Nuclear Physics and Particle Therapy

Giuseppe Battistoni,
INFN, Milano, Italy

NN 2015

ENLIGHT
European Network for
Light Ion Hadron Therapy

INFN Istituto Nazionale di Fisica Nucleare

RD H

Outline

- Basic principles
- Diffusion in the world and actual implementation
- The relevant nuclear physics:
  - The nuclear processes involved
  - The impact of fragmentation
  - Particle interactions and the uncertainties on range
  - Nuclear reactions as a tool for on-line monitoring
  - Modelling of nuclear reactions: the role of Monte Carlo codes in particle therapy
  - Some experimental results
  - Towards additional choices of nuclei for therapy
- Conclusions and Perspectives

Recent important reviews in the nuclear physics community

Nuclear Physics European Collaboration Committee (NuPECC)

Nuclear Physics for Medicine

Hadron Therapy (Charged Particle Therapy) is not the only important case of successful application of nuclear physics to medicine, however it represents a paradigmatic case of a topic in between research and actual cinical practice, where the contribution coming from nuclear physicists is fundamental

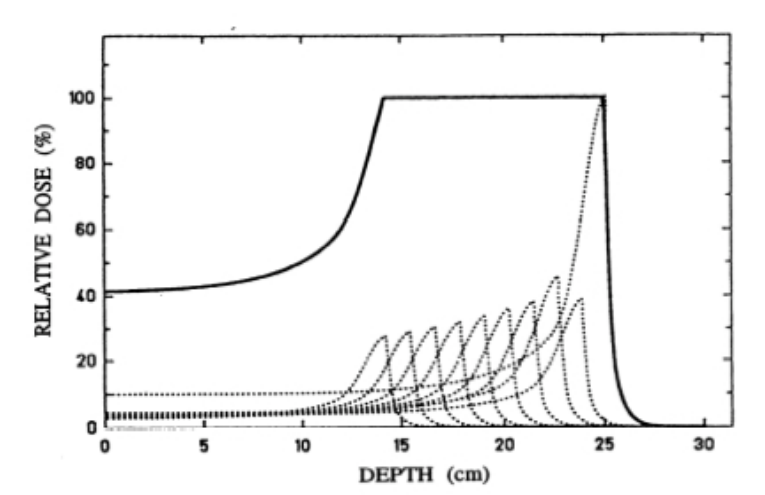
There is still a significant fraction of people in the clinical community who consider hadrontherapy (ion therapy) too complicated, too expensive, not able to reach in practice the expected high level of precision

