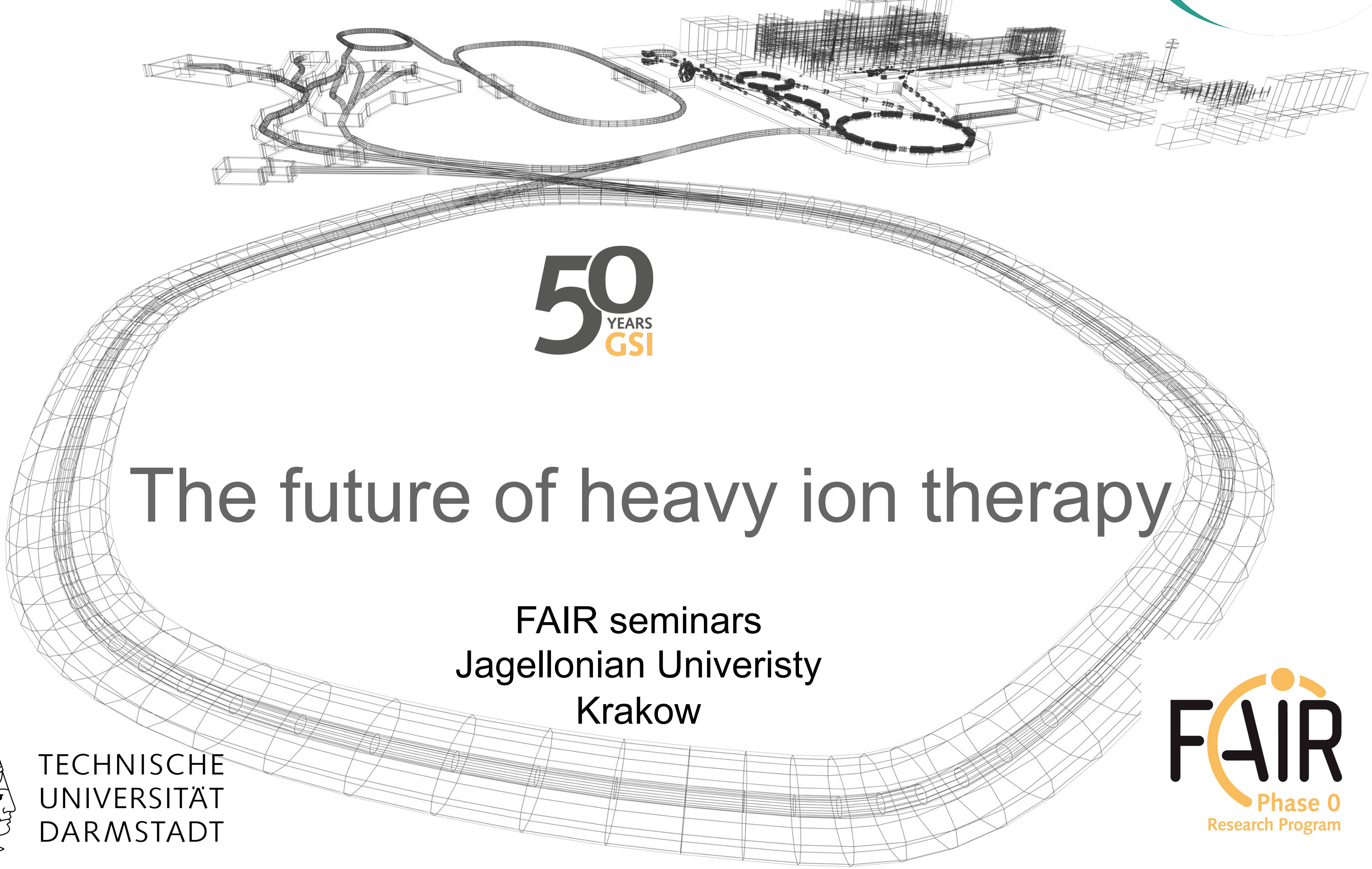
Marco Durante

Director, Biophysics Department



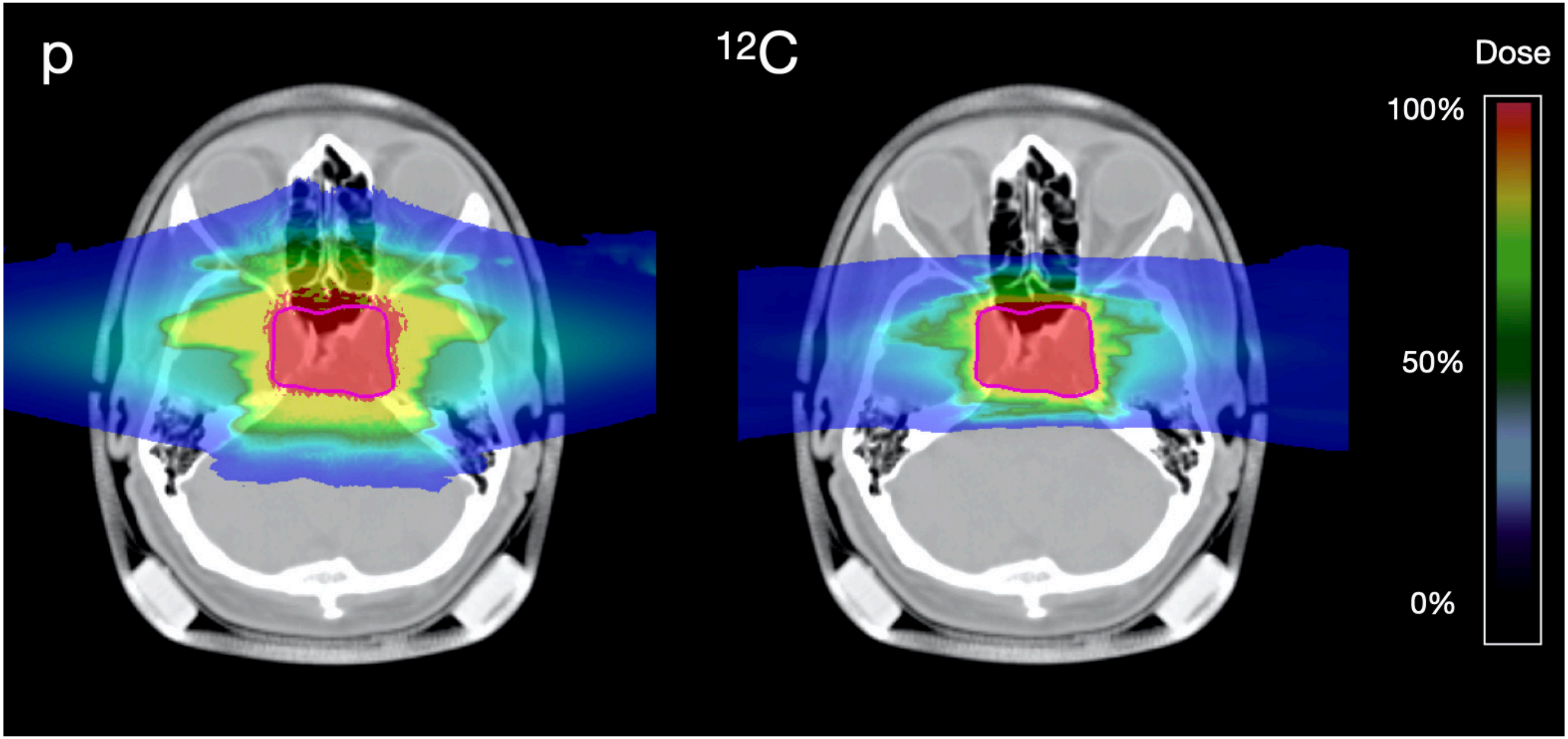
The future of heavy ion therapy

FAIR seminars
Jagellonian Univeristy
Krakow

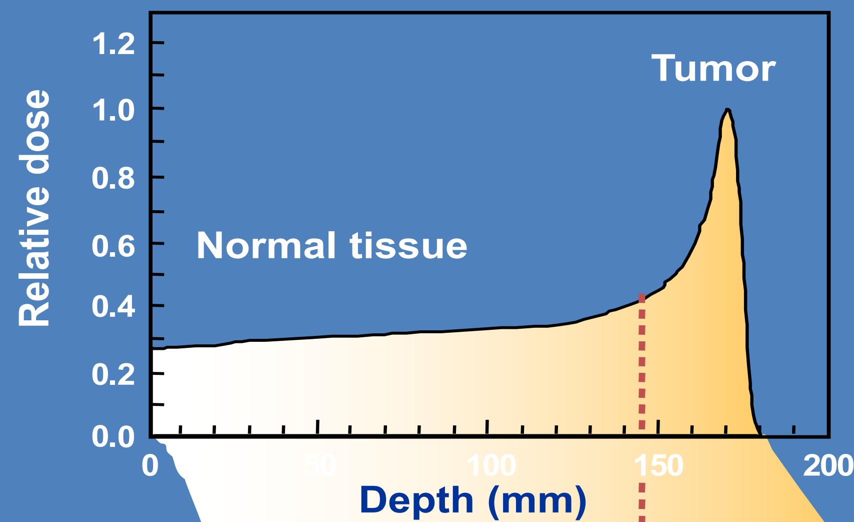
TECHNISCHE UNIVERSITÄT DARMSTADT

FAIR Phase 0 Research Program

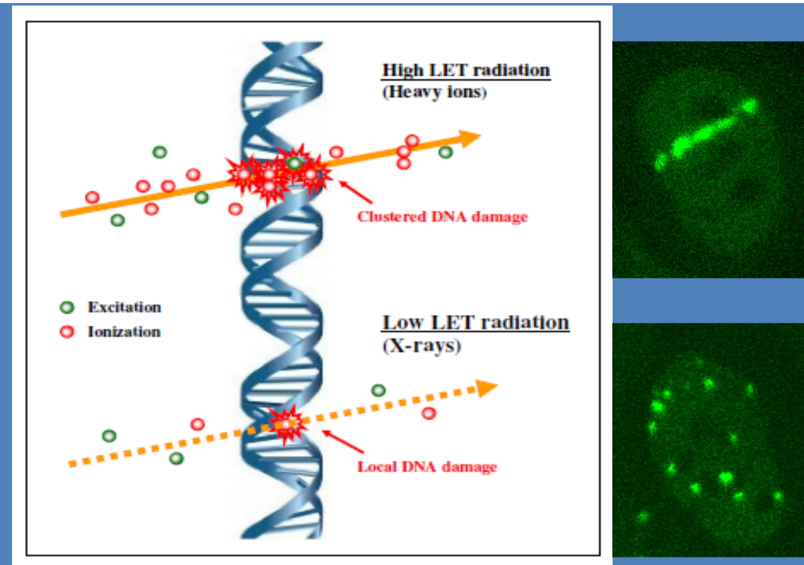
The physical advantages of heavy ions



Durante, Debus & Loeffler, *Nat. Rev. Phys*. 2021



Energy	high	low
LET	low	high
Dose	low	high
RBE	≈ 1	> 1
OER	≈ 3	< 3
Cell-cycle dependence	high	low
Fractionation dependence	high	low
Angiogenesis	Increased	Decreased
Immune effects	Weak	Strong



Potential advantages

High tumor dose, normal tissue sparing

Effective for radioresistant tumors

Effective against hypoxic tumors

Radioresistant (S) phase cells are sensitized

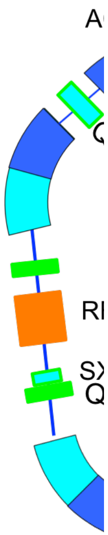
Fractionation spares normal tissue more than tumour

