NEW APPLICATIONS OF POSITRON-EMITTING NUCLEI IN MEDICAL IMAGING AND TREATMENT AT GSI

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GSI, Darmstadt, Germany

The 19th International Conference on Electromagnetic Isotope Separators and Related Topics (EMIS 2022)

Daejeon, South Korea, 3 to 7 October 2022

HEAVY ION RADIOTHERAPY: SHORT HISTORY

FAIR Phase 0 Research Program

Super-FRS EC

1946

Robert Wilson first proposed heavy ions for cancer treatment

1957 –1992

Lawrence Berkeley National Lab, US

Radiotherapy with H and heavier ions up to Ne

1990-2005

GSI, Germany

Clinical trials of Radiotherapy with C

Raster magnetic scanning system

PET range verification

1994 - present

National Institute of Radiological Sciences (NIRS), Japan

Radiotherapy with C at HIMAC

2009 - present

Heidelberg ion-beam therapy centre (HIT), Germany

MEDICAL APPLICATIONS OF RADIOACTIVE ION BEAMS

1980 –1992

Lawrence Berkeley National Lab, US

Positron emitting RIB

As low dose probe beam

1990 - 1992

GSI, Germany

Investigations on PET imaging using radioactive ion-beam was

2000 - present

National Institute of Radiological Sciences (NIRS), Japan

Investigations on

Positron emitting isotopes of C & O

2015 - present

CERN-ISOLDE ,

KU Leuven, Belgium &

Med Austron, Austria

mass separated 11Carbon for PET-aided hadron therapy

Promed

PRISMAP

2021 - present

GSI, Germany

Biomedical Applications of Radioactive ion Beams

ERC Advanced Grant

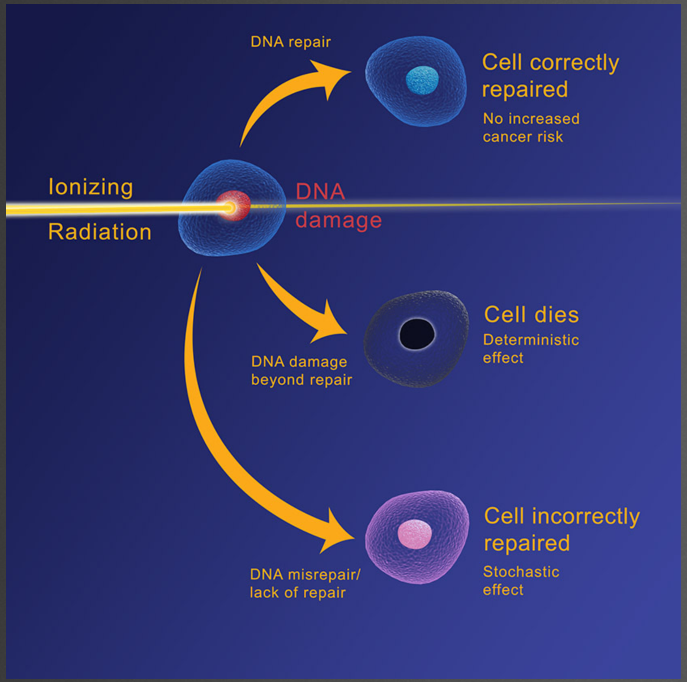
B·A·R·B

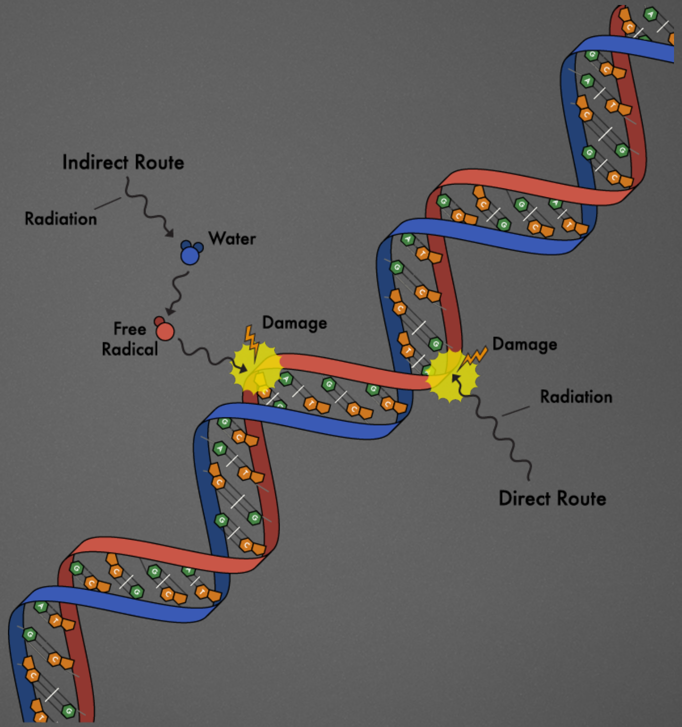
erc European Research Council

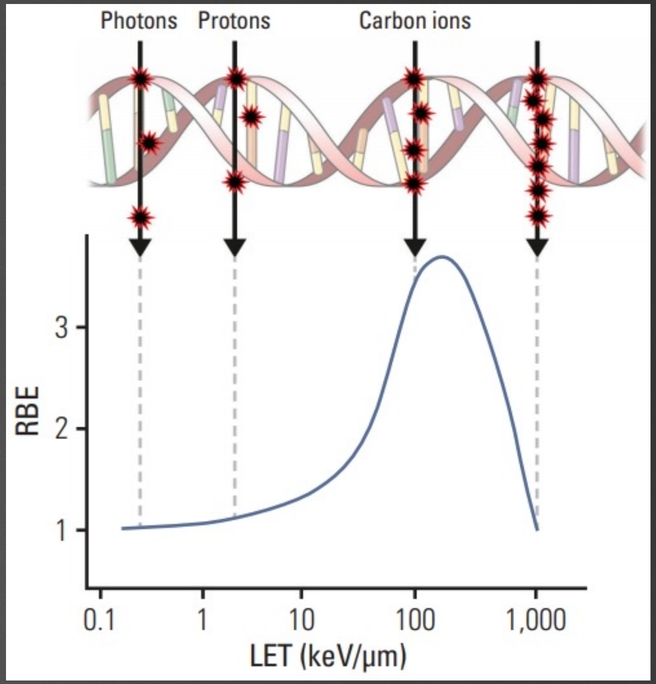
RADIOTHERAPY

Treatment of cancerous tumors using ionizing radiation

- Direct and indirect interaction with DNA







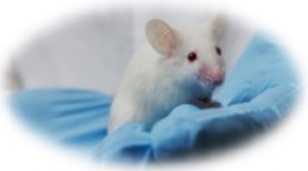
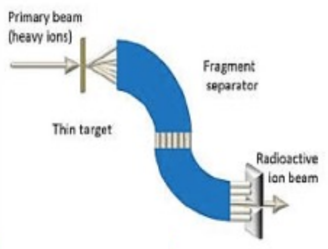
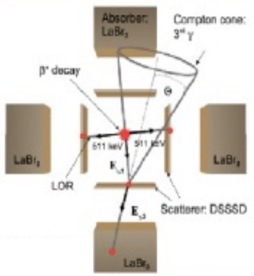
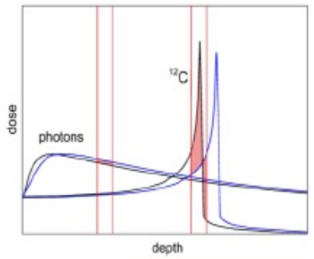
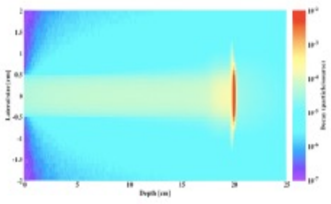
High Linear Energy Transfer (LET) ➤ ionizes water into H and OH radicals over a very short track

Heavy ions ➤ predominantly direct effect ➤ less dependent on free radical production and oxygen concentrations.

Image courtesy: Duke University Medical Center, Canadian Nuclear Safety Commission

ERC ADVANCED GRANT BARB

BIOMEDICAL APPLICATIONS OF RADIOACTIVE ION BEAMS

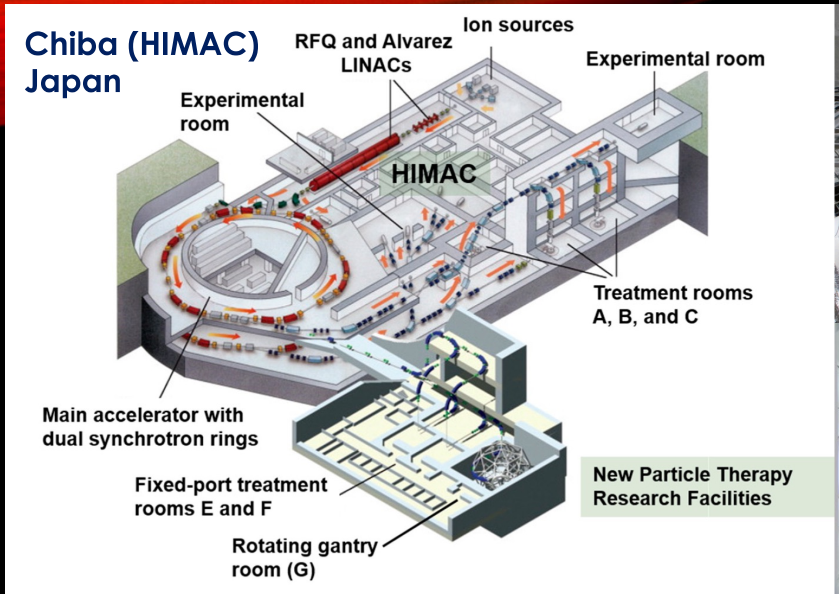
OBJECTIVES	Measure maximum achievable intensity for ^{12}C- and ^{16}O-derived RIB	Design hybrid γ-PET detector superior to state-of-the-art PET	Select best high-intensity RIB for therapy	Define maximum accuracy and resolution for RIB CPT	Validate therapeutic potential of RIB in animals
					
METHODOLOGY	Produce light RIB using fragment separator at FAIR	Development of hybrid γ-PET detector through collaboration with LMU	Conduct biophysical dosimetric studies in phantoms and mammalian cells	Visualize RIB using BASTEI PET camera and hybrid γ-PET detector	Assess tumour growth post-irradiation in soft-tissue sarcoma model
					
OUTCOMES	**Production of high-intensity RIB for first-time therapeutic use**	**Real-time imaging and monitoring of high-intensity RIB**	**Identification of RIB suitable for therapeutic applications**	**Unprecedented imaging accuracy for therapeutic beam delivery**	**Improved precision of RIB CPT for cancer and other indications**

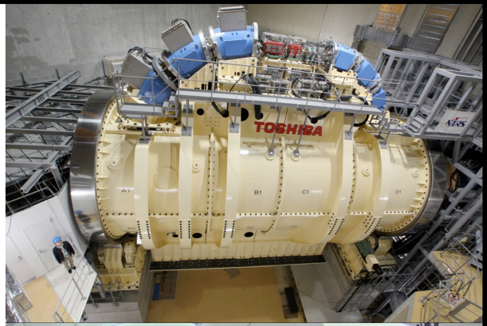
M. Durante
Principal investigator

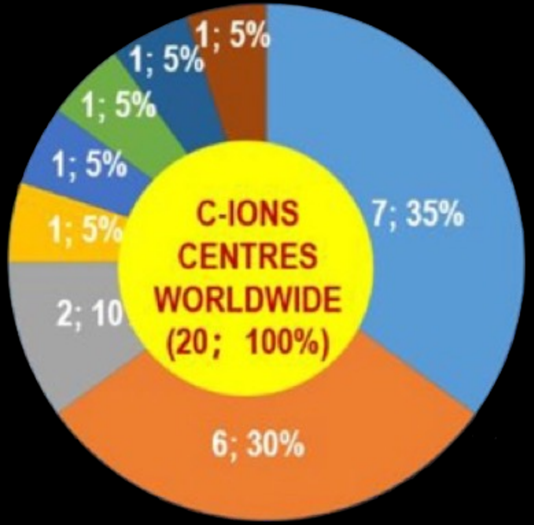
K. Parodi
Co-PI/WPL: Imaging

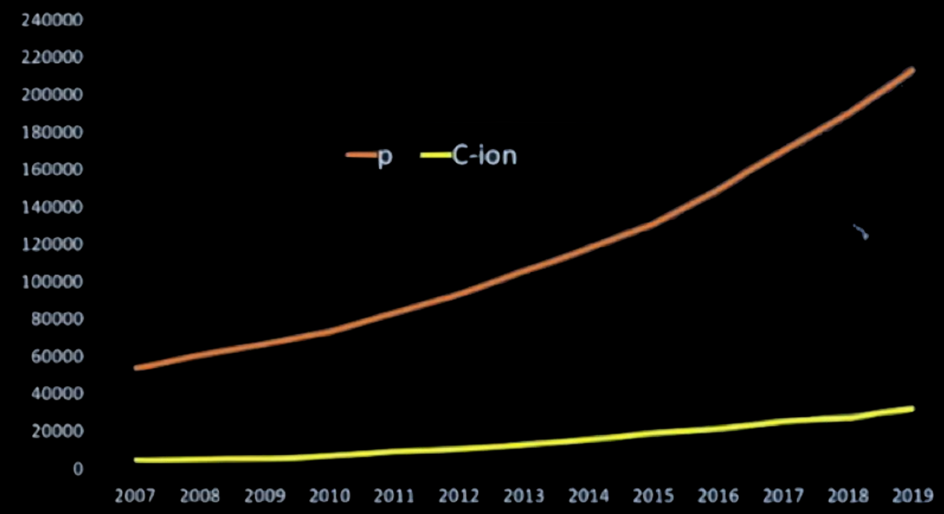
C. Scheidenberger
WPL: RIB production

HEAVY ION MEDICAL ACCELERATORS





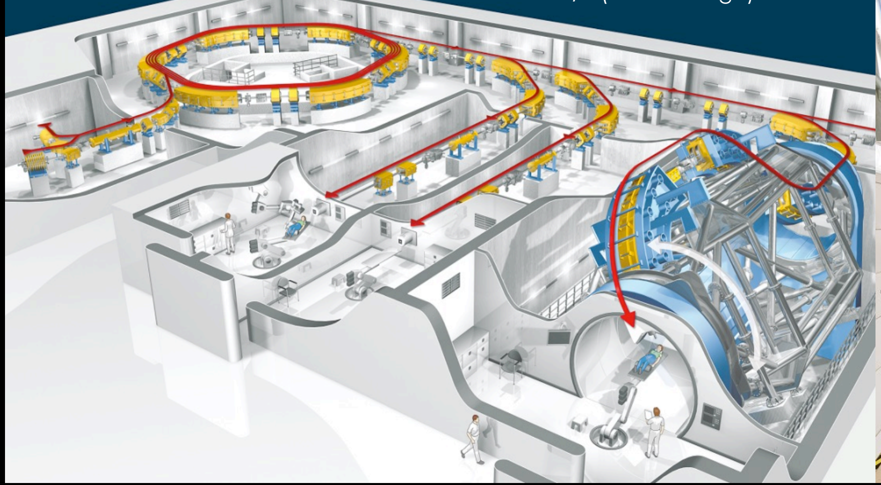




Patients treated with protons and C-ions worldwide

Heidelberg (HIT) Germany

- Compact Synchrotron
- 2 Horizontal beams
- ScanningGantry
- QA- Room
- p, He, C, O,...
- E<430MeV/u (~30cm range)

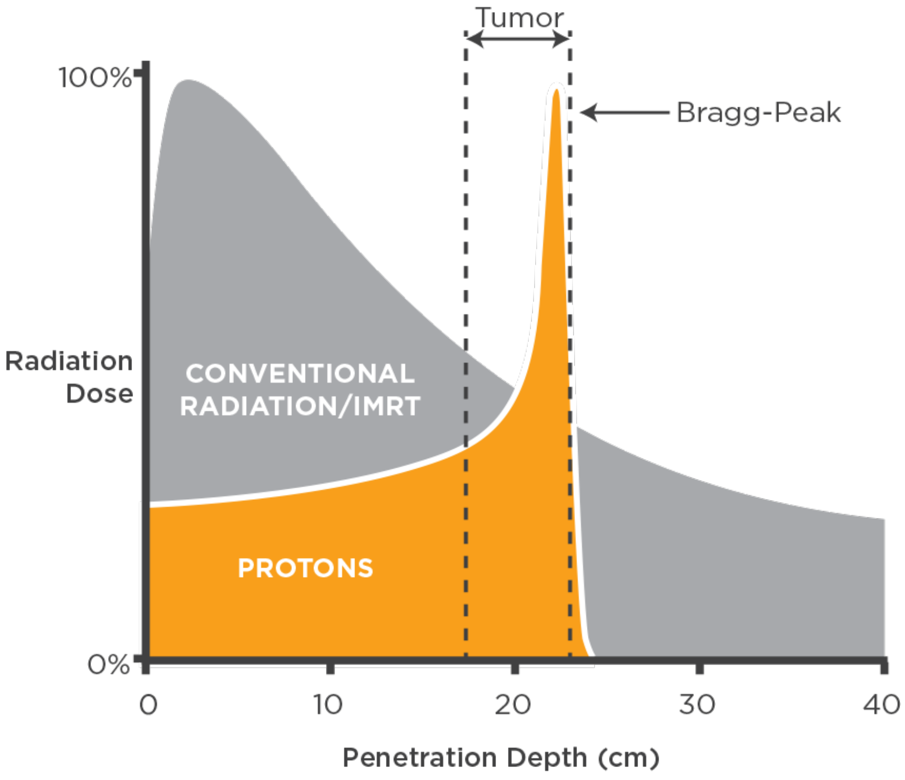


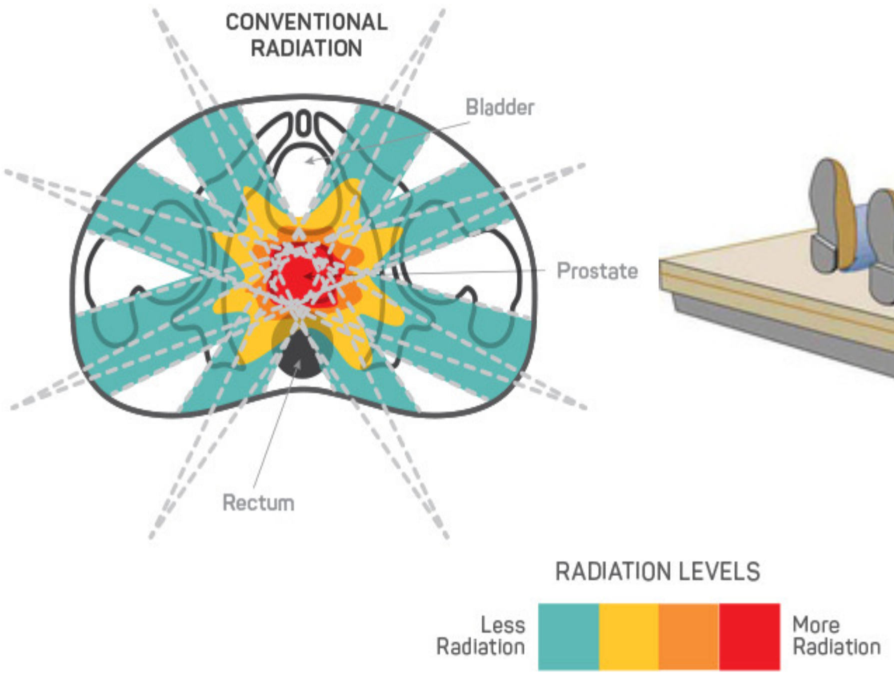
Wang, Xiaolin, et al. Frontiers in Oncology 11 (2021): 2603.

