Research and Development in Charged Particle Therapy

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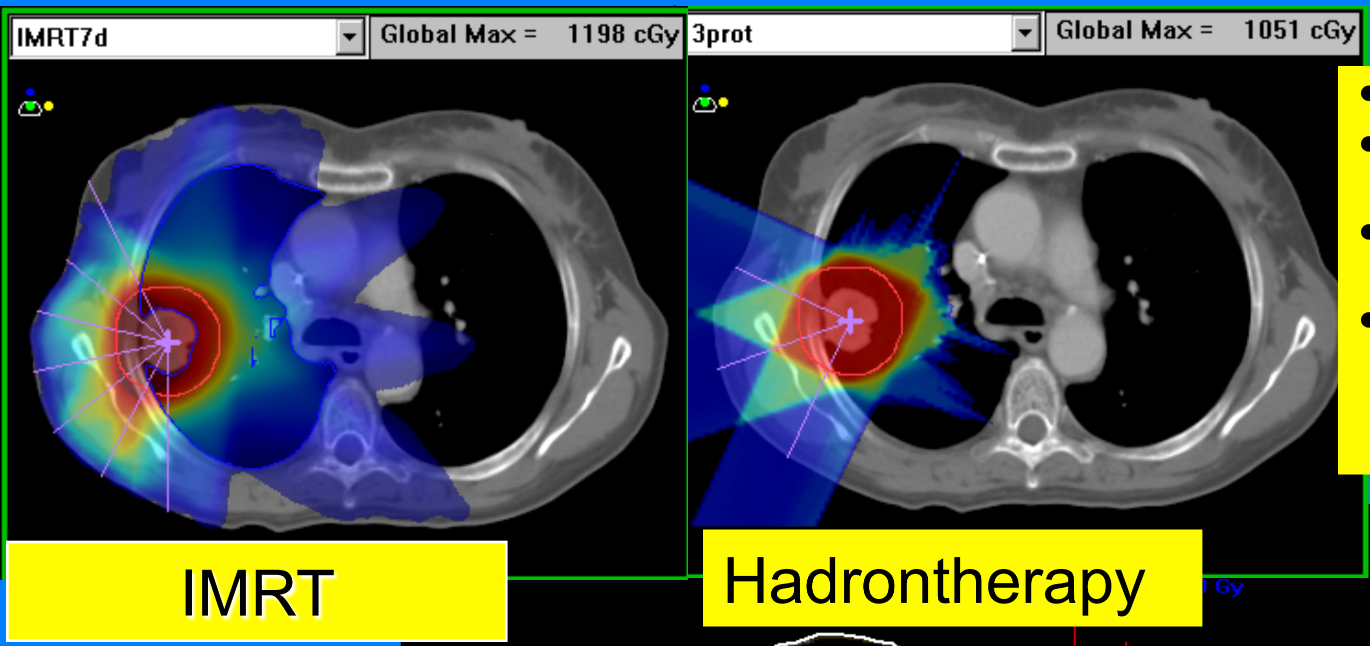
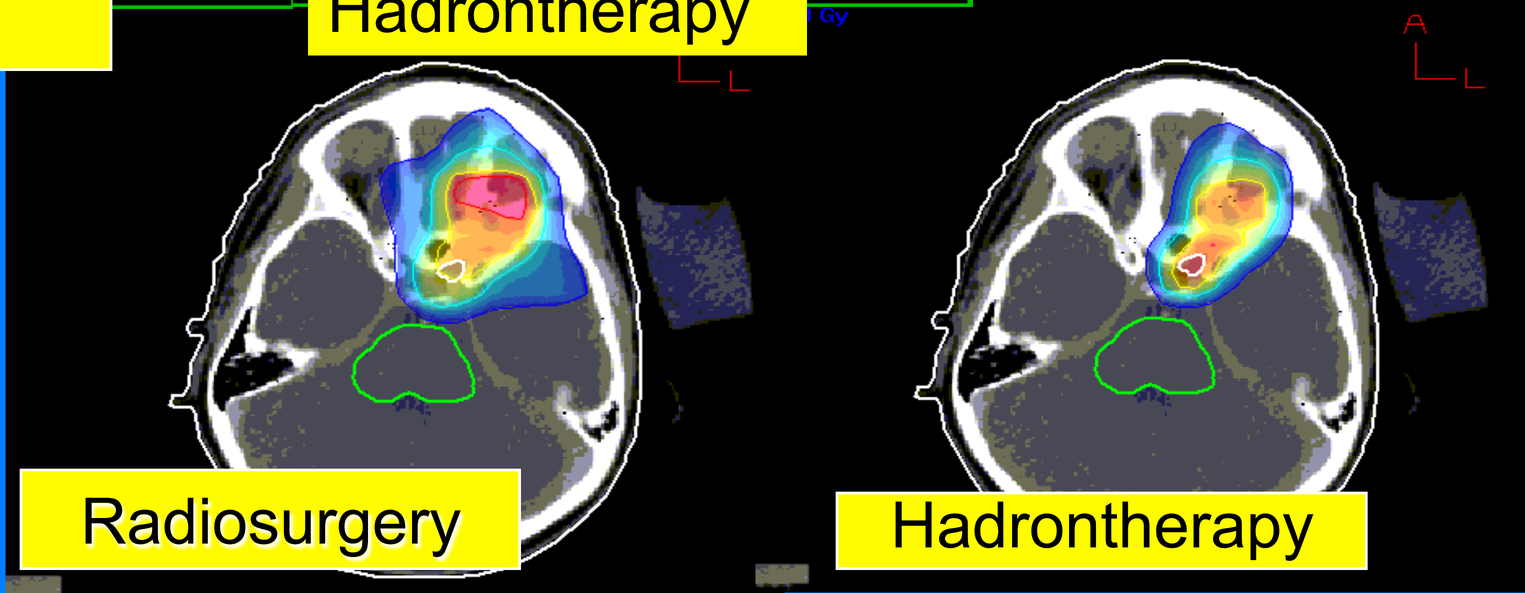
ENLIGHT
European Network for Light Ion Hadron Therapy

INFN Istituto Nazionale di Fisica Nucleare

Advantages of Charged Particle Therapy



- Reduced NCTP
- Length of track function of the beam energy
- Dose decrease rapidly after the Bragg Peak
- Accurate conformal dose to tumour with Spread Out Bragg Peak



Nuclear projectiles

protons: 50-250 MeV

RBE ~ 1.1 *(under discussion…)*
accelerated by cyclotrons or synchrotrons

^{12}C: 60-400 MeV/u

Higher RBE → well suited for radio-resistant tumors
reduced no. of fractions
reduced lateral spread with respect to protons

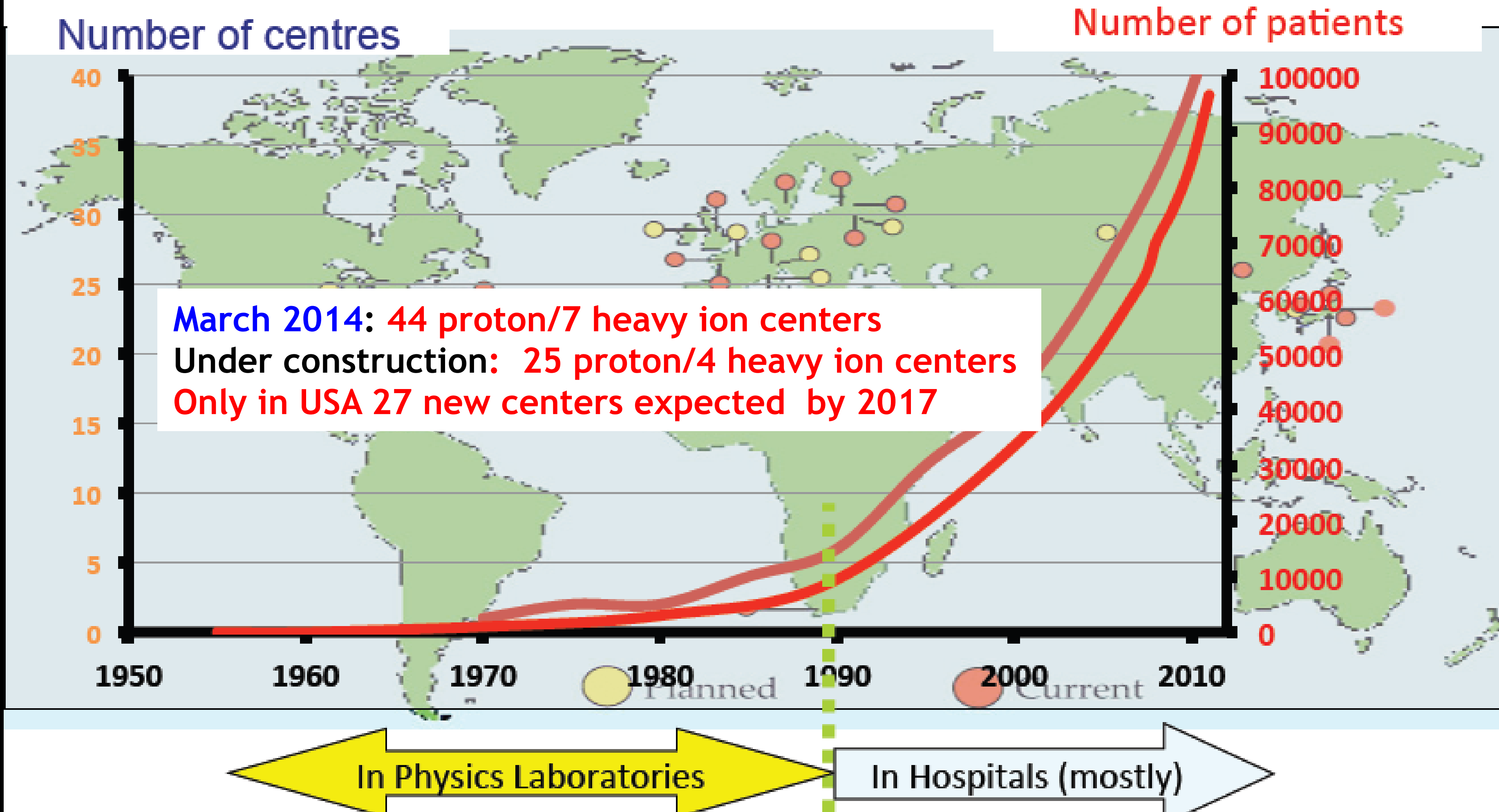
However:
accelerated by larger machines
Nuclear Fragmentation
heavier gantries and magnets…

Future Options under considerations:

^{4}He (50-300 MeV/u): negligible fragmentation, higher RBE than protons, but more limited lateral scattering

^{16}O (100-500 MeV/u): to be used in particular case where high-LET is needed

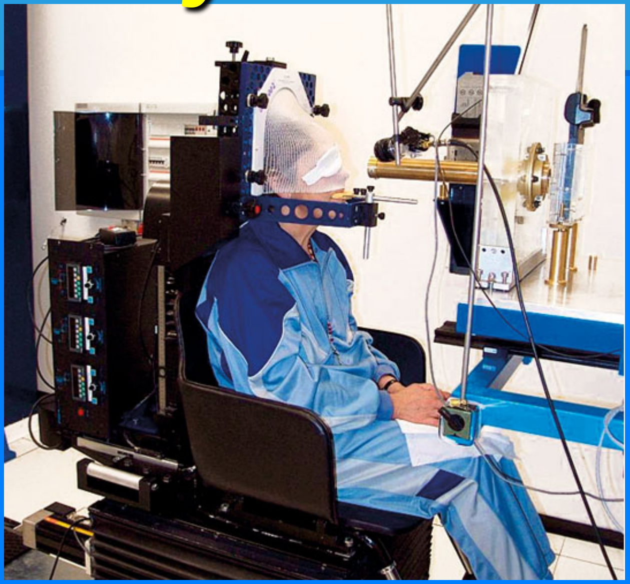
Charged Particle Therapy in the world



~2014: **122499 treated patients: 105743 with p,** mainly in USA, 53532
13119 with ^{12}C, mainly in Japan, 10993;

+ 46,000 in the past 5 years ≈ 10,000 patients per year

HadronTherapy in Italy



CATANA @INFN-LNS

- **353 patients since 2002**

(see G.Cuttone's talk)

