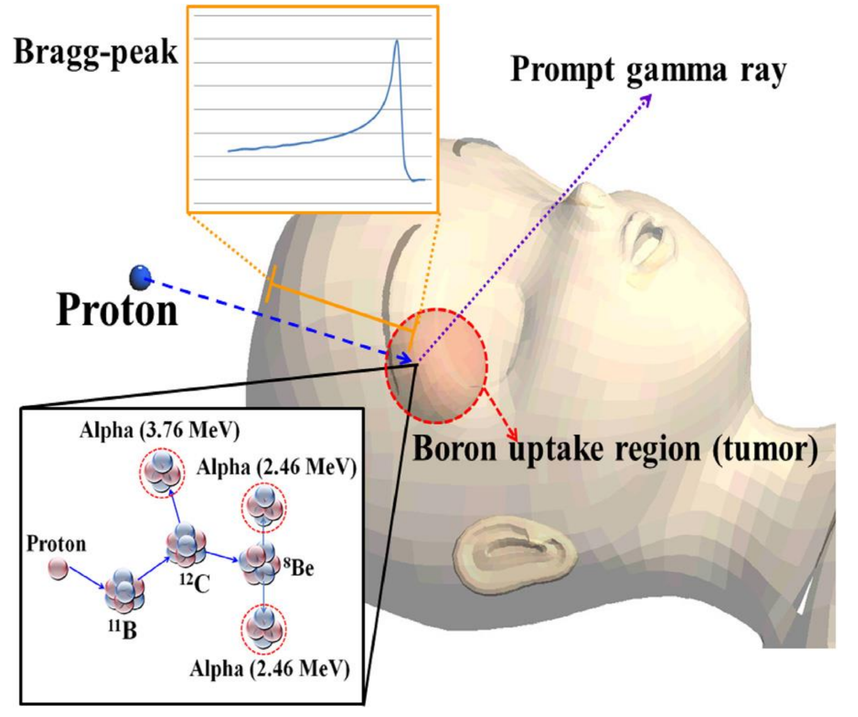
2013-17 **COST action** – common effort accelerated experimental research toward clinical application

Potental indication: GBM, DIPG, Osteo-, chondro sarcomas, soliter-, oligo-metastasis, epilepsy, radio-immunotherapy

Delivery: single-, oligo fraction (≤3), sequential-, integrated-boost, reirradiation

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)

It splits into alpha particle of 3.76 MeV and beryllium (8Be).

Subsequently, the beryllium is divided into the two alpha particles of 2.74 MeV

In silico- and in vitro studies on BPFEPT

D. Adam and B. Bednarz, SU-F-T-140**: Assessment of the proton boron fusion reaction for practical radiation therapy applications using MCNP6,** *Med. Phys.* **43 (**2016) 3494

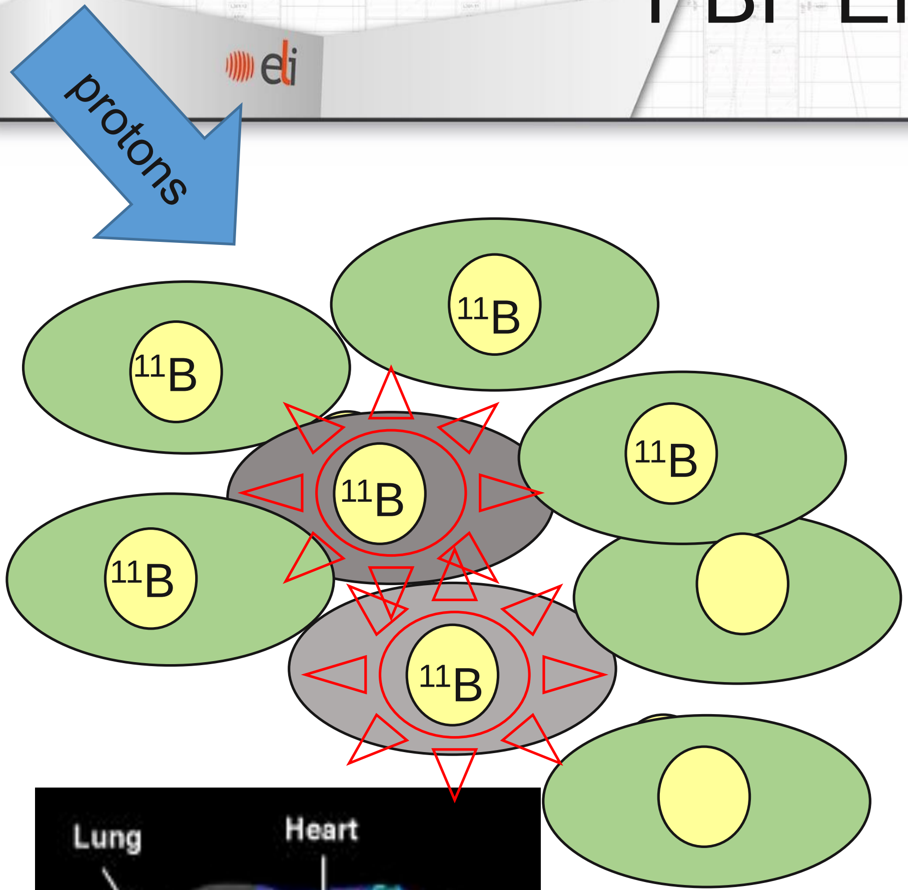
Jung JY, Yoon DK, Barraclough B, Lee HC, Suh TS, Lu B **Comparison between proton boron fusion therapy (PBFT) and boron neutron capture therapy (BNCT): a Monte Carlo study.** Oncotarget. 2017 Feb 25

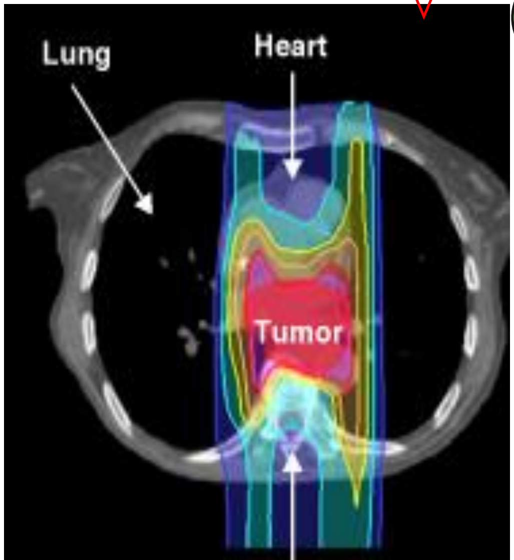
GAP Cirrone L Manti, D Margarone, L Giuffrida, A. Picciotto, G. Cuttone, G. Korn, V. Marchese, G. Milluzzo, G. Petringa, F. Perozziello, F. Romano, V. Scuderi**, Nuclear fusion enhances cancer cell killing efficacy in a protontherapy model** Med. Phys.2018.02

↓

Both chromosoma abberation analysis and colony forming assay confirmed the enhanced effectivity of BPF in cell cultures using natural (80% ^{11}B containing) BSH at a 62 MeV proton source