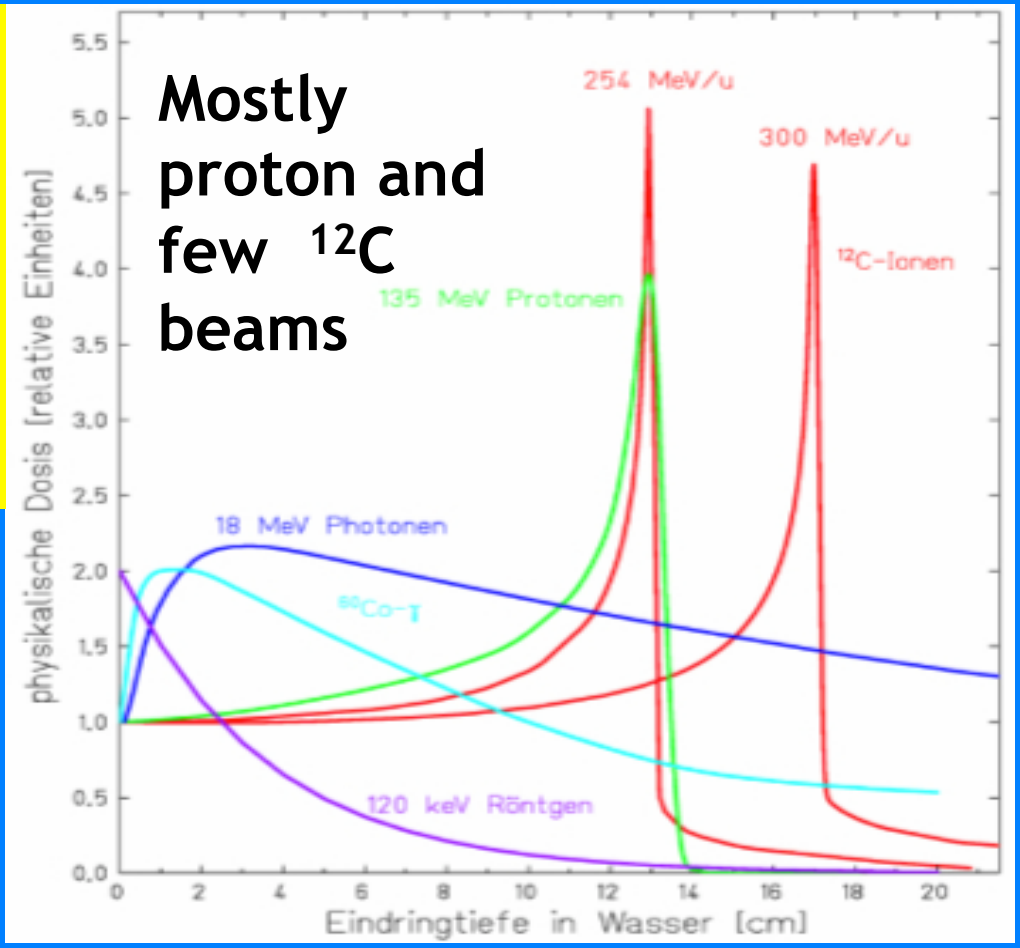
BASIC principles

Advantages of charged particle therapy

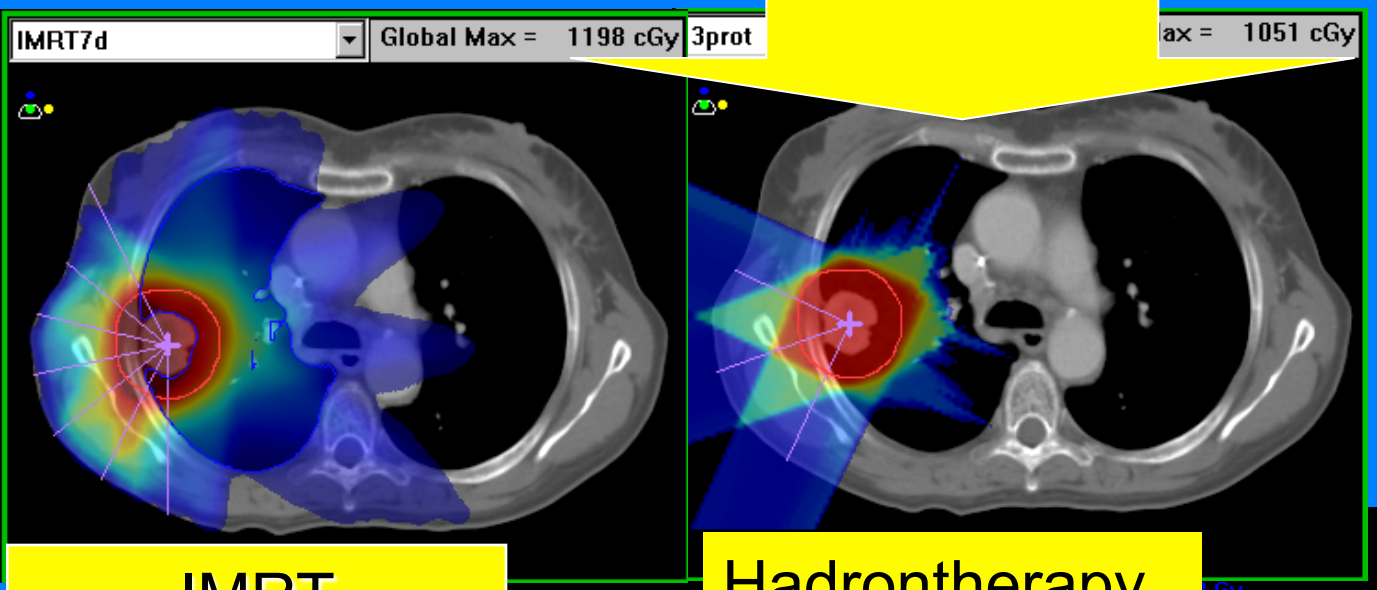
The highest dose released at the end of the track, sparing the normal tissue

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



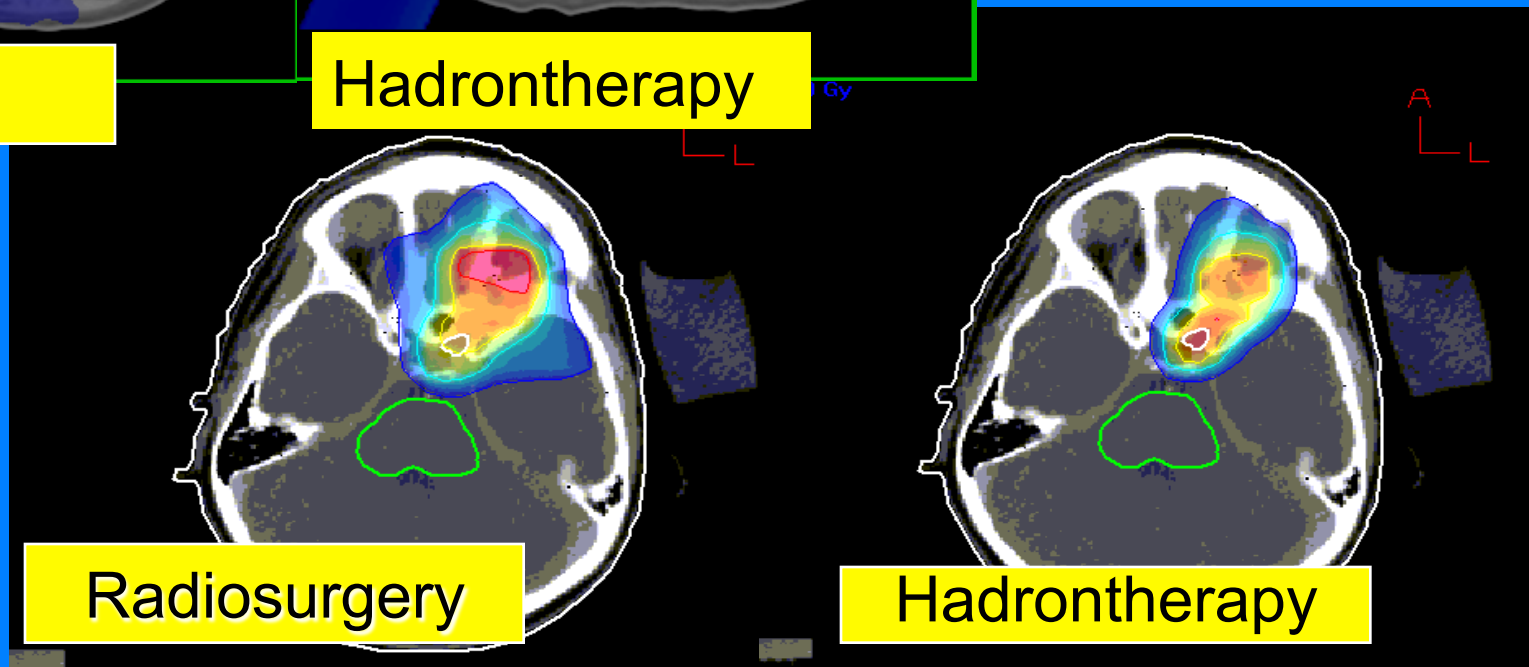


Selectivity



IMRT

Hadrontherapy



Radiosurgery

Hadrontherapy

The start of Hadrontherapy

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

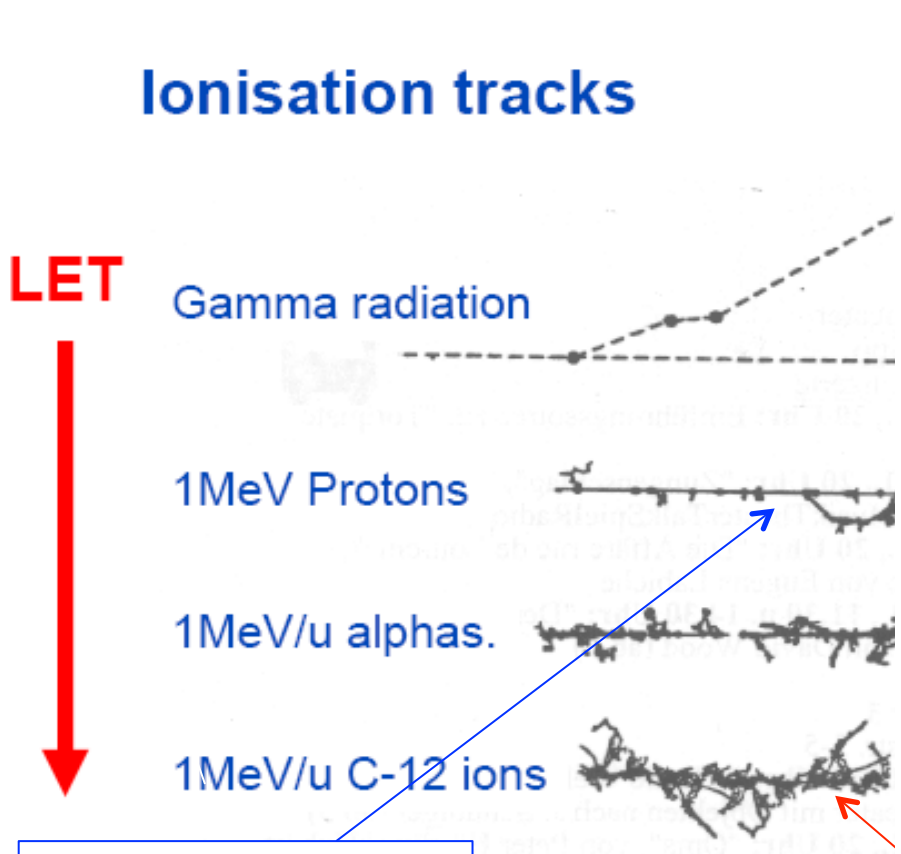
EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles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