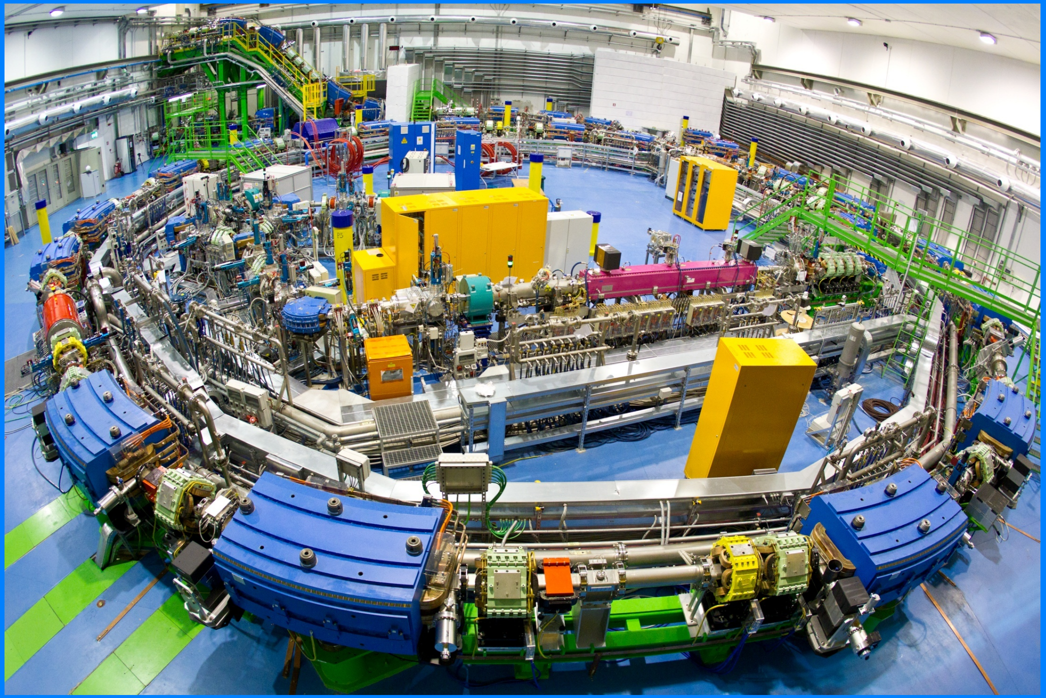
CNAO in Pavia

- **650 patients, 75% with C**

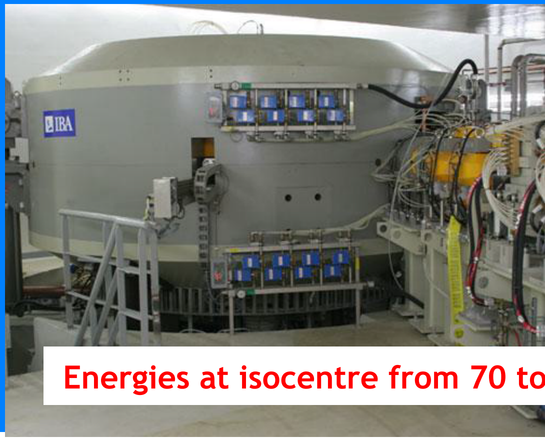
(see S.Rossi's talk)

p: max 250 MeV; ~10^9 p/s

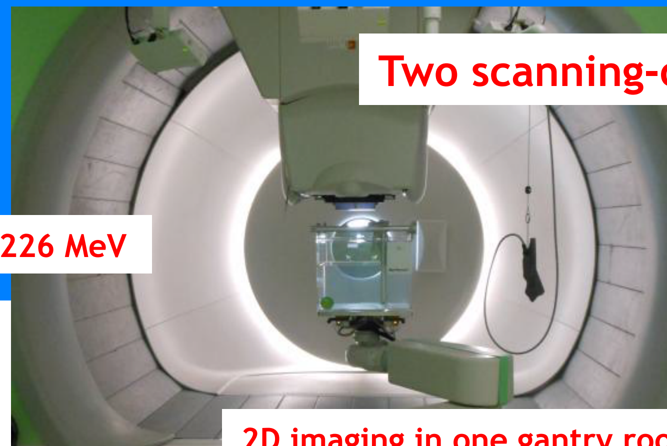
^{12}C: max 400 MeV/u; ~ 10^8 p/s



New Proton Therapy in Trento (Italy)

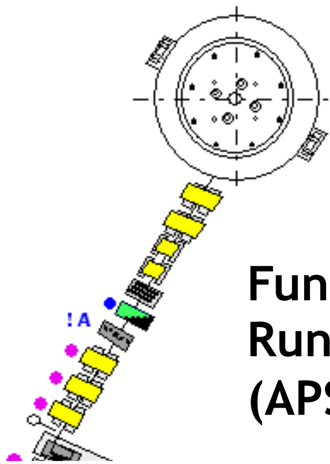


Energies at isocentre from 70 to 226 MeV

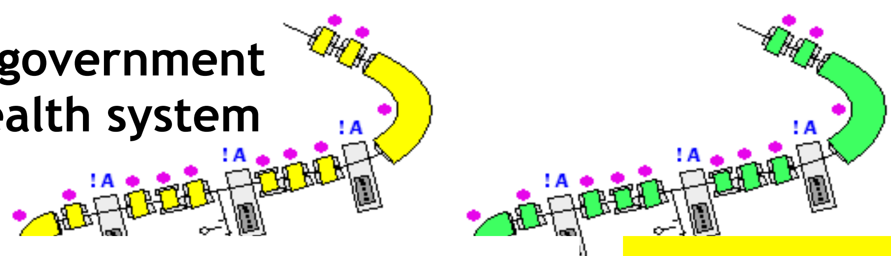


Two scanning-only 360° gantries

2D imaging in one gantry room
Ct on rail being installed in the second gantry room

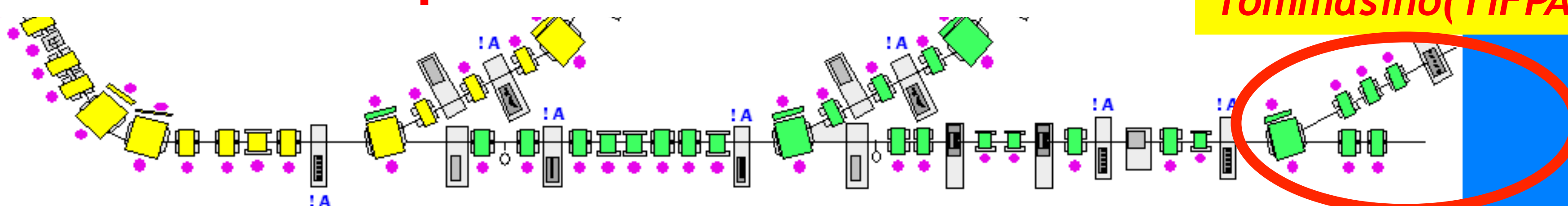


Funded by the local government
Run by the public health system (APSS)



First patient treated on 22 Oct. 2014
30 completed at 20/05/15

Research Area: see contribution by F. Tommasino(TIFPA)



The contribue of phyics to particle therapy

There is still a significant fraction of people in the clinical community who consider hadrontherapy (ion therapy) too complicate, too expensive, not able to reach in practice the expected high level of precision

Randomized clinical trials

Nuclear Physics European Collaboration Committee (NuPECC)

Nuclear Physics for Medicine

paradigmatic case of a topic in between research and actual clinical practice, where the contribution coming from physicists is fundamental

Towards improved Charged Particle Therapy (1):

- Reduction of range uncertainties
  - Imaging
  - Monitoring techniques in real time (nuclear physics)
- Radiobiology
  - Reduction of uncertainties. Models vs. Experimental data. Mechanisms?
  - Cancer stem cells
  - Hypoxia and related treatment strategies
  - in vivo + in vitro investigations
- Enhanced Particle Therapy
  - Combined treatments (ex. chemotherapy + PT)
  - Gold Nanoparticles
- Treatment Planning
  - Coupling to improved radiobiological
  - Other variables considered in optimization (ex.: Oxygen Enh. Ratio)
  - adaptive plannig; 4D planning (moving organs)
  - tumor tracking
  - fast MC-based planning

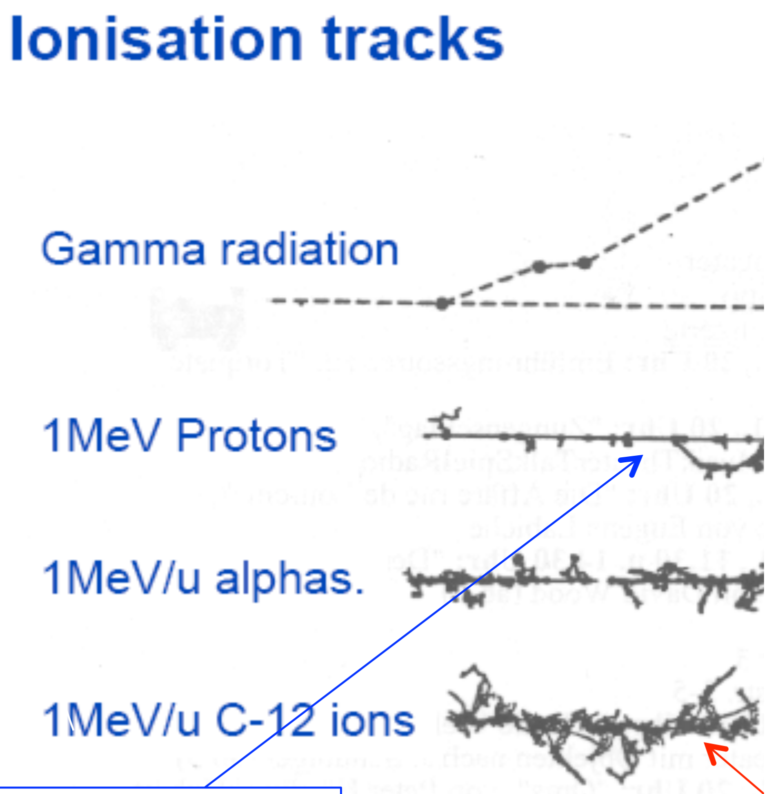
Towards improved Charged Particle Therapy (2):

- **Personalized treatments:**
  - **LET or RBE "painting" (aiming at hypoxical/radioresistant regions)**
  - **Image guided PT**
- **Use of new nuclear species (O, He, …)**
- **Hypofractionation, Radiosurgery**
- **Nuclear fragmentation and related experimental data** ***(see next talk by V. Patera)***
- **Monte Carlo development**
- **Ultrafast treatments -> Higher intensity beams**
- **Accelerator developments and cost reduction**
  - **New components (for instance: more performant ion sources)**
  - **Compact acceleration systems**
  - **New detectors for beam monitoring**
  - **Future: new acceleration techniques towards more compact structures**

→ Laser driven Plasma acceleration: a future option?

Interdisciplinary aspects: Physics and Biology

LET



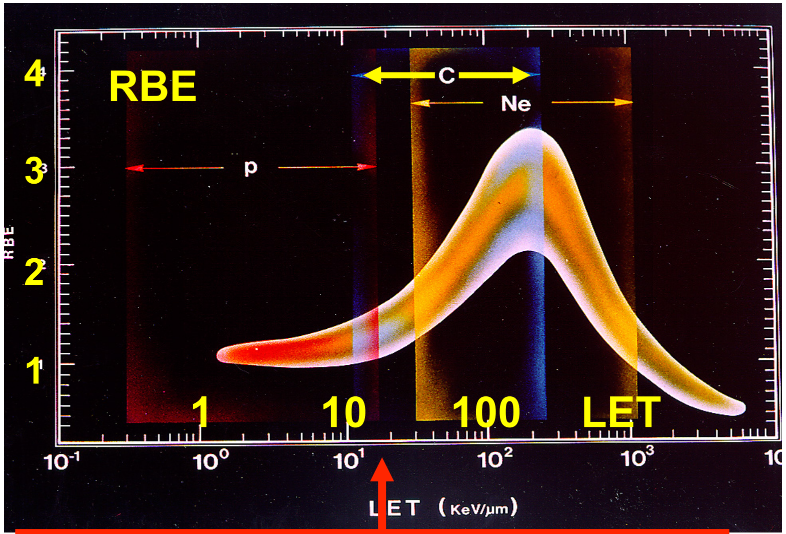
p on the Bragg peak
when Rres ~ 0.2 mm
E ~ 4 MeV
LET ~ 10 keV/µm
<d> ~ 4 nm

^{12}C on the Bragg peak
when R_{res} ~ 1 mm
E ~ 17 MeV/u
LET ~ 140 kev/µm
<d> ~ 0.3 nm

