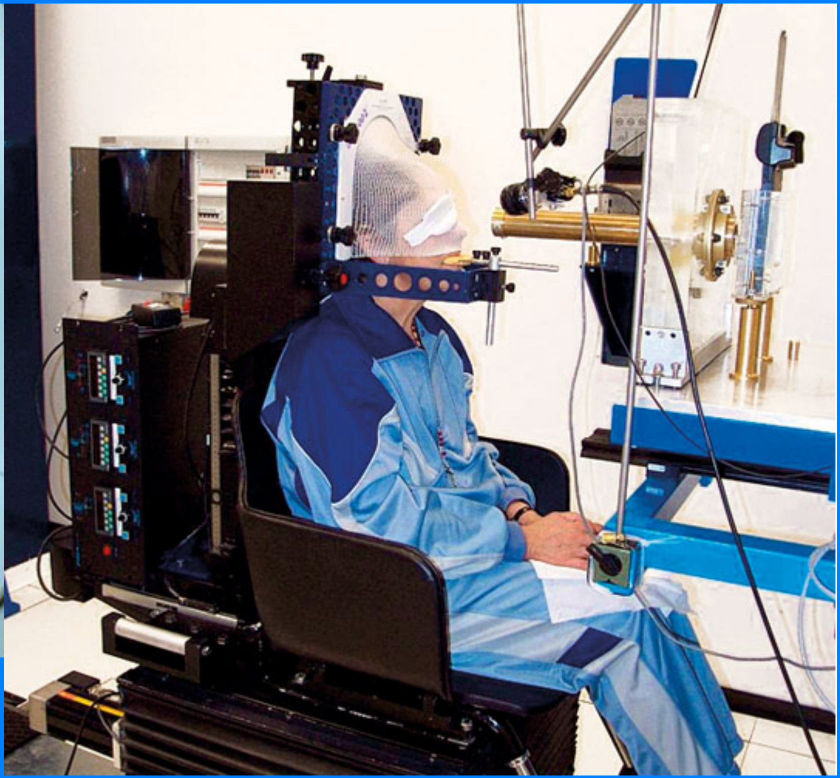


Nuclear Physics and Hadrontherapy

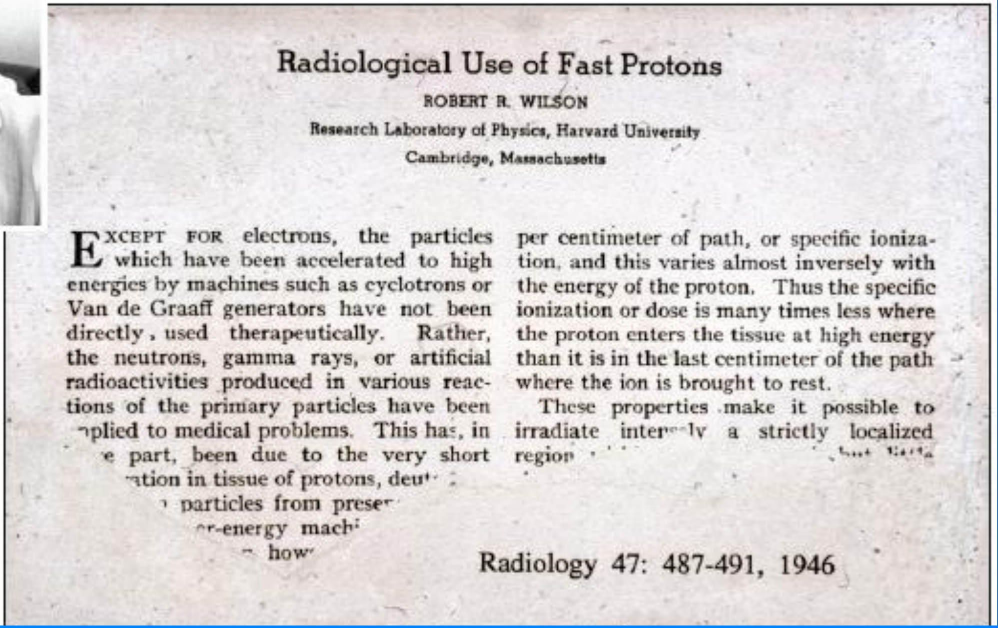
Giuseppe Battistoni,
INFN, Milano, Italy

European Network for
Light Ion Hadron Therapy

Hadrontherapy: the history

Hadron RT was proposed by Robert Wilson in 1946

R.R. Wilson, "Foreword to the Second International Symposium on Hadrontherapy," in Advances in Hadrontherapy, (U. Amaldi, B. Larsson, Y. Lemoigne, Y., Eds.), Excerpta Medica, Elsevier, International Congress Series **1144**: ix-xiii (1997).



Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University

Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly, used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been …plied to medical problems. This has, in …e part, been due to the very short …ation in tissue of protons, deu… …particles from prese… …r-energy mach… …how…

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate inter…ly a strictly localized region …

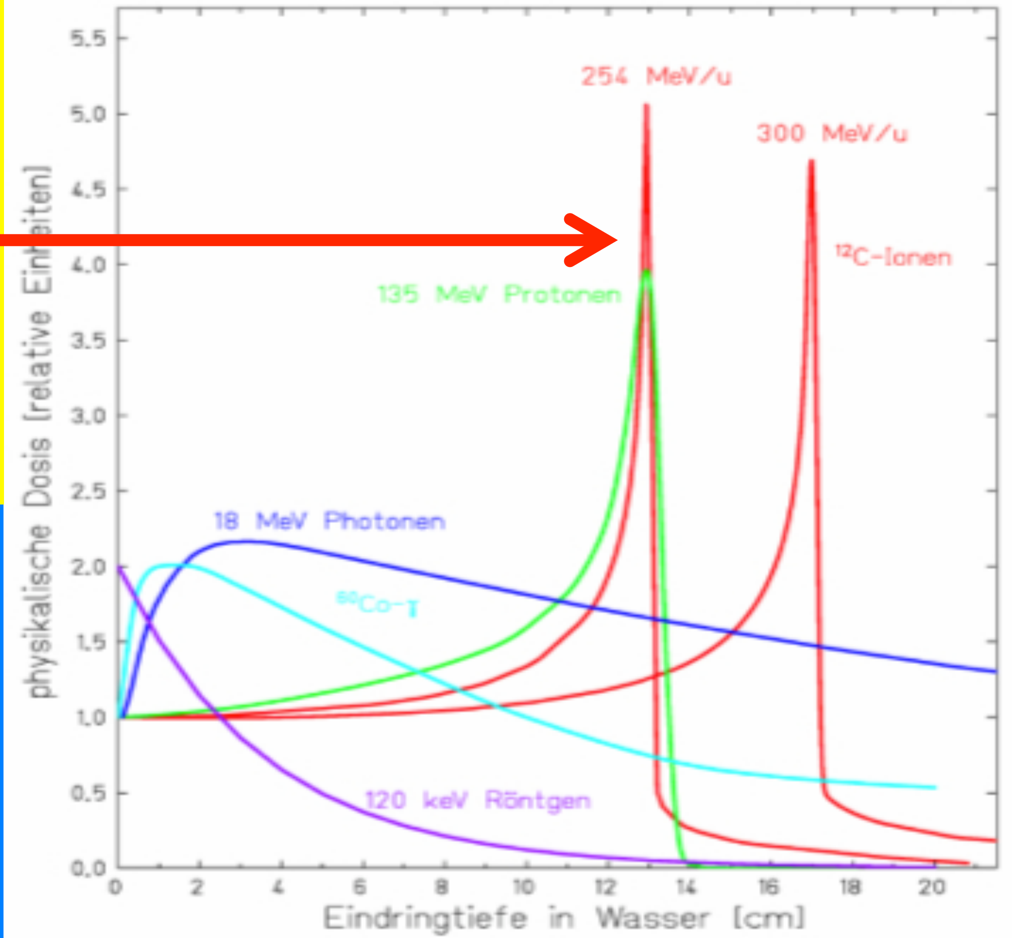
Radiology 47: 487-491, 1946

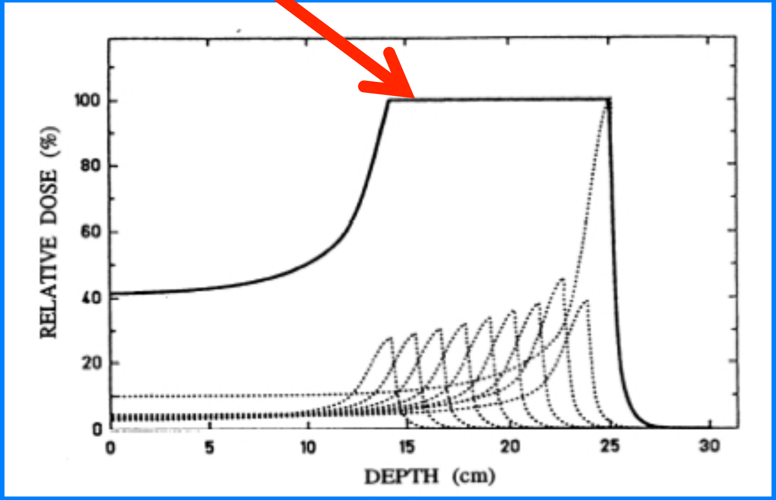
1954 - Berkeley treats the first patient and begins extensive studies with various ions
1957 - first patient treated with protons in Europe at Uppsala
1961 - collaboration between Harvard Cyclotron Lab. and Massachusetts General Hospital
1993 - patients treated at the first hospital-based facility at Loma Linda
1994 - first facility dedicated to carbon ions operational at HIMAC, Japan
2009 - first European proton-carbon ion facility starts treatment in Heidelberg

Charged Particle Therapy (hadrontherapy): the advantages

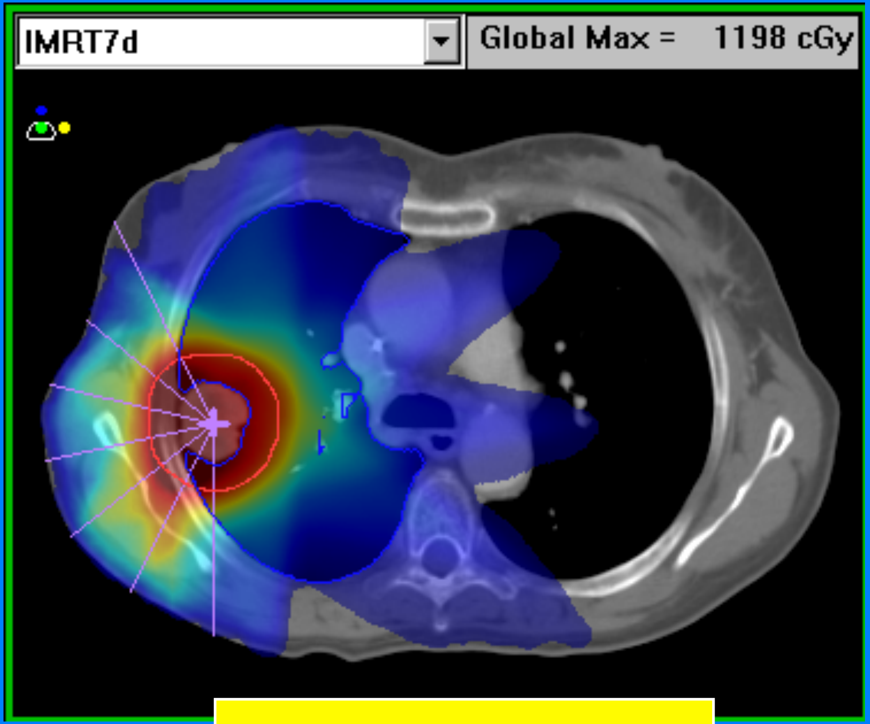
The highest dose released at the end of the track, sparing the normal tissue

- 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 (SOBP)**



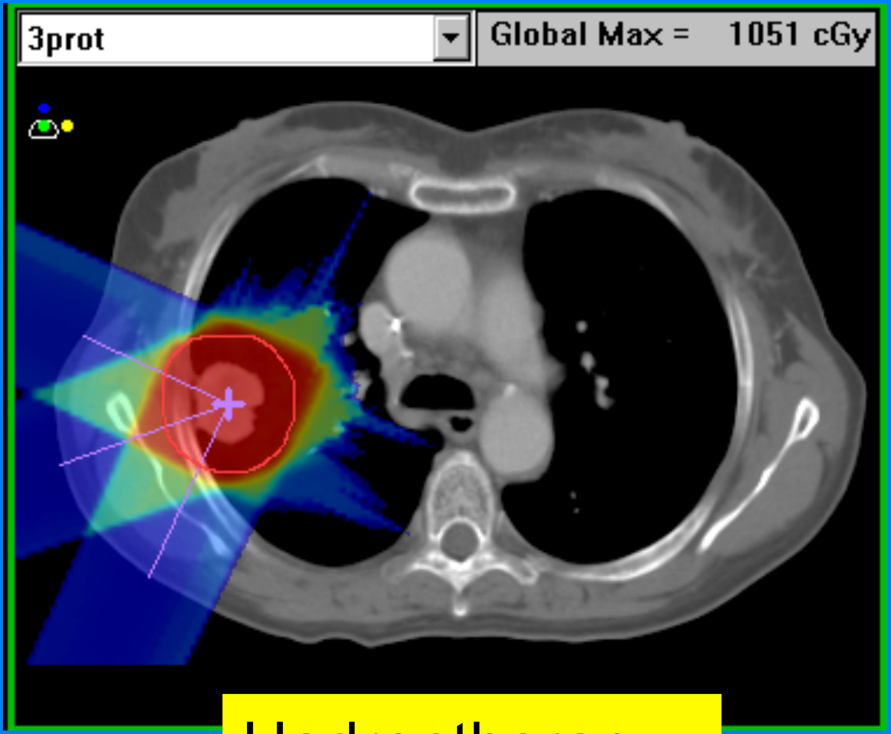


Selectivity


IMRT7d

Global Max = 1198 cGy

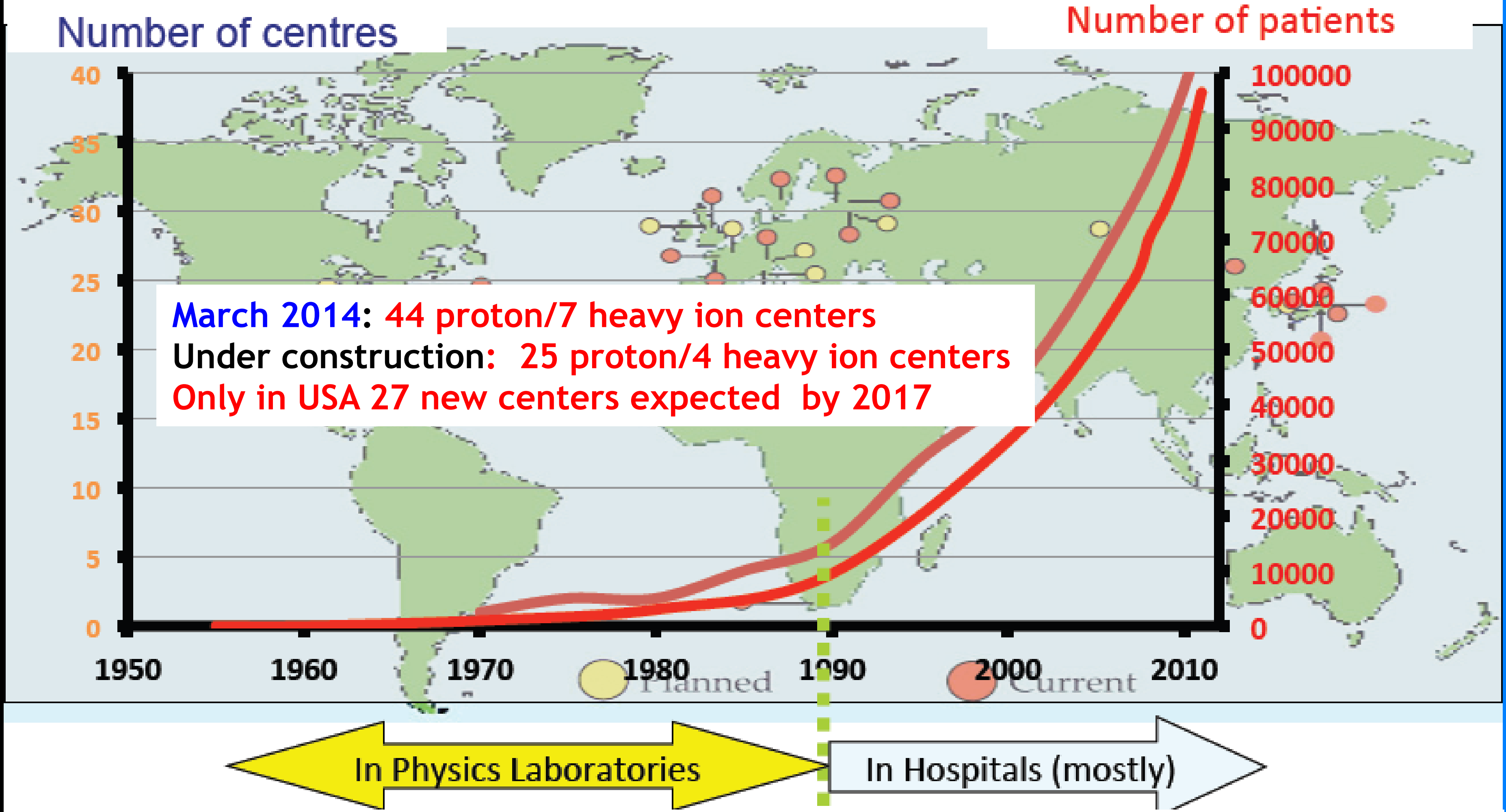
IMRT


3prot

Global Max = 1051 cGy

Hadrontherapy

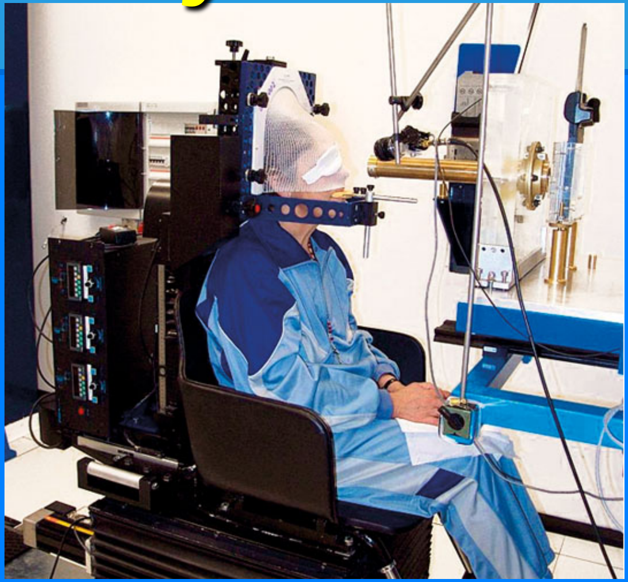
Charged Particle Therapy in the world



March 2014: 44 proton/7 heavy ion centers
Under construction: 25 proton/4 heavy ion centers
Only in USA 27 new centers expected by 2017

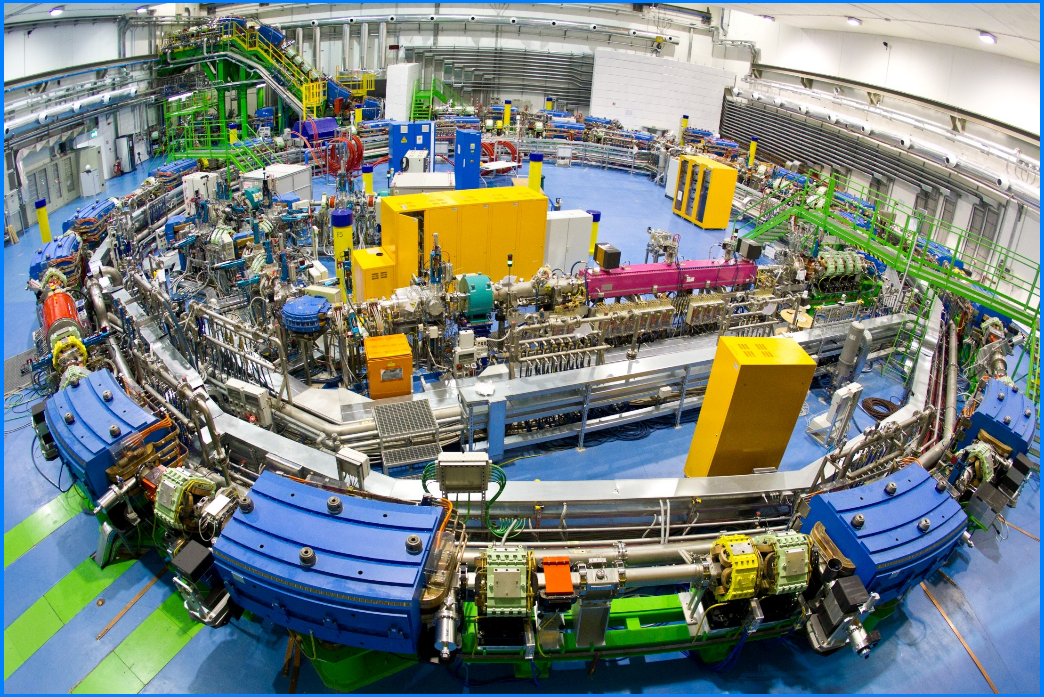
~2014: 122499 treated patients: 105743 with p, mainly in USA, 53532
13119 with ^{12}C, mainly in Japan, 10993;
+ 46,000 in the past 5 years ≈ 10,000 patients per year

HadronTherapy in Italy



CATANA @INFN-LNS

- 353 patients since 2002



CNAO in Pavia

- 650 patients, 75% with C

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

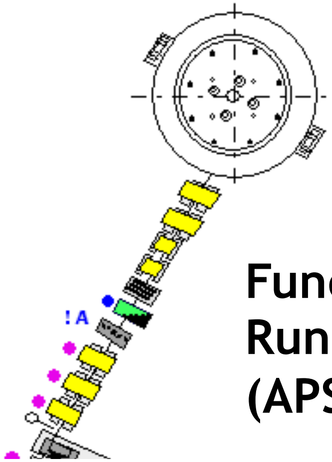
^{12}C: max 400 MeV/u; ~ 10^8 p/s

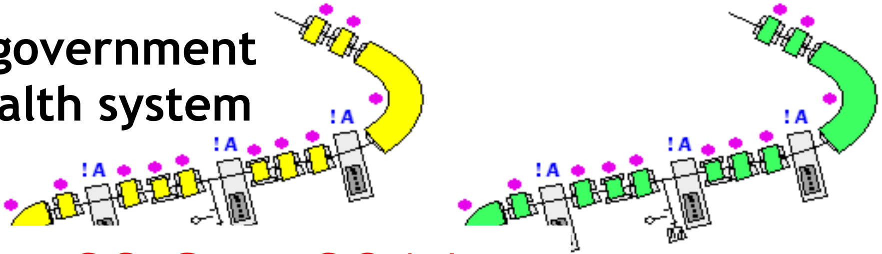
New Proton Therapy in Trento (Italy)

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

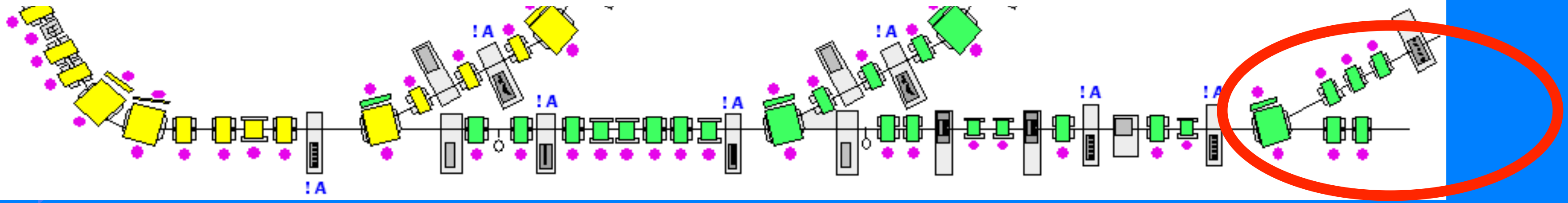




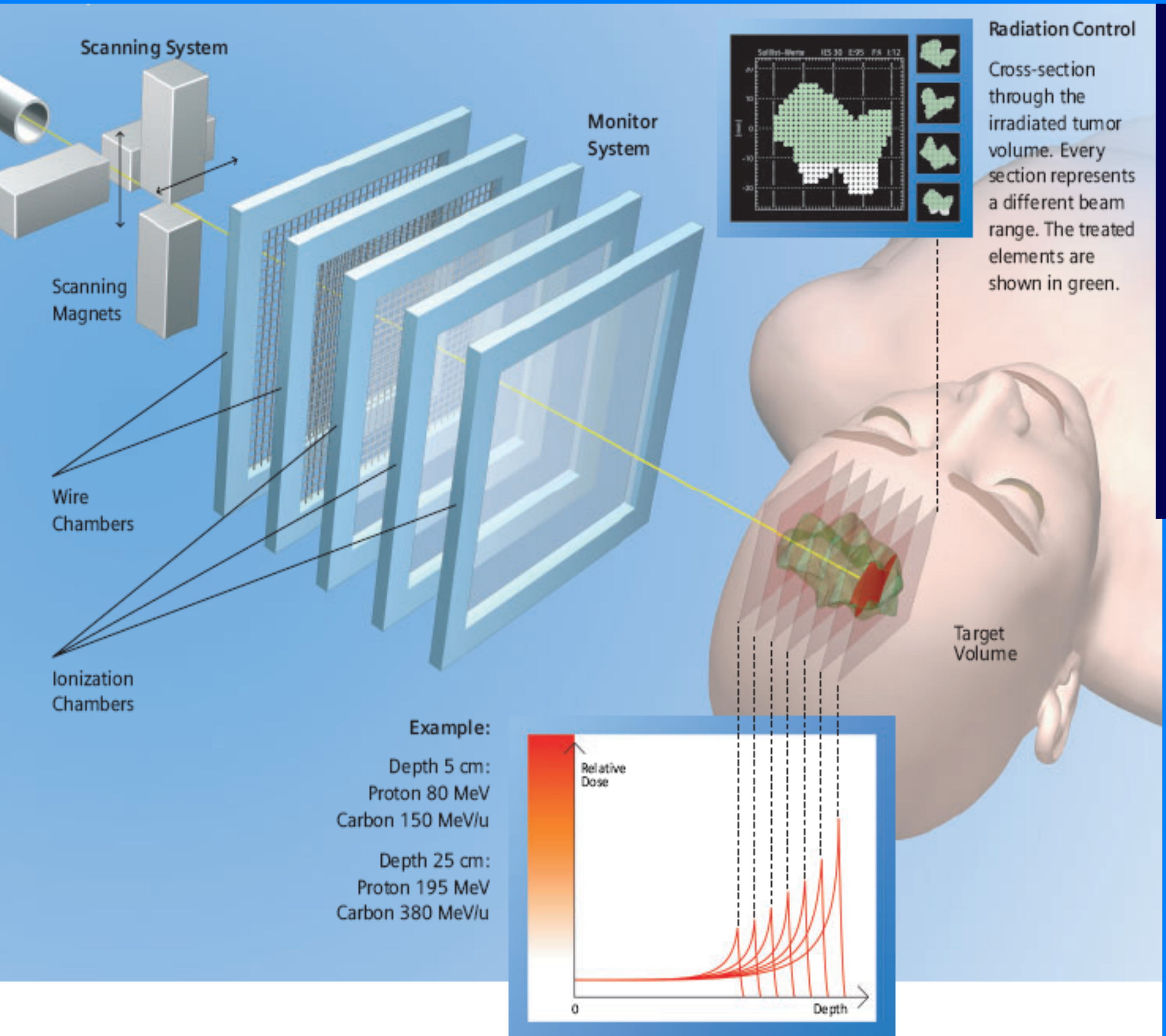
Funded by the local government
Run by the public health system (APSS)

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

Research Area



Beam Technology & Dose delivery to tumor: The Raster Scan method ("Active Scanning")

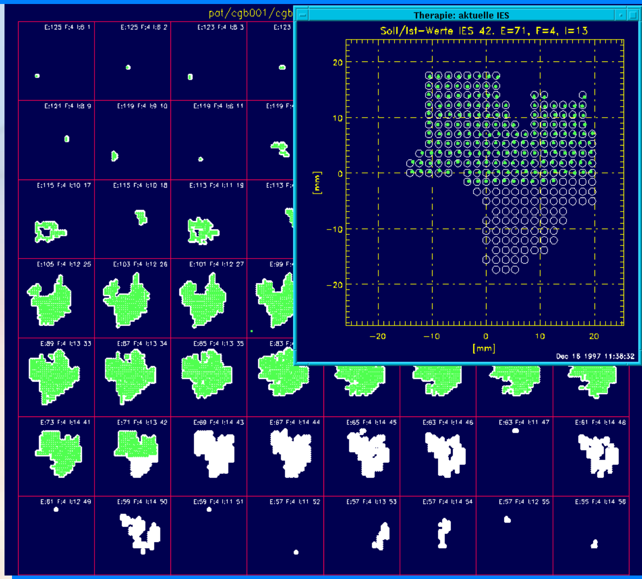


Cross-section through the irradiated tumor volume. Every section represents a different beam range. The treated elements are shown in green.