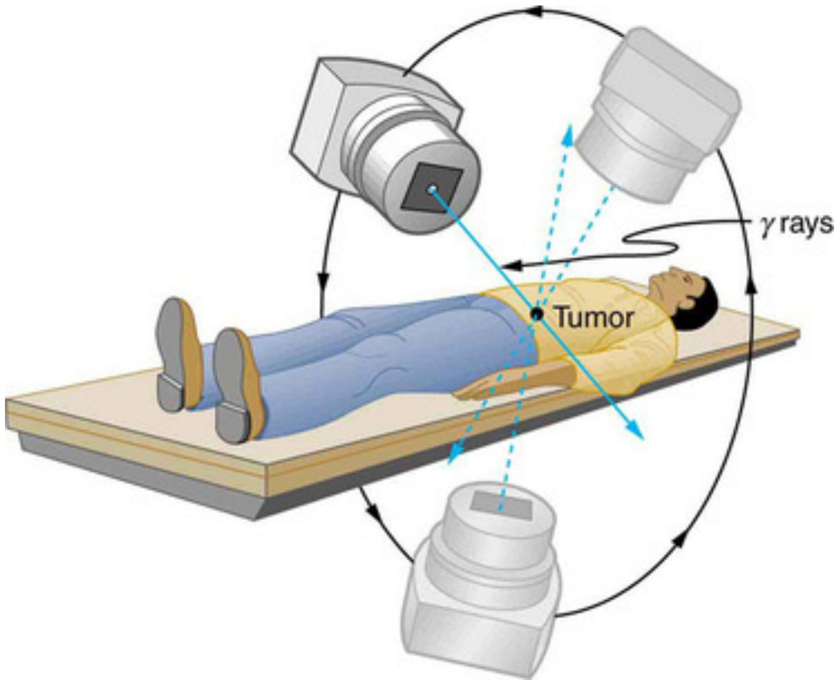
RADIATION DOSE: PHOTON VS. IONS

Photons

Exponential absorption of dose with depth





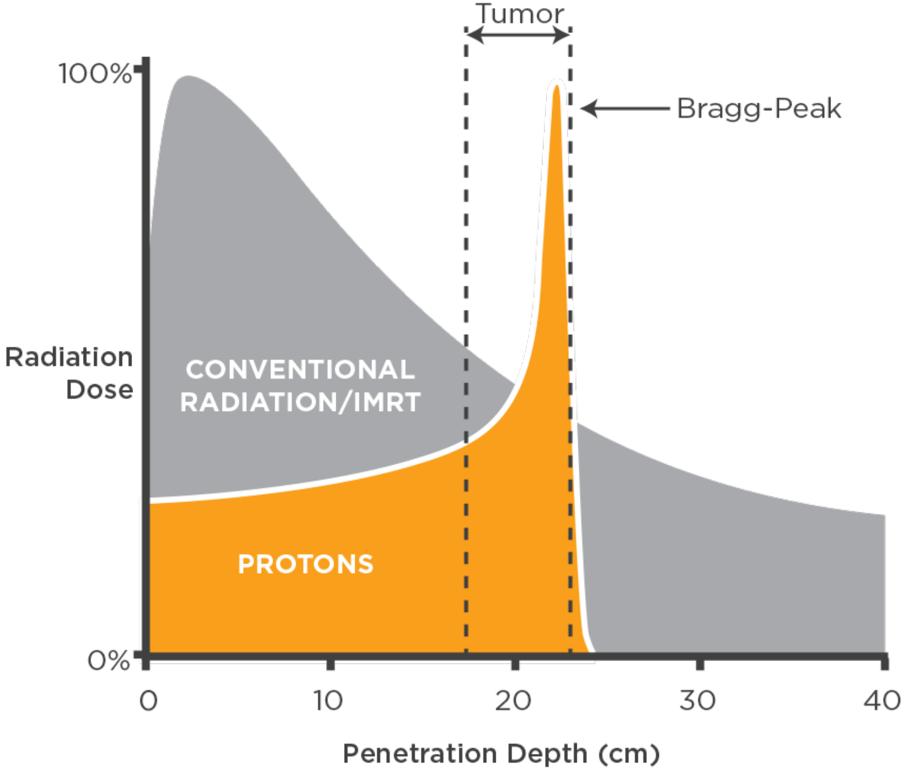


The National Association for Proton Therapy, US

RADIATION DOSE: PHOTON VS. IONS

Ion beams

Increase in energy deposition with penetration depth up to the sharp maximum at the end of their range



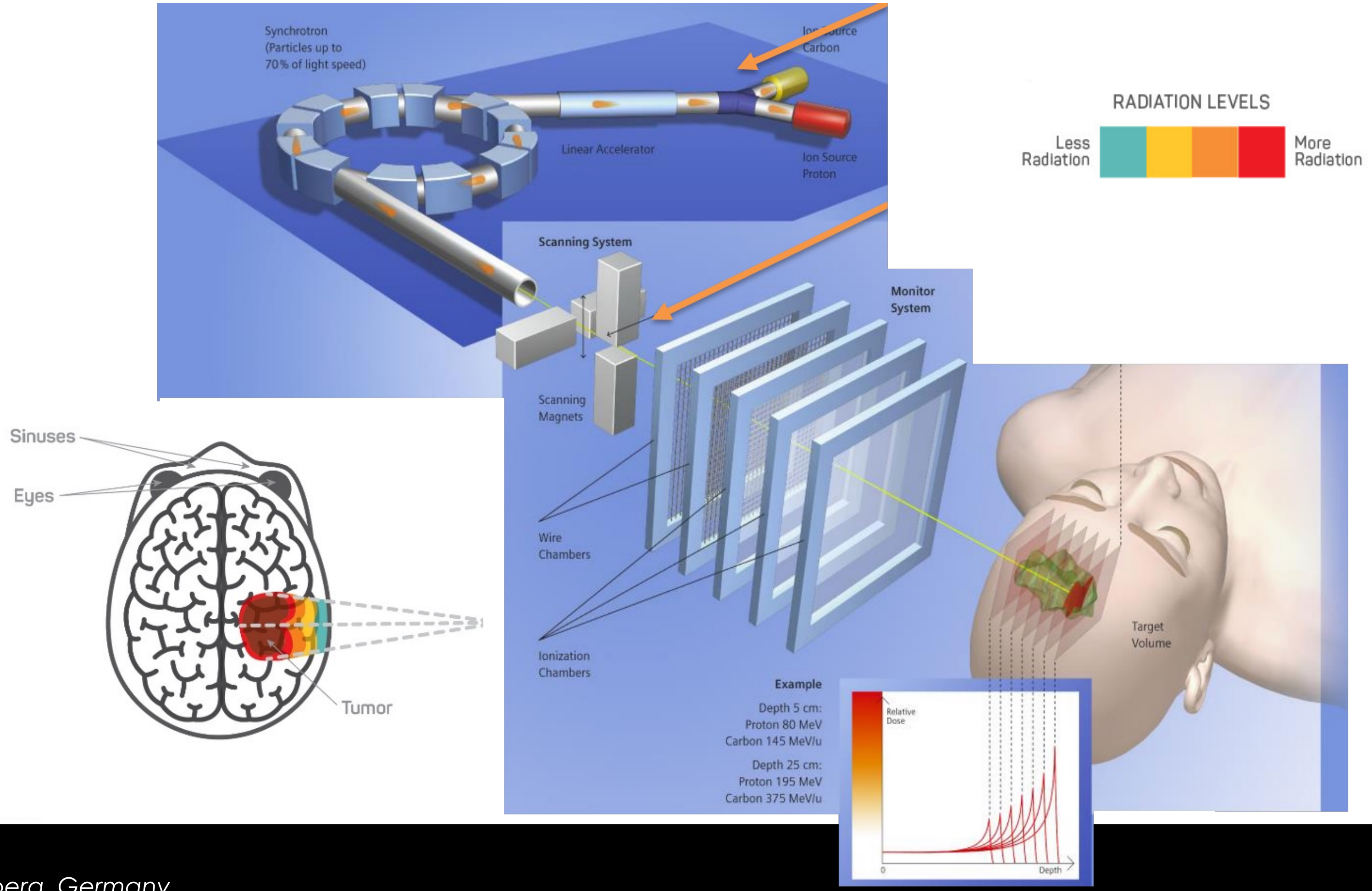


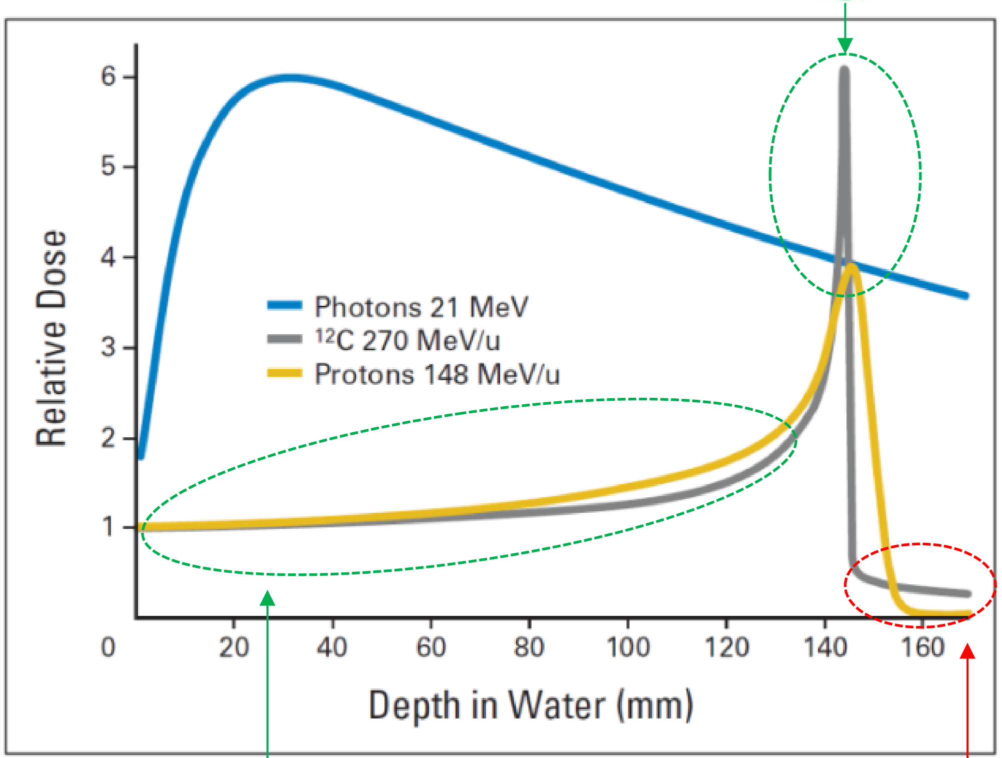
Image courtesy: The National Association for Proton Therapy, US, HIT Heidelberg, Germany

PROTON VS. HEAVIER IONS

FAIR Phase 0 Research Program

Super-FRS EC

Conformity advantages

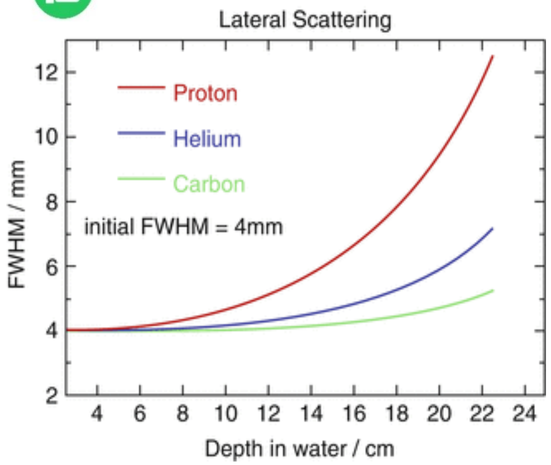


Lower entrance channel dose

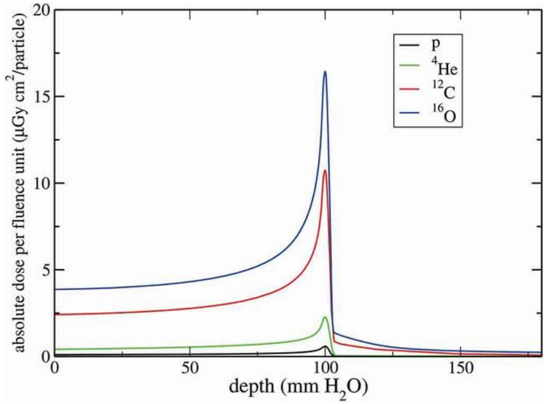
higher exit channel dose

heavier masses

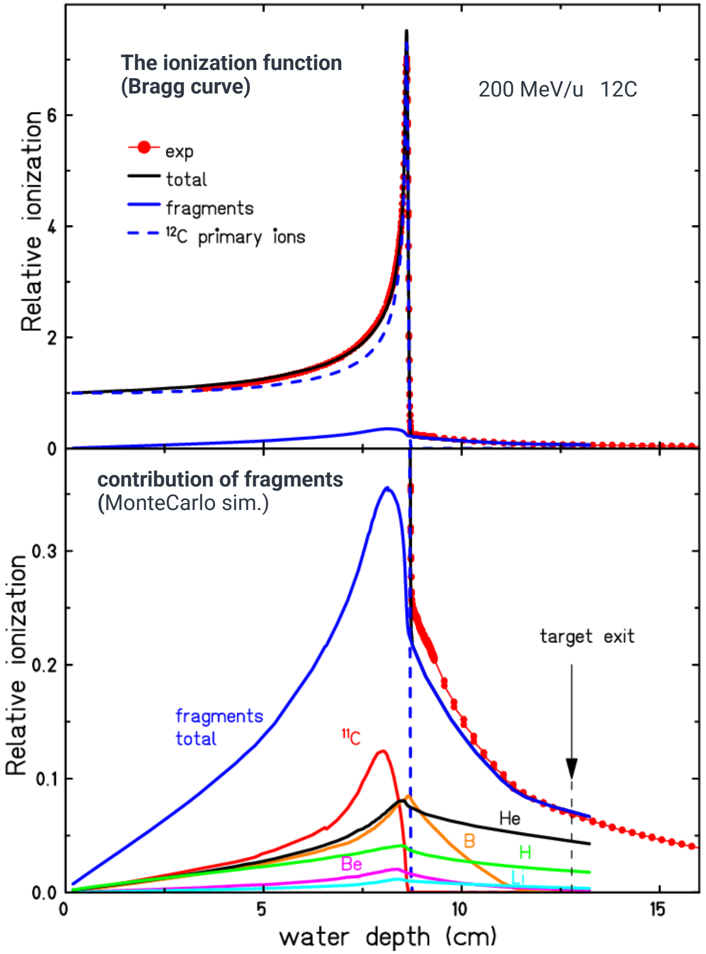
Scatter less



Higher Absolute dose per unit fluence

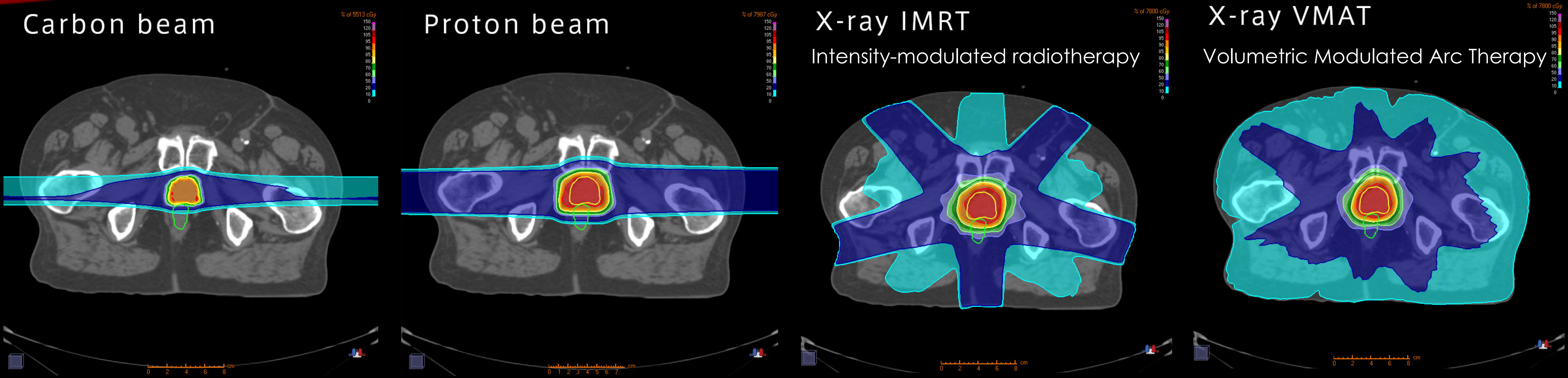


Fragmentation



Tommasino, Francesco et al. *International journal of particle therapy* 2.3 (2015): 428-438., Gunzert-Marx, K., et al. *New journal of physics* 10.7 (2008): 075003.

