Nuclear Physics Mid Term Plan in Italy

LNF – Session

Frascati, December 1st - 2nd 2022

Nuclear Physics
Mid Term Plan in Italy

Treatment monitoring and optimization

Treatment monitoring
- **Beam monitoring (x-y position and intensity)**
- **Range verification (depth)**

Treatment optimization
- **Boron Neutron Capture Therapy (also monitoring)**
- **Target Nuclear fragmentation**

Piergiorgio Cerello

INFN, Sezione di Torino, Torino, Italy

INFN
Istituto Nazionale di Fisica Nucleare

Nuclear Physics Mid Term Plan in Italy

LNF – Session

Frascati, December 1st - 2nd 2022

Nuclear Physics Mid Term Plan in Italy

Treatment monitoring and optimization

Treatment monitoring

- Beam monitoring (x-y position and intensity)

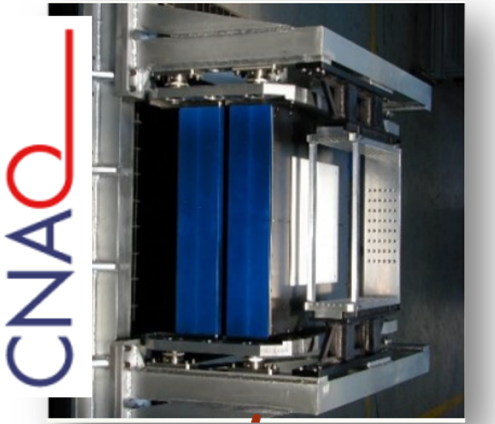
Piergiorgio Cerello

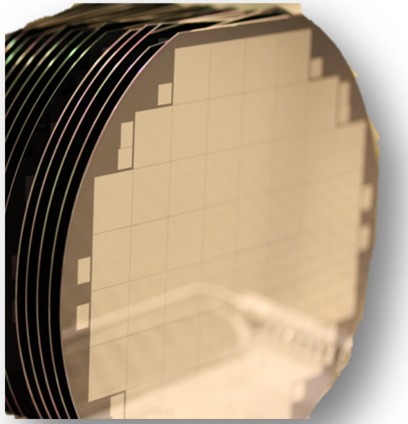
INFN, Sezione di Torino, Torino, Italy

Istituto Nazionale di Fisica Nucleare

Beam monitoring in particle therapy

IONIZATION CHAMBERS		SOLID STATE DETECTORS





Collection times ~ 100 μs	→	~ ns
Sensitivity ~ 10^4 protons	→	single protons
Time resolution ~ no/poor	→	< 100 ps
Not suitable for fast scanning modalities and timing applications	→	proton counting timing applications

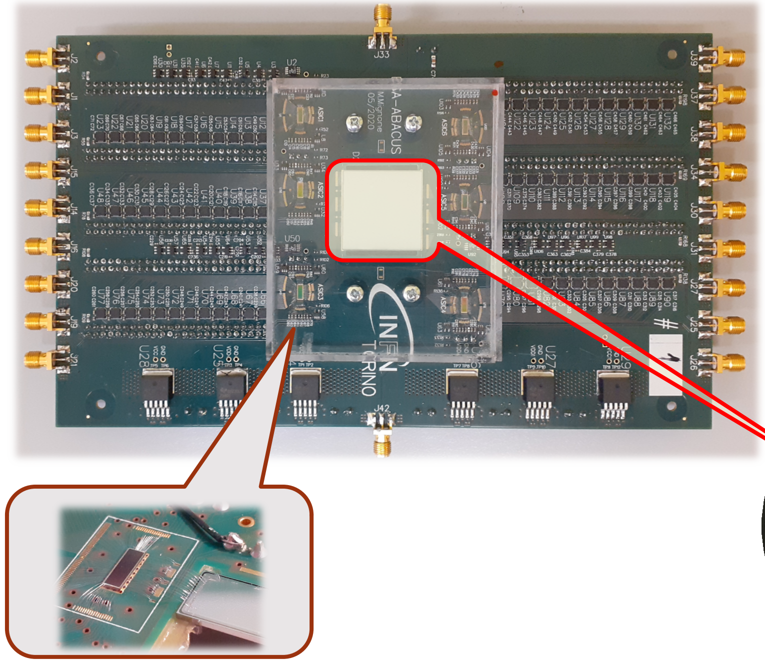
Main issues at $\phi = 10^{10}$ p/cm^{2}s

- **Signal pile-up**
  → fast sensors & readout
  → segmentation
- **Radiation tolerance**
  → manufacturing strategies
  → damage compensation

Courtesy of Roberto Sacchi

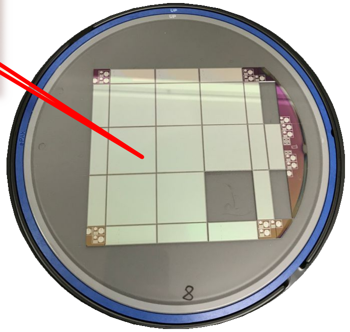
Beam monitoring in particle therapy

2.7×2.7 cm^2 active area (144 strips)



ABACUS ASIC (24 ch)

MOVEIT sensors



R&D on Frontend readout and DAQ system

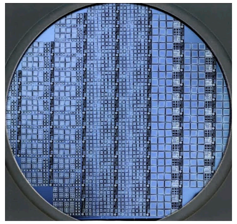
- 6 ABACUS front-end ASICs, 3 FPGA boards
- Counting rate up to 100 MHz with < 2% pileup inefficiency
- For larger rates, inefficiency measurement implemented in FPGA

R&D on new silicon detectors

- LGAD for proton beams
- thin planar silicon sensors for C ions

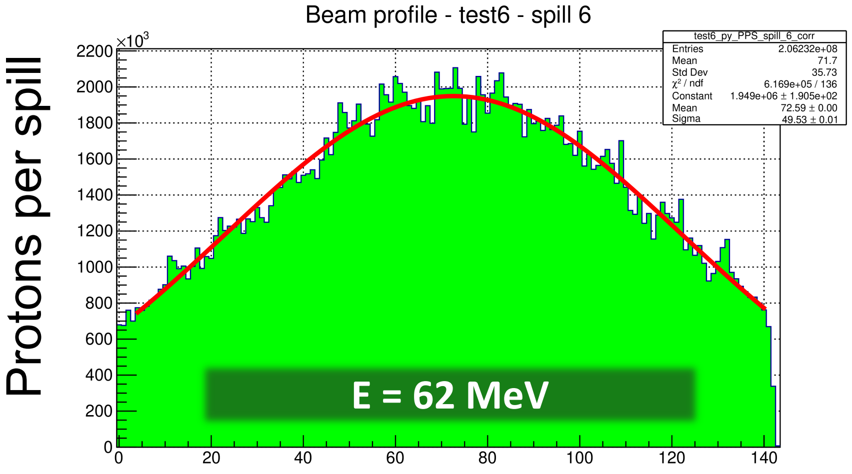
Superconducting Ion Gantry

Collaboration with INFN-EXFLU project

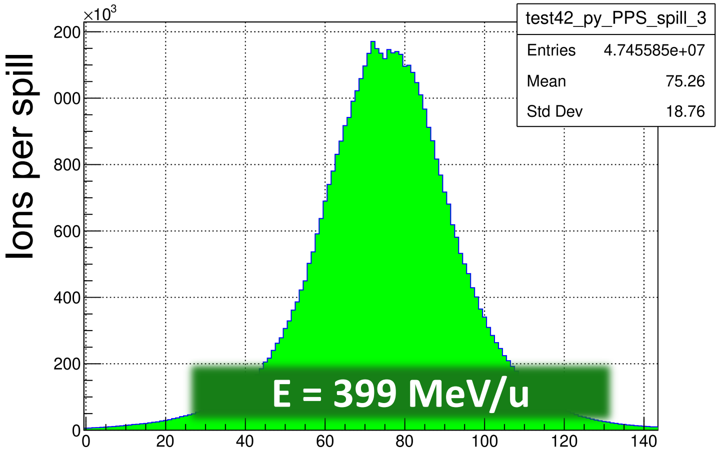


Courtesy of Roberto Sacchi

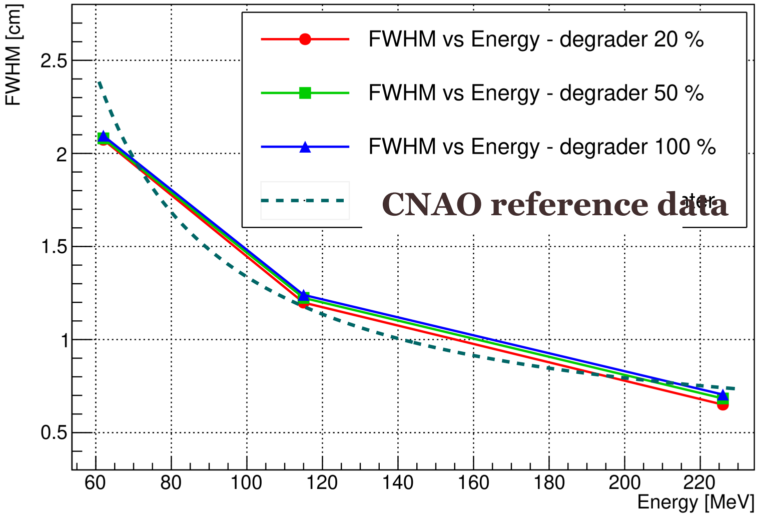
Beam profiles measured at CNAO

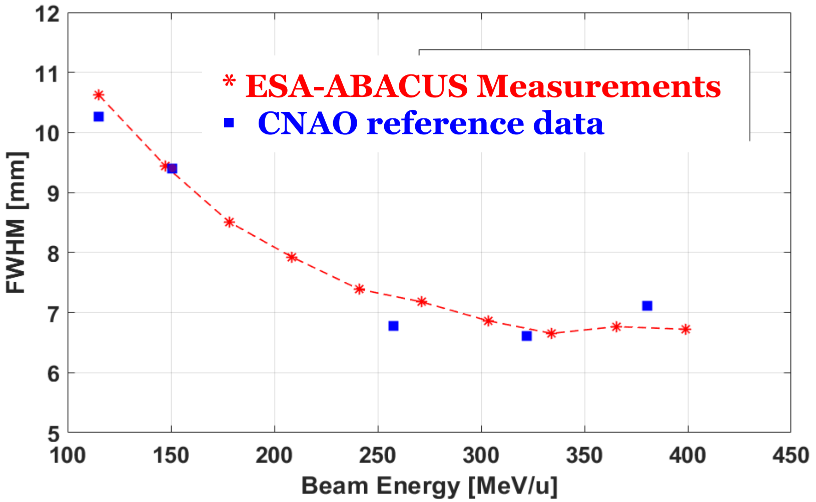


PROTONS



CARBON IONS





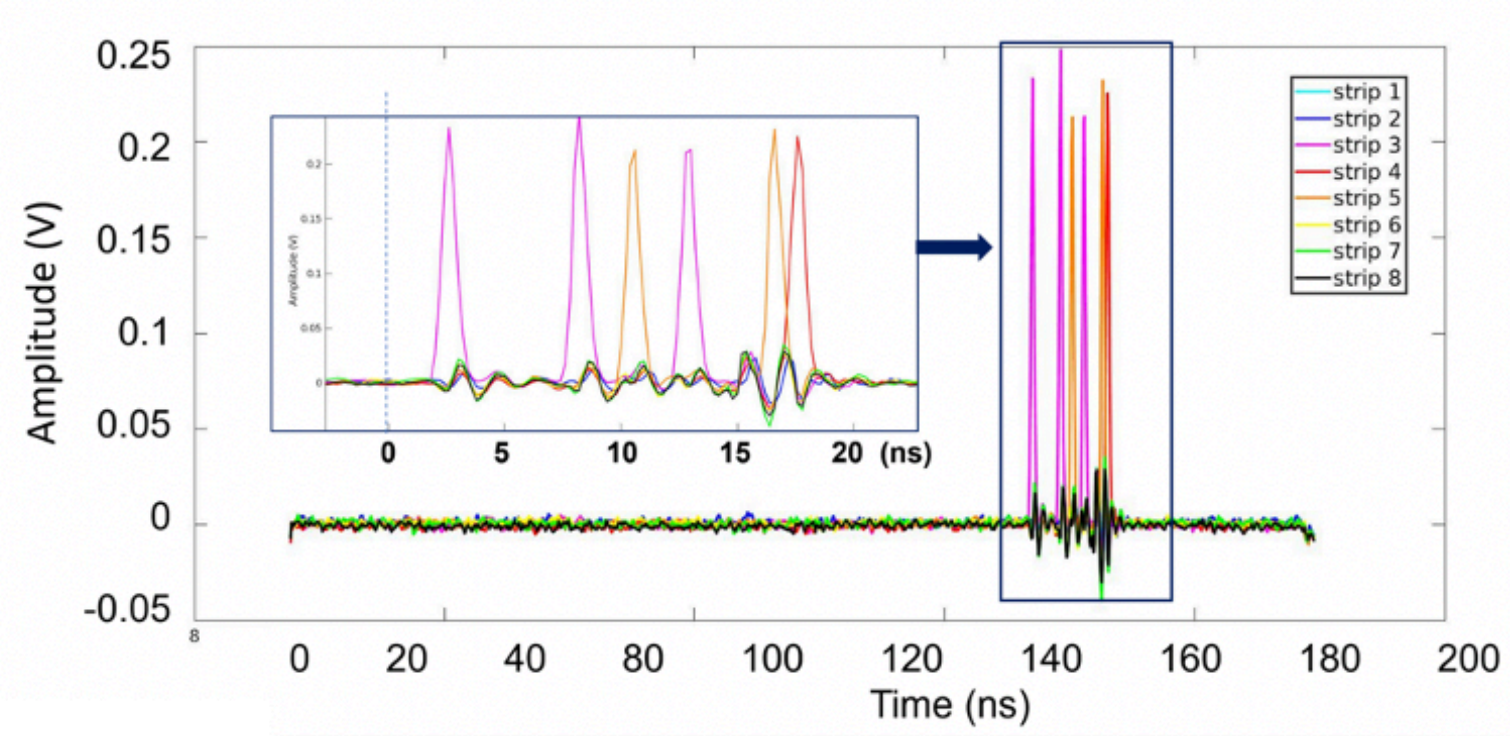
Superconducting Ion Gantry

Courtesy of Roberto Sacchi

Beam Time profile

Carbon ions, 399 MeV/u

30 ns

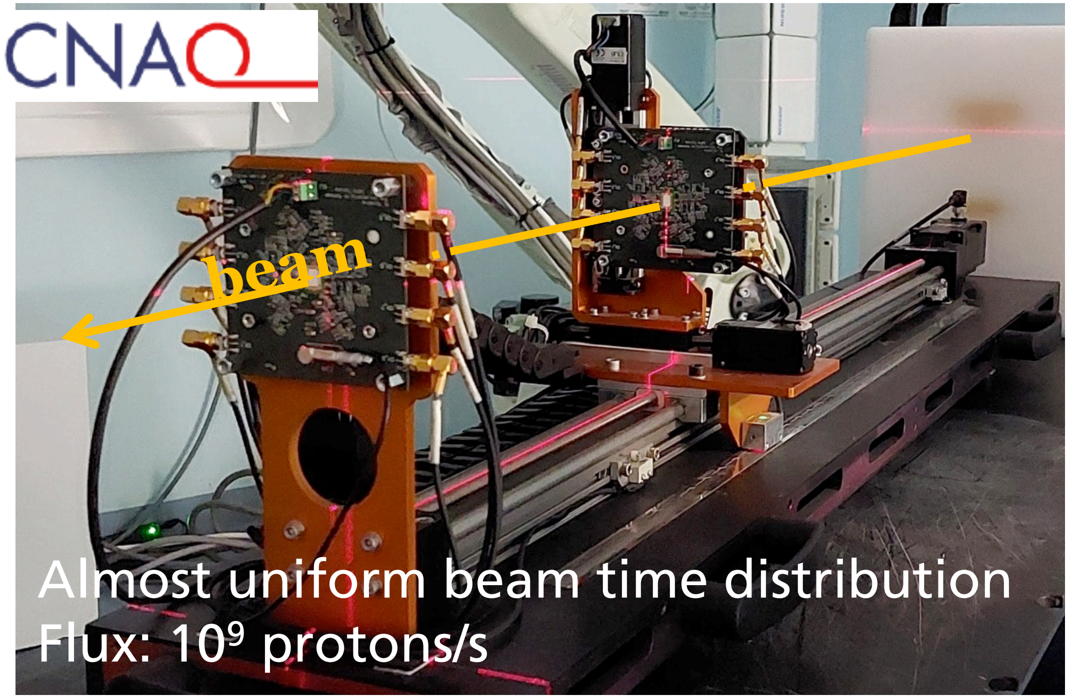


Single proton identification and timing

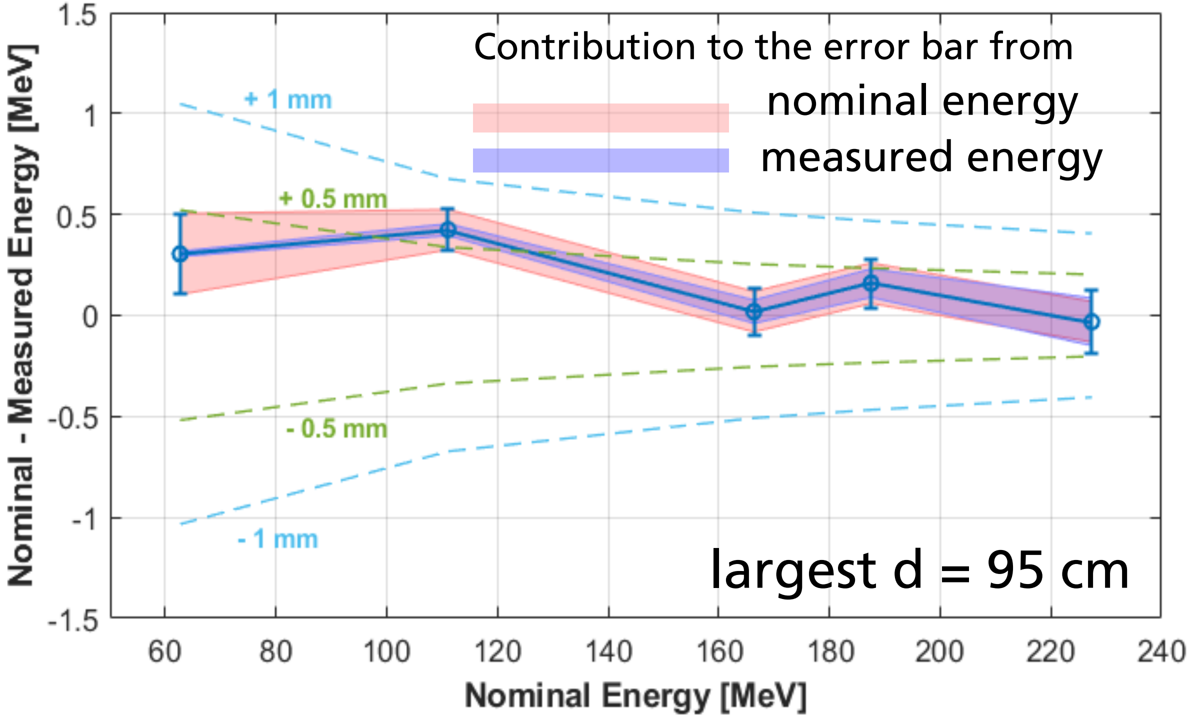
Superconducting Ion Gantry

Courtesy of Roberto Sacchi

Beam Energy profile



Single hit time resolution: ~40 ps < σ < ~75 ps



ToF statistical uncertainty < 1 ps can be achieved with 50k coincidences
→ ~ 1 ms active acquisition
→ ~ 3 s detector irradiation

Superconducting Ion Gantry

Courtesy of Roberto Sacchi

Nuclear Physics Mid Term Plan in Italy

LNF – Session

Frascati, December 1^{st} - 2^{nd} 2022

Treatment monitoring and optimization

Treatment monitoring

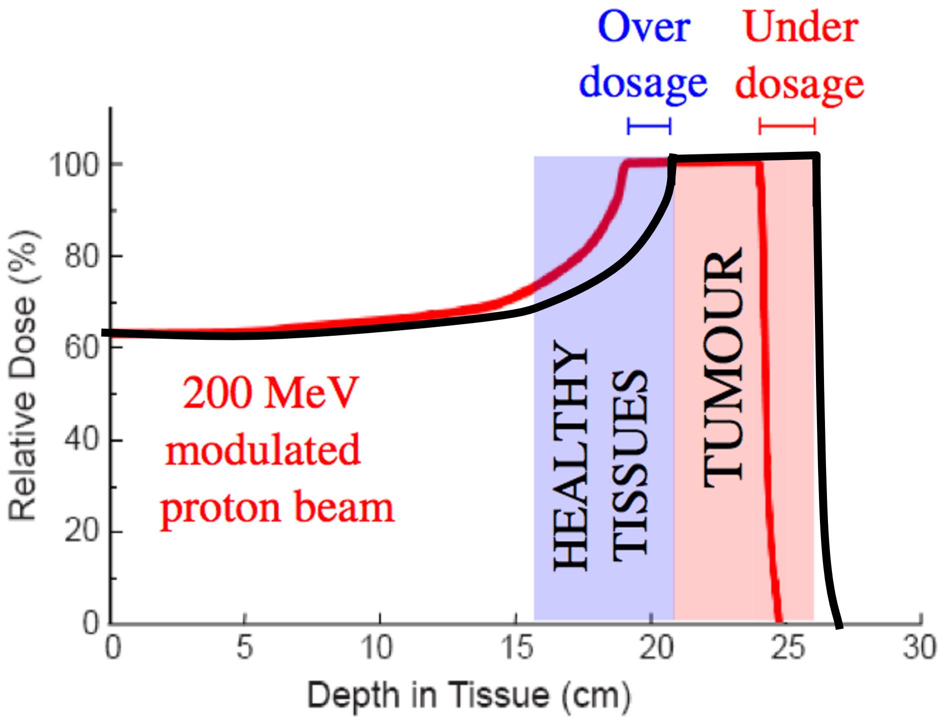
- Range verification (depth)