Example:

Depth 5 cm:
Proton 80 MeV
Carbon 150 MeV/u

Depth 25 cm:
Proton 195 MeV
Carbon 380 MeV/u



In use at CNAO, Heidelberg, MedAustron, Trento, etc.

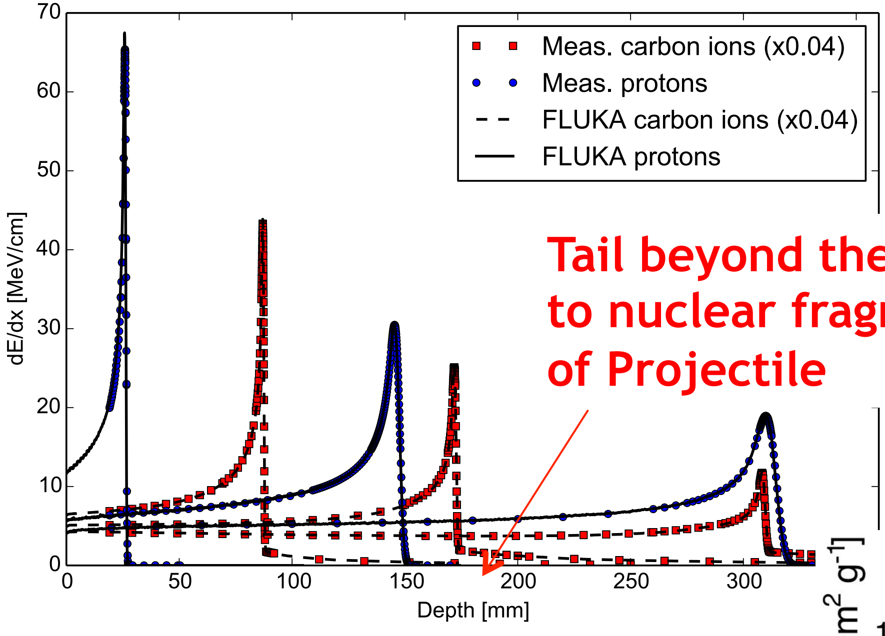
Physics of Bragg Peak

important at Low Energy dE/dx:

- ○ Shell Corrections

High order corrections

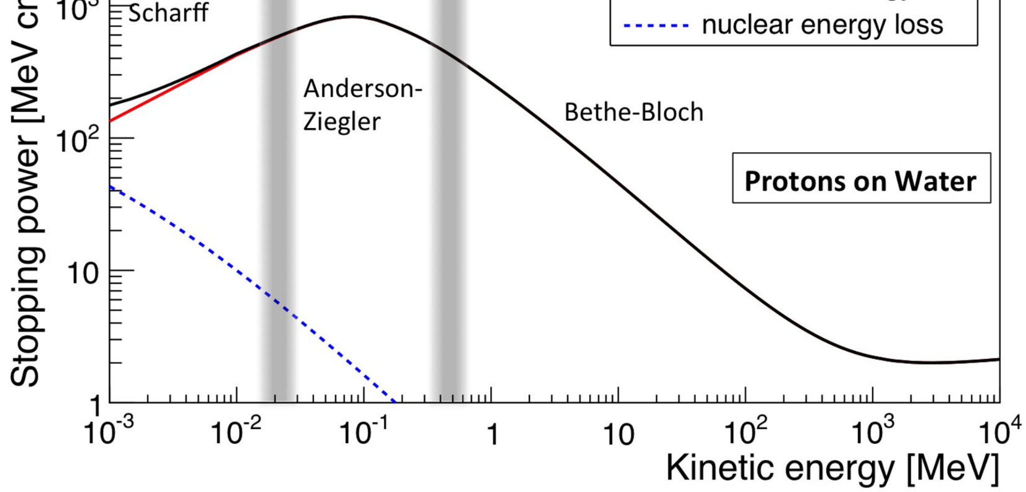
- ○ Barkas correction (∝ z^3)
- ○ Bloch correction (∝ z^4)
- ○ Mott corrections



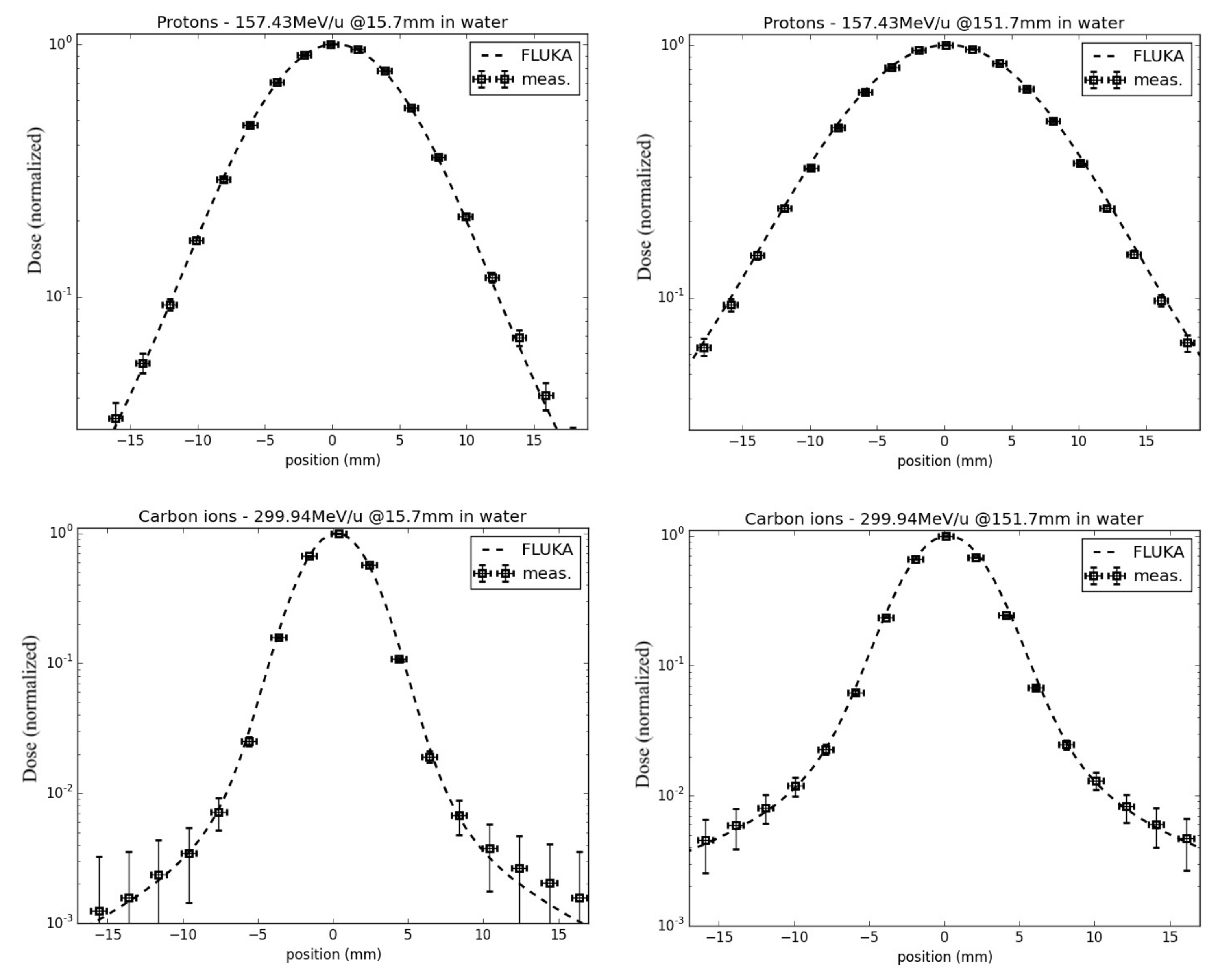
Tail beyond the Peak due to nuclear fragmentation of Projectile

dominated by interaction with electrons

MCS, Energy loss fluctuations and <u>nuclear interactions do affect the shape!</u>

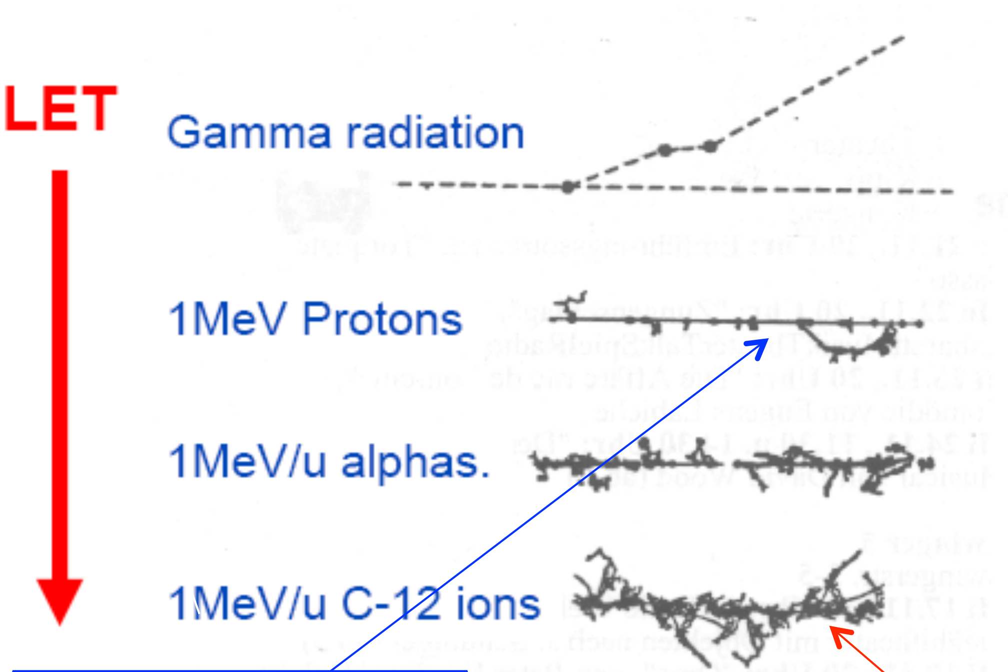


Lateral Spread (MCS not enough…)



Interdisciplinary aspects: Physics and Biology

Ionisation tracks



LET

Gamma radiation

1MeV Protons

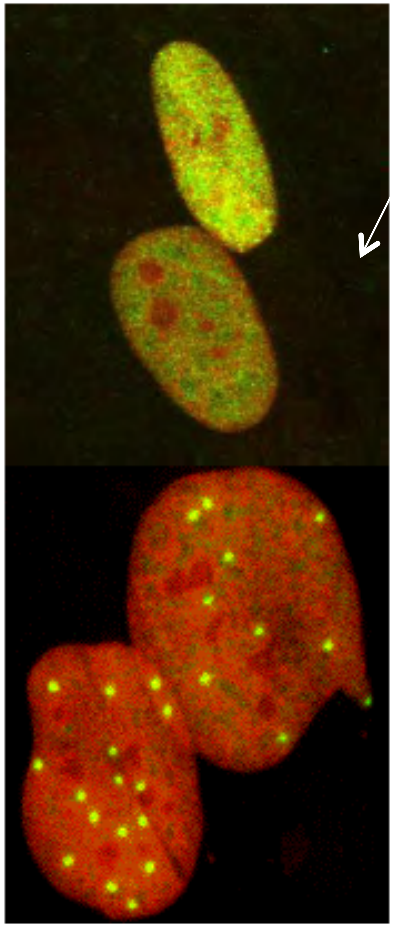
1MeV/u alphas.

1MeV/u C-12 ions

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

Damage in nucleus



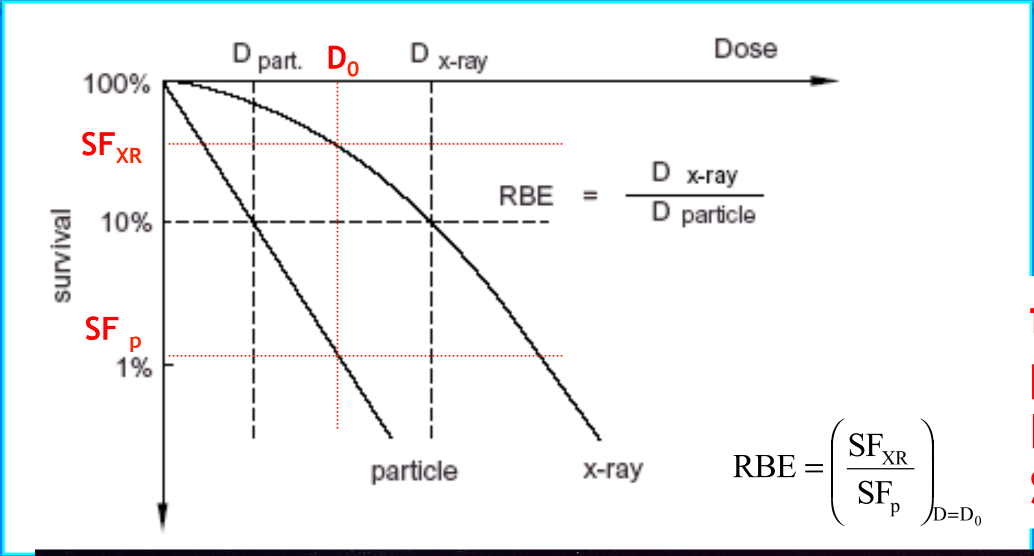
Low LET

Homogeneous deposition of dose

High LET

Local deposition of high doses

Radio Biological Effectivness (RBE)



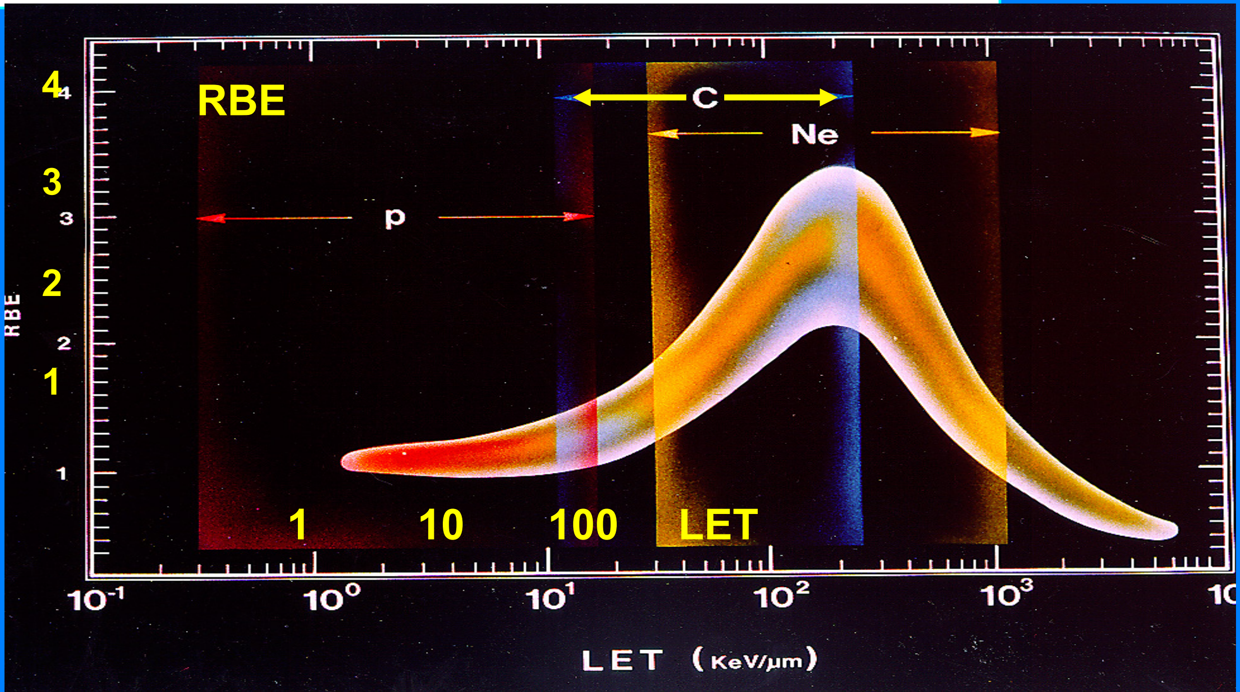
$$RBE = \left(\frac{SF_{XR}}{SF_p}\right)_{D=D_0}$$

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

for a given type of biological end-point and its level of expression.

For example:

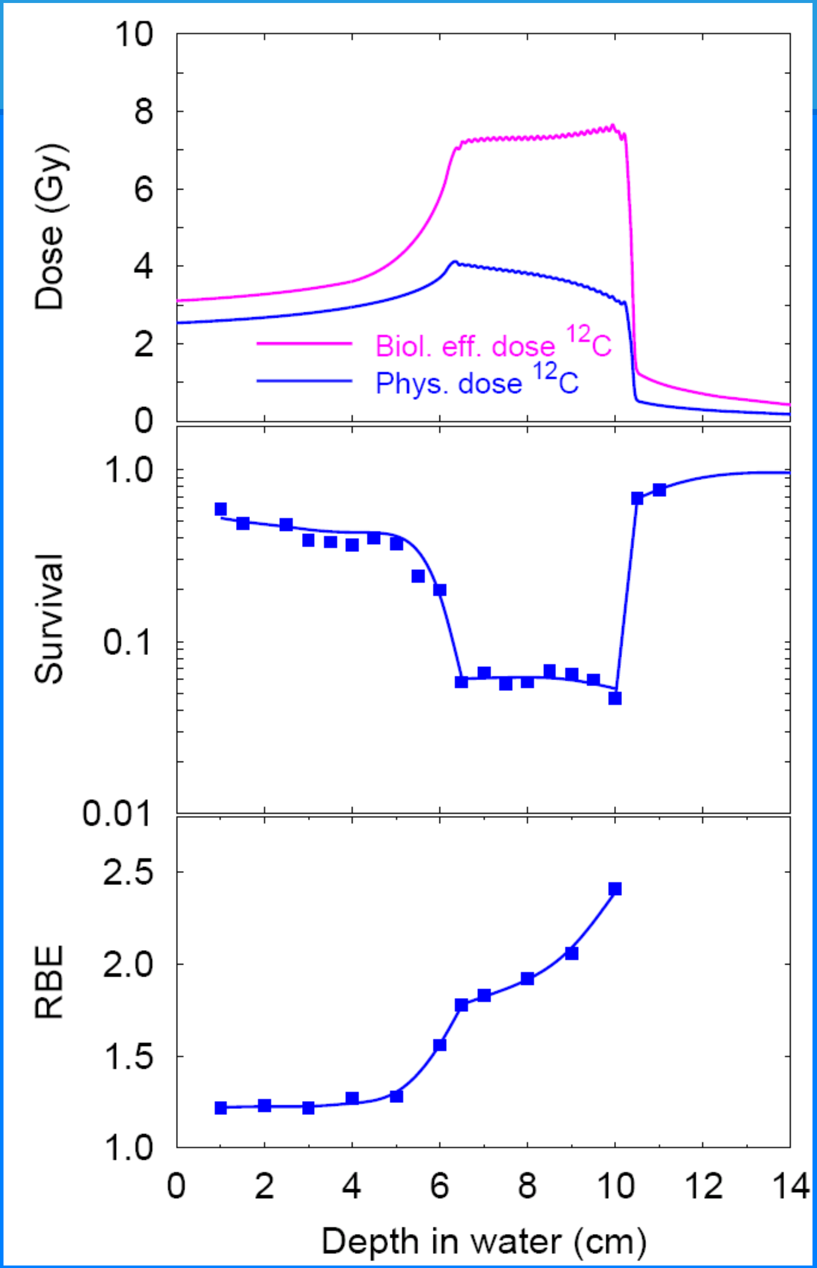
Survival Fraction of 10%



G. Battistoni

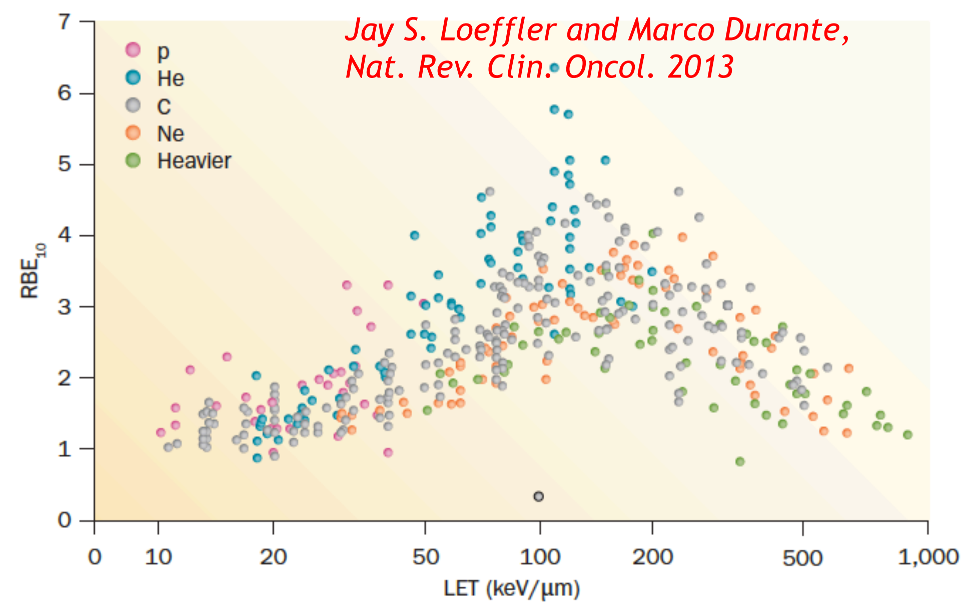
Biological Dose

In case of non constant RBE the optimization of Spread Out Bragg Peak has to be done considering the RBE-weighted dose and not the physical one!



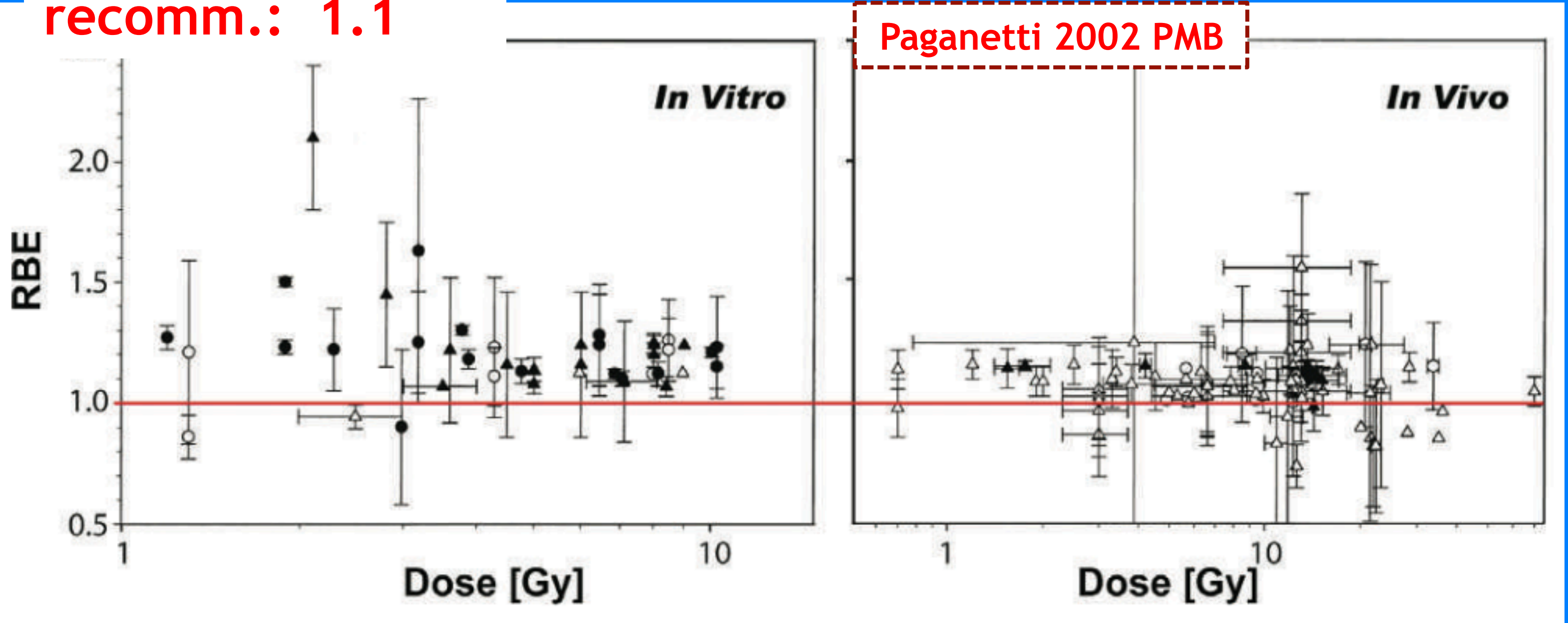
Radiobiology

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



Jay S. Loeffler and Marco Durante, Nat. Rev. Clin. Oncol. 2013

RBE of protons
recomm.: 1.1



Paganetti 2002 PMB

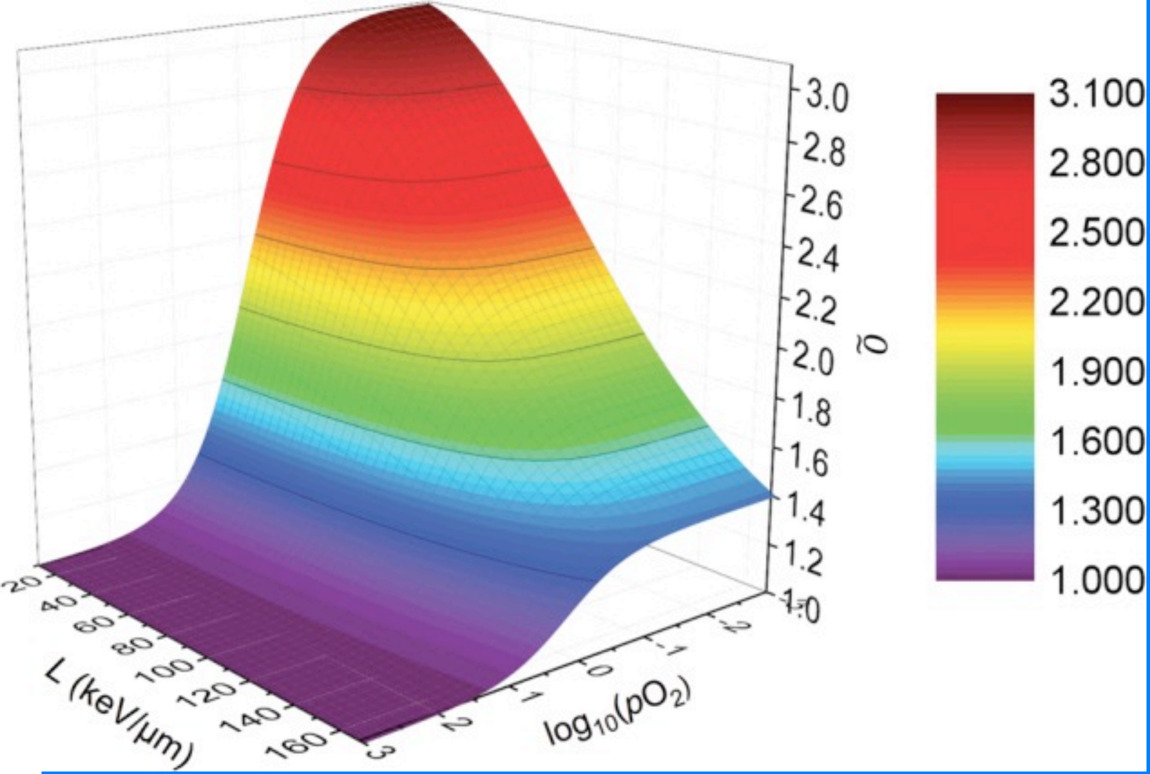
New Paradigm for Proton Radiobiology (Girdhani 2013 Radiat Res) → **Protons and photons present distinct physics and biological properties at Sub-Cellular, Cellular and Tissue level**

Oxygen Enhancement Ratio

Ionizing Radiation generates complex damages to DNA structure mainly throught the action of Free Radicals ROH

The presence of Oxygen is a crucial parameter

Hypoxial tumors are radioresistant



$$OER = \frac{D_{hypoxic}}{D_{oxigenated}}$$

Laura Antonovic et al.