CARBON BEAM RADIOTHERAPY



- High tumor dose, normal tissue sparing
- Effective for radioresistant tumors
- Effective against hypoxic tumor cells
- Increased lethality in the target because cells in radioresistant (S) phase are sensitized

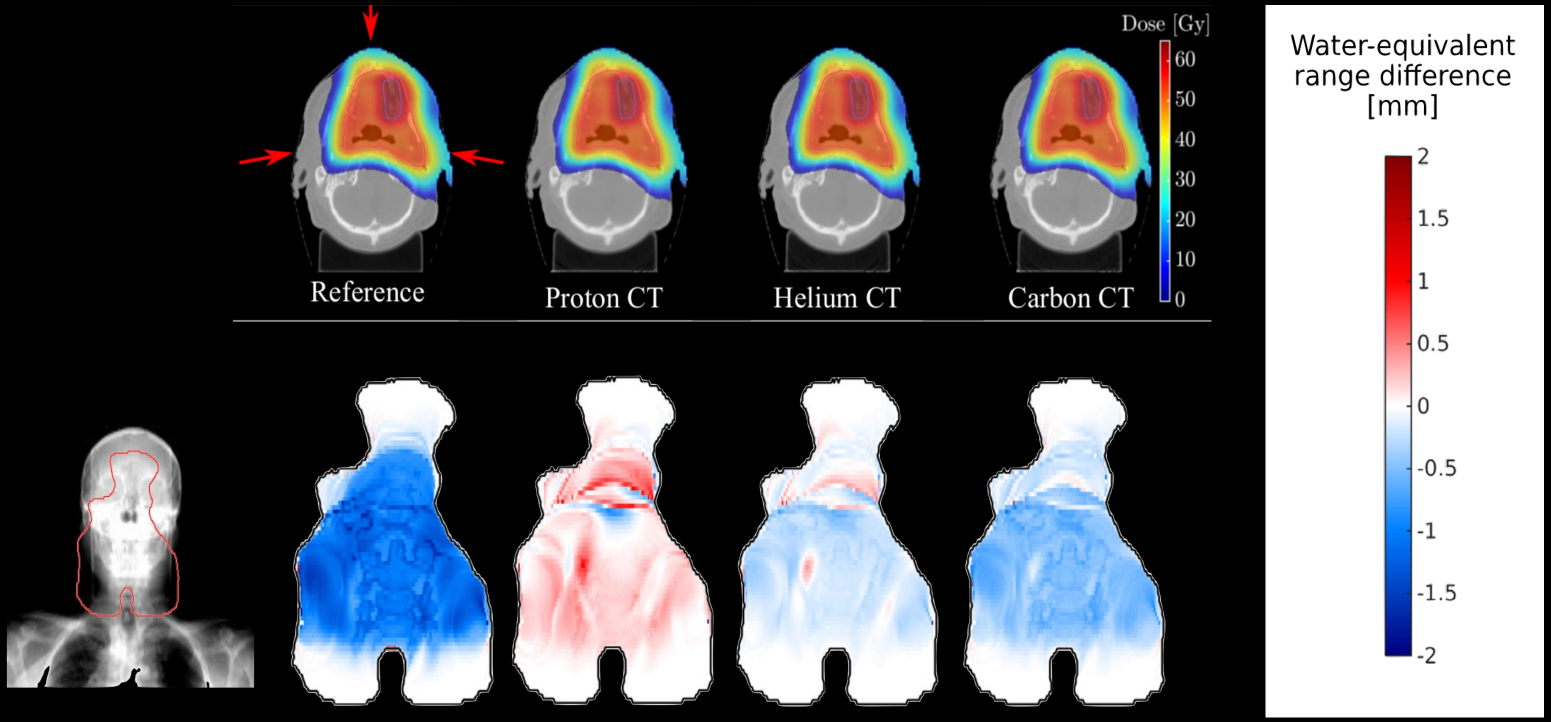
Image courtesy: Osaka Heavy Ion Therapy Center & Durante & Loeffler, Nature Rev Clin Oncol 20

ION BEAM THERAPY : CHALLENGES

Range uncertainties

Highly conformal ►Low tolerance for treatment planning error

- Inherent uncertainties in the conversion from X-ray CT data to particle range
- Anatomical changes



water-equivalent proton range variations for recalculation based on iCTs and xCT with respect to the optimized dose using the reference plan

Sebastian Meyer et al 2019 Phys. Med. Biol. 64 125008

RANGE UNCERTAINTIES: WAY FORWARD

Tumor tracking & Treatment verification

Tumor tracking

- 4D CT

Motion detection

- X-ray stereo projections
- External surrogates combined with adaptive correlation models
- Soft-tissue imaging (ultrasound, MRI)
- Particle radiography

Motion tracking

- Lateral compensation (magnet steering)
- Depth compensation (moving degrader vs static degrader)

Treatment verification

Range verification with RIB of positron emitters and Positron emission tomography (PET)

- Off-line PET dosimetry
- In-beam PET dosimetry
- Prompt radiation measurement

B · A · R · B

BIOMEDICAL APPLICATIONS OF RADIOACTIVE ION BEAMS

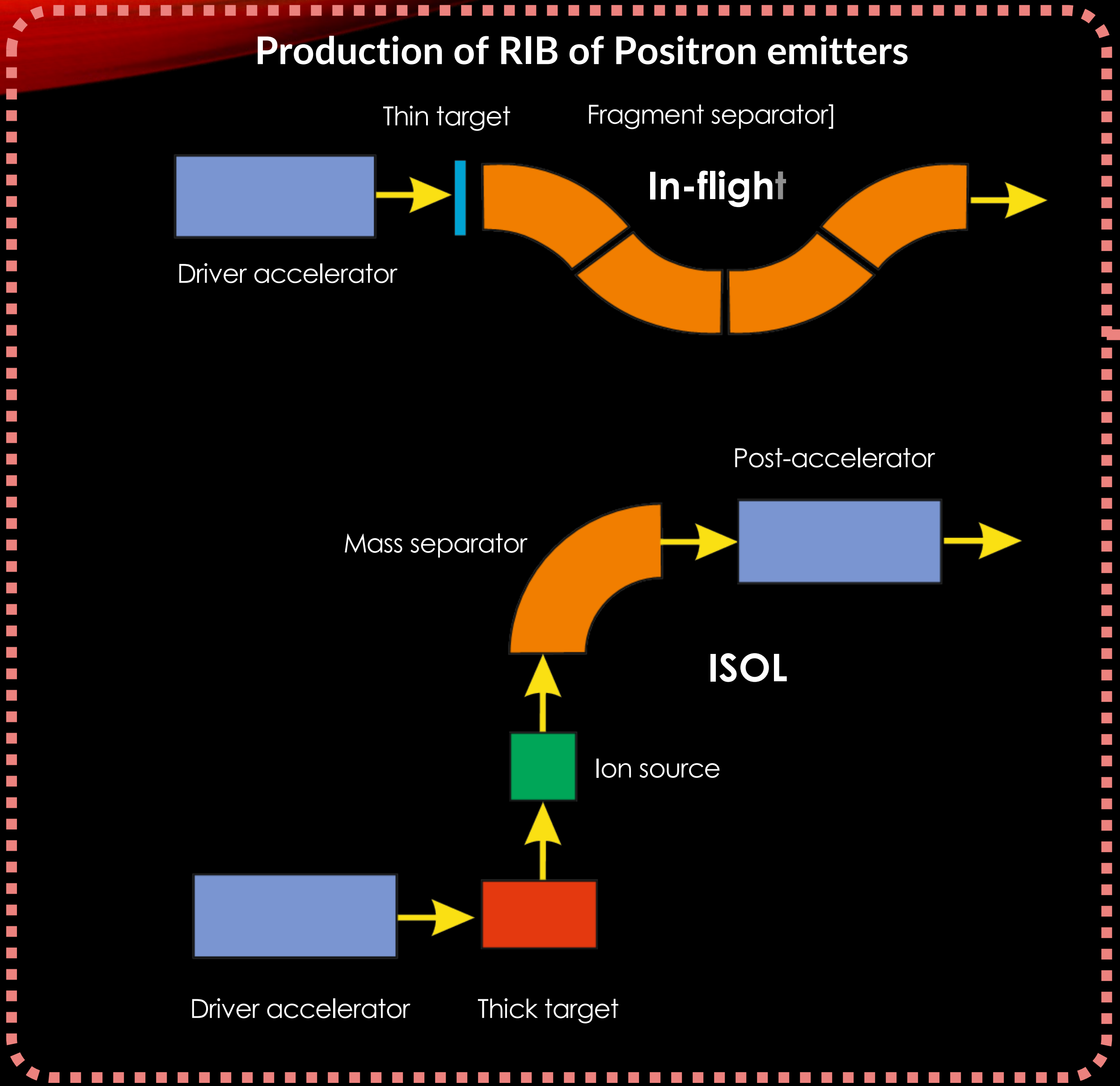
Radiotherapy with positron emitters e.g. ^{11}C, ^{10}C, ^{15}O, ^{14}O

Riboldi *et al.*, *Lancet Oncol*. 2012

FAIR Phase 0 Research Program

Super-FRS EC

RADIOTHERAPY WITH POSITRON EMITTERS



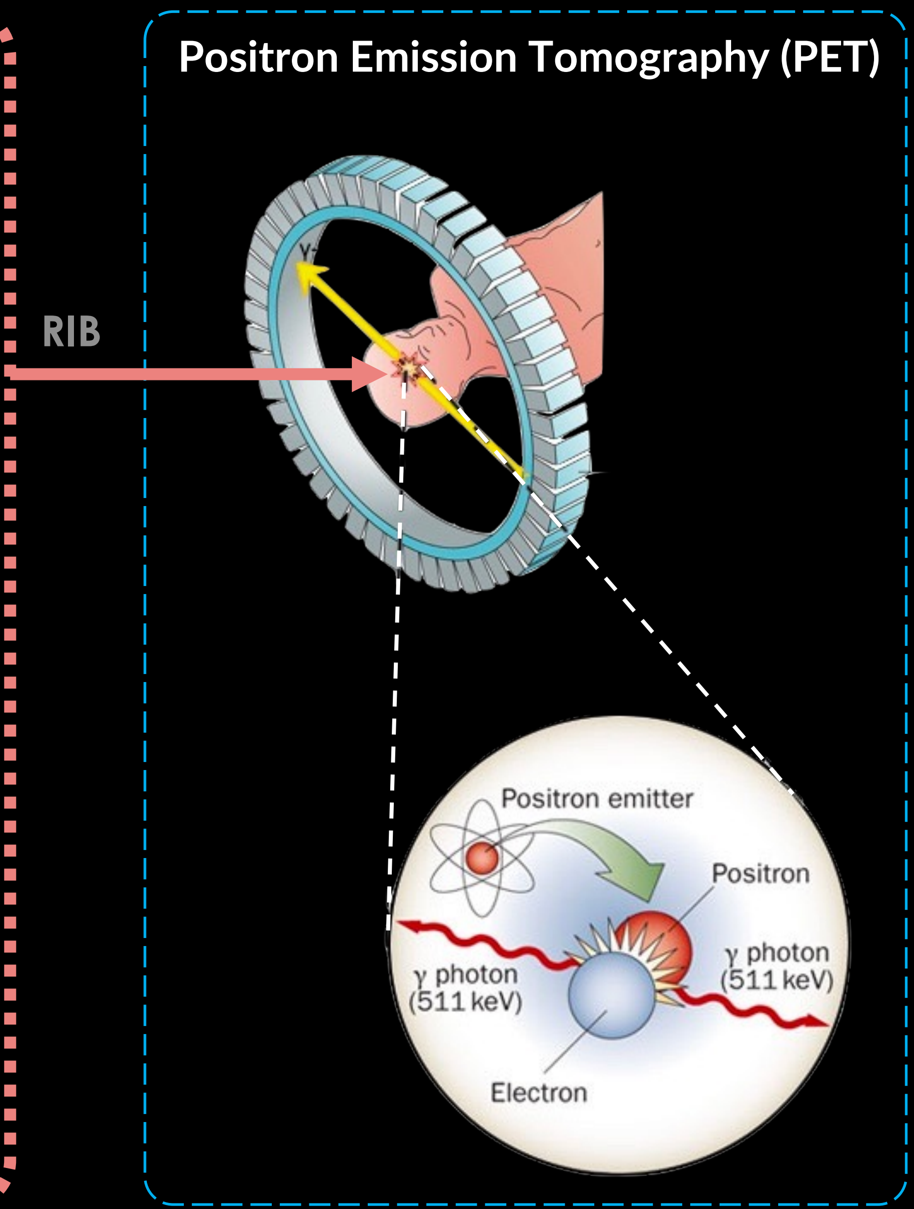
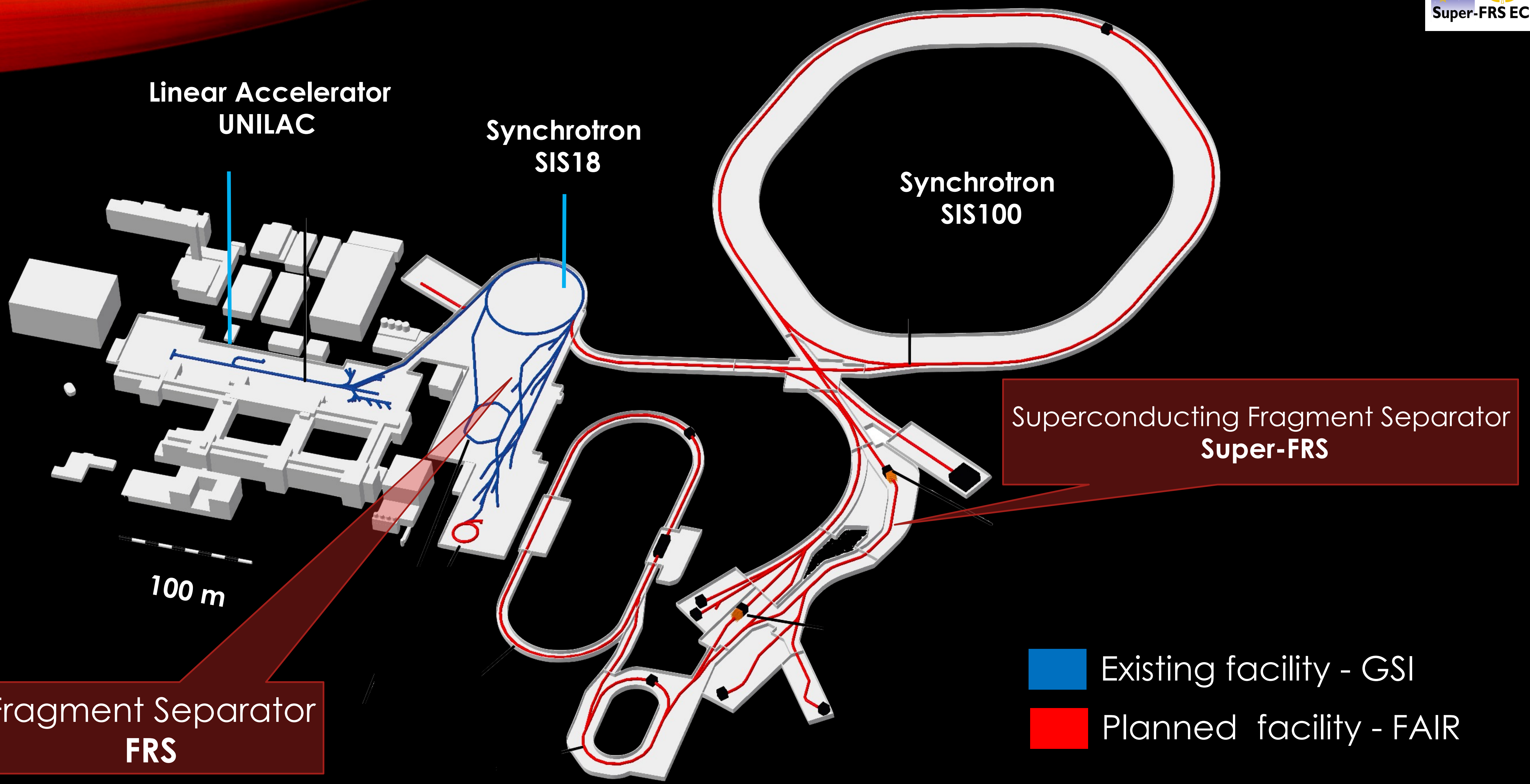