PBF Enhanced Proton Therapy PBFEPT





In addition to selective

proton therapy

High spatial resolution

High LET,

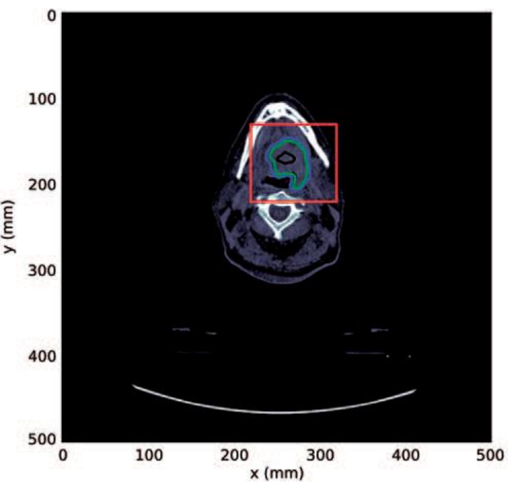
High RBE

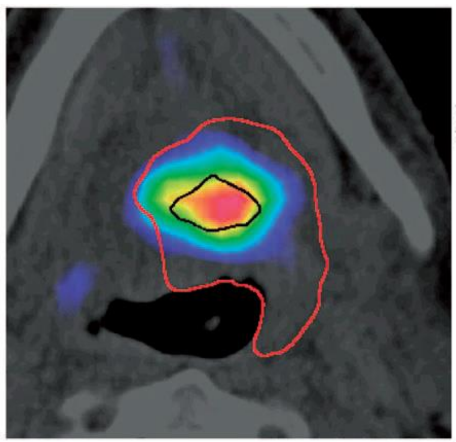
Low OAR

Binary approach

Dose- and LET-painting with PBFEPT

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

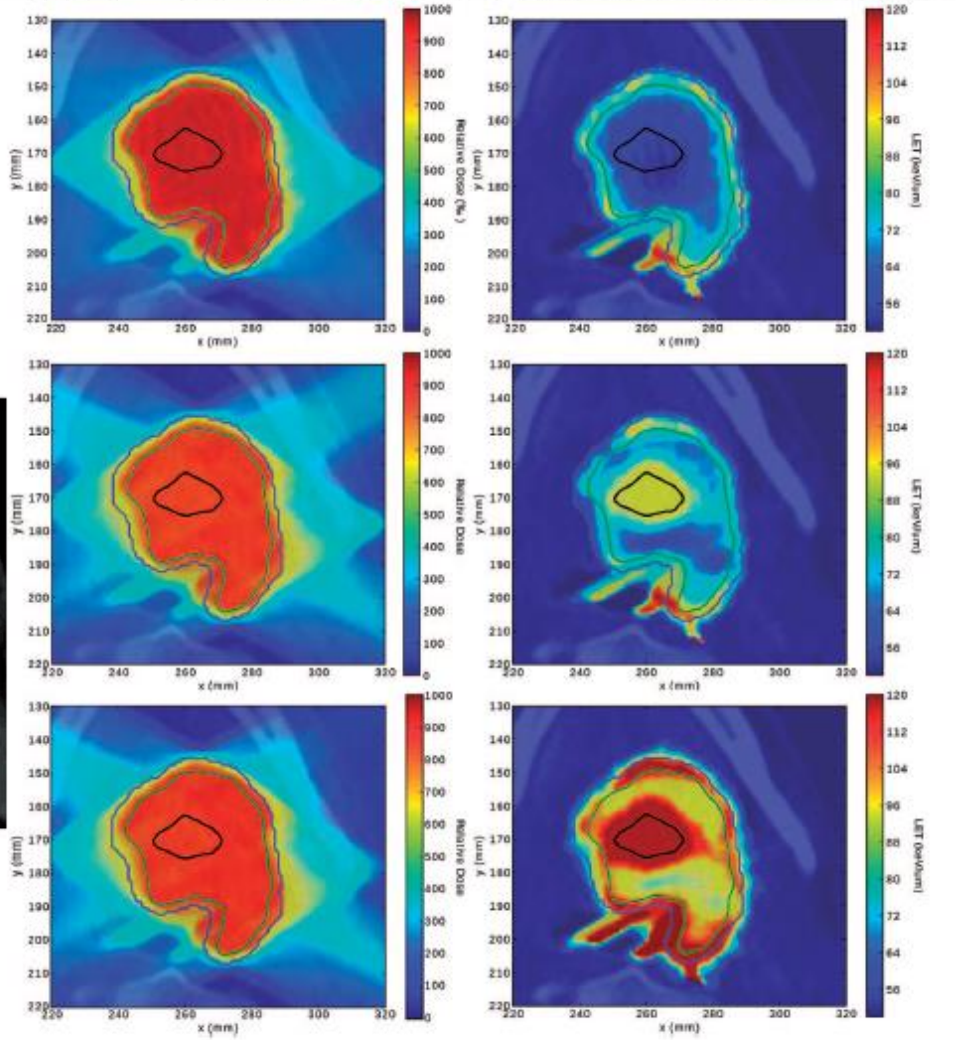
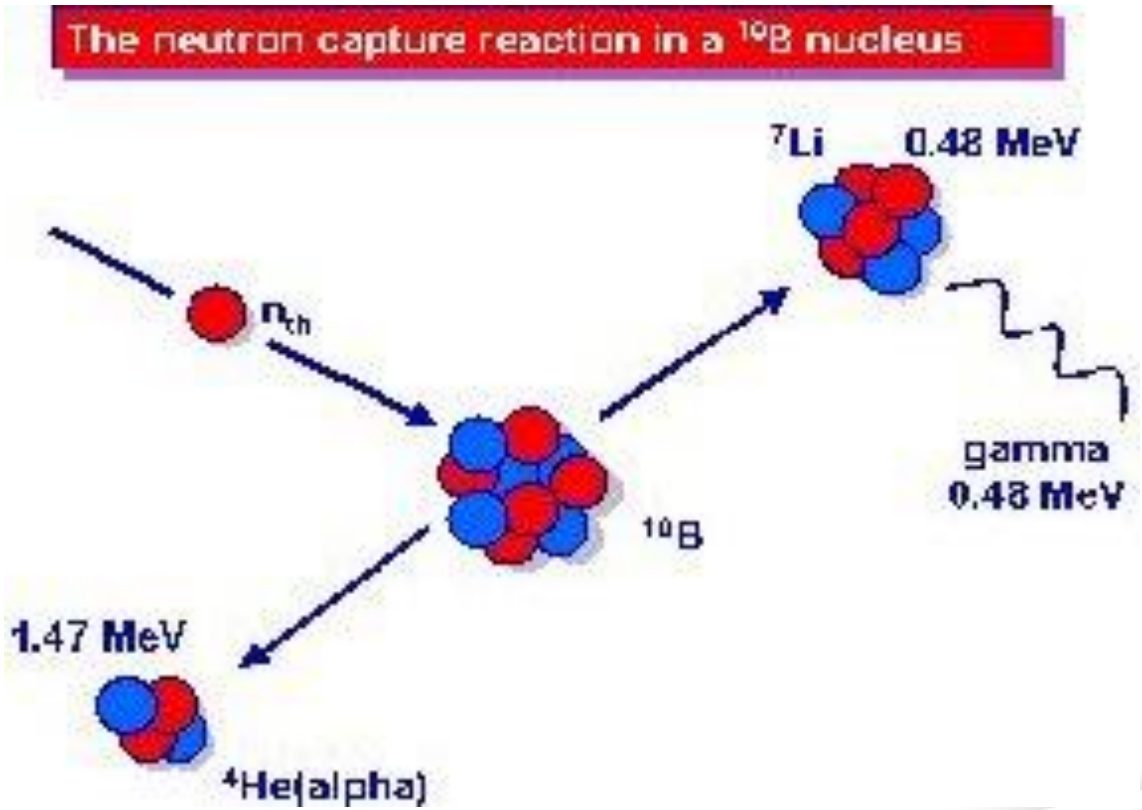


Figure 3. Dose and dose-averaged LET profiles shown in left and right column, respectively. First row is a carbon-12 ion plan using four conventional fields with homogeneous dose. The highest LET is then found at the rim of the SOBPs as seen in the upper right figure. LET-painting, as shown in the middle 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.

Boron Neutron Capture Therapy (BNCT)

Thermal neutrons captured by high probability by ^{10}B

desintegrates into two particles .



The two particles α and 7Li absorption ranges in tissue (~9 mm and ~5 mm respectively). All the energy is released inside the tumor cell