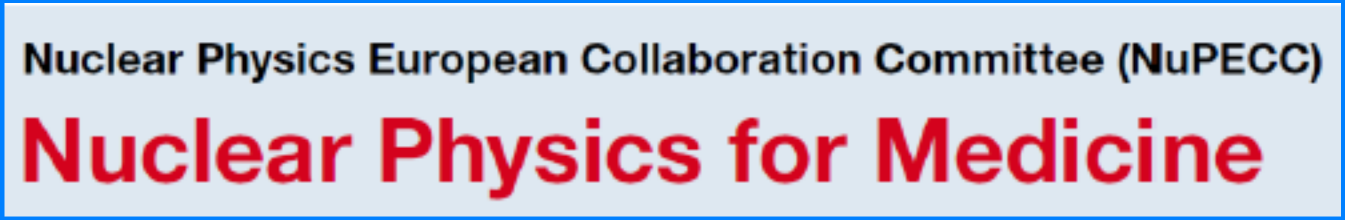
J Radiat Res. 2014 Sep; 55(5): 902-911.

The contribue of phyics to particle therapy development

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 are required

NuPECC


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

Nuclear projectiles currently used

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

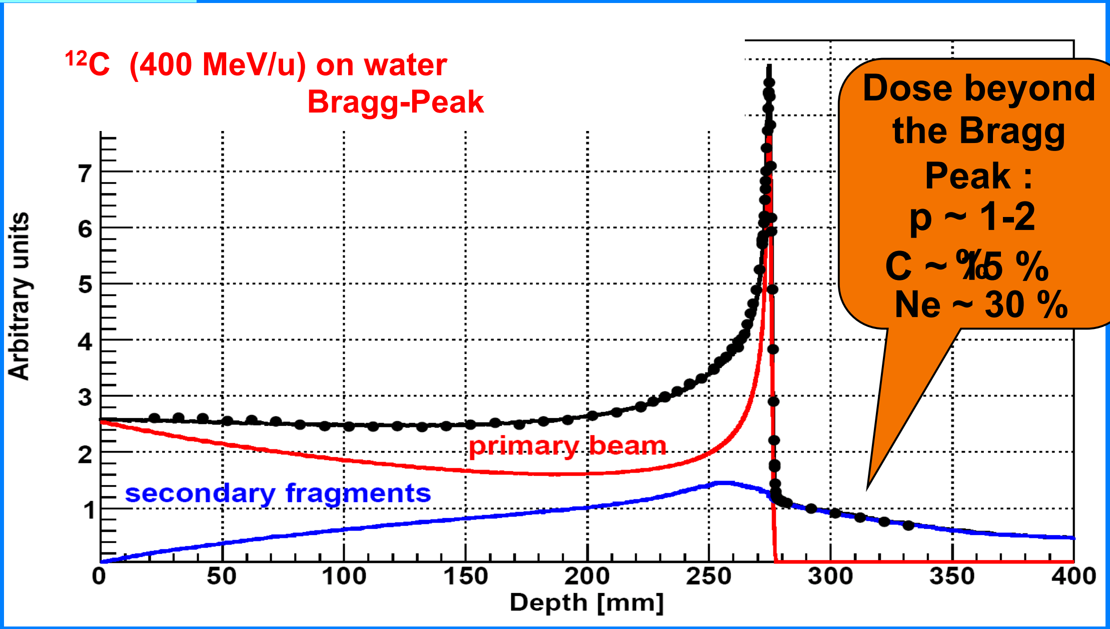
^{16}O (100-500 MeV/u): to be used in particular case where high-LET is needed

Heavier is better? *Fragmentation!*

Dose release in healthy tissues with possible long term side effects, in particular in treatment of young patients ➔must be carefully taken into account in the Treatment Planning System

- ✓ **Production of fragments with higher range vs primary ions**
- ✓ **Production of fragment with different direction vs primary ions**

- ✓ *Mitigation and attenuation of the primary beam*
- ✓ *Different biological effectiveness of the fragments wrt the beam*



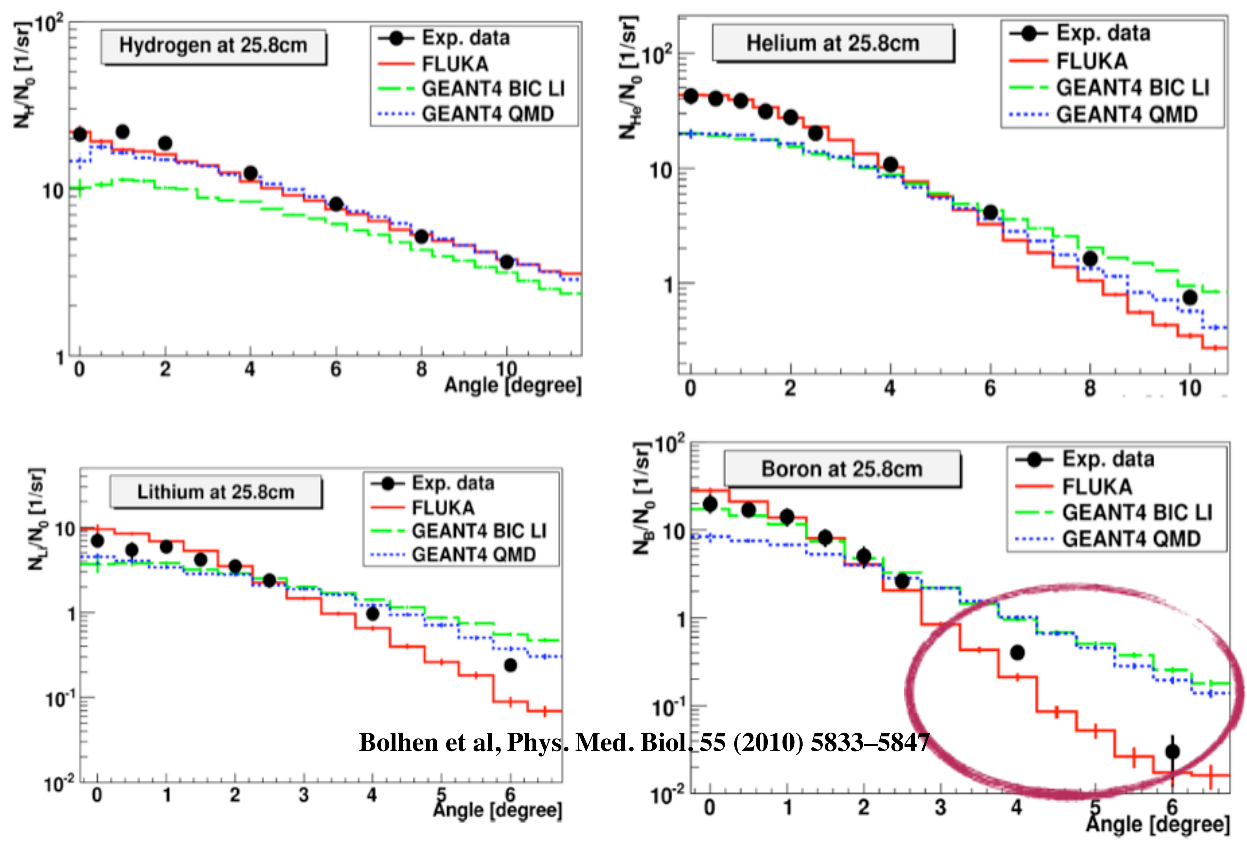
Dose beyond the Bragg Peak :
p ~ 1-2 %
C ~ 15 %
Ne ~ 30 %

Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

Courtesy of Andrea Mairani

Data - MC comparison: ^{12}C ions

Differential/double-differential quantities (vs angle and/or energy)

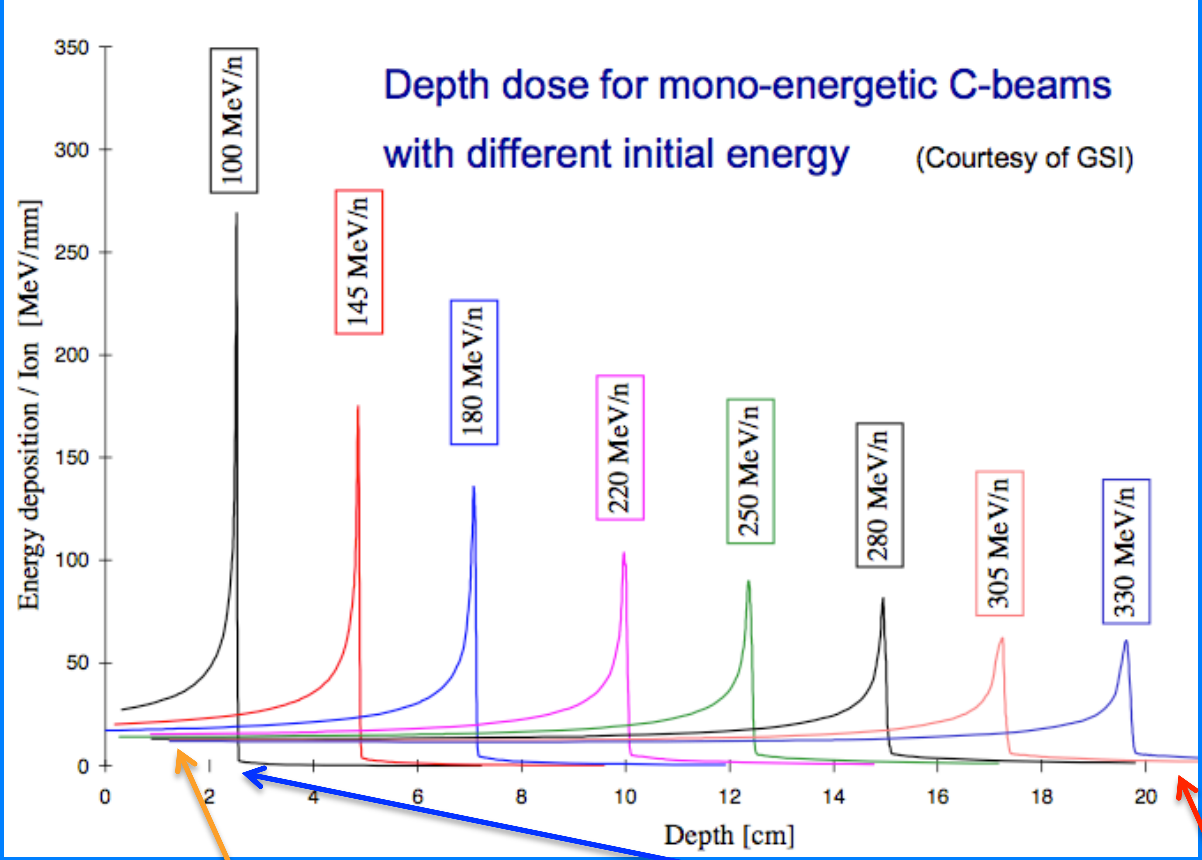


Bolhen et al, Phys. Med. Biol. 55 (2010) 5833–5847

NB: the accuracy on delivered dose MUST be of the order of few %

Some MC benchmarks:
Sommerer et al. 2006, PMB
Garzelli et al. 2006, JoP
Pshenichnov et al. 2005, 2009
Mairani et al. 2010, PMB
Böhlen et al. 2010, PMB
Hansen et al. 2012, PMB

Recent thin target, Double Diff Cross Section C-C measurements



The community is exploring the interesting region for therapeutic application, in particular for the ^{12}C beam.

Yet there is a lot of energy range to explore in the range 150-350 AMeV (i.e. 5-17 cm of range…)

LNS 62AMev C beam (2009)

GANIL 95AMev C beam - E600 collaboration (2011)

GSI 400Mev C beam FIRST experiment (2011)

Towards improved Charged Particle Therapy (1):

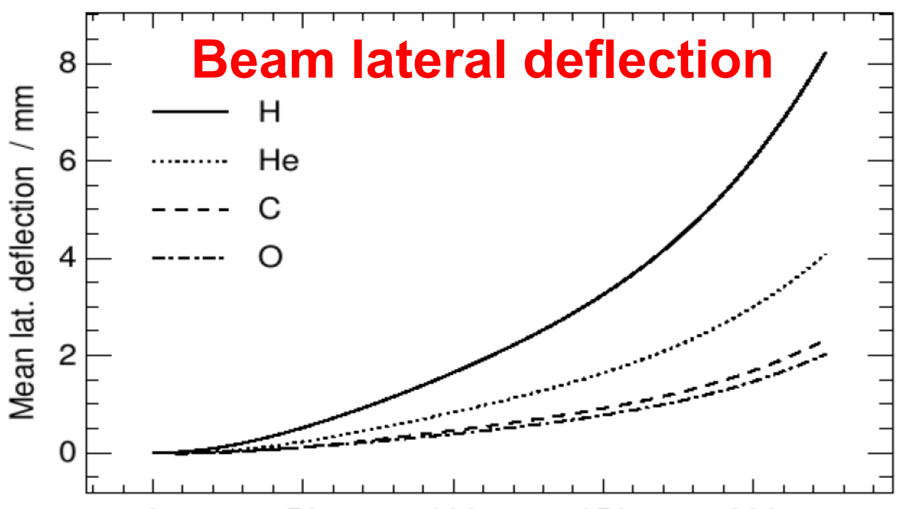
- Radiobiology
  - Reduction of uncertainties. Models vs. Experimental data. Mechanisms?
  - Hypoxia and related treatment strategies
  - in vivo + in vitro investigations
- Treatment Planning
  - Coupling to improved radiobiological
  - Other variables considered in optimization (ex.: Oxygen Enh. Ratio)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

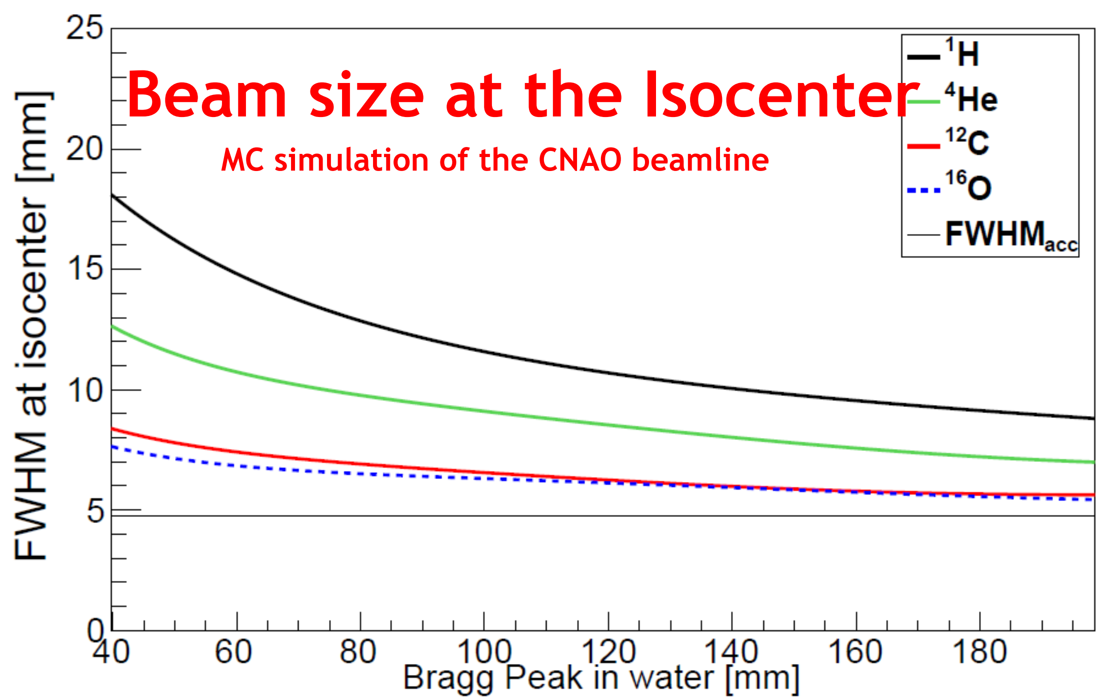
Towards improved Charged Particle Therapy (2):

- Personalized treatments:
  - LET or RBE “painting” (aiming at hypoxical/radioresistant regions)
  - Image guided PT
- Use of new nuclear species (O, He, …)
- Nuclear fragmentation and related experimental data
- 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 and dose delivery systems
  - Future: new acceleration techniques towards more compact structures

⇨ Laser driven Plasma acceleration: a future option?

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

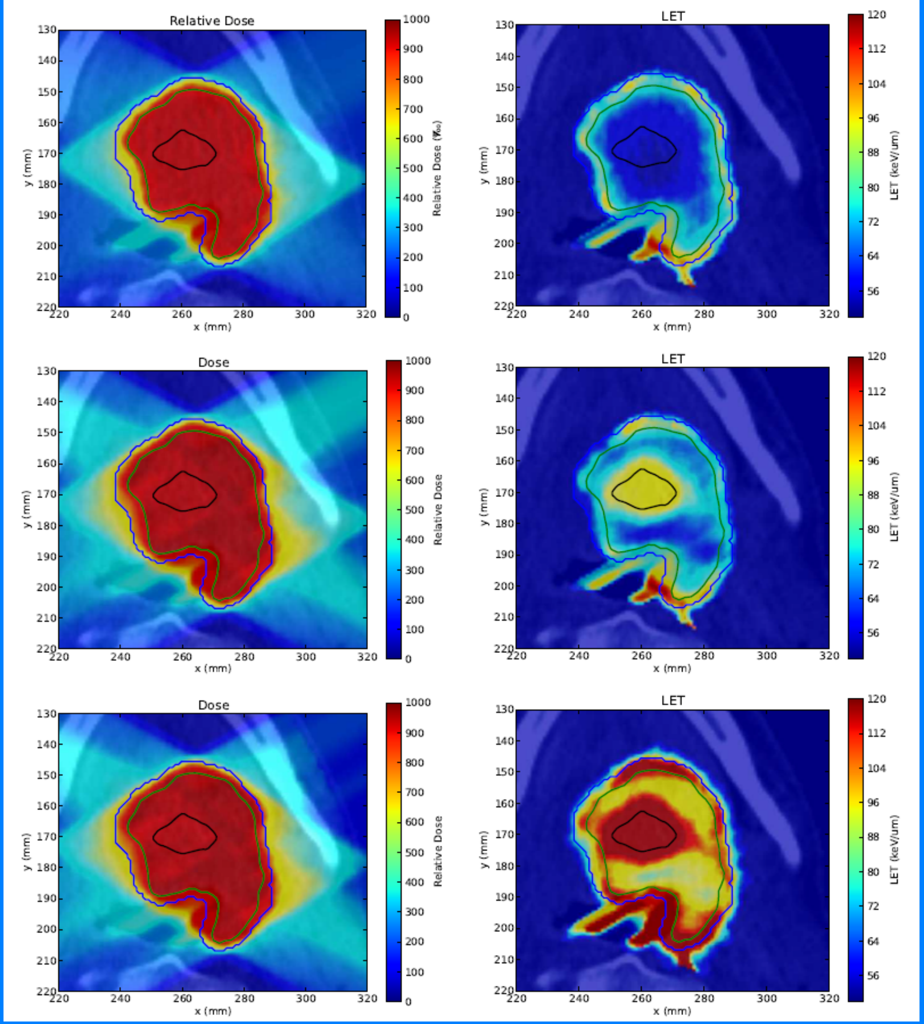
The high LET of the ^{16}O beam is effective against radio-resistant hypoxic tumors (low Oxygen Enhancement Ratio)

Carbon 4 Flat fields

Carbon 4 Dose LET painted

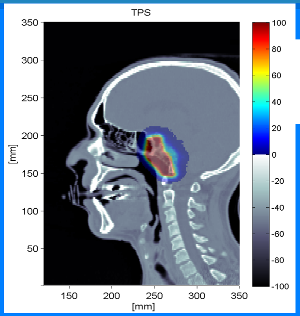
ions heavier than ^{12}C may be necessary in order to reduce the OER to sufficient levels. ^{16}O along with a slight dose boost could be a promising candidate when targeting hypoxic structures of 1 - 4 cm 3 in size. In vitro and in vivo radiobiologic experiments are needed to proceed towards clinical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

Software: Treatment Planning

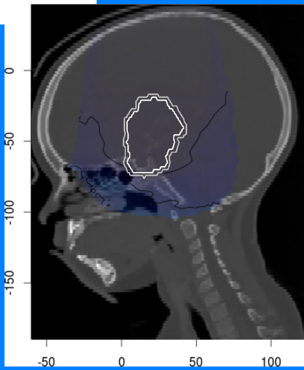


(Effective) Dose Optimization

Imaging:
CT scan
and/or PET-CT)

Electron density

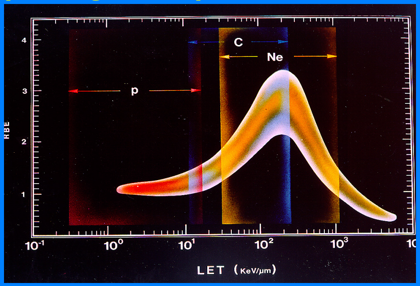
Radiotherapist:
identification of Target Volume
and of Organs at Risk

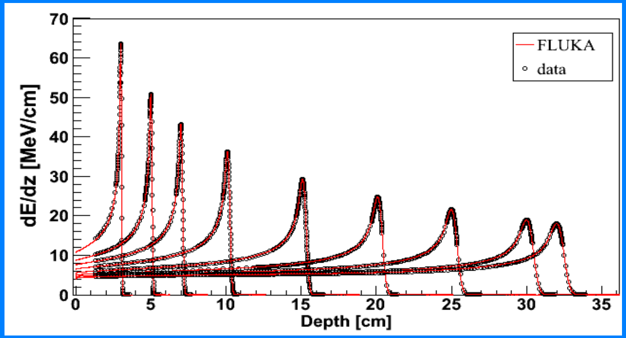


Radiobiology:
RBE parameters
OER (not yet…)

Nuclear Physucs:
Dose vs Depth
hadrone/nucleus scattering:
fragments etc.

Treatment Planning System





Intensity, position and energies
to be delivered
to patient

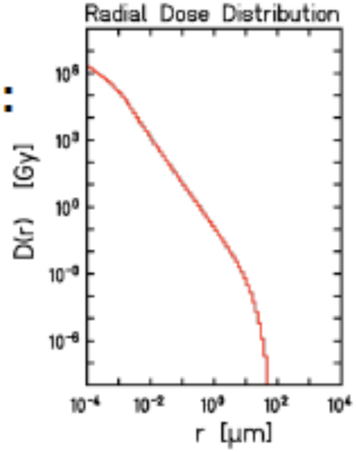
Radiobiological modelling

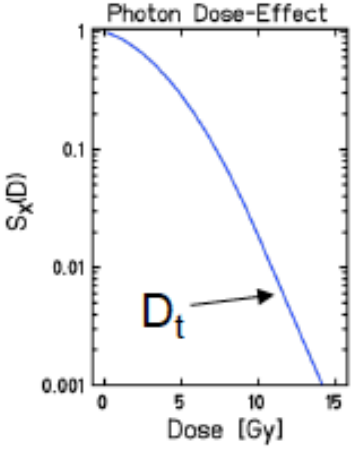
Physics

Radial Dose Distribution:

Monte-Carlo (Krämer), Experimental Data

$$D(r) \propto \frac{1}{r^2}$$





Biology

Photon Response Curve:

additional assumptions for large doses

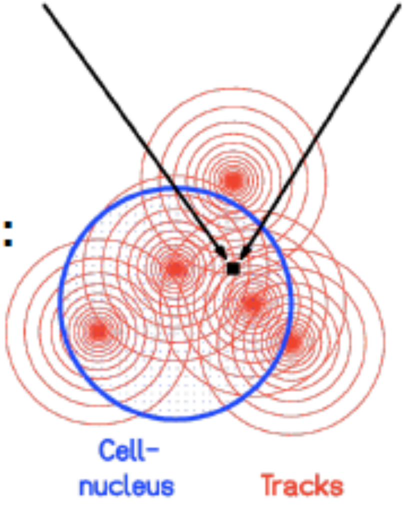
$$S = e^{-(\alpha D+\beta D^2)}, \quad D < D_t$$

$$S = e^{-s_{\max}\eta(D-D_t)}, \quad D \ge D_t$$

Geometry

Target (cell nucleus):

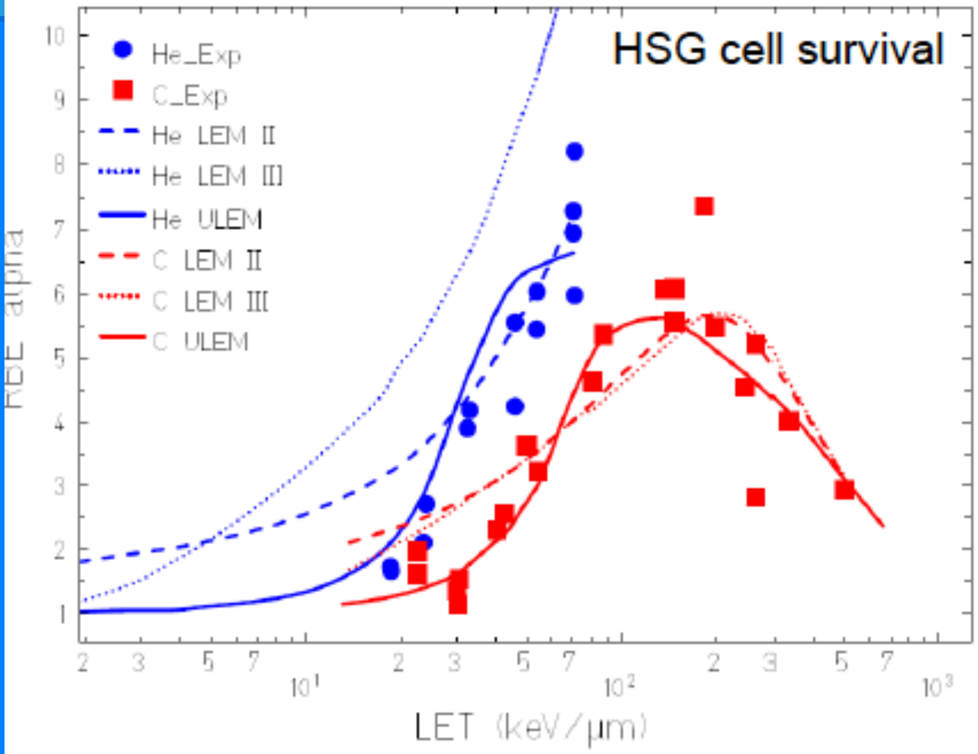
Experimental Data

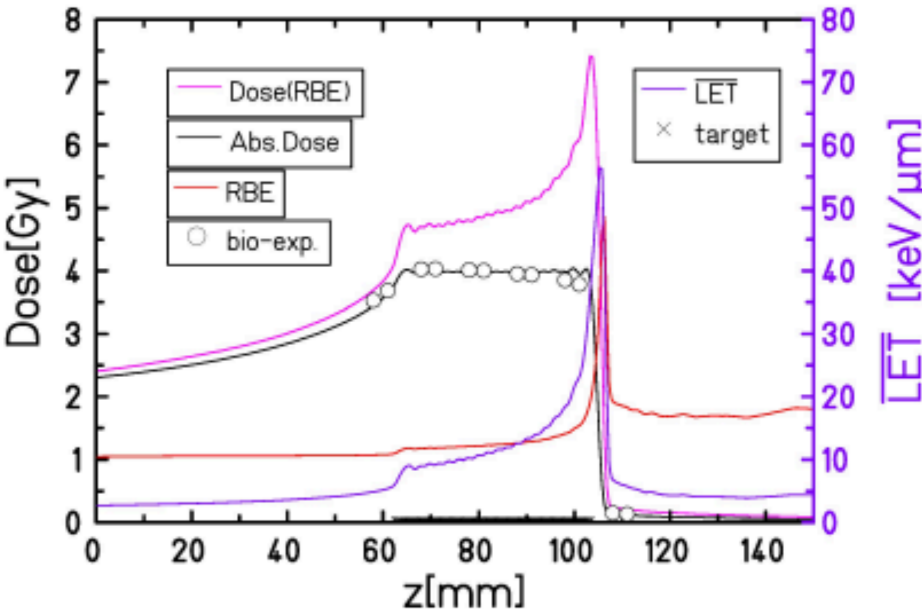


Local Effect (Ions) = Local Effect (Photons)