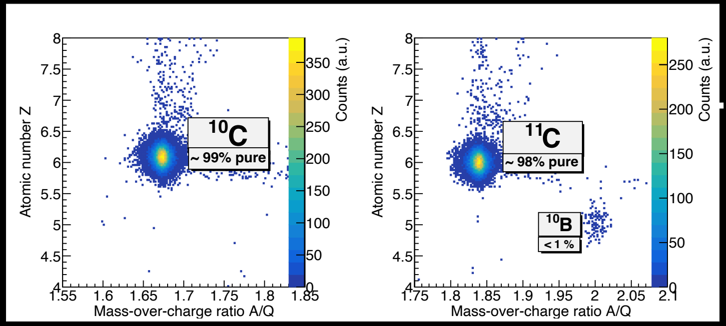
Image courtesy: HIT, Heidelberg

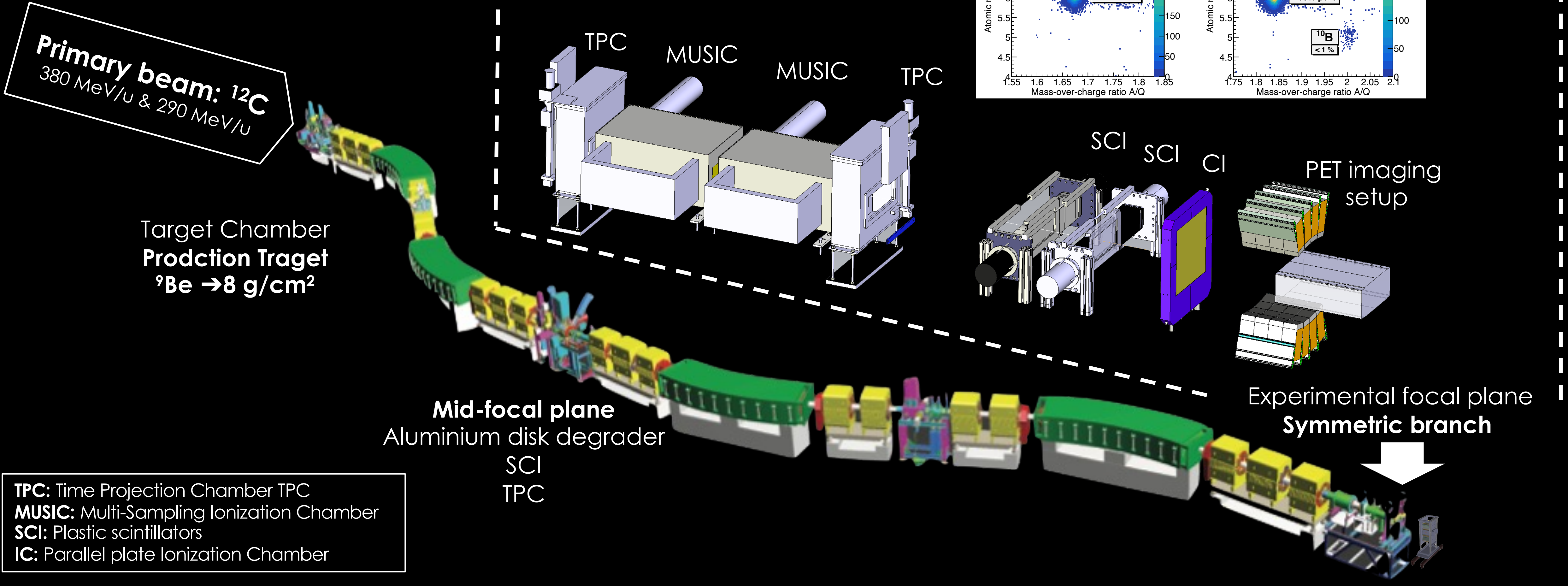
RADIOACTIVE ION BEAMS AT GSI AND FAIR



PRESENT EXPERIMENTS AT FRS

- Low intensity run to obtain particle ID using FRS detectors
- High intensity irradiation for PET imaging





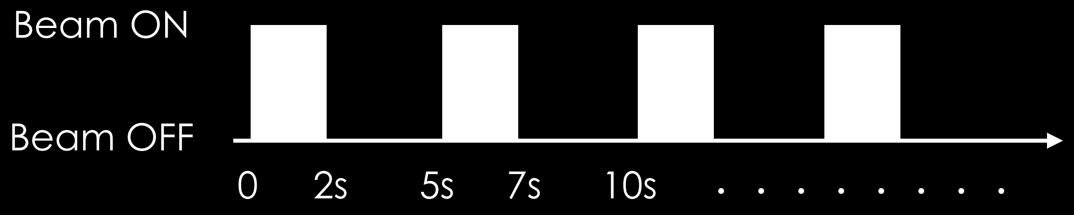
TPC: Time Projection Chamber TPC
MUSIC: Multi-Sampling Ionization Chamber
SCI: Plastic scintillators
IC: Parallel plate Ionization Chamber

IN-FLIGHT SEPARATED POSITRON EMITTERS AT FRS

Beam time: 2020 February

Stable primary beam: 10^9 ions/spill ^{12}C
Secondary beams : ^{11}C, ^{10}C
Secondary beam purity: 94 to 99%
Secondary beam intensity: 10^6-10^7 ions/spill

Spill structure



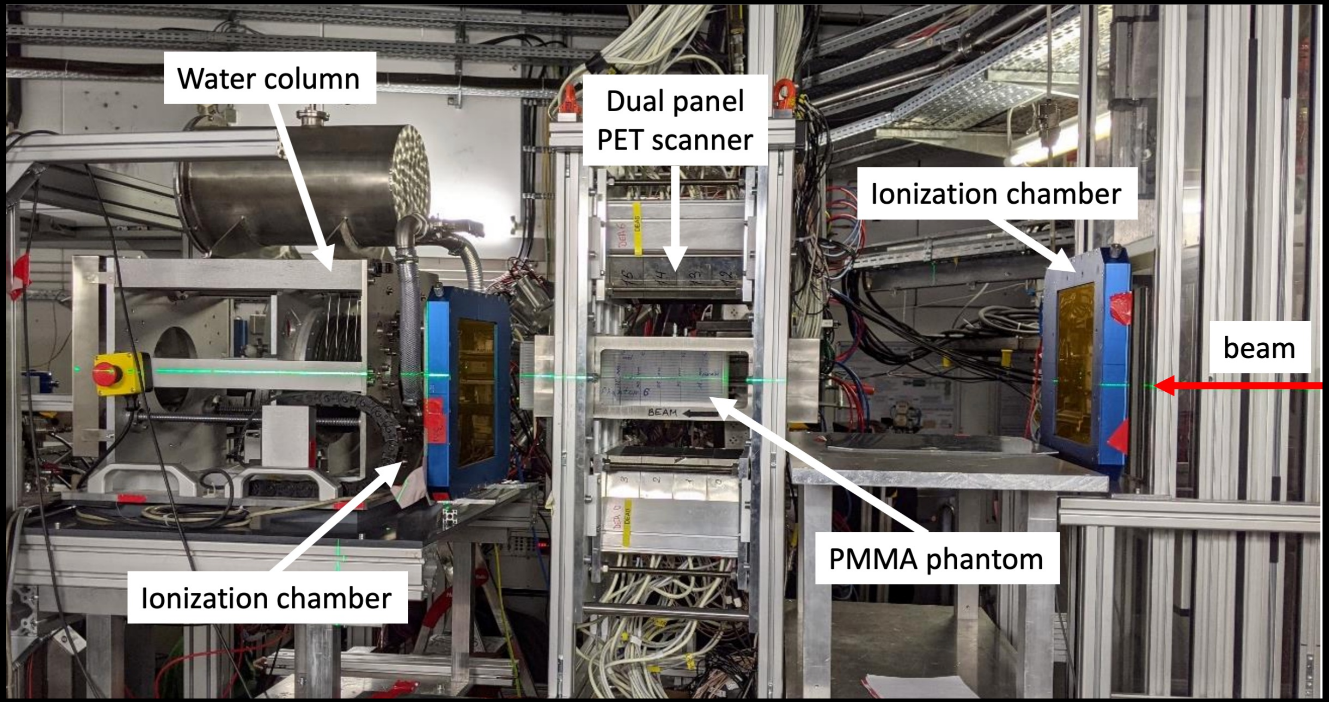
High energy irradiation
Primary beam energy: 390 MeV/u
Δp/p of secondary beam : 0.13 to 0.42%

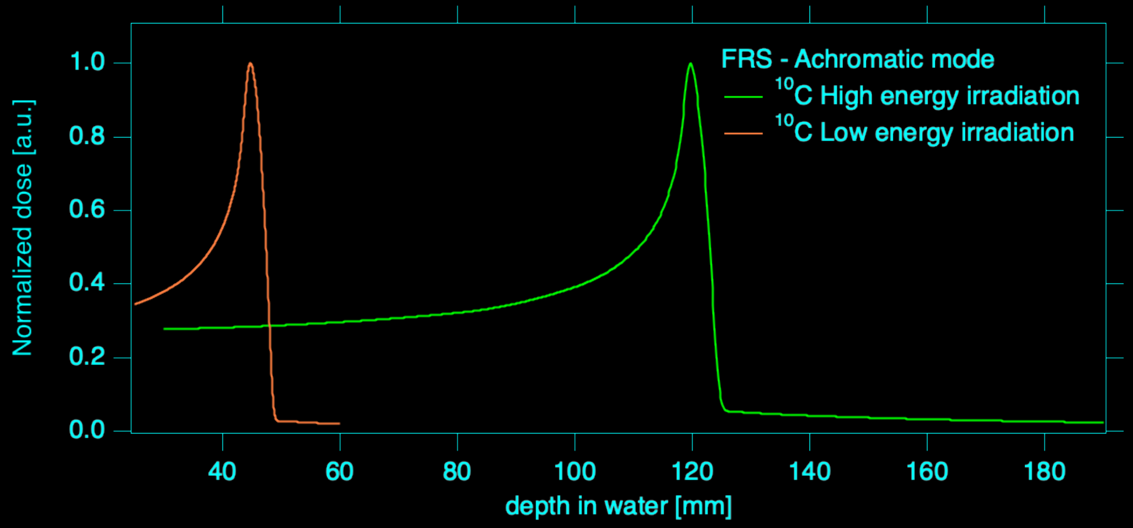
Low energy irradiation
Primary beam energy: 280 MeV/u
Δp/p of secondary beam : 0.25 to 0.74%

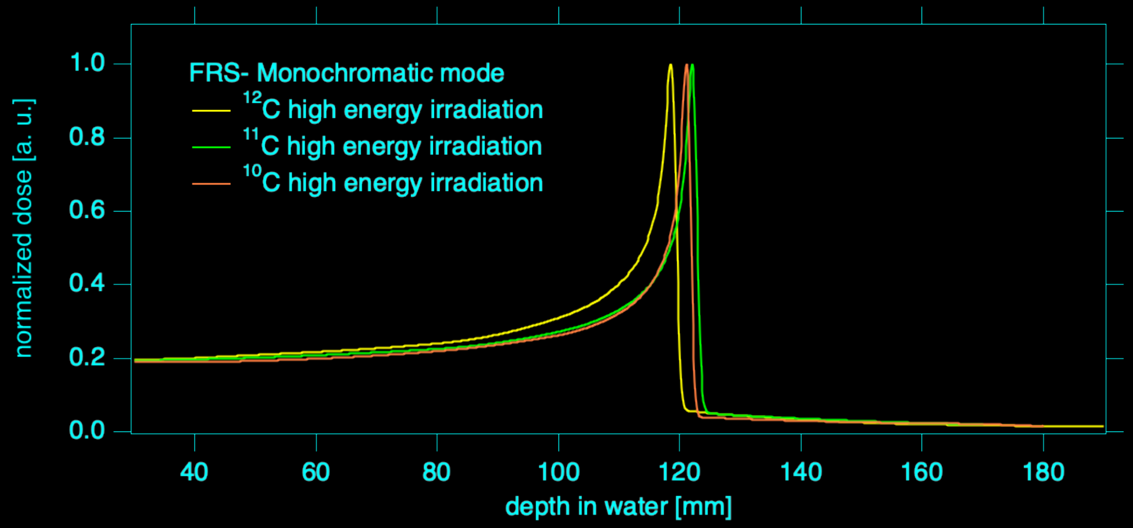
isotope	half-life[min.]	Energy [MeV/u]	Expected Range in water [mm]
12C	stable	138.8	45
11C	20.4	146.71	45
10C	0.321	155.75	45
12C	stable	240.2	120
11C	20.4	258.49	120
10C	0.321	272.53	120

DEPTH DOSE PROFILES MEASUREMENTS

PET imaging: Dual panel PET scanner: Uni. Groningen
Range and Bragg curve measurements : GSI-Biophysics variable thickness water column
BARB Prompt gamma and PET detector test: LMU





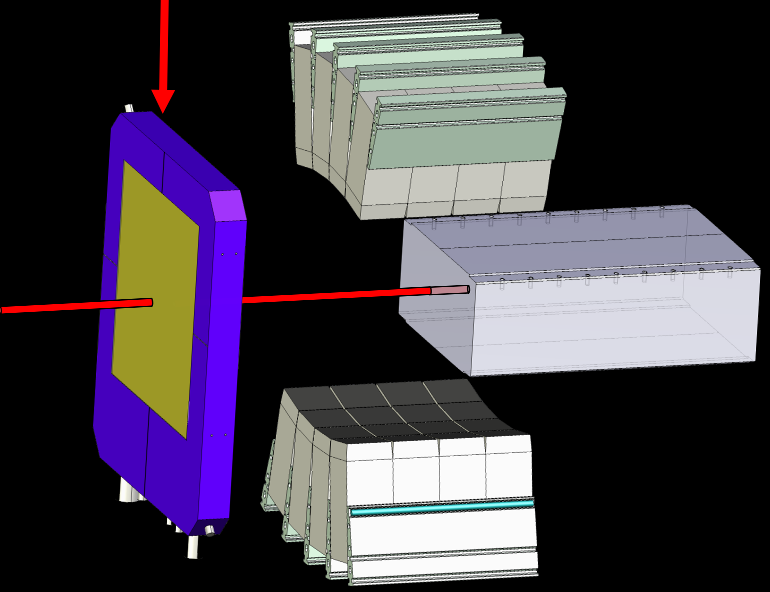


Boscolo, D., Kostyleva, D., Schuy, C., Weber, U. et al., *NIMA*, 167464.

INTENSITY MONITORING AND PET IMAGING

Parallel plate ionization chamber (IC)

Dual-panel PET scanner



Detetcor: LSO (lutetium oxyorthosilicate doped with cerium) scintillation crystals + PMT

Eenergy window of 435-650 keV

Time window: 4.1 ns

Dual-panel PET scanner

Parallel plate ionization chamber (IC)

Gas filled IC with high rate capability

Biophysics, GSI

PET SCANNER

1/6th of a SiemensBiograph mCT clinical scanner

University Medical Center Groningen

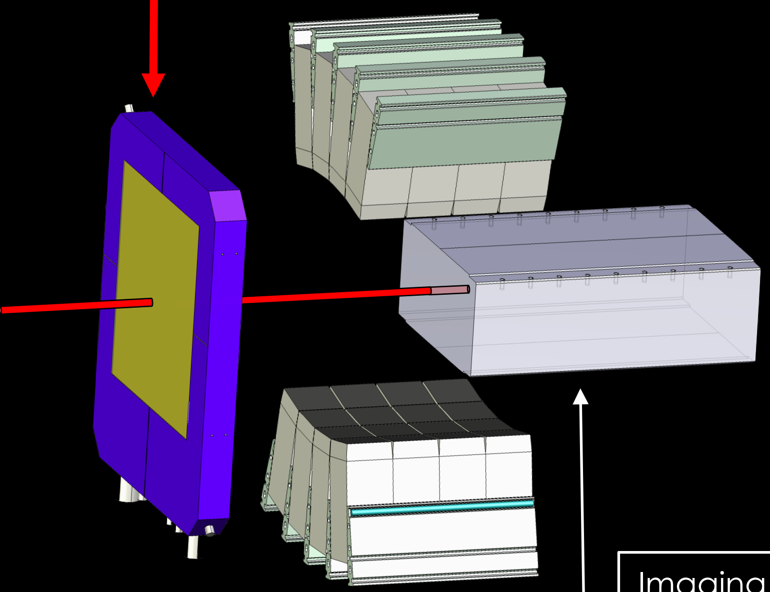
umcg

PET IMAGING EXPERIMENT AT FRS

D. Kostyleva, S. Purushothaman, P. Dendooven, E. Haettner, C. Scheidenberger et al., Phys. Med. & Bio. (Submitted)

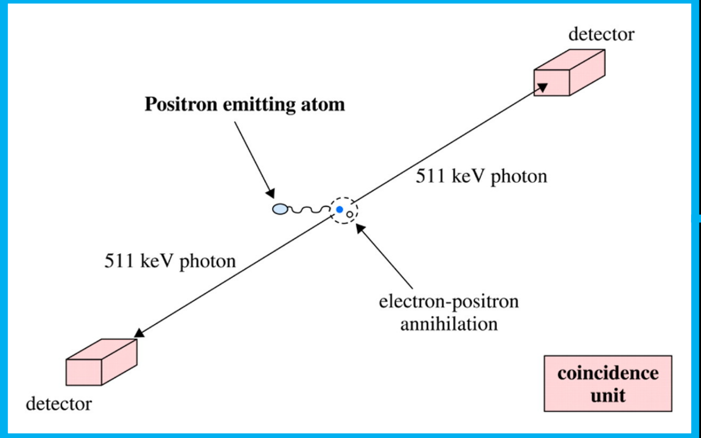
Parallel plate ionization chamber (IC)