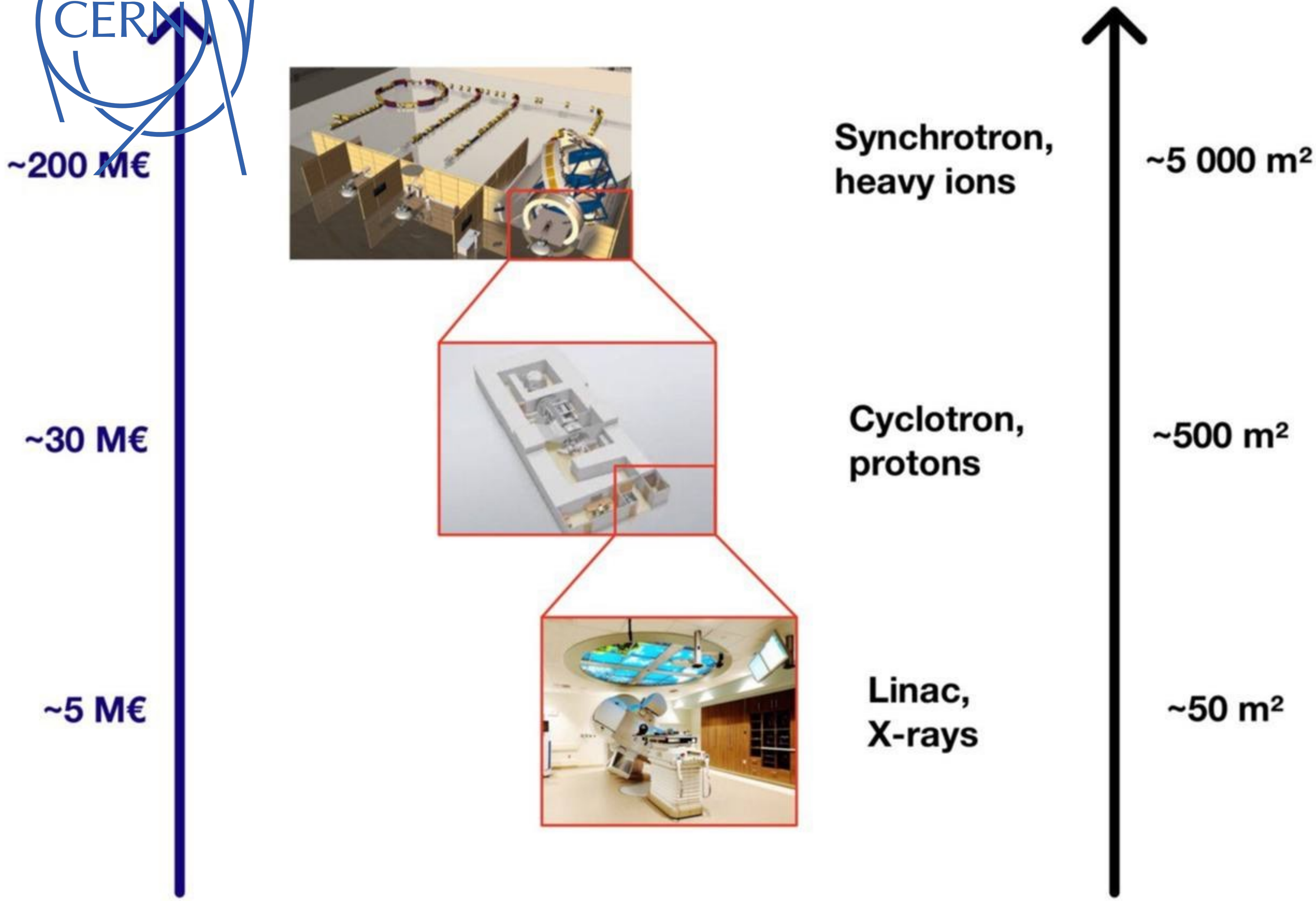
Reduced angiogenesis and metastatization

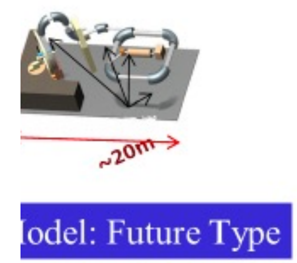
Systemic effects in combination with immunotherapy

Durante & Loeffler, *Nat. Rev. Clin. Oncol.* 2010

New compact accelerators for biomedical applications







Durante, Debus & Loeffler, *Nat. Rev. Phys*. 2021

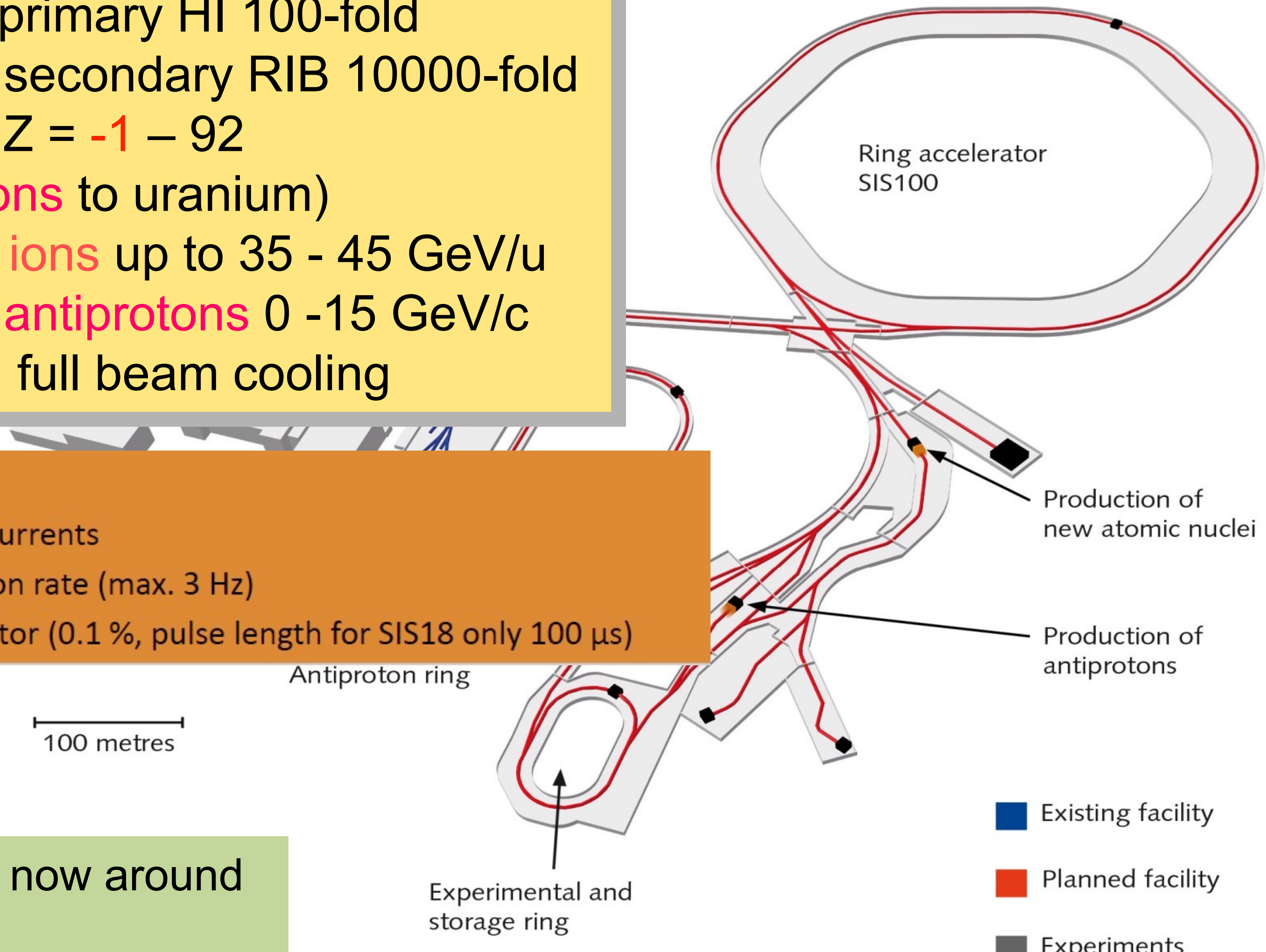
NEW NUCLEAR PHYSICS ACCELERATORS: FAIR, ELI, SPIRAL2, SPES, NICA, RAON,….

FAIR

Future Beams:
Intensity: primary HI 100-fold
secondary RIB 10000-fold
Species: Z = -1 – 92
(anti-protons to uranium)
Energies: ions up to 35 - 45 GeV/u
antiprotons 0 -15 GeV/c
Precision: full beam cooling

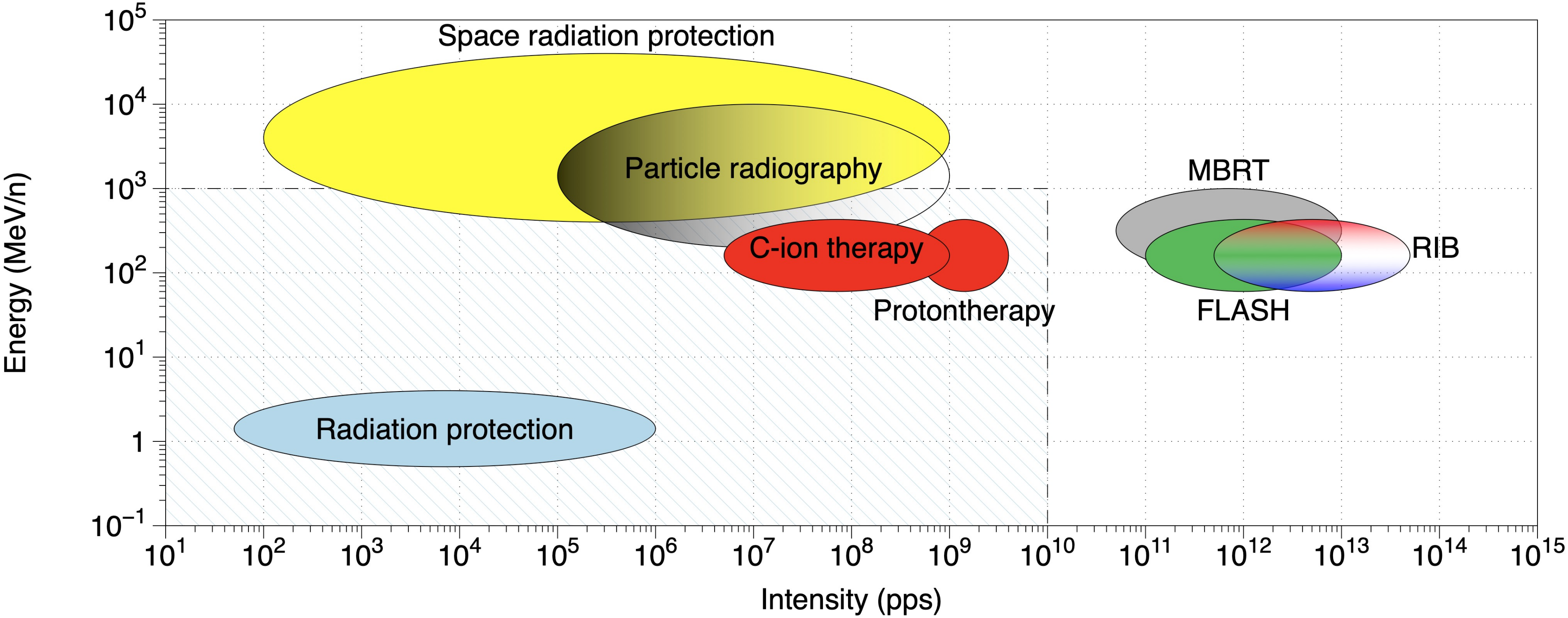
FAIR

- high beam currents
- low repetition rate (max. 3 Hz)
- low duty factor (0.1 %, pulse length for SIS18 only 100 µs)