LEM-I, Scholz et al., *Rad. Environ. Biophys.* 1997; LEM-IV, Elsässer *et al.*, *IJROBP* 2010

Radiobiological modelling





SOBP, He-ions

Krämer *et al.*, *Med. Phys.* 2015 (submitted)

Exp. Data:	Furusawa et al., Rad. Res. 2000
LEM II:	Elsässer et al., Rad. Res. 2007
LEM III:	Elsässer et al., IJROBP 2008
LEM IV:	Elsässer et al., IJROBP 2010

Mostly used one

Other available model: Microdosimetric Kinetic Model (MKM, Hawkins 2009)
Example: planKIT (TPS from INFN-IBA development)

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**

proton based imaging system (pCT):

Conventional X ray tomographies taken before the proton treatment session and in a different setup. Precision improvement if positioning and treatment could be done in one go

Treatment planning is defined using X-CT *but* protons and photons interact differently with matter. Direct measure of the stopping power maps with same particles used to irradiate

The method

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

***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.**

S(E,x,y) is obtained by solving the tomographic equation *(Wang, Med.Phys. 37(8), 2010: 4138)*

$$\int_{Path} S(x,y,E_0)\,dl = \boxed{\int_{E_{res}}^{E_0} \left[\frac{S}{\rho}(H_2O,E_0) \Big/ \frac{S}{\rho}(H_2O,E) \right] dE}$$

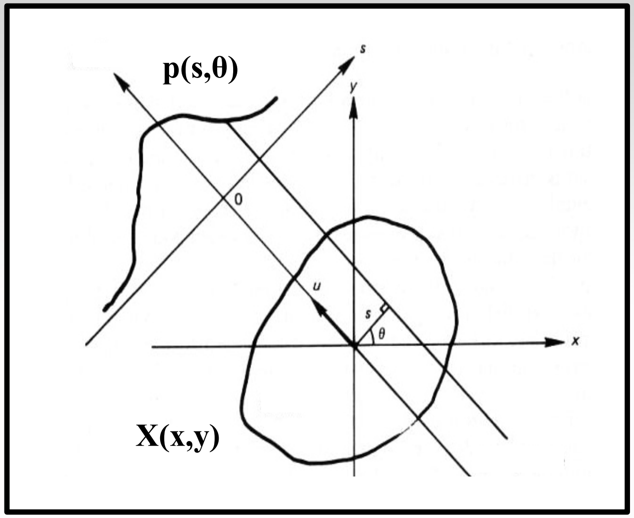
Unknown stopping power distribution (at E_0)

«projection»

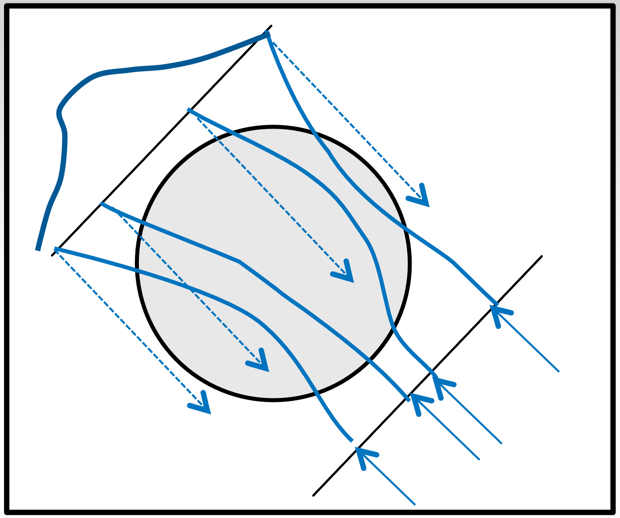
Evaluation of the "projection" term (through numerical integration starting from tables (ex. NIST) in H_2O and using the measured E_{res}

Photon vs. Proton CT

Photon CT



Proton CT (pCT)



Due to the presence of MCS, the **Filtered Back Projection (FBP)** algorithm, that back-projects the measured data on straight parallel lines perpendicular to the projection direction, is not suited for pCT image reconstruction.

A description of the proton path must be included in reconstruction to increase spatial resolution.

$$p(s,\theta)=\iint_{-\infty}^{+\infty} X(x,y)\,\boxed{F}(s+x\,sen\theta-y\cos\theta)\,dx\,dy$$

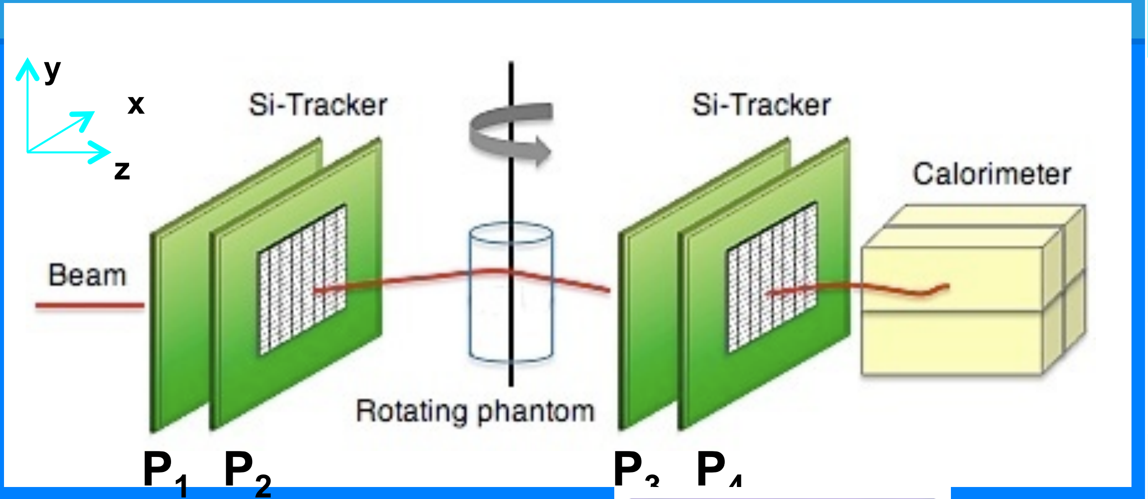
Modified Radon Transform: F contains the physical model

→

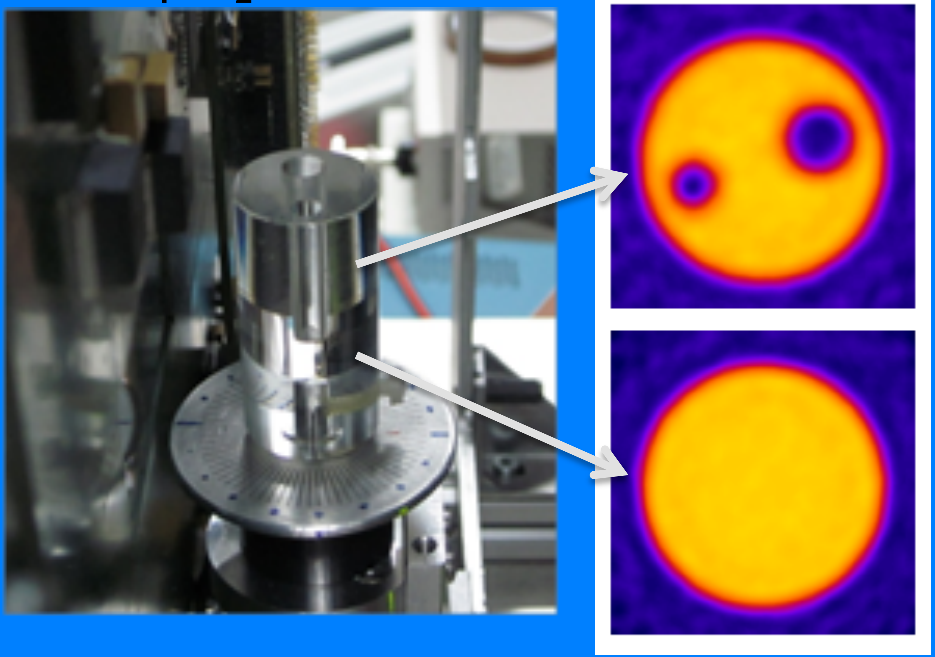
$$p_j = F_j^k X_k$$

Linear system of equations to be solved with iterative techniques (ART, SART…)

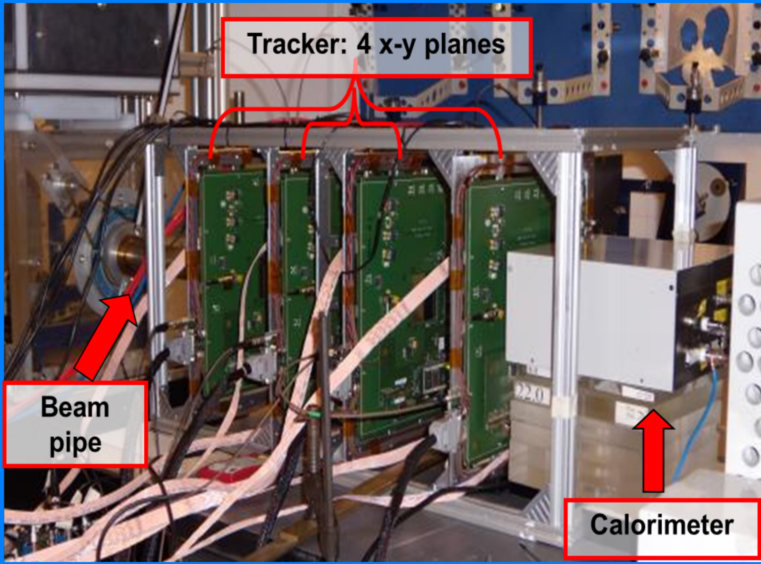
Proton CT: the INFN approach (Fi-LNS-Ct-Ca)



PARAMETER	VALUE
Proton beam kinetic energy	~300 MeV
Proton beam rate	1 MHz
Spatial resolution	< 1 mm
Electronic density resolution	<1%
Detector radiation hardness	>1000 Gy
Dose per scan	< 5 cGy

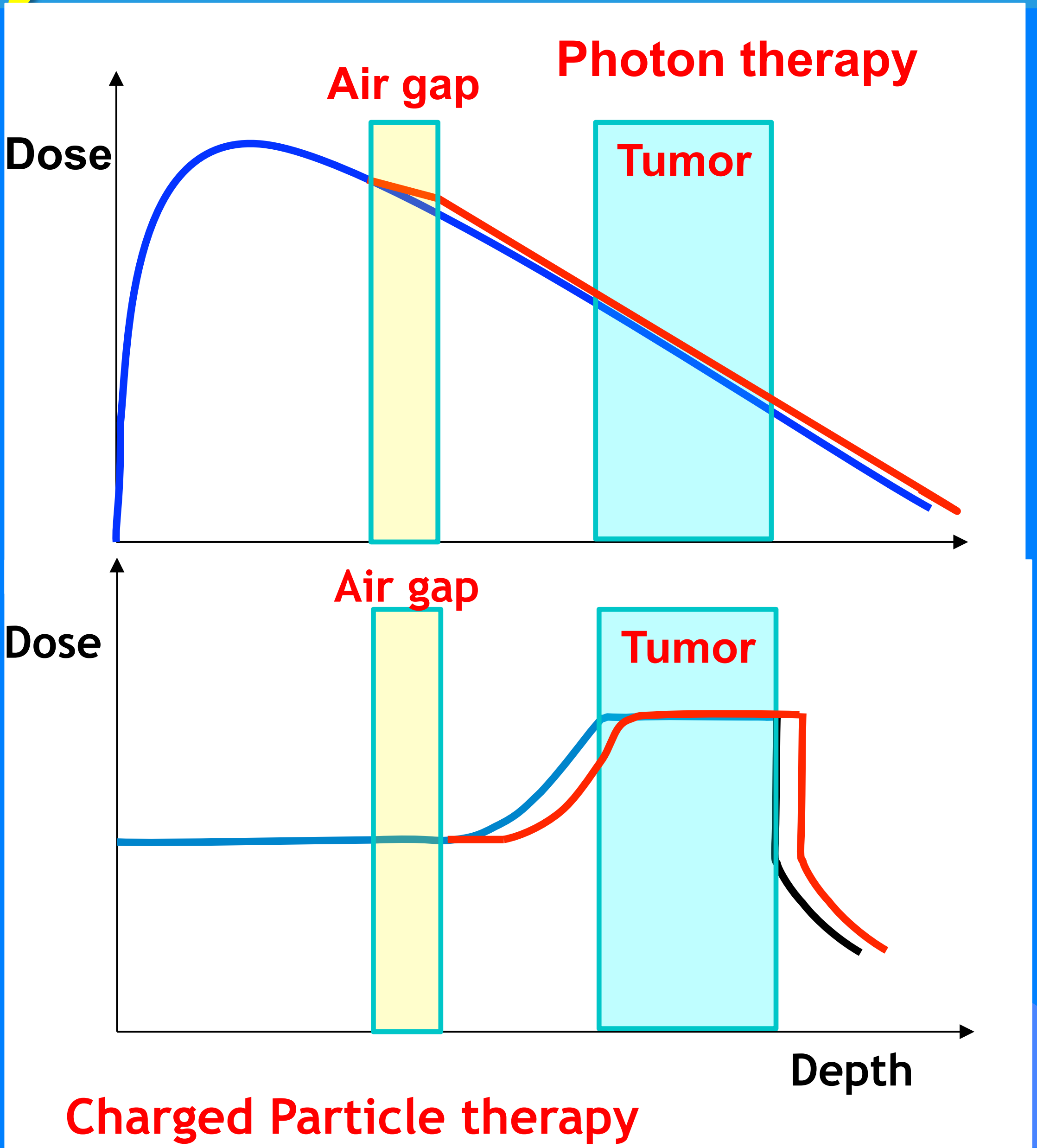


Proof of principle at 60 MeV LNS p beam



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

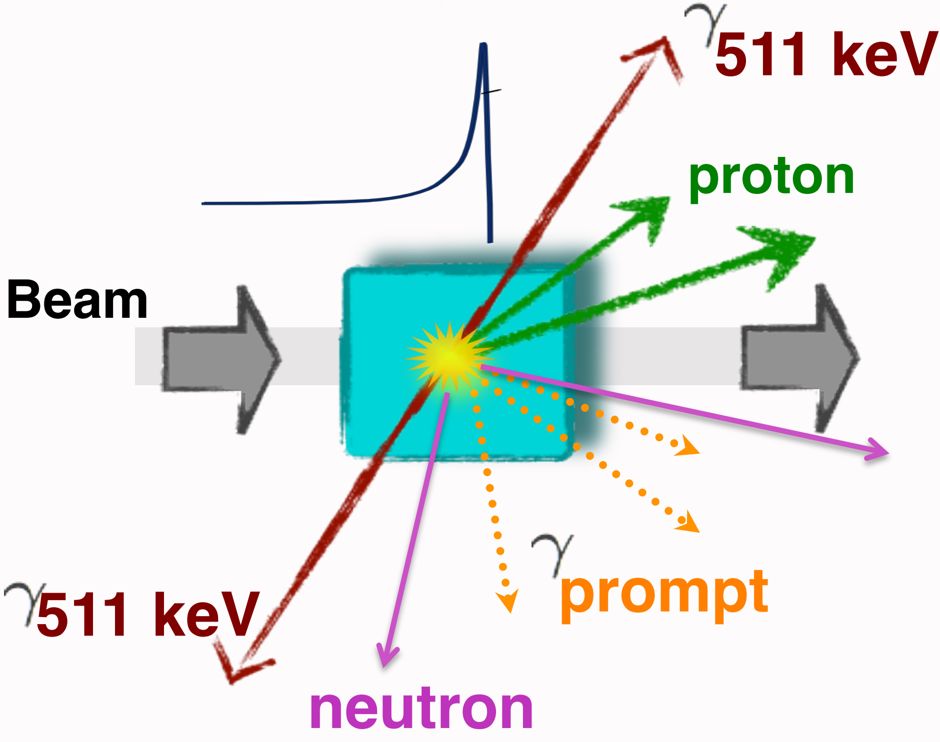


Help from Nuclear Physics: exploiting secondary products

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

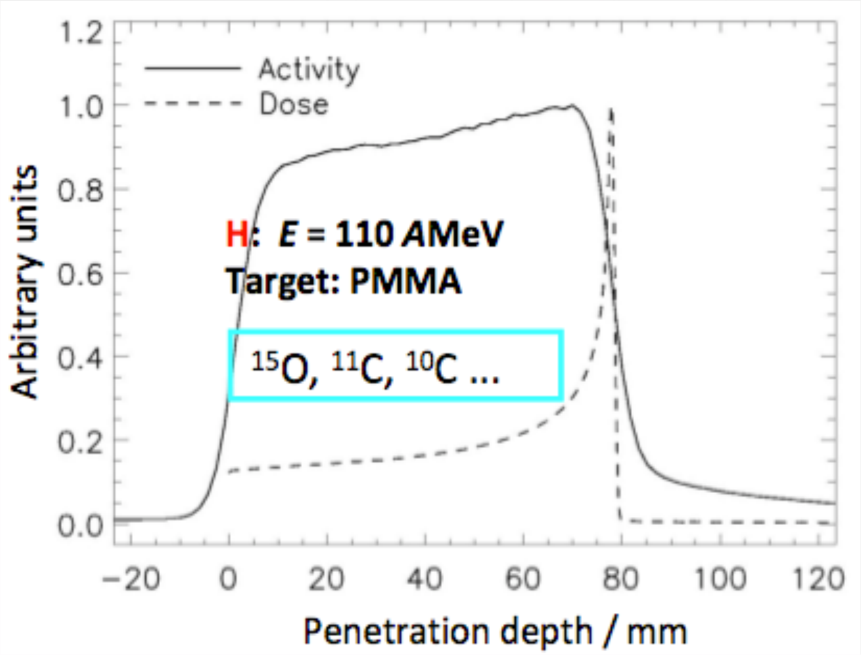


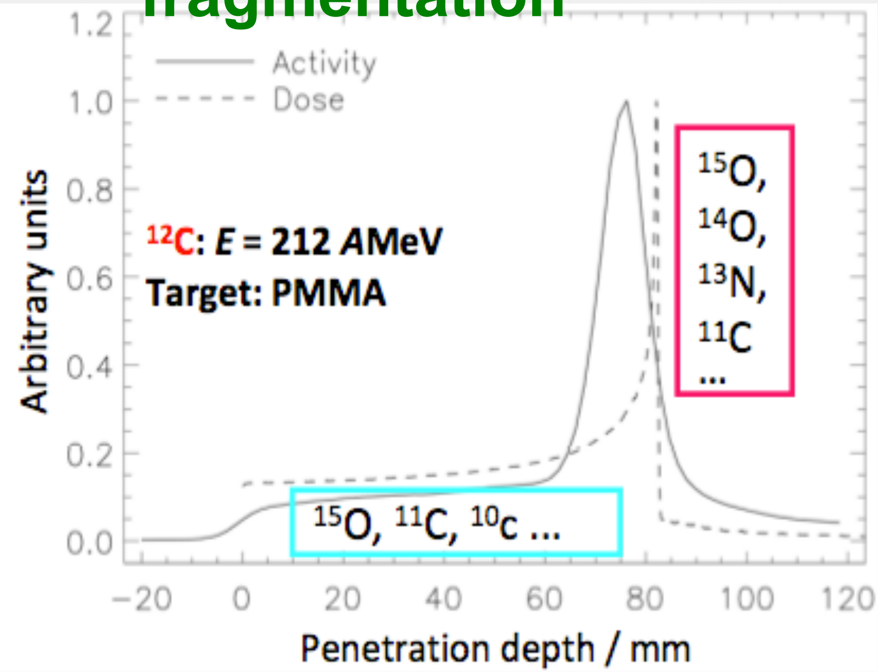
Correlation between β^+ activity and dose

Therapy beam	^{1}H	^{3}He	^{7}Li	^{12}C	^{16}O	Nuclear medicine
Activity density / Bq cm^{-3} Gy^{-1}	6600	5300	3060	1600	1030	$10^4 - 10^5$ Bq cm^{-3}

Target fragmentation

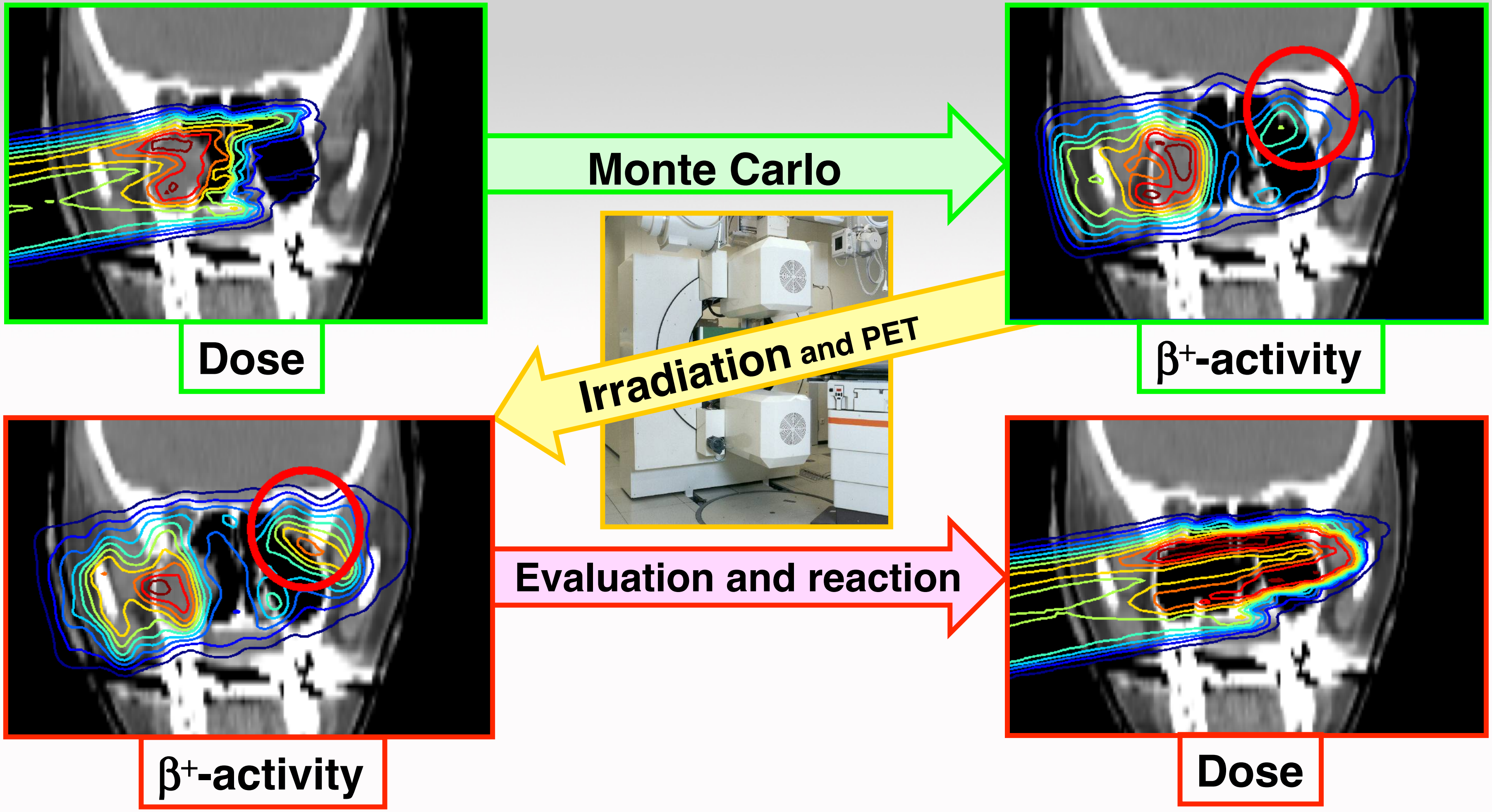
Projectiles & target fragmentation





In-Vivo range measurement with PET: workflow and potential

W. Enghardt et al.: Radiother. Oncol. 73 (2004) S96



Monte Carlo

Dose

β^+-activity

Irradiation and PET

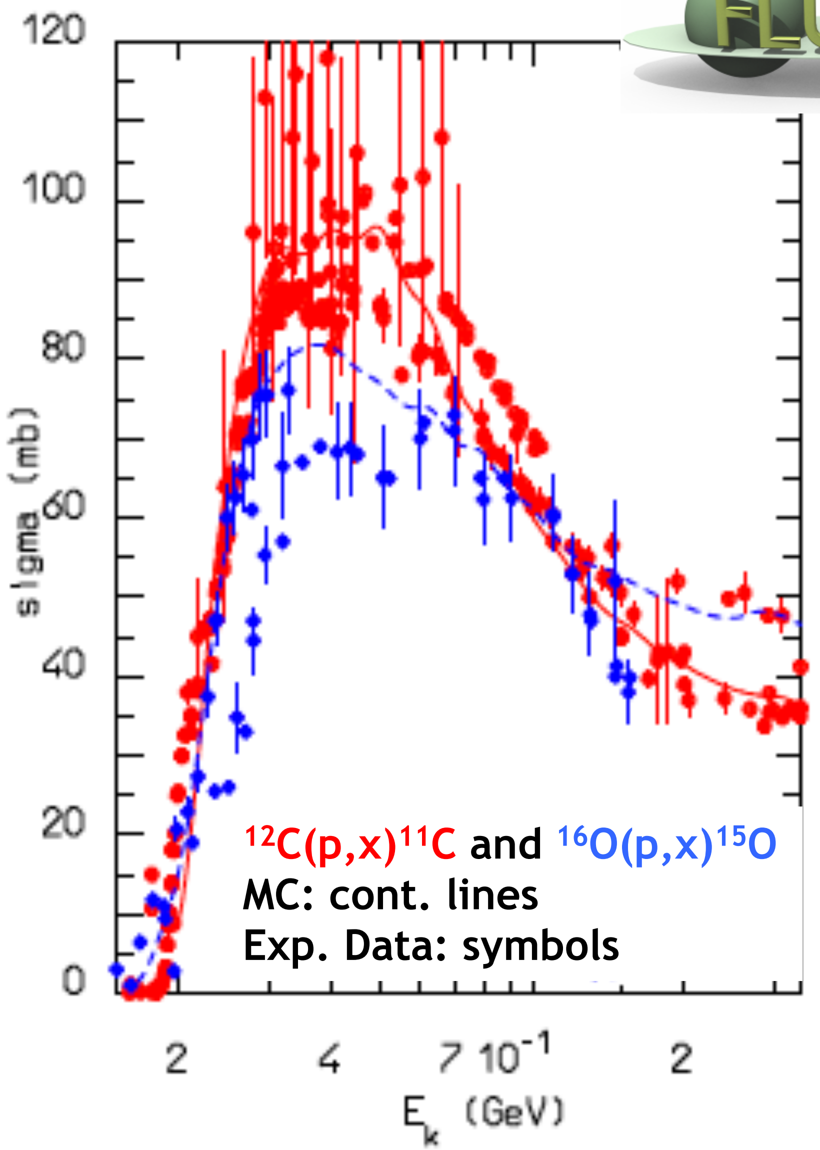
β^+-activity

Evaluation and reaction

Dose

Problem to solve: Metabolic Washout! In-beam measurement is really necessary, but difficult. Trade-off: in-room or off-room measurement after irradiation (Heidelberg for example)