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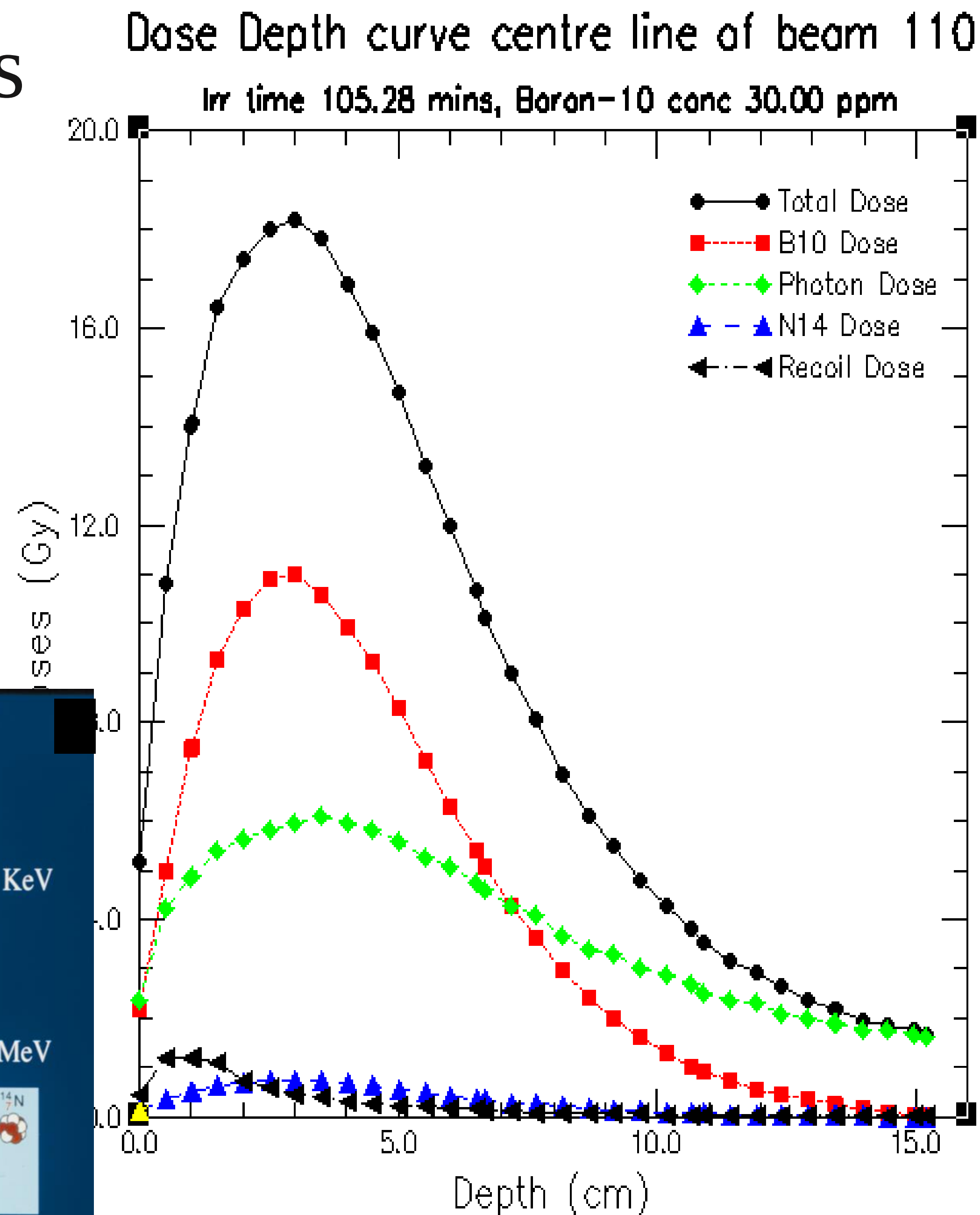
Neutron beam requirements for BNCT

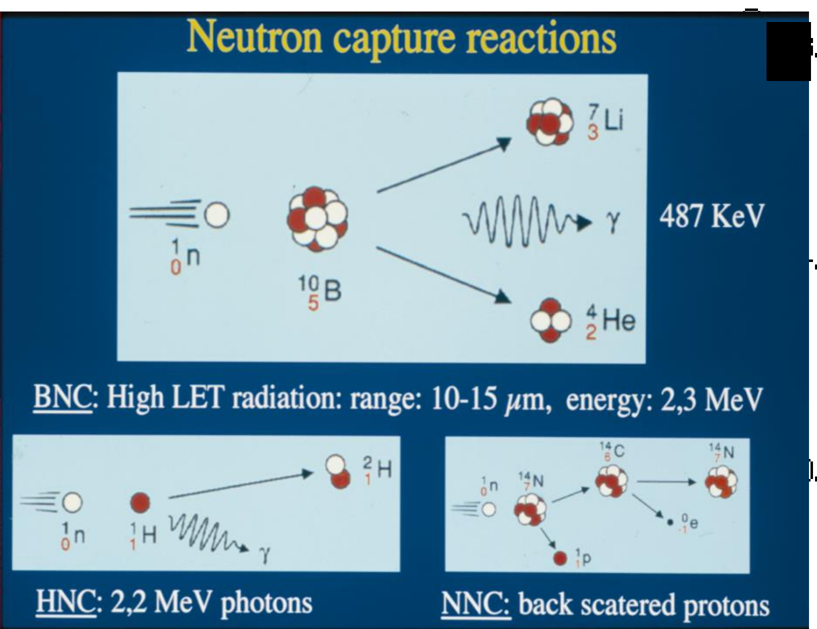
• epithermal neutron flux	$\cong 10^9$ neutrons/cm^2s (at the therapy position)
• neutron energy	~ 1 eV to ~ 10.0 keV
• gamma dose rate	$\leq$ 1.0 Gy/hr
• fast neutron dose rate	$\leq$ 0.5Gy/hr
• current:flux (J/Φ) ratio	> 0.8

- the parameter J/Φ reflects the forward directionality (degree of collimation) of the beam of neutrons, which equals 0.5 for a completely isotropic beam and 1.0 for a purely parallel beam

Dose components

- D_{Boron}
- $D_{Nitrogen}$
- D_{Photon}
- $D_{neutron}$





Clinical application of BNCT

N>200

HFR Research reactor

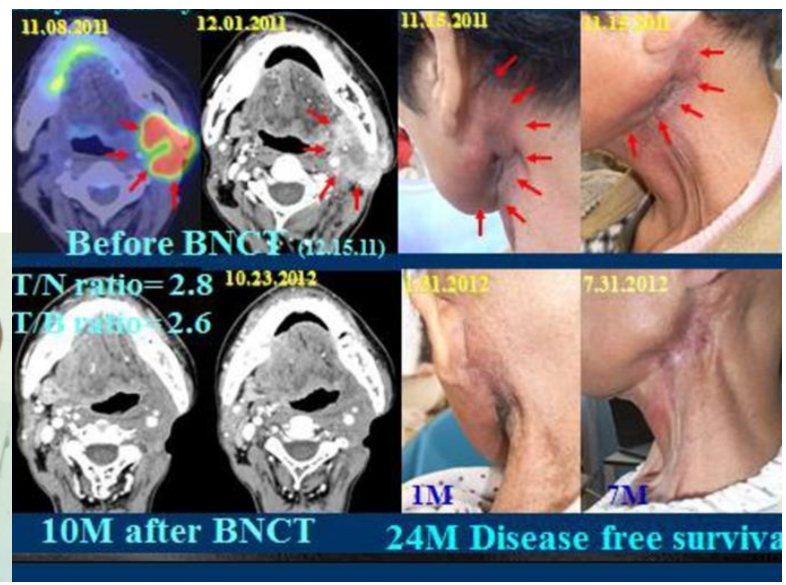
GBM ^{10}B carrier BSH

$Na_2B_{12}H_{11}SH$

Malignant melanoma

^{10}B carrier: BPA+BSH

Extracorporal liver BNCT — BPA



Recurrent H&N tumors

^{10}B carrier: BPA

Boro-phenylalanin

Neutron sources for BNCT

Nuclear reactors

Charged particle accelerators

Compact neutron generators

LINAC based neutron source

High power laser facilities may provide
via (p, n) reaction intense epithermal neutron beam

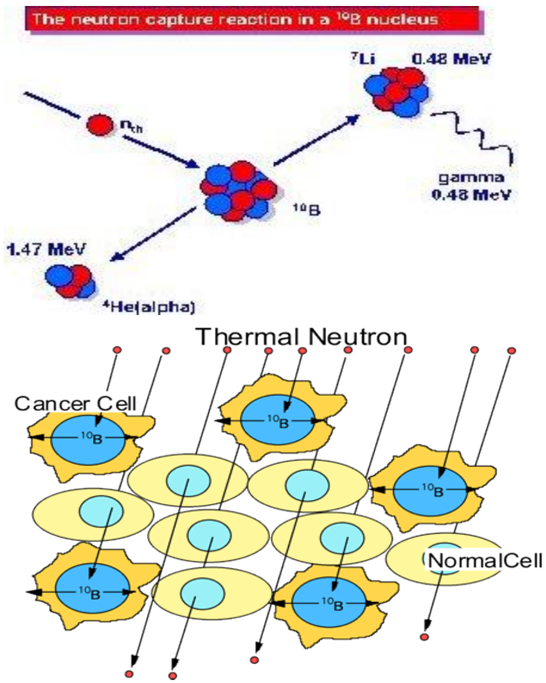
eli attosecond

Binary modality hadron therapy

Boronated agents for BNCT and BPCEPT

Katalin Hideghéty, Szilvia Brunner, Andrew Cheesman, Emilia Rita Szabó, Róbert Polanek, Daniele Margarone, Tünde Tőkés, Károly Mogyorósi **^{11}Boron delivery agents for Boron Proton Capture Enhanced Proton Therapy (BPCEPT)** – Anticancer Research submitted