Dual-panel PET scanner



Imaging phantom: PMMA : (C5O2H8)n

Dual-panel PET scanner



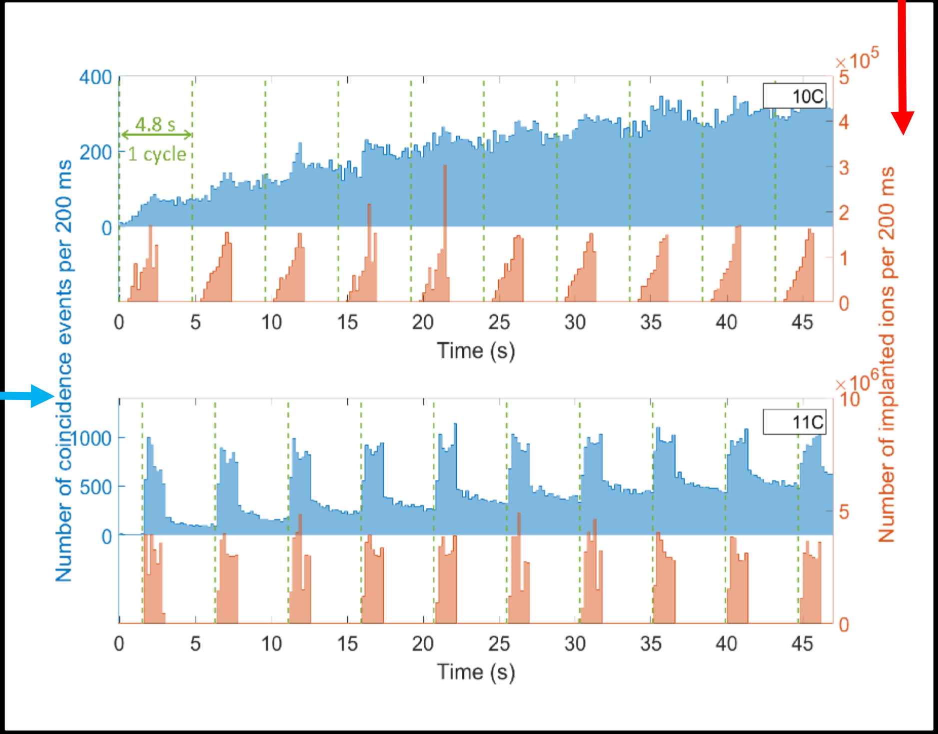
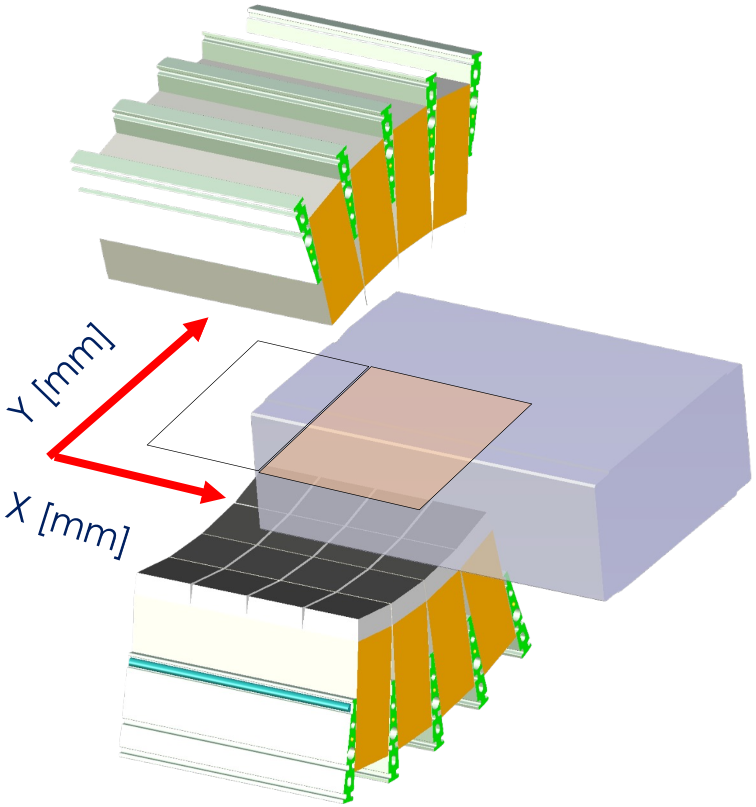
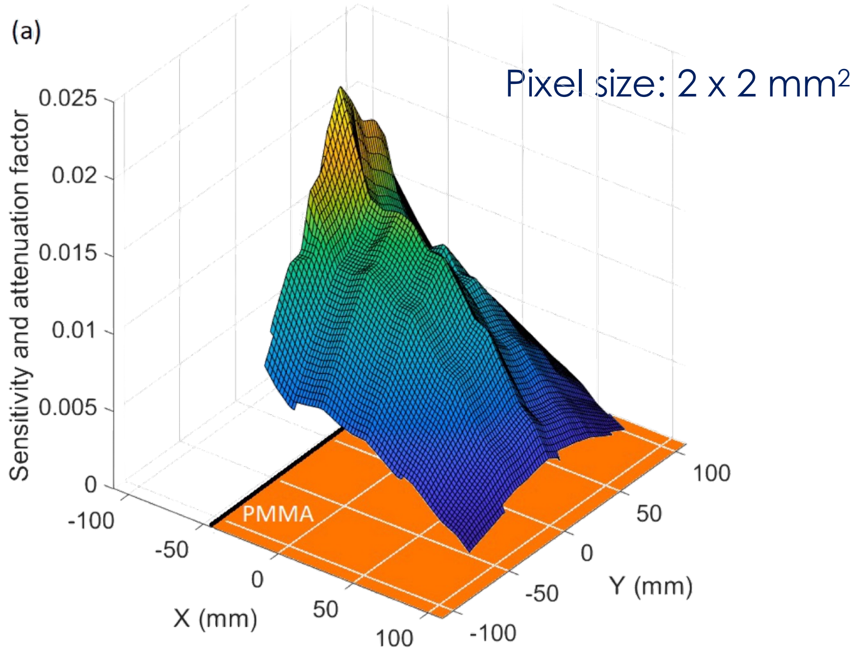


IMAGE RECONSTRUCTION

Image plane



2D Sensitivity correction

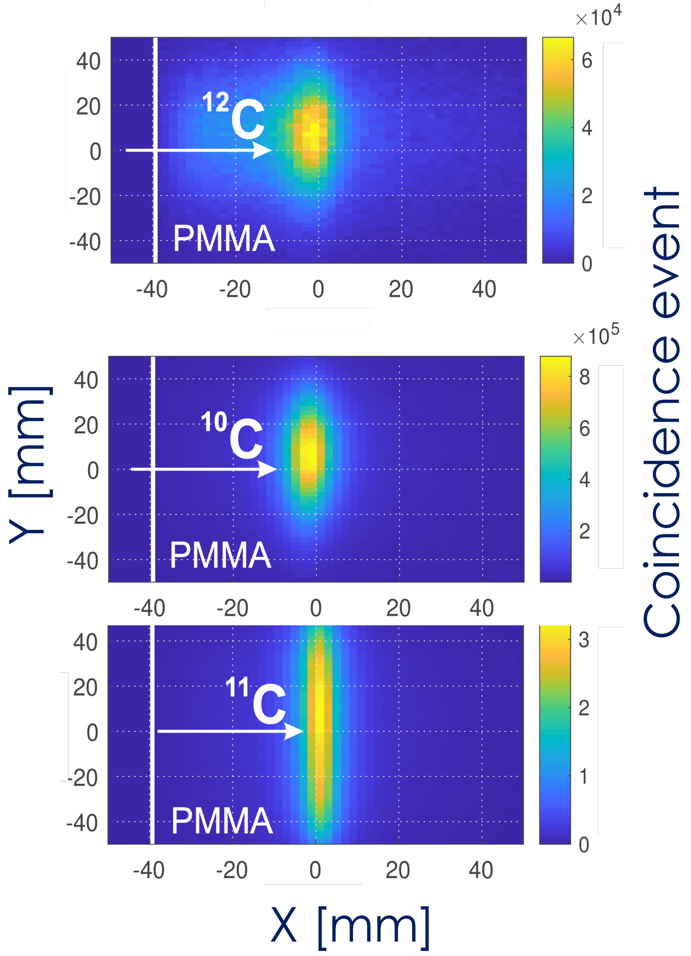


^{12}C → 138.8 MeV/u (achromatic)

^{11}C → 146.71 MeV/u (monoenergetic)

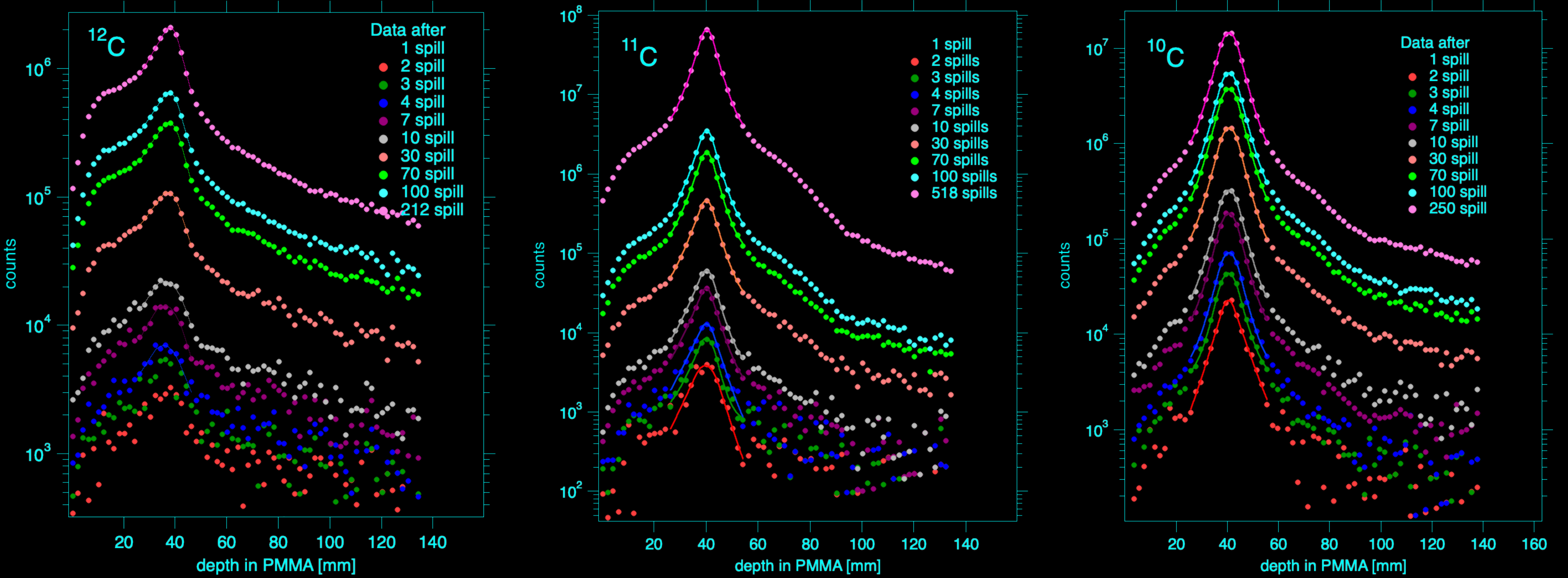
^{10}C → 155.75 MeV/u (achromatic)

2D PET image



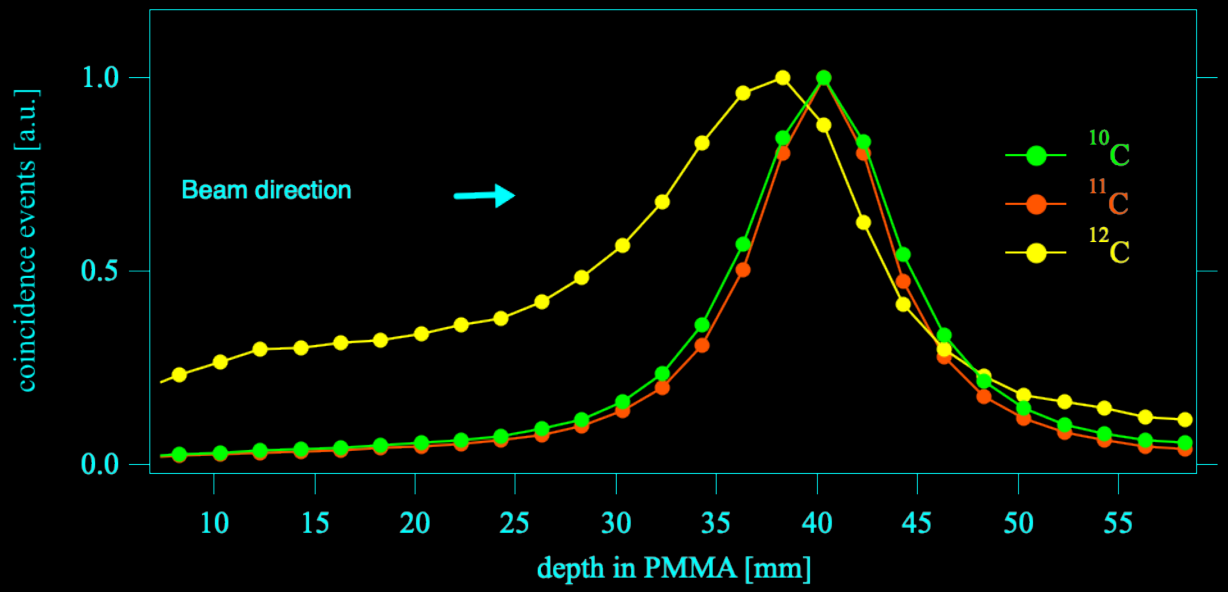
EVOLUTION OF PET PROFILE DURING IRRADIATION

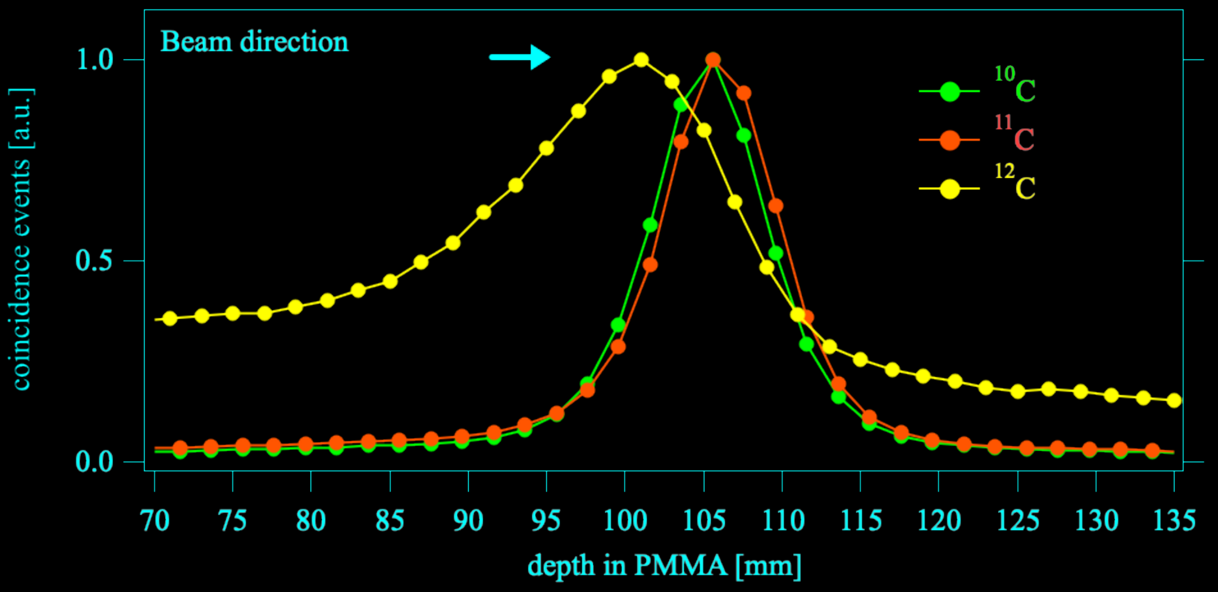
Cumulative evolution of data during irradiation : PET profiles



COMPARISON: 12C VS 11,10C PET IMAGE PROFILES

- **Experiments at therapy relevant implantation depths**
- **Beam energy tuned to have same rages for 12, 11 and 10C**





12C PET image peak

- Peak position defined by projectile fragments
- Mismatch between PET image Peak and projectile range
- Image intensity defined by fragmentation cross-section
  - 1 order of magnitude lower than 11C
  - 2 orders of magnitude lower than 10C