Piergiorgio Cerello

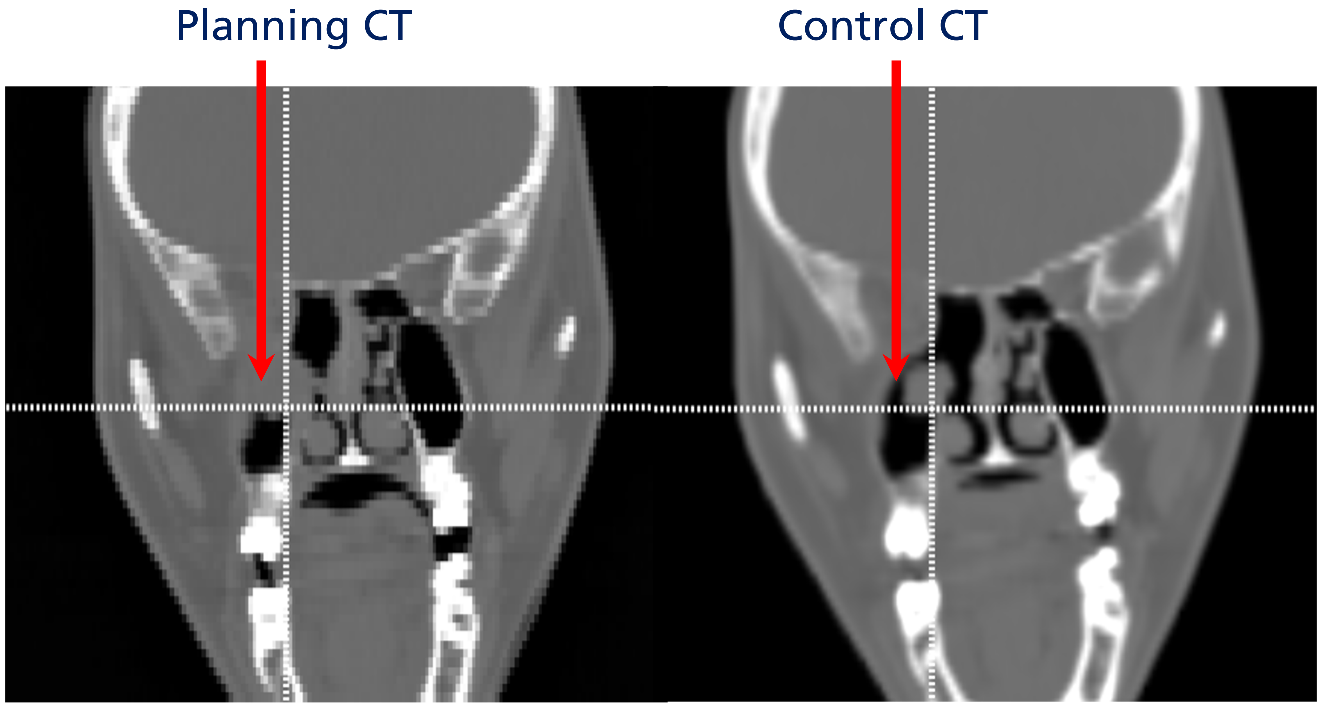
INFN, Sezione di Torino, Torino, Italy

In-vivo range verification in particle therapy

Main clinical motivation: detection of inter-fractional morphological changes

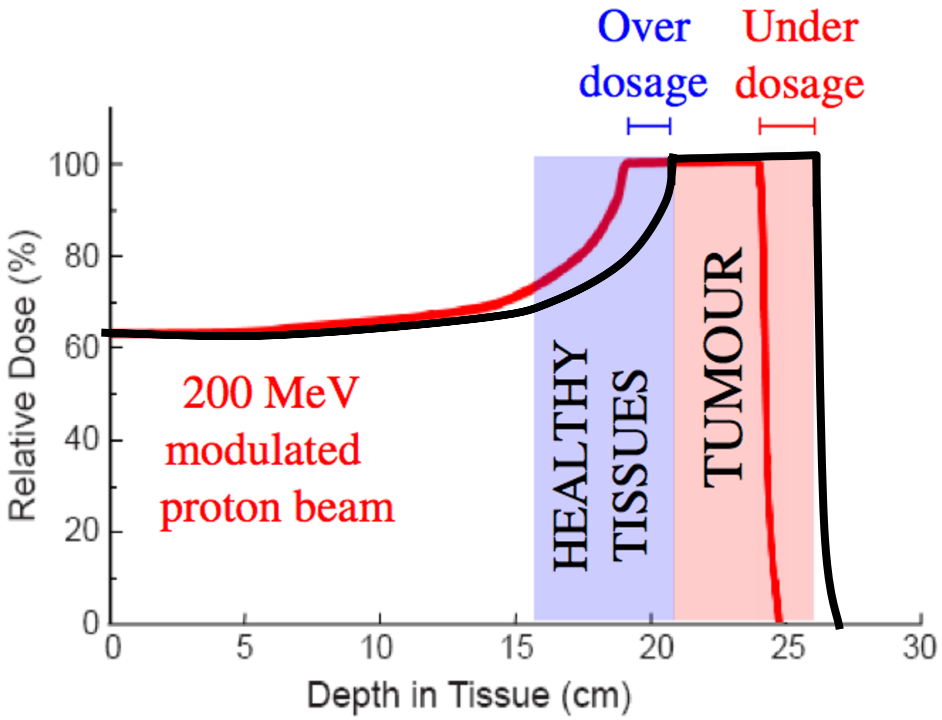


Zhu X, Fakhri GE. *Theranostics. 2013;3(10):731-740.*

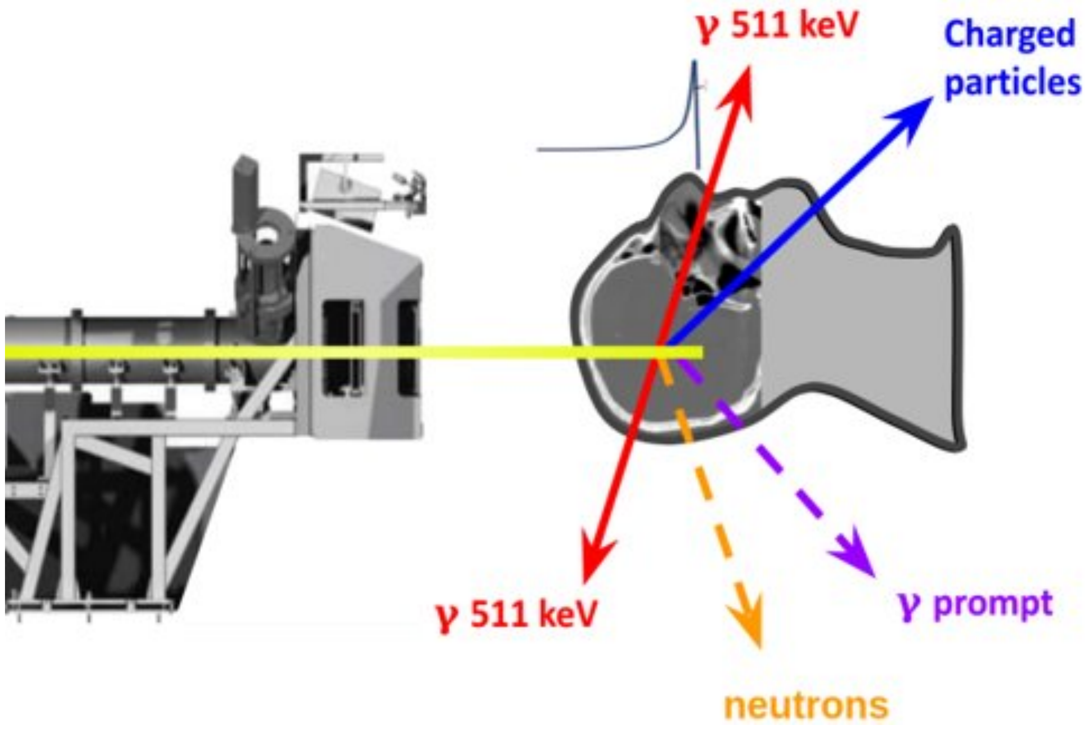


In-vivo range verification in particle therapy

Main clinical motivation:
detection of inter-fractional morphological changes

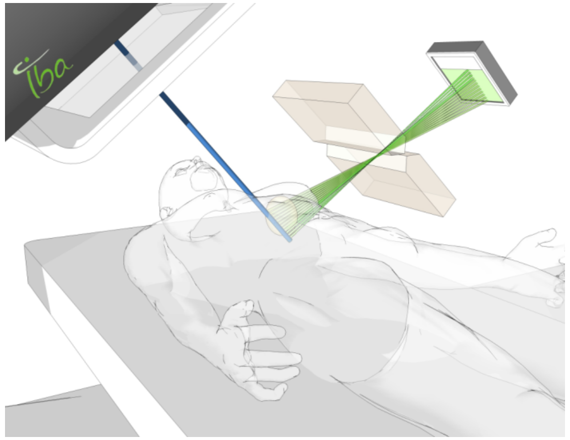


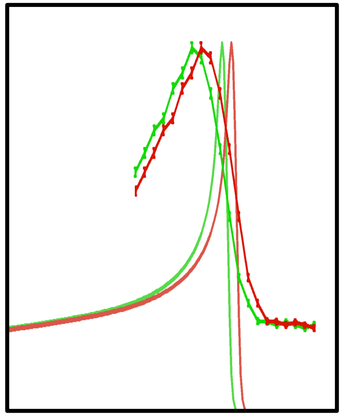
Zhu X, Fakhri GE. *Theranostics. 2013;3(10):731-740.*



passive signals from beam/tissue nuclear interactions

In-vivo range verification: prompt gamma imaging



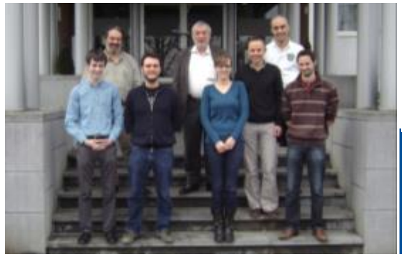


Measurement of the proton beam range in the patient in PBS mode

Camera configuration

Knife-edge slit collimation and 1D detection of gamma-ray profiles

Collimator, software, positioning, project PI



Detector and Electronics

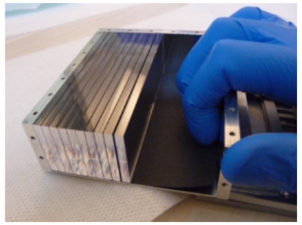
Clinical partner

and others…

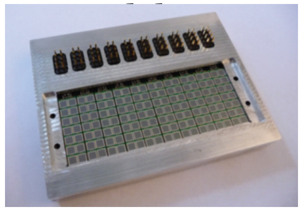
Courtesy of Carlo Fiorini

Clinical trial

In-vivo range verification: prompt gamma imaging



500 cm³ LYSO



SiPMs readout

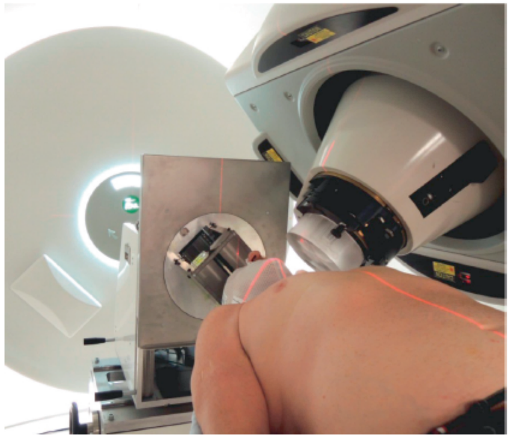
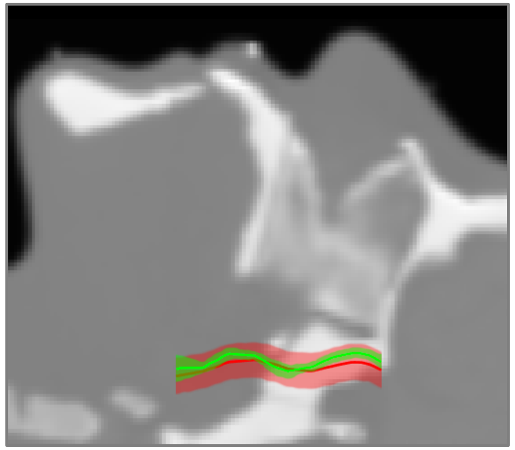
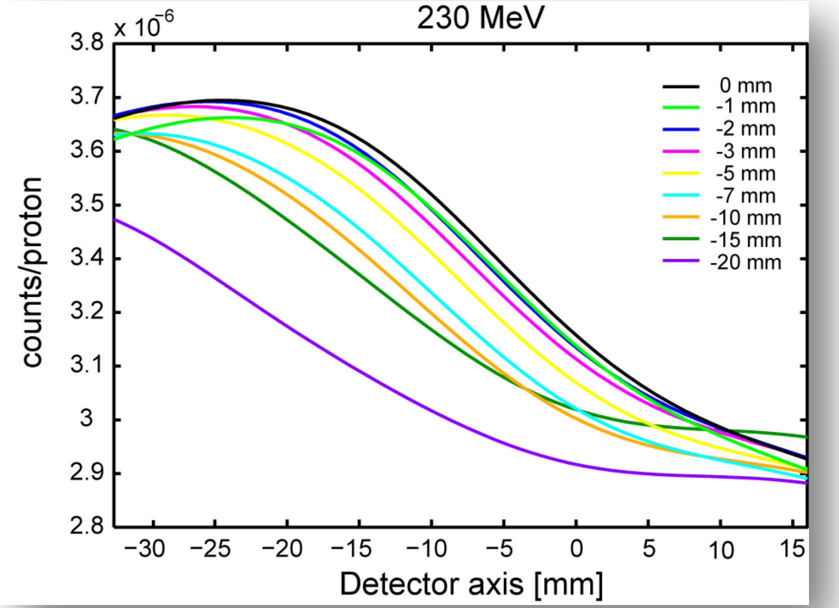


Fig. 1. PGI slit camera trolley (upper row) and its application during patient treatment (lower row).

beam



Planning uncertainty > **5 mm**
(margin of 3.5% + 2 mm)
Measurement uncertainty (1.5σ)
≈ **2.0 mm**



Shift measurements

C.Richter, et al., "First clinical application of a prompt gamma based in vivo proton range verification system", Rad. Onco. 2016;118:232–7.
Y.Xie, et al., "Prompt gamma imaging for in vivo range verification of pencil beam scanning proton therapy", Int J Rad. Oncol Biol Phys 2017;99:210–8.

Courtesy of Carlo Fiorini

The InSide Project

2010 - 2011

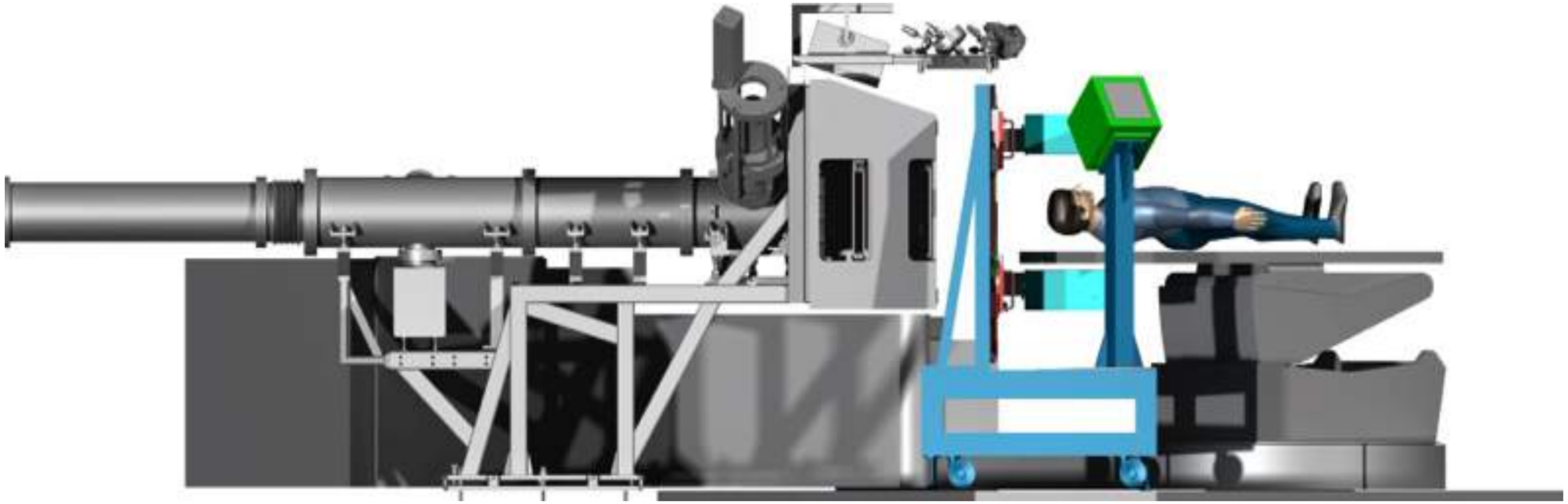
INnovative Solutions for In-beam DosimEtry in particle therapy

In-beam PET

- positron emitters
- proton and carbon in-vivo verification

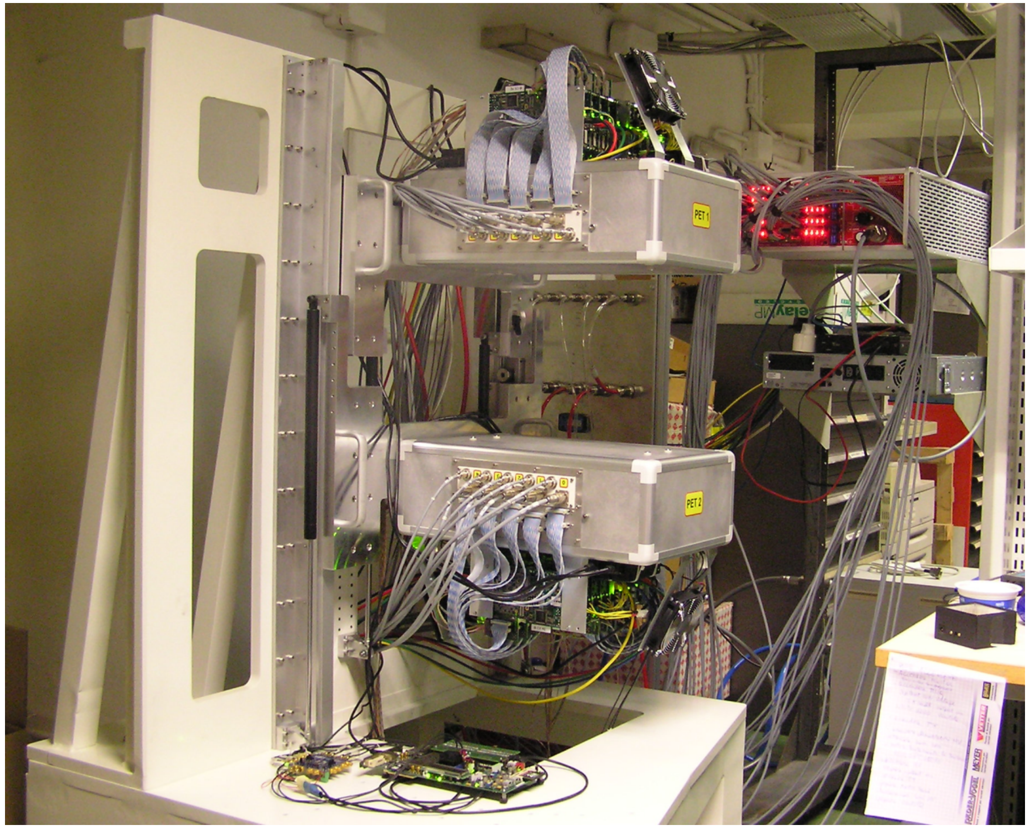
Dose Profiler

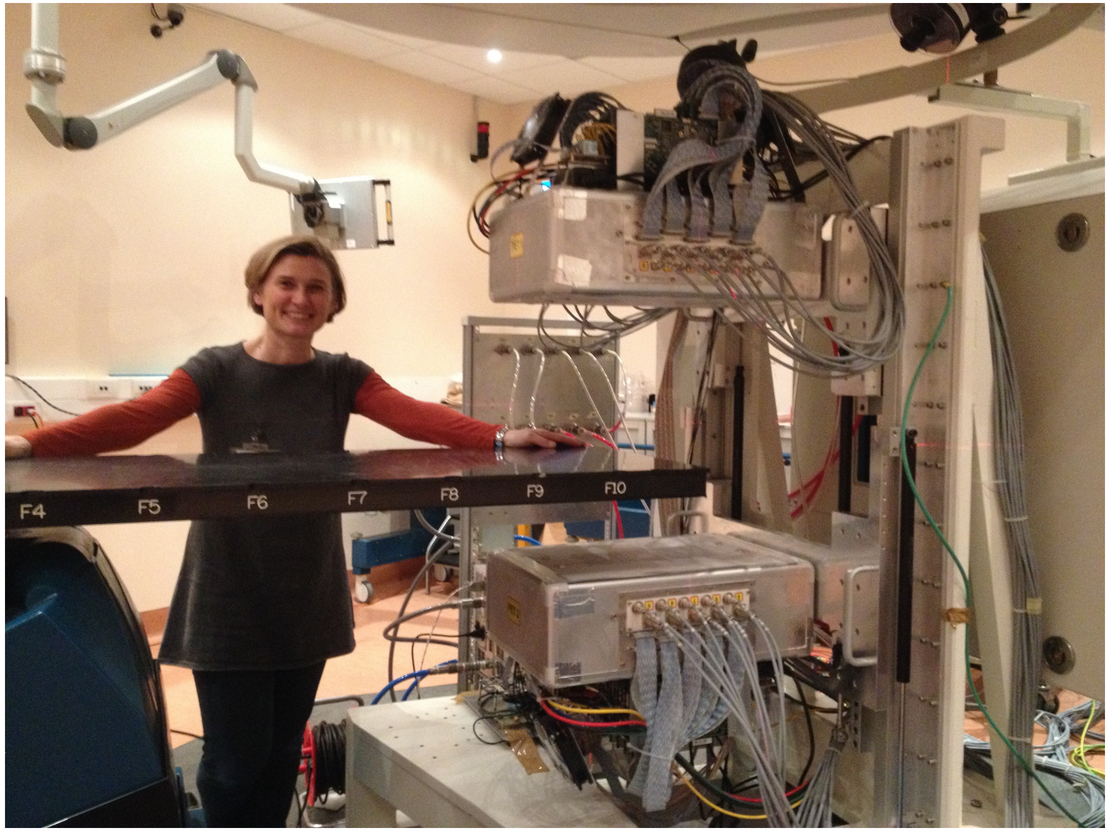
- secondary protons
- carbon ion in-vivo verification