Some relevant processes

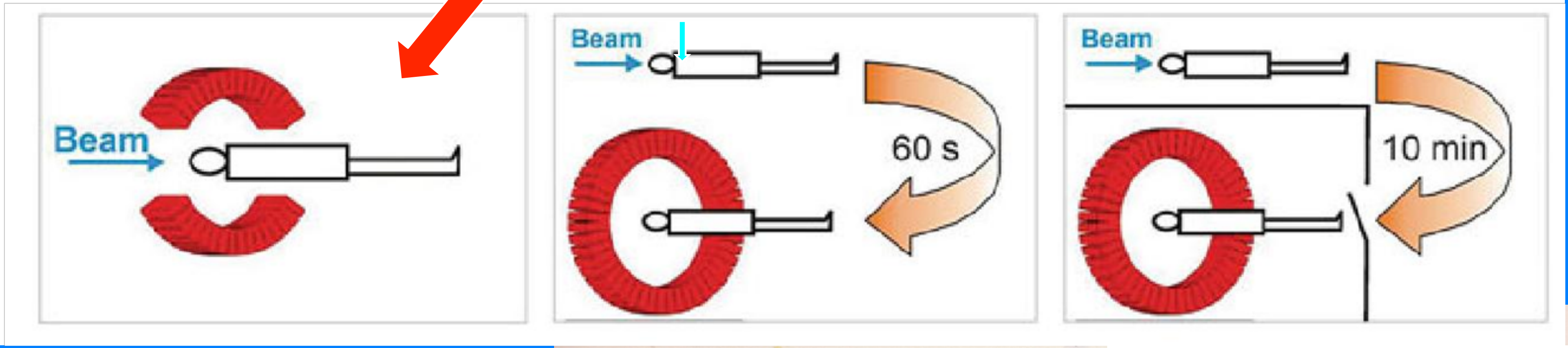


Isotope production cross sections (in mb) for the fragmentation of 86 MeV/n 12C ion projectiles on a carbon target. Data are compared to FLUKA predictions, integrated over the measured angular range. The experimental uncertainty is on the order of 10%

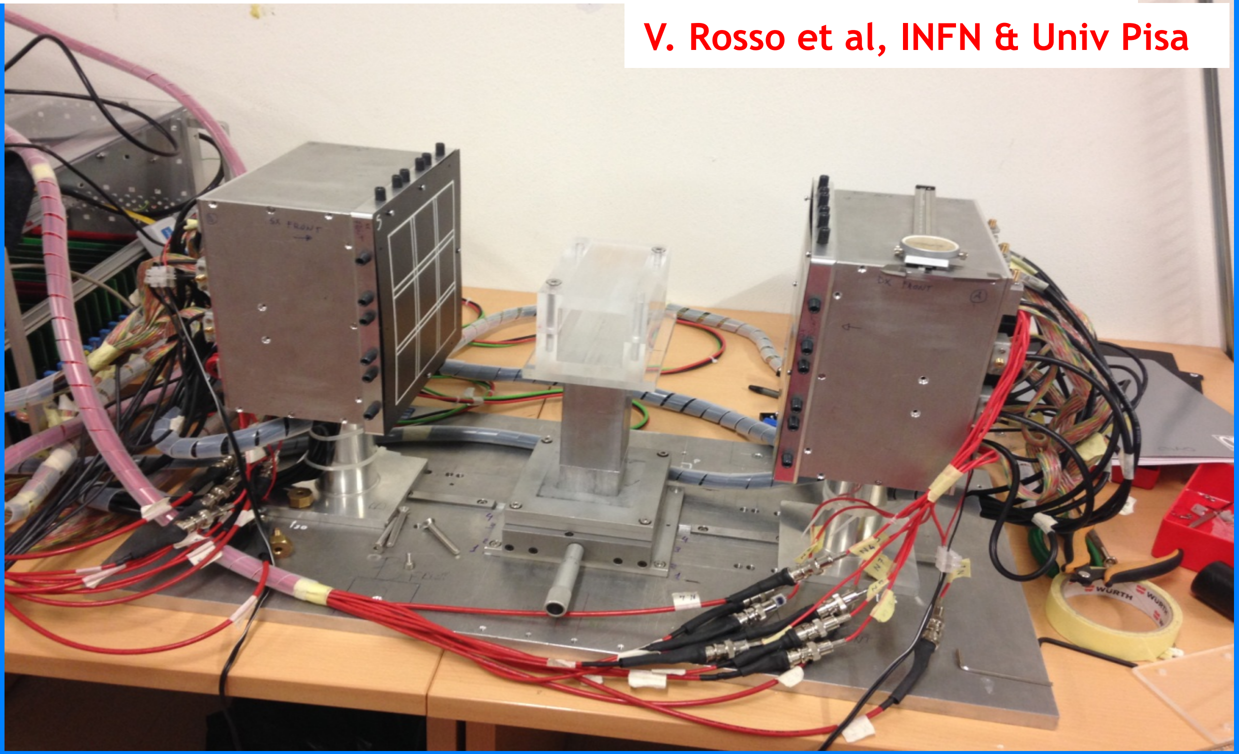
	$T_{1/2}$ (s)
^{11}C	1221.84
^{15}O	122.24
^{13}N	597.9
………	………………

Towards real in-beam measurement

- In-beam
- In-room
- Off-room



First INFN approaches

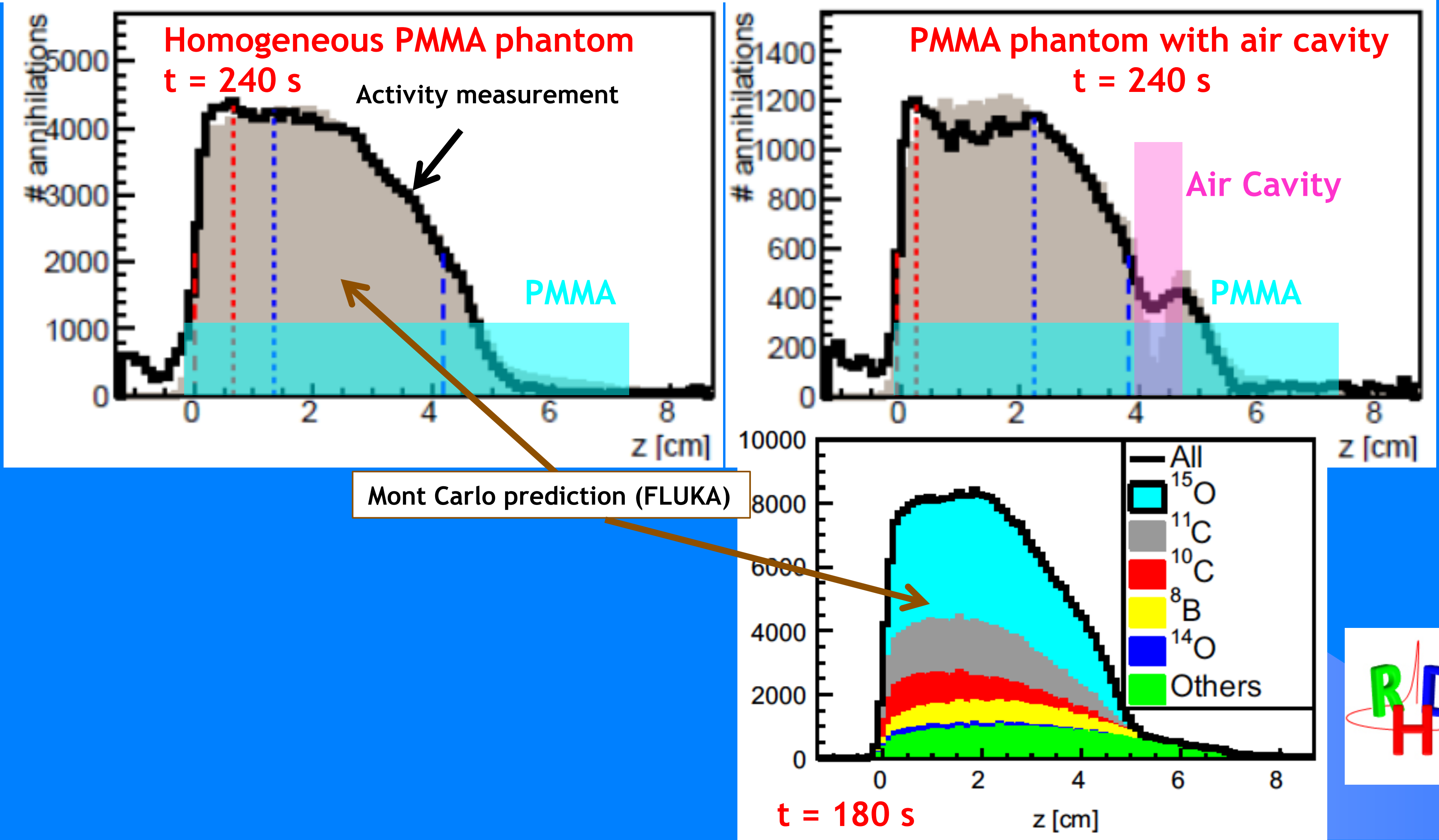


V. Rosso et al, INFN & Univ Pisa

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*

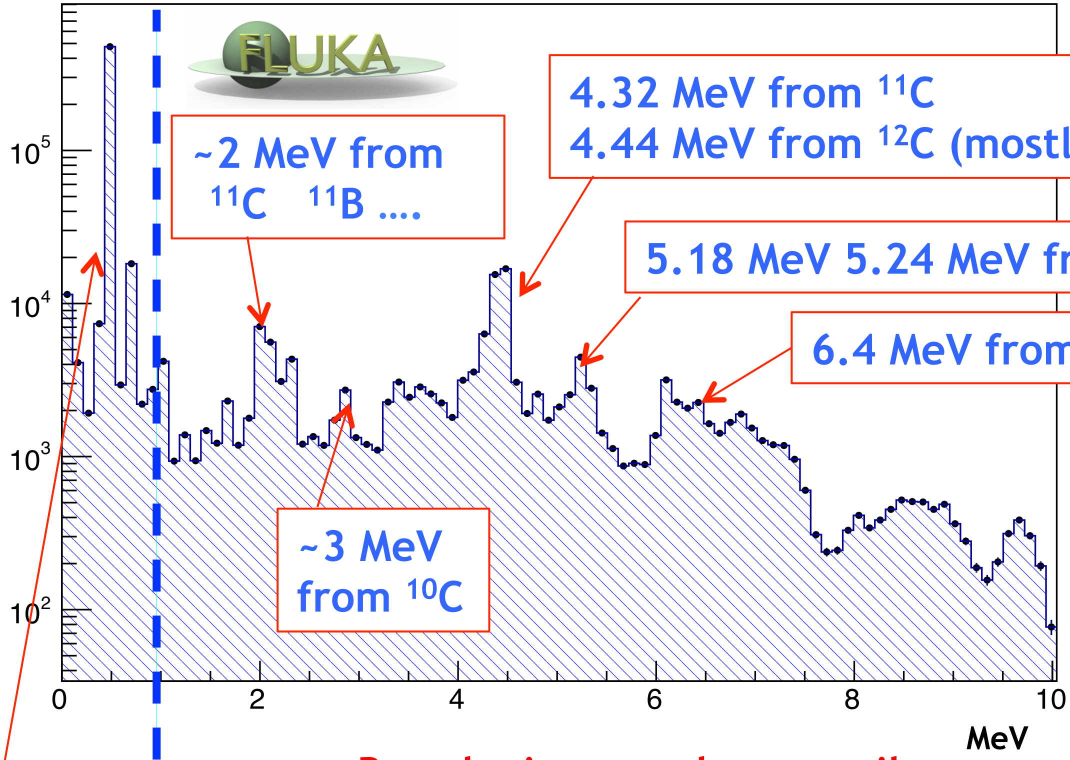
2 Gy uniform dose in 3x3x3 cm^3
17 energies: 62.3 - 90.8 MeV
146 s



Mont Carlo prediction (FLUKA)

Exploiting "prompt" de-excitation γ's

MC: γ Energy spectrum produced by p impinging on a PMMA target



~2 MeV from
^{11}C ^{11}B ….

4.32 MeV from ^{11}C
4.44 MeV from ^{12}C (mostly from O fragmentation)

5.18 MeV 5.24 MeV from ^{15}O

6.4 MeV from ^{16}O

~3 MeV
from ^{10}C

0.511 MeV from
e^+ annihilation

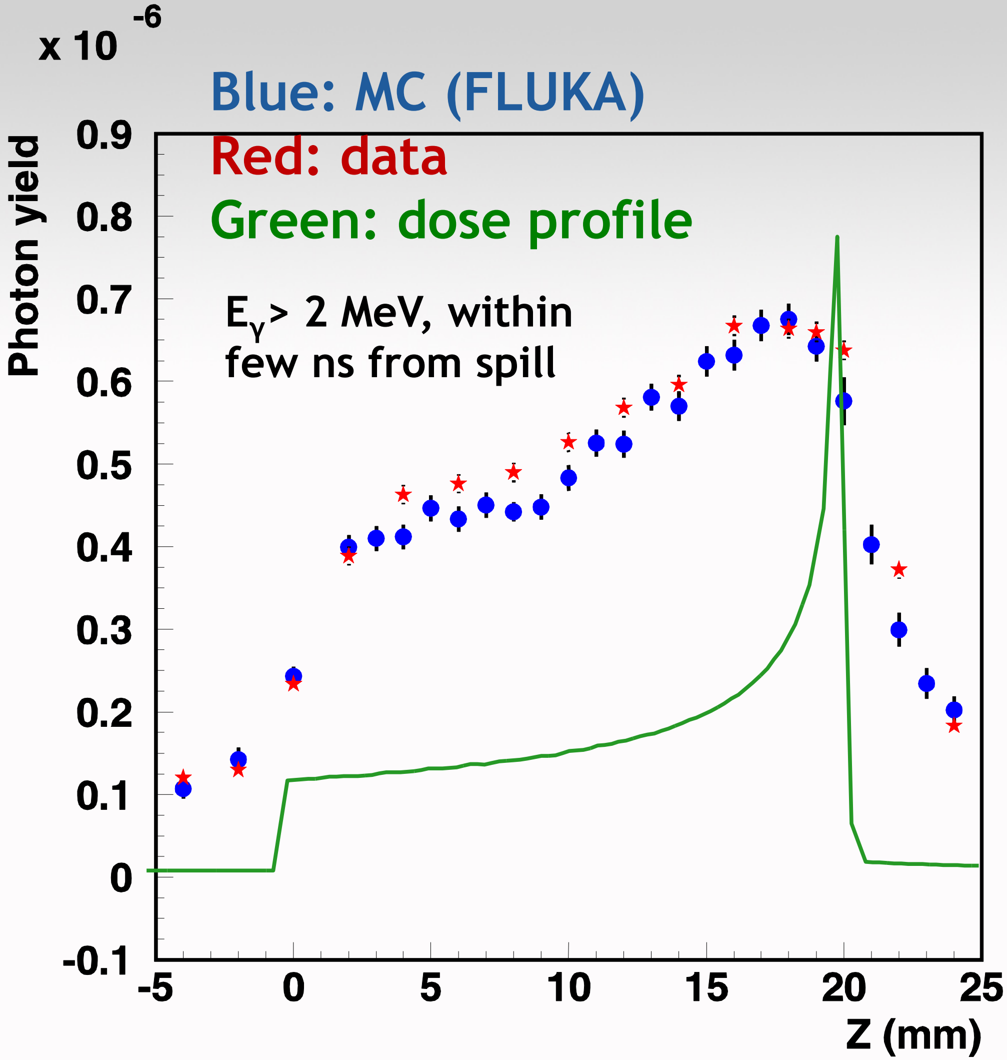
Broadening: nuclear recoil

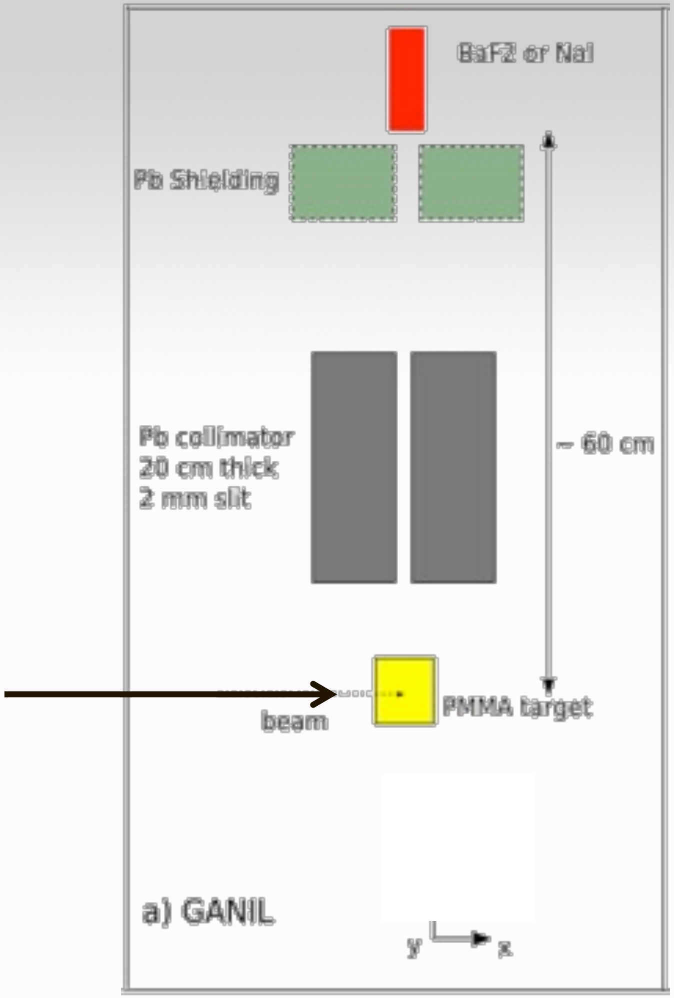
- $4 \cdot 10^9$ /fraction (2 Gy) 🙂
- γ-energy: 0… ~8 MeV ☹

not suited for standard
gamma-imaging devices
of nuclear medicine

Huge background from neutrons and γ's produced by neutrons.
TOF: not easy to implement in clinical practice

Prompt Photon Yield test @ GANIL
^{12}C 95 MeV/n in PMMA at 90°

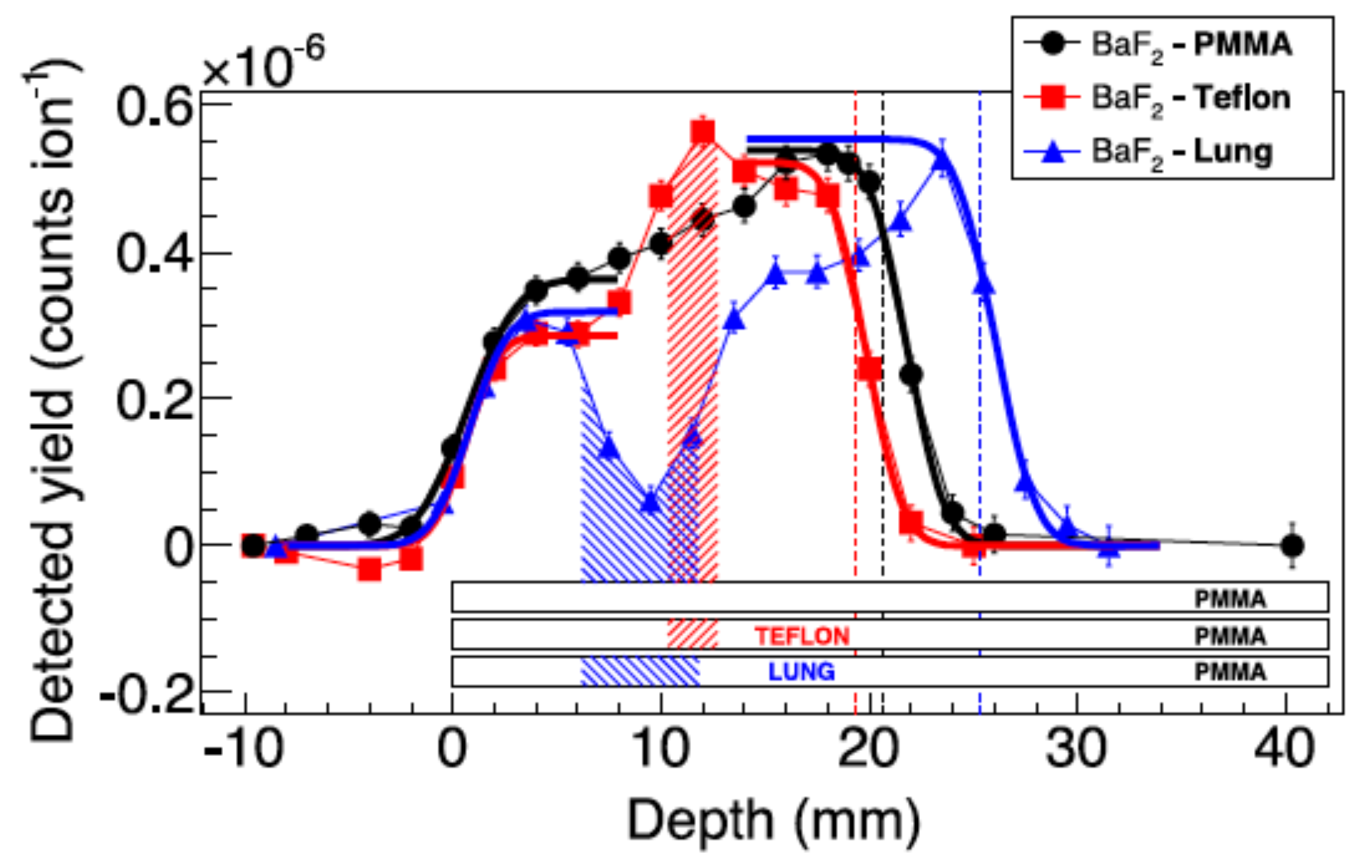




[sketch and exp. data taken from F. Le Foulher et al IEEE TNS 57 (2009),
E. Testa et al, NIMB 267 (2009) 993.

Spotting structures with prompt photon detection

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

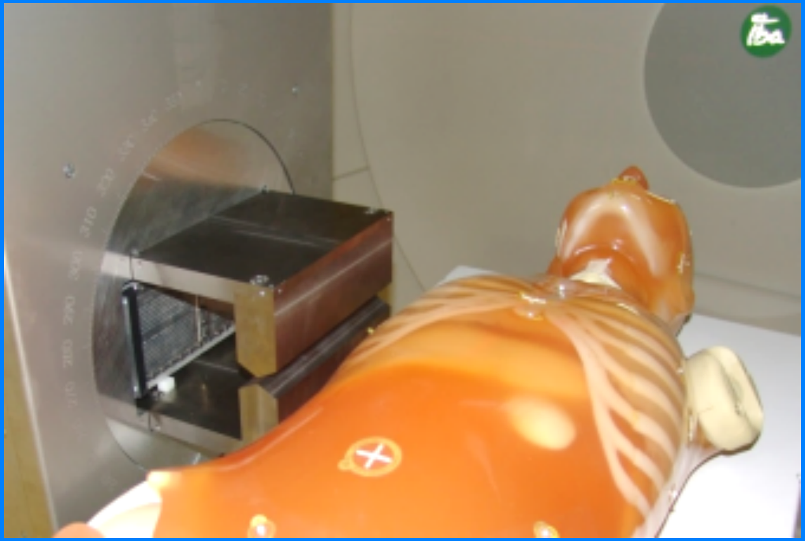


Key issue is the detection efficiency when trying to backtrack the γ

- Collimated detection approach suffers for reduced statistics)
- Compton camera approach suffers for low detection/reconstruction efficiency

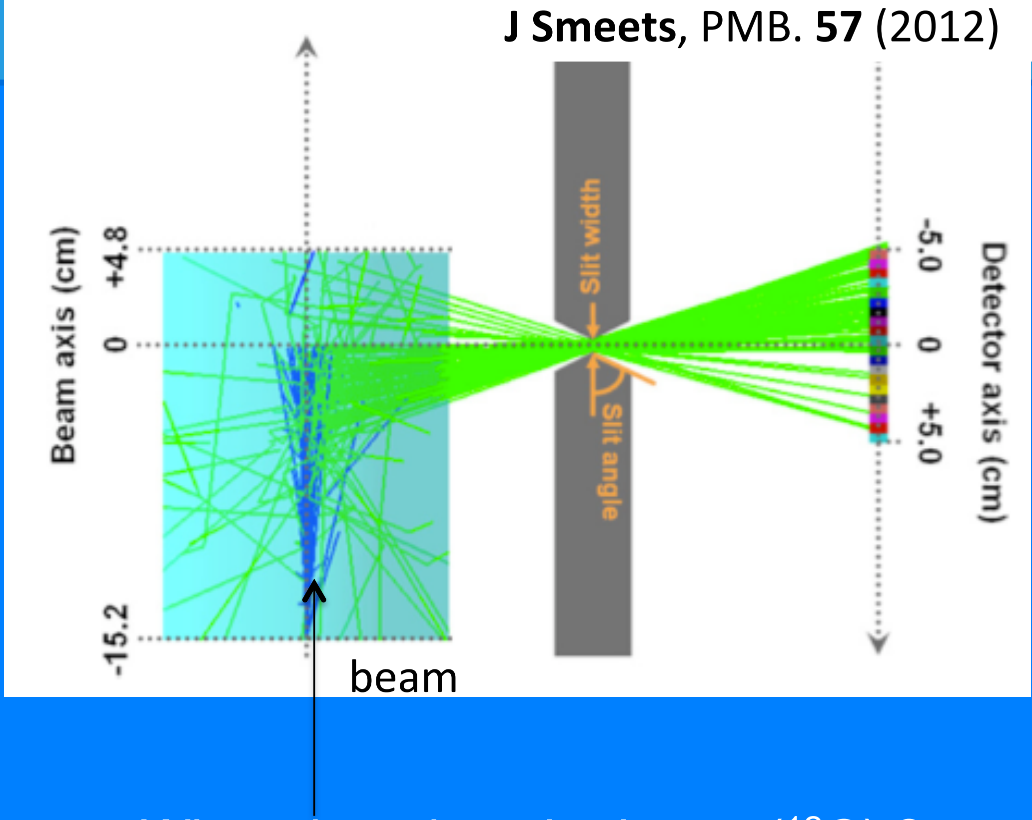
Range monitor for proton beam: Knife-Edge slit camera

Near to clinically practice: IBA, Politecnico & Xglab spinoff from Milano



Many groups working also on:

- **electronic collimated (Compton) camera**
- **Multi-slit collimated camera**



J Smeets, PMB. **57** (2012)

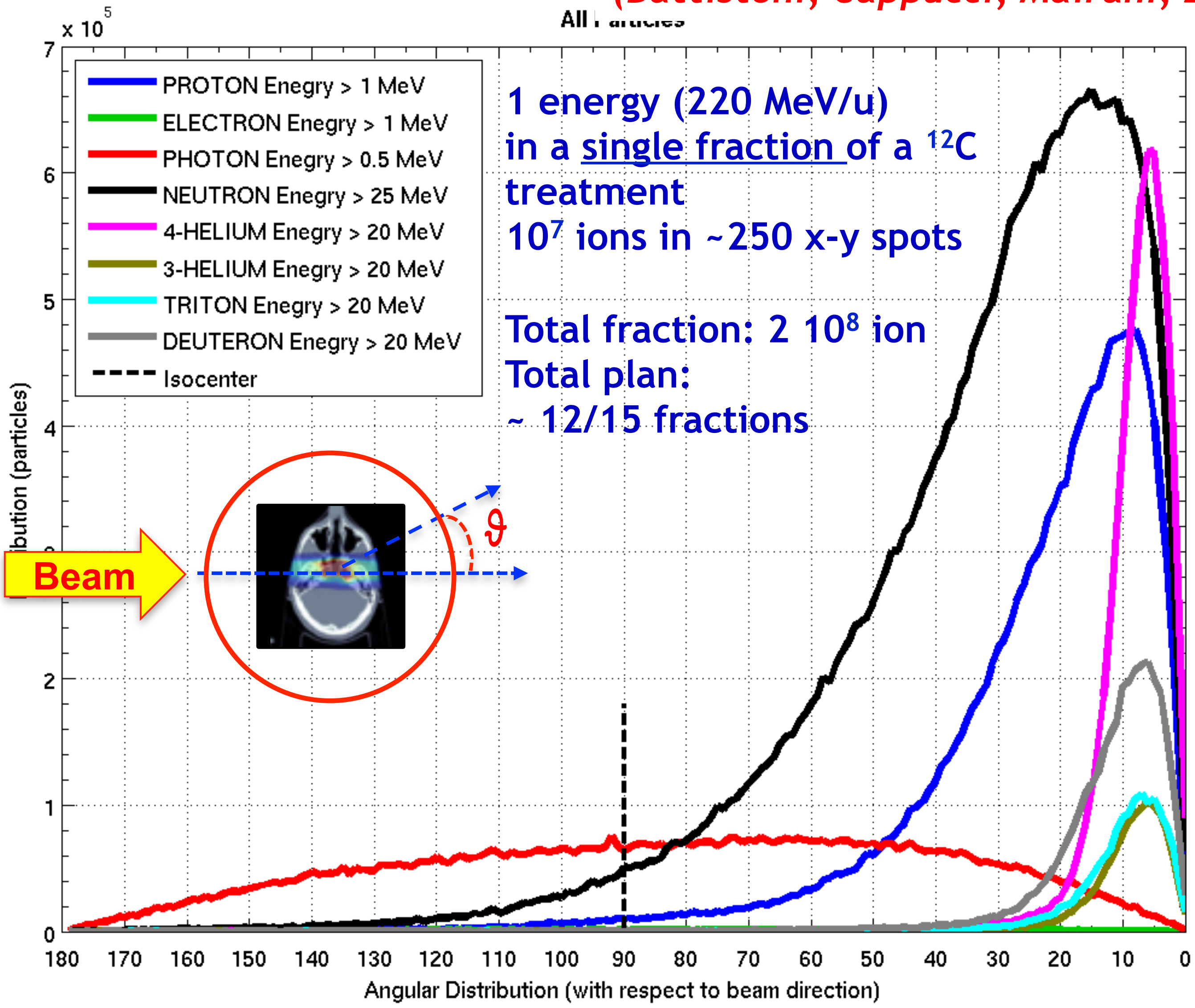
What about heavier beam (^{12}C) ? LET grows as Z^2 and the nuclear interaction increase with A. Thus, for the given dose, ^{12}C gives:

- **less prompt γ than proton**
- **more background than proton**

How many particles/fragments out of a patient?