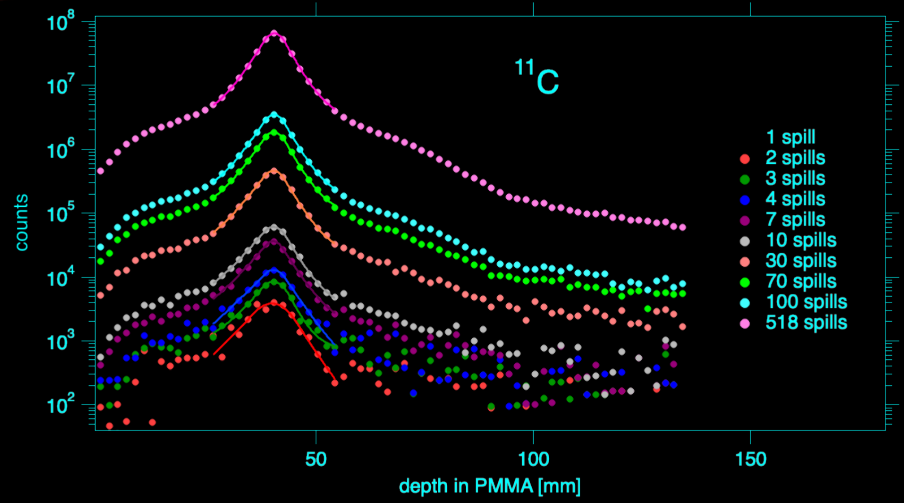
10 and 11C PET image peak

- Peak position defined by mean range of projectiles

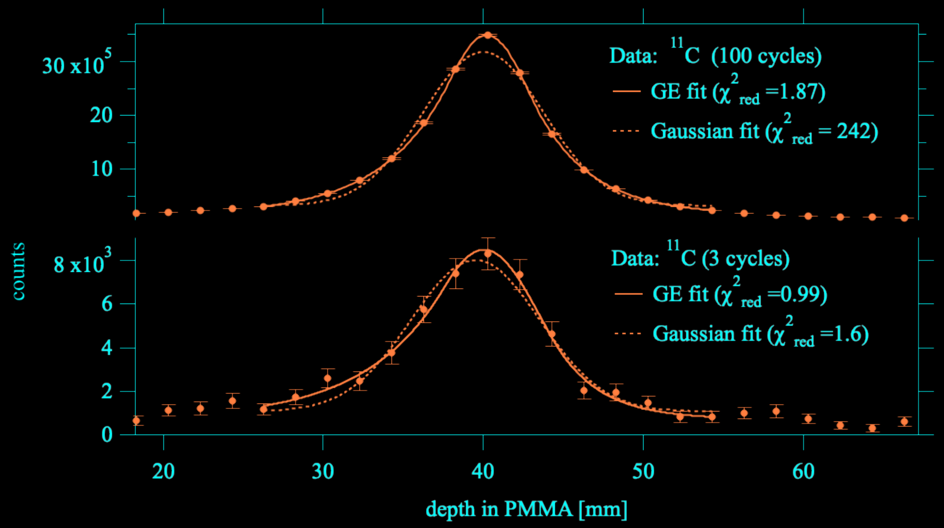
DATA ANALYSIS PROCEDURE

FAIR Phase 0 Research Program
Super-FRS EC

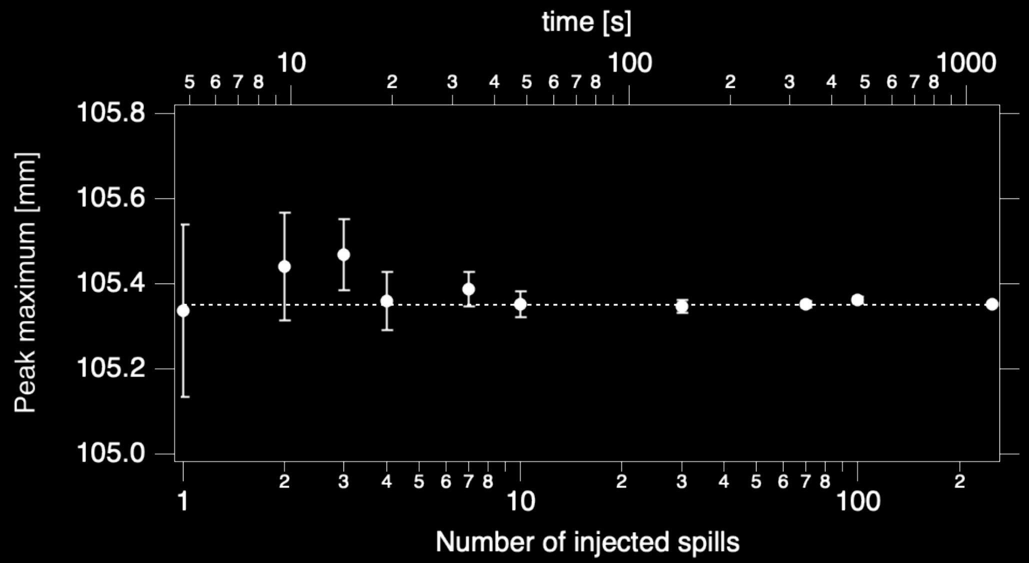
Extract time evolution of PET image profiles

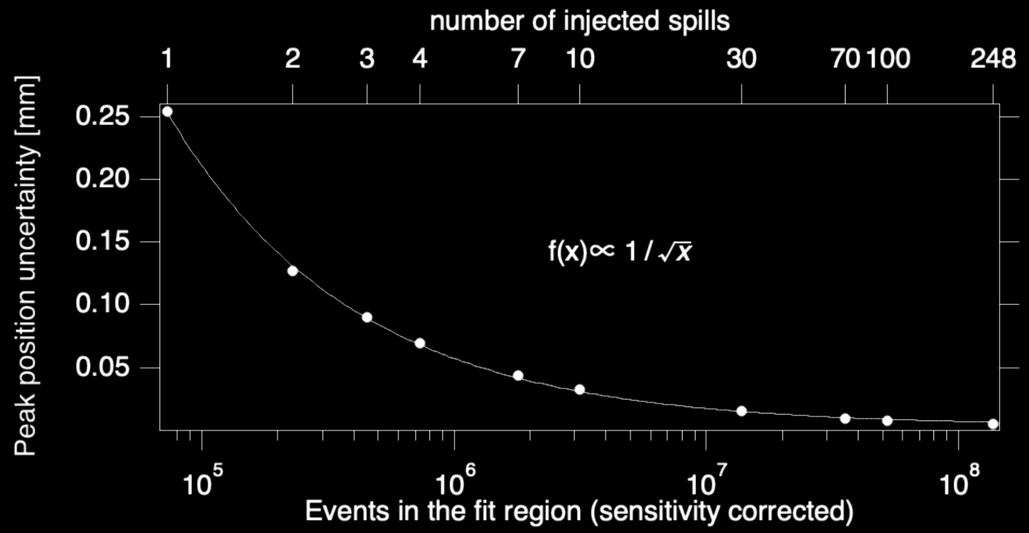


Peak shape analysis to extract peak position and uncertainty



Evolution of peak position and uncertainties

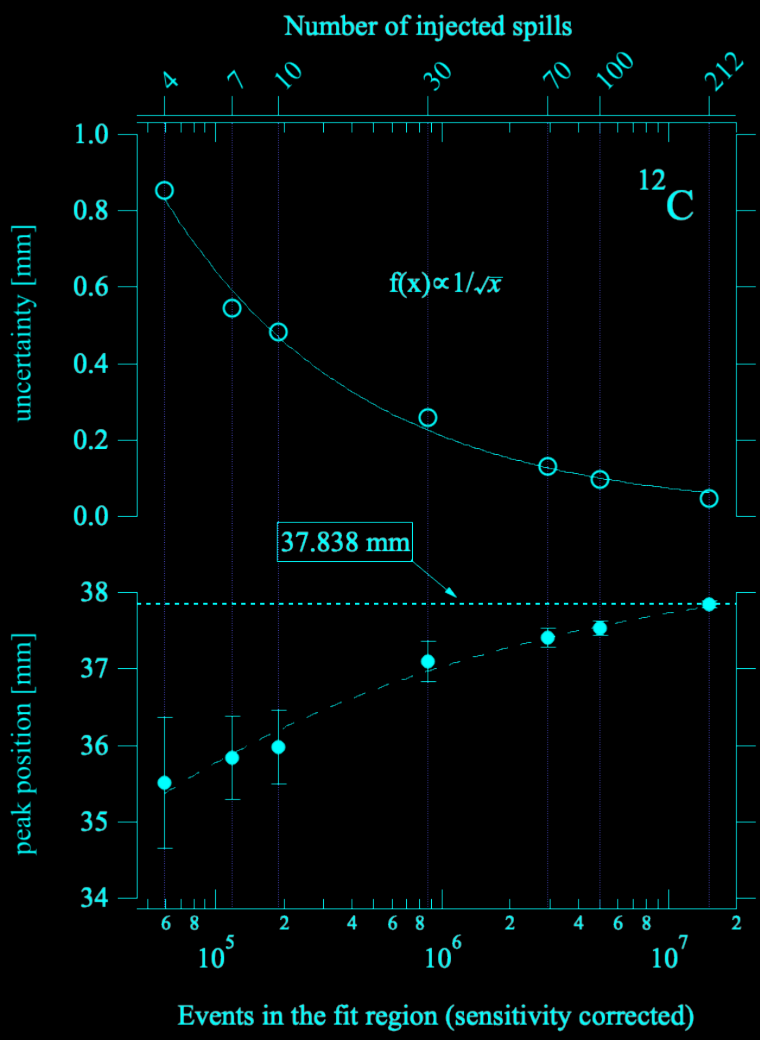




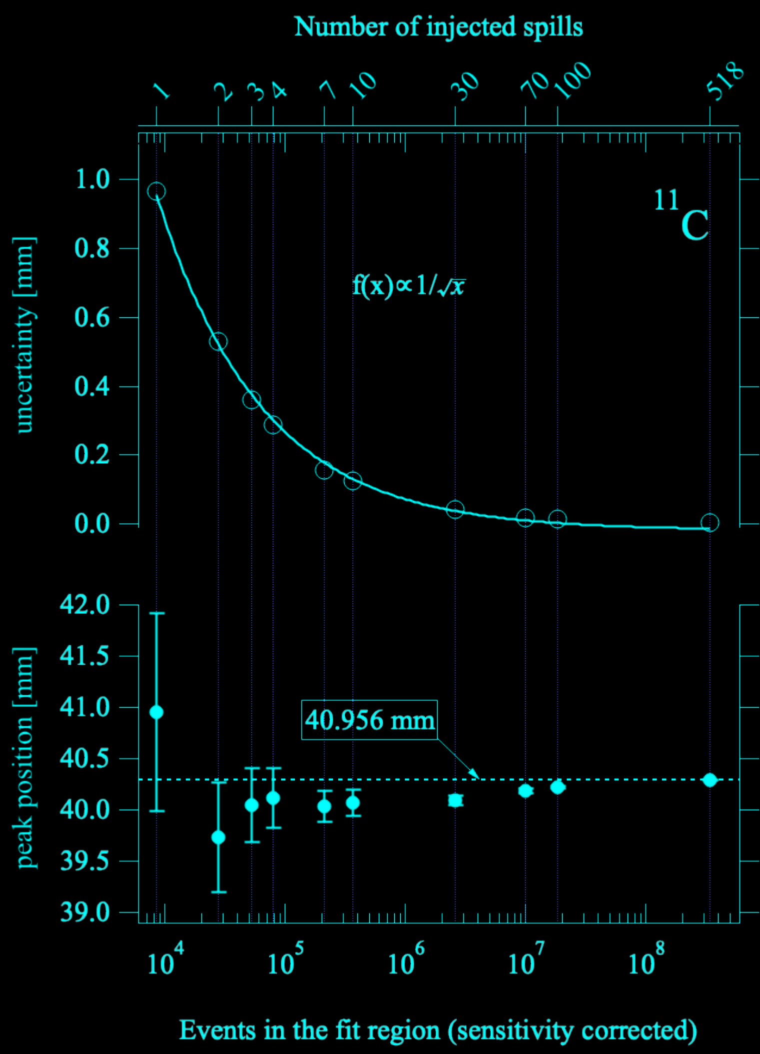
EVOLUTION OF PET PROFILE DURING IRRADIATION

Cumulative evolution of data during irradiation: positions and associated uncertainties