Relative Biological Effectivness

$$R.B.E. = \left(\frac{D_{RX}}{D_r} \right)_{SF=SF_0}$$

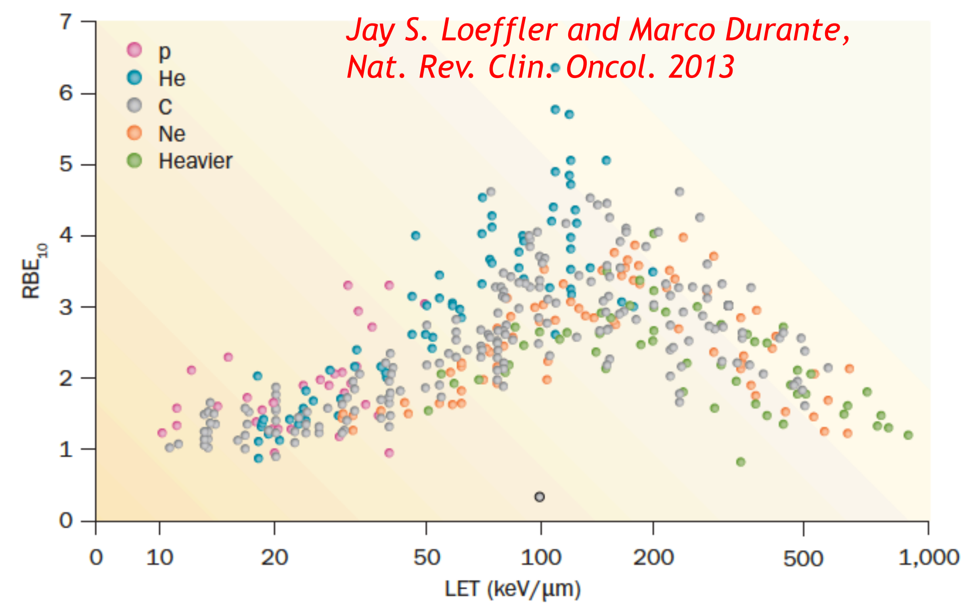
for a given type of biological end-point and its level of expression.
For example:
Survival Fraction of 10%



10 – 20 keV/µm = 100 – 200 MeV/cm =
20 – 40 eV/(2 nm)

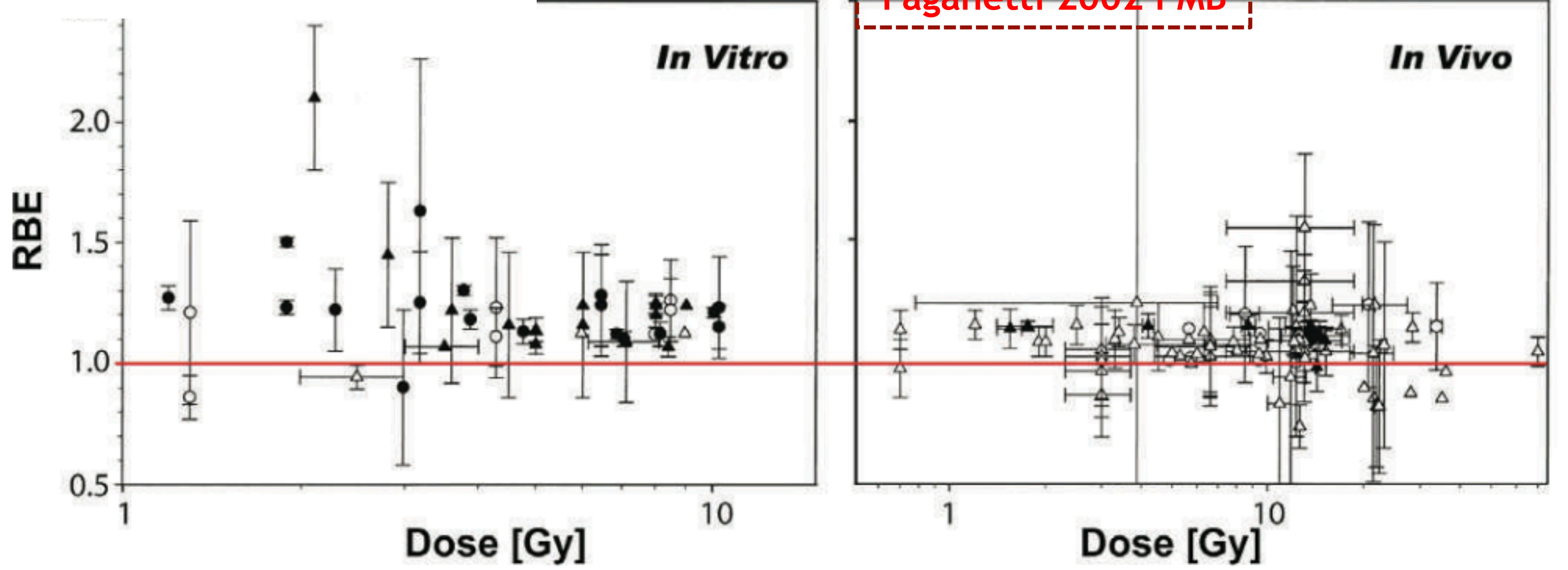
Radiobiology

RBE versus LET from published experiments on *in vitro* cell lines. RBE is calculated at 10% survival.



RBE of protons?

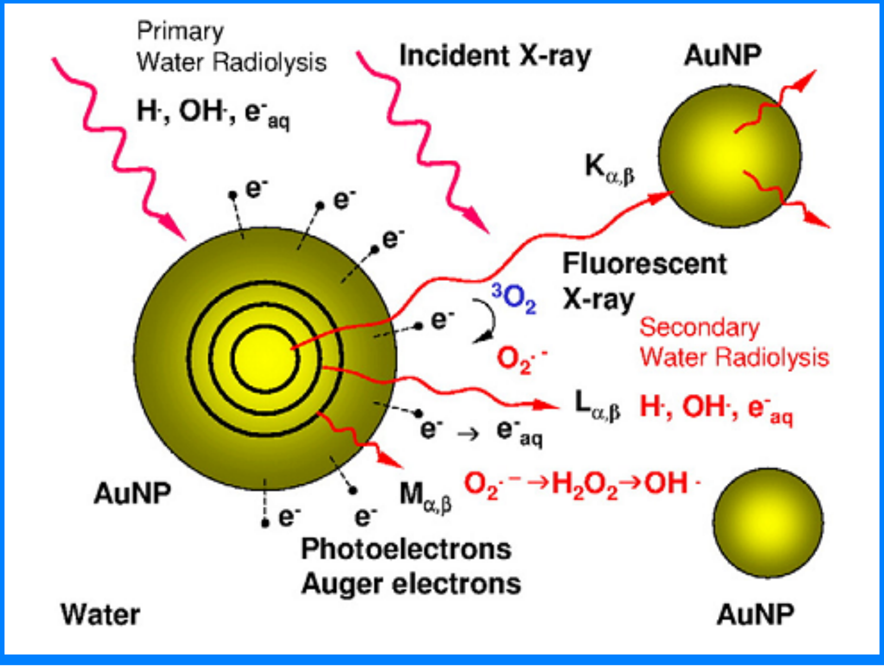
recomm.: 1.1



New Paradigm for Proton Radiobiology (Girdhani 2013 Radiat Res) → **Protons and photons present distinct physics and biological properties at Sub-Cellular, Cellular and Tissue level**

Enhanced Particle Therapy

Enhancement by Gold NanoParticles: ROS?



Specific research activity for PT under way in INFN (To & Pi)

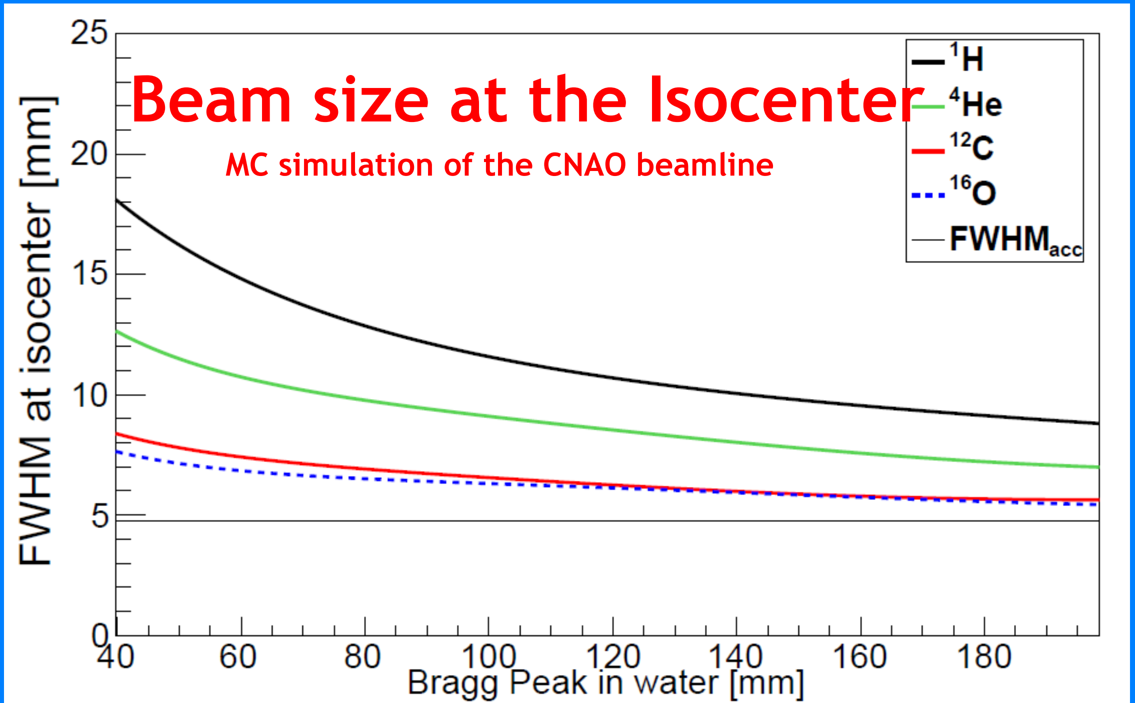
Combine effect of charged particles irradiation and anticancer drugs in cultured tumor cells.(INFN Milano and Roma 3, INT, CNAO)

-to improve locoregional tumour control and to reduce distant failure
-to reduce the total treatment Dose in radiosensitive patients

in vitro studies

see contribution by M. Lafiandra (Univ. & INFN-Mi)

New ion beams for therapy



Carbon vs Oxygen LET painting

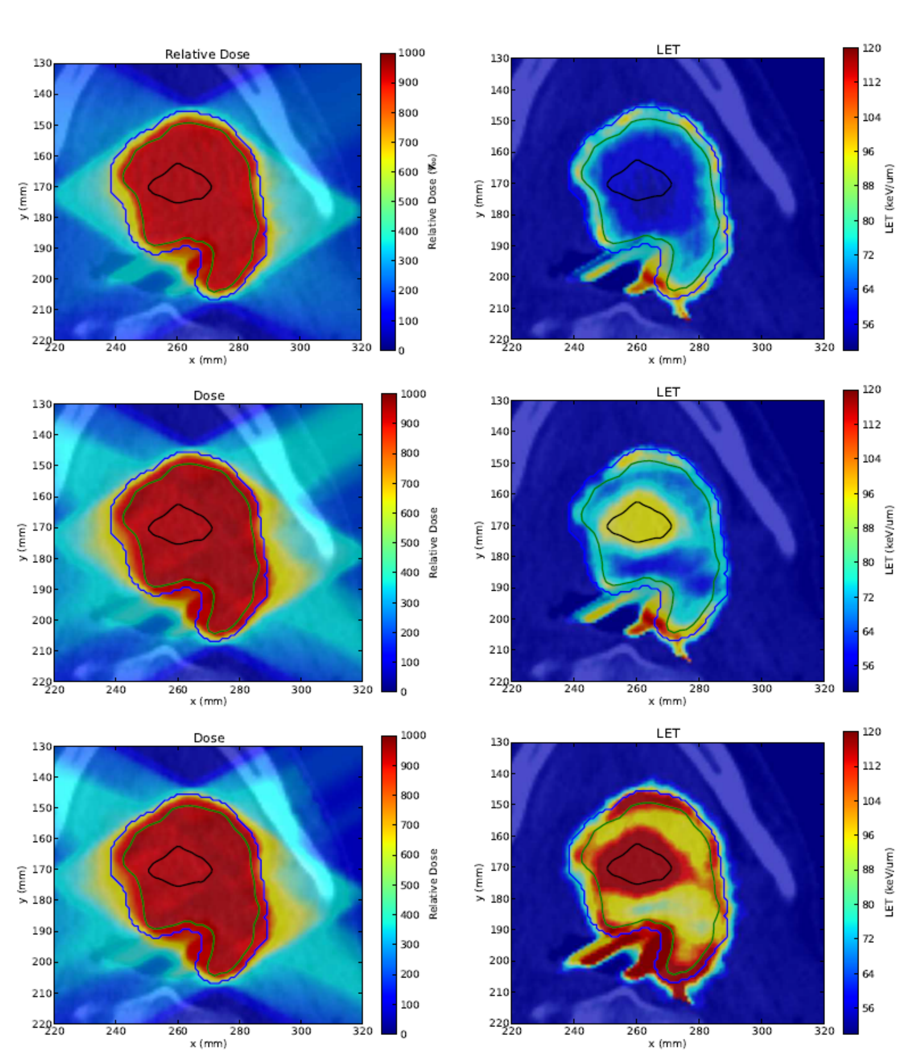
Redistribution of LET, to be maximized in a target volume applying different dose ramped fields

Carbon 4 Flat fields

Carbon 4 Dose LET painted

ions heavier than ^{12}C may be necessary in order to reduce the OER to sufficient levels. ^{16}O along with a slight dose boost could be a promising candidate when targeting hypoxic structures of 1 – 4 cm 3 in size. In vitro and in vivo radiobiologic experiments are needed to proceed towards clinical trials necessary to validate the true potential of LET-painting.