INFN CNAO

InSide



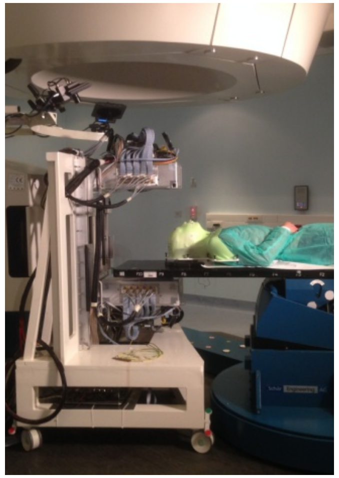


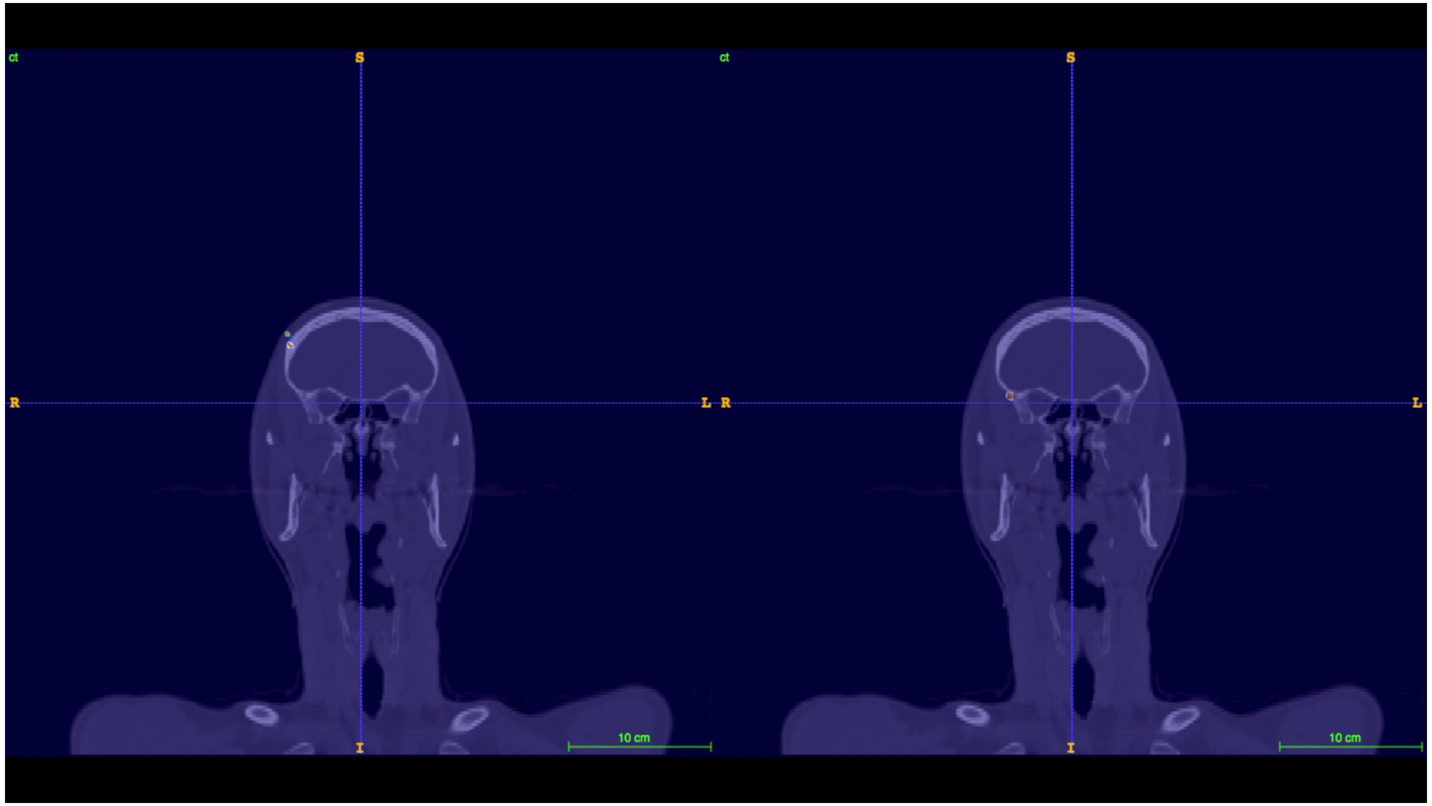
PET built @ INFN–Torino in January 2016

First test @ CNAO on February, 7th, 2016

InSide First clinical test @CNAO, 1-2 Dec. 2016

Dec, 1st Dec, 2nd





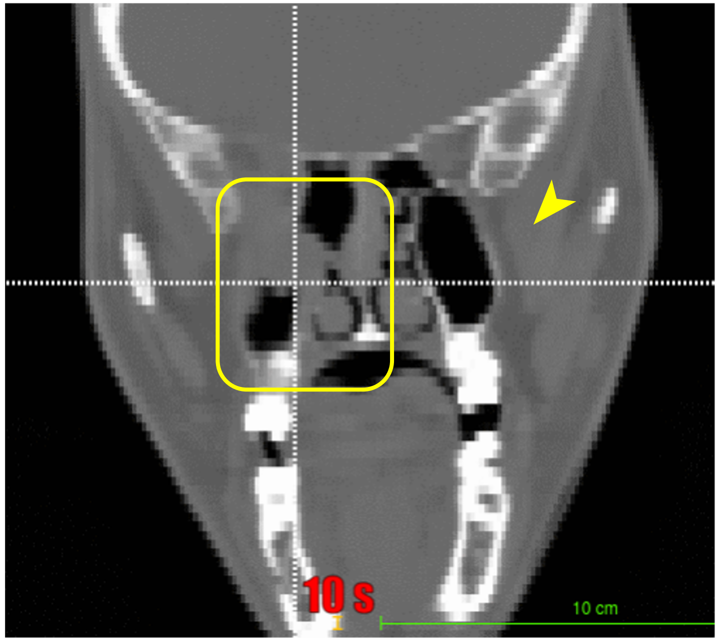
Carcinoma of the lacrimal gland
3.7 10^{10} protons
[66.3, 144.4] MeV/u
(28-29)/30 fractions, 2.2 GyE
Vertex field

V. Ferrero et al., "Online proton therapy monitoring: clinical test of a Silicon photo-detector based in-beam PET", Nature Scientific Reports **8**, Article number: 4100 (2018)

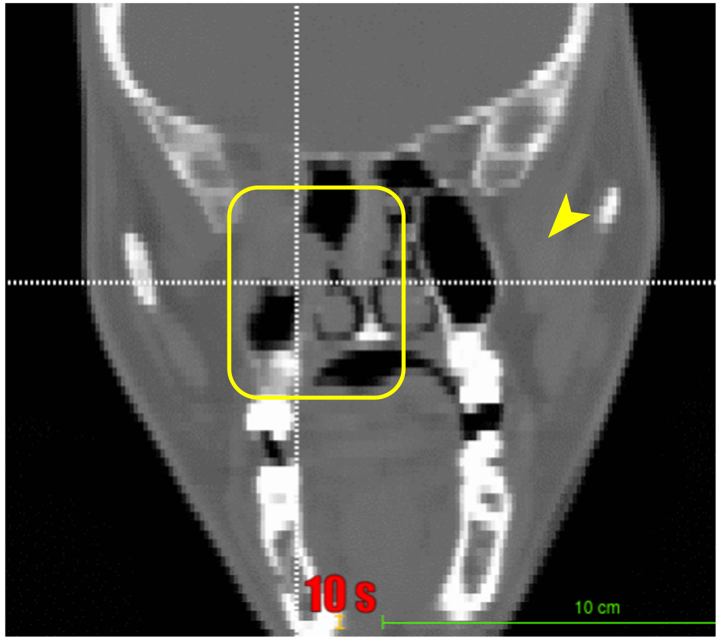
The INSIDE clinical trial

in-beam Positron Emission Tomography

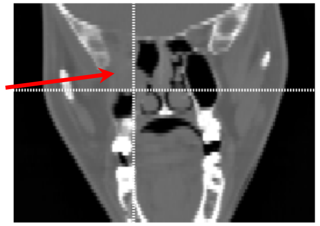
in-beam PET image - 2 fx



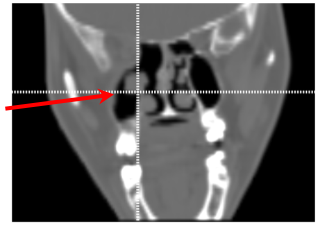
In-beam PET image - 21 fx



Planning CT



Control CT



Courtesy of Elisa Fiorina

ClinicalTrials.gov NCT03662373

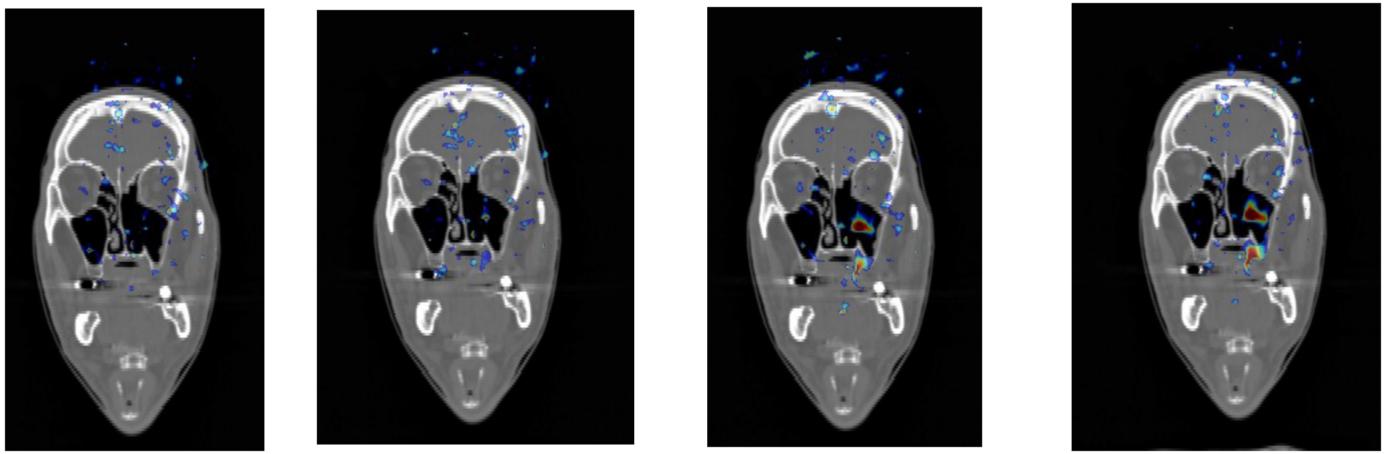
In-beam PET Dose comparison: Gamma analysis

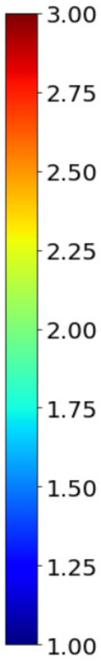
- less sensitive than dose difference to high-dose-gradient regions
- clinically irrelevant features are smoothed out

$$\Gamma(\vec{r_e},\vec{r_r}) = \sqrt{\frac{|\vec{r_e}-\vec{r_r}|^2}{r^2} + \frac{|D_e(\vec{r_e}) - D_r(\vec{r_r})|^2}{D^2}}$$

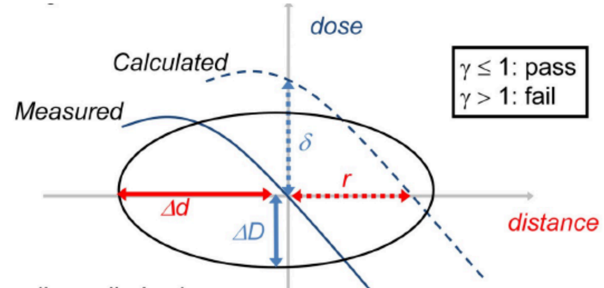
$$\gamma(\vec{r_e}) = min\,\{\Gamma(\vec{r_r},\vec{r_e})\}\ \forall\ \vec{r_r}$$

0 ml vs 0 ml   0 ml vs 3.8 ml   0 ml vs 7.3 ml   0 ml vs 13.1 ml





Gamma index value



Generally applied values are:
ΔD = 3% of dose maximum as dose-difference
Δd = 3 mm as distance-to-agreement (DTA)
T=Threshold, often 10% of max dose

Patient: Squamous Cell Carcinoma (SCC)
proton therapy, cavity emptying, CTV 40ml, 60 Gy

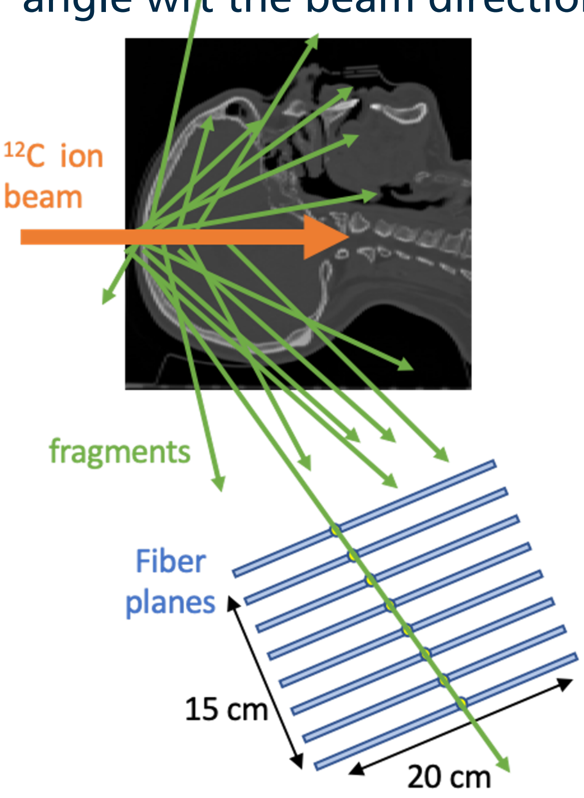
- Treatment and scanner simulated with FLUKA Monte Carlo code
- Image reconstruction with MLEM algorithm

Courtesy of Aafke Kraan

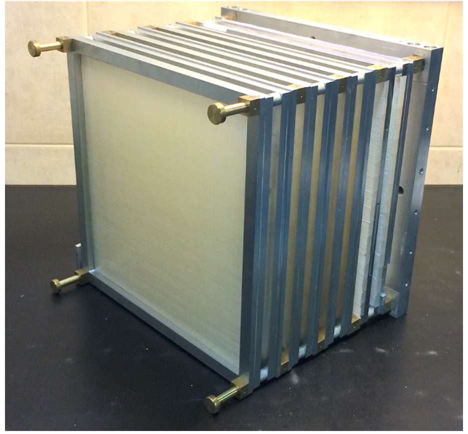
InSide

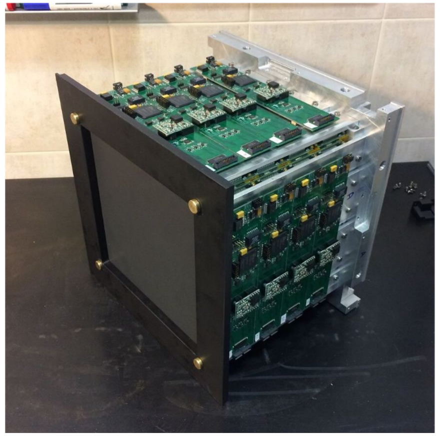
Dose profiler

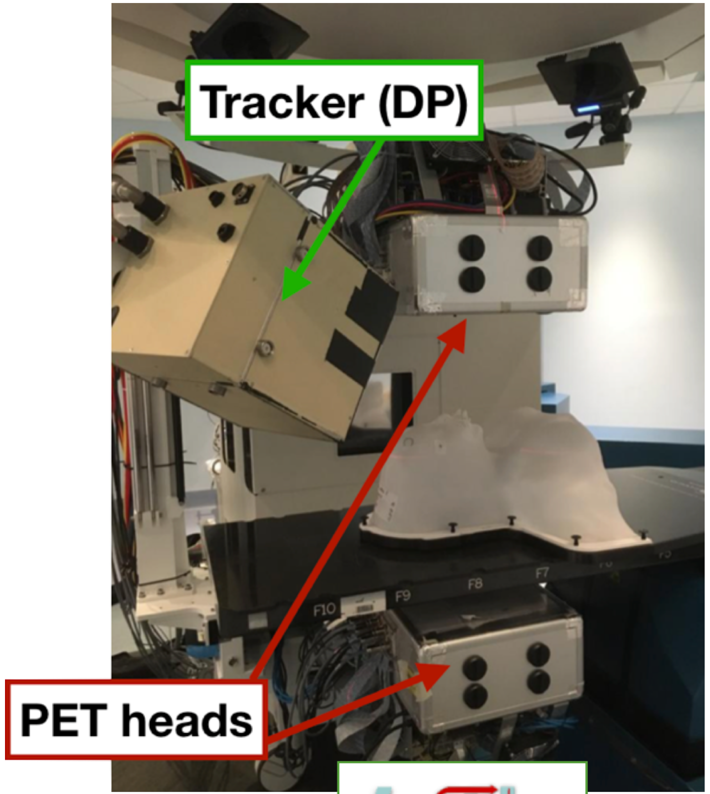
Detection of charged secondary fragments emitted @ large angle wrt the beam direction



8 planes composed of 2 orthogonally oriented layers of plastic scintillating fibres
SiPM read-out



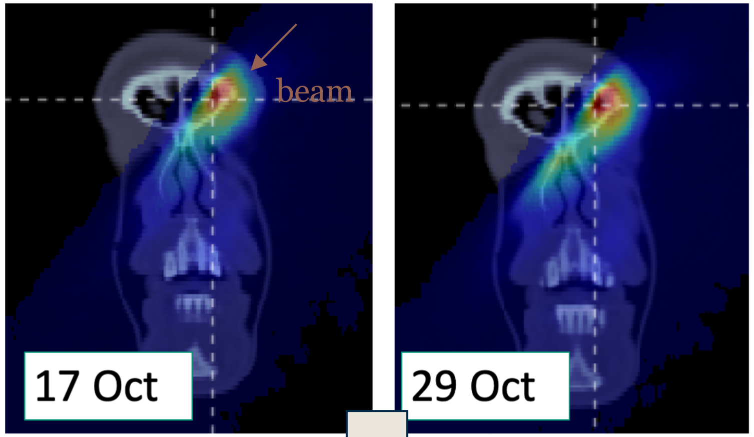




Courtesy of Alessio Sarti

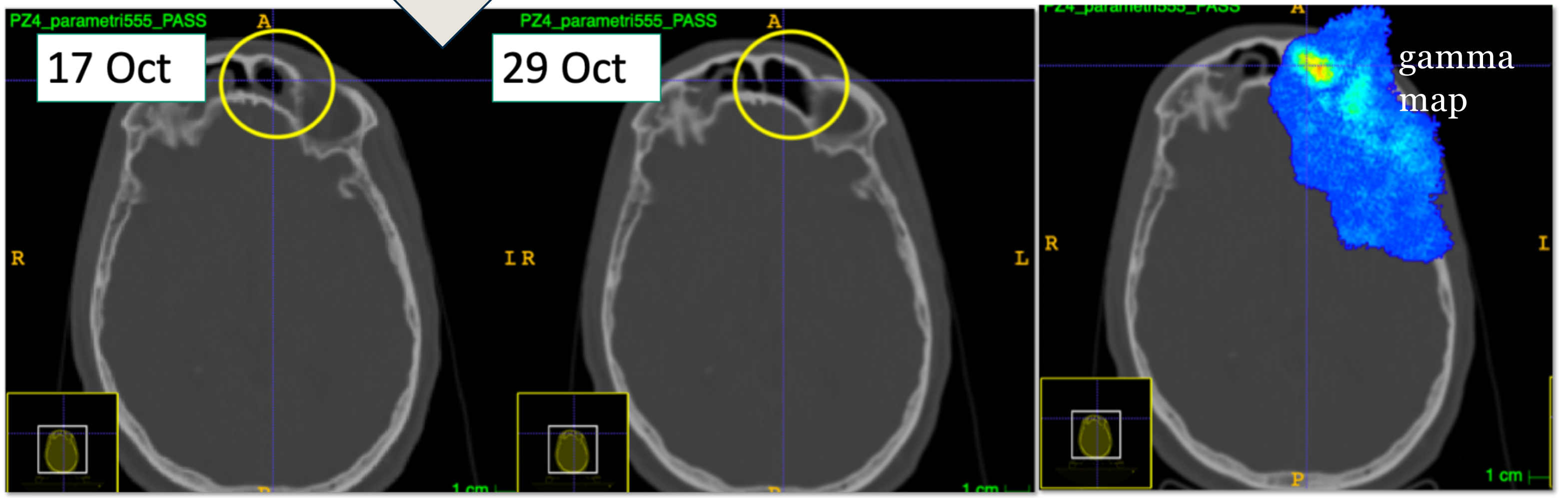
The INSIDE clinical trial

Dose profiler



- 3D emission map of fragments collected during the treatment delivery

- **Gamma test (9mm/10%)** has been used for voxel to voxel comparison



Courtesy of Alessio Sarti

ClinicalTrials.gov NCT03662373

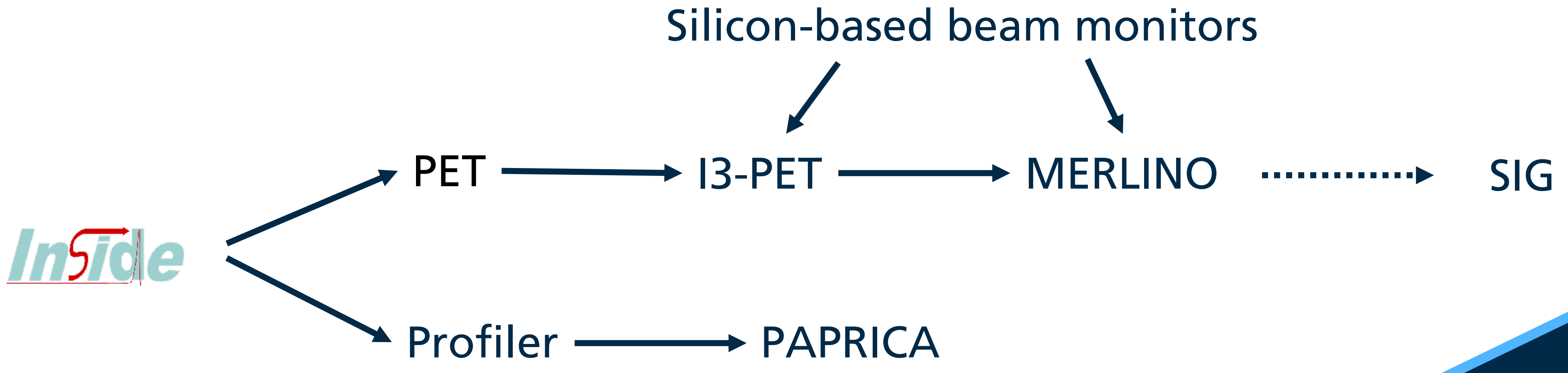
InSide is unique, but it still has limitations