BNCT Selective, cell-targetted energy deposition



Clinical data available (>200 patients)

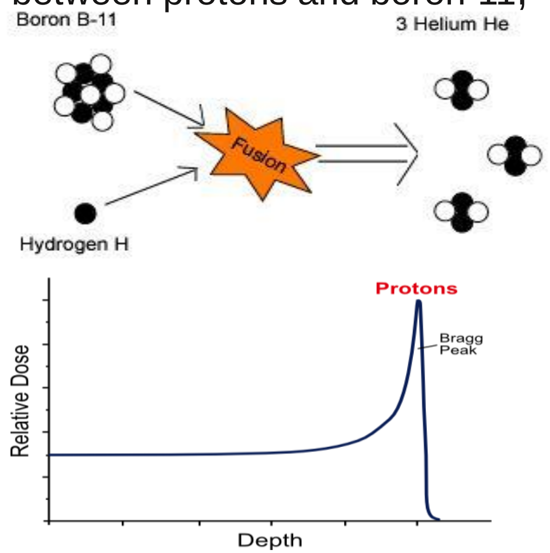
High LET,

High RBE

Binary

approach

BPF ^{11}B (p, 3α) reaction occurs between protons and boron-11,



The highest cross-section occurs with protons around 600-700 keV corresponding to the Bragg peak

Starting experiments

Laser driven particle beams

X-UV, X-ray photons

Very high energy electron

Protons
Carbon ions

Integrated facilities with particle selection

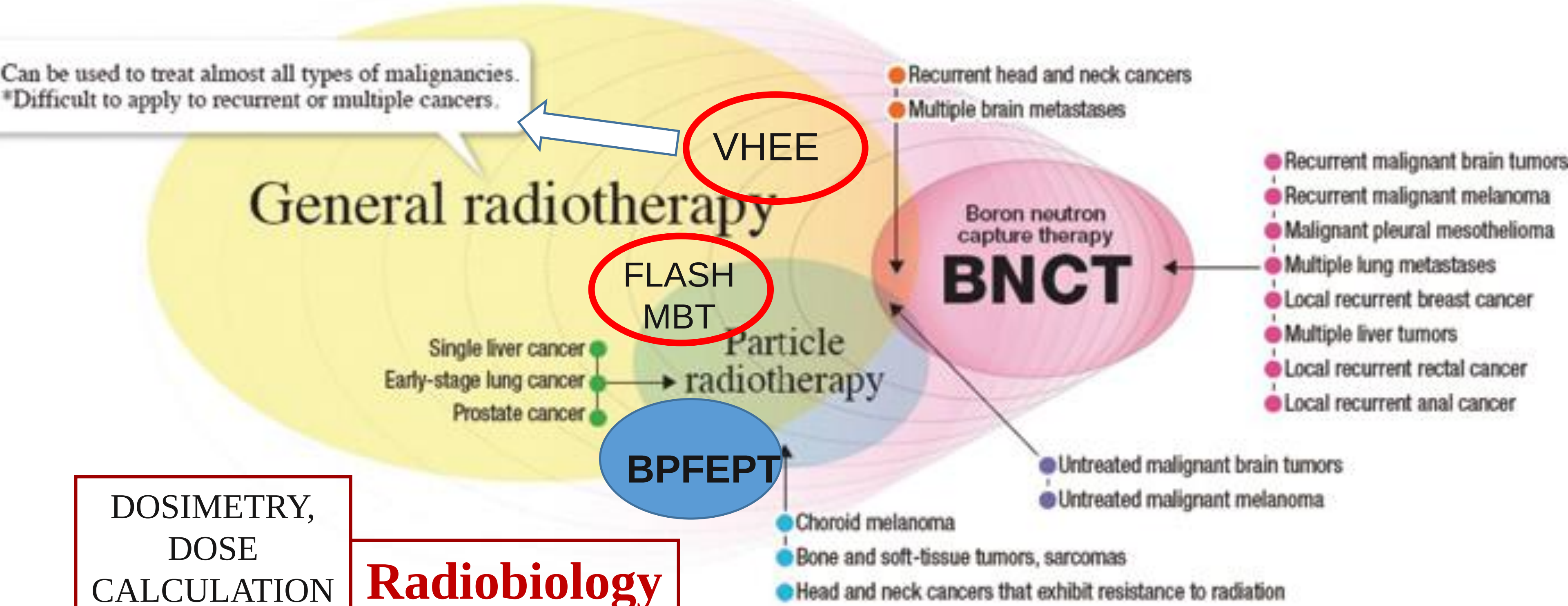
Ultra short pulses

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

High repetition rate

Ultra high time and spatial resolution

Emerging approaches



DOSIMETRY, DOSE CALCULATION

Radiobiology

Effects on normal tissue / tumor response

RBE of pulsed, ultraintense beams

BNCT, BPCEPT $^{10}B/^{11}B$ carriers

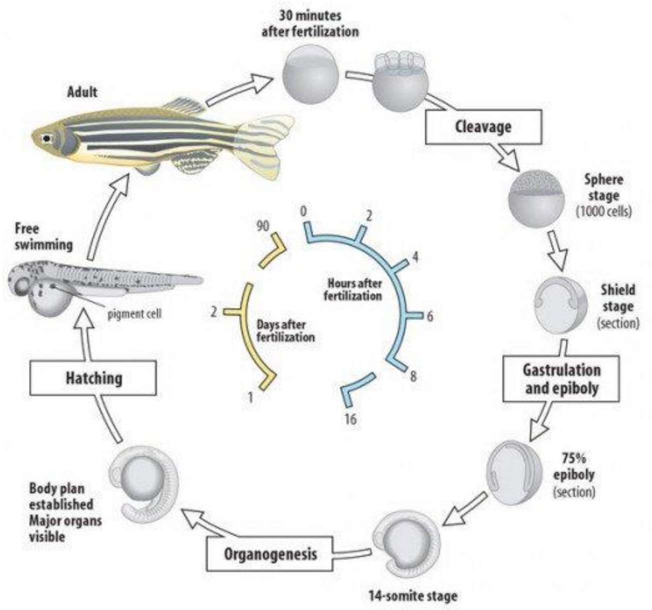
MRT Flash

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

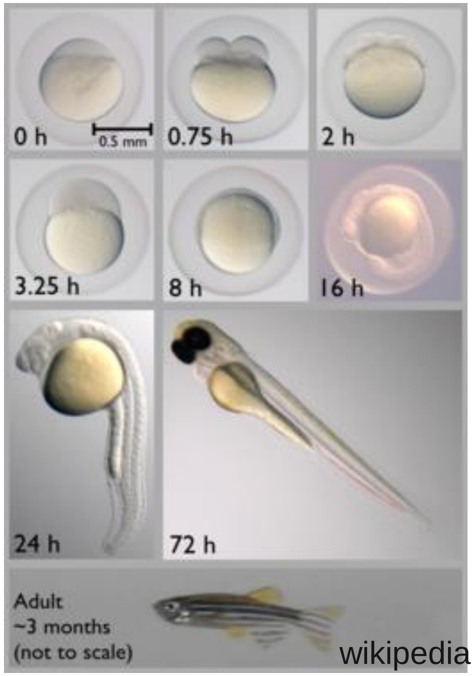
Novel vertebrate model

Advantages

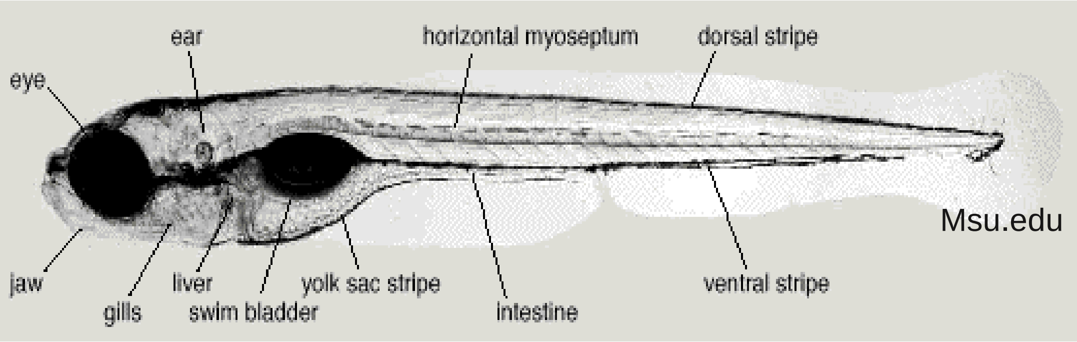
- Easy to handle, good reproduction captivity
- Body transparency (embryo and larva)
- External fertilization
- Rapid embryonic development
- Genomic similarity to the human genome
- Availability of several transgenic lines
- High resilience



helda.helsinki.fi



wikipedia



Msu.edu

Establishment of zebrafish embryo system for radiobiology studies

Definition of the emryo related factors (type, age,handling)