Oxygen 4 Dose LET painted



Bassler, Toftegaard, Luhr, Sorensen, Scifoni, Krämer, Jäckel, Mortensen, Petersen, Acta Oncol 2014

Uncertainties related to particle range

The error intrinsic in this conversion (due to $\mu(\eta_e,Z)$ dependency on atomic number and electron density) is the principal cause of proton range indetermination (3%, up to 10 mm in the head)

[Schneider U. (1994), Med Phys. 22, 353]

AAPM 2012: **main obstacle to proton therapy becoming mainstream:**

- **35 % unproven clinical advantage of lower integral dose**
- **19 % never become a mainstream treatment option**
- **33 % range uncertainties**

A new imaging approach:

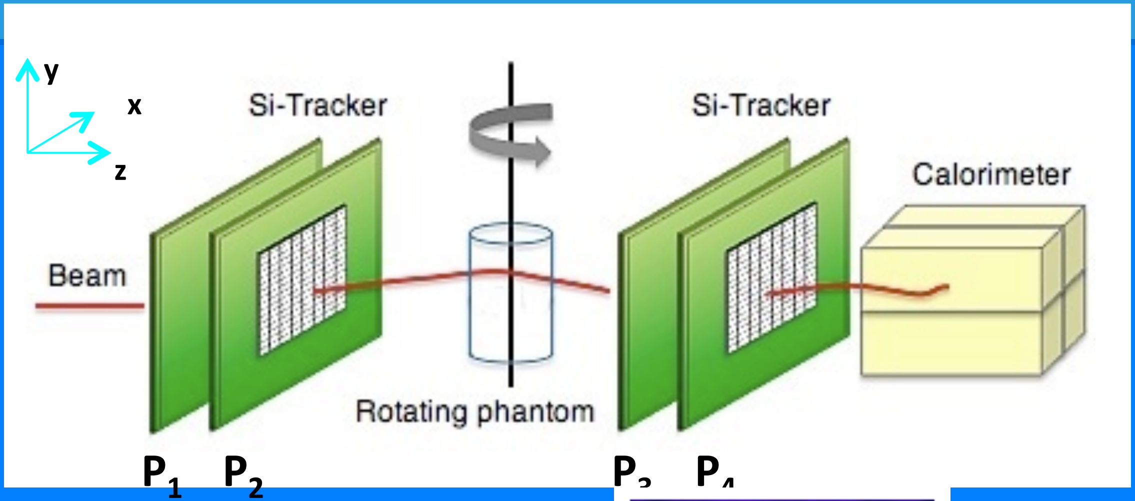
from Computed Tomography using X rays to Proton Computed Tomography (pCT)

$$\int_L \eta_e(\vec{r})\, d\vec{r} = K \int_{E_{out}}^{E_{in}} \frac{dE}{S(E)}$$

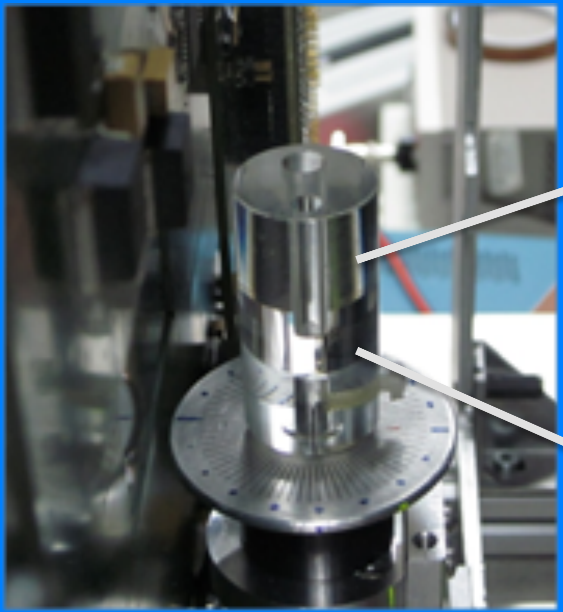
E_{in} is the incident proton energy and E_{out} is the proton energy after traversing through the object, $S(E)$ is the proton stopping power, and K is a constant.

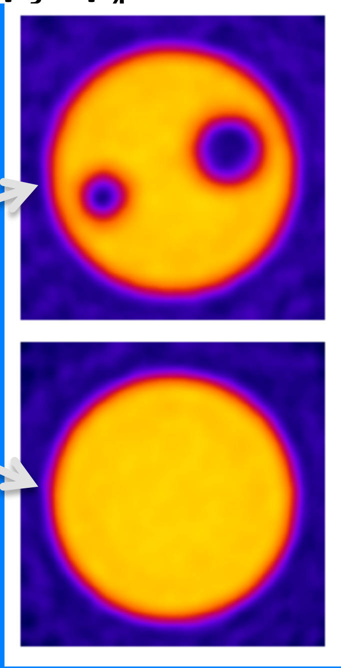
Proton CT: the INFN approach

INFN
Fi-Ct-LNS



Low Energy test
PMMA phantom
36 projection steps:
0° → 360°
An average of 950000 events per projection
E_0=62MeV INFN-LNS
Filtered Back Projection



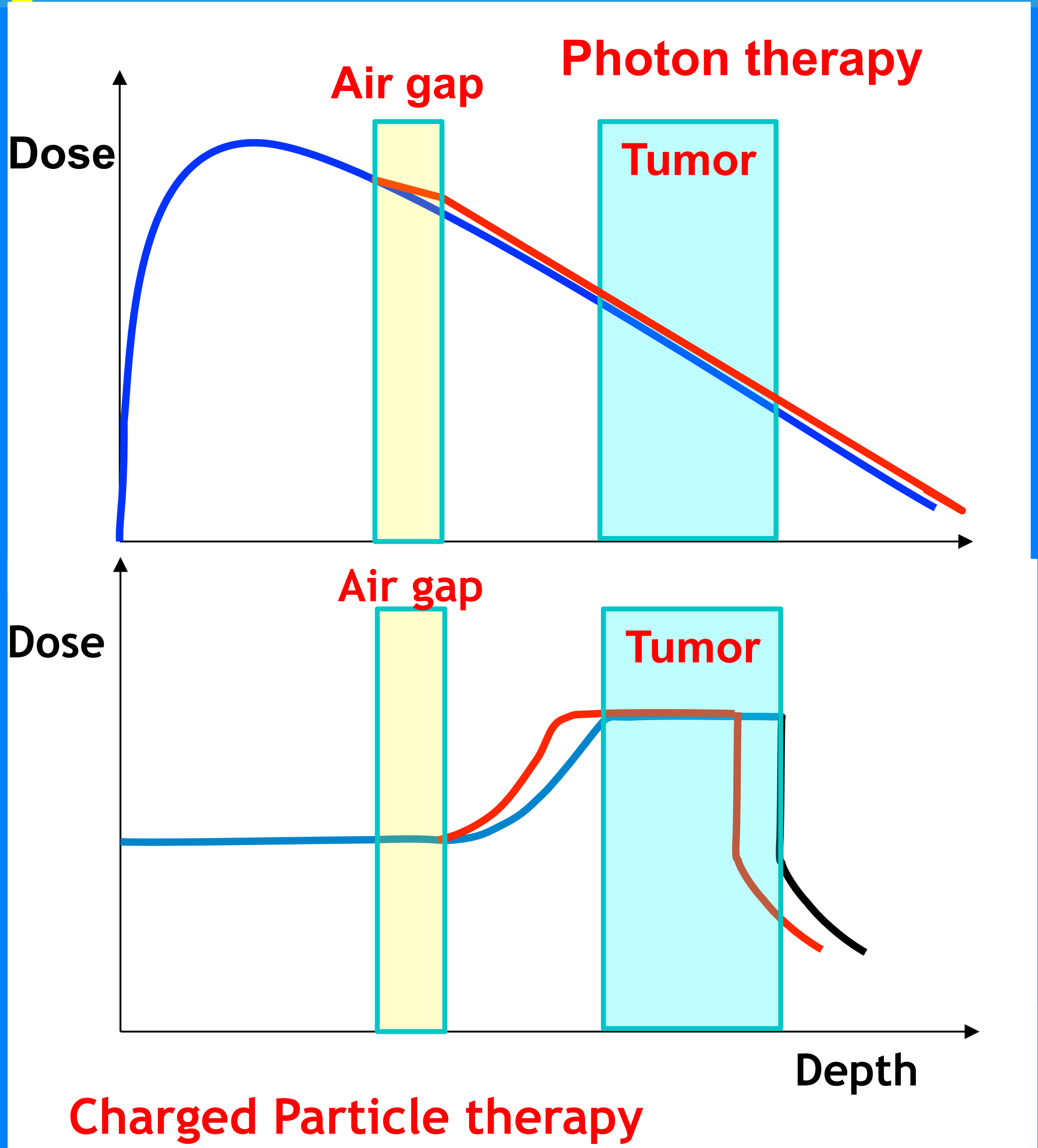


(see contribution by C. Civinini (INFN-Fi)

Key issues: appropriate reconstruction algorithms to produce tomographic images. More complicate that with X-Rays!

The need for in-vivo monitoring of particle therapy

Again uncertainties:
a) dose calculation
b) imaging artefacts, positioning errors
c) Organ motion
d) Anatomic/physiologic variations

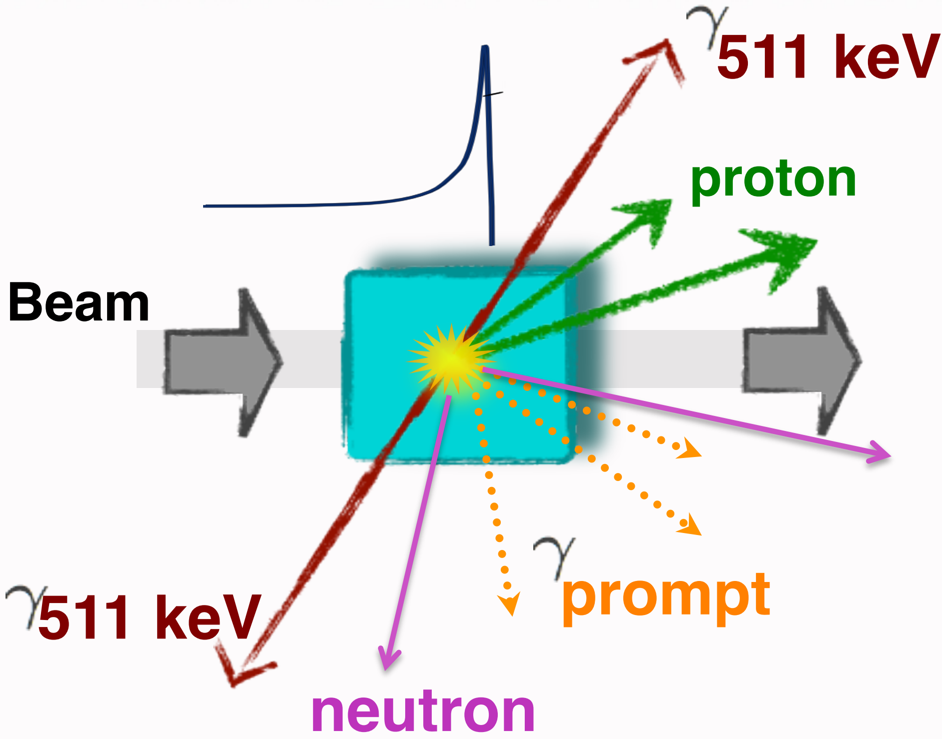


Help from Nuclear Physics: exploiting secondary products

The therapeutic beam is absorbed inside the patient: a monitor device can rely on secondaries, generated by the beam coming out from the patient. The p, ^{12}C beams generate a huge amount of secondaries: prompt γs, PET- γs, neutrons and charged particles/fragments