Incomplete PET ring

- Bad resolution on the vertical coordinate
- Sub-optimal statistics

Dose profiler not suitable for proton treatments

- no charged fragments

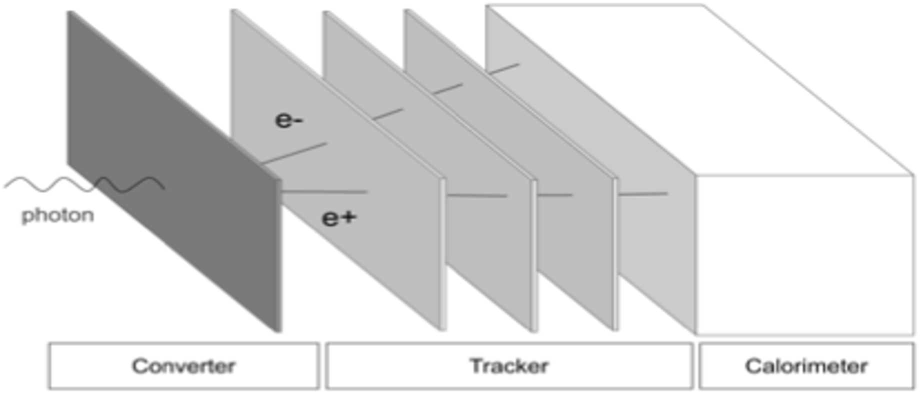


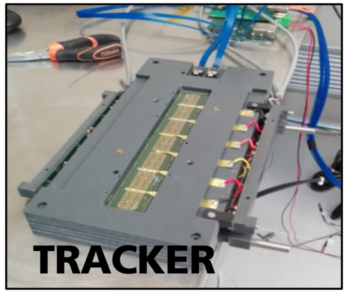
The PAPRICA project

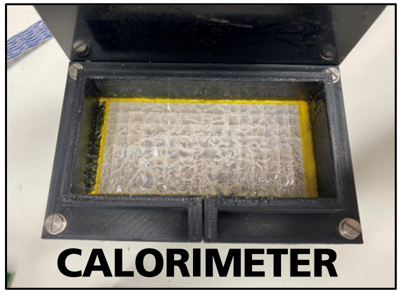
in-vivo monitoring of inter-fraction morphological variations
with prompt photons (E > 4MeV) detection through the pair production mechanism

Prototype design (~ 5x20 cm^2 total surface)

Converter: LYSO fibres, 1.5x1.5x50 mm^3 each
Tracker: 3 planes of **ALPIDE pixels** (27x29x100 μm^3)
Calorimeter: **EJ-200** plastic scintillator rods, 6x6x50 mm^3 each

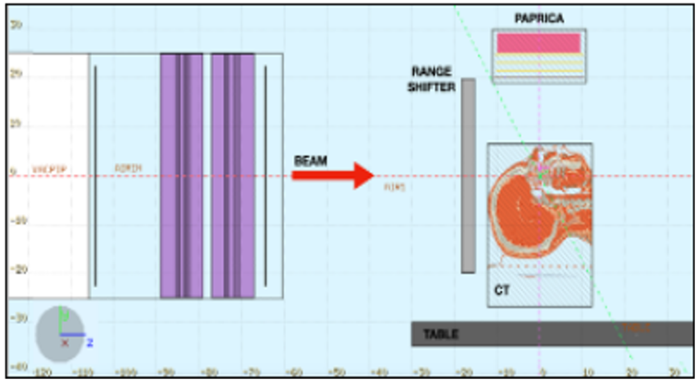


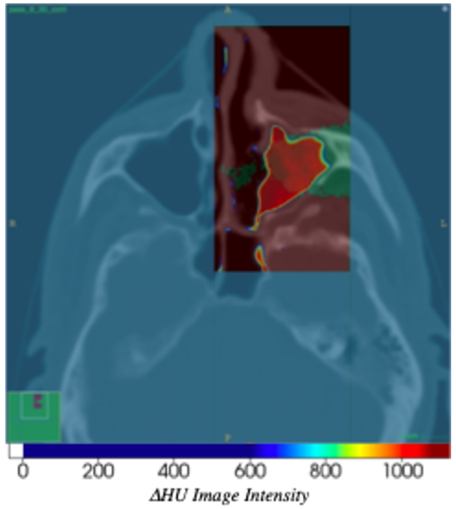




Courtesy of Ilaria Mattei

Expected performance from FLUKA Monte Carlo simulation, on patients from the INSIDE clinical trial

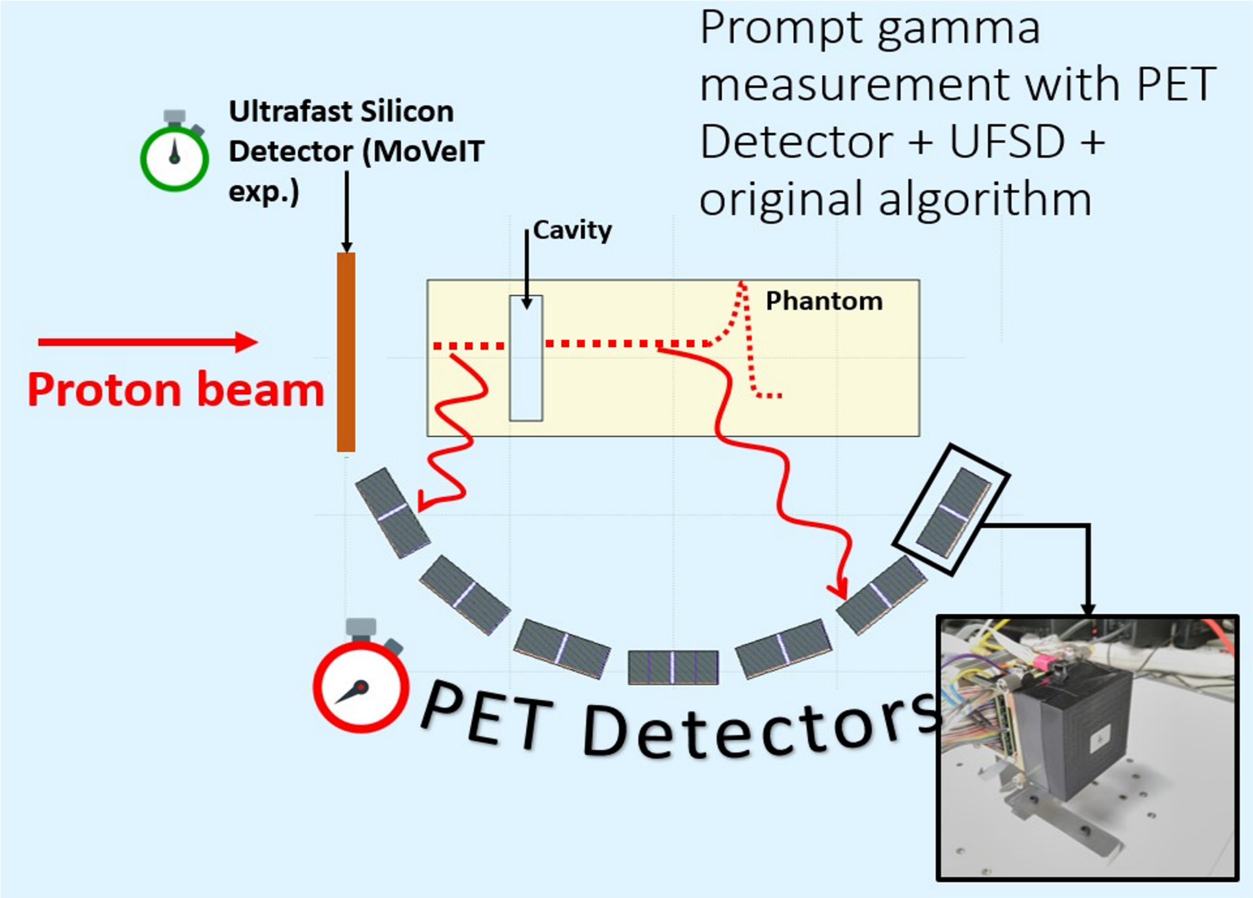




PAPRICA spots morphological variations
- in 2/2 replanned patients
- in 0/4 not replanned patients

Innovative In-beam Imaging: the I3PET project

monitoring of Positron Emitters & Prompt Photons with the same PET detector



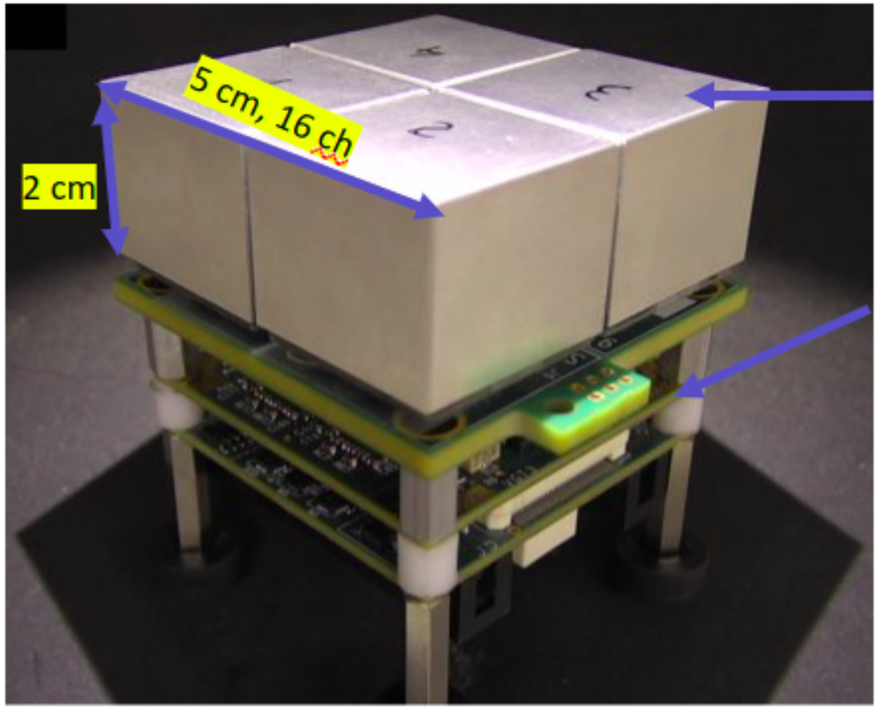
Prompt Gamma Timing (PGT)

Integration and synchronization of the beam monitoring system with range verification detectors

Courtesy of Francesco Pennazio

Innovative In-beam Imaging: the I3PET project

monitoring of Positron Emitters & Prompt Photons with the same PET detector

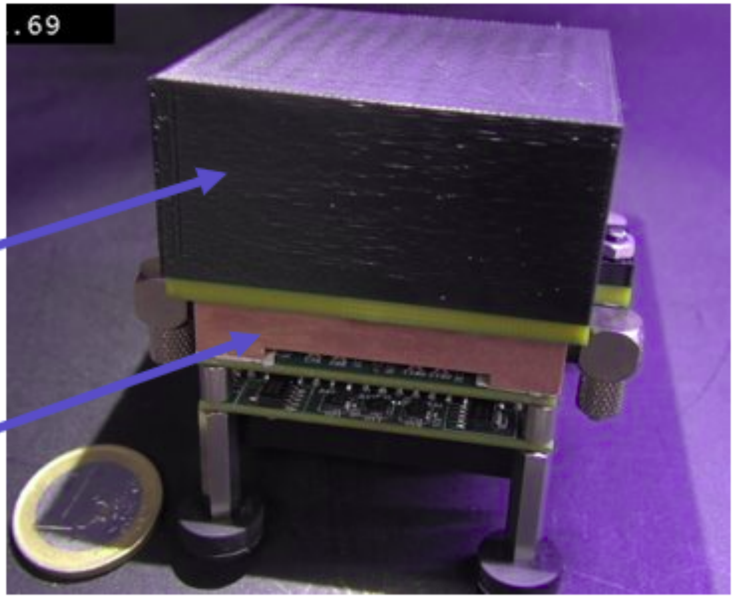


4x Hamamatsu 64 channels commercial PET modules

TETRATOFPET2 board

3D printed cover

Copper dissipator for water cooling



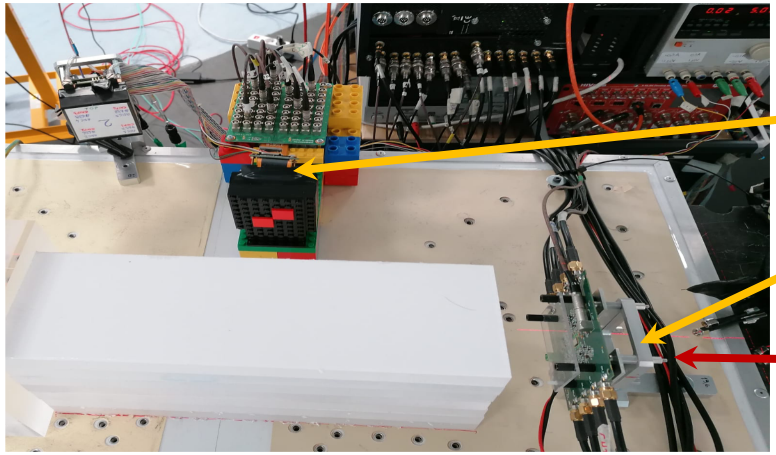
Courtesy of Francesco Pennazio

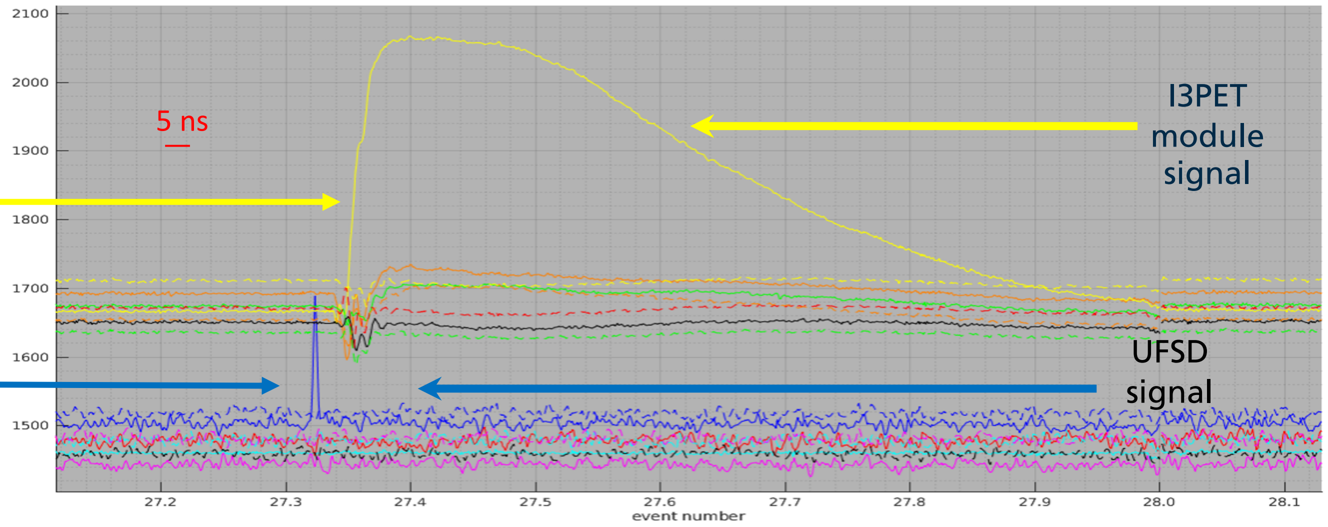
Innovative In-beam Imaging: the I3PET project

monitoring of Positron Emitters & Prompt Photons with the same PET detector

First I3PET proton beam test (June 2021):
primary-secondary radiation coincidences identified!!!

- Trigger on PET detector
- Joint DAQ

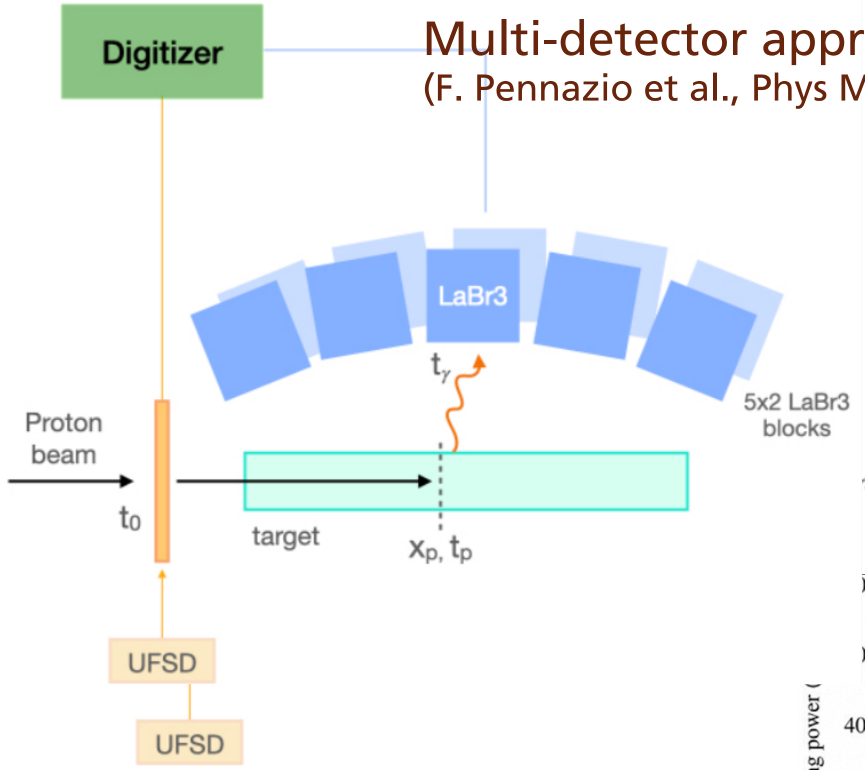


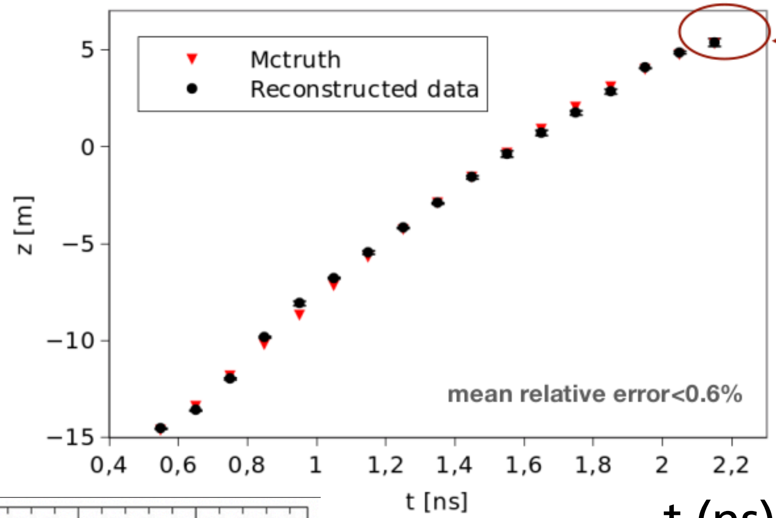


Courtesy of Francesco Pennazio

MERLINO: From PGT to stopping power!

Measurement of the EneRgy Loss for IN-vivo Optimization in particle therapy
Multi-detector approach relying on the SER-PGT reconstruction algorithm
(F. Pennazio et al., Phys Med Biol 2022)





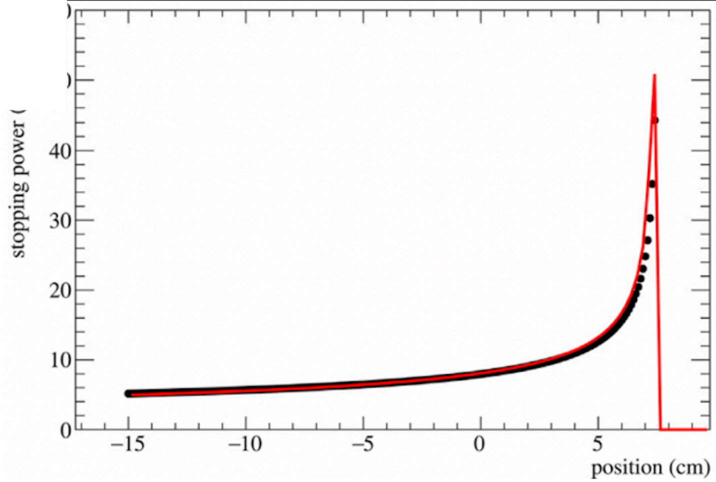
particle range

t (ns)

... but we have the whole (z,t) distribution: proton motion study

↓

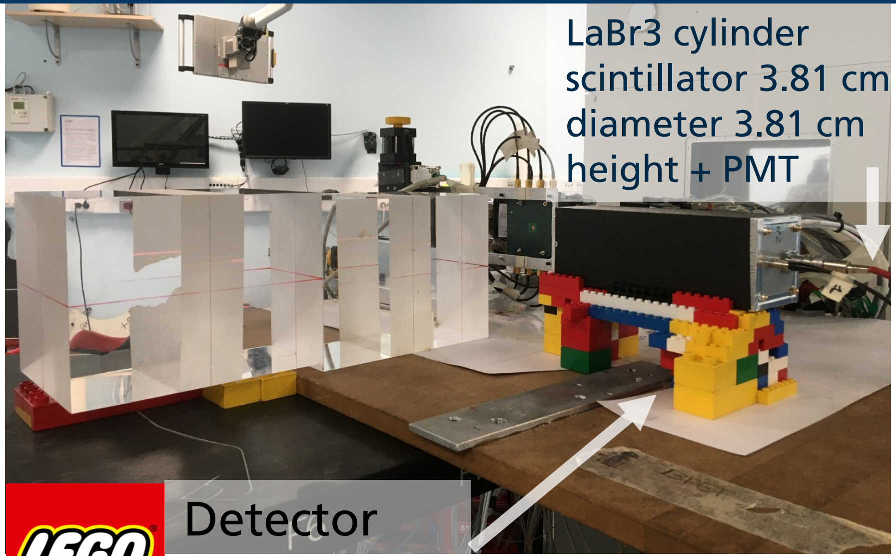
stopping power evaluation

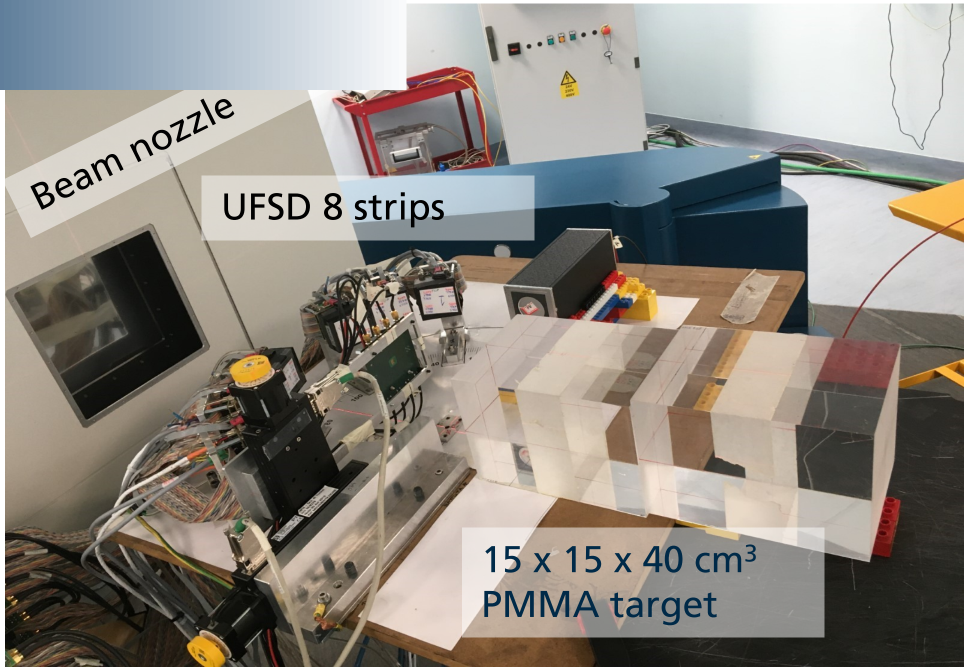


The Bragg curve (in-vivo!!!)