Price tag now around
3 G€

Biomedical applications: opportunities from new accelerators



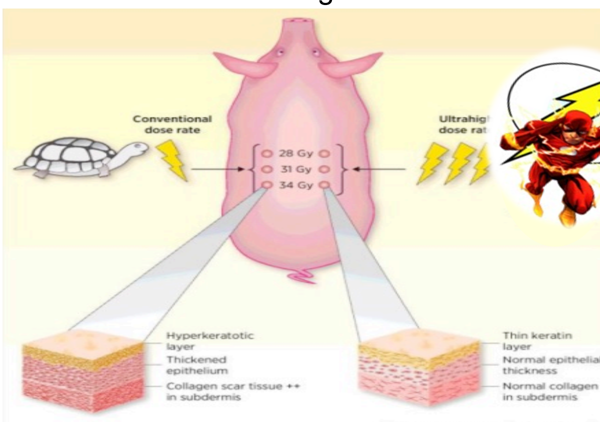
Patera *et al., Front. Phys*. 2020

- 250 participants from 27 countries in 5 continents

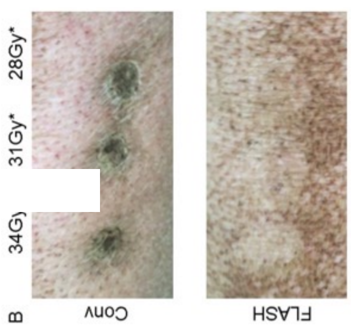
High intensity

The FLASH Effect evidence

- Decreasing of the normal tissue response



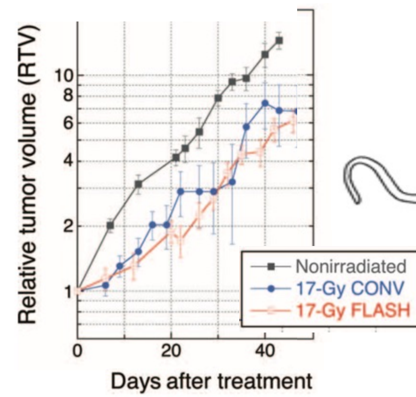
Vozenin et al. 2019, Clin. Canc. Res.



CONV

FLASH

- Preservation of the tumor responses



V. Favaudon et al. 2014, Sci. Transl. Med.

The first clinical result

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland

1a : Day 0

1b : 3 weeks

1c : 5 months

- multiresistant CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface.

  Localized skin RT previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments.

  Treatment given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT.

  Prescribed dose to the PTV = 15 Gy, in 90 ms.

  Results: At 3 weeks, i.e. at the peak of the reactions, a grade 1 epithelitis (CTCAE v 5.0) along with a transient grade 1 oedema (CTCAE v5.0) in soft tissues surrounding the tumor were observed.

  Clinical examination was consistent with the optical coherence tomography showing no decrease of the thickness of the epidermis and no disruption at the basal membrane with limited increase of the vascularization.

  In parallel, the tumor response was rapid, complete, and durable with a short follow-up of 5 months

FLASH „boom“

The Hottest Topic in Radiation Oncology!

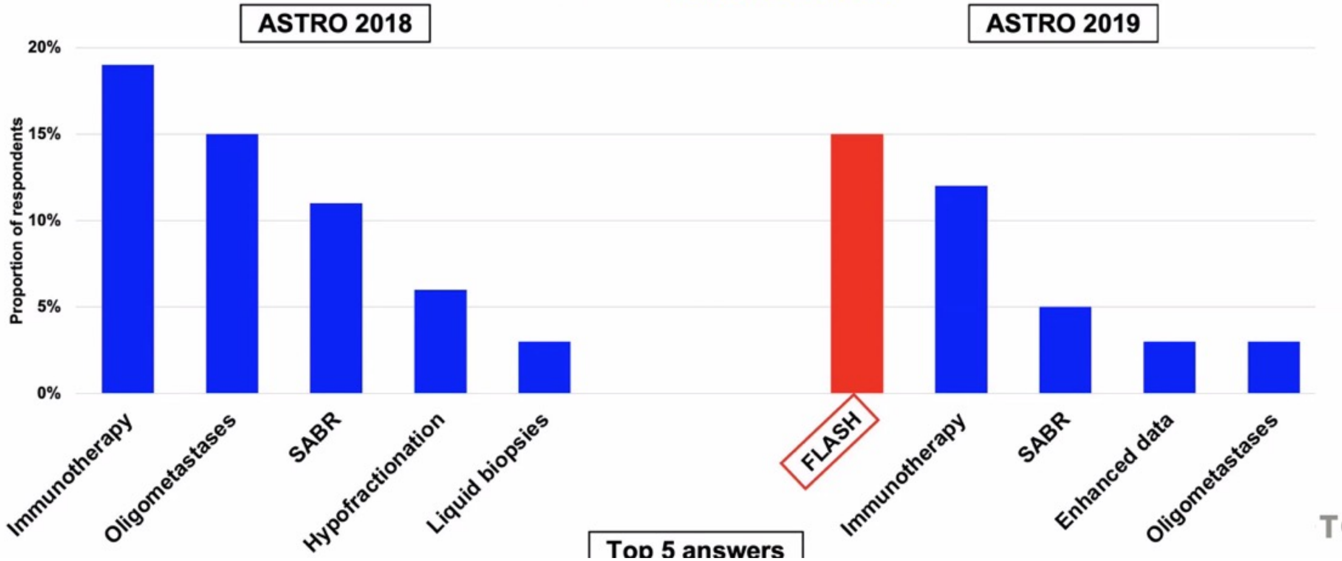
ARTICLE IN PRESS

International Journal of Radiation Oncology biology • physics
www.redjournal.org

EDITORIAL

Responses to the 2018 and 2019 "One Big Discovery" Question: ASTRO Membership's Opinions on the Most Important Research Question Facing Radiation Oncology...Where Are We Headed?

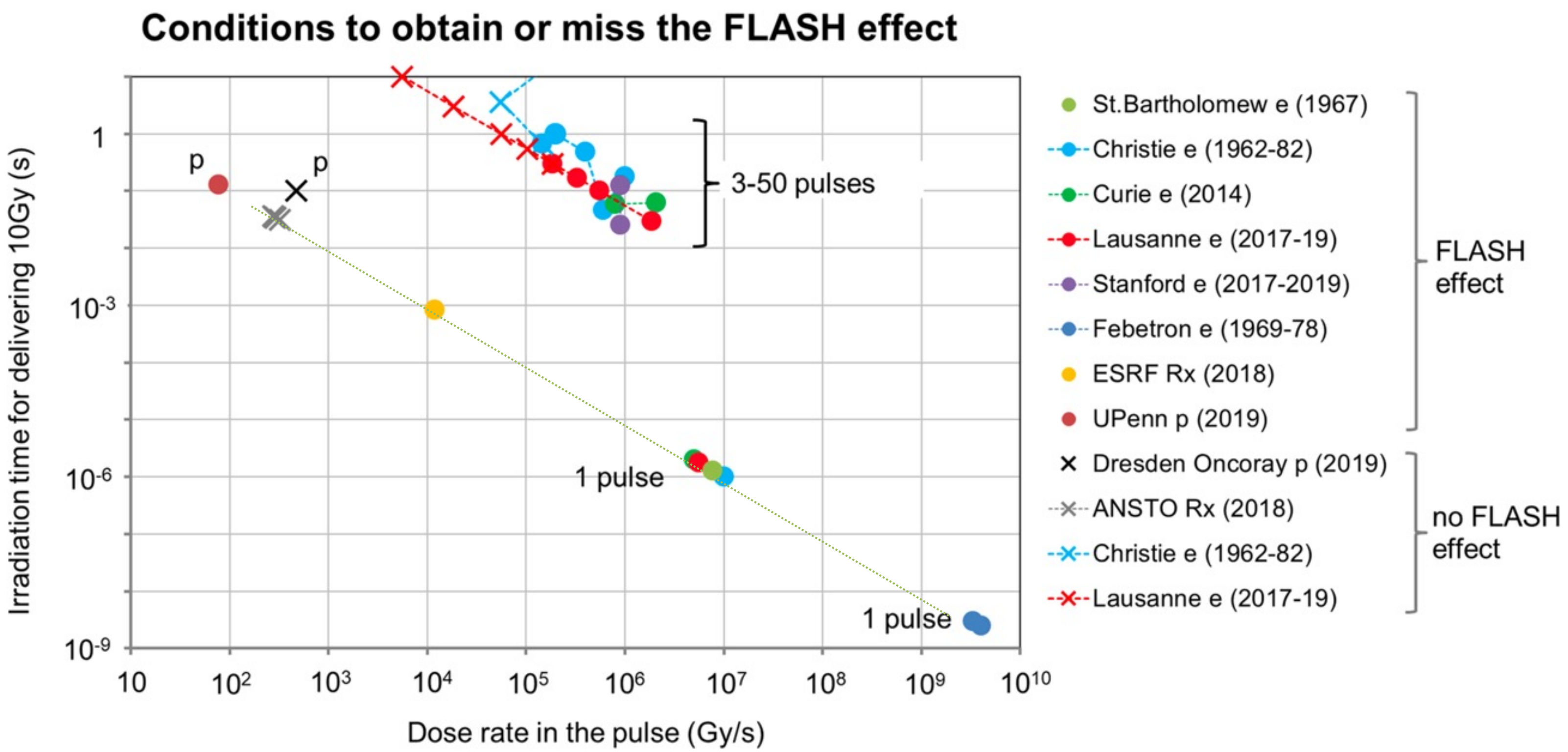
ASTRO Meeting Survey:
What is the One Big Discovery that needs to be translated into the clinic RIGHT NOW?