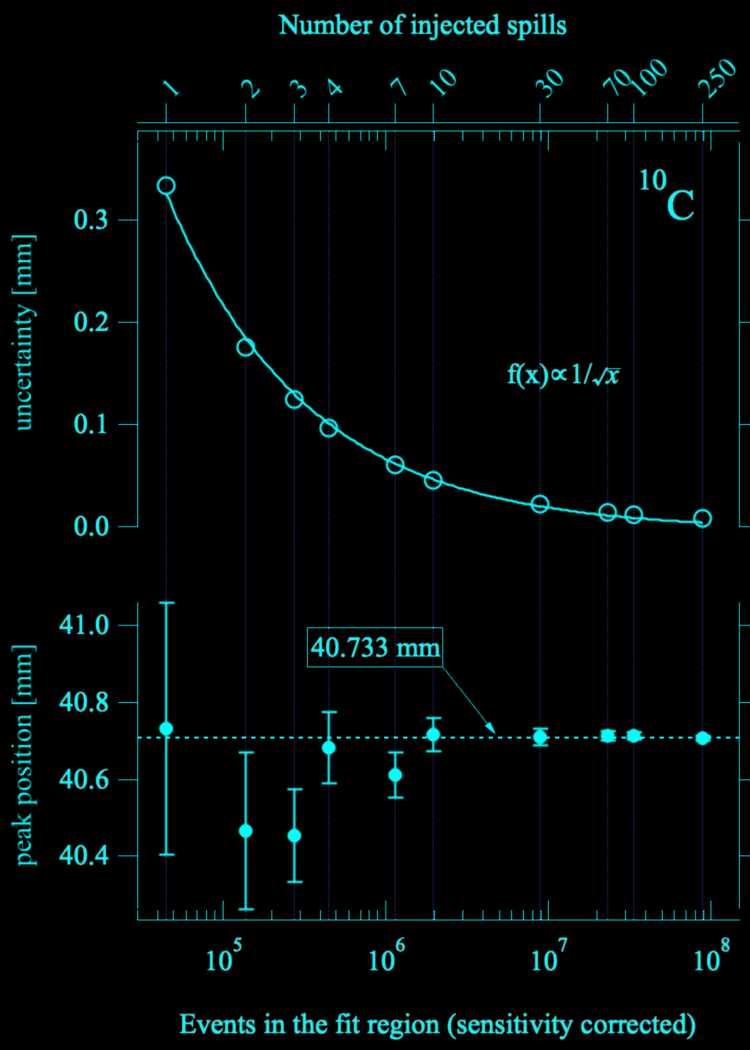
^{12}C



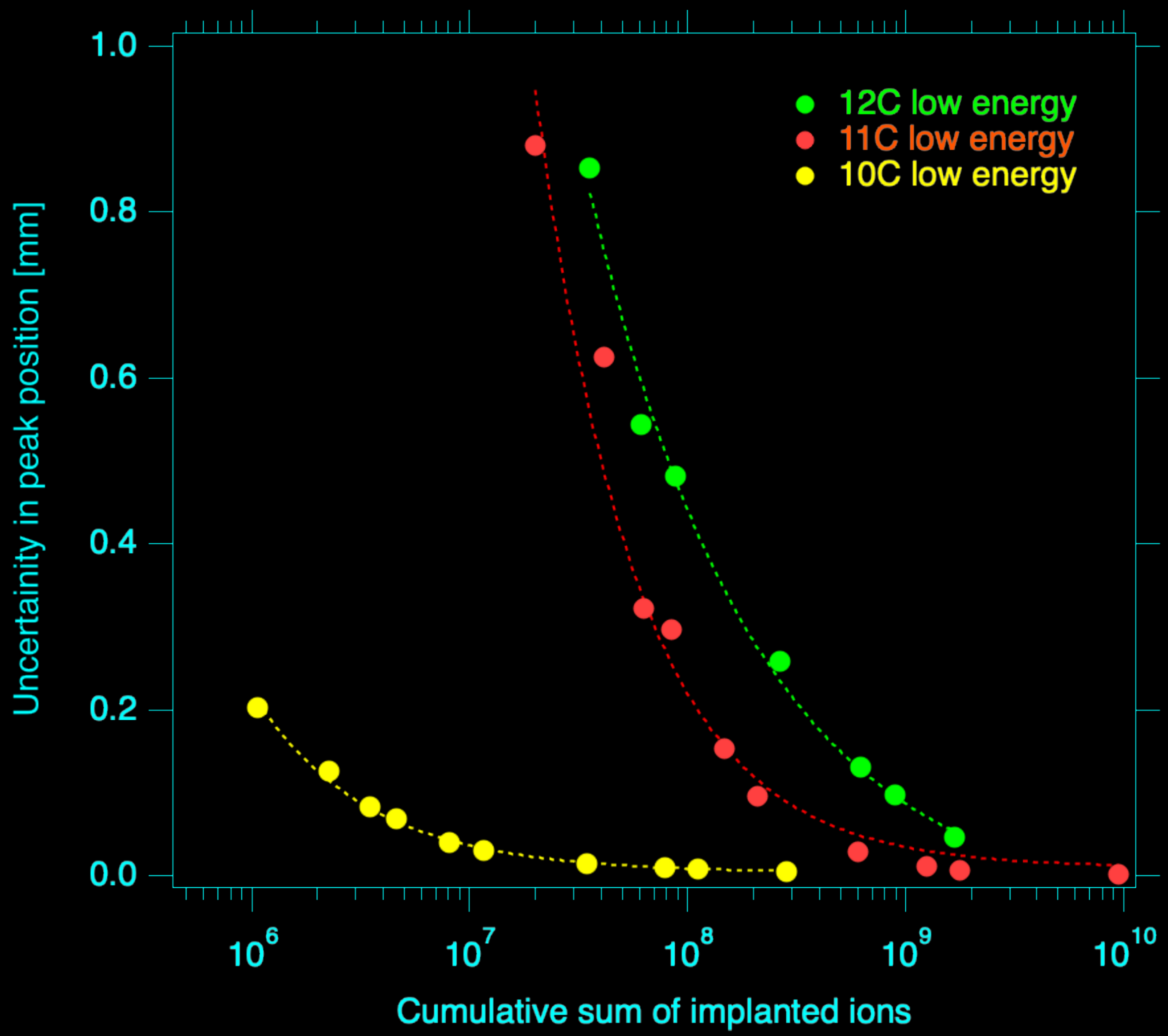
^{11}C

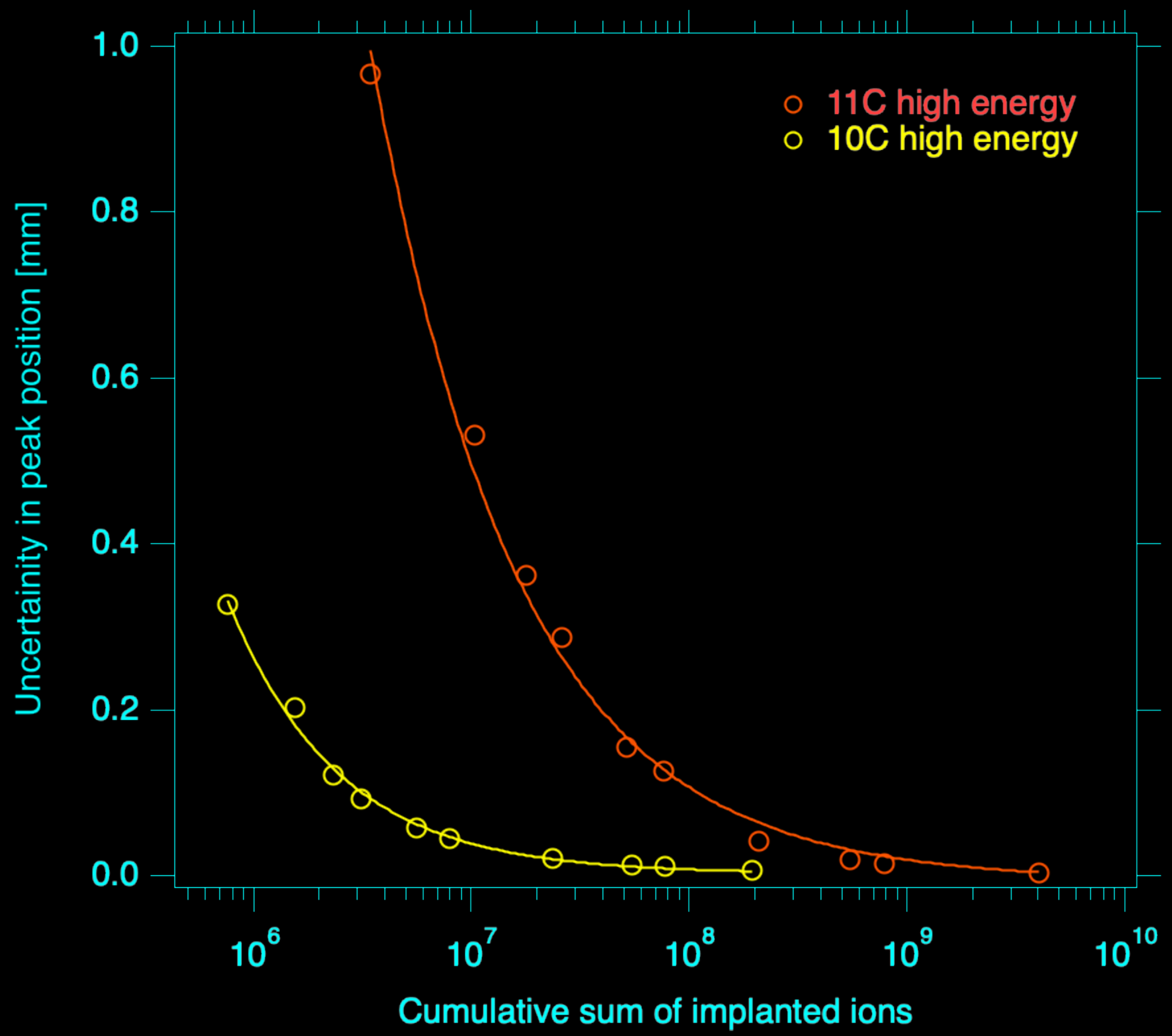


^{10}C



DATA ANALYSIS: SUMMARY





CONCLUSIONS AND OUTLOOK

10C

⇒ Accurate range verification with a single spill

⇒ Best candidate for **“real-time”** PET range verification

⇒ Range uncertainty dominated by systematic error (~ 1mm)

⇒ Lower production cross-section ⇒ High intensity primary beam

11C

⇒ ISOL type production feasible ⇒ Easier technical realization (?)

⇒ Longer half life requires higher dose (compared to 10C) before reliable range verification

12C

⇒ Mismatch between PET peak and range

⇒ Time evolving PET image peak ⇒ Not a candidate for real time PET range verification

THANKS

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H. Geissel, I. Ozoemelam, C. Schuy
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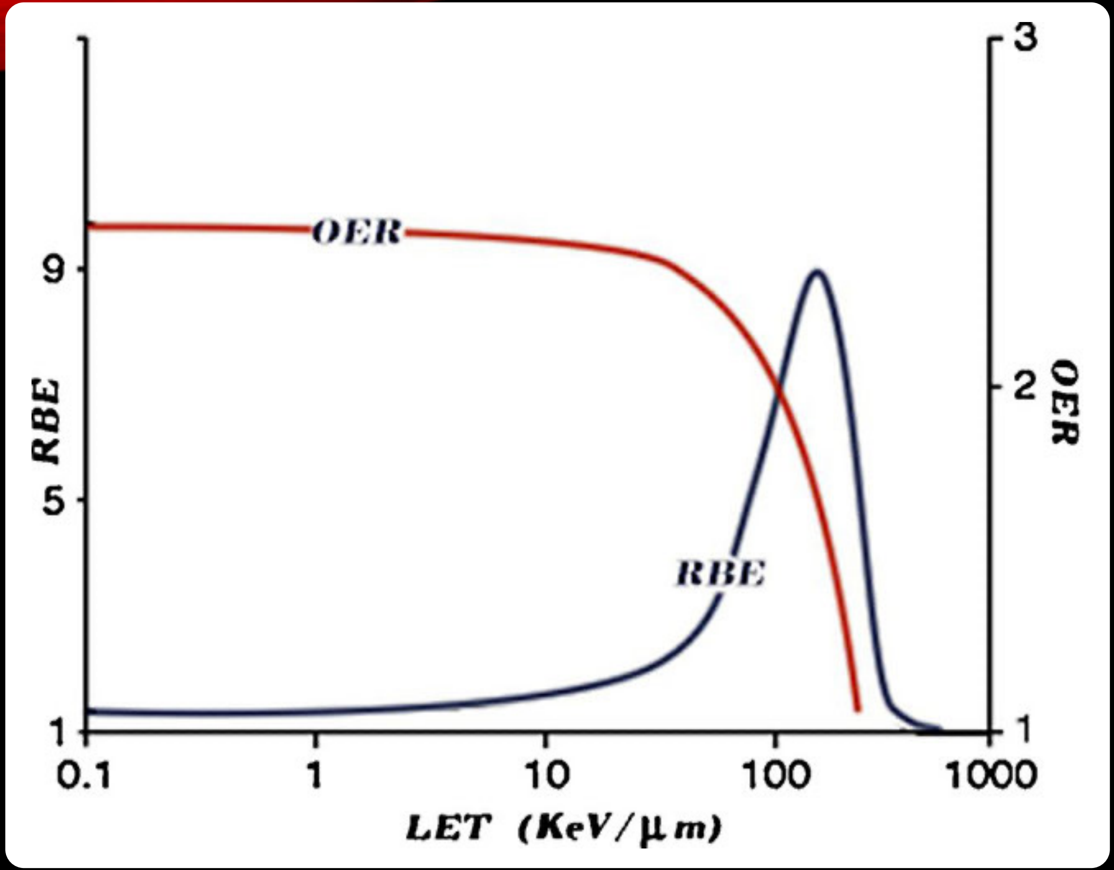
H. Weick J. Zhao, M. Durante , K. Parodi
&
Super-FRS Experiment Collaboration

GSI FAIR Phase 0 Research Program NUSTAR Super-FRS EC APPA erc B · A · R · B LMU Ludwig-Maximilians-Universität München umcg

RADIATION THERAPY: BIOLO GICAL QUALIFIERS



LET = Linear Energy Transfer
D = Distance between ionization

Low LET

< 20 keV/µm ► D > DNA size

High LET

> 20 keV/µm ► D < DNA size

Very high LET

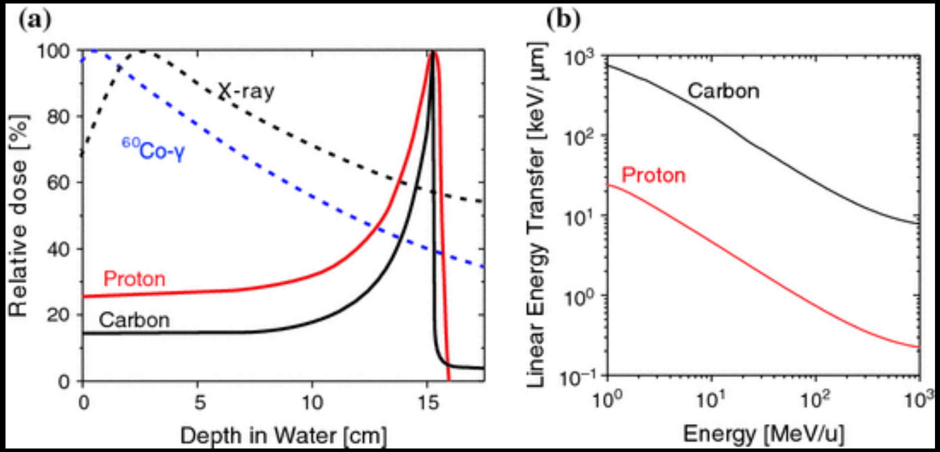
> 1000 keV/µm ► D < DNA size + excess energy

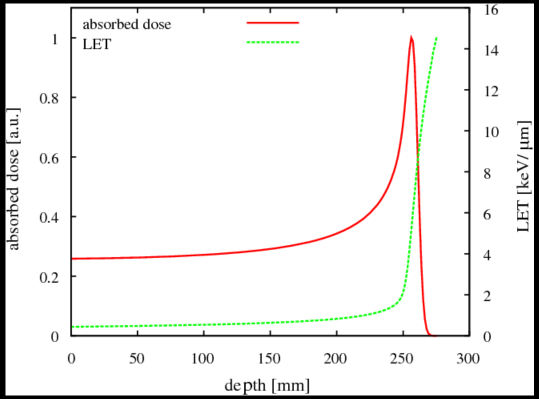
Particle	Cobalt gamma rays	protons	Heavy ions
Maximum LET	10 keV/µm	100 keV/µm	1000 keV/µm

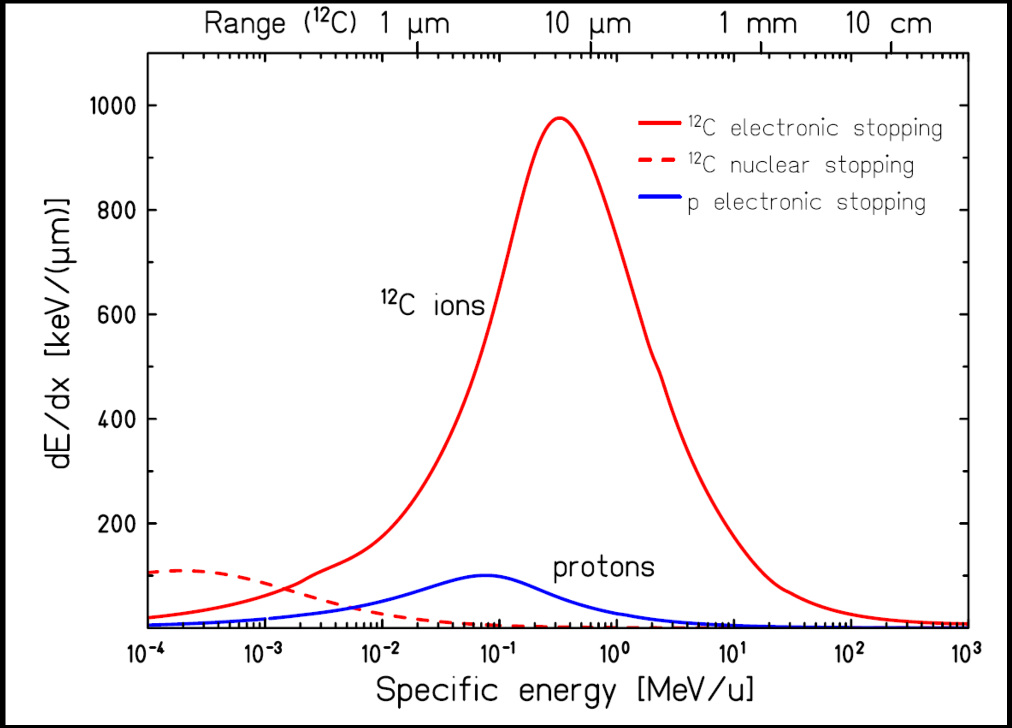
Zhou, O. D. G. (2010). Biophysical and Radiobiological Aspects of Heavy. Rev. Clin. Oncol, 7, 37-43.

ENERGY DEPOSITION MECHANISM: IONS

Charged particles demonstrate an increase in energy deposition with penetration depth up to the sharp maximum at the end of their range, known as a Bragg peak.







Therapy beam energy evolution direction

Linear Energy Transfer (LET)

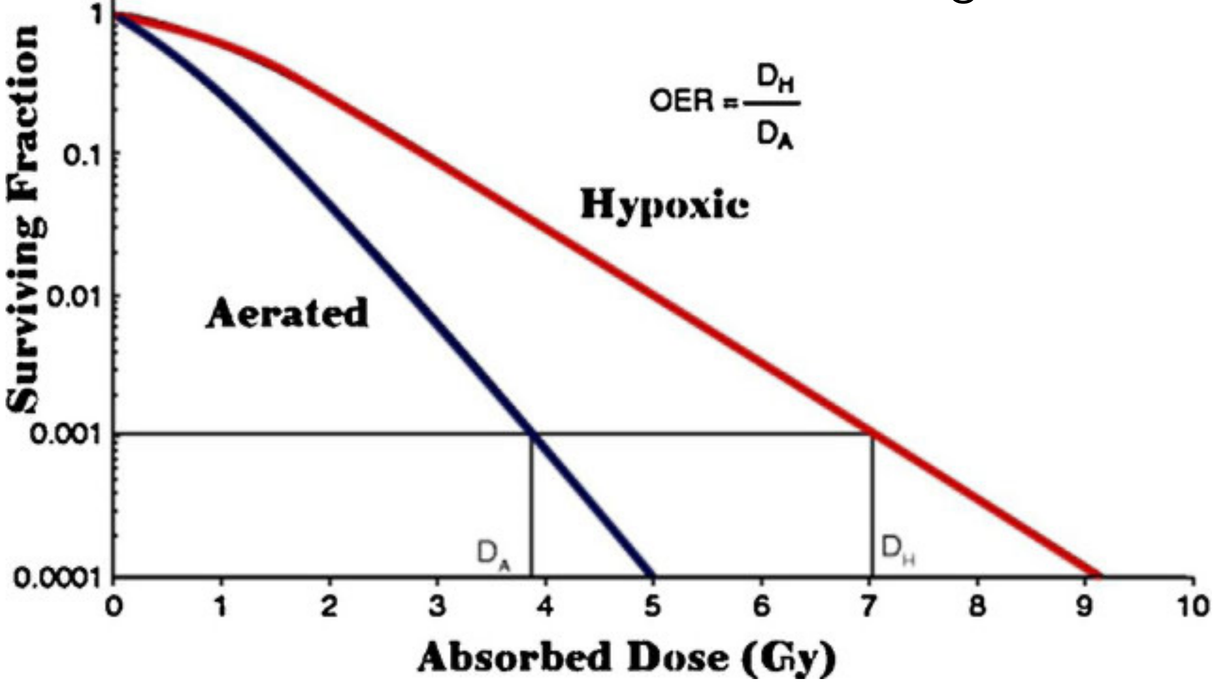
Energy that an ionizing particle transfers to the material traversed per unit distance

Schardt, Dieter et al., *Reviews of modern physics* 82.1 (2010): 383.

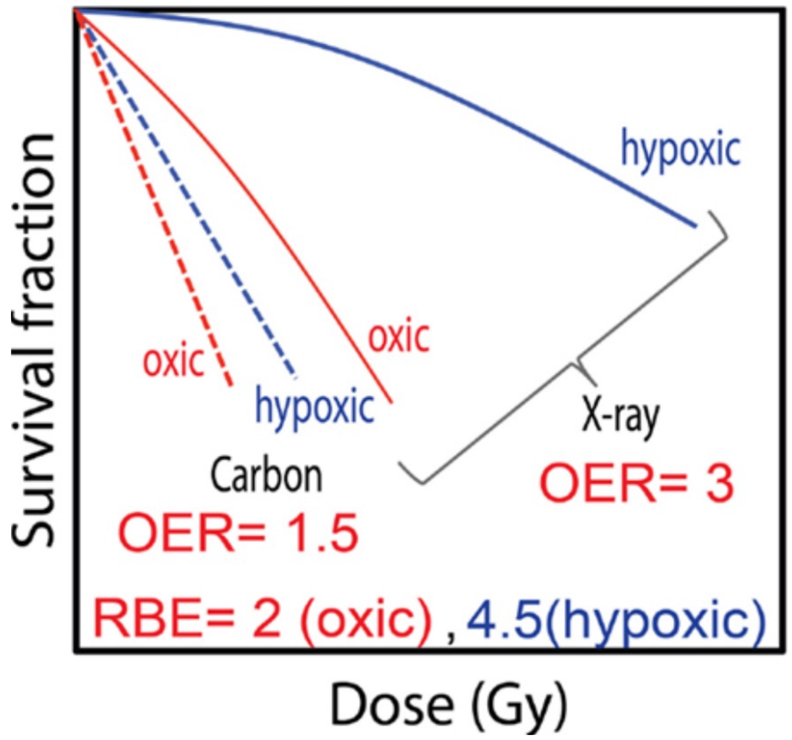
OXYGEN ENHANCEMENT RATIO (OER)

Additional oxygen abundance creates additional free radicals and increases the damage to the target tissue.