Validation of dose dependent biological endpoints (cell cultures/small animals)

- survival, morphological deterioration
- histopathological changes
- Molecular damages (gammaH2AX, caspase3)
- molecular pathway activation (RTPCR)

Irradiation parameters: setup, dose delivery, dose escalation, fractionation,

Observation (period, frequency, assessment, documentation /photo/

Quatitative measurements

Automatisation

Irradiation of zebrafish embryos

LINAC

Age: 24 hpf

In: plates/tubes/plastic bags

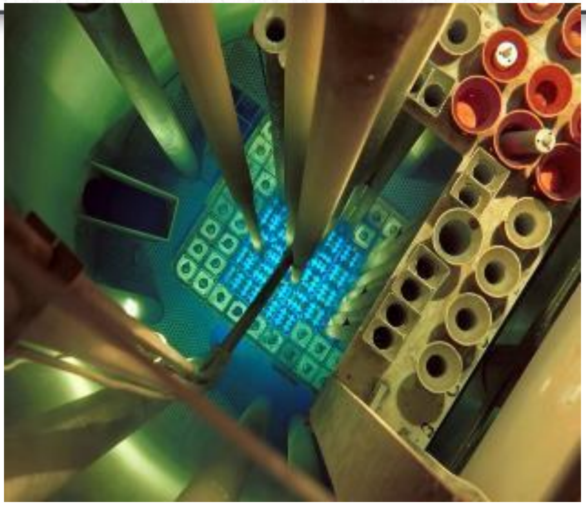
6 MV foton- 0 Gy, 5 Gy, 10 Gy, 15 Gy, 20 Gy

<En=1 MeV> hasadási neutron

0 Gy, 1,25 Gy, 1,875 Gy, 2 Gy, 2,5 Gy

p(18 MeV)+Be,<En>=3.5 MeV ciklotron neutron

2 Gy, 4 Gy, 6,8 Gy, 8,12 Gy, 10,28 Gy

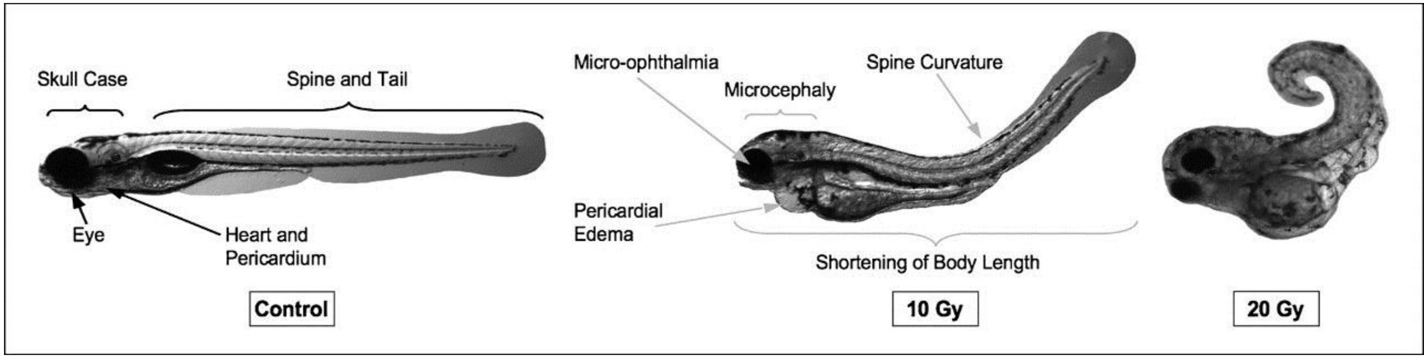


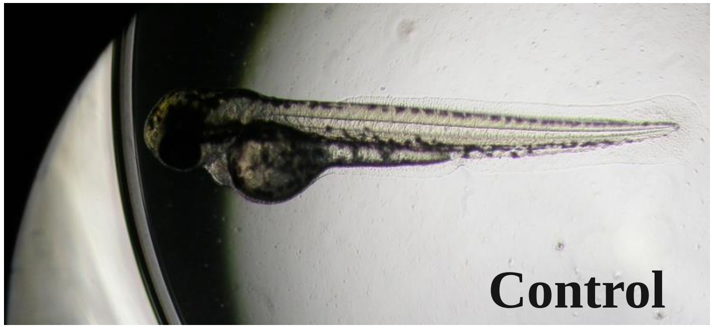
Fission neutron- research reactor

ATOMKI cyclotron

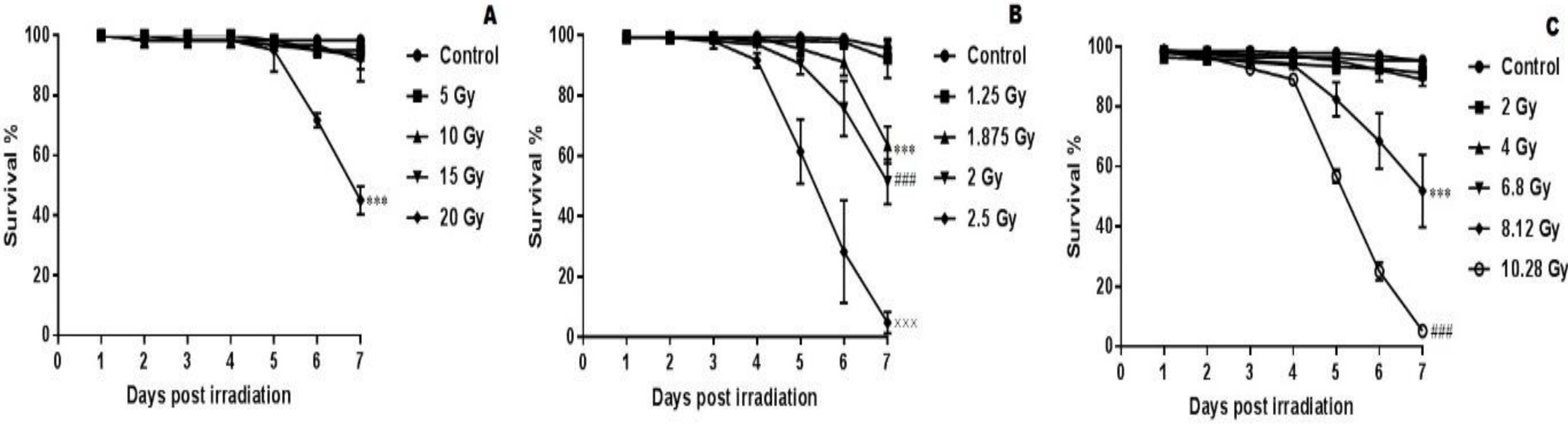
End points of zebrafish embryo experiments