Radiology 47: 487-491, 1946

1954 - Berkeley treats the fi st 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

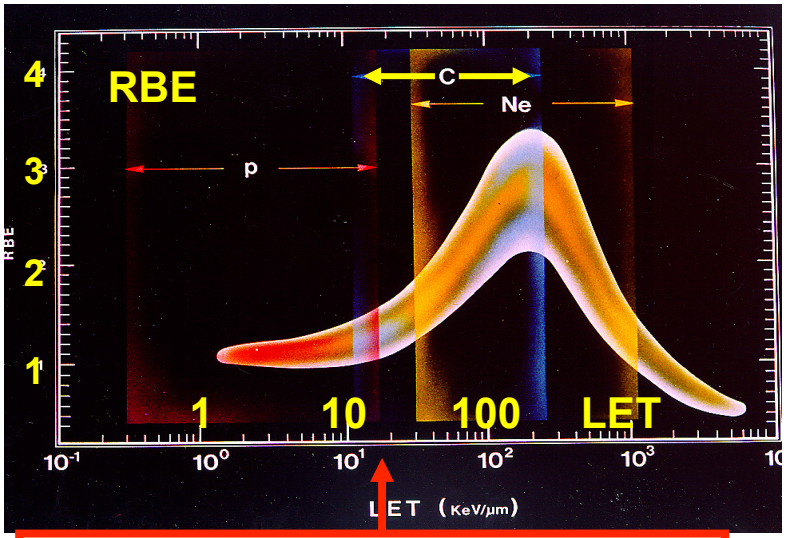
Interdisciplinary aspects: Physics and Biology



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)

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

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…

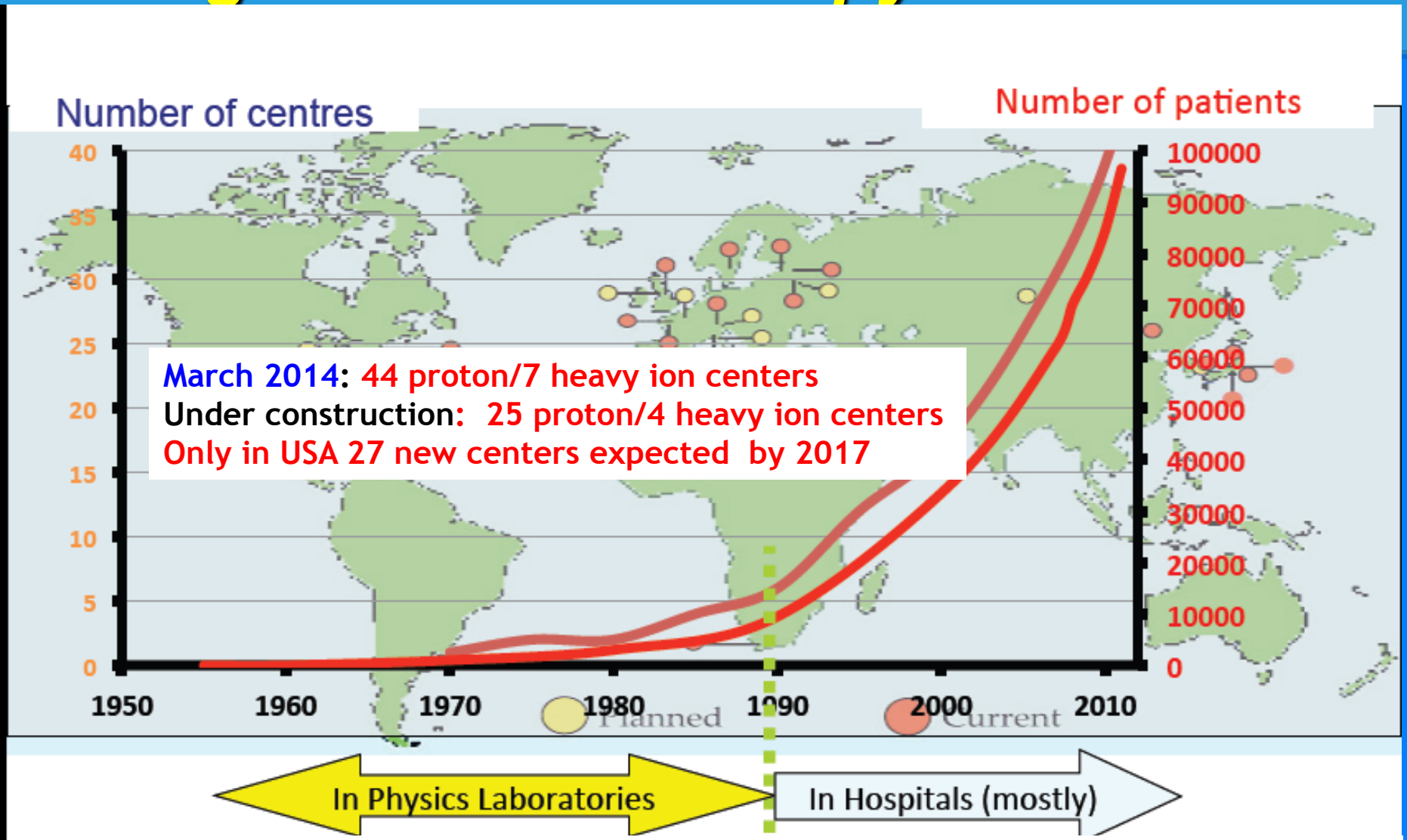
Future Options under considerations:

^{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

HadronTherapy in the world

Charged Particle Therapy in the world

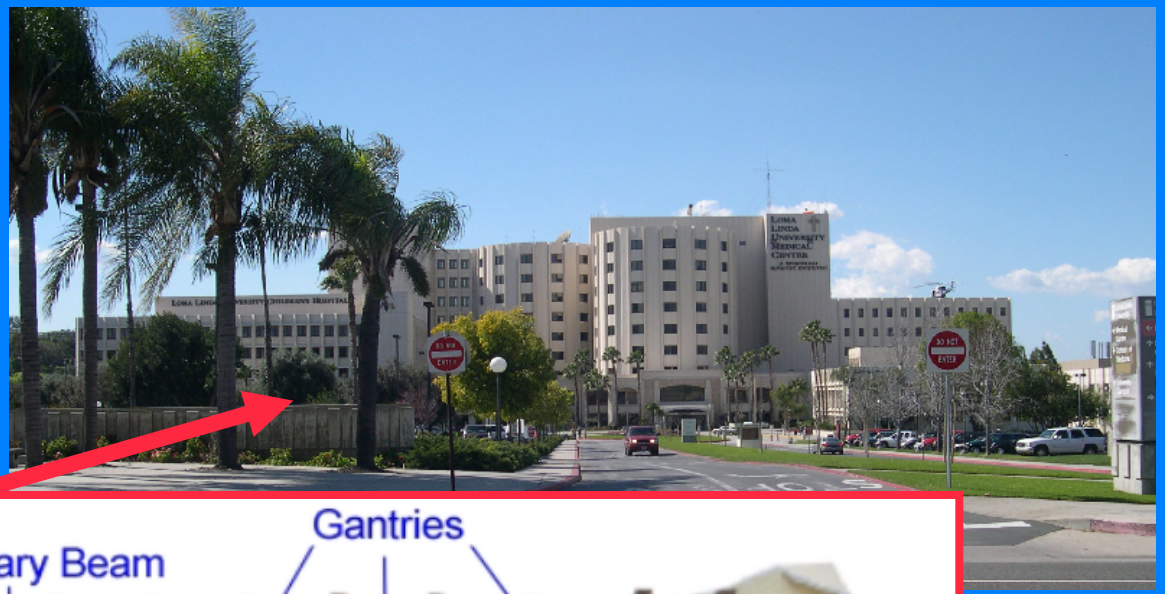


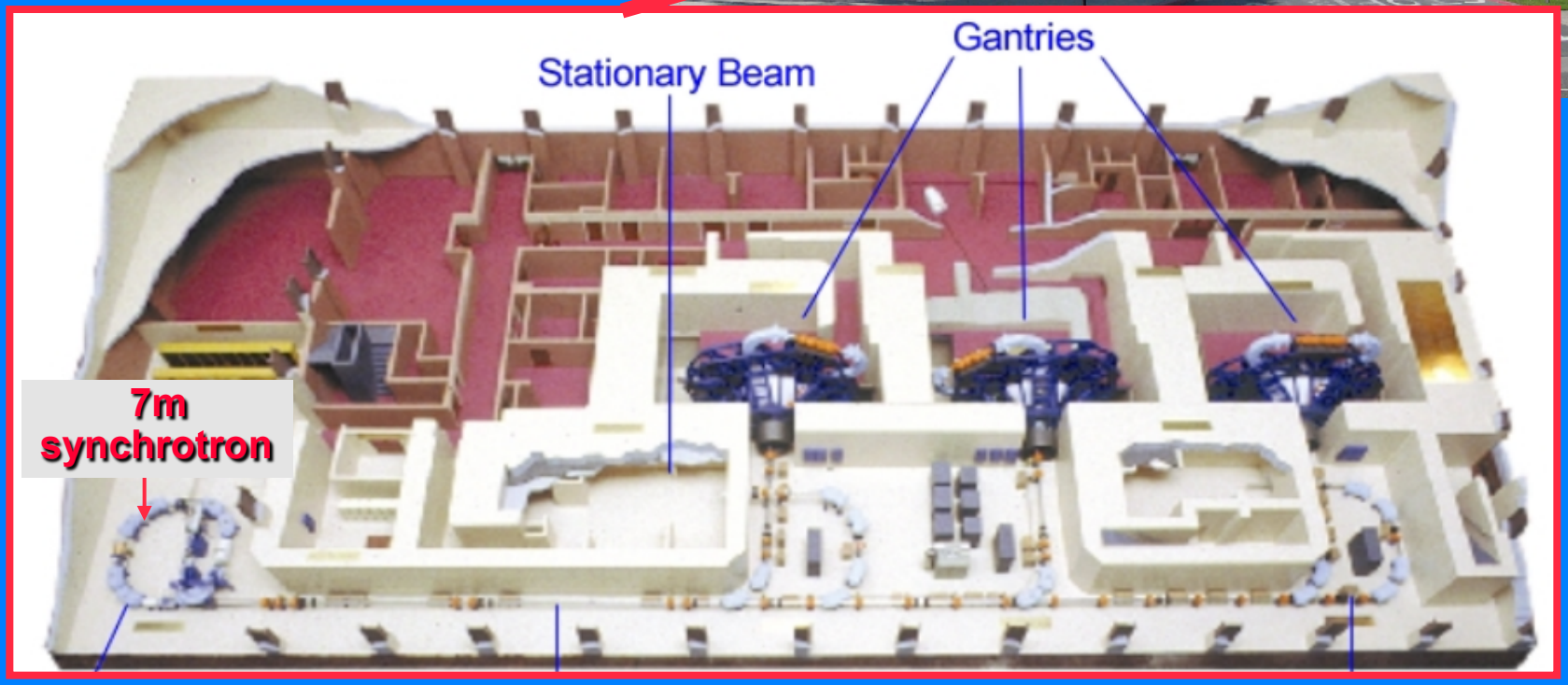
~2014: 122499 treated patients: 105743 with p, mainly in USA, 53532
13119 with ^{12}C, mainly in Japan, 10993;