- A frequent condition especially in badly vascularized large tumor
- One of the main challenges in RT



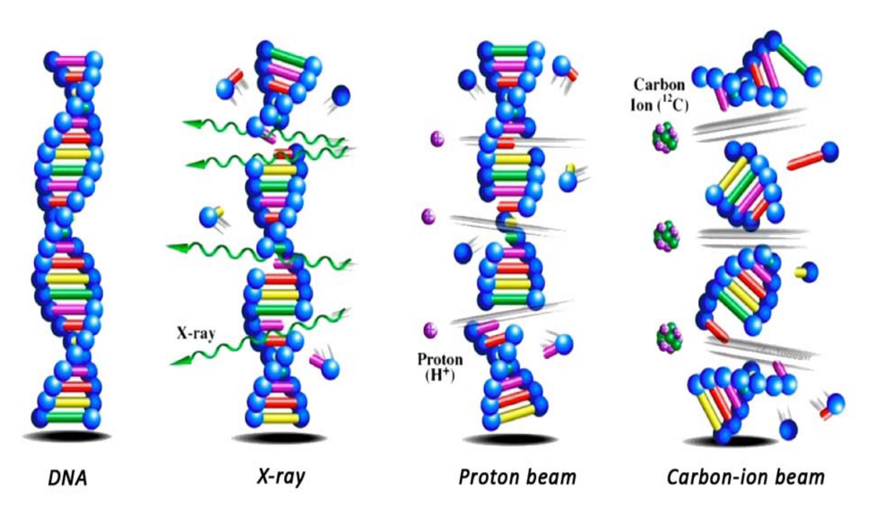
Photon vs. Carbon ions



Zhou, O. D. G. (2010). Biophysical and Radiobiological Aspects of Heavy. Rev. Clin. Oncol, 7, 37-43.

RADIOTHERAPY CANDIDATES

LET = Linear Energy Transfer
D = Distance between ionization



Low LET

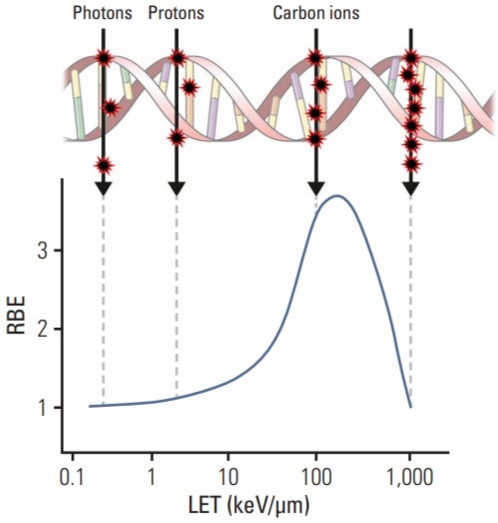
< 20 keV/µm ► D > DNA size

High LET

> 20 keV/µm ► D < DNA size

Very high LET

> 1000 keV/µm ► D < DNA size + excess energy



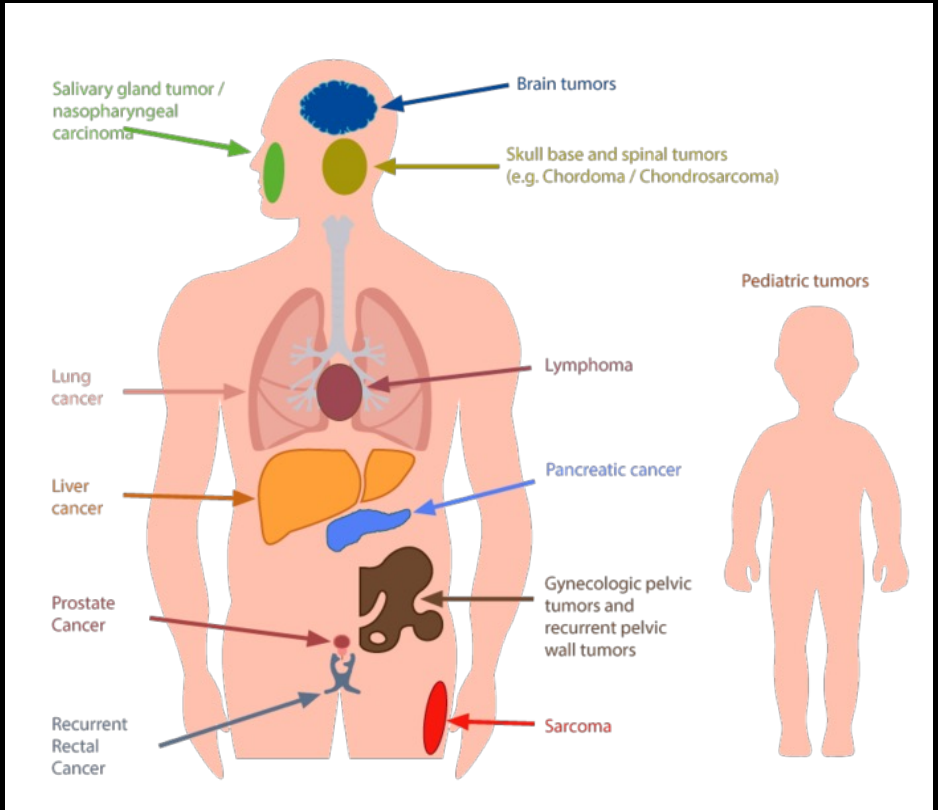
Particle	60Co gamma rays/bremsstrahlung photons	protons	Heavy ions
Maximum LET	10 keV/µm	100 keV/µm	1000 keV/µm

High LET ➤ ionizes water into H and OH radicals over a very short track
Heavy ions ➤ predominantly direct effect ➤ less dependent on free radical production and oxygen concentrations.

Arena, Carmen, et al. , Acta Astronautica 104.1 (2014): 419-431.

ION BEAM RADIOTHERAPY: STATUS

Proton Therapy: By the end of 2017, a total of ~175,000 patients had been treated
Carbon beam therapy: By mid 2017, more than 15,000 patients have been treated



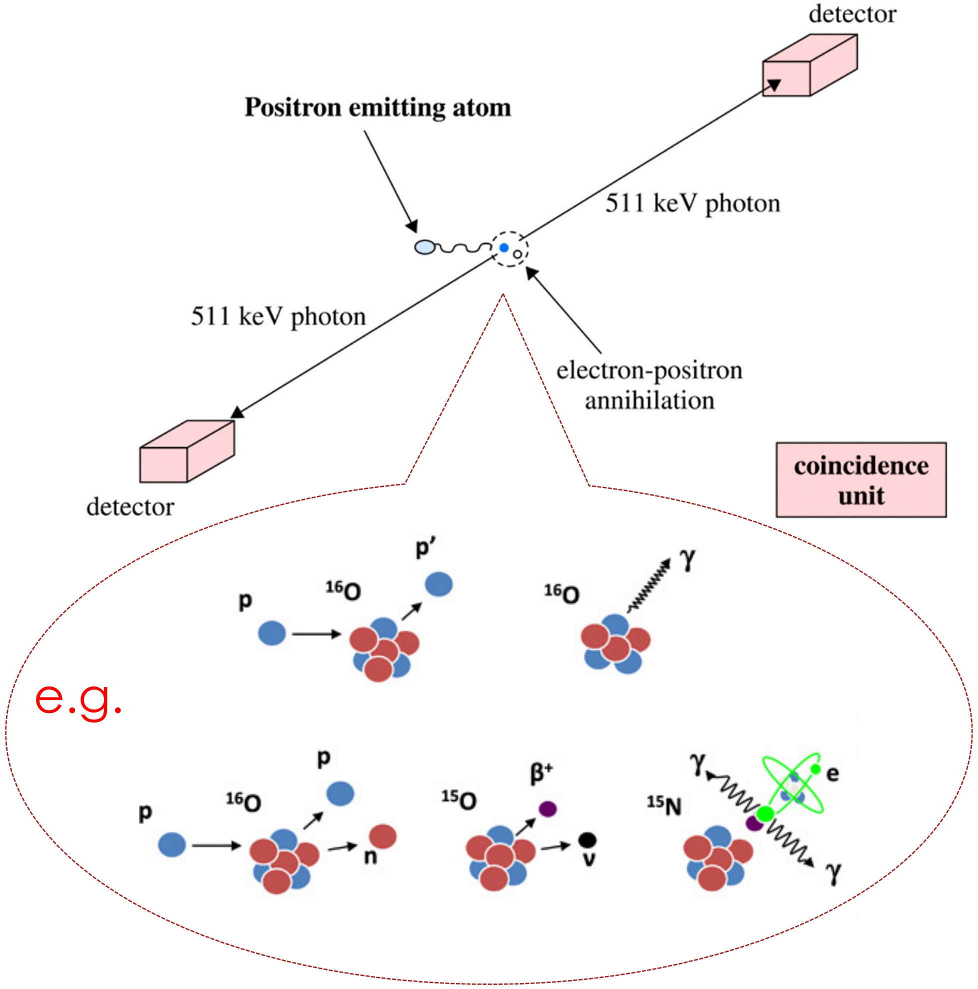
Cancers for which ion radiation is favorable, especially deeply placed tumors that can be treated effectively or those where particular care is necessary for the surrounding tissues

Heidelberg Ion Beam Therapy Center

Durante, Marco et al., *Nature Reviews Clinical Oncology* 14.8 (2017): 483.

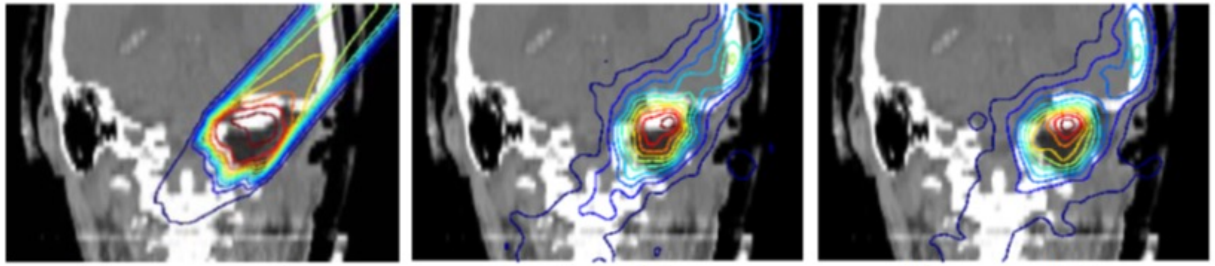
RANGE VERIFICATION

Range verification by positron-emission tomography (PET)



PET isotopes produced by Fragmentation of tissue and therapy ions

Positron emitting nuclide	Half-life	Yield (%)	Percentage of total yield (%)
^{11}C	20min	13.437	71.14
^{10}C	19s	1.681	8.9
^{15}O	121.8s	2.375	12.57
^{14}O	91s	0.359	1.9
^{13}N	10min	0.806	4.27
^{12}N	11ms	0.213	1.13
^{8}B	770ms	0.017	0.09



Treatment plan | Predicted β^+-activity | Measured β^+-activity

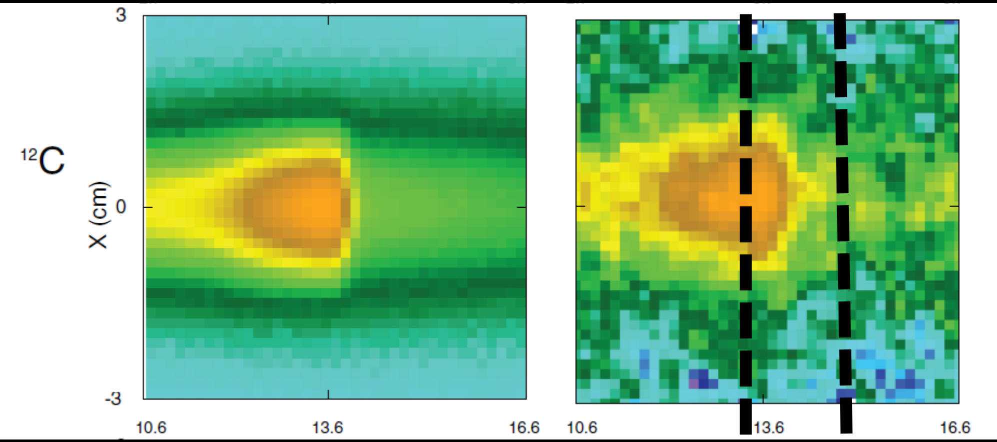
Paganetti, Harald, ed. *Proton therapy physics*. CRC press, 2018

Camici, Paolo G., Heart 83.4 (2000): 475-480.

NEXT GENERATION HEAVY-ION THERAPY: POSITRON EMITTING ION BEAMS

- **3D reconstruction by back projection**
- **Positron emitter distribution neither proportional nor equivalent to the dose distribution**

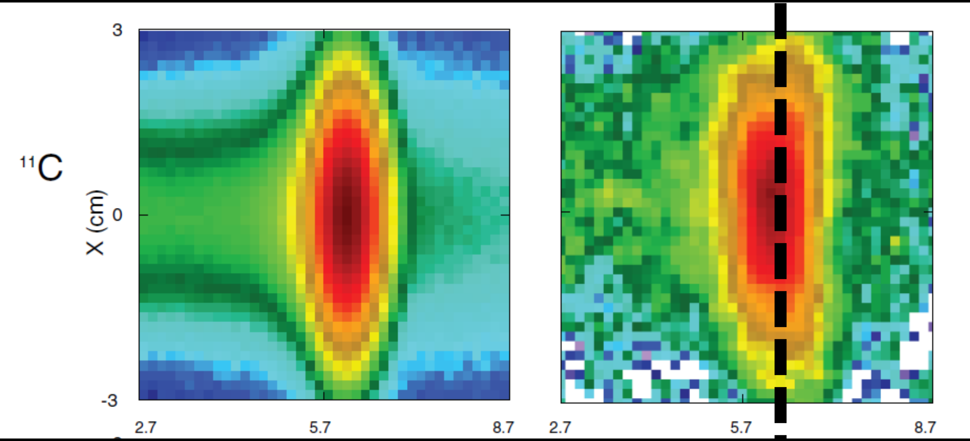
PET peak Bragg peak



Monte Carlo simulation Experiment

Stable ^{12}C ion beam stopped in tissue equivalent material

Matching
PET activity & Bragg peak

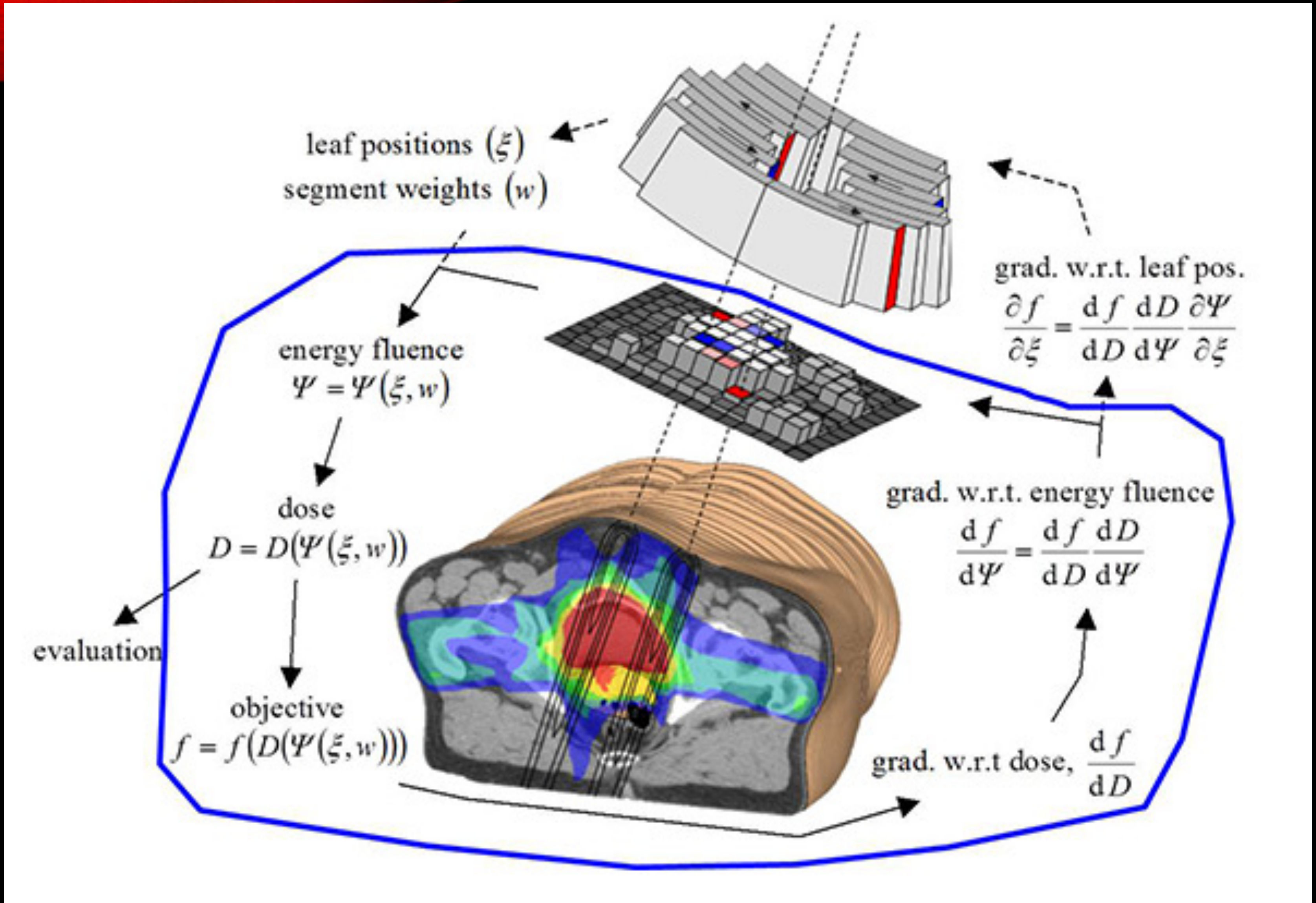


Monte Carlo simulation Experiment

Radioactive positron emitting ^{11}C ion beam stopped in tissue equivalent material

R S Augusto *et al* 2018 *Phys. Med. Biol.* **63**

RADIOTHERAPY OPTIMIZATION PROCESS



Rudbeck Laboratory, at BMC and at Uppsala University Hospital.