detection of malformation and survival





RBE of fission neutron and of p(18 MeV)+Be fast neutron

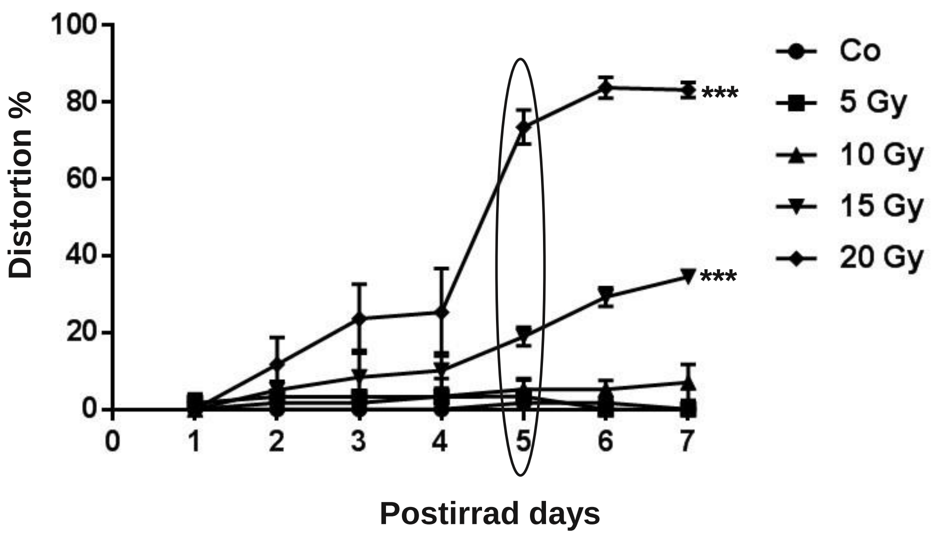


fission neutron LD50: 2Gy / photon LD50: 20Gy **RBE =10**

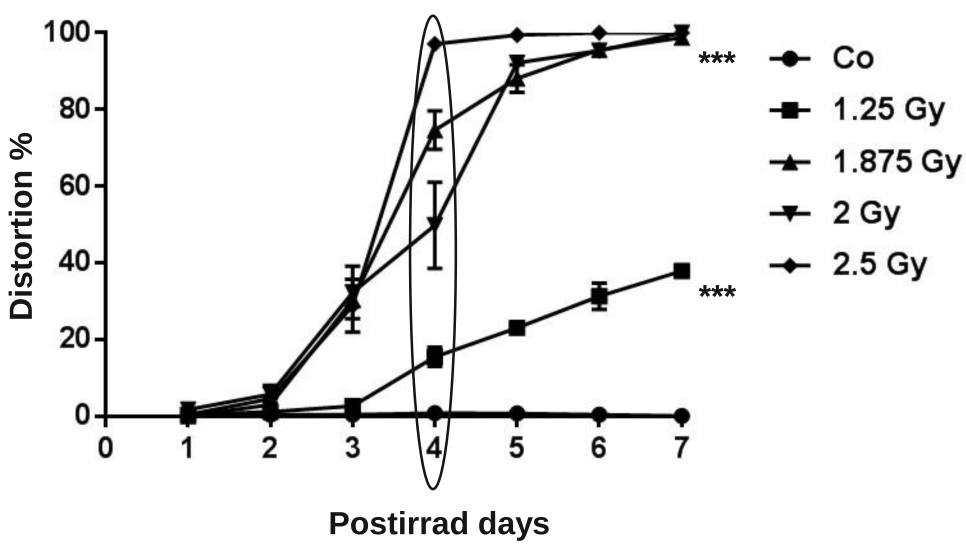
p(18 MeV)+Be fast neutron LD50:8Gy / photon LD50: 20Gy **RBE = 2,5**

Developmental deterioration

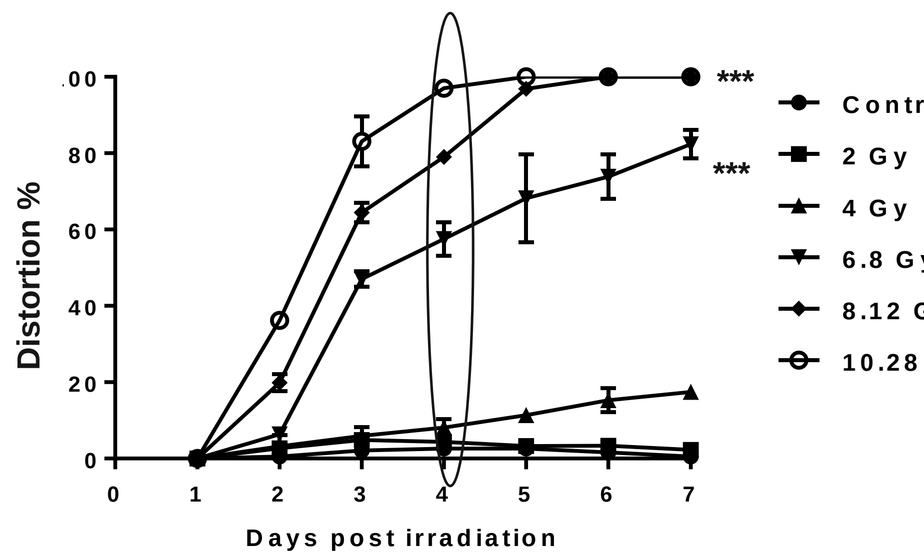
Photon (6 MV)



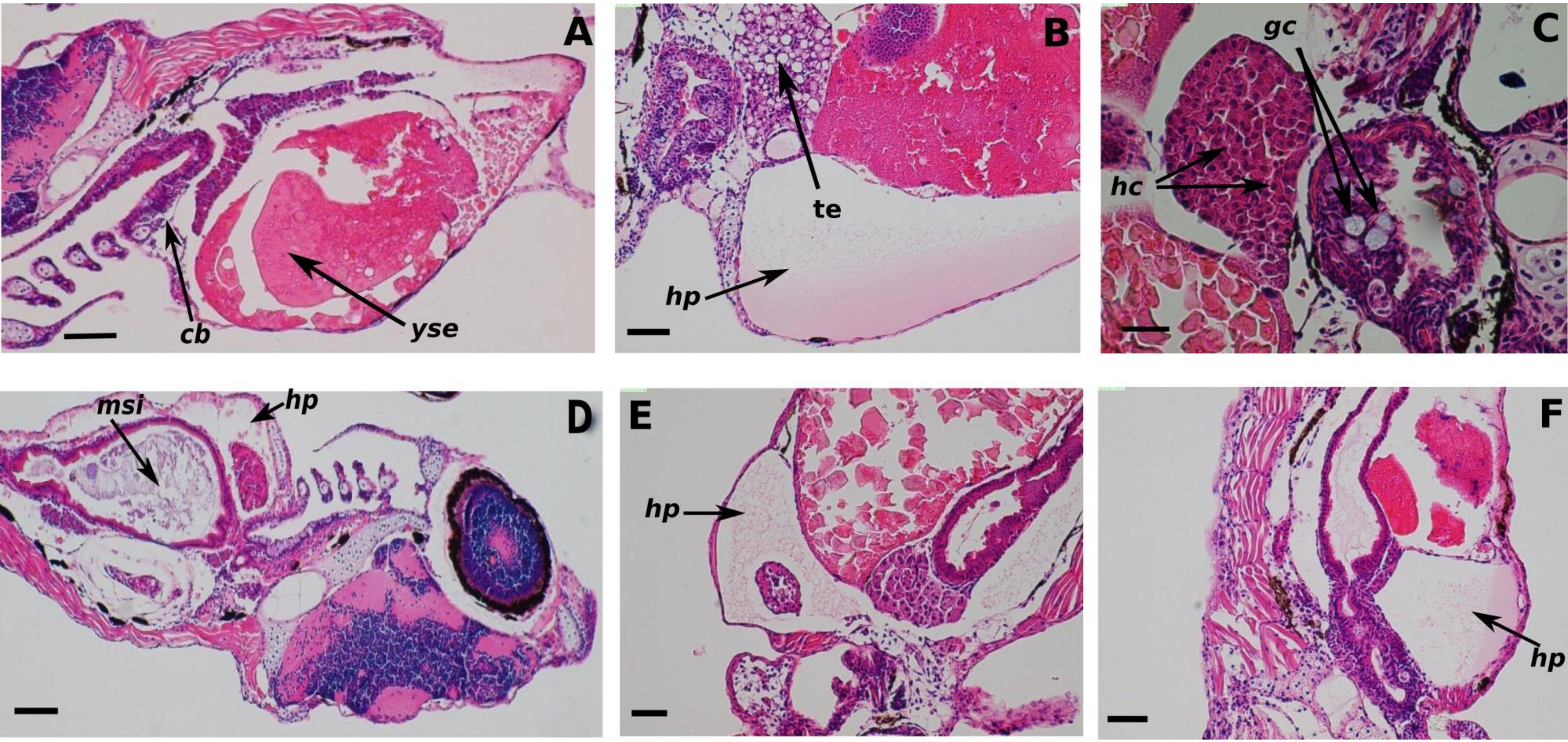
Fission neutron (1 MeV)



Cycl. neutron (p(18 MeV+Be)