Courtesy of Veronica Ferrero

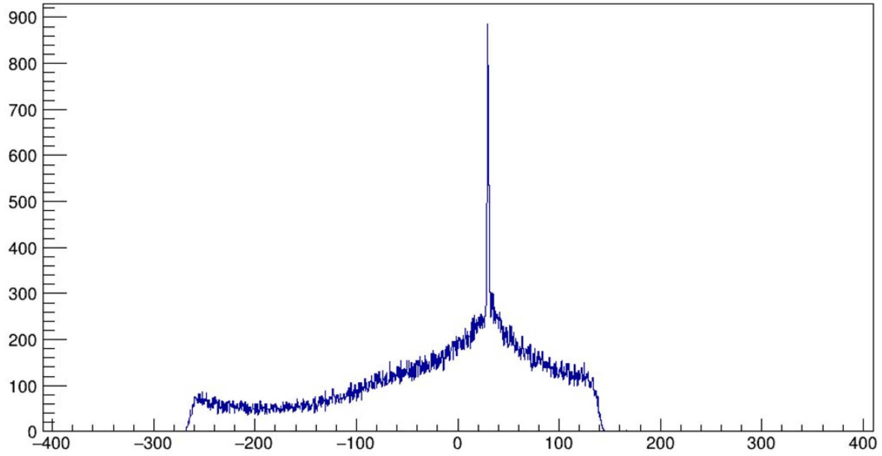
MERLINO: From PGT to stopping power!





227 MeV protons on PMMA
Beam average rate 10^7 pps

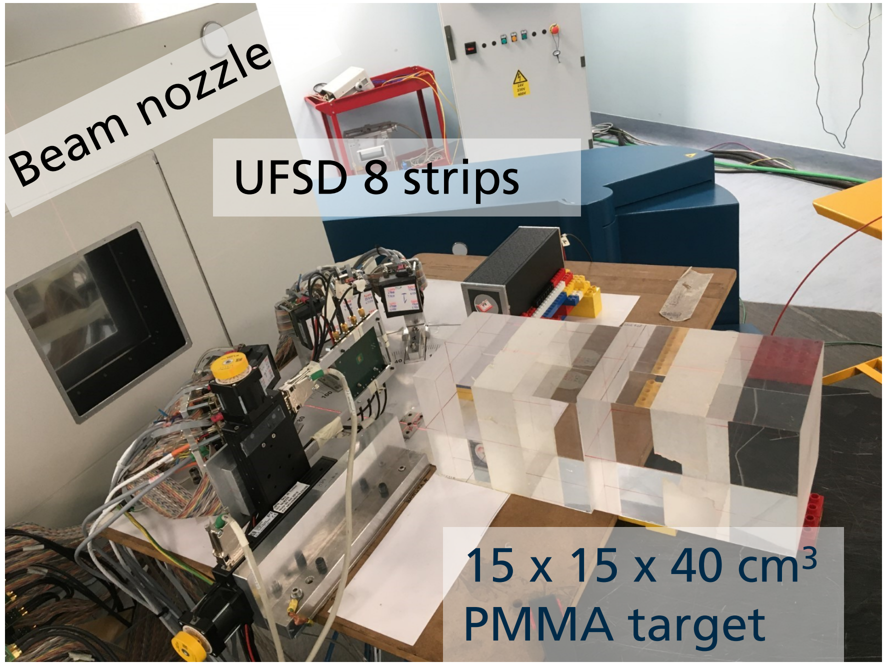
LaBr3 – UFSD time coincidences

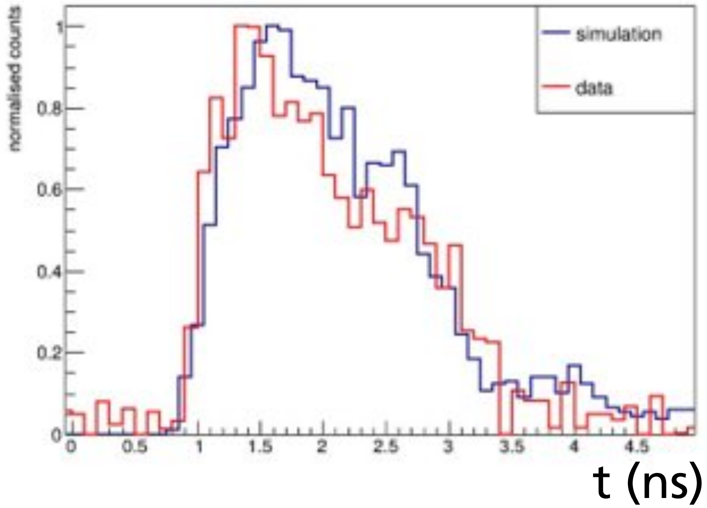


t (ns)

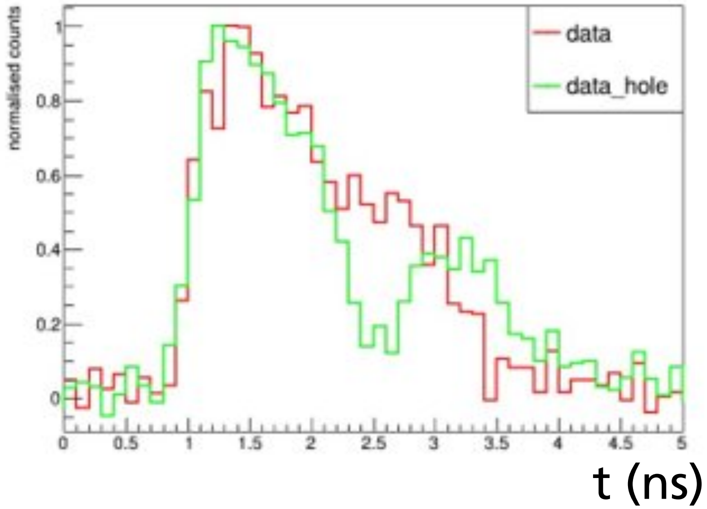
Courtesy of Veronica Ferrero

MERLINO: From PGT to stopping power!





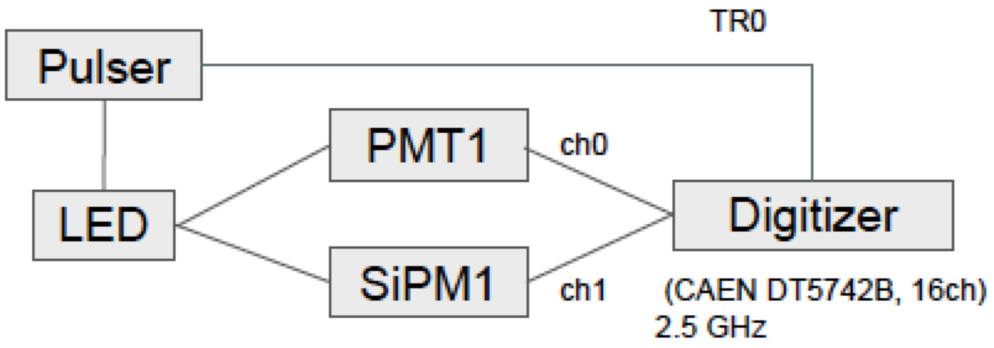
Data vs. simulation

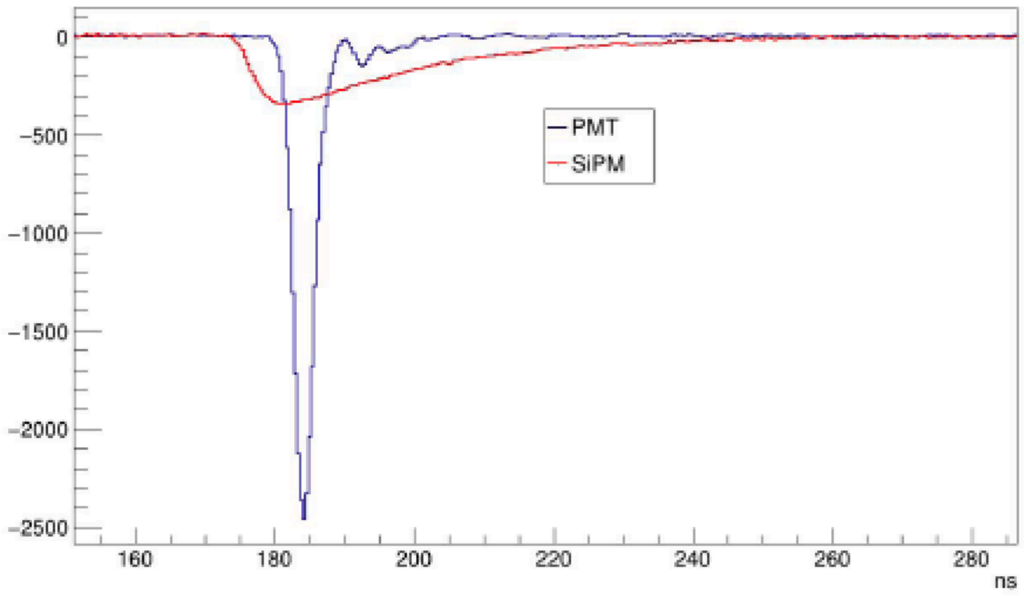


Data with(out) hole

Courtesy of Veronica Ferrero

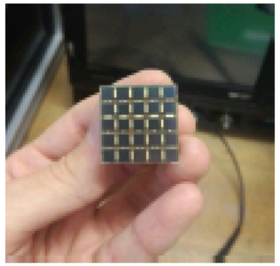
MERLINO: From PGT to stopping power!

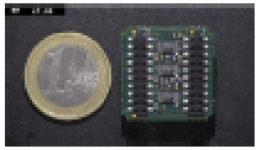




SiPM tile developed by FOOT collaboration (FBK):
5x5 channels

SiPM Type			Tile		
Technology	Cell size (µm)	SiPM size (mm²)	Tile size (mm²)	# SiPMs	Resin
RGB-HD	15	16	24x24	25	Epoxy





Board by M. Mignone: sum of channels output

SiPM signal: rise time ~5 ns, total duration ~80 ns

PMT signal is about 13 times higher than SiPM signal at the same LED intensity

SiPM gain (value by FBK): 4E5

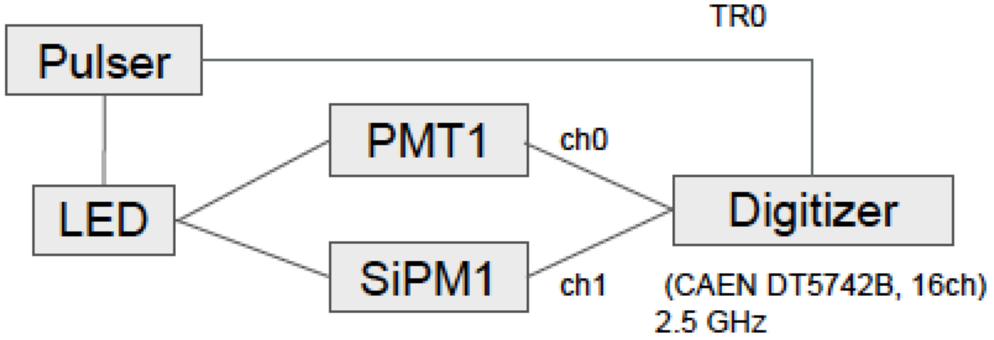
MERLINO

FOOT

FONDAZIONE BRUNO KESSLER

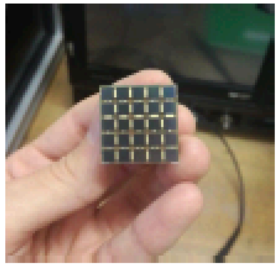
Courtesy of Veronica Ferrero

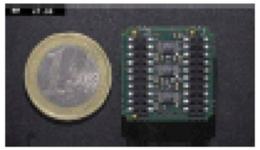
MERLINO: From PGT to stopping power!



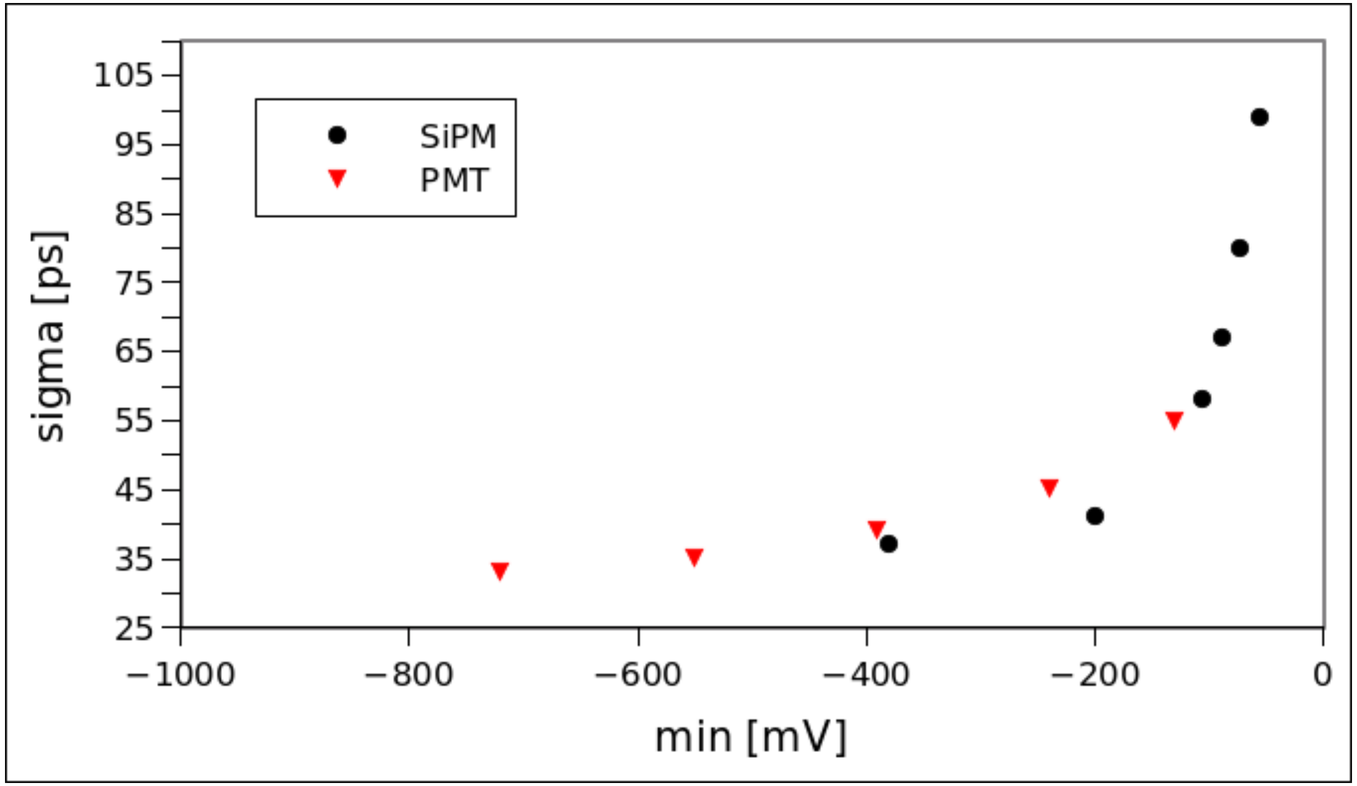
SiPM tile developed by FOOT collaboration (FBK):
5x5 channels

SiPM Type			Tile		
Technology	Cell size (µm)	SiPM size (mm²)	Tile size (mm²)	# SiPMs	Resin
RGB-HD	15	16	24x24	25	Epoxy



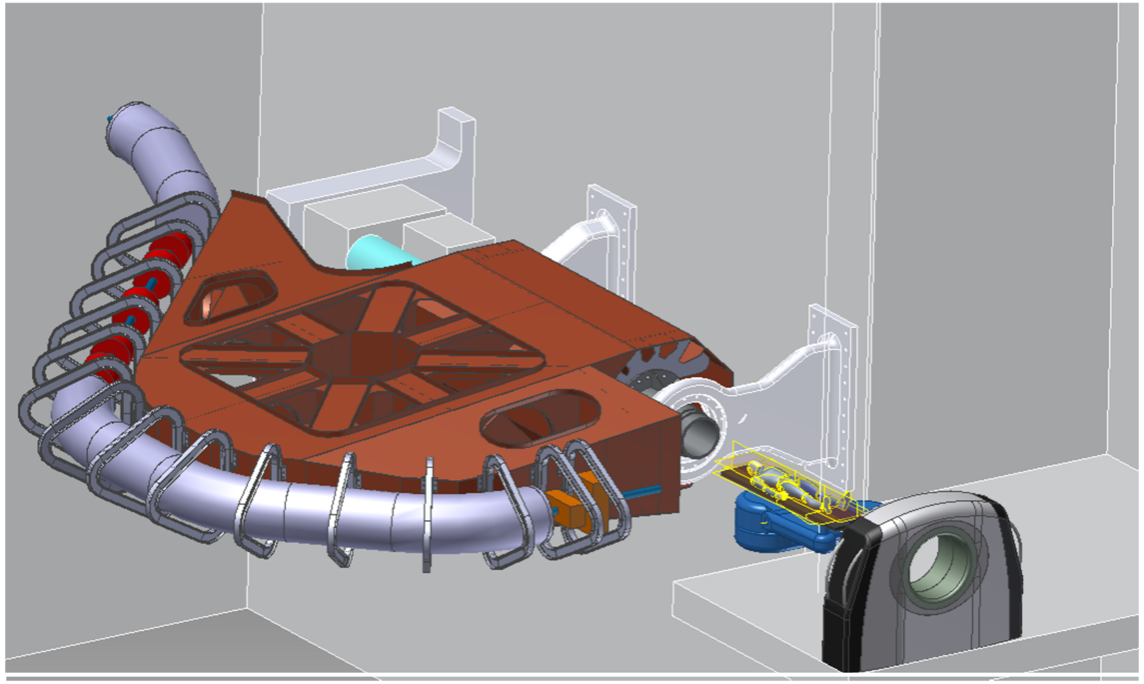


Board by M. Mignone: sum of channels output



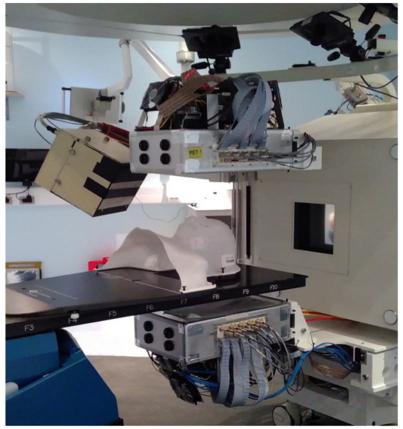
Courtesy of Veronica Ferrero

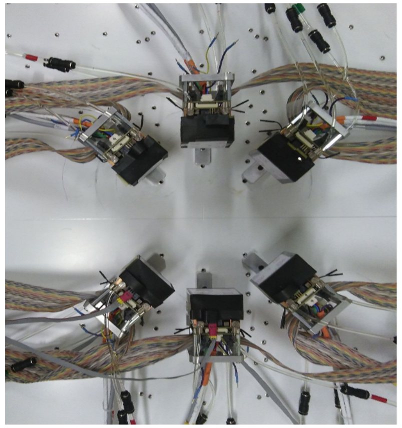
Superconducting Ion Gantry



- study, design and test the prototype of the in-vivo RVS for the SIG ion gantry
- design a full system that meets the clinical requirements

...from...





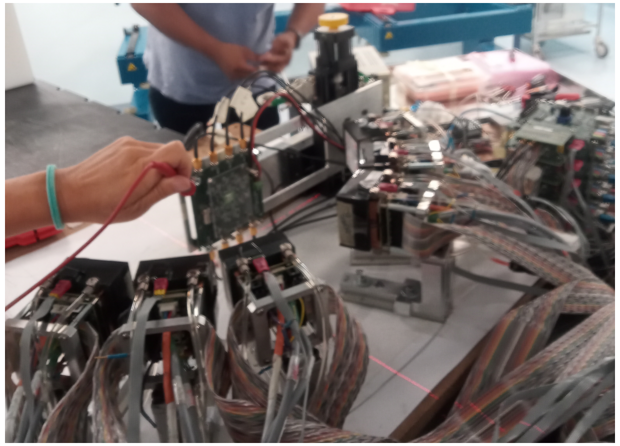
...towards...