MC simulation of a 12C treatment plan on a patient (CNAO)

(Battistoni, Cappucci, Mairani, 2014)

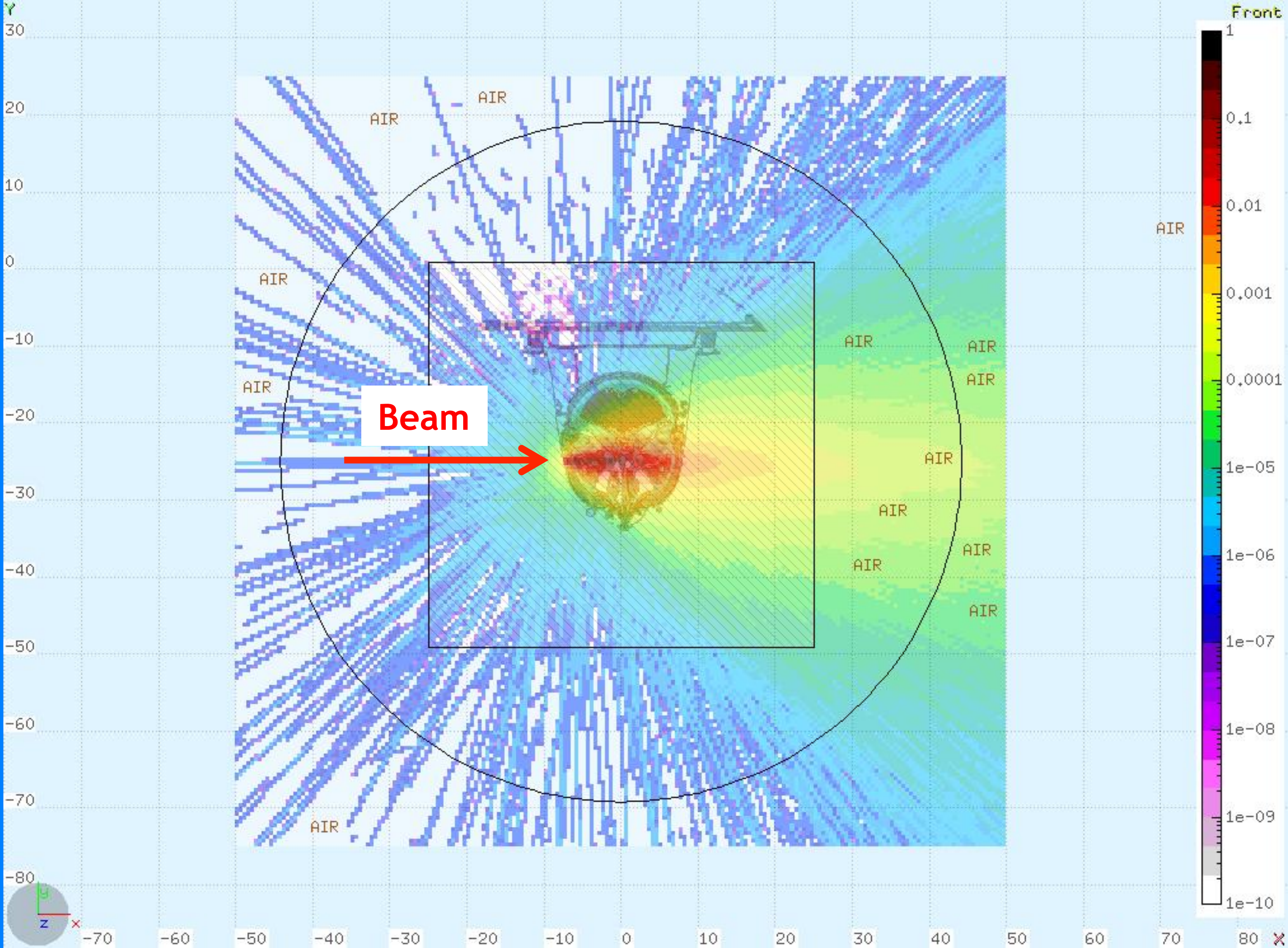


1 energy (220 MeV/u)
in a single fraction of a ^{12}C treatment
10^7 ions in ~250 x-y spots

Total fraction: 2 10^8 ion
Total plan:
~ 12/15 fractions

How many particles/fragments out of a patient?

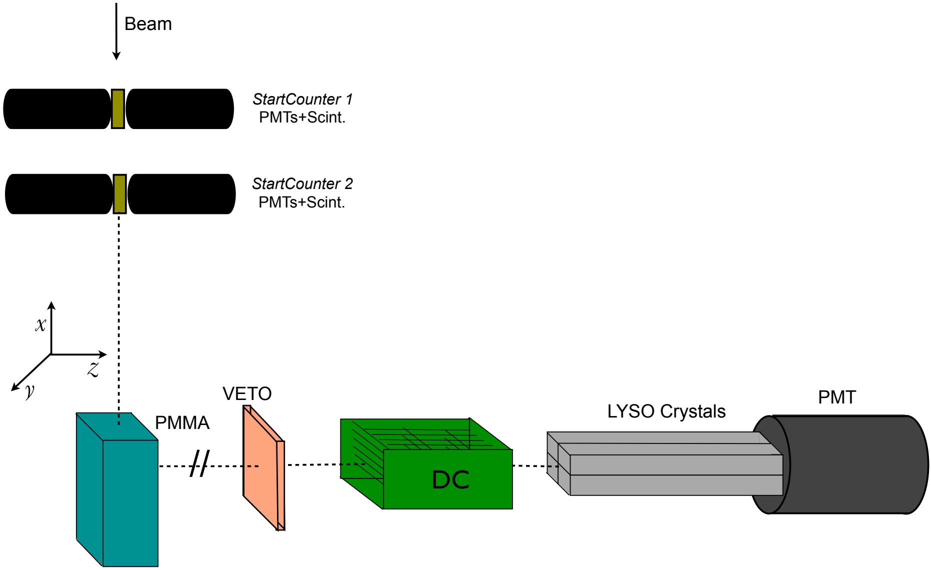
MC simulation of a 12C treatment plan on a patient (CNAO)
(Battistoni, Cappucci, Mairani, 2014)

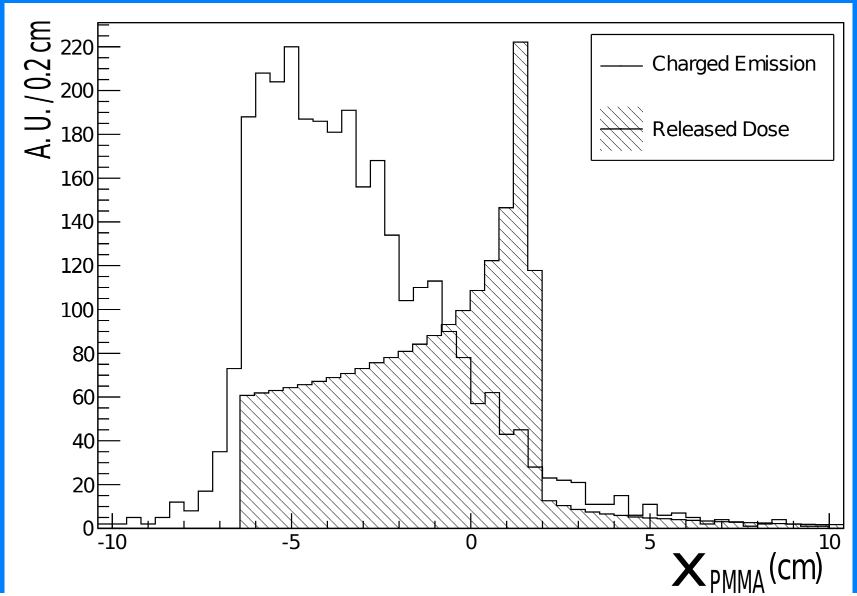


Use of charged secondary production

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

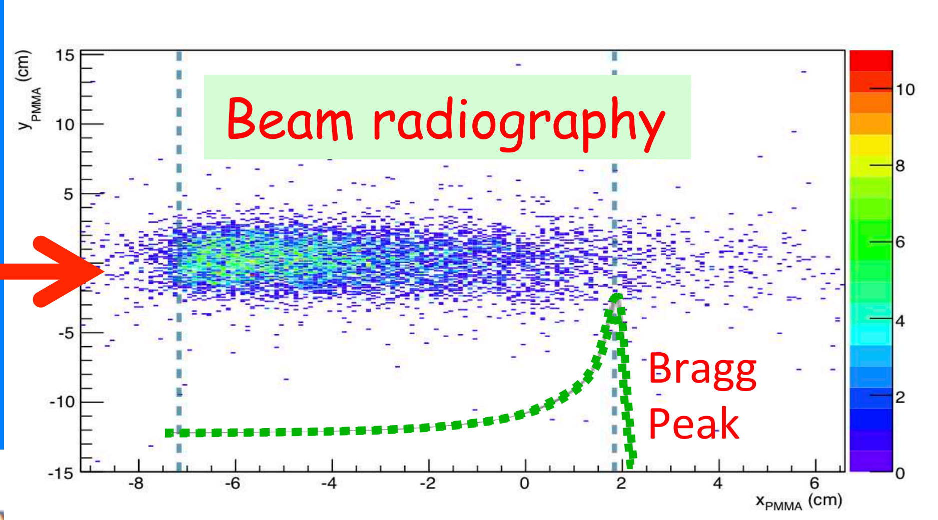
Charged secondary produced at 90^0 by ^{12}C 220 MeV/u at GSI





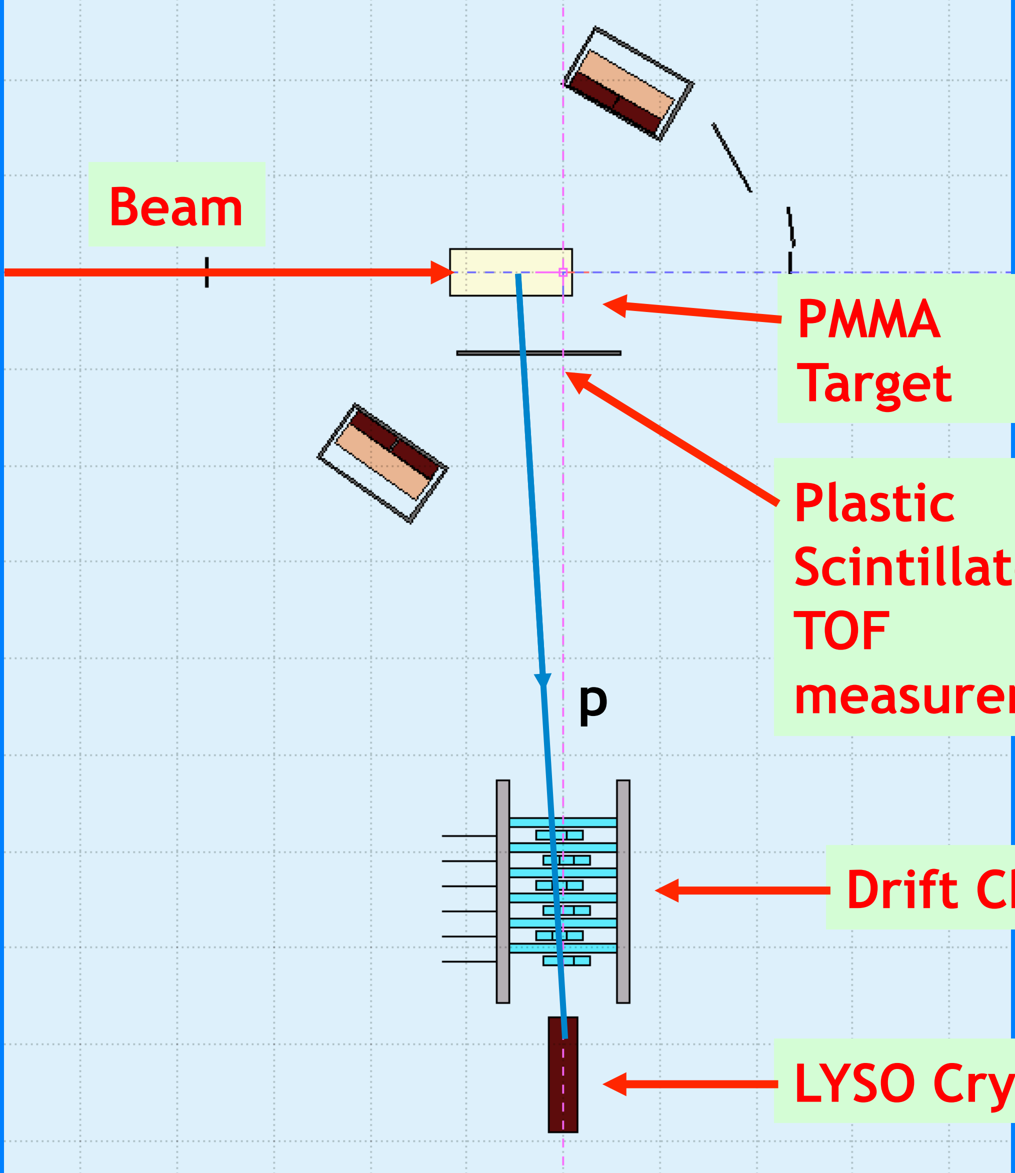
Beam

Beam



$$\frac{dN_p}{N_C d\Omega}(\theta = 90^\circ) = (1.83 \pm 0.02_{\text{stat}} \pm 0.14_{\text{sys}}) \times 10^{-} sr^{-}$$

Recent test at Heidelberg with He, C and O beams: Prompt γ and Charged particles Detection



Beam

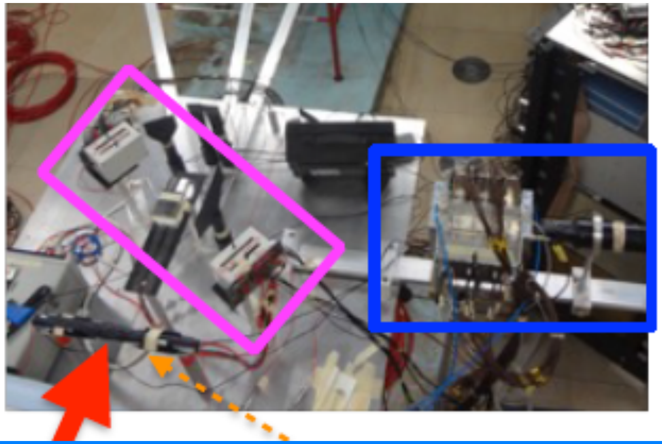
PMMA Target

Plastic Scintillator for TOF measurement

Drift Chamber

LYSO Crystal

G. Battistoni, F. Bellini, F. Collamati, E. De Lucia, M. Durante, R.Faccini, M. Marafini, I. Mattei, S. Morganti, R. Paramatti, V. Patera, D. Pinci, A. Rucinski, A. Russomando, A. Sarti, A. Sciubba, M. Senzacqua, E. Solfaroli Camillocci, M. Toppi, G. Traini, C. Voena

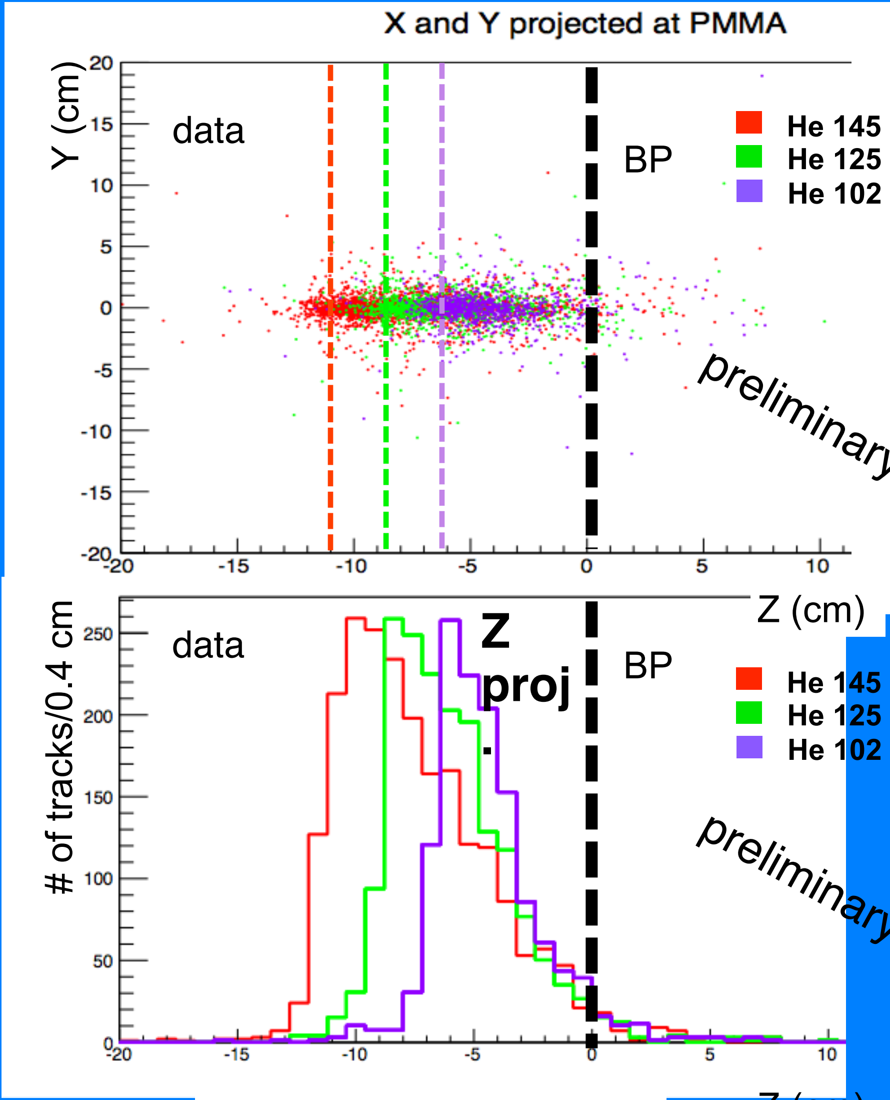


BP monitoring with He beams

- 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
- $\phi = dN_{all}/(N_{ions}\, d\Omega)$

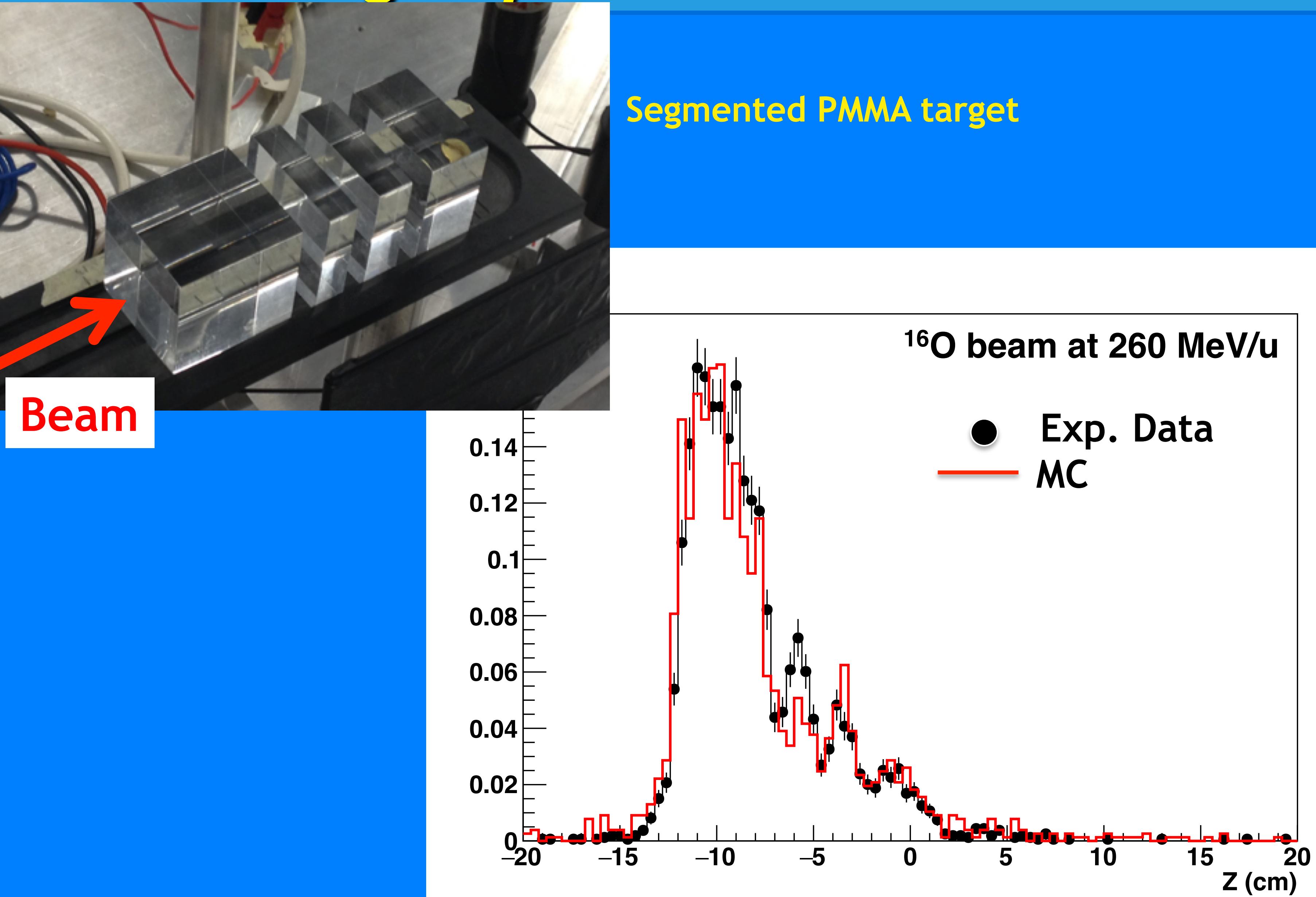
Beam type/E	**ϕ 90° (10^{-3})**
He 102	**0.6**
He 125	**0.7**
He 145	**1**
C 160	**1**
C 180	**2**
C 220	**3**
O 210	**3**
O 260	**5**
O 300	**10**

preliminary



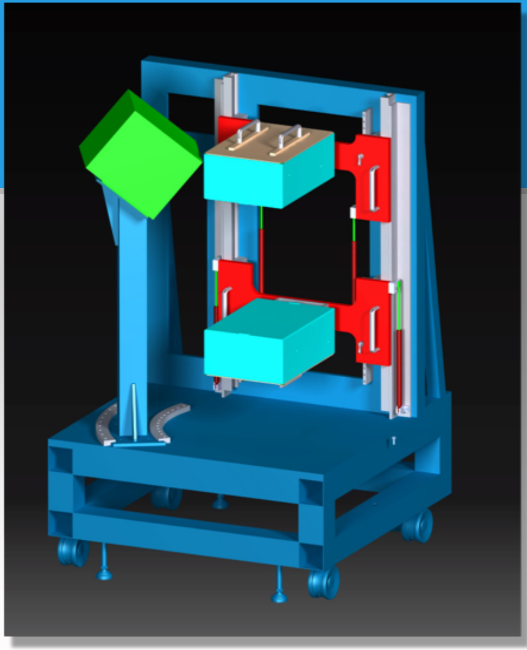
different PMMA thickness !!