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

Loma Linda University Medical Center

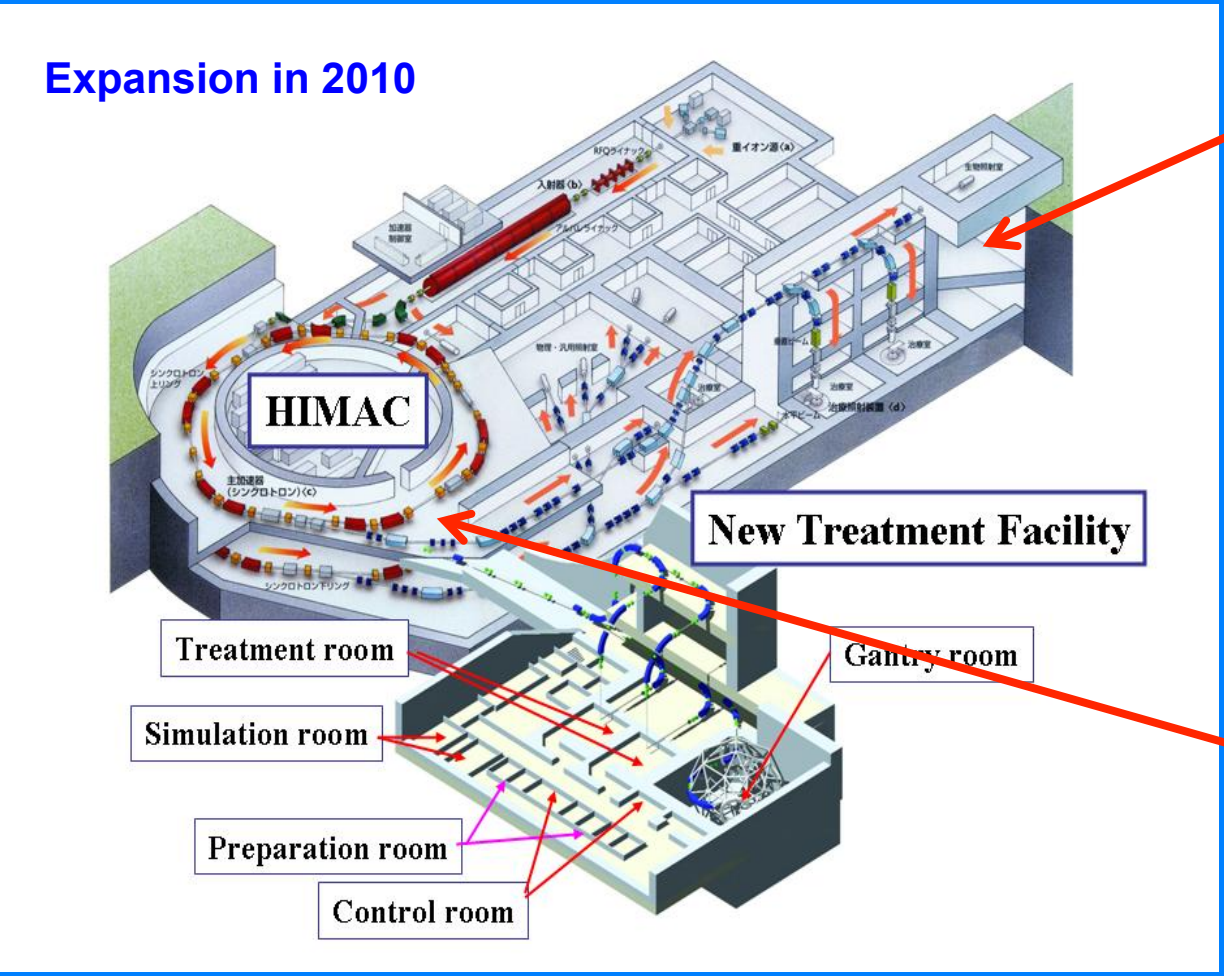
160 session/day





HIMAC

Heavy Ion Medical Accelerator in Chiba



3 treatment rooms
1 experimental room

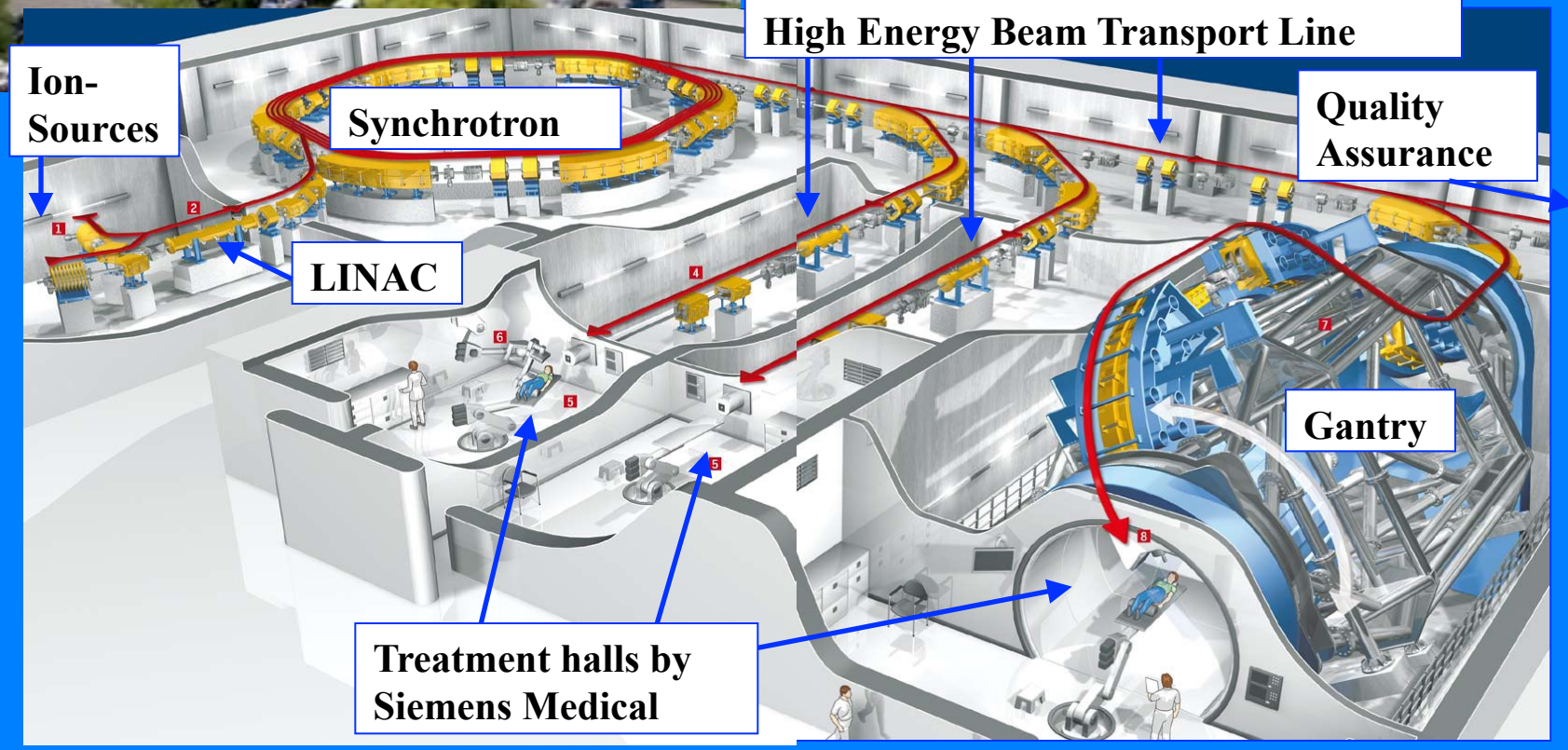
2 synchrotrons
800 MeV/u,
therapy and
nuclear physics