Histopathology analysis



cb- ceratobranchials
yse- yolk sac edema/ szíkhólyag ödéma
hp-

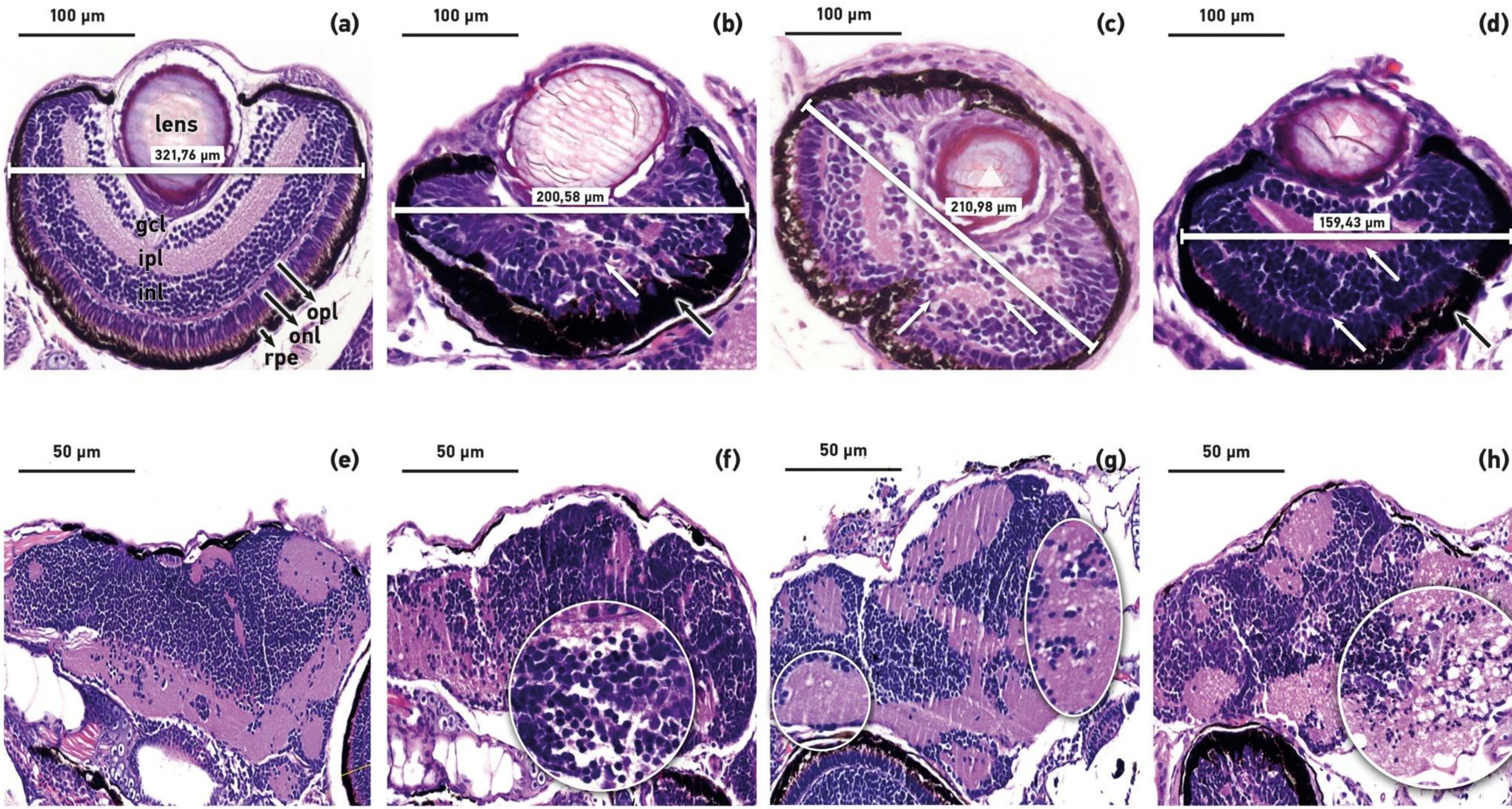
Eye and brain tissue

Control

20 Gy- 6 MV Foton

2 Gy- Fission neutron <EN=1 MeV>

8.12 Gy- Cyclotron neutron (p(18 MeV)+Be,<EN> =3.5 MeV



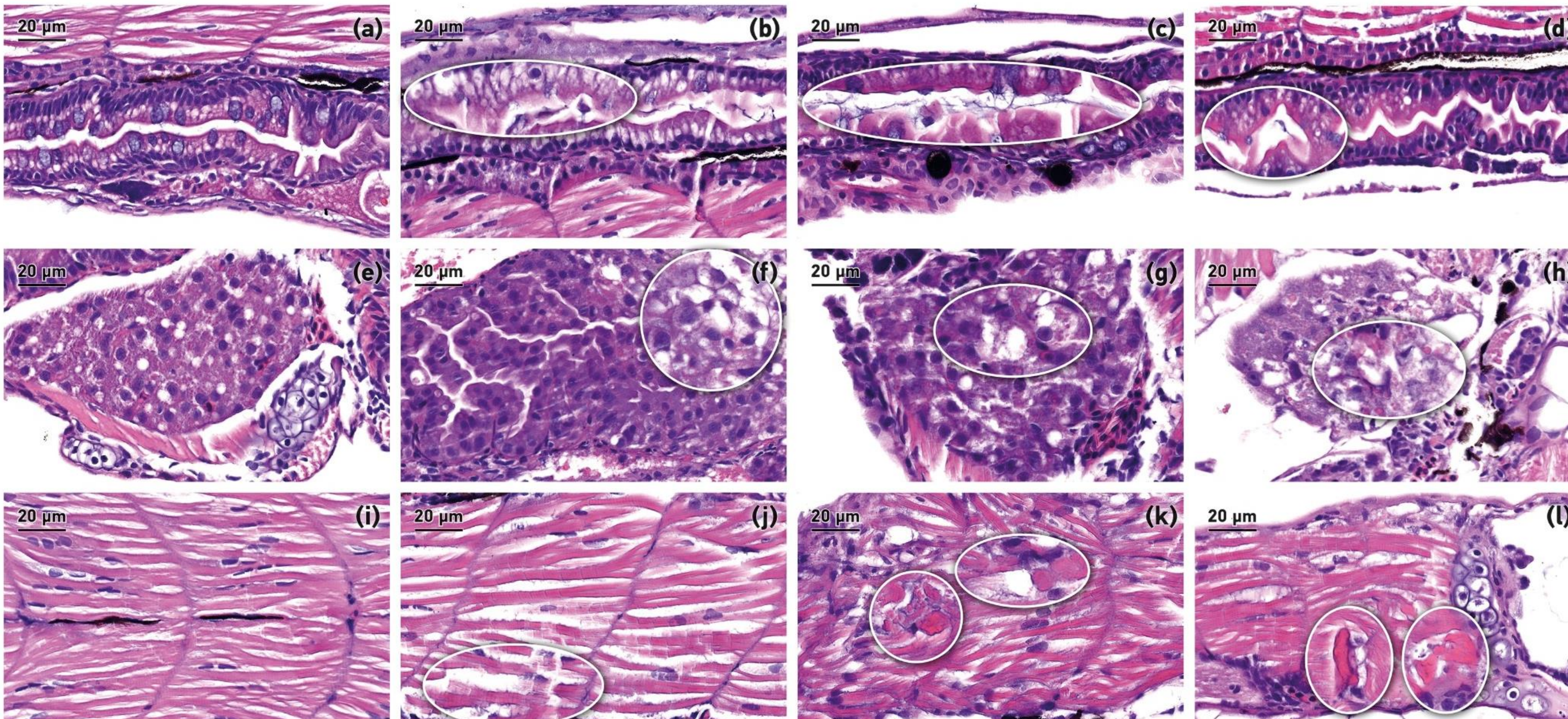
Small intestine, liver, muscle tissue

Control

20 Gy- 6 MV Photon

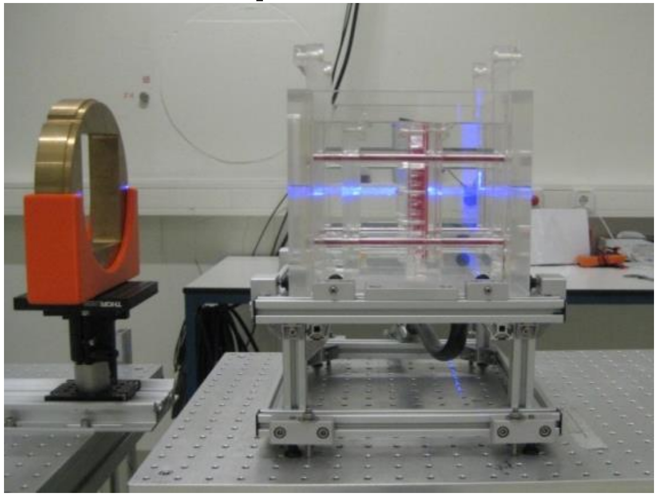
2 Gy- Fissioni neutron <EN=1 MeV>

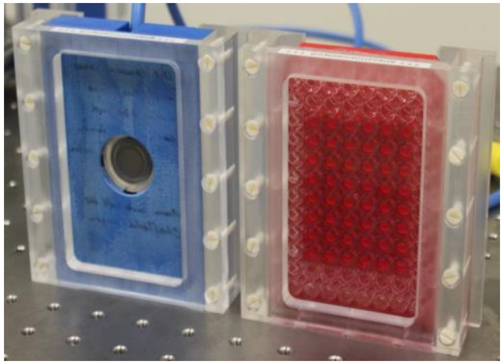
8.12 Gy- Cyclotron neutron (p(18 MeV)+Be,<EN> =3.5 MeV