TON CENTER

Parameters for FLASH/noFLASH

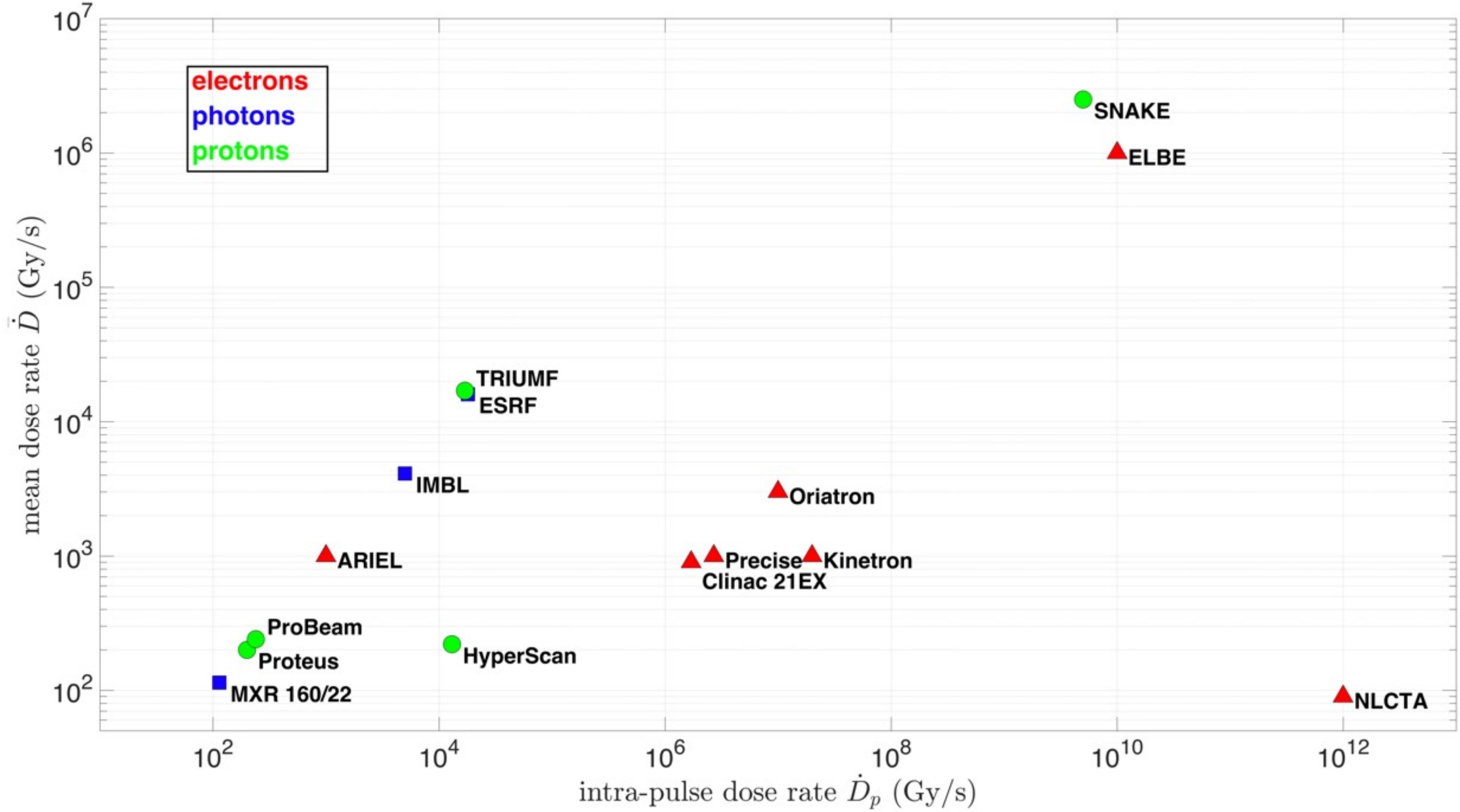
Figure 1



$$T_{10} = \frac{10}{\dot{D}} = \frac{10}{\dot{n}\dot{D}_p t_p}$$

Montay-Gruel et al. Clin Cancer Res 2020

Employed facilities



Esplen et al. Phys.Med. Biol. 2020

Multi-energy raster scanning lasts too long for FLASH

Particle beam scanning and FLASH

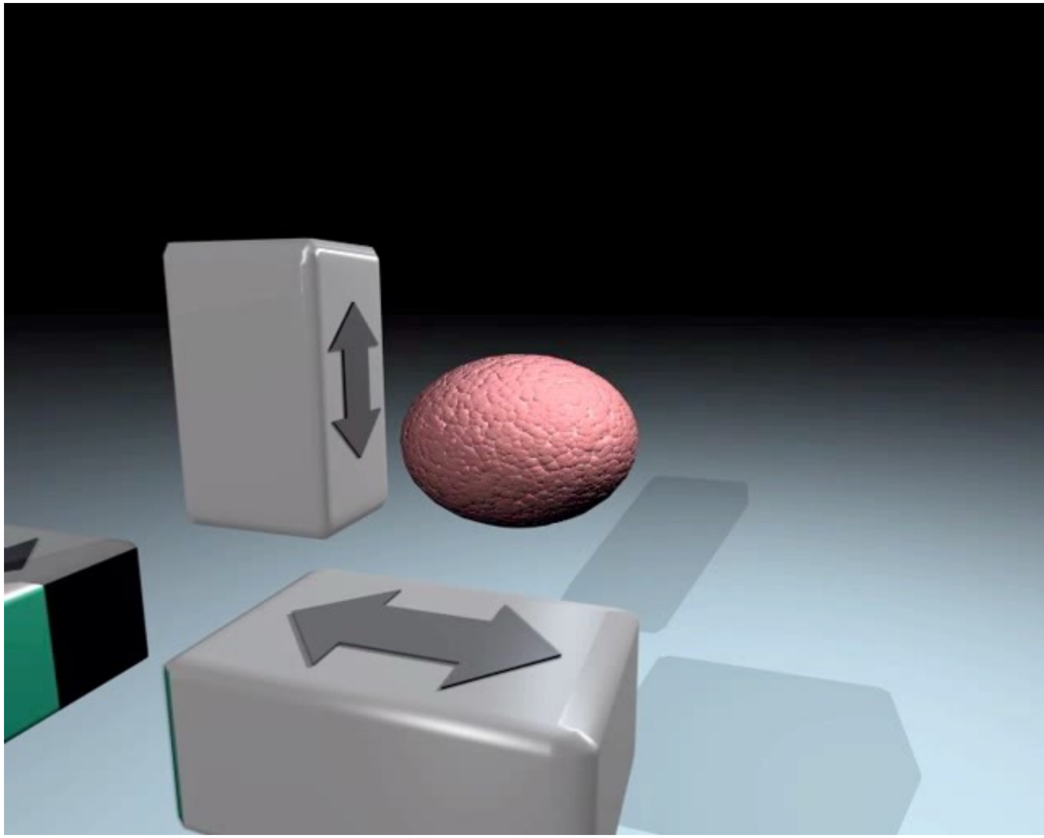
- Synchrotron Cycle > 1 sec , normally ~ 5-10 sec
- each energy step requires a new cycle

- However for FLASH
  8 Gy with 40 Gy/s
  should by appied in **t < 200 ms**

⇨ the normal multi-layer raster scanning
for 3D conformal irradiation
does not work

(neither for proton cyclotron, IBA, VARIAN …)

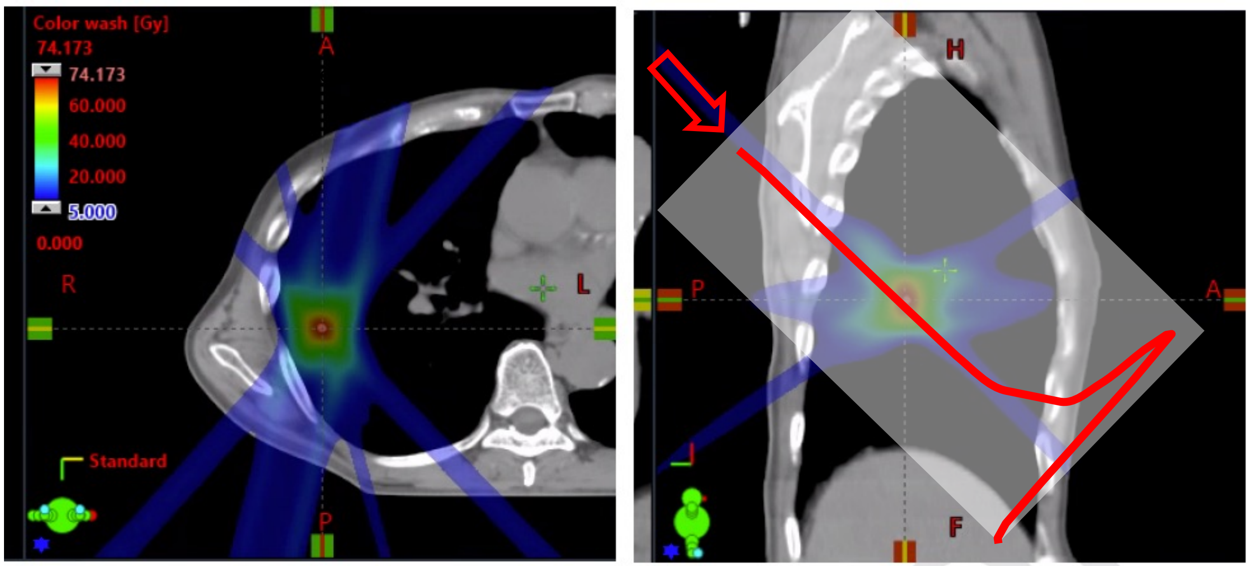
⇨big issue for FLASH in particle therapy



Durante *et al., Nat. Rev. Phys*. 2021

Transmission beam technique

- Using 244 MeV proton transmission beam (VARIAN proton machine)
- Penetration of the whole patient with the beam



Issues:

- Not conformal as IMPT (scanning)
- SOBP advantage lost
- Higher integral Dose
- Many fields and long irradiation time for the treatment

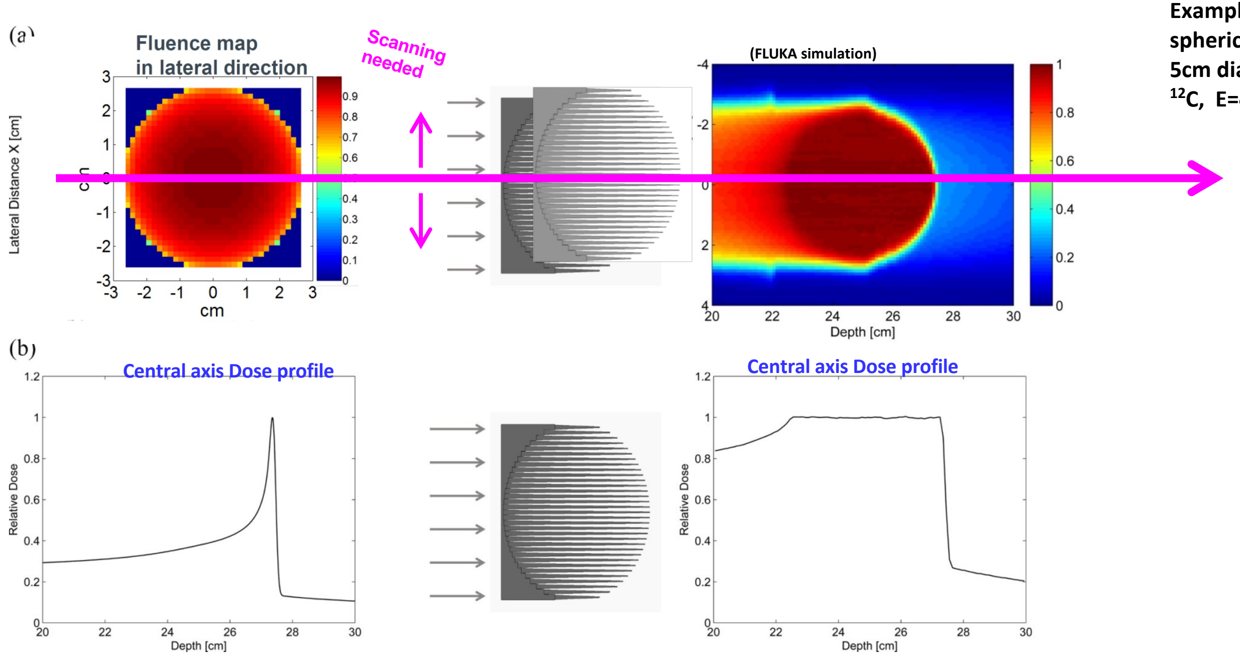
However:

Clinical study started
Treatment of symptomatic Bone Metastases
Cincinnati Proton Centre

van Marlen et al., Int J Radiat Oncol Biol Phys 2020

VU VRIJE UNIVERSITEIT AMSTERDAM

Beam application with 3D Range Modulators: Single-energy Irradiation

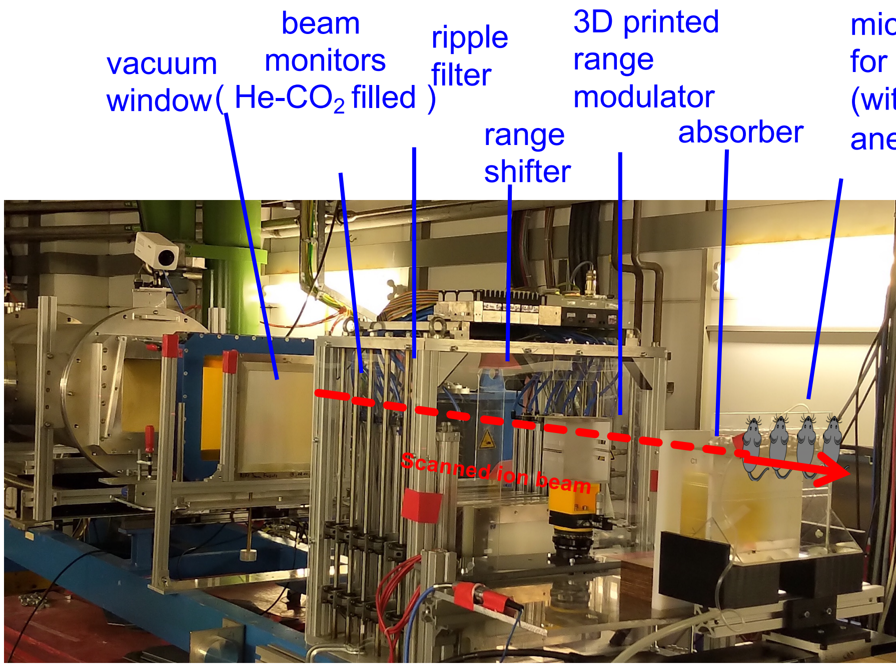


Example for a spherical target volume, 5cm diameter, ^{12}C, E=400 MeV/u

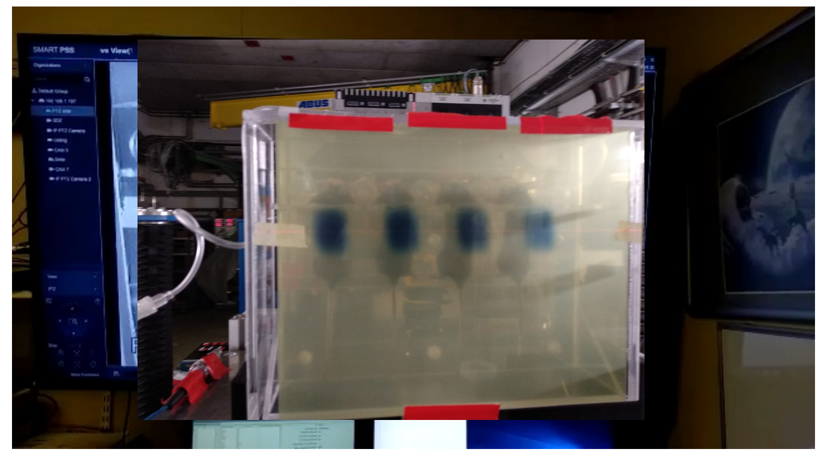
Simeonov *et al., Z. Med. Phys.* 2020

FLASH with C-ions - 2019

C-ion FLASH



D= 18 Gy



-HIT ≈ 5×10^8 ions per spill
⇨ 8 Gy | 50 Gy/s for 10 × 10 mm^2

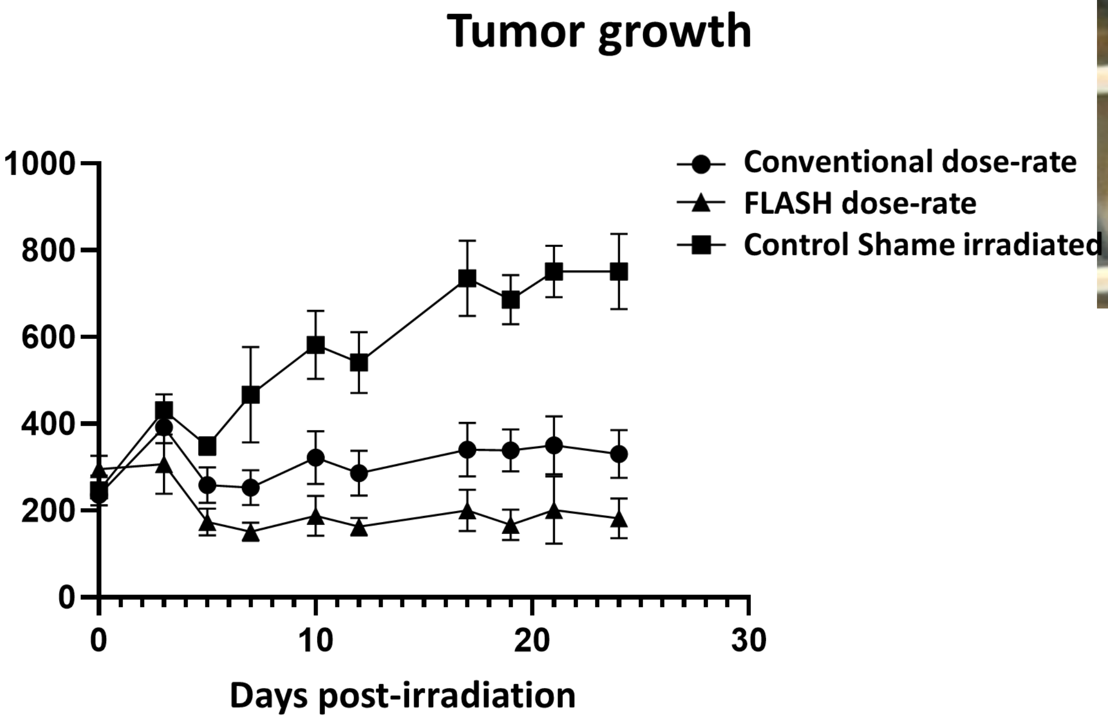
-GSI > 5×10^9 ions per spill (reliable)
⇨ 18 Gy | 100 Gy/s for 20 × 20 mm^2

Tinganelli *et al., Int. J. Radiat. Oncol. Biol. Phys*. 2021
Weber *et al., Med. Phys*. 2021

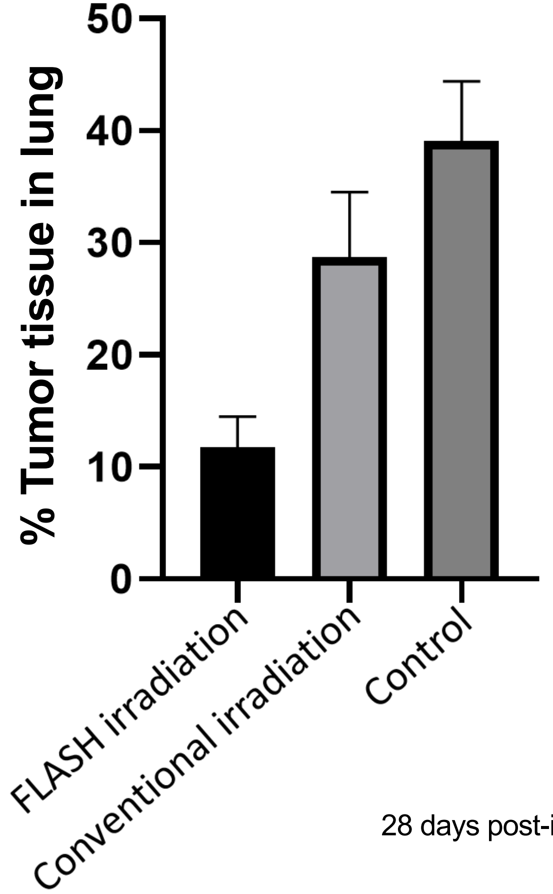
Preliminary results

Skin exfoliation in:

4/6 animals irradiated with conventional
1/7 animal irradiated with FLASH

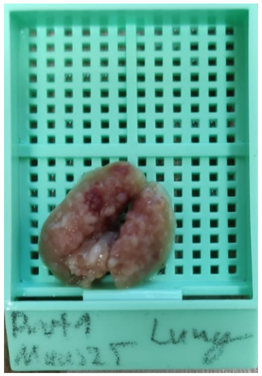


Lung Metastasis form limb osteosarcoma



28 days post-irradiation

Normal lung

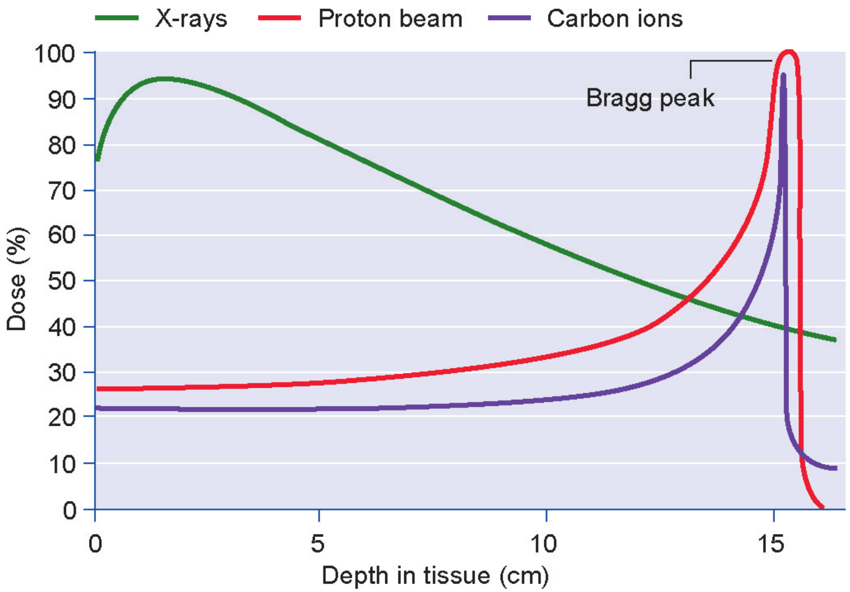


Unirradiated tumor

Irradiated tumor

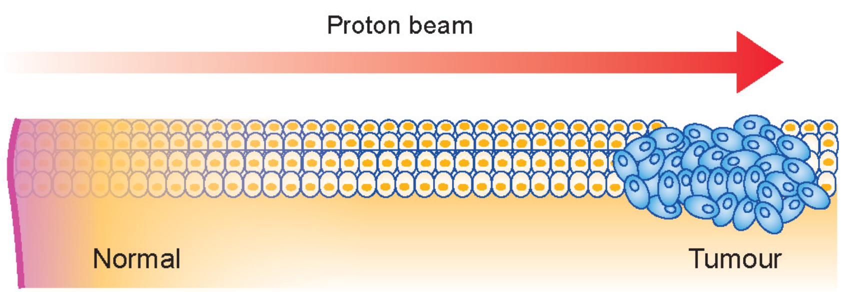
Durante *et al., Radiother. Oncol., submitted*