Activity of β^+ emitters is the baseline approach

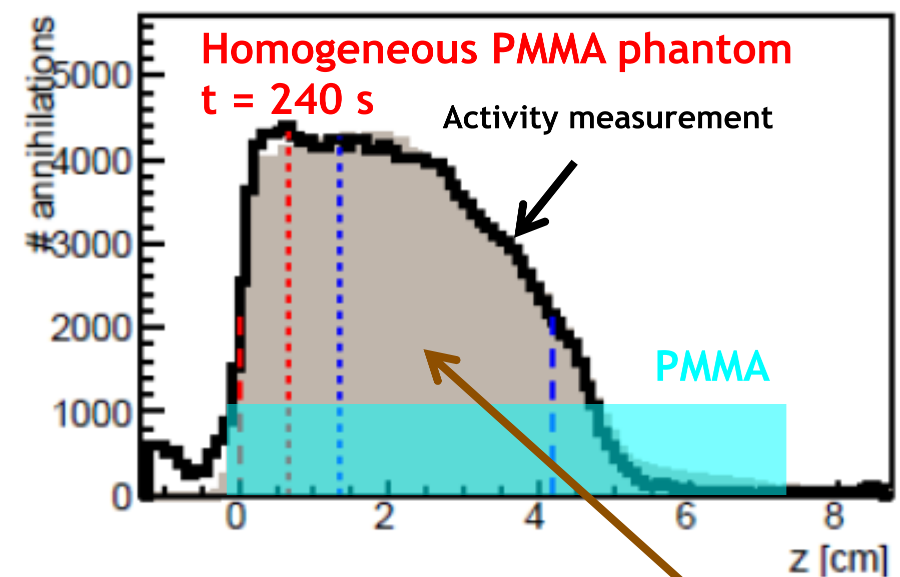
- Isotopes of short lifetime ^{11}C (20 min), ^{15}O (2 min), ^{10}C (20 s) with respect to conventional PET (hours)
- Low activity asks for quite a long acquisition time (some minutes at minimum) with difficult in-beam feedback
- Metabolic wash-out, the β^+ emitters are blurred by the patient metabolism

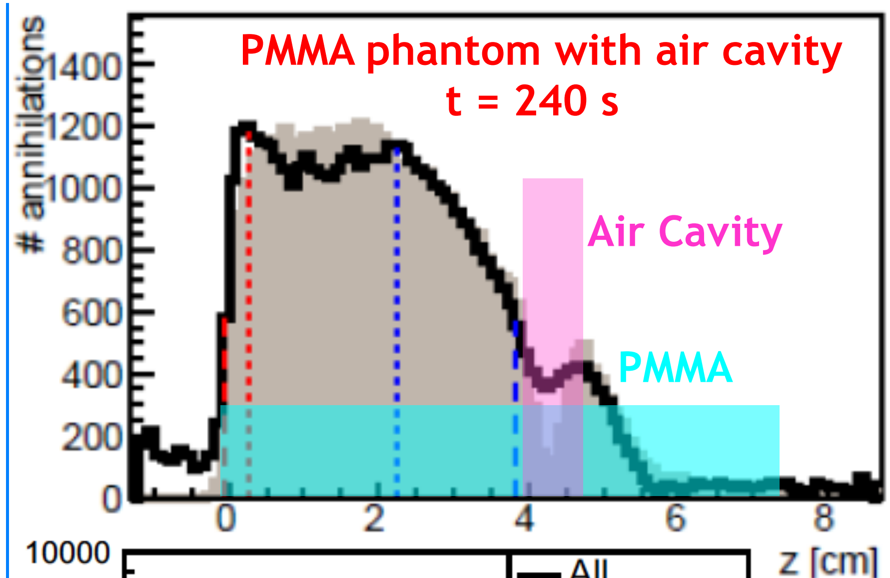


Spotting structures with β⁺ activity measurement in-beam (proton beam at CNAO)

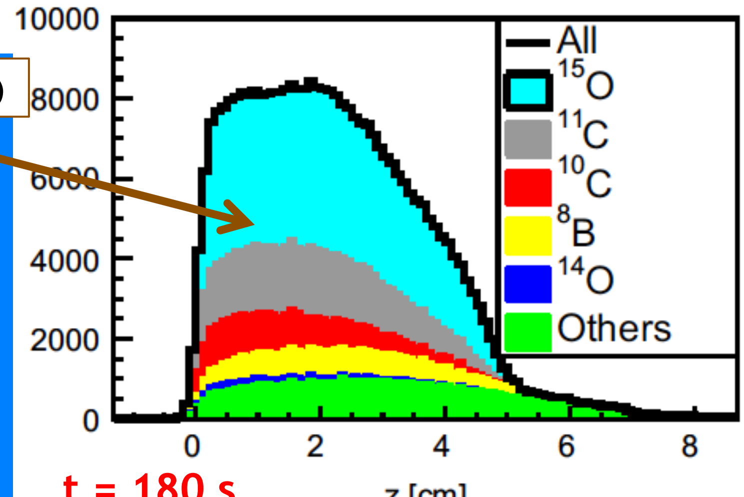
A.C. Kraan, G. Battistoni, N. Belcari, N. Camarlinghi, M. Ciocca, A. Ferrari, S. Ferretti, A. Mairani, S. Molinelli, M. Pullia, P. Sala, G. Sportelli, A. Del Guerra, V. Rosso, NIM A *786, (2015) 120-126*

2 Gy uniform dose in 3x3x3 cm^3
17 energies: 62.3 - 90.8 MeV
146 s





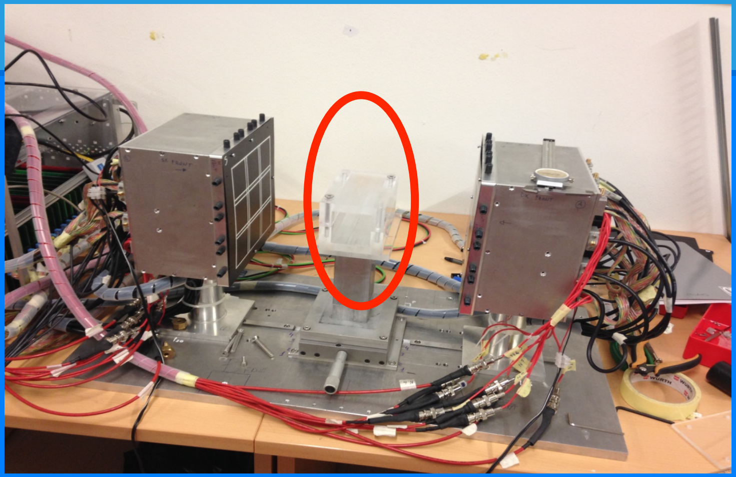
Mont Carlo prediction (FLUKA)



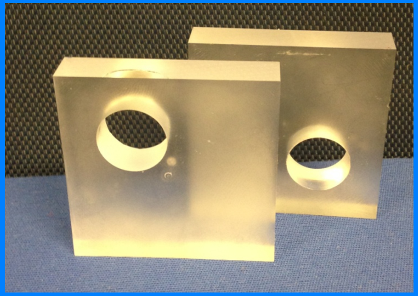
t = 180 s

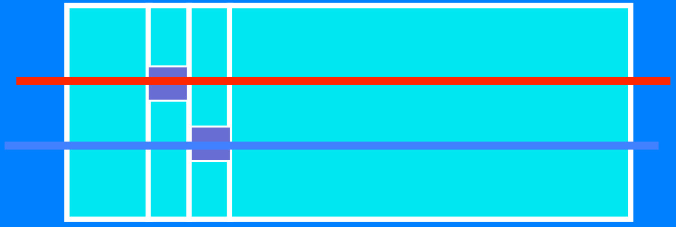
In-beam PET is a base-line solution but:
➡ Hard to go really "online" which is necessary to avoid "metabolic washout"
must sustain high rates (PET + prompt γ + n)

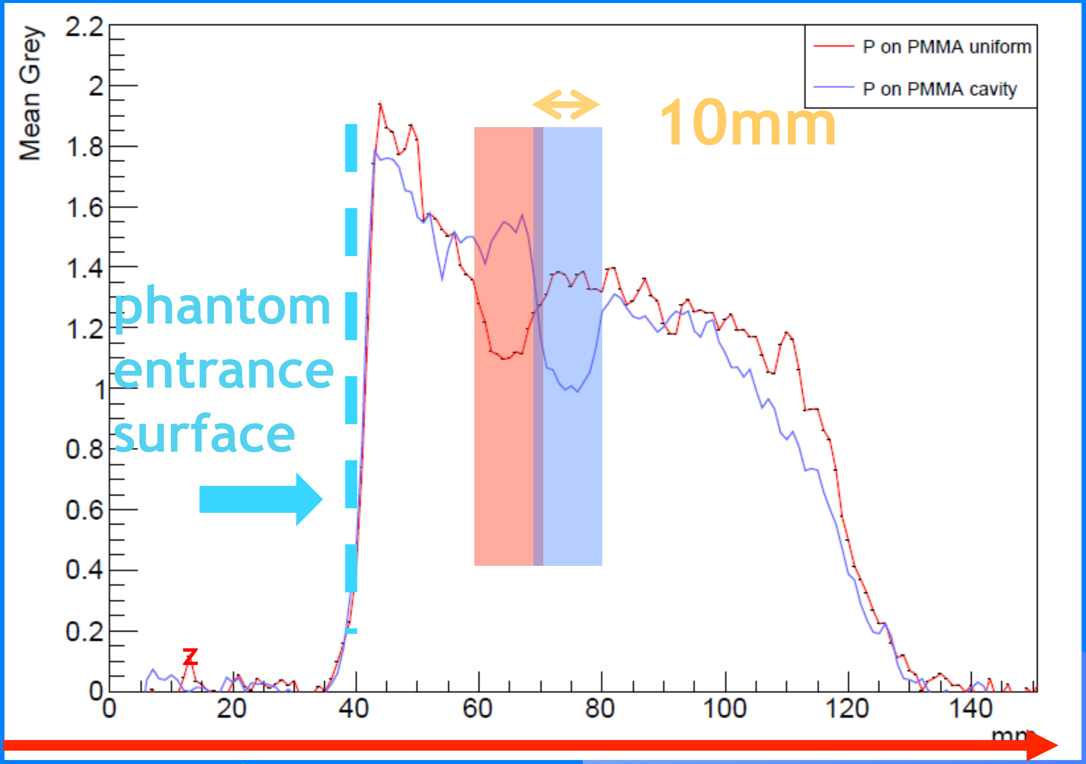
Test with Carbon Plan at CNAO



see contribution by F. Collini (Univ. Siena & INFN-Pi)