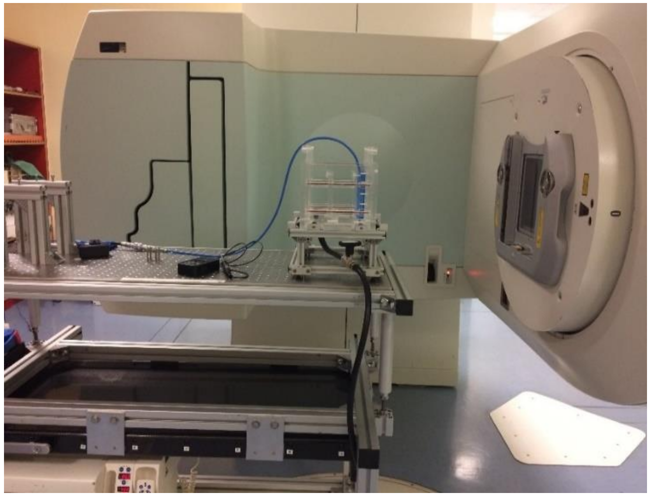
Collaboration with OncoRay, and HZDR

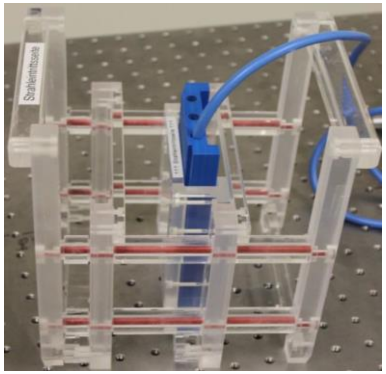
150 MeV proton source





6 MV photon (ref. Source)

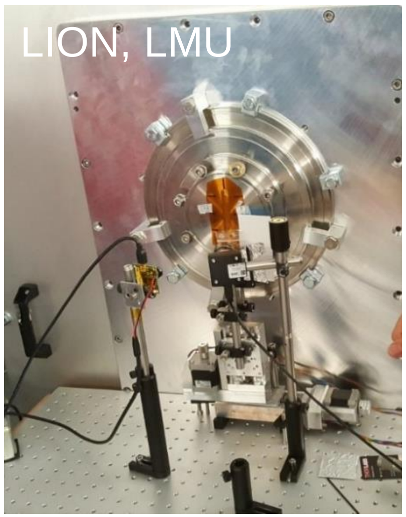


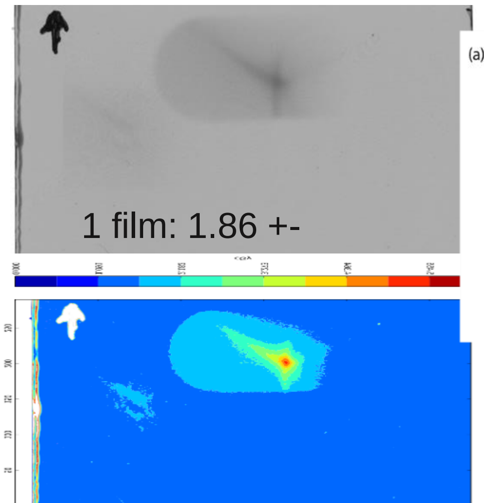


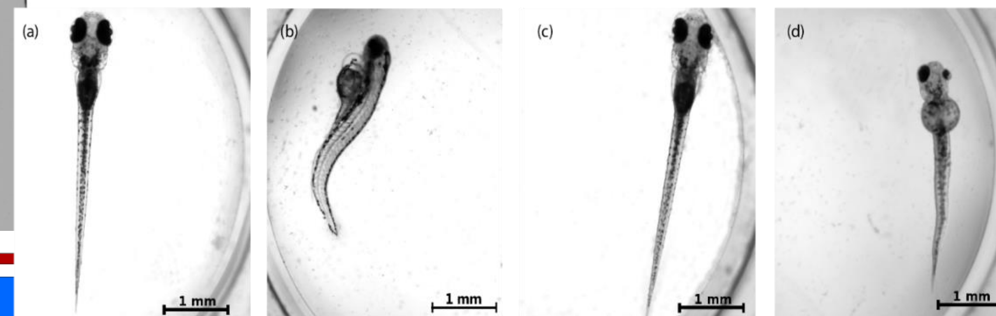
Experiments on

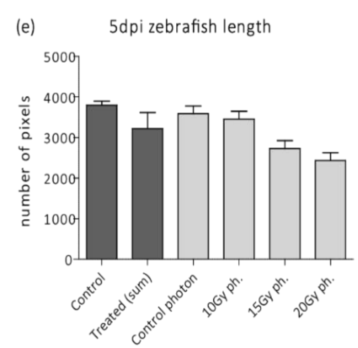
- proton RBE at the plato and mid of SOBP
- laser driven proton irradiation
- FLASH effect

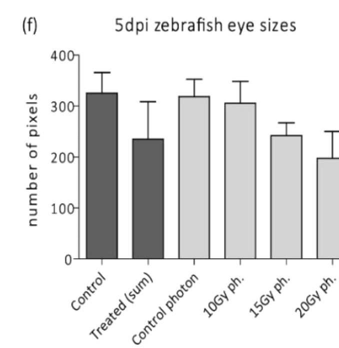
Feasibility experiment at the LION facility at LMU

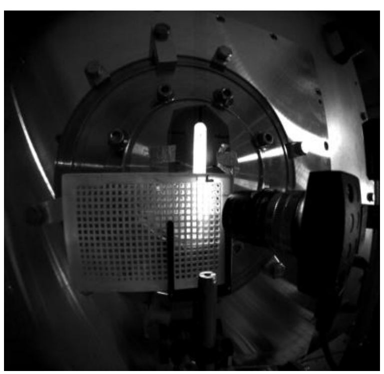


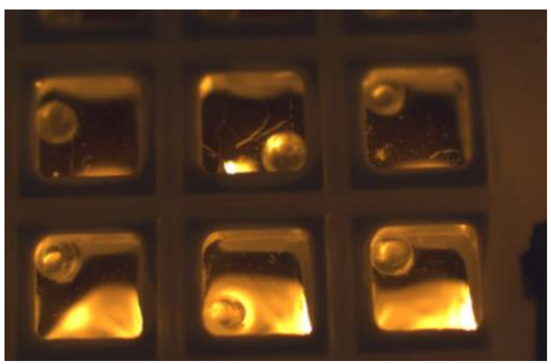












Further technical improvements may open the possibilities for **micro beam irradiation** development

Laser driven ionizing radiation

Pulsed mode/ Ultraintense beam /Ultrashort dose delivery

short treatment time

- without increased entrance (skin) dose
- no need for internal organ motion management
- immunoRT

high temporal resolution

(adaptive response, FLASH RT)

- high spatial resolution
- Intensity modulation with higher resolution
- Microbeam RT

Potential for charged particle/neutron and multiple particle beams

Improved dose distribution,

BNCT, BPCEPT

Dose and LET painting

ELI-ALPS
BIOMEDICAL APPLICATION GROUP

attosecond

Thank you

LMU, Munich
Laser-driven proton beam

HZDR
Laser-driven proton beam

OncoRay, Dresden
Proton (IBA)

INFN, Catania
Proton beam

PTC, Prague
Proton beam

Univ.Gödöllő
Fish laboratory

BME
Neutron beam

ATOMKI
Neutron beam

KFKI
Neutron beam

University of Szeged

MEDICAL PHYSICS AND IINFORMATICS
Fish lab. Chemical dosimetry, RT planning

ONCOTHERAPY
Dosimetry, LINAC ref. photon, electron radiation

PHYSIOLOGY
neurovascular function

EXPERIMENTAL SURGERY
Radbiol. Lab., malonaldehyd.

DERMATOLOGY
Cell culture and genetic lab

PATHOLOGY
Histology, immunohistochem.

RADIOLOGY
small animal MRI

PHARMACOGNOSIA
Radiation modifiers

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SZÉCHENYI 2020

Hungarian Government

European Union
European Regional Development Fund

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