detecting inhomogeneities with charged particles



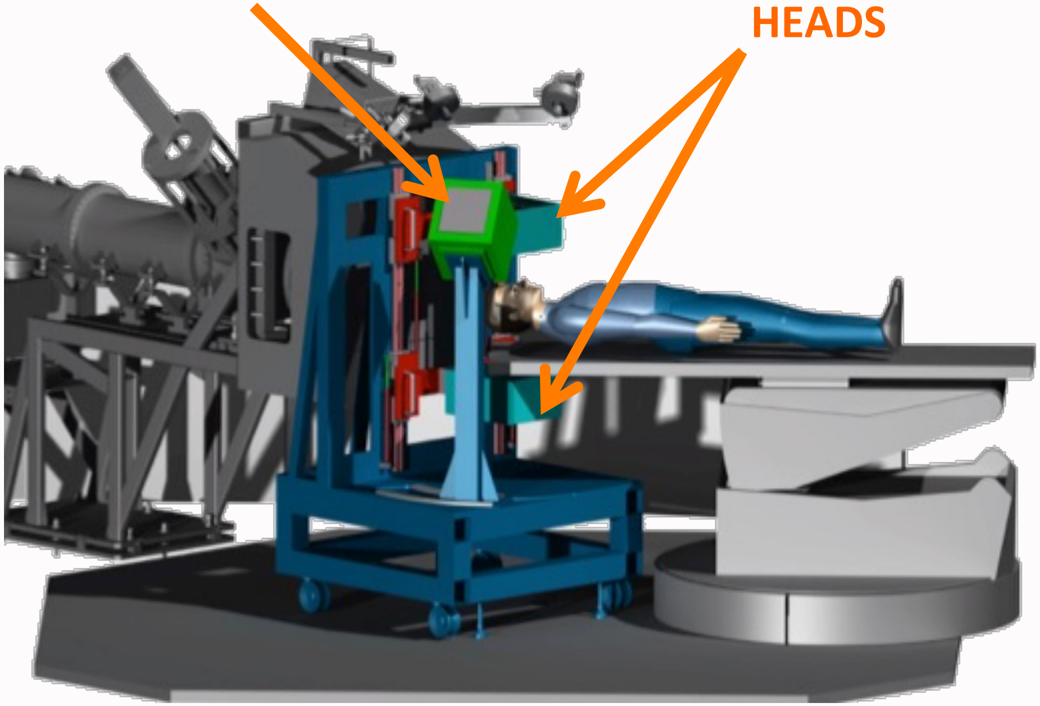
Segmented PMMA target

The InSide Project @CNAO



INnovative **S**olutions for **I**n-beam **D**osim**E**try in Hadrontherapy

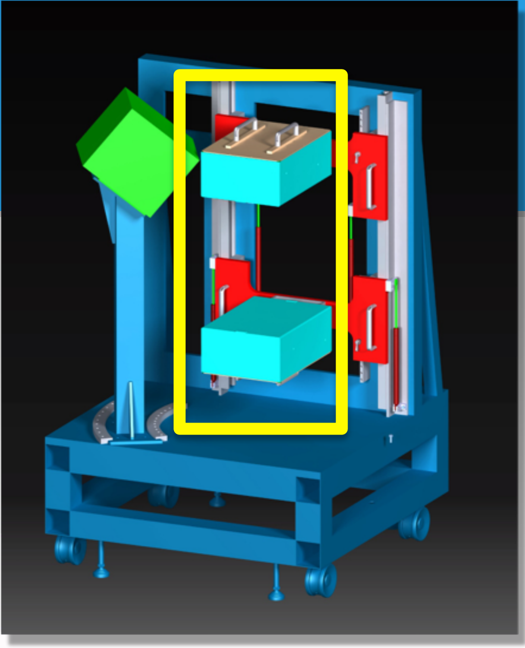
Funds: PRIN + Centro Fermi + INFN (RM1-TO-MI-PI)



proton emission
Tracker +
Calorimeter =
DOSE PROFILER

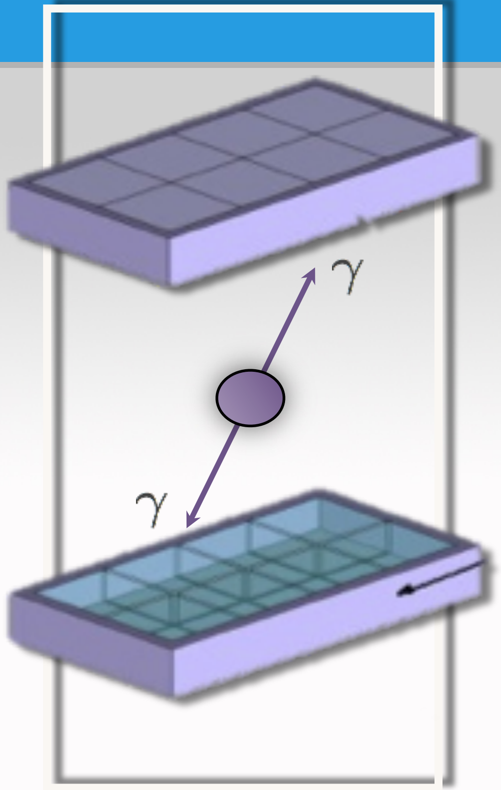
β^+ activity distribution
IN-BEAM PET HEADS

- Dual signal operation
- integrated in treatment room
- Provide in-beam feedback on beam range
- Challenge: fusion of charged and PET information



The INSIDE PET system

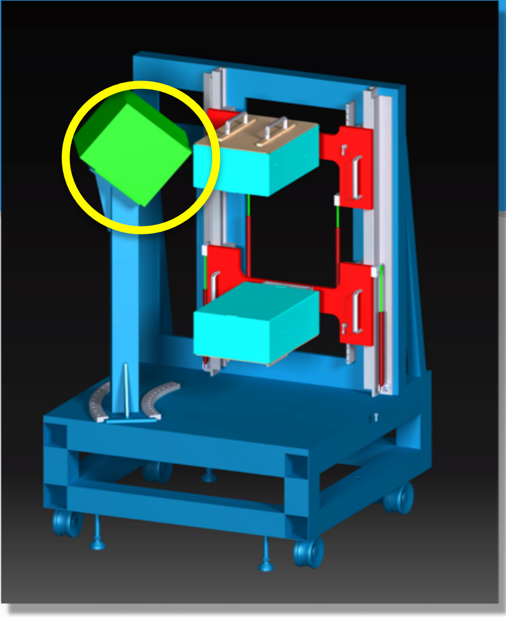
- Detectors to measure the 511 keV back-to-back photons in order to reconstruct the β^+ activity map.
- Two planar panels: 10 cm x 20 cm wide => 2 x 4 detection modules;
- 1-2 mm resolution expected along the beam path



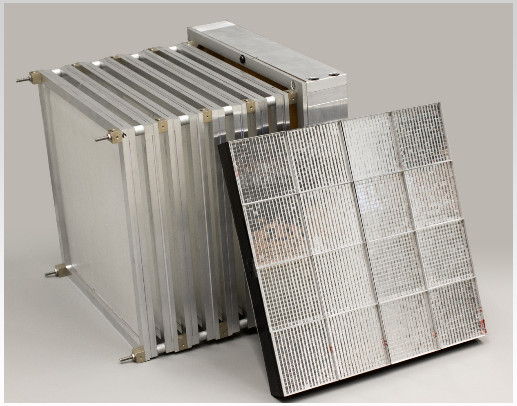
Each module = pixelated LSO matrix 16 x 16 pixels, 3 mm x 3 mm crystals (pitch 3.1mm)

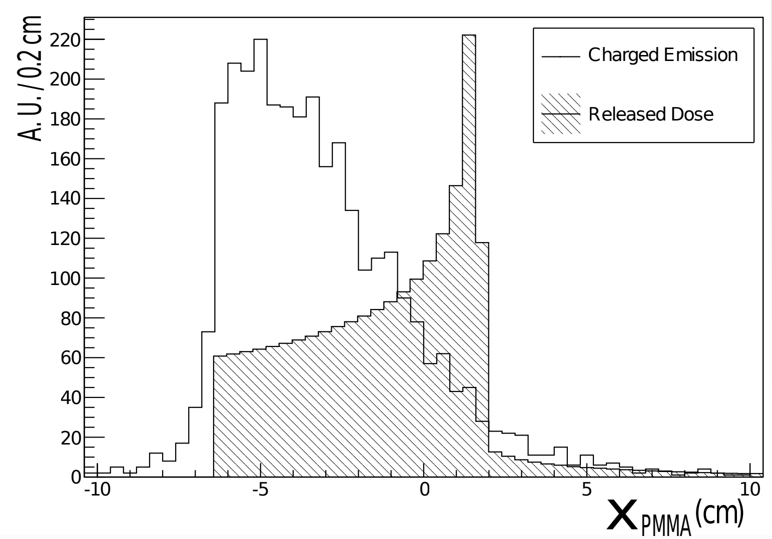
LYSO matrix readout: array of SiPM (16x16 pixels) coupled one-to-one.

Custom TOF-PET asic (Courtesy of M. Rolo, LIP and ENDOTOFPET EU project)



The INSIDE charge Profiler



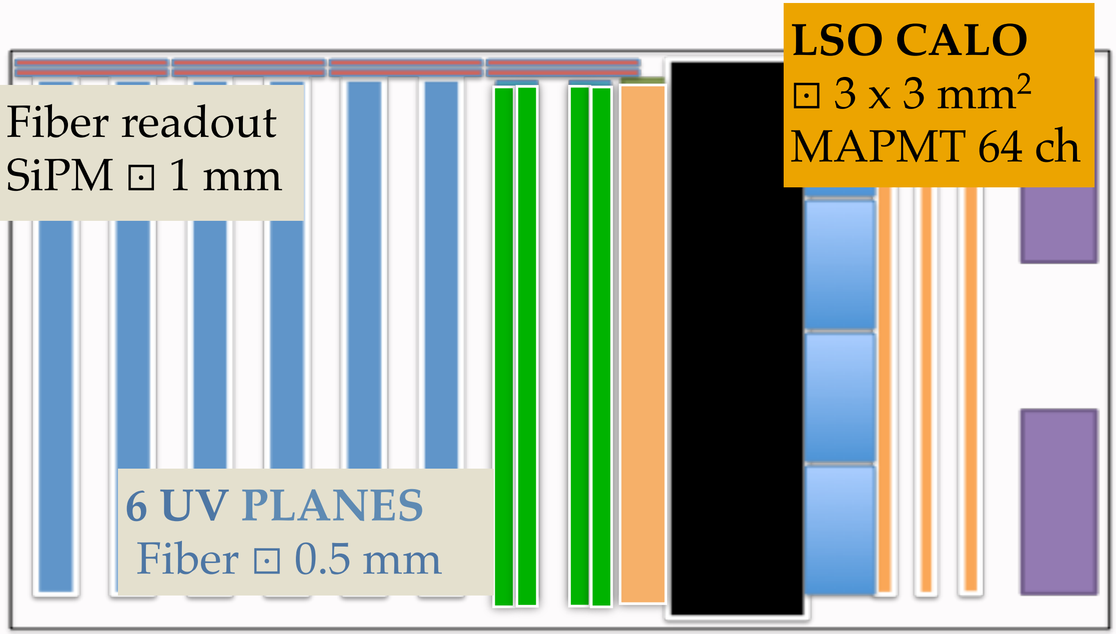


Tracker: back-tracking of secondary protons to the beam line

Calo: select higher energy protons to minimize MS in the patient.

Reconstruction: deconvolution of absorption inside the patient from the emission shape

Calibration: BP position vs Emission shape parameters

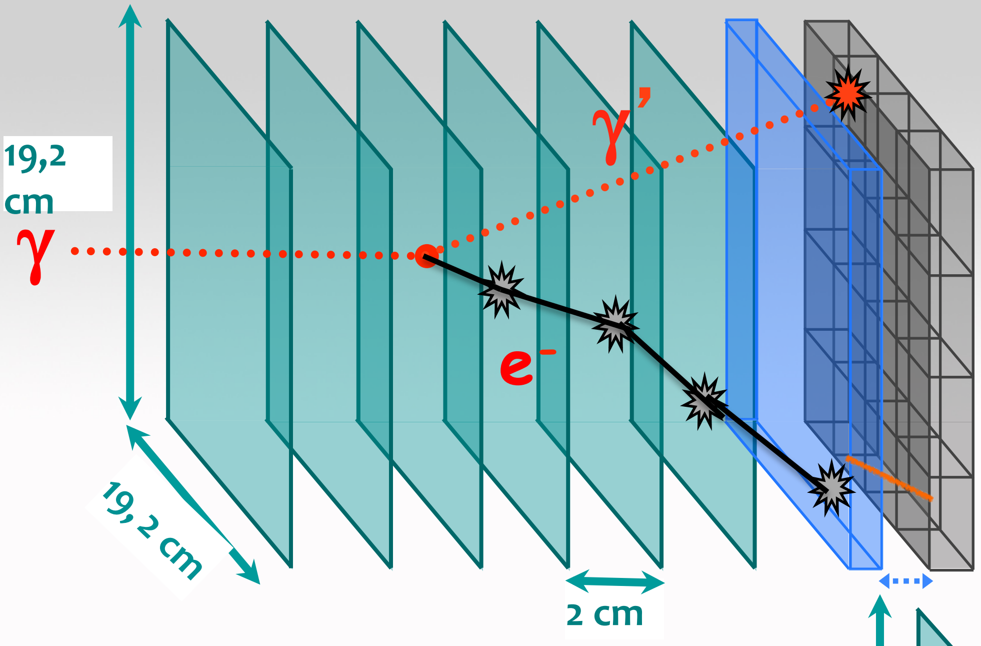


LSO CALO
⊡ 3 x 3 mm^2
MAPMT 64 ch

Fiber readout
SiPM ⊡ 1 mm

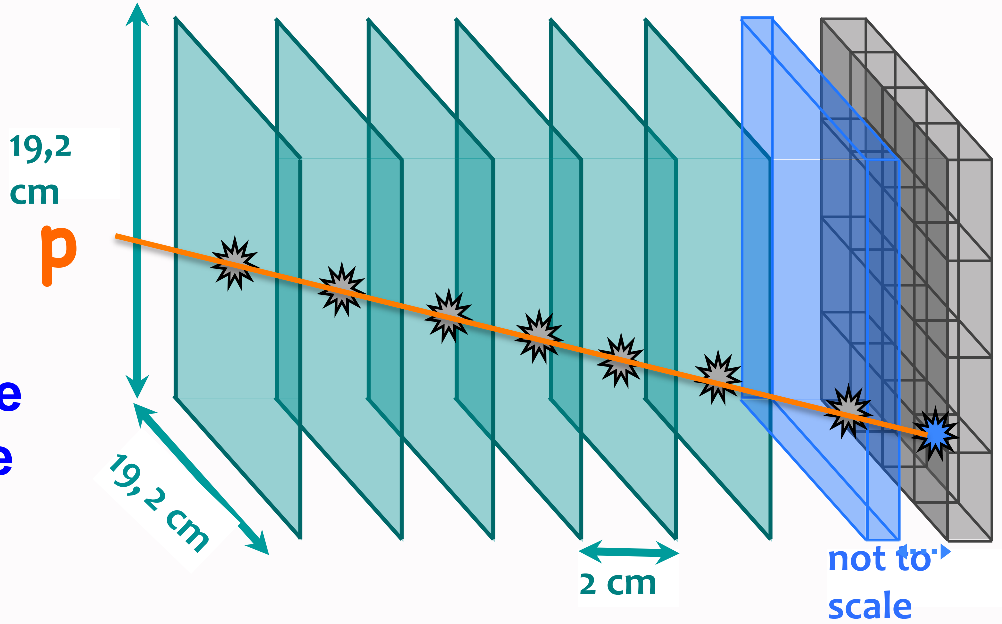
6 UV PLANES
Fiber ⊡ 0.5 mm

INSIDE Dose Profiler



“dual mode” detector

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



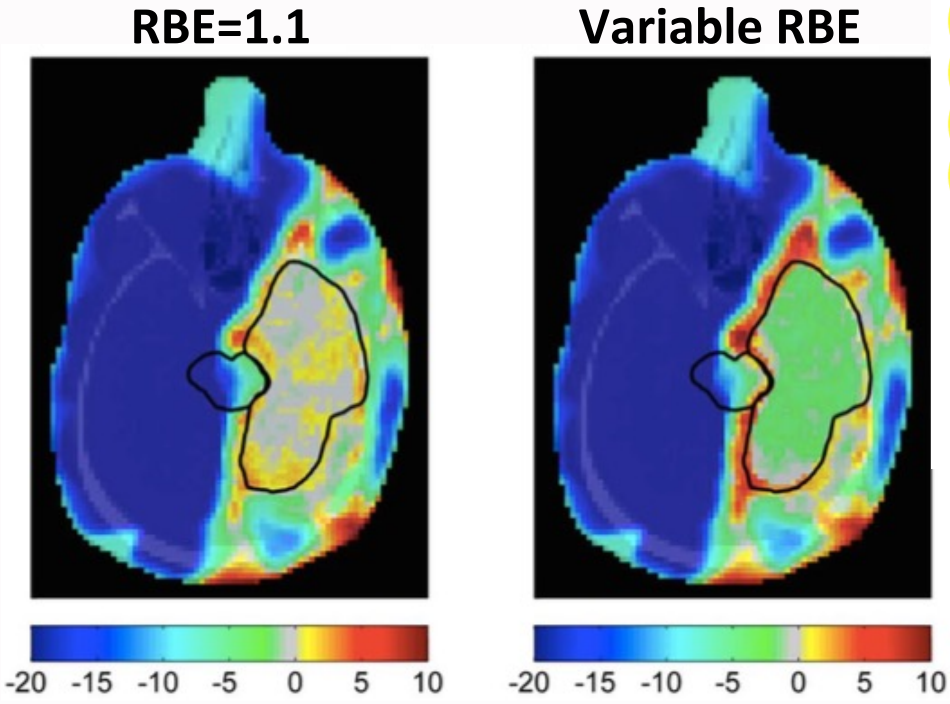
Heavy charged secondary cross all TRK planes up to LYSO crystals

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

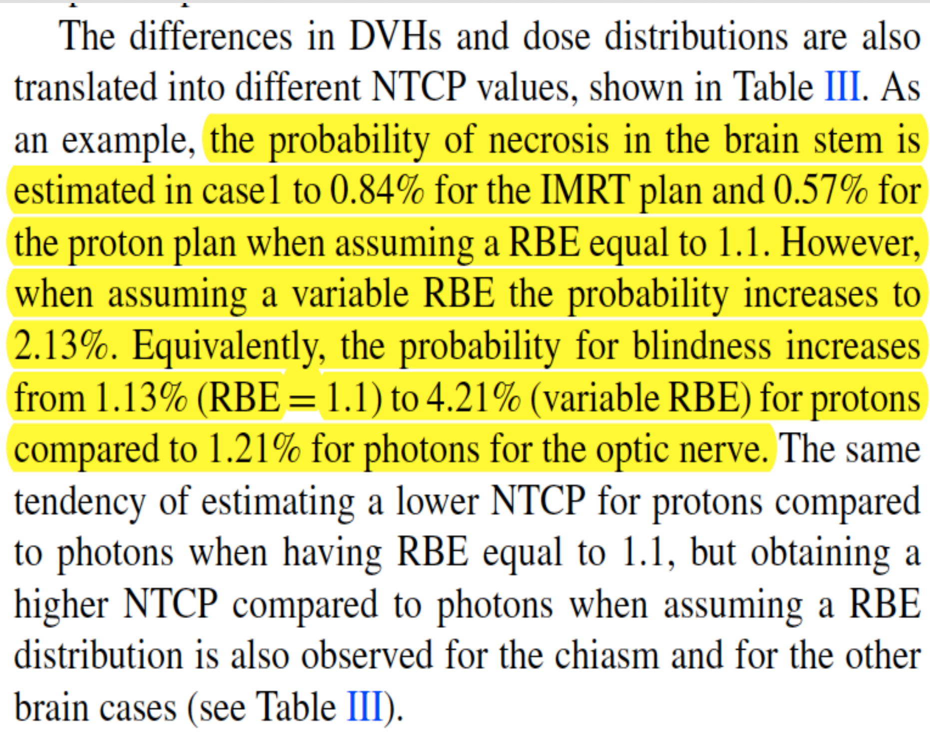
Target fragmentation & proton RBE

Currently the contribution of target fragments and of the increasing RBE near the PB is implicit (ICRU reccommendation RBE=1.1)

Lately has been pointed out possible impact of variable proton RBE on clinical NCTP values


RBE=1.1

Variable RBE

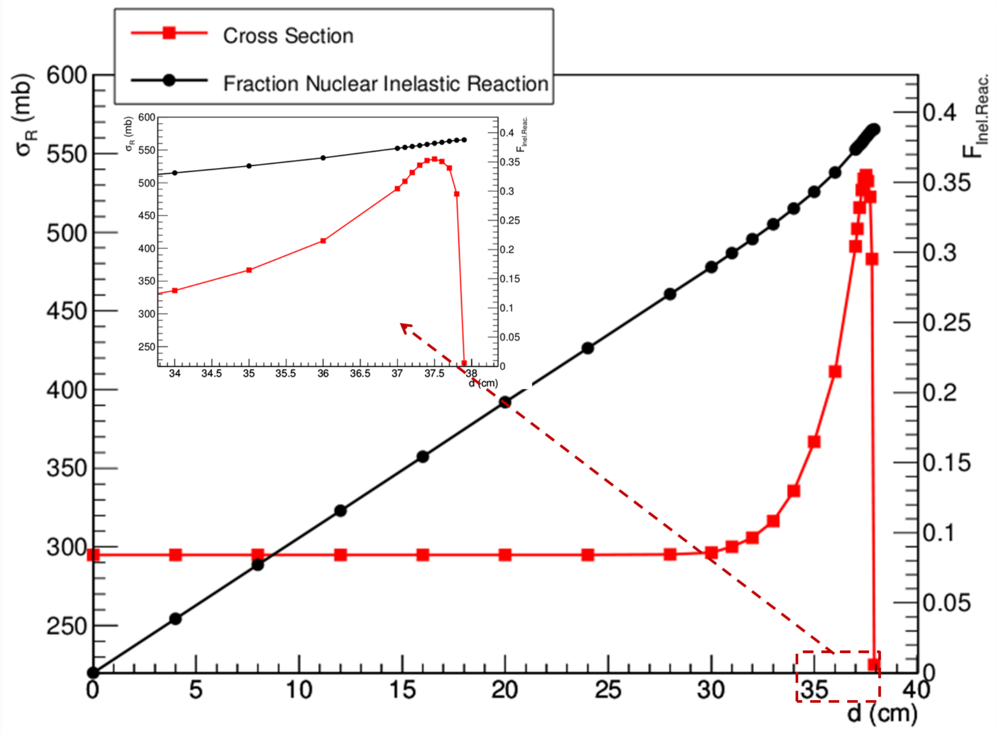

The differences in DVHs and dose distributions are also translated into different NTCP values, shown in Table III. As an example, the probability of necrosis in the brain stem is estimated in case1 to 0.84% for the IMRT plan and 0.57% for the proton plan when assuming a RBE equal to 1.1. However, when assuming a variable RBE the probability increases to 2.13%. Equivalently, the probability for blindness increases from 1.13% (RBE = 1.1) to 4.21% (variable RBE) for protons compared to 1.21% for photons for the optic nerve. The same tendency of estimating a lower NTCP for protons compared to photons when having RBE equal to 1.1, but obtaining a higher NTCP compared to photons when assuming a RBE distribution is also observed for the chiasm and for the other brain cases (see Table III).

Wedenberg 2014 Med Phys

Target fragmentation & PT: is it an issue?

The target fragmentation could be relevant (only?) for proton beam treatment. The proton inelastic scattering on patient nuclei (C,O,N) produces Z≤8 fragments with low energy -> very high LET and very good at cell killing (very high RBE)

Example : analytic approximation of p -> H_2O @250 MeV

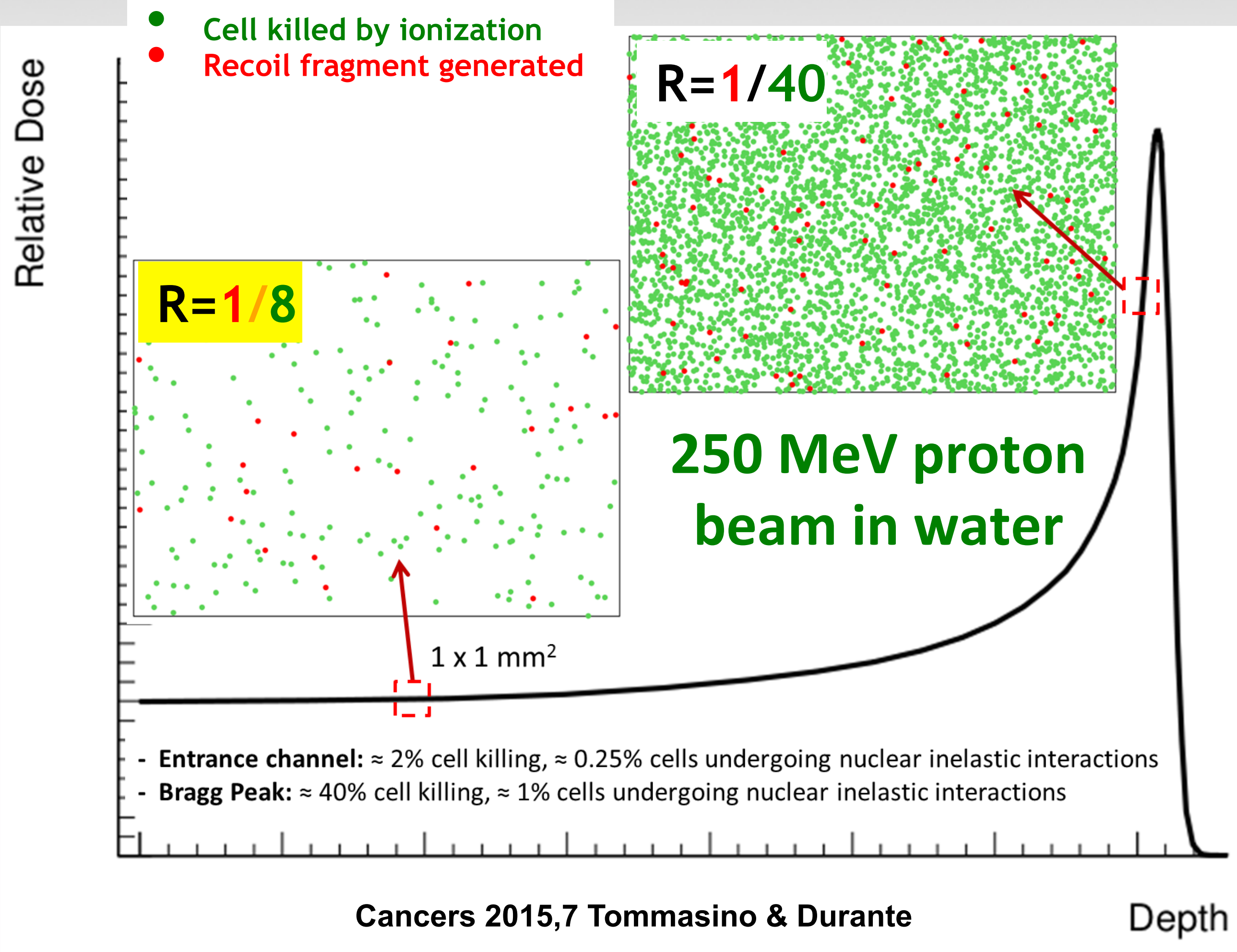


Bradt-Peters formula (Sihver 2009 Radiat Meas)

- **In water, about 1% cm^{-1} of protons undergo inelastic nuclear interactions**
- **In a typical treatment, this corresponds to about 20% of the primary beam**
- **60% of the energy deposited by recoil in charged fragments**
- **40% in neutrons and photons out of the field**

Target fragmentation & PT: when is it an issue?

Target fragmentation in proton therapy: gives contribution also outside the tumor region!



- **Entrance channel:** ≈ 2% cell killing, ≈ 0.25% cells undergoing nuclear inelastic interactions
- **Bragg Peak:** ≈ 40% cell killing, ≈ 1% cells undergoing nuclear inelastic interactions

Cancers 2015,7 Tommasino & Durante

About 10% of biological effect in the entrance channel due to secondary fragments

Largest contributions of recoil fragments expected from He, C, Be, O, N

See also dedicated MC studies:

- **Paganetti 2002 PMB**
- **Grassberger 2011 PMB**

Focus on C,O,N(p,X) scattering & heavy fragment production @100-250 MeV

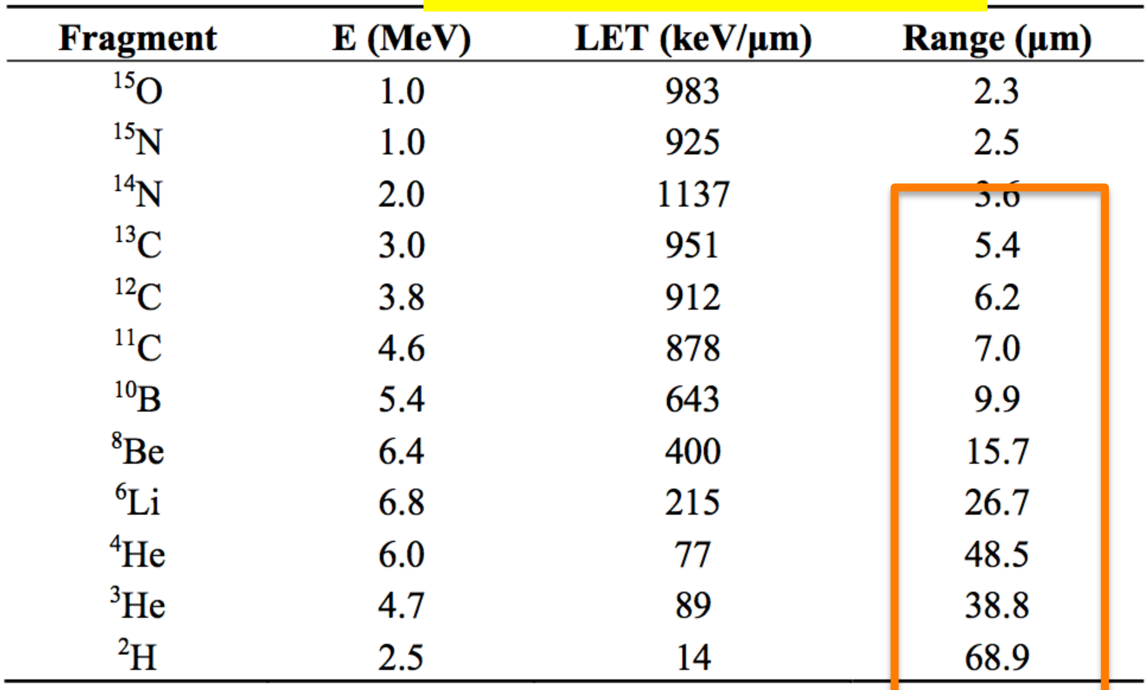
The proton-nucleus elastic interaction and the light fragment production, namely p,d,t and He(?), are quite well known..