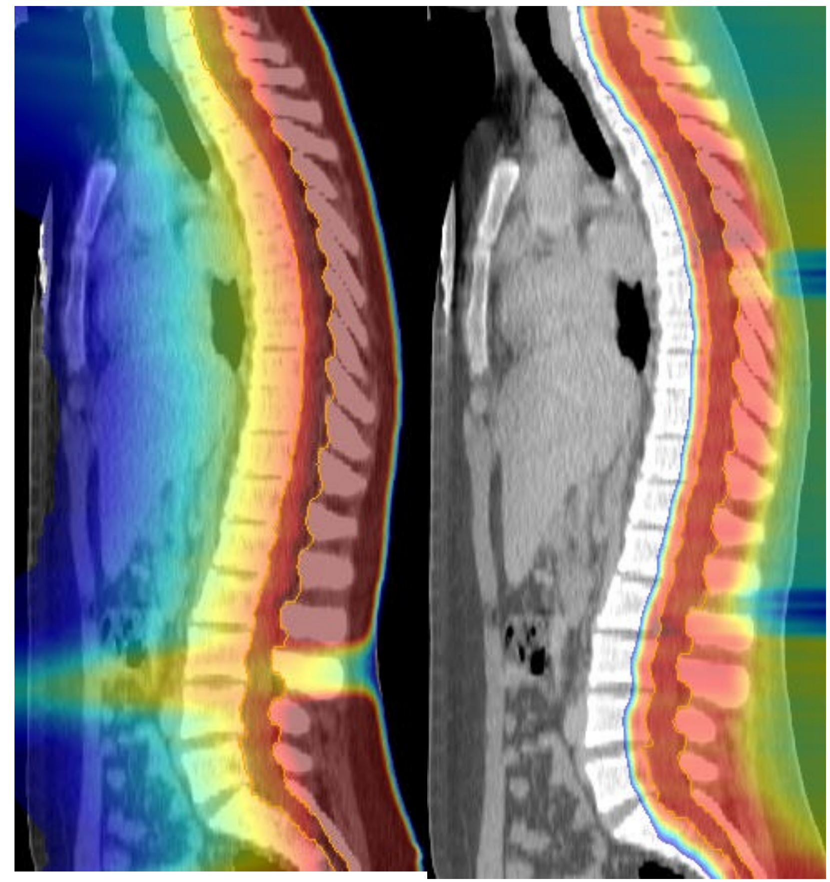
Bragg peak in particle therapy



High-energy
Low dose
Low-LET
Fractionation sparing
RBE ~1
OER~3

Low-energy
High dose
High-LET
Little fractionation effect
RBE >1
OER <3

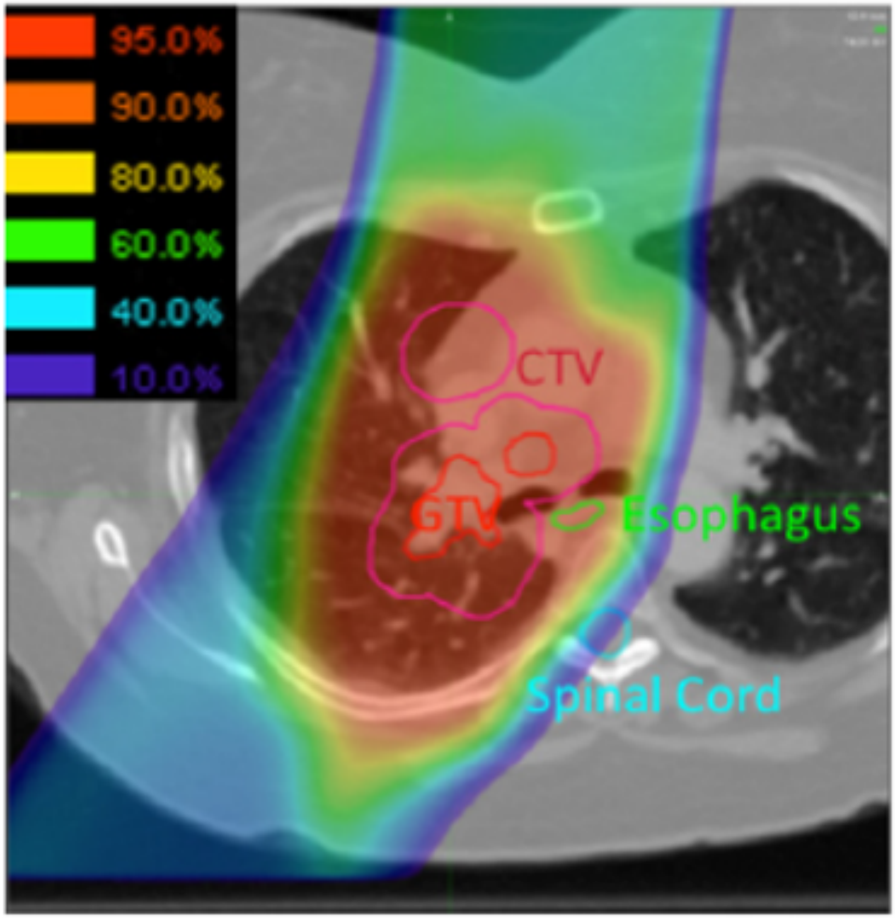


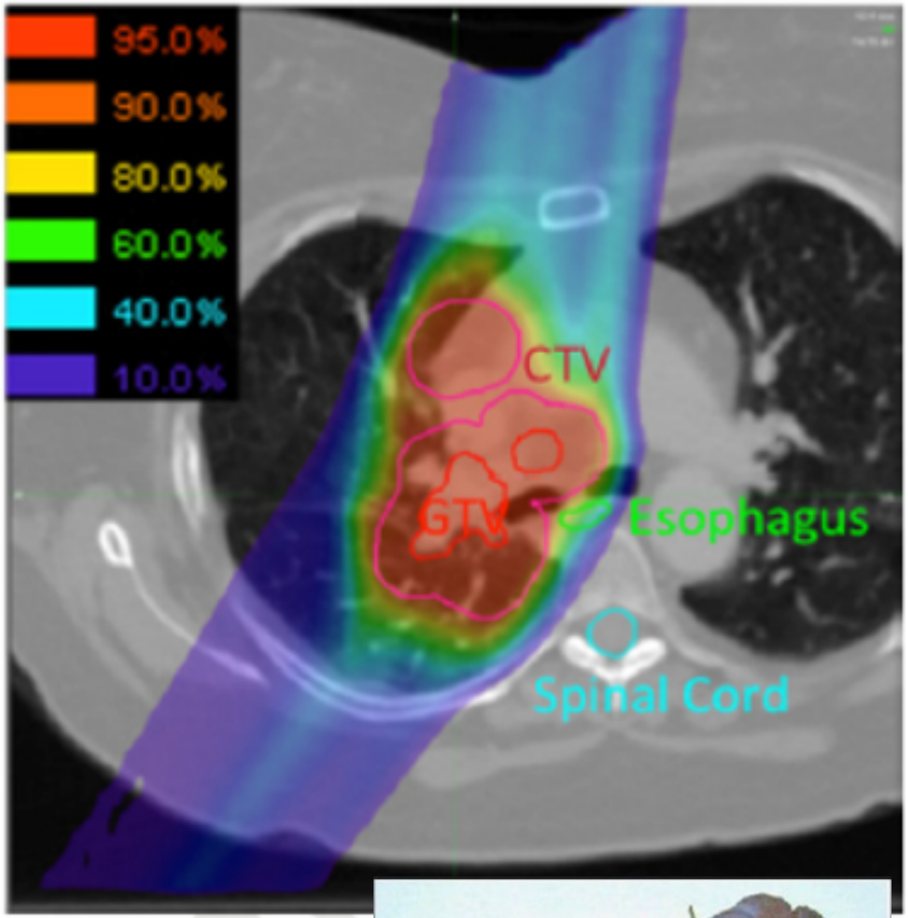


X-rays Protons

Durante, Br. J. Cancer 2019

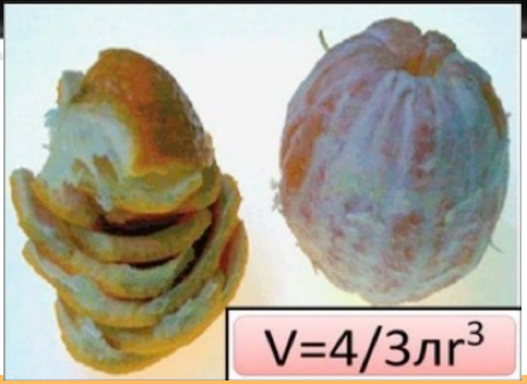
Range uncertainty jeopardizes the Bragg peak precision





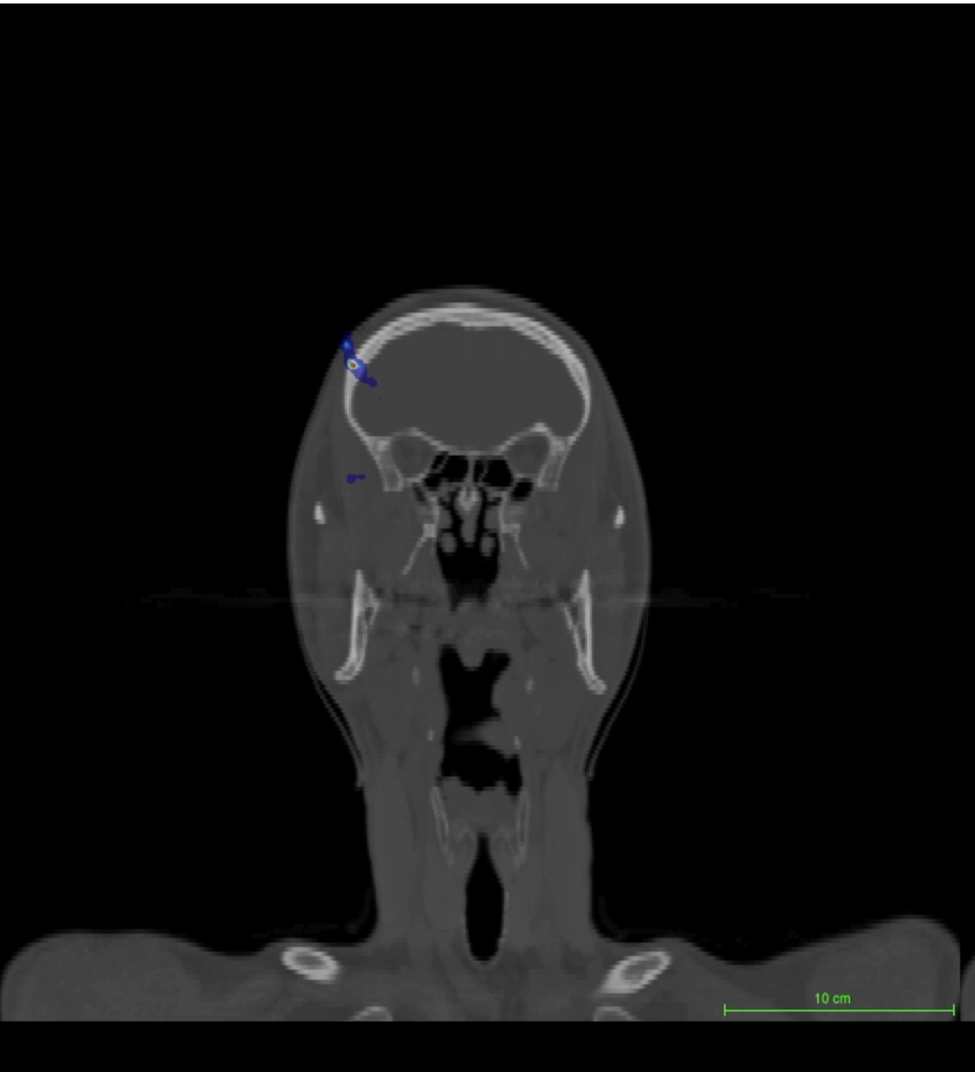
Durante & Flanz, *Semin. Oncol*. 2019

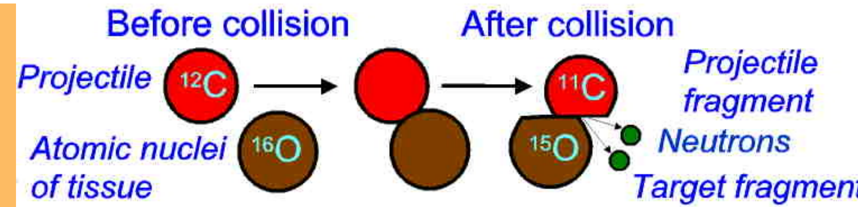
Total margins ~ 1 cm compared
to a proton penumbra ~ 2 mm