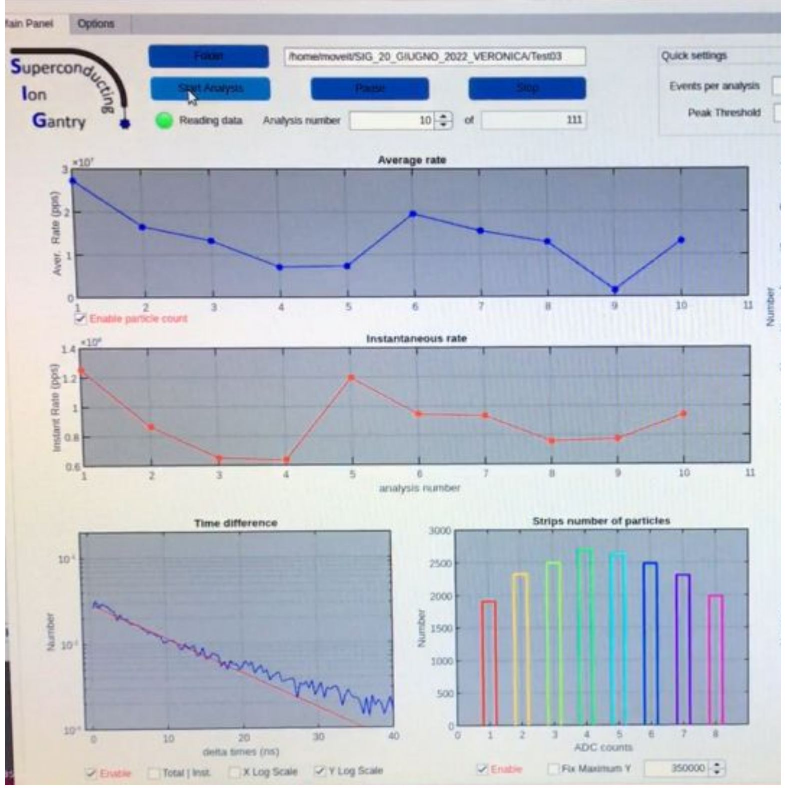
Superconducting Ion Gantry

Courtesy of Elisa Fiorina

Superconducting Ion Gantry

PGT acquisition



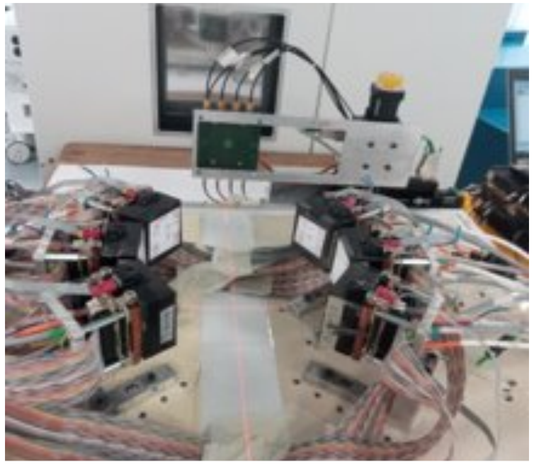


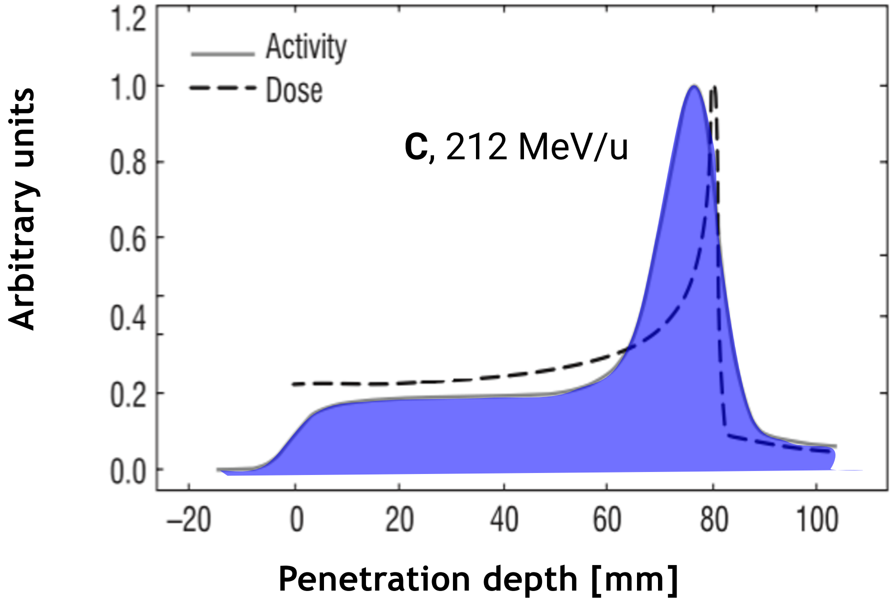
Superconducting Ion Gantry

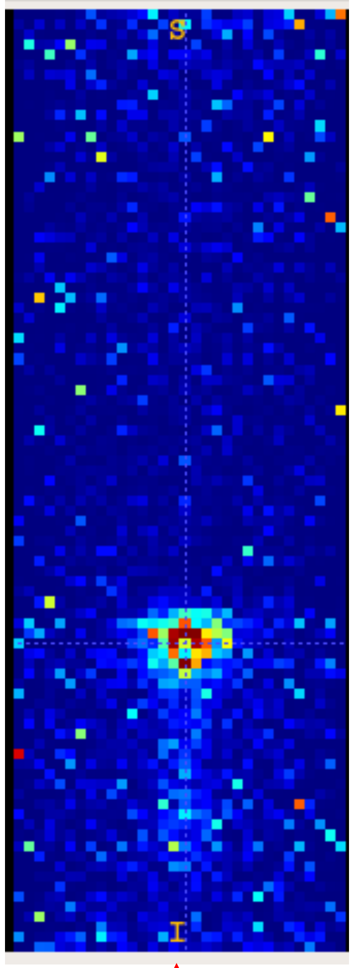
Courtesy of Elisa Fiorina

Superconducting Ion Gantry

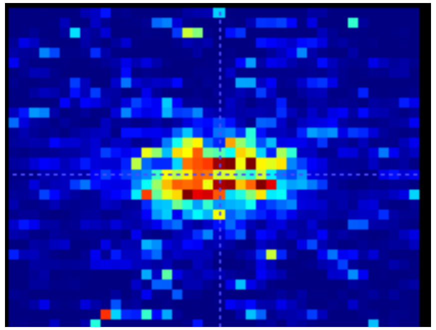
PET acquisition







Carbon beam



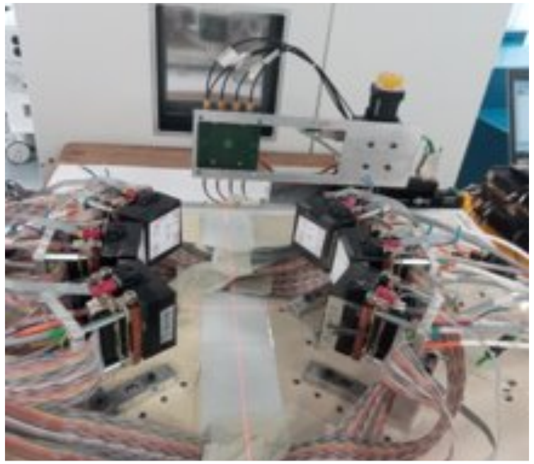
Single spot
144.10 MeV/u
(inter spill)

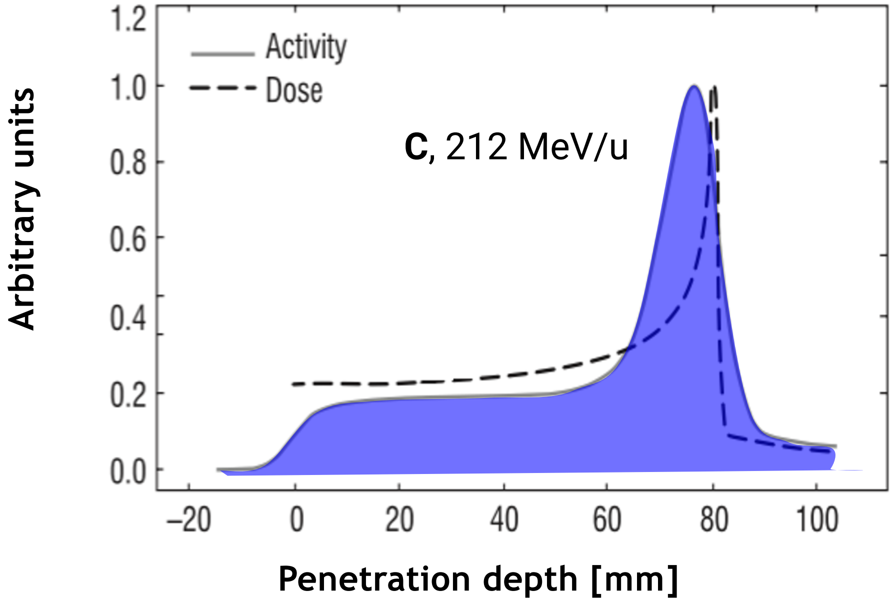
Superconducting Ion Gantry

Courtesy of Elisa Fiorina

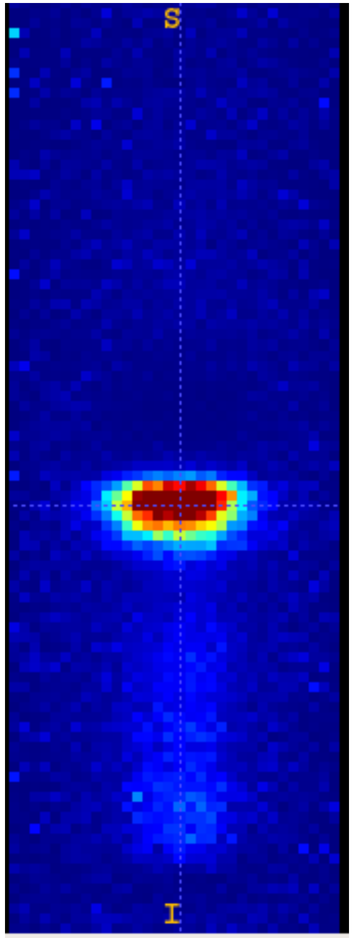
Superconducting Ion Gantry

PET acquisition

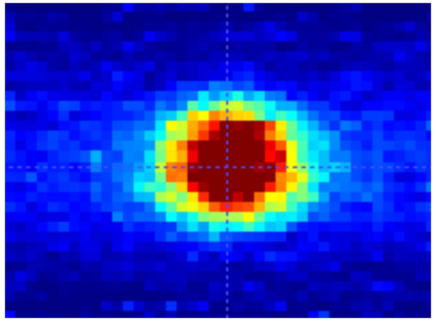




Courtesy of Elisa Fiorina



Carbon beam



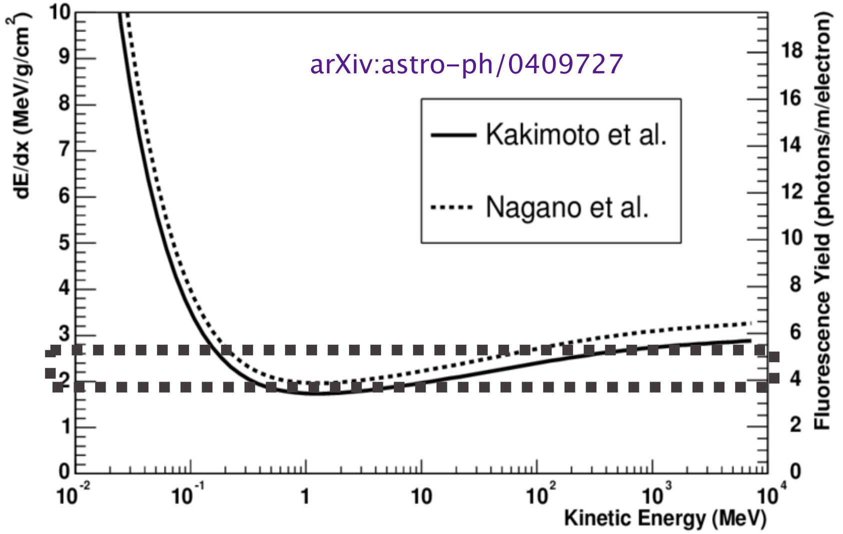
2D scanning
178.28 MeV/u
(after treatment)

Fluorescence-based beam monitor for FLASH RT

Real time beam monitoring (intensity and direction) is required

Standard detectors (i.e., ionization chambers) not suitable in FLASH regime

- discharges
- dose-dependent effects



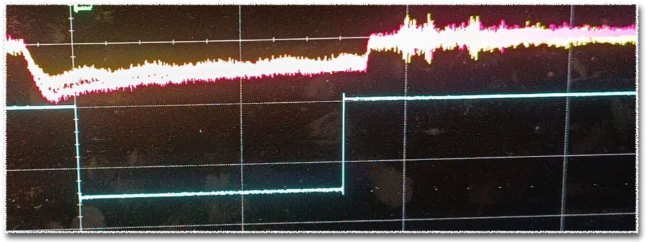
- air fluorescence to detect electron current and measure its characteristics
- emission of optical photons from molecular excitation with an almost constant yield over a wide energy range
- air as a medium minimizes the material thickness on the beam line

FLASH Radiotherapy with hIgh Dose-rate particle beAms

Courtesy of Alessio Sarti

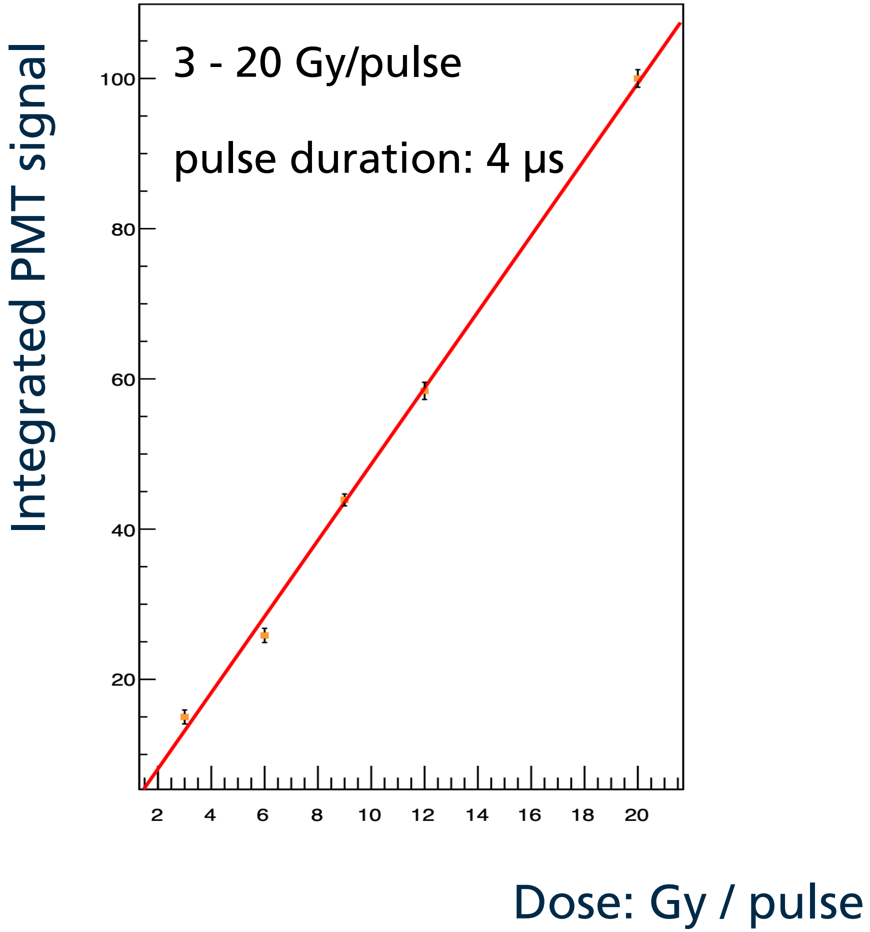
Fluorescence-based beam monitor for FLASH RT

- Proof of principle using the ElectronFlash machine, by Sordina IORT Technologies S.p.A.
- air volume (2x2x60 cm^3) enclosed by a thin layer of tedlar, light sensors on the edges



Courtesy of Alessio Sarti

Fluorescence-based beam monitor for FLASH RT



- Optimize the light detection system to make it more stable and precise, and reduce the risk of saturation
- Optimize design with MC simulations
- Aim: monitor the intensity of typical FLASH pulses making a 2D mapping of the beam with a spatial resolution ≈mm

FLASH Radiotherapy with hIgh Dose-rate particle beAms

Courtesy of Alessio Sarti

Treatment monitoring and optimization

Piergiorgio Cerello

INFN, Sezione di Torino, Torino, Italy

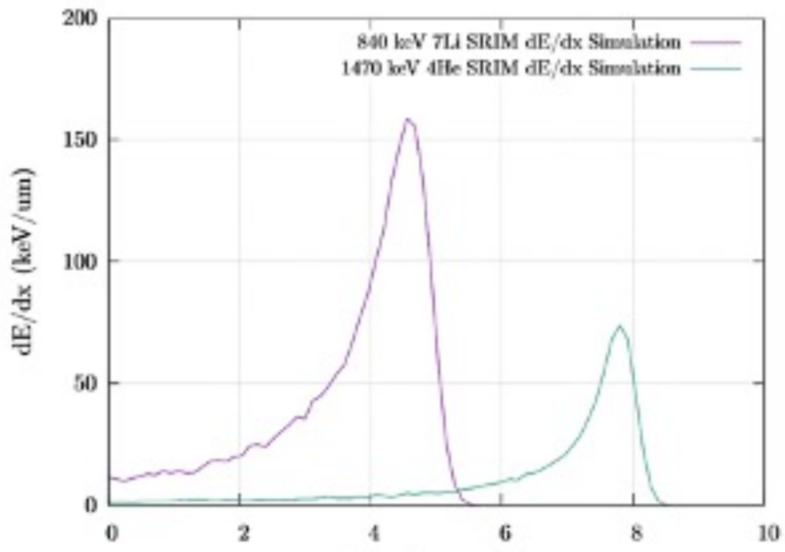
Treatment optimization

- Boron Neutron Capture Therapy

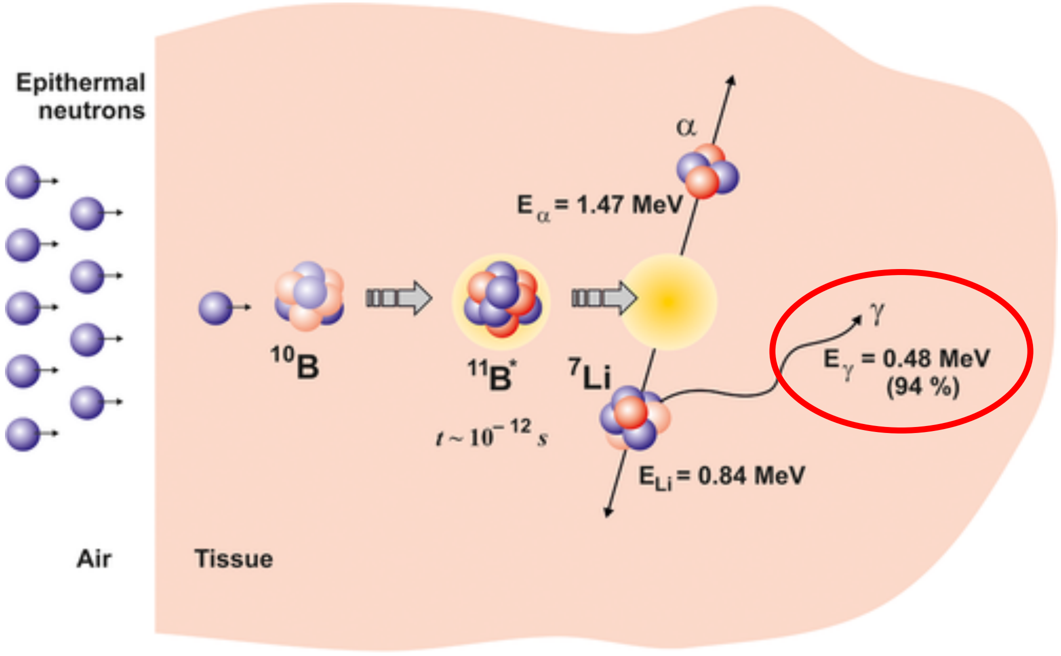
Boron Neutron Capture Therapy (BNCT)

- neutron flux on ^{10}B-enriched target tissue
- high LET secondaries produced in $^{10}B(n,\alpha)^{7}Li$

- highly effective at cell level



Charged particles Range (μm)



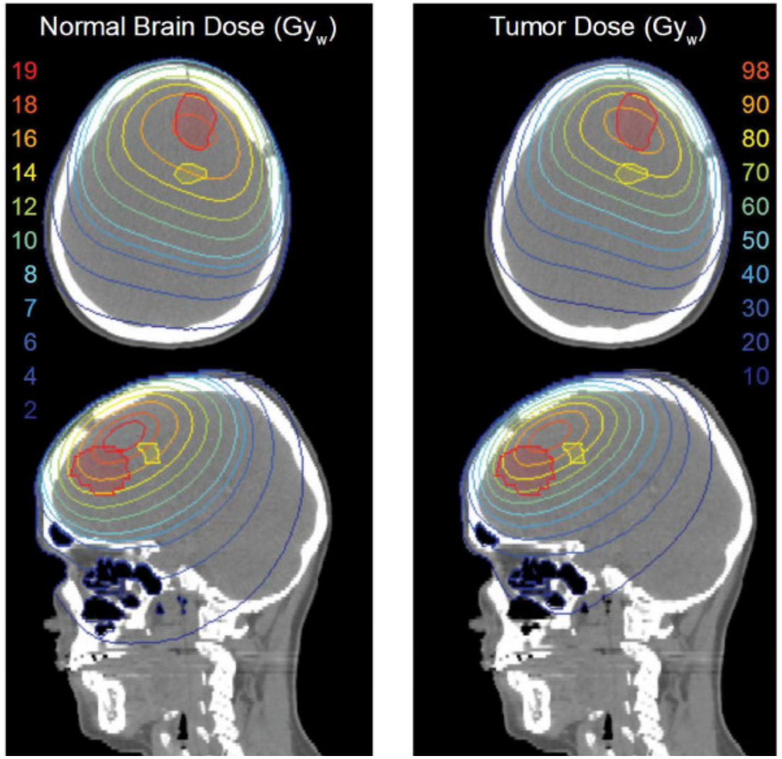
BNCT dosimetry: the present limit

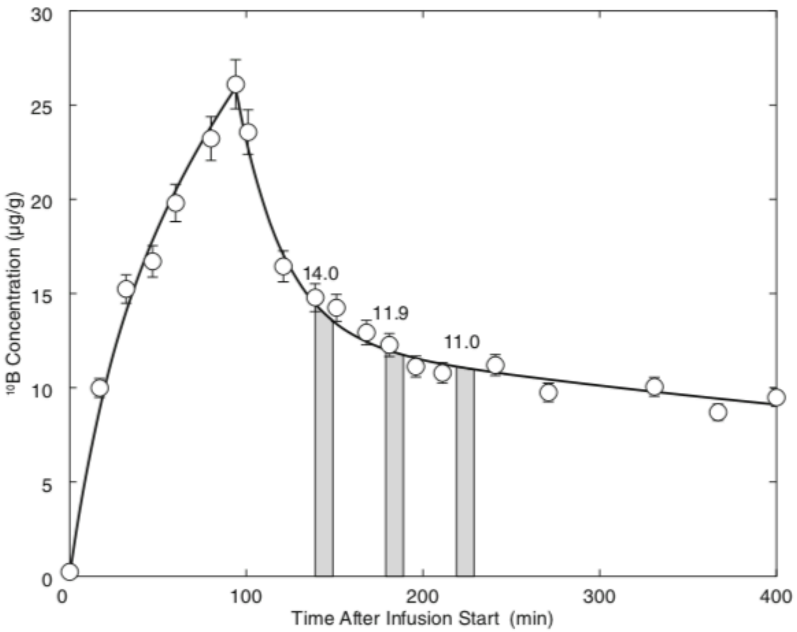
"therapeutic" dose due to ^{10}B accumulation $dD(x,y,z) \sim n_{10B}(x,y,z) \cdot \Phi(x,y,z)dV$