HIT - Heidelberg

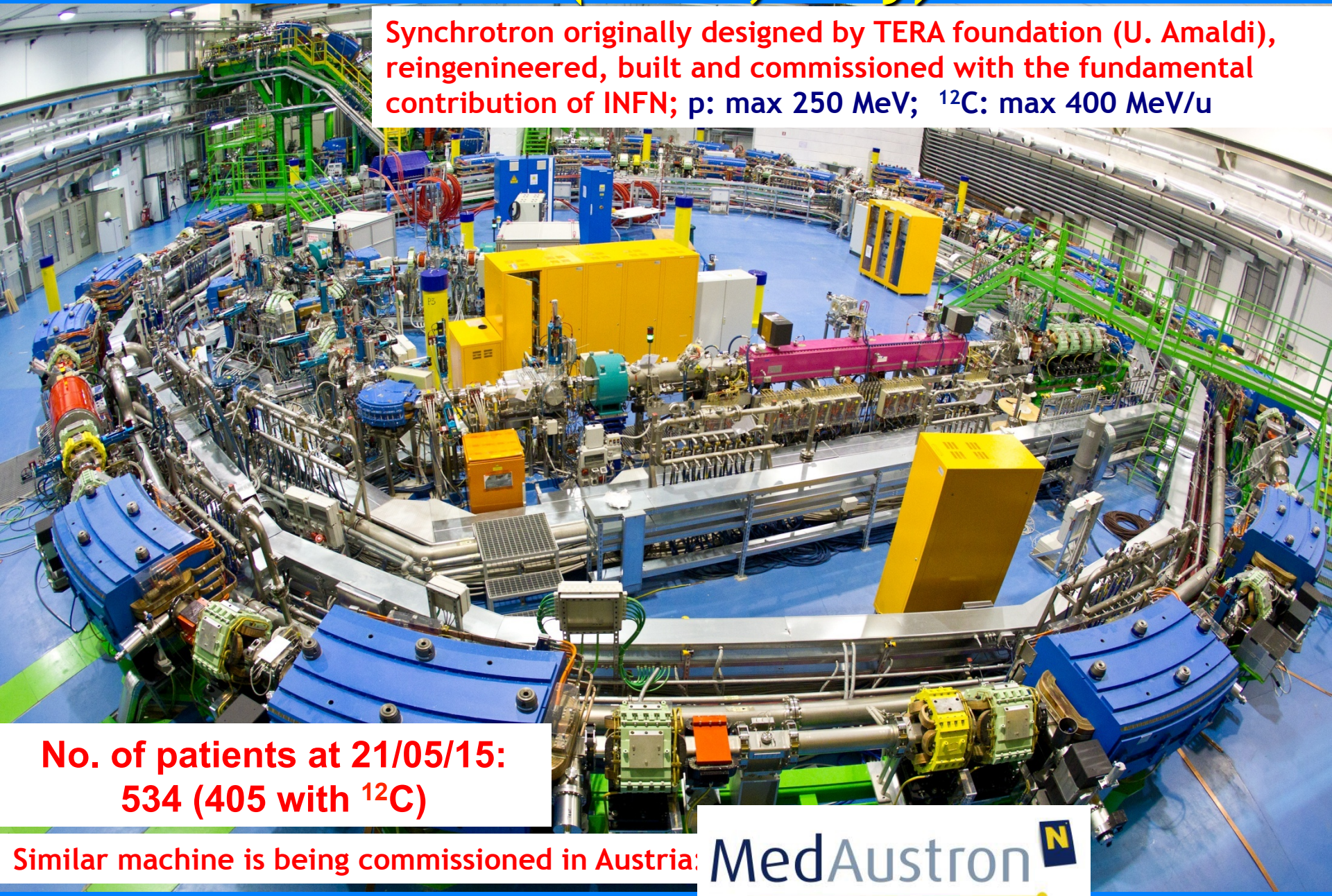
HIT
Heidelberger Ionenstrahl-Therapiezentrum

First patient: end 2009

So far >2.000 patients



CNAO (Pavia, Italy)