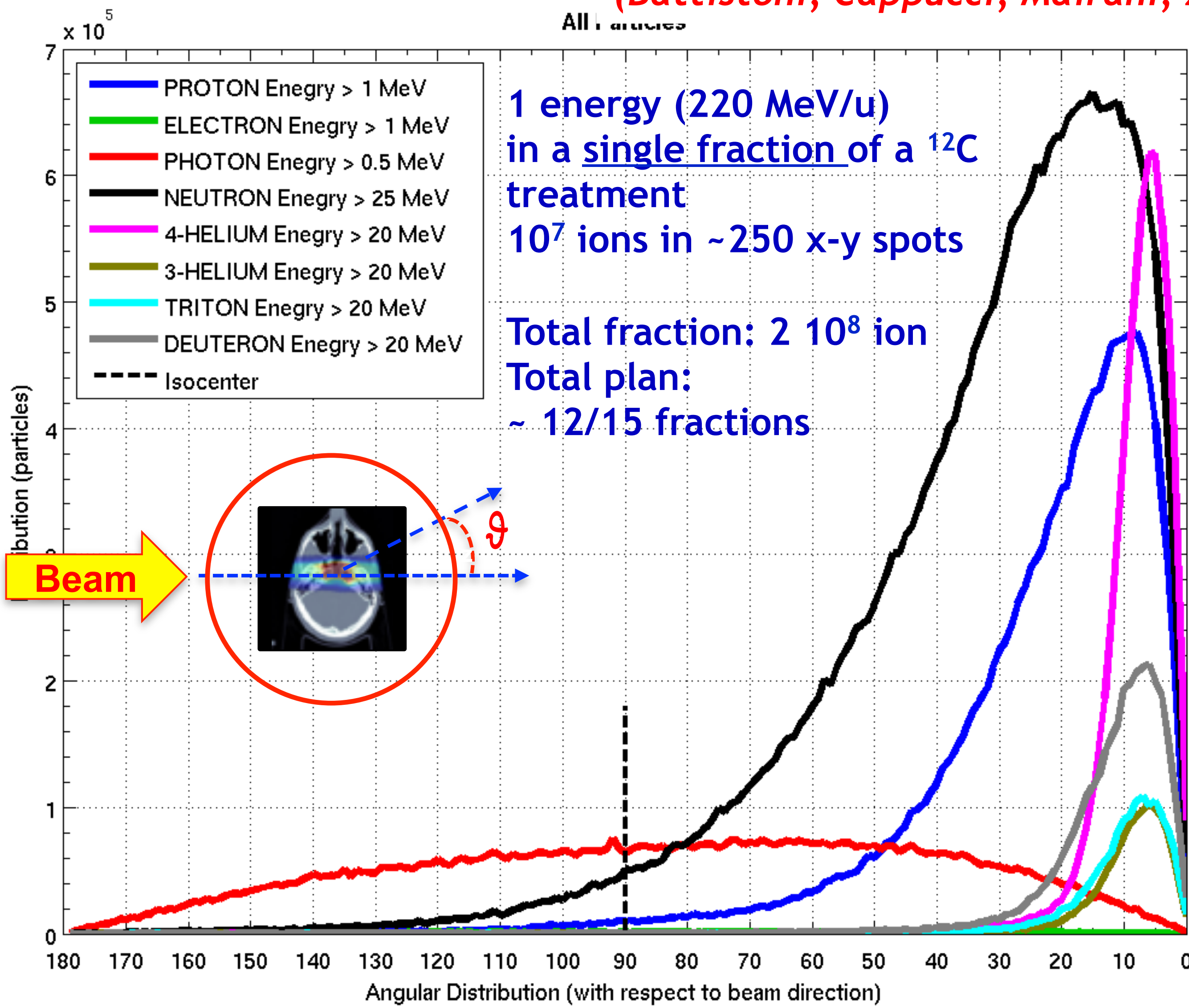




V. Rosso et al,
presented at 13° Pisa Meeting on Advanced Detectors 2015
Paper in prepariation

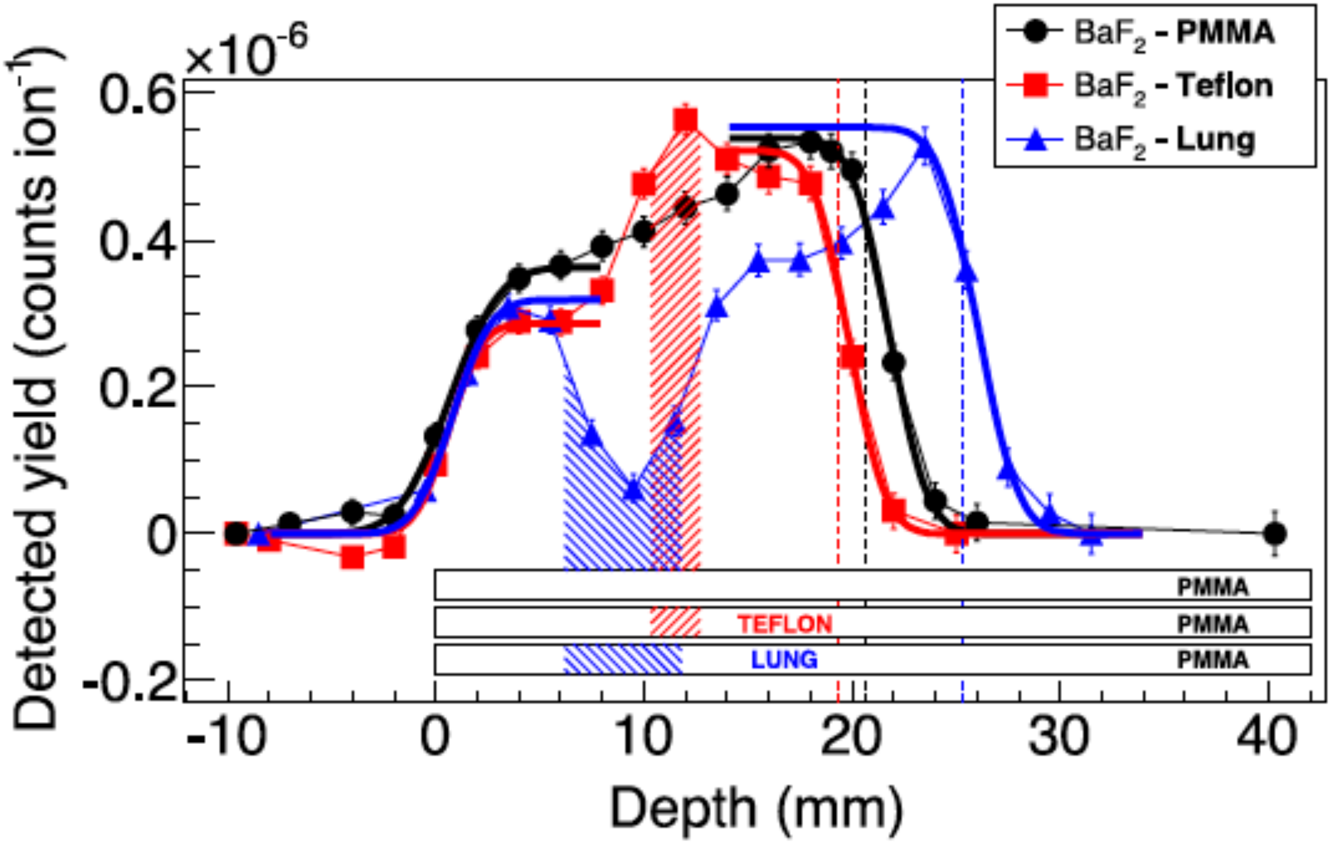
How many particles/fragments out of a patient?

MC simulation of a 12C treatment plan on a patient (CNAO)
(Battistoni, Cappucci, Mairani, 2014)



Exploiting "prompt" nuclear de-excitation photons

M. Pinto, et al, Med. Phys. 42 (5), May 2015



- $4 \cdot 10^9$ /fraction (2 Gy)
- γ-energy: 0… ~8 MeV

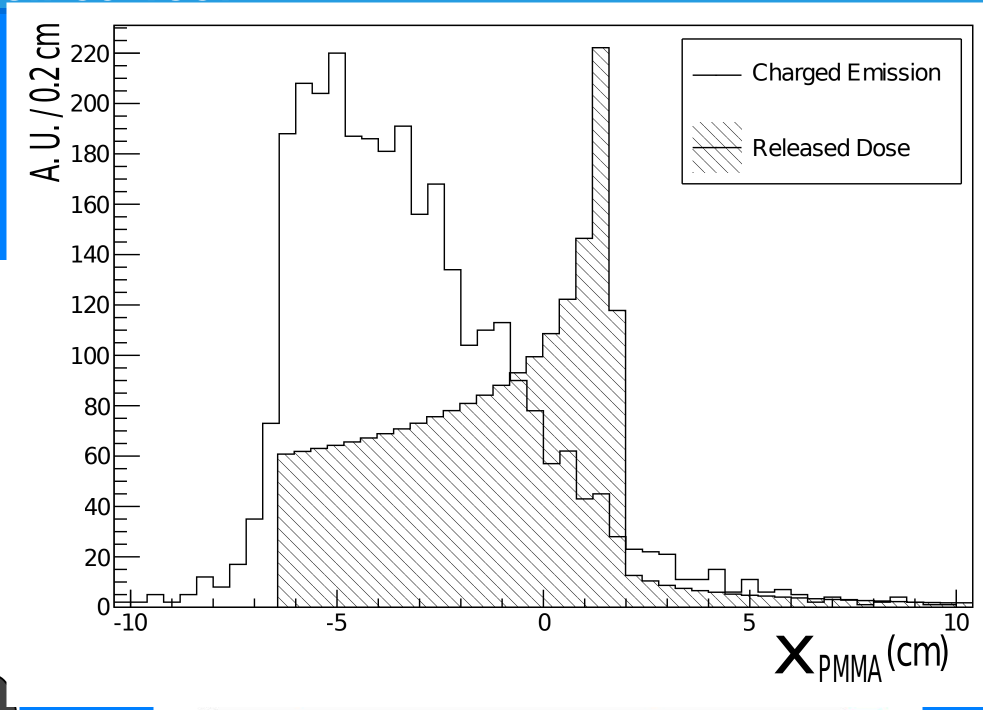
not suited for standard gamma-imaging devices of nuclear medicine

Key issue is the detection efficiency when trying to backtrack the γ
- Collimated detection approach suffers for reduced statistics)
- Compton camera approach suffers for low detection/reconstruction efficiency

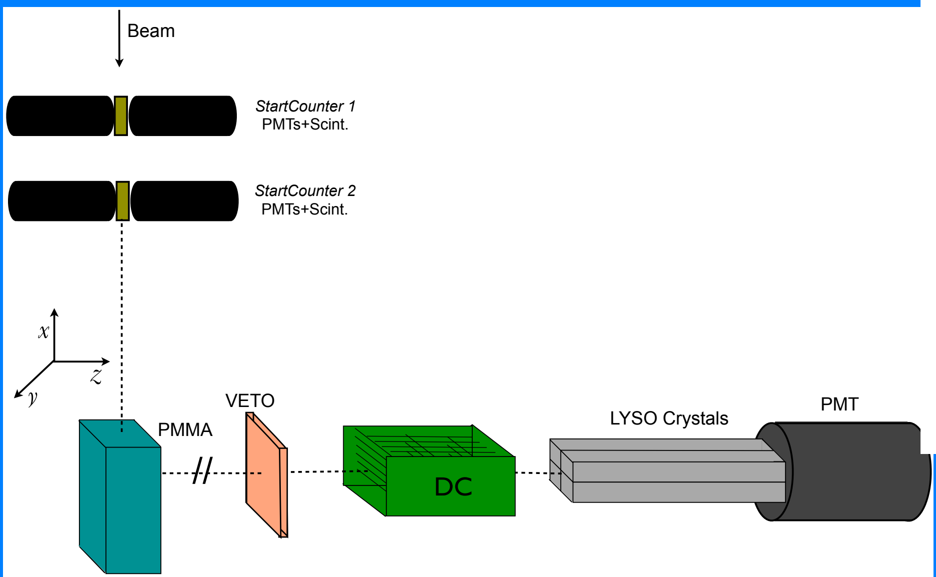
→ New IBA system for proton therapy ready for the market