Verellen et al., *Nat. Rev. Cancer*. 2007

In-situ range verification with PET





fondazione CNAO

The FAIR program on RIB-PET

European Research Council

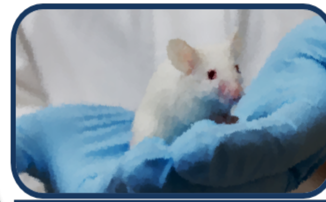
METHODS

(1) Light RIB production

(2) Physical & (3) Biological dosimetry of RIB

(4) Development of a novel hybrid PET detector

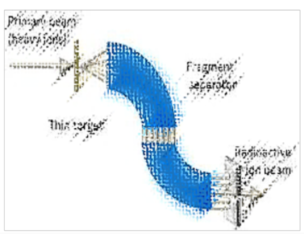
(5) RIB visualization (in phantoms)



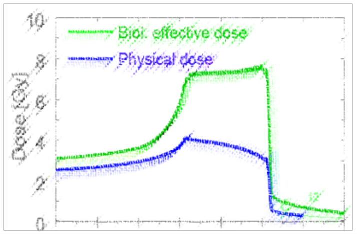
(6) Biological proof-of-concept (in animals)

OBJECTIVES

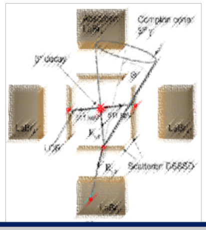
Acceleration of high-intensity and –energy light RIB



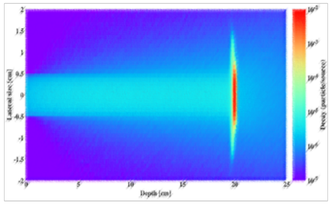
Selection of the best RIB for therapy



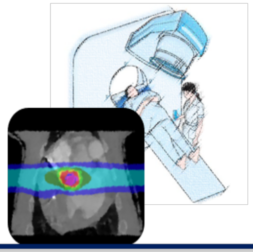
Prototype of the new online detector for small animals



Maximum accuracy achievable with RIB



proof-of-concept validation animals



OUTCOMES

Physics: *Novel FRS use with light ions*

Dosimetry and Radiobiology: *RIB Bragg peak and RBE*

Engineering: *Novel hybrid γ-PET detector*

Imaging: *reaching a precision below 0.3 mm with RIB*

Cancer therapy: *More precise cancer treatment*

Other disease areas: *New precision CPT treatment option*

Medium-risk / unique use | **Low-risk / key outcome** | **High-risk / high gain** | **Pivotal milestone** | **Major impact**

B • A • R • B

BIOMEDICAL APPLICATIONS OF RADIOACTIVE ION BEAMS

Radioactive Ion Beams (RIB) for simultaneous treatment and range verification

European Research Council

B · A · R · B
BIOMEDICAL APPLICATIONS OF RADIOACTIVE ION BEAMS

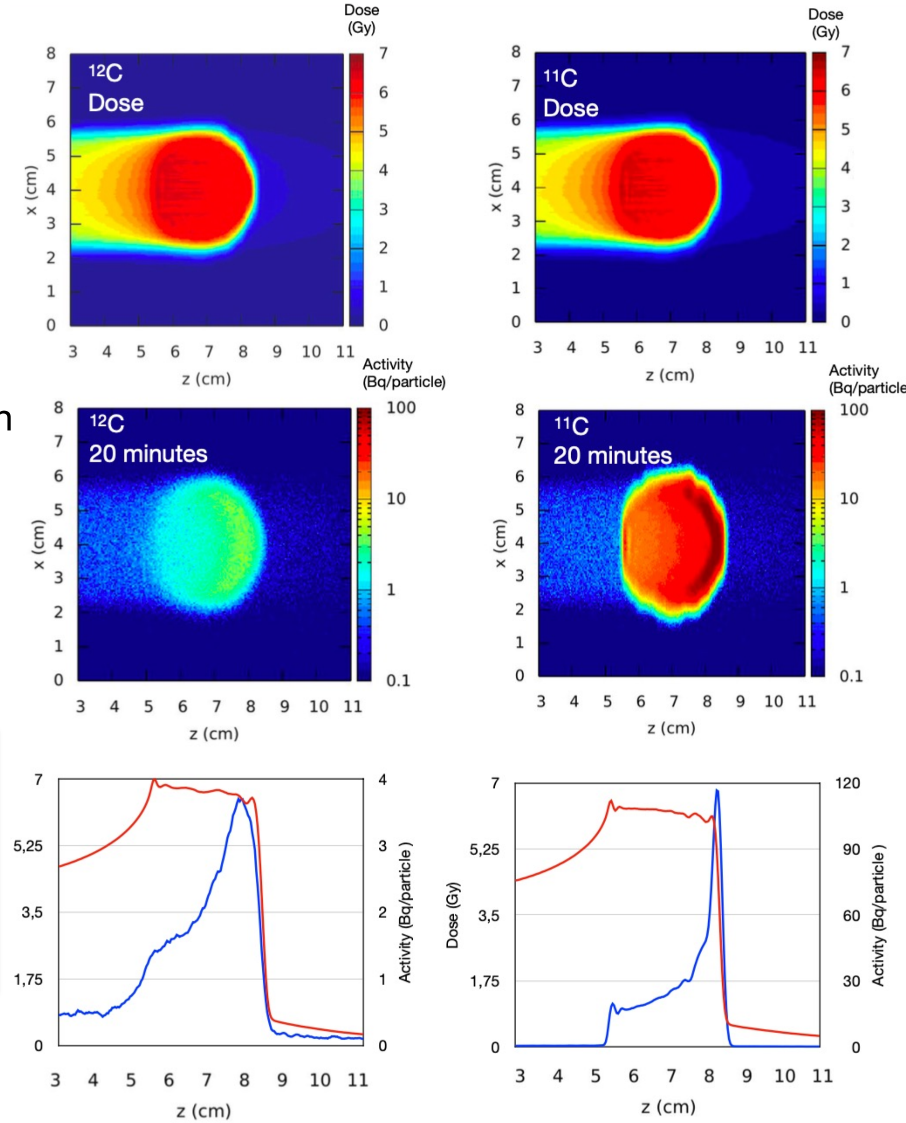
www.gsi.de/BARB

- Improved count rate (one order of magnitude larger than for stable ions)
- Improved correlation between activity and dose
- Reduced washout blur thanks to short lived isotopes

Hampered by the low intensities achievable

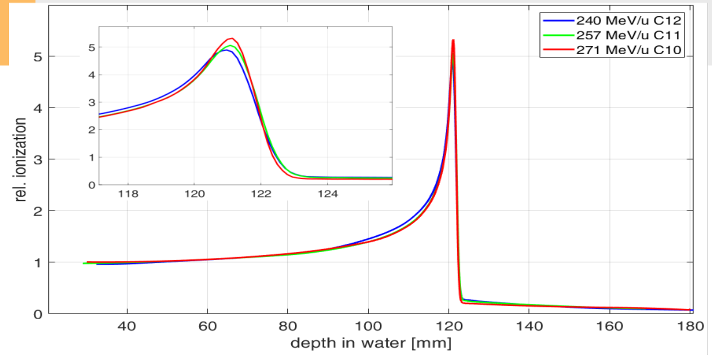
RIB therapy is now revived thanks to the construction of therapy compatible high-intensity accelerators.

e.g. FAIR Phase 0 at GSI (Darmstadt, Germany)

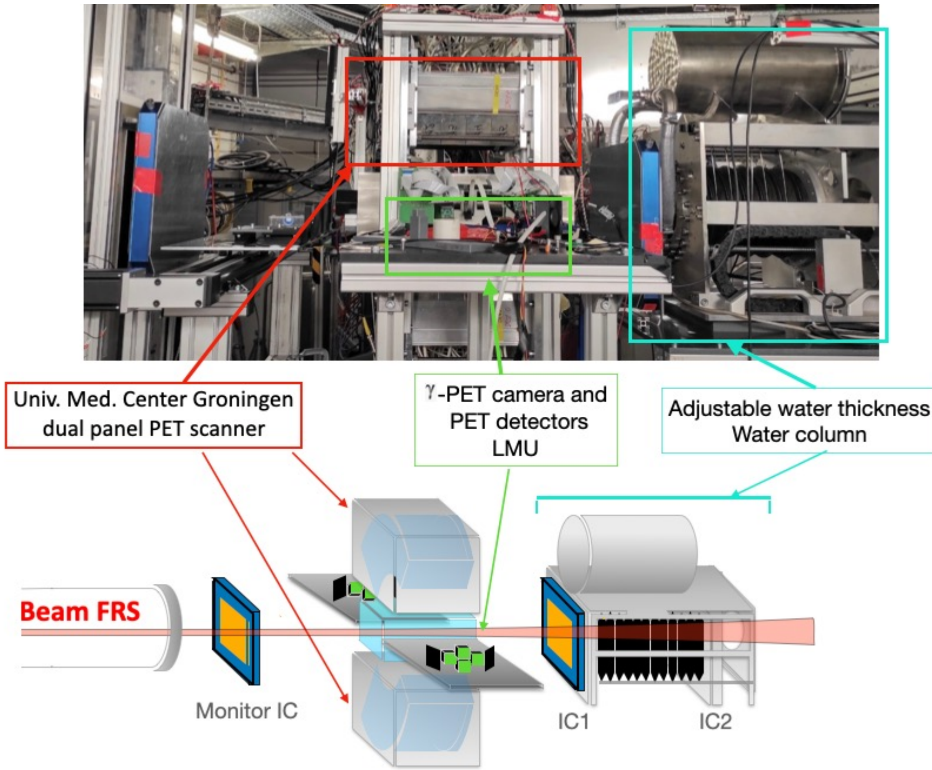


Boscolo *et al., Front. Oncol*. 2021

www.gsi.de/BARB

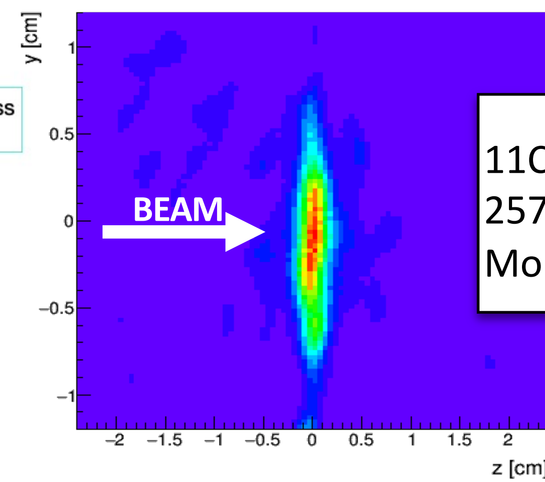


BARB: first experimental tests in June 2021



Isotopes:	^{10}C	^{11}C	^{12}C
Half-life (min):	0.322	20.36	stable
Intensities:	~10^6 pp/s	~10^7 pp/s	~10^8 pp/s