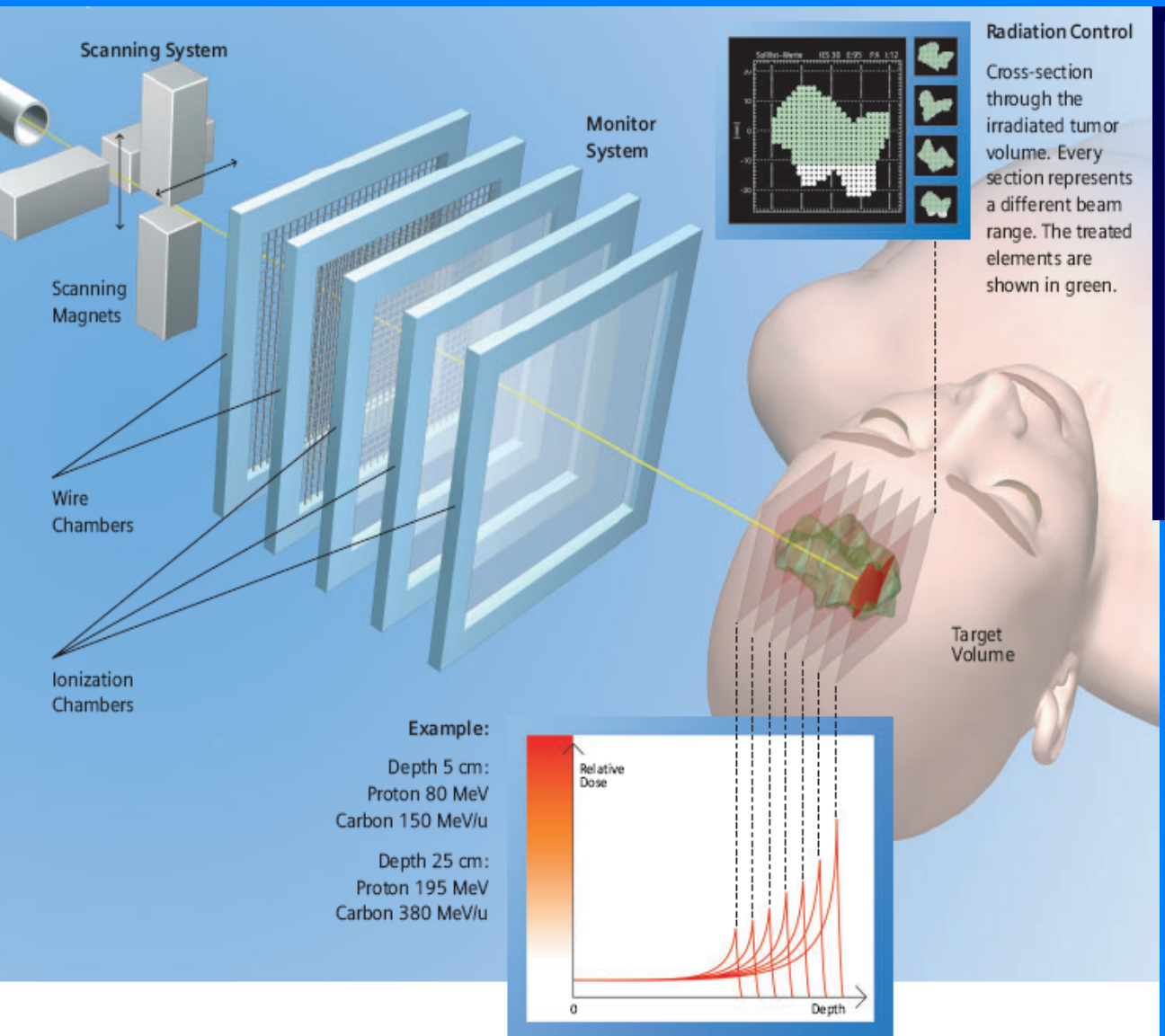


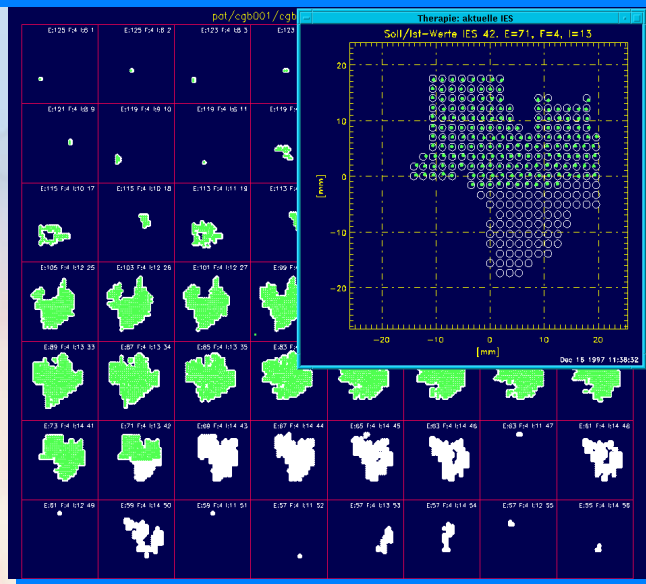
Synchrotron originally designed by TERA foundation (U. Amaldi), reingenineered, built and commissioned with the fundamental contribution of INFN; p: max 250 MeV; ^{12}C: max 400 MeV/u

No. of patients at 21/05/15: 534 (405 with ^{12}C)

Similar machine is being commissioned in Austria: MedAustron

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



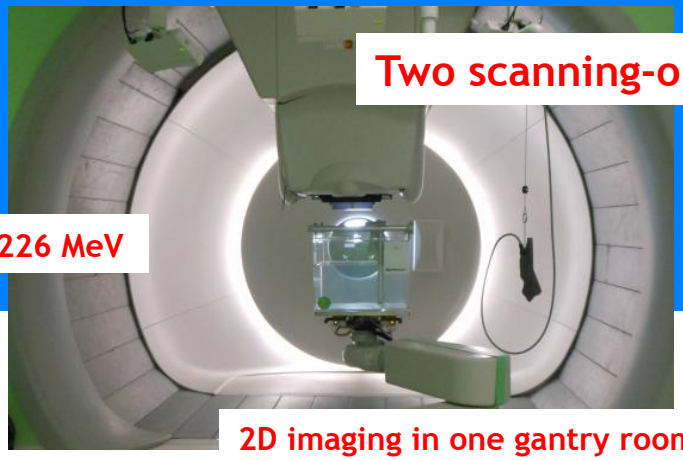


Typically:

p: ~10^9 p/s
^{12}C: ~ 10^8 p/s

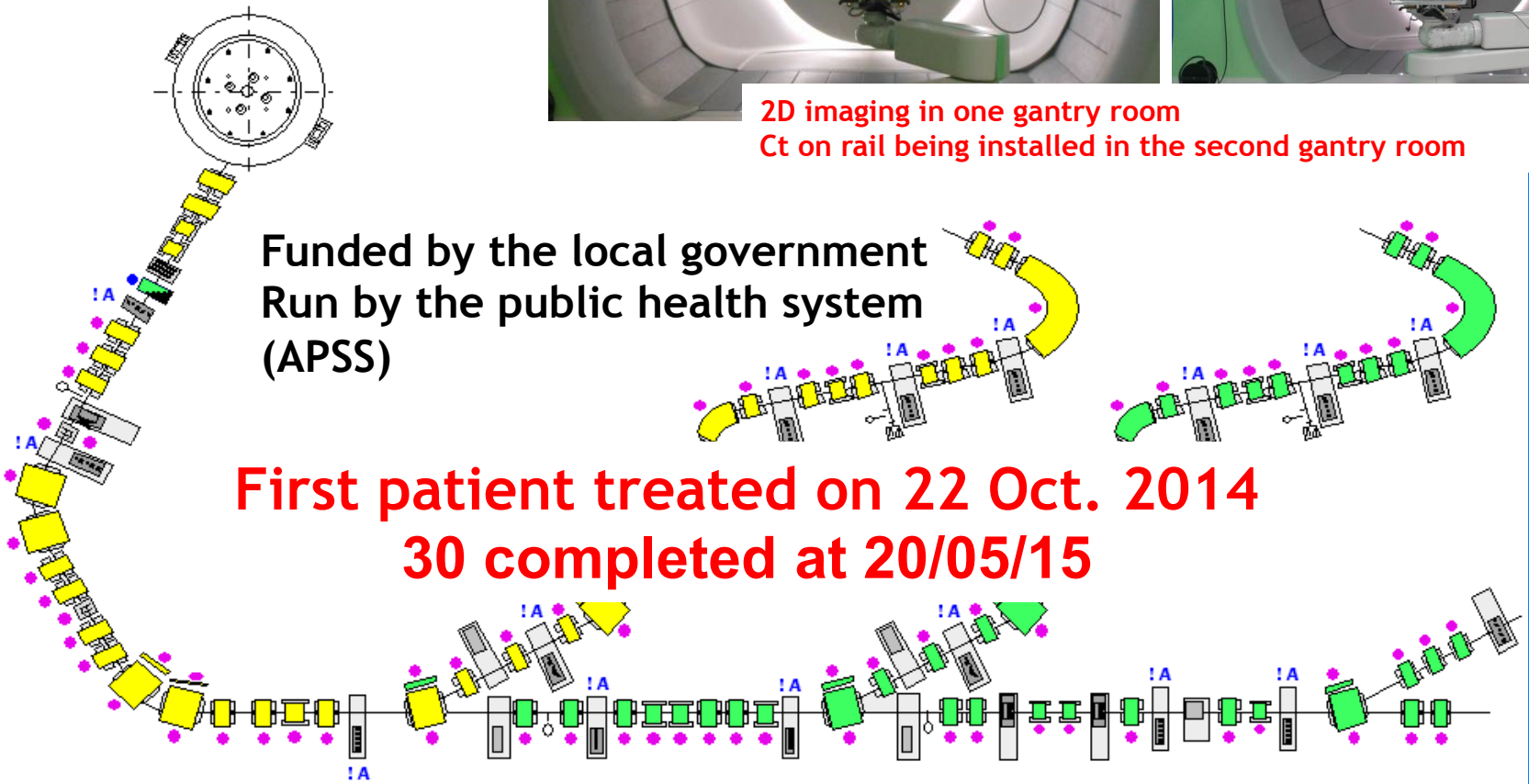
New Proton Therapy in Trento (Italy)

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

HadronTherapy and Nuclear Physics

Nuclear reactions: what does really matter?

Proton therapy

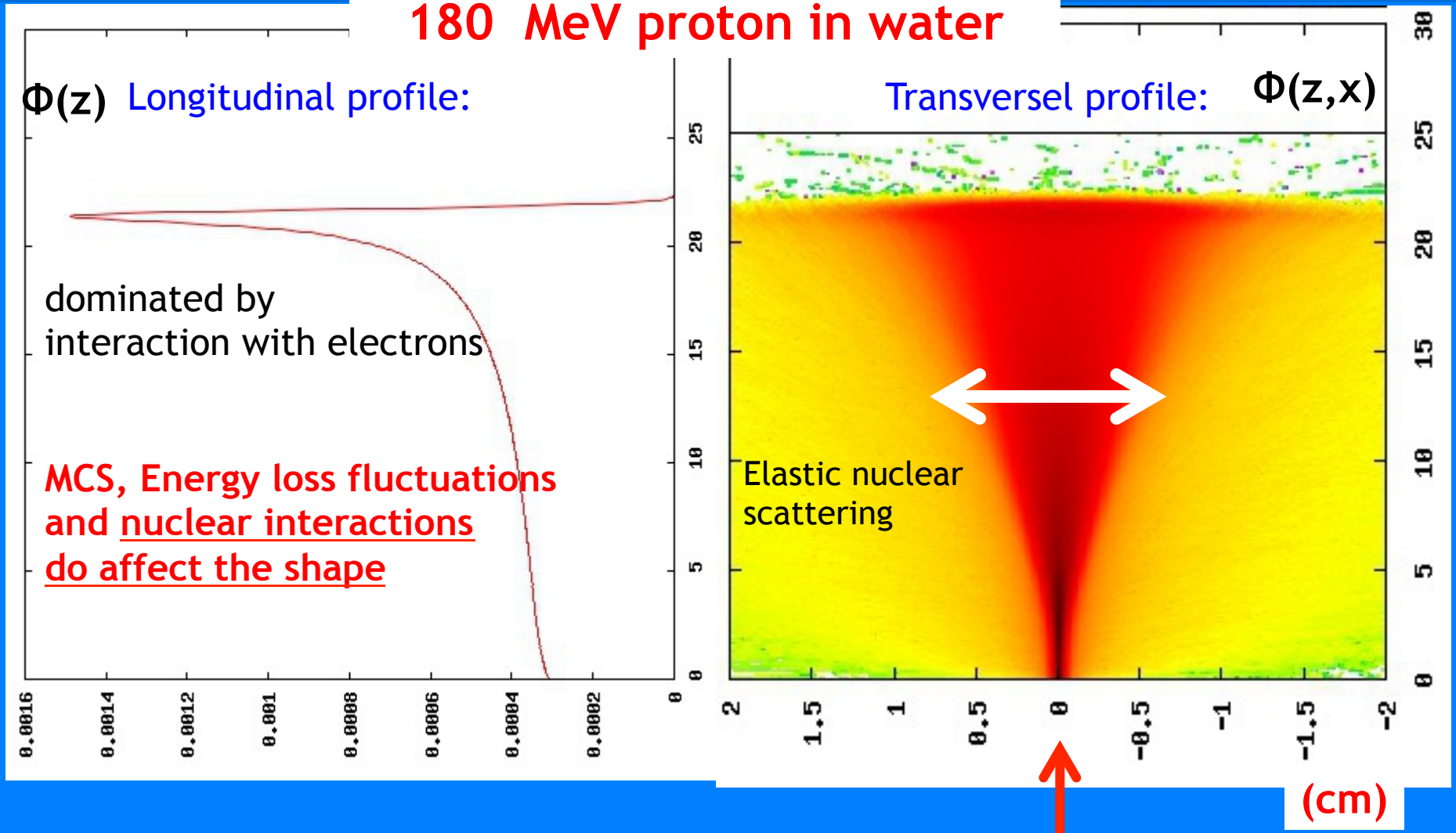
- ✓ Reaction cross sections (beam attenuation)
- ✓ Elastic cross sections
- ✓ Particle (p,n,α..) emission
- ✓ Production of radioactive isotopes in the target (Positron emitters)
- ✓ Nuclear de-excitation of target

Therapy with ions:

- ✓ Reaction cross sections (beam attenuation)
- ✓ Projectile Fragments (α included) production
- ✓ Particle emission, p, others
- ✓ Production of radioactive isotopes in the target AND rad. projectile fragments
- ✓ Nuclear de-excitation of target AND of projectile and its fragments

The physics of Bragg Peak

180 MeV proton in water