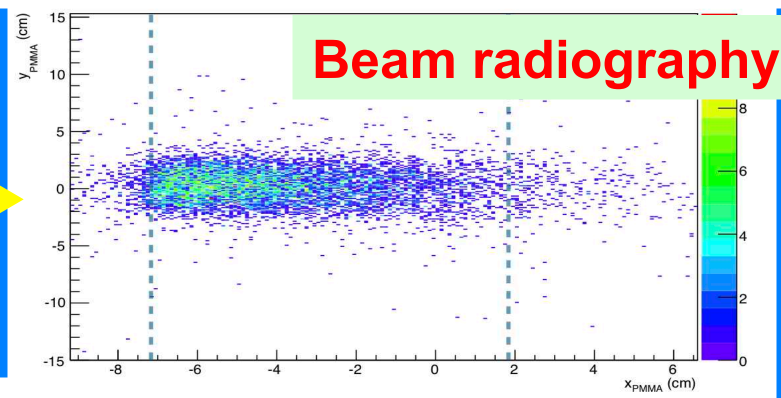
Use of charged secondary production

L. Piersanti et al. 2014 *Phys. Med. Biol.* 59 1857



Charged secondary produced at 90^0 by ^{12}C 220 MeV/u at GSI





Beam

Beam

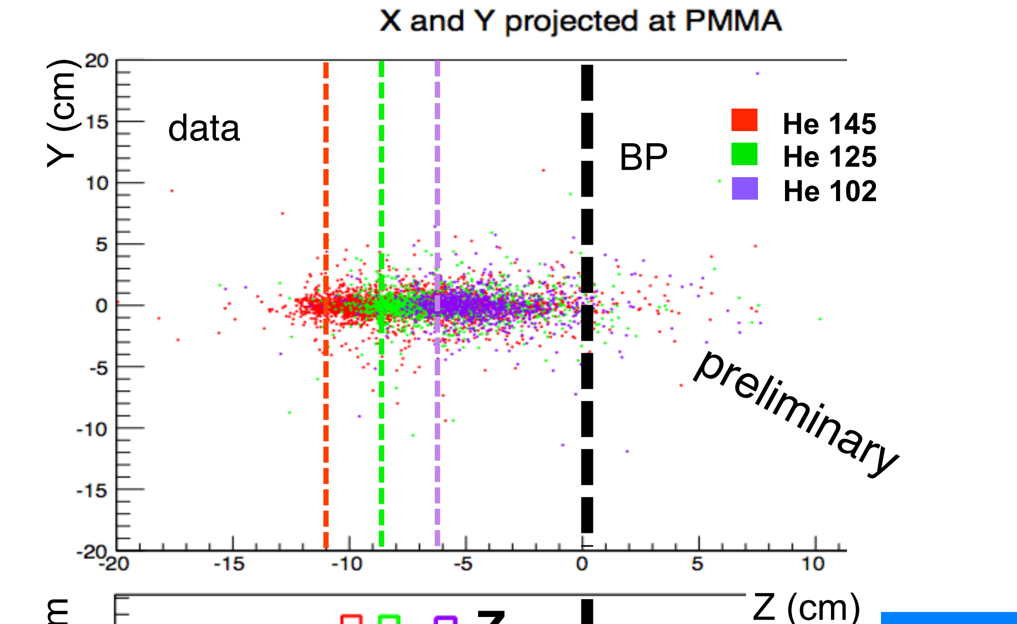
$$\frac{dN_{\rm p}}{N_{\rm C}d\Omega}(\theta = 90°) = (1.83 \pm 0.02_{\rm stat} \pm 0.14_{\rm sys}) \times 10^{-3}\ sr^{-1}$$

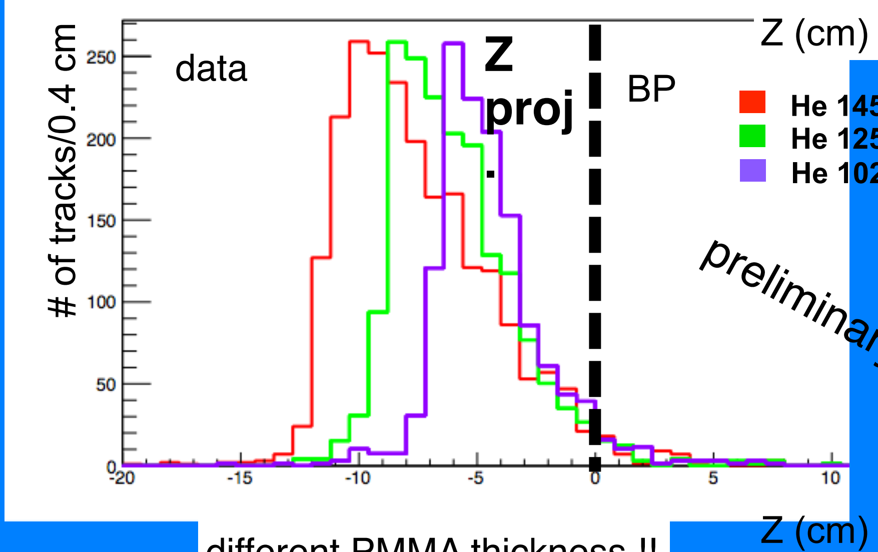
BP monitoring on He beams

- A non negligible production of charged particles at large angles is observed for all beam types
- The emission shape is correlated to the beam entrance window and BP position as already measured with ^{12}C
- $\phi = dN_{all}/(N_{ions}\, d\Omega)$

Beam type/E	φ 90° (10^{-3})
He 102	0.6
He 125	0.7
He 145	1
C 160	1
C 180	2
C 220	3
O 210	3
O 260	5
O 300	10

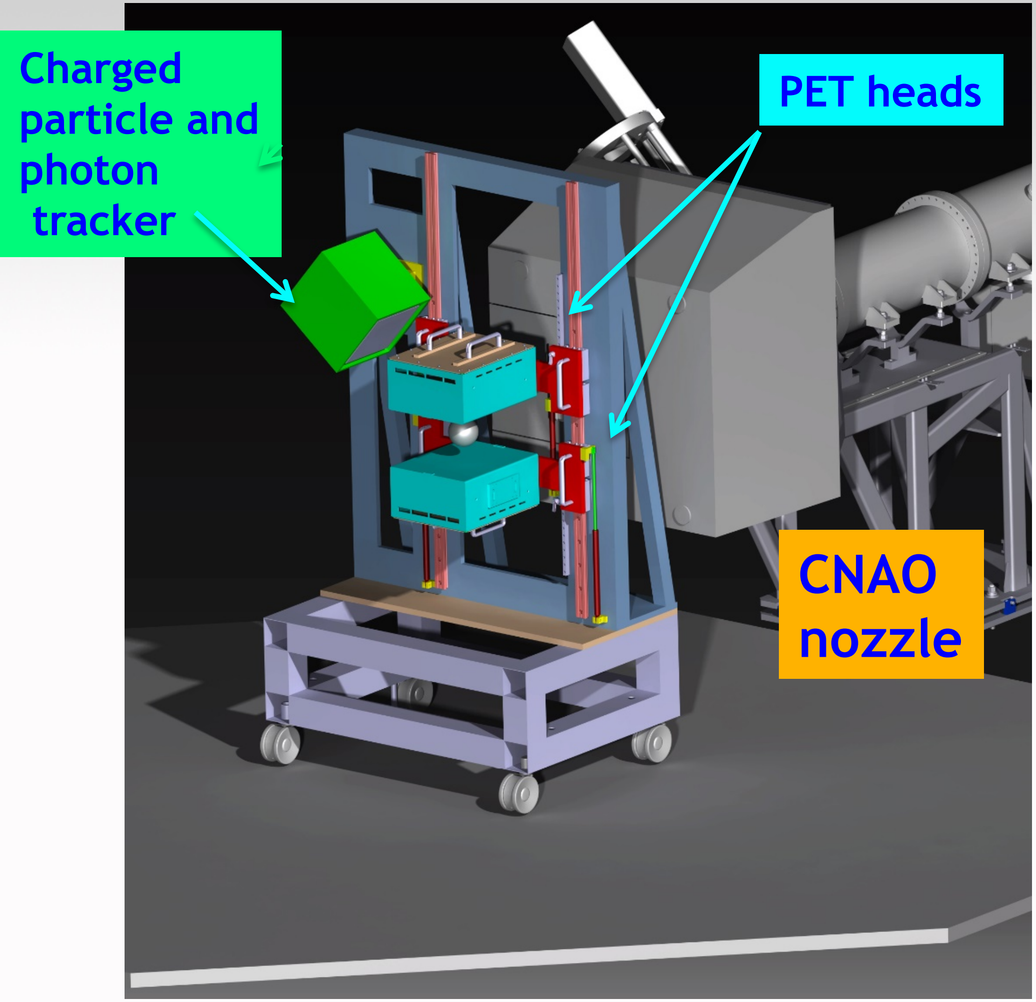
preliminary





different PMMA thickness !!

The InSide Project



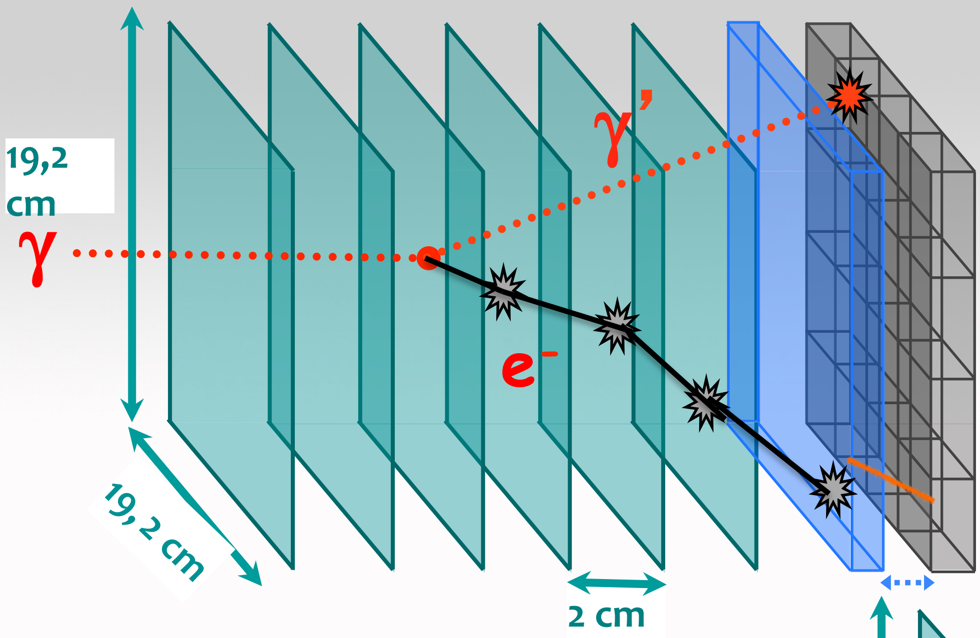
INnovative Solutions for In-beam DosimEtry in Hadrontherapy

see contribution by M.A. Piliero (Univ. & INFN-Pi)

Designed to:

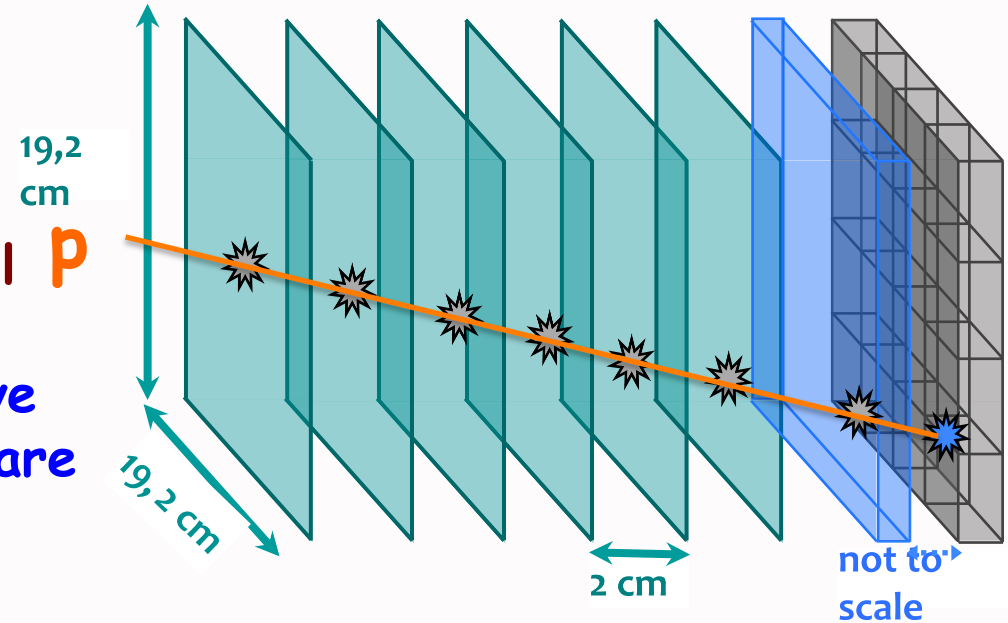
- be operated in-beam
- provide an IMMEDIATE feedback on the particle range