BUT…..

“Heavy” (A≥4) fragment emission energy and angle largely unknown.

Very low energy-short range fragments.

$P\text{->}H_2O$ @ 200 MeV

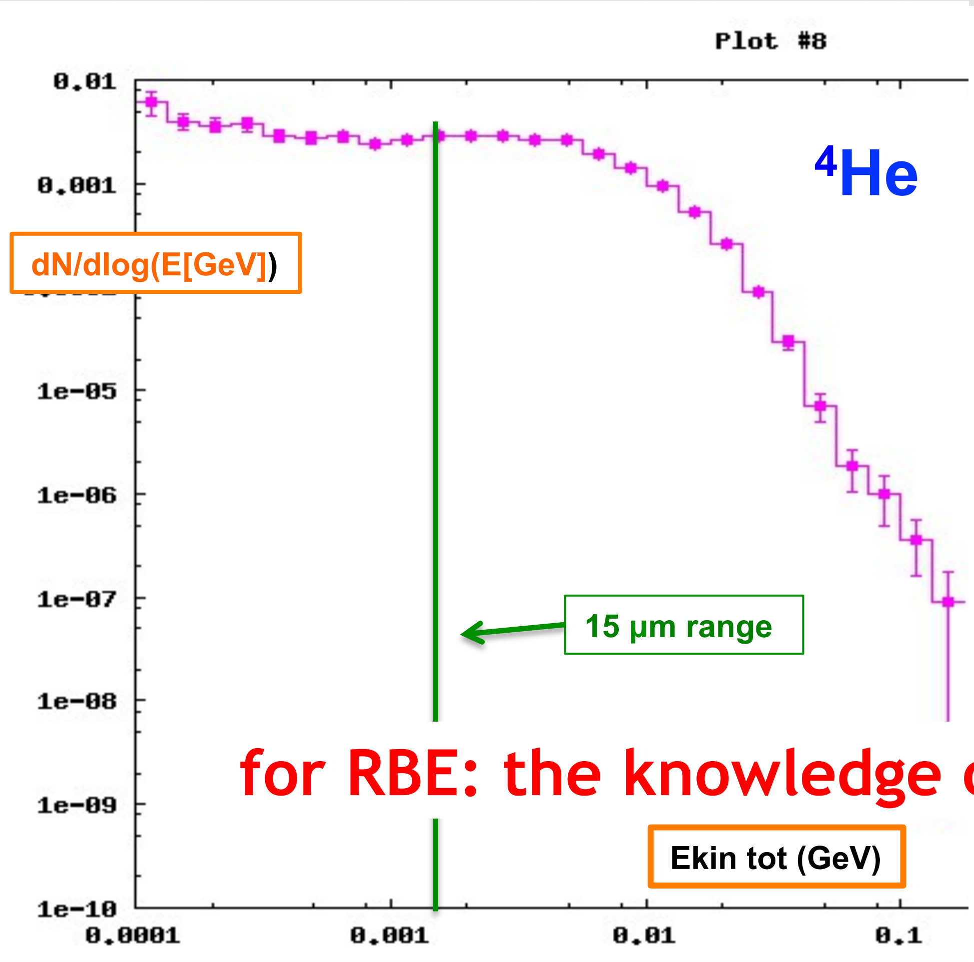


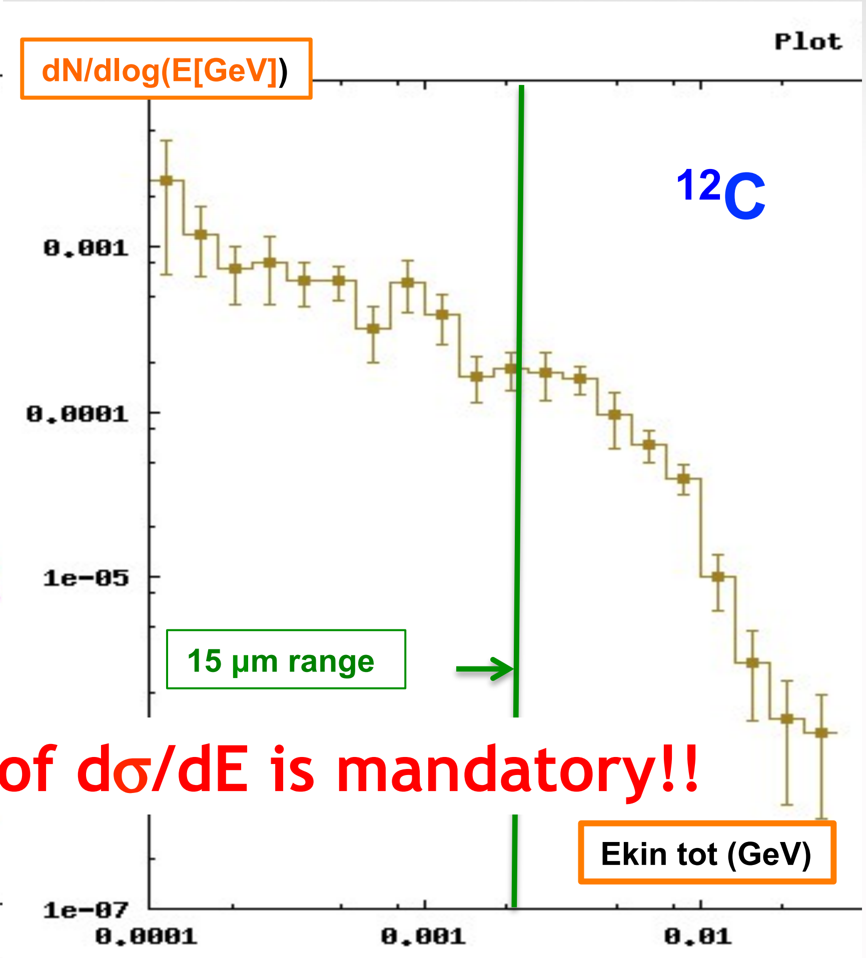
Fragment	E (MeV)	LET (keV/µm)	Range (µm)
^{15}O	1.0	983	2.3
^{15}N	1.0	925	2.5
^{14}N	2.0	1137	3.6
^{13}C	3.0	951	5.4
^{12}C	3.8	912	6.2
^{11}C	4.6	878	7.0
^{10}B	5.4	643	9.9
^{8}Be	6.4	400	15.7
^{6}Li	6.8	215	26.7
^{4}He	6.0	77	48.5
^{3}He	4.7	89	38.8
^{2}H	2.5	14	68.9

Cancers 2015,7 Tommasino & Durante

p scattering on Brain tissue @200 MeV

MC (FLUKA) prediction of production of heavy fragments for 200 MeV p on “BRAIN” : production of He & C





for RBE: the knowledge of dσ/dE is mandatory!!

Inverse kinematic strategy

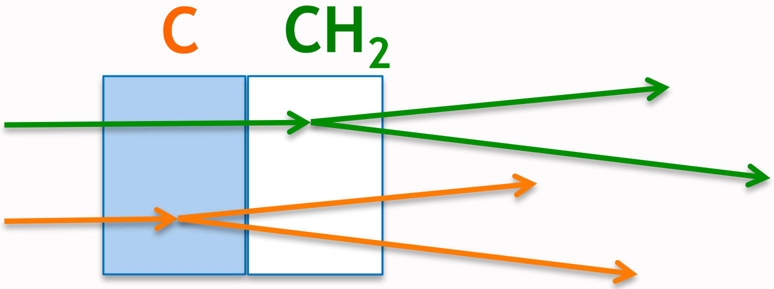
Target fragments travel few μm in the target-> difficult to directly detect them, even for very thin target (10 μm?)

let's shoot a β=0.6 patient (C,O,N nuclei) on a proton at rest and measure how it fragments!!

Then if we measure the X-section, provide we apply an inverse velocity transformation, the result should be the same.

- **Use (as patient) beams N, O, C ions with β= 0.6 ➔ Ekin=200 A MeV.**
- **The heavy fragment (all but p,d,t,He) has ~200 MeV/nucleon kinetic energy and are forward peaked**

H target difficult!!
A possible solution is to use twin targets. The fragmentation cross section can be obtained by subtraction.



New target fragmentation Experiment?

The community is starting to think at target fragmentation experiment: new contributors are welcome!

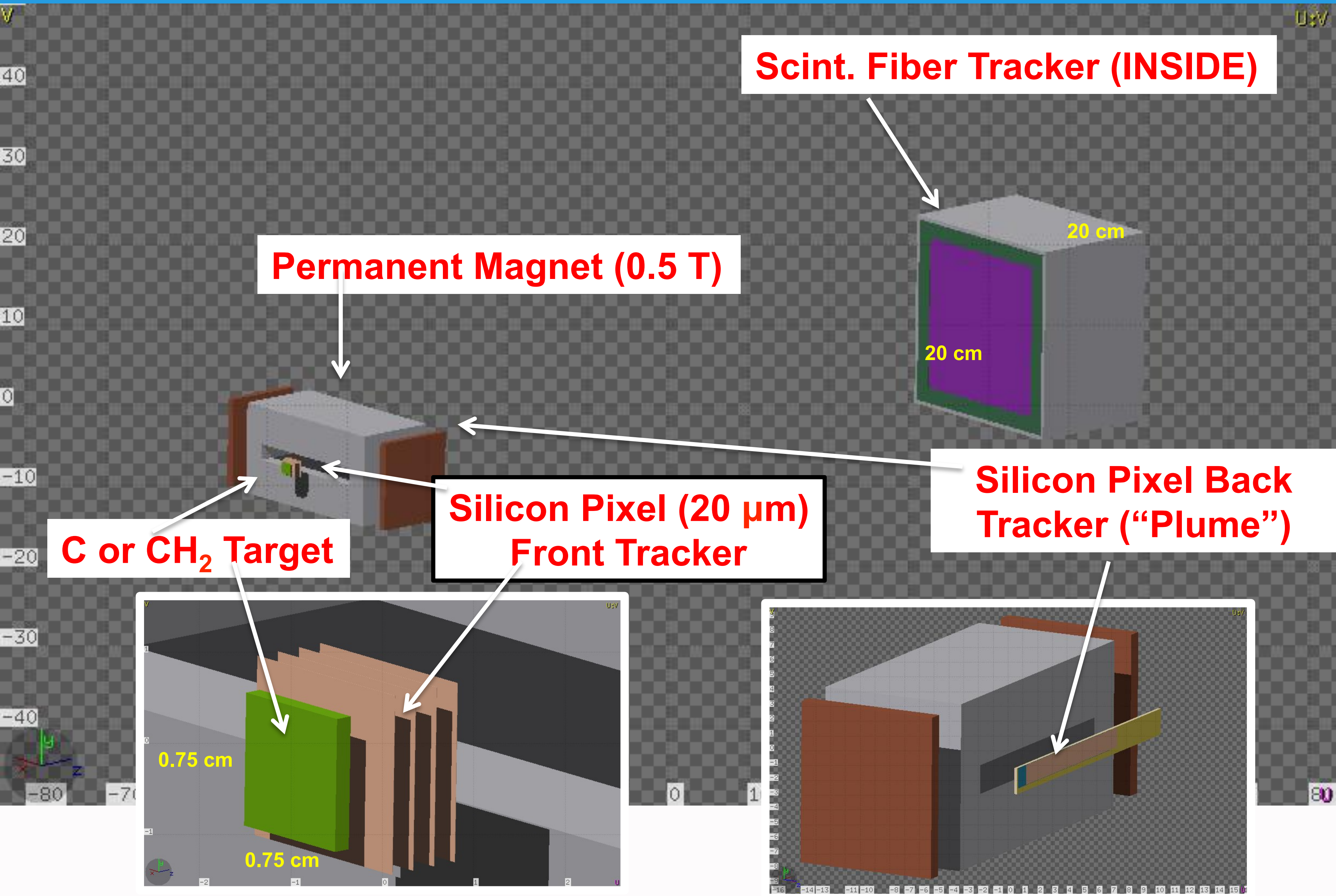
- **Challenging measurement**
- **A first meeting dedicated to this opportunity/challenge held in Villa Tambosi (TN) in July 2015 , near TIFPA**
- **Beam available in Europe: HIT, CNAO, GSI(?)**

FramentatiOnOf Target

FOOT

A possible Set Up

(Prin2015 proposal: POP)



Scint. Fiber Tracker (INSIDE)

Permanent Magnet (0.5 T)

Silicon Pixel Back Tracker (“Plume”)

Silicon Pixel (20 μm) Front Tracker

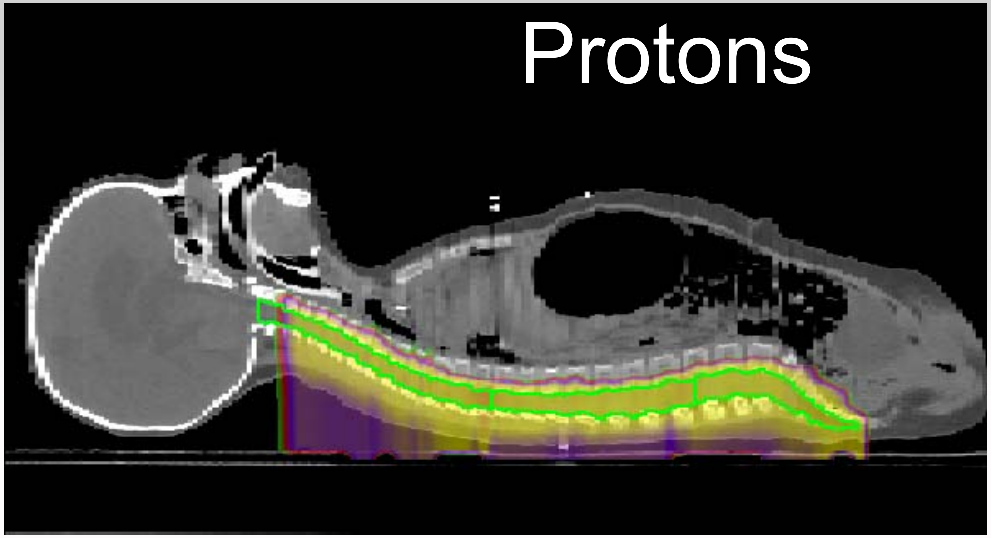
C or CH$_2$ Target

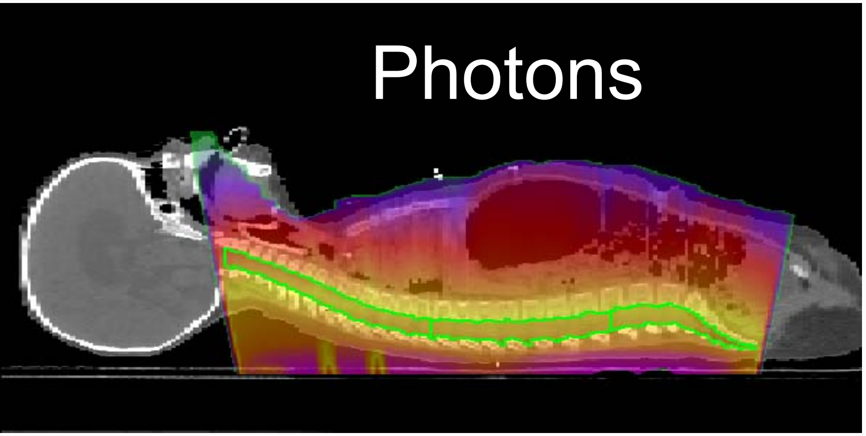
PT, secondary cancers, pediatric tumors

Secondary primary malignancies account for ~16% of risk for all cancer surviving patiens. Radiotherapy is one of the causes

Secondary effect of diffuse dose could be relevant for pediatric tumor, where the expected life span is longer.

The **neutron contribution is particularly difficult to model** and to be taken into account in TPS (environment, beam halo, etc..



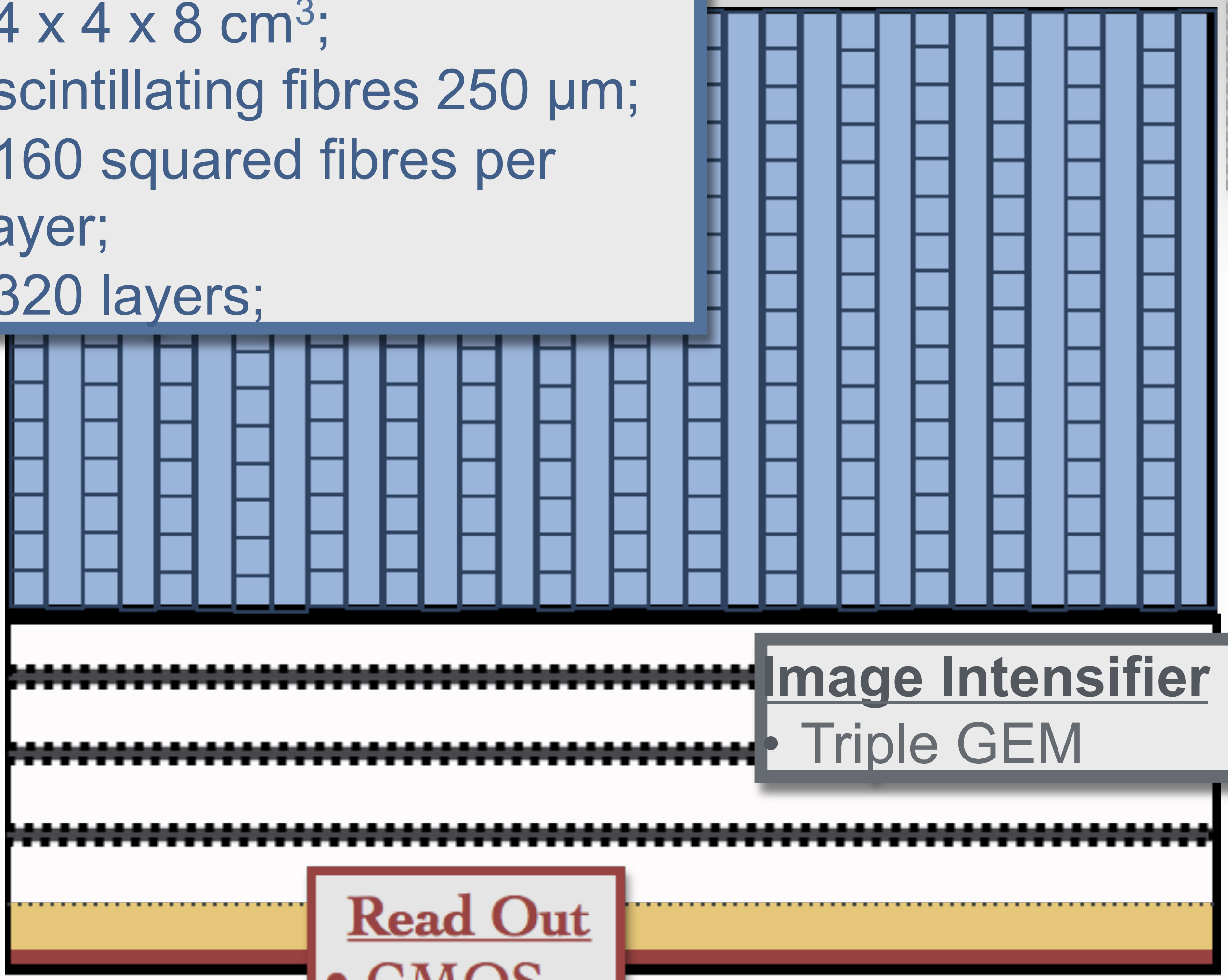


In PT neutron flux dominates, by orders of magnitude, the total secondary flux. Neutrons directly produced by the beam in PT are mainly ultra fast neutrons [20-200 MeV]

Accurate n production X-section by ^{12}C beam (or other nuclei) on (O,C), with angle and energy distribution, are still incomplete.

Neutron monitoring during PT is particularly difficult, (no directionality, scattering from environment, probabilistic release of energy, PID?, etc..)

MOnitor for Neutron Dose in hadrOntherapy



Plastic Scintillator

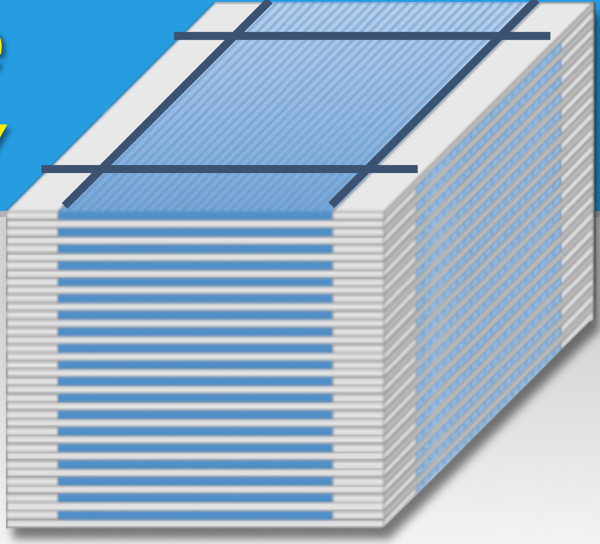
- 4 x 4 x 8 cm^3;
- scintillating fibres 250 µm;
- 160 squared fibres per layer;
- 320 layers;

Image Intensifier

- Triple GEM

Read Out

- CMOS



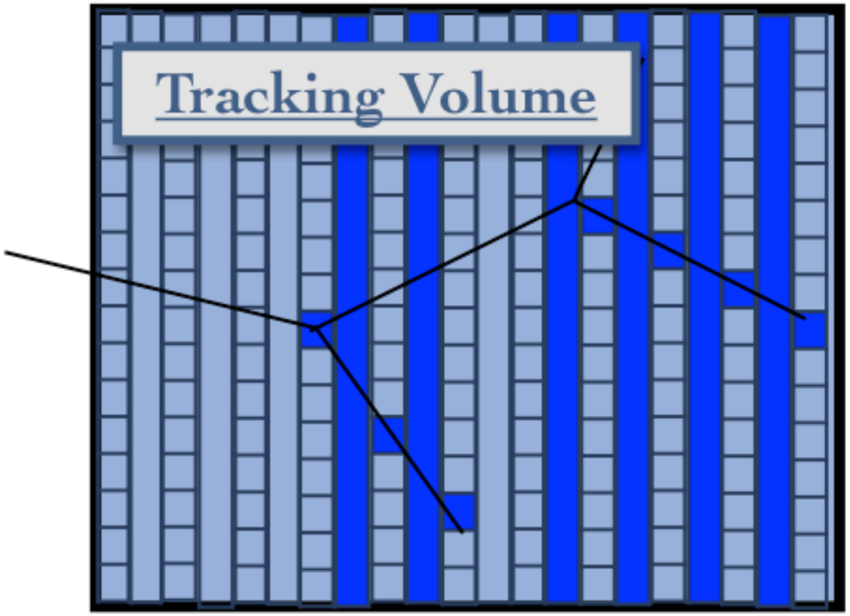
TRACKING the neutron !!

- ✧ Neutron tracking device efficient in the 20:300 MeV range
- ✧ Efficiency in 10^{-2} – 10^{-3} range
- ✧ Funded by SIR 2014+INFN Young Grant 2015

MOnitor for Neutron Dose for hadrOntherapy

Tracking Detector

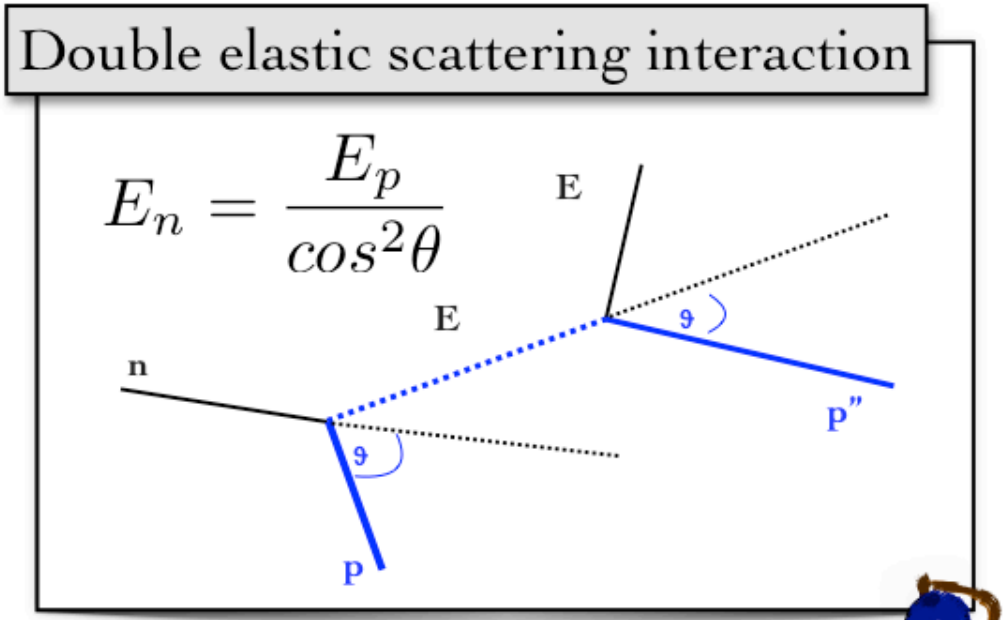
JINST M.Marafini et al 2015



Plastic Scintillator
- 20 x 20 x 20 cm^3;
- scintillating fibres 250 μm;
- 800 squared fibres per layer;
- x-y layer orientation;

Neutron
- E_{kin}=[20-200] MeV
- Inter. length. ~ 1m

Proton mean path
- E_{kin} = 100 MeV=> 8 cm
- E_{kin} = 10 MeV=> 0.1 cm



Double elastic scattering interaction

$$E_n = \frac{E_p}{cos^2\theta}$$

Monte Carlo codes: the need for exp. data

MC are becoming more and more fundamental for:

- **startup and commissioning of new facilities and beam line stuides**
- **database generation for Treatment Planning System commissioning**
- **Treatment Planning verification (and correction)**
- **Prediction and analysis of secondary production by hadron beams for monitoring purposes**
- **Study of detector response**

Main important features

- **Physics**
- **Overcaming Water Equivalent approximations**
- **Accurate 3D tracking**
- **Detailed description of actual patient geometry: → CT images directly read as input**

Main Challenges: Nuclear physics models and exp cross sections for validation, Coupling with Radiobiological models, Computing time…

Fast calculations and dose verification

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

15th SEPTEMBER , 2014

WORLD'S FIRST PT SPECIFIC CBCT GOES CLINICAL

- patient positioning
- geometry match
- delivery uncertainties

GPU calculation approaches

Two lines of development

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

2. Fast MC-based Treatment Planning optimization/recalculation

Thank you for the attention

Acknowledgmentes:
V. Patera, M. Marafini, A. Sarti, A. Schiavi (INFN & Univ. Roma 1), M. Durante (INFN Tifpa), A. Mairani,
R. Orecchia, M. Pullia S. Rossi (CNAO), M. Schwarz (APSS, Trento), A. Ferrari, (CERN), P.Sala (INFN Mi),
G. Bisogni (INFN & Univ. Pisa), M. Bruzzi, C. Civinini (Univ. & INFN Firenze)
and in the general the colleagues from RDH-IRPT coll., FLUKA coll.

"Physics is like sex: sure, it may give some practical results, but that's not why we do it. "
R. Feynmann