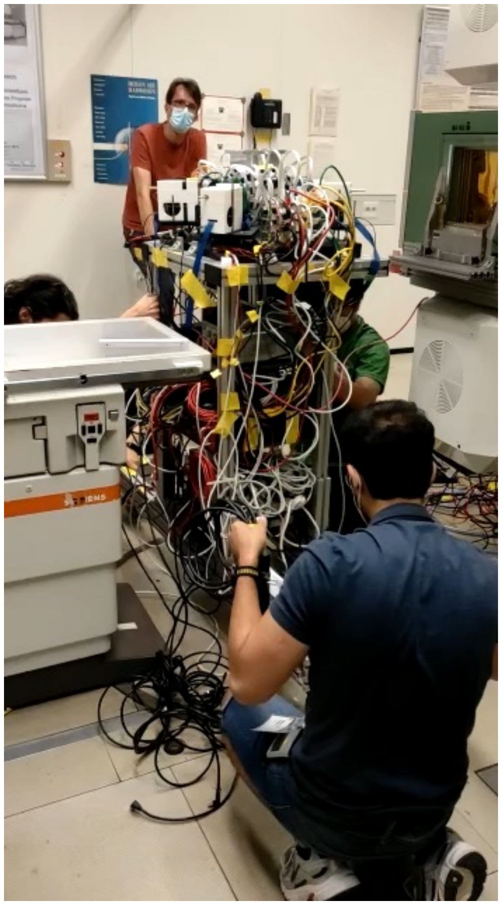
Energy:	~270 MeV/u and ~135 MeV/u
Imaging phantoms:	PE and PMMA
FRS ion optical modes	Monochromatic and achromatic

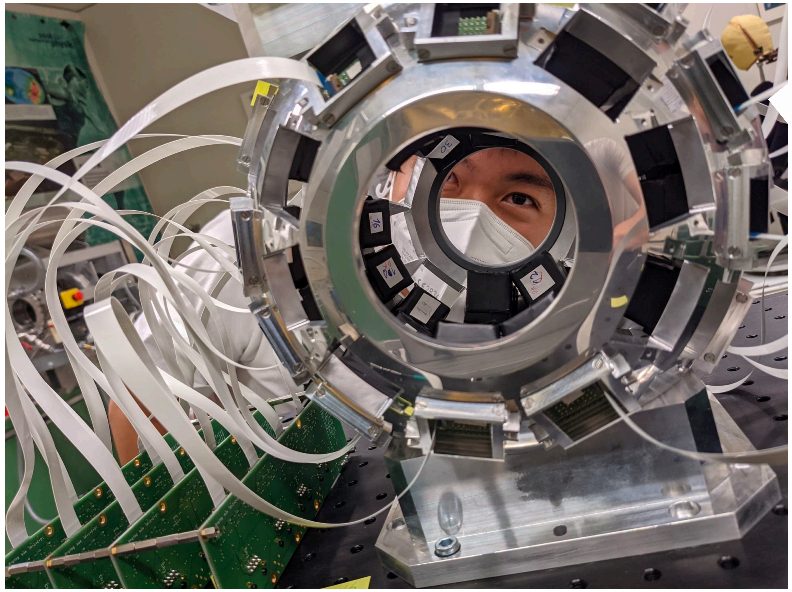


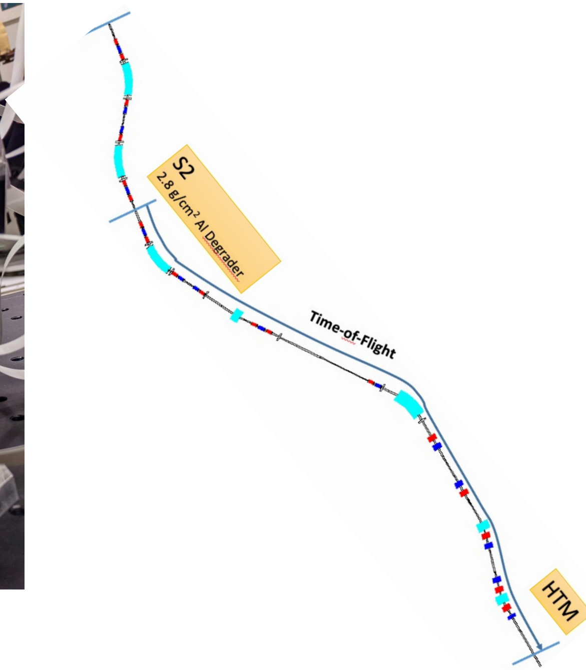
PET image

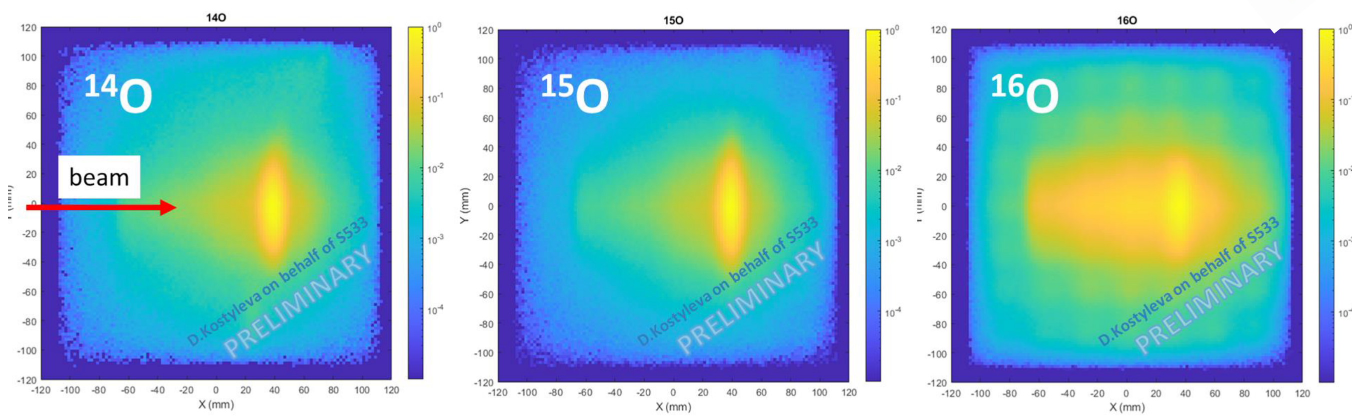
11C beam,
257 MeV/u
Monochromatic mode

FAIR-phase-0 2021 - BARB: commissioning of the FRS-Cave M beamline and test of the new γ-PET detector





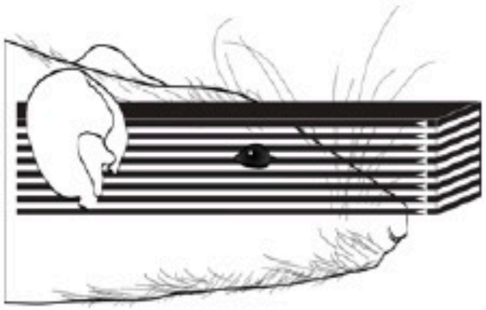




PET image

Mini- or microbeam radiotherapy

- CNS tissue can tolerate very high doses *(hundreds of Gy)* if the radiation is delivered in arrays of microbeams
  - Brookhaven National Lab (USA), 1950 +
  - European Synchrotron Radiation Facility (France), 2006 +
  - Established with deuteron beams, synchrotron x rays, carbon ions, and protons



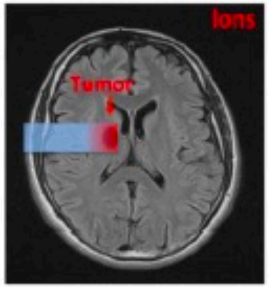
Rat brain irradiated with ~0.7-mm synchrotron x-ray minibeams with ***170 Gy in-beam dose in single fractions***. No side effects were seen in 7 month observation period post RT.
(Dilmanian et al. 2006)

Terminology evolving to describe dimensions

Microbeams **~ 1 - 100 microns**

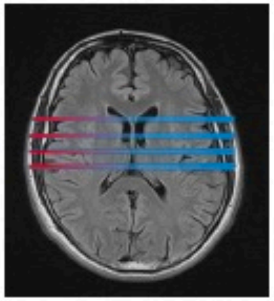
Minibeams **~ 100 microns - 1 mm**

*HADRON*MBRT: an innovative therapeutic approach



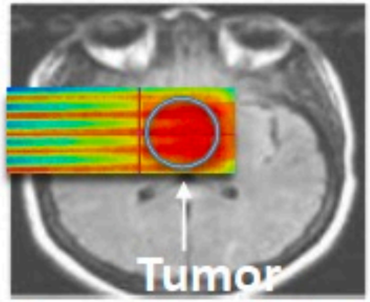
Charged particles

+



Minibeam radiation therapy (MBRT)

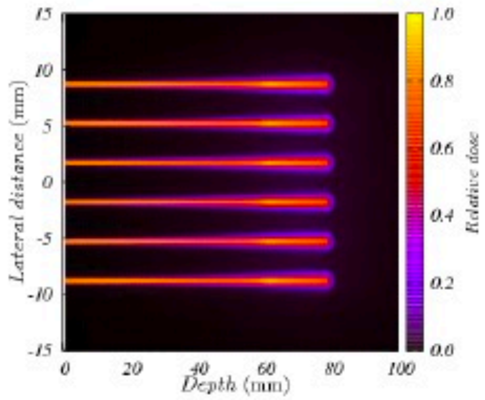
Proton MBRT



Prezado et al. 2013

- Reduction of skin toxicity
  Girst et al 2015, Prezado et al 2017
- Reduction of neurotoxicity
  Prezado et al. 2017
- Increased therapeutic index in glioma-bearing rats
  Prezado et al 2018

Heavy ions MBRT



- Reduced MSC:
  -High Peak-to-valley ratios -
  -Valleys no degraded by nuclear frag.

Peucelle et al. 2015
Gonzalez et al. 2018

Conclusions

- FAIR and other new accelerators (e.g. NICA, RAON, SPIRAL2, ELI…) offer new opportunities for biomedical research
- Both high energy and high intensity can have important applications in different fields such as space radiation protection and particle therapy
- Space radiation research is urgently needed to allow a safe exploration of the solar system
- High intensity (FLASH, RIB, minibeams,…) can provide breakthrough in particle therapy
- The Biophysics Collaboration at FAIR is open to contributions, ideas, proposals from the whole scientific community

Thanks you very much!

www.gsi.de/biophysik

Thank you!

JAGIELLONIAN UNIVERSITY IN KRAKÓW

Funding agencies

HELMHOLTZ GEMEINSCHAFT

Bundesministerium für Bildung und Forschung

NIH National Institutes of Health

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Horizon 2020
European Union Funding for Research & Innovation