INSIDE Dose Profiler: prompt secondaries



"dual mode" detector

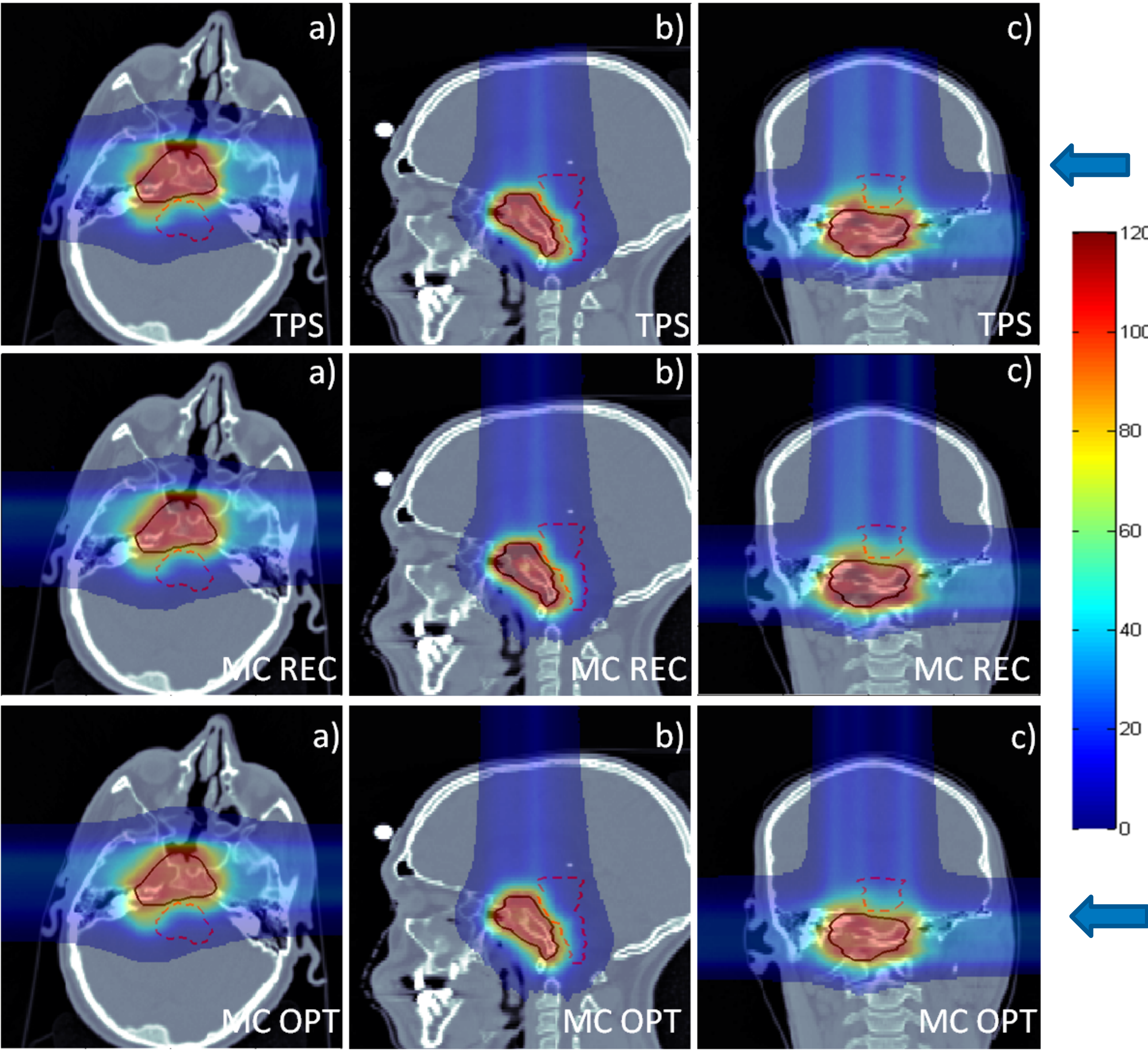
- Compton camera for prompt photons (Eg~1-10 MeV)
- Tracking device for charged secondaries (E_{kin} ~ 30-130 MeV)



Heavy charged secondary cross all TRK planes up to LYSO crystals

Electrons from Compton event have winding tracks (mul. scatt.) and are not detected in the LYSO

Monte Carlo for TP verification and optimization



The Syngo TPS prescription

MC fw simulation of TPS prescription

Mairani A, et al.
PMB 58 (2013) 2471-2490

3-port chordoma case treated with protons at CNAO

Result of MC Optimization

Fast calculations and dose verification

In-room imaging for patient positioning Cone-Beam CT (CBCT)

- patient positioning
- geometry match
- delivery uncertainties

see contribution by A.Vignati (INFN-To) about RIDOS project

Two lines of development
(GPU calculation approach)

1. Dosimetric verification of TP on the day of treatment and possibly its fast recalculation

2. Fast MC-based Treatment Planning optimization/recalculation

Beam monitoring developments in view of new high-intensity beams

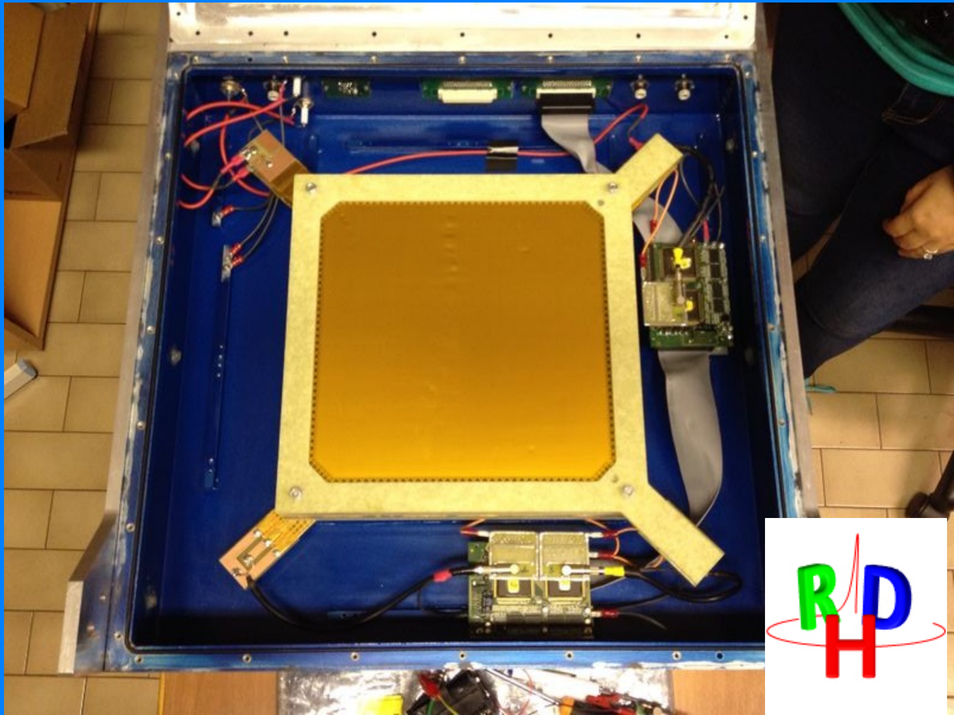
Development of monitor chamber for high intensity beam:

- Pulsed beam with duty-cycle of the order of 10^{-3}
- Pulse intensity 10^3 times higher than the continuos beam
- In this operation condition standard ionization chambers are inefficient because of space charge recombination.

INFN-To:

Innovative monitor based on

- New multigap ionization chamber with different gap geometry (0.5,1,1.5 cm) can be used to correct the response saturation
- New dedicated integrated electronic must be designed and produced to deal such a high current

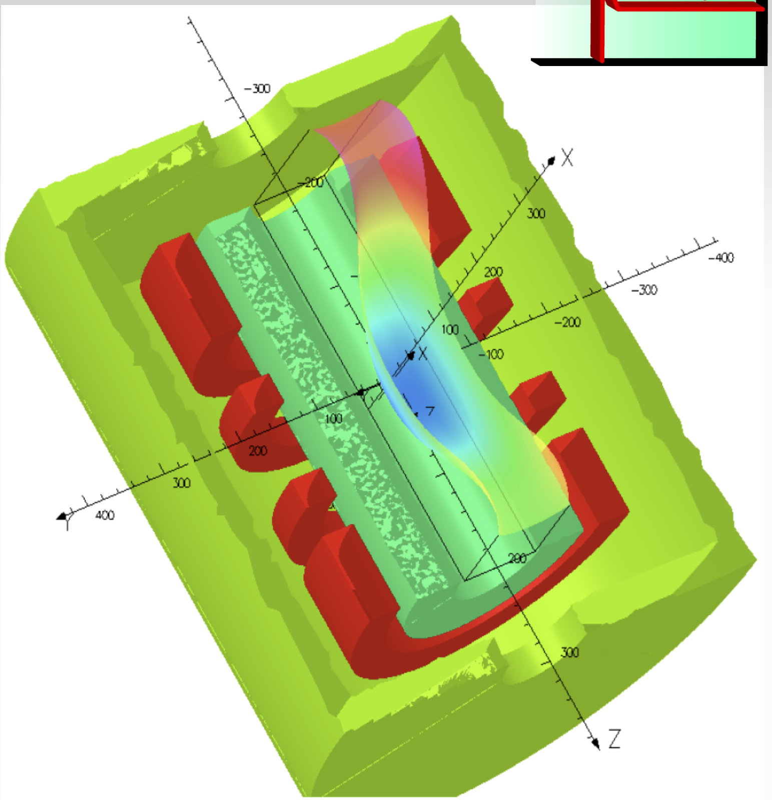


see contribution by F. Fausti (Politec. & INFN-To, De.Tec.Tor.) Premio Guglielmo Marconi per Trasf. Tec.

AISHa - Advanced Ion Source for Hadrontherapy
INFN - LNS

AISHA is a hybrid ECRIS: the radial confining field is obtained by means of a permanent magnet hexapole, while the axial field is obtained with a **Helium-free superconducting system.**

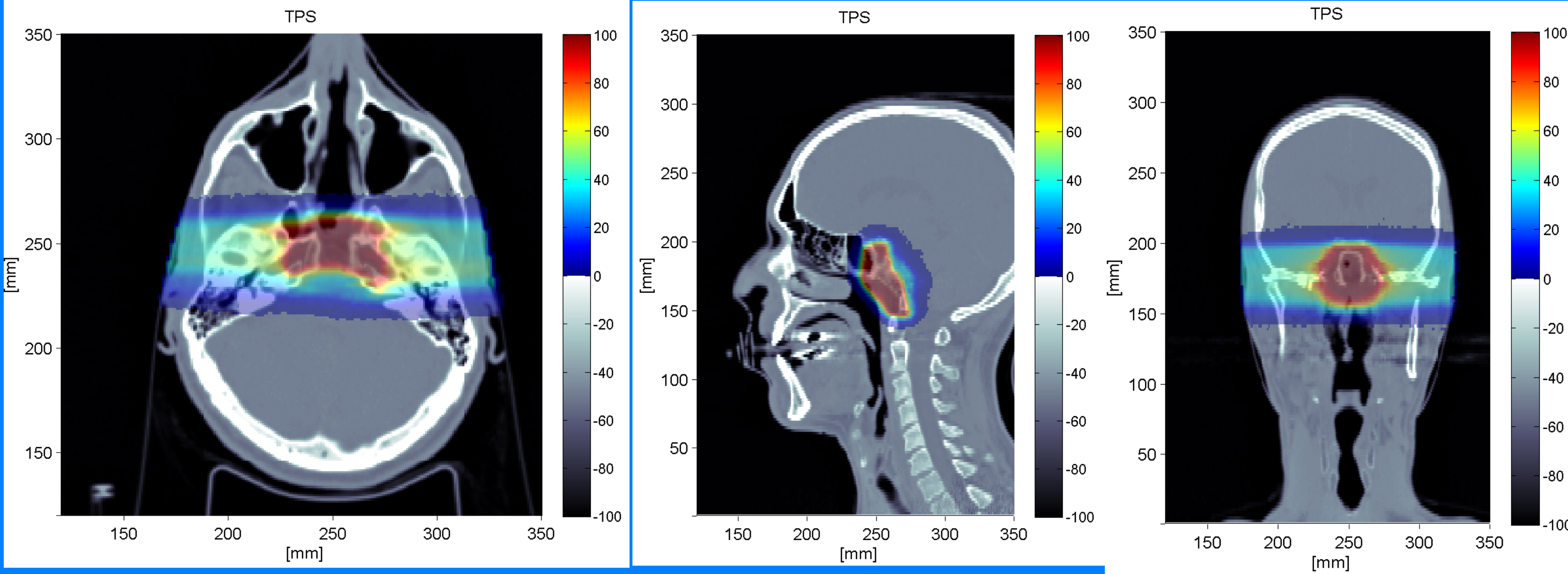
The **operating frequency of 18 GHz will permit** to maximize the plasma density by employing commercial microwave tubes meeting the <u>needs of the installation in hospital</u> environments.



Radial field	1.3 T
Axial field	2.7 T - 0.4 T - 1.6 T
Operating frequencies	18 GHz – 21 GHz
Operating power	1.5 + 1.5 kW

Ion beam production (eμA)

Ion	Supernanogan (14 GHz)	AISHa (18 GHz + TFH)	ASIA (24 GHz + TFH)
H^+	2000	4000	//
$^{3}He^+$	800	2000	//
$^{12}C^{4+}$	250	800	2000
$^{18}O^{6+}$	400	1000	2500



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