- thermal neutron flux @ tumour site
- ^{10}B distribution @ irradiation time

are presently measured indirectly - huge uncertainties on dose estimation

Monte Carlo-based Treatment Planning Systems (TPS) validated through TE-phantom measurements





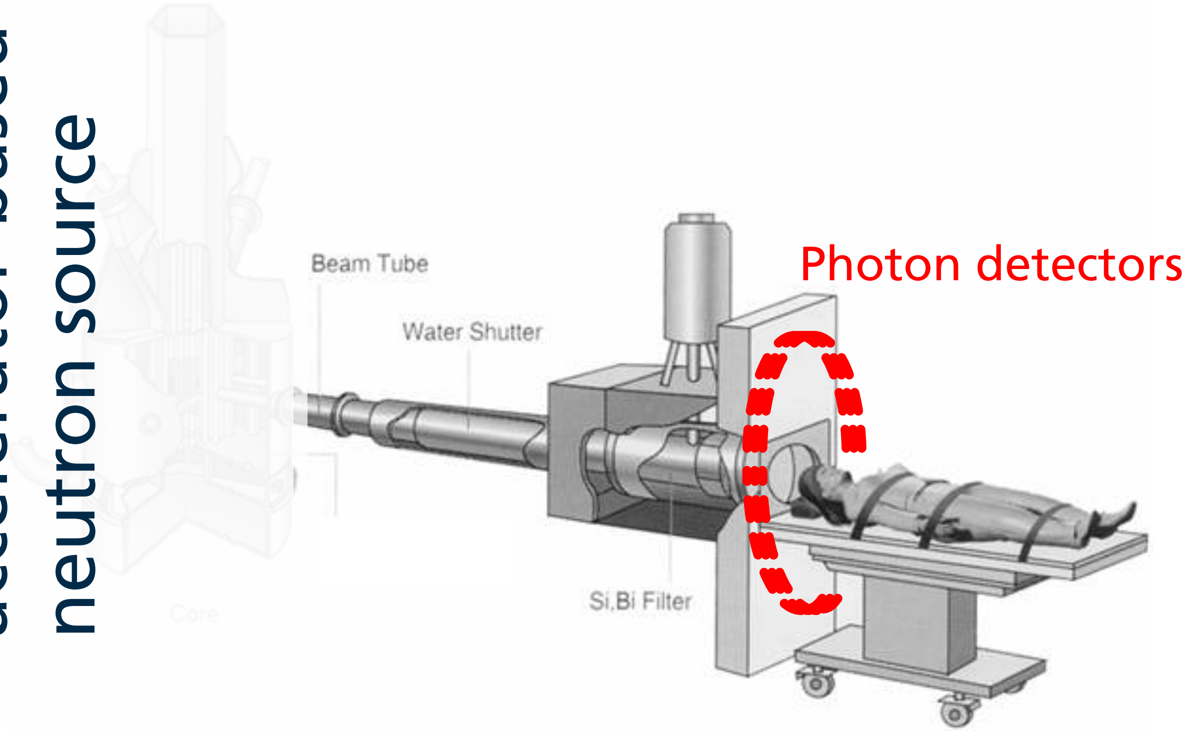
^{10}B concentration from blood samples and ICP-AES or MS, coupled with pharmacokinetic models

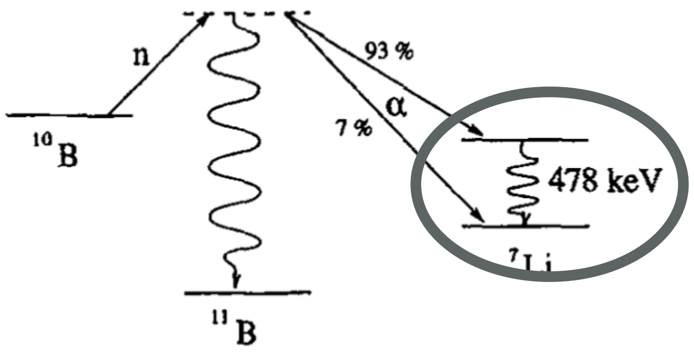
Courtesy of Nicoletta Protti

in vivo BNCT dosimetry by single photon detection

"therapeutic" dose $dD(x,y,z) \sim n_{B10}(x,y,z) \cdot \Phi(x,y,z)dV \sim \underline{dI_{\gamma}(x,y,z)}$

accelerator-based neutron source





Real time measurement of ^{10}B reaction rate

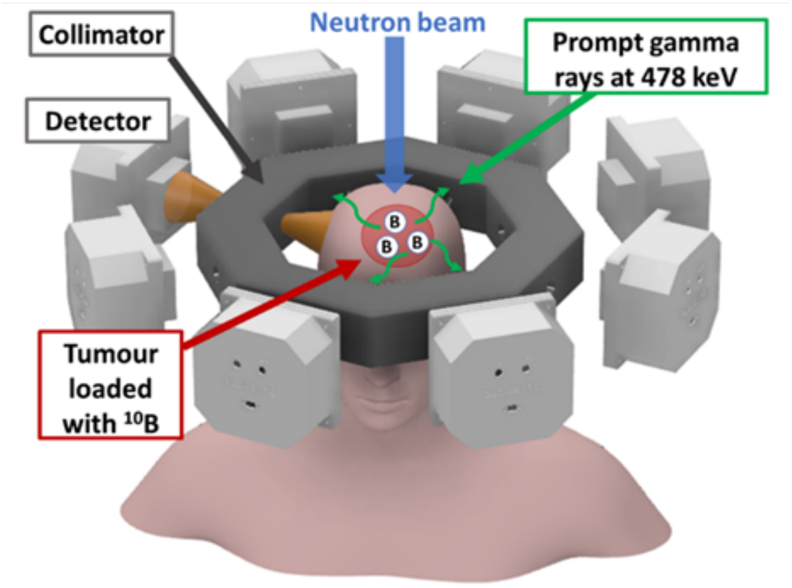
- multiple detectors = multiple projections
- BNCT-SPECT or Compton Camera
  - voxel size < 1 cm^3
  - statistical uncertainty < 10% @478 keV
  - ^{10}B reaction rate > 10^6 cm^{-3}s^{-1}

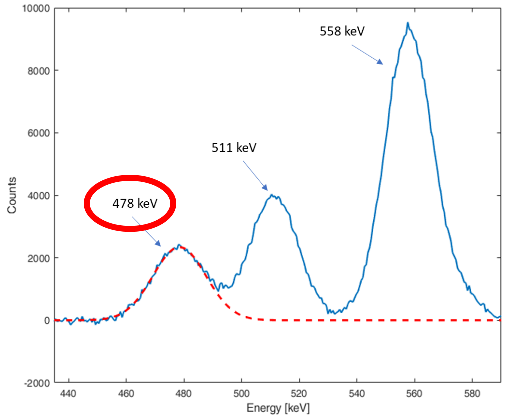
Challenges:

- mechanical collimator effective @ 478 keV
- intense n+γ background (2.2 MeV γ rays from ^{1}H captures)
- compact and portable system to adapt to patient's position

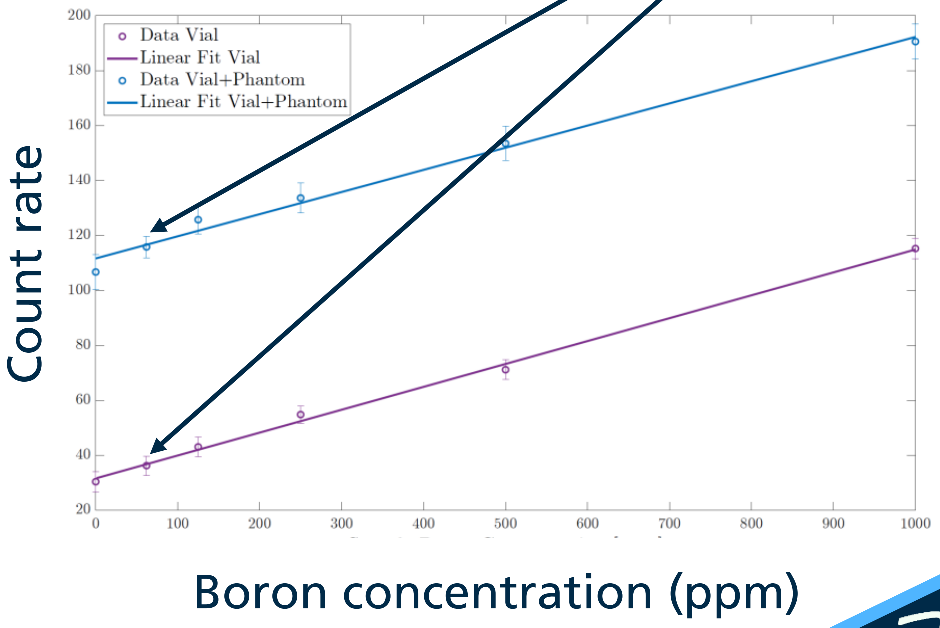
Courtesy of Nicoletta Protti

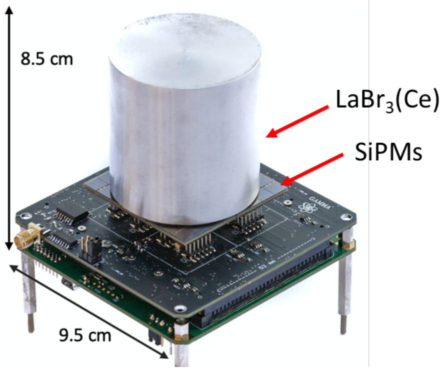
BENEdiCTE (Boron Enhanced NEutron CapTurE)

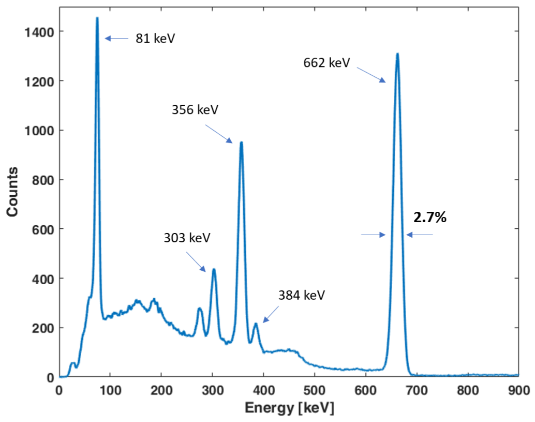




Minimum ^{10}B-concentration of 60ppm detected at Lena (Pavia)





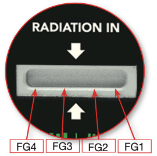


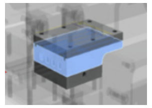
Courtesy of Carlo Fiorini

SPECT and Compton Imaging

CdZnTe room-temperature semiconductor detectors: the cutting-edge technology for small field of view scanners

DoseCapture modules for BNCT-SPECT (ENTER-BNCT project INFN + UNIPV Dipartimento di Eccellenza)





(i) an array of 4 Frisch Grid (FG) CZT detectors

(ii) ^{6}Li-enriched neutron shield surrounding the array to reduce the (n,γ) reactions of ^{113}Cd (~12% natural abundance)

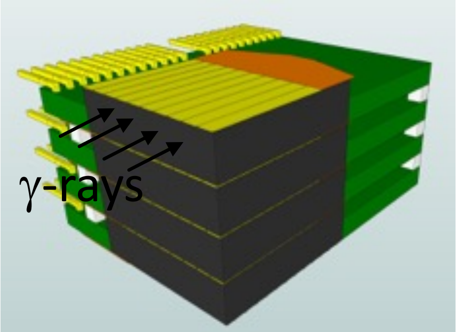
(iii) a square 4 holes Pb collimator to select the photon direction

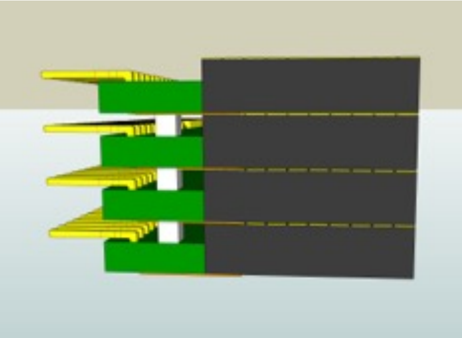
(iv) proprietary digital electronics for acquisition, correction and analysis

S.Fatemi et al., NIM-A 903: 134-139 (2018)

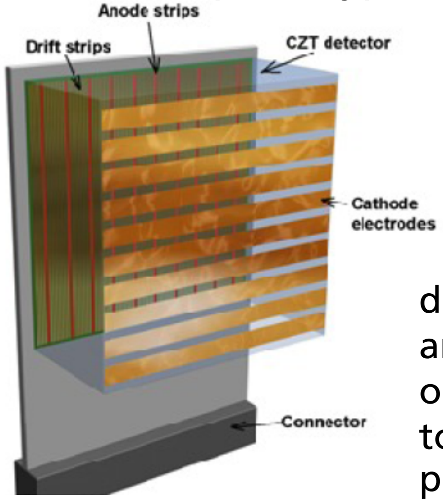
Courtesy of Nicoletta Protti

"single stage" Compton Camera 3D CZT detectors (3CaTS project)





3D-CZT prototype, 20x20x20 mm^3



drift strip detectors: anode-cathode orthogonal strips to have a virtual pixel

L. Abbene et al., J Synchrotron Rad 27: 1564-1576 (2020)
L. Abbene et al., Sensors 22:1502 (2022)

Nuclear Physics Mid Term Plan in Italy

LNF – Session

Frascati, December 1st - 2nd 2022

Nuclear Physics
Mid Term Plan in Italy

Treatment monitoring and optimization

Piergiorgio Cerello

INFN, Sezione di Torino, Torino, Italy

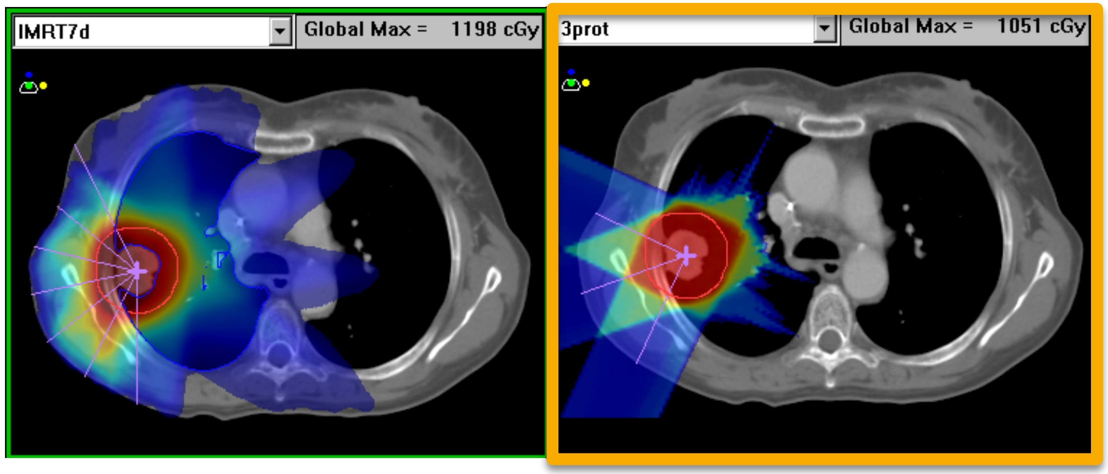
Treatment optimization

- Nuclear fragmentation

Istituto Nazionale di Fisica Nucleare

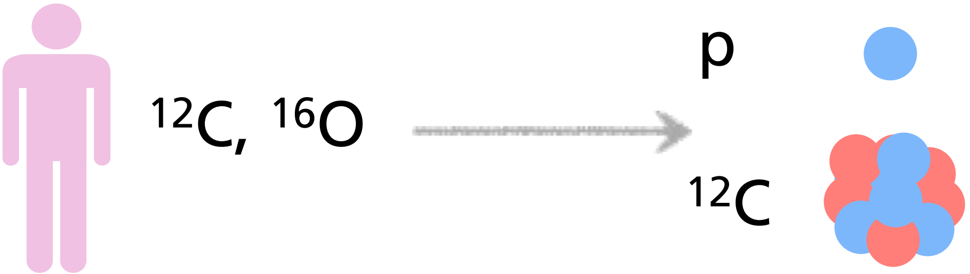
FragmentatiOn Of Target (FOOT)

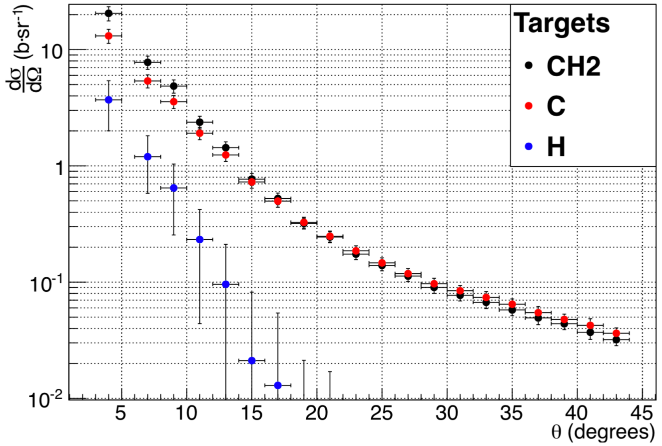
Particle therapy: E < 500 MeV/u



the contribution of tissue fragmentation in the entrance channel was not measured (yet)

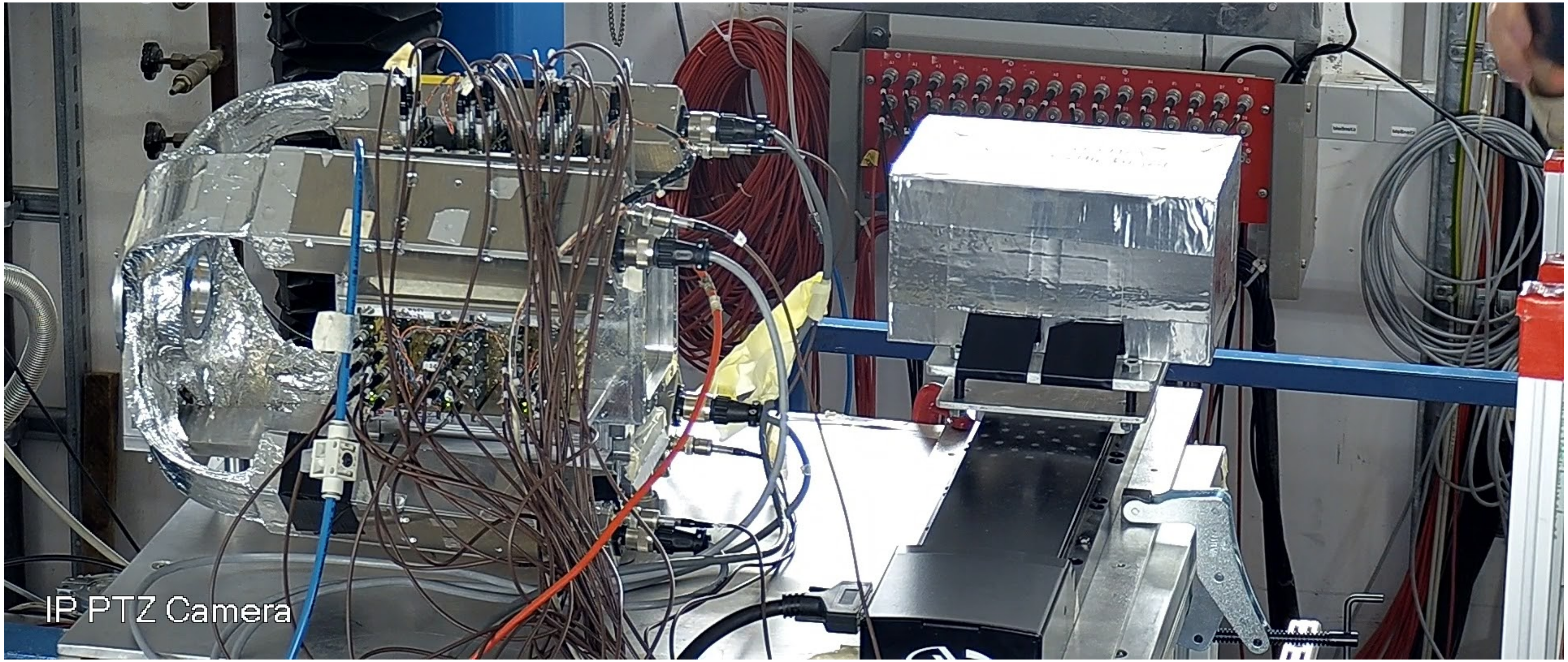
Inverse kinematics





$$\frac{d\sigma}{d\Omega}(H) = \frac{1}{4} \cdot \left(\left(\frac{d\sigma}{d\Omega}(C_2H_4)\right) - 2 \cdot \frac{d\sigma}{d\Omega}(C)\right)$$

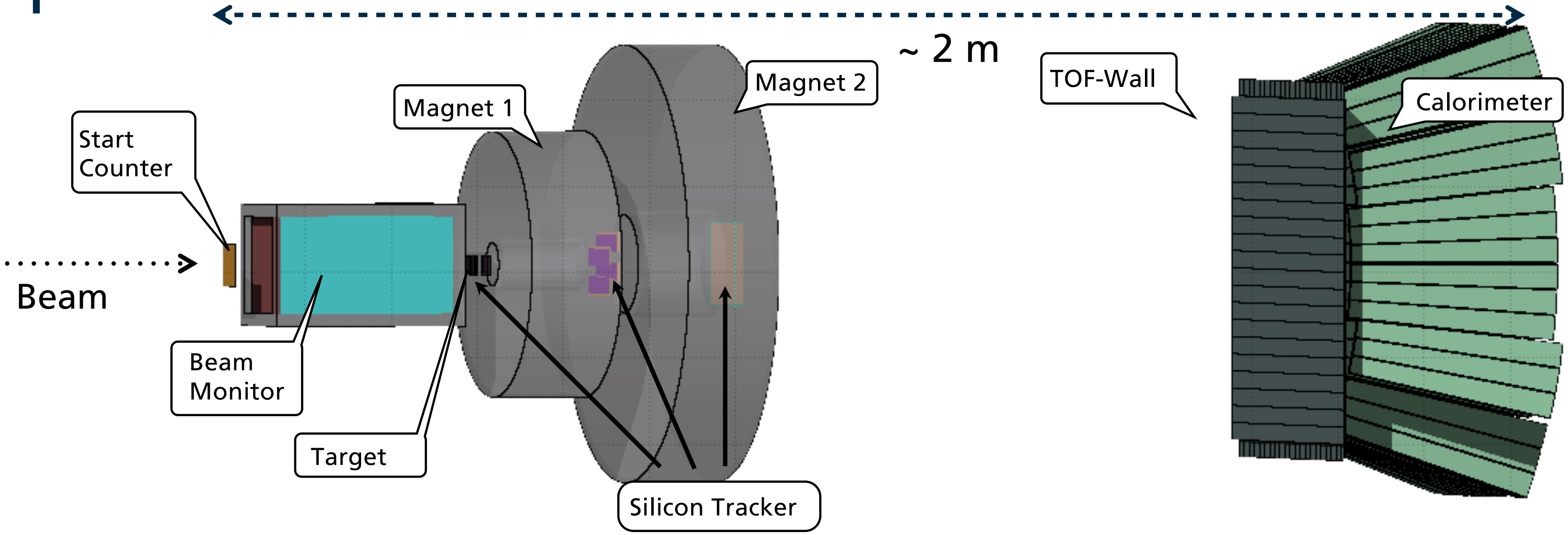
Emulsion Spectrometer*

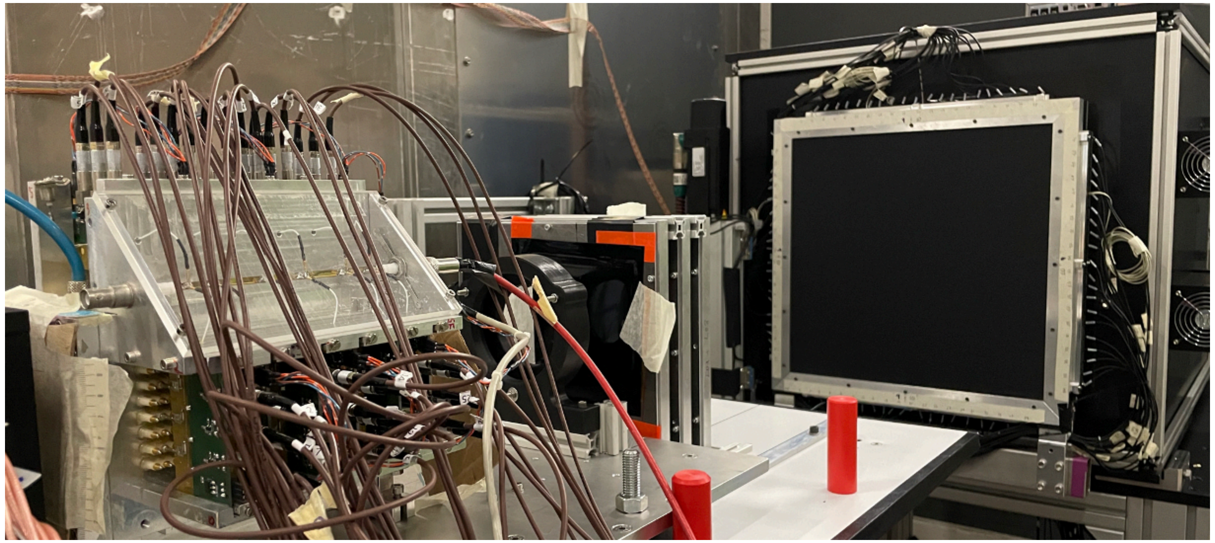


- Large acceptance
- Low statistics

*already covered by L. Servoli

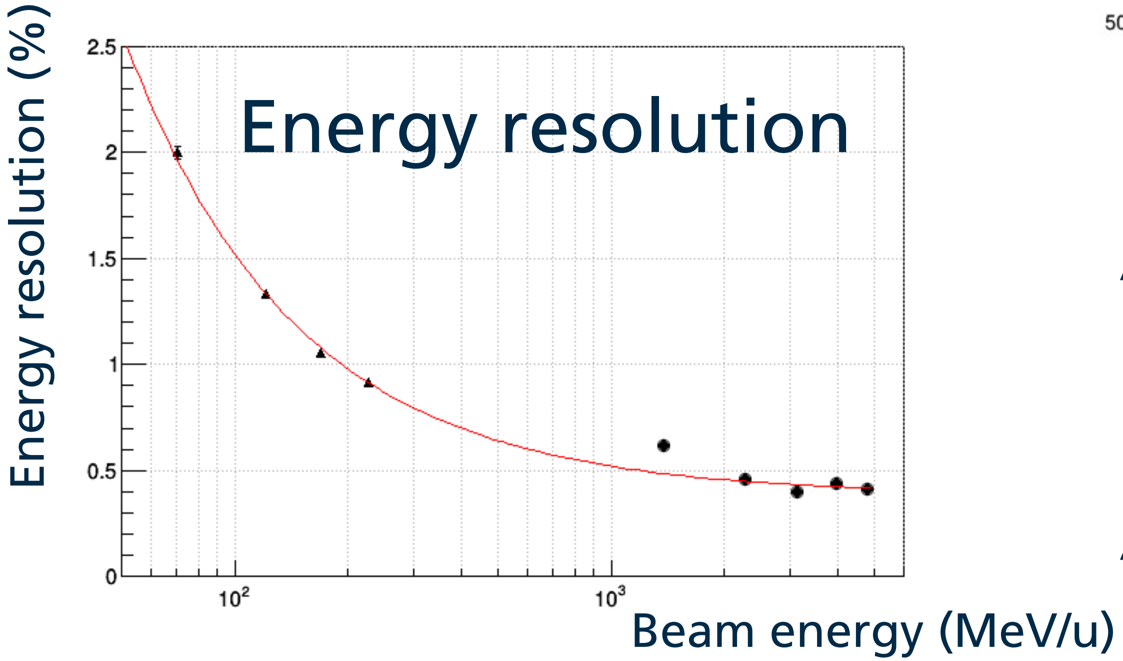
Electronic Spectrometer

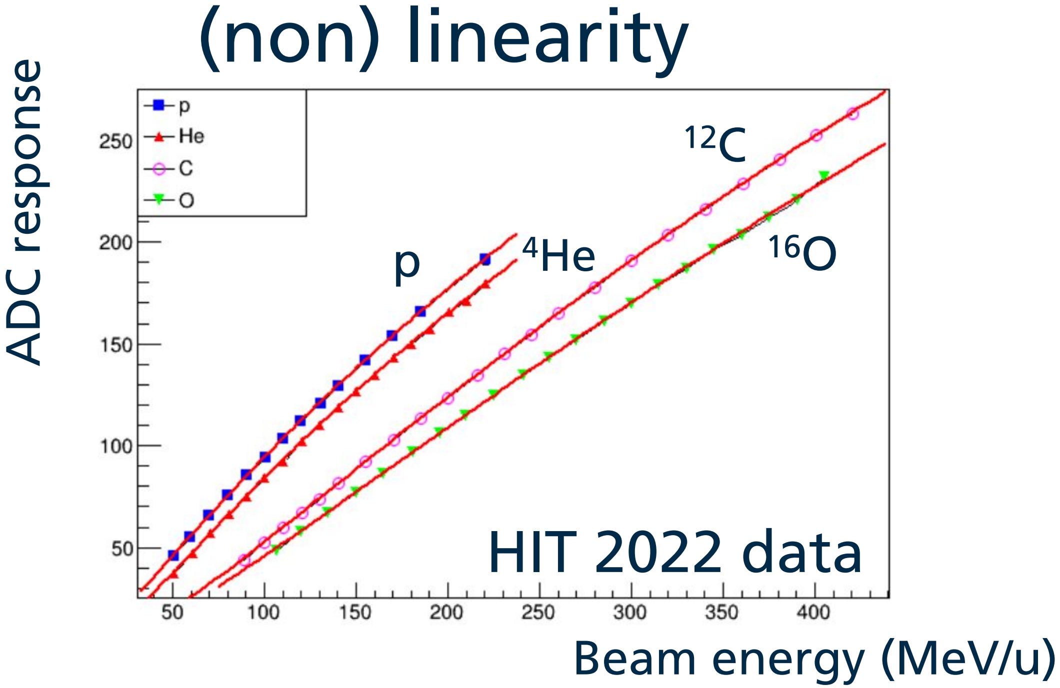




- Forward acceptance (~ 11 degrees)
- High statistics

BGO Calorimeter





$ADC(E) = aE^2 / (1 + bE + cE^2)$

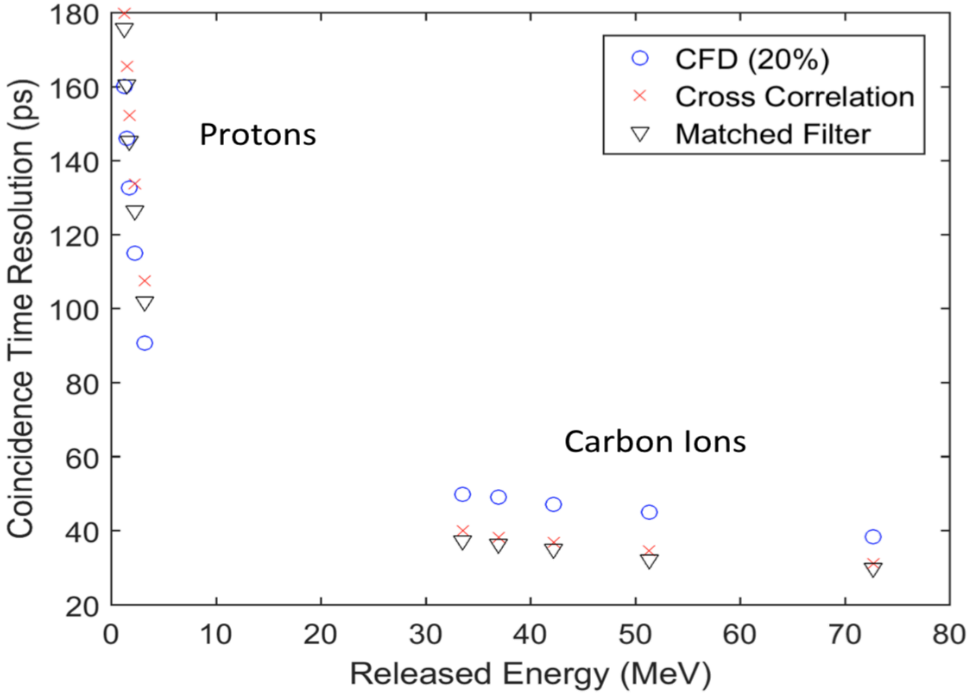
$|E_{fit} - E_{ADC}| / E_{fit} < 1\%$

A (Z?) dependence

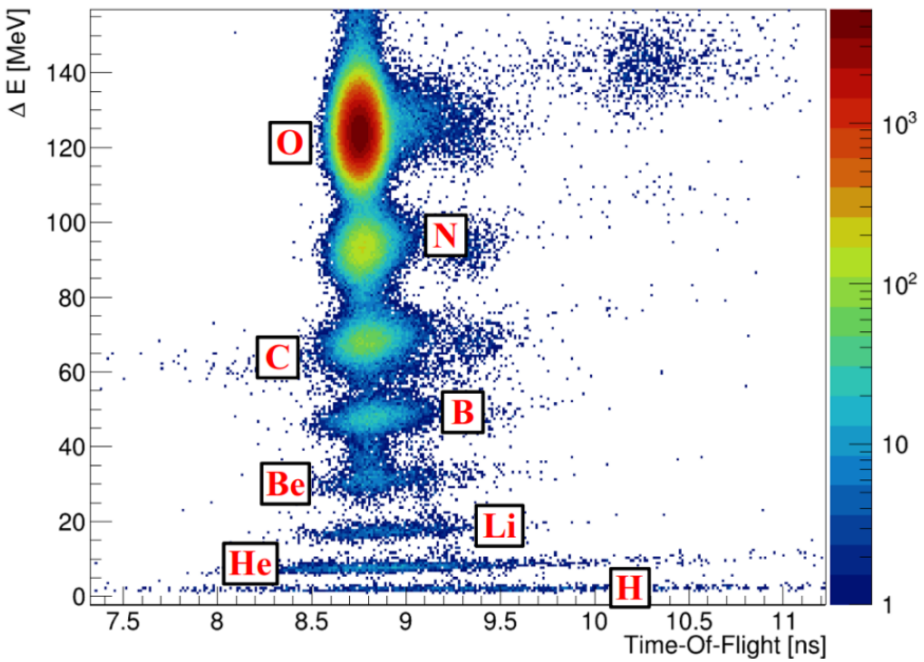
Courtesy of Nazar Bartosik

Time of Flight & dE/dx – Z resolution

CNAO 2019 data: p,^{12}C Coincidence Time Resolution



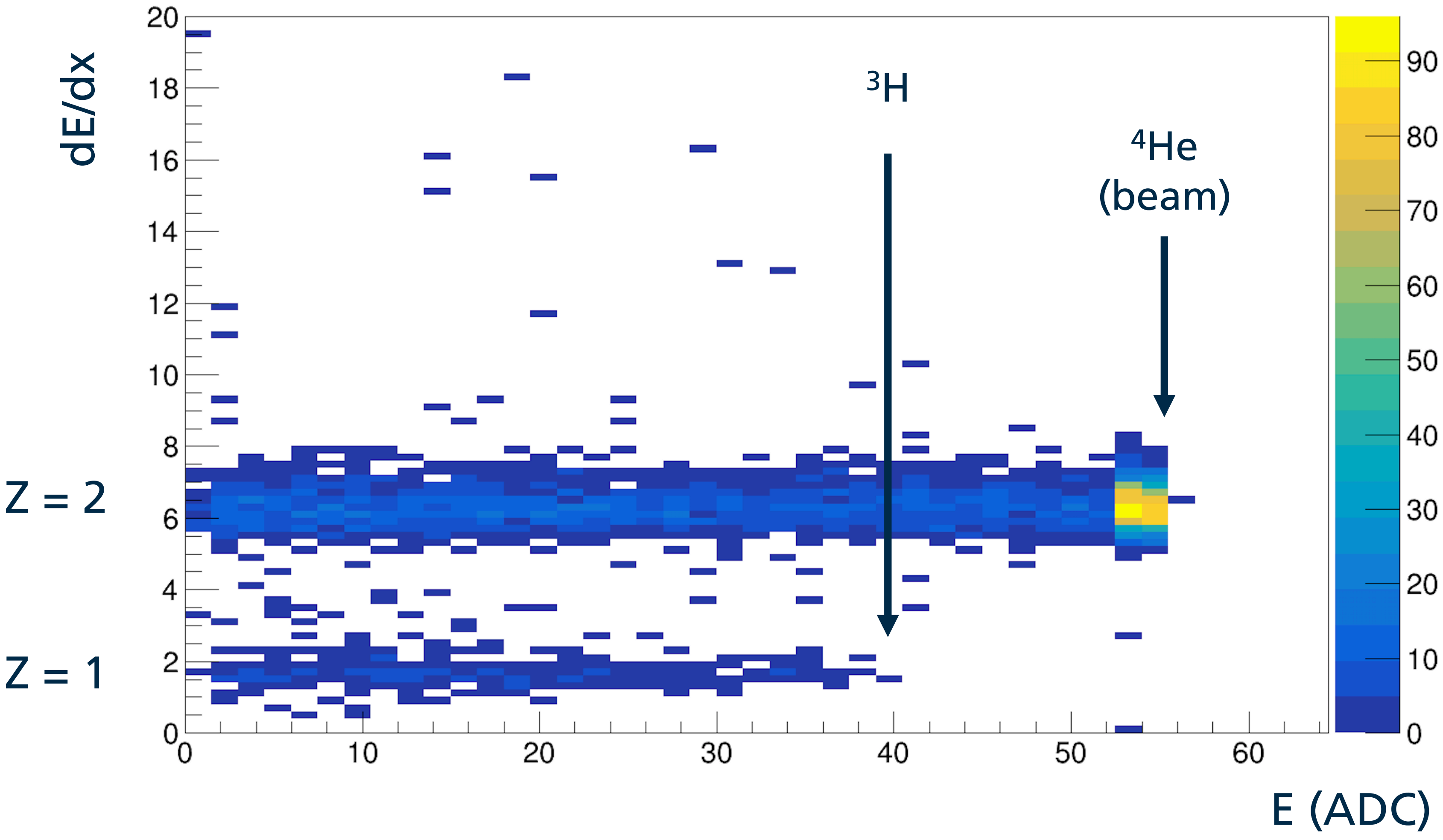
GSI 2021 data 400 MeV/u ^{16}O on 5mm carbon



Courtesy of Matteo Morrocchi

dE/dx vs. Energy – A resolution

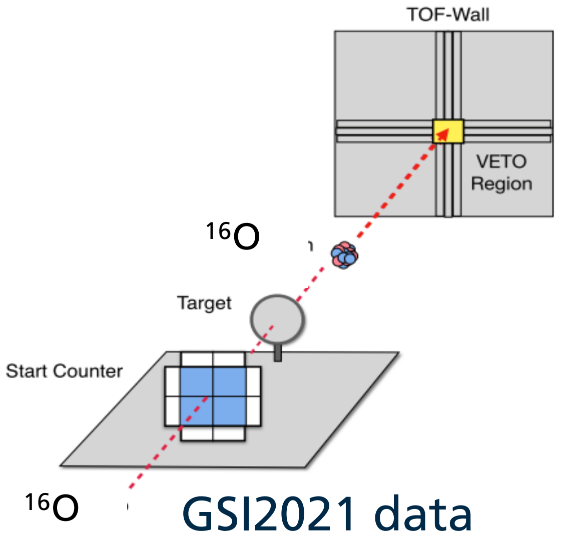
Heidelberg2022 Data taking: $^{4}He + ^{12}C$



Courtesy of Roberto Zarrella

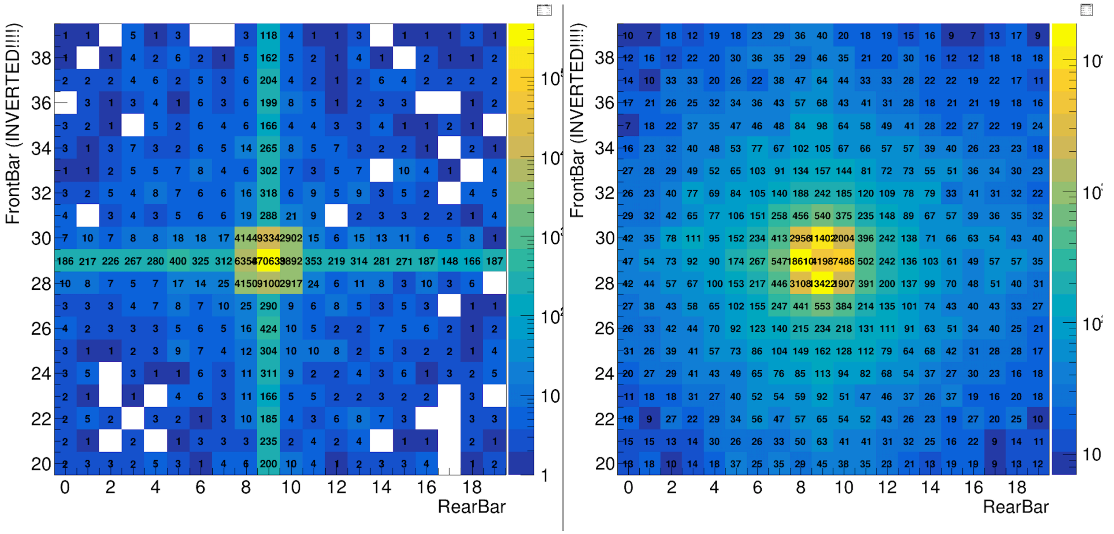
Trigger

Fragmentation events are at a level of few % → how to enhance them?

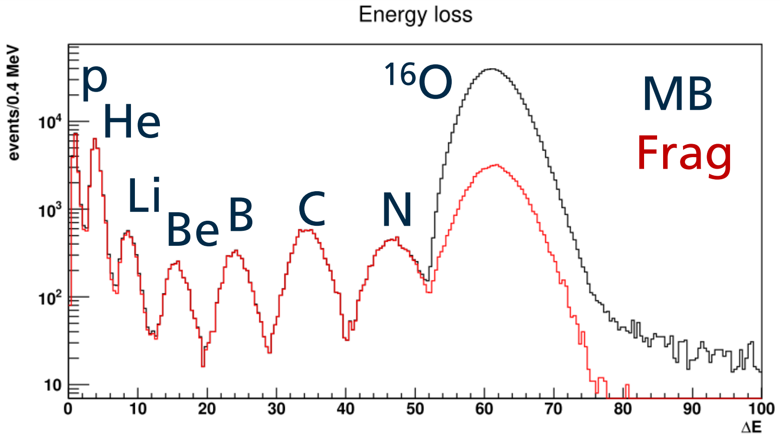


GSI2021 data

TofWall Hitmaps



Minimum bias Fragmentation



Trigger efficiency (%)

H	He	Li	Be	B	C	N	O
95.7± 0.2	98.2± 0.1	99.1± 0.2	99.3± 0.2	99.6± 0.1	99.8± 0.1	98.2± 0.1	8.46± 0.03

^{16}O rejection factor 11.8 ± 0.1

Courtesy of Luca Galli

Contributions by:

Nazar Bartosik
Veronica Ferrero
Elisa Fiorina
Carlo Fiorini
Luca Galli
Aafke Kraan
Ilaria Mattei
Matteo Morrocchi
Francesco Pennazio
Nicoletta Protti
Roberto Sacchi
Alessio Sarti
Valentina Sola
Roberto Zarrella

on behalf of their teams / collaborations

Summary: Key issues for the near future

- Beam monitoring

silicon detectors radiation resistance and size

Superconducting Ion Gantry

- Range Verification

direct Bragg peak measurement: time of flight resolution

pair-production PAPRICA

air fluorescence

FLASH Radiotherapy with hIgh Dose-rate particle beAms

MERLINO

Superconducting Ion Gantry

- Boron Neutron Capture Therapy

SPECT & Compton imaging

ENTER-BNCT,
3CaTS

- Fragmentation

cross section measurements: time of flight resolution, energy in the non-linear regime, magnet & silicon tracker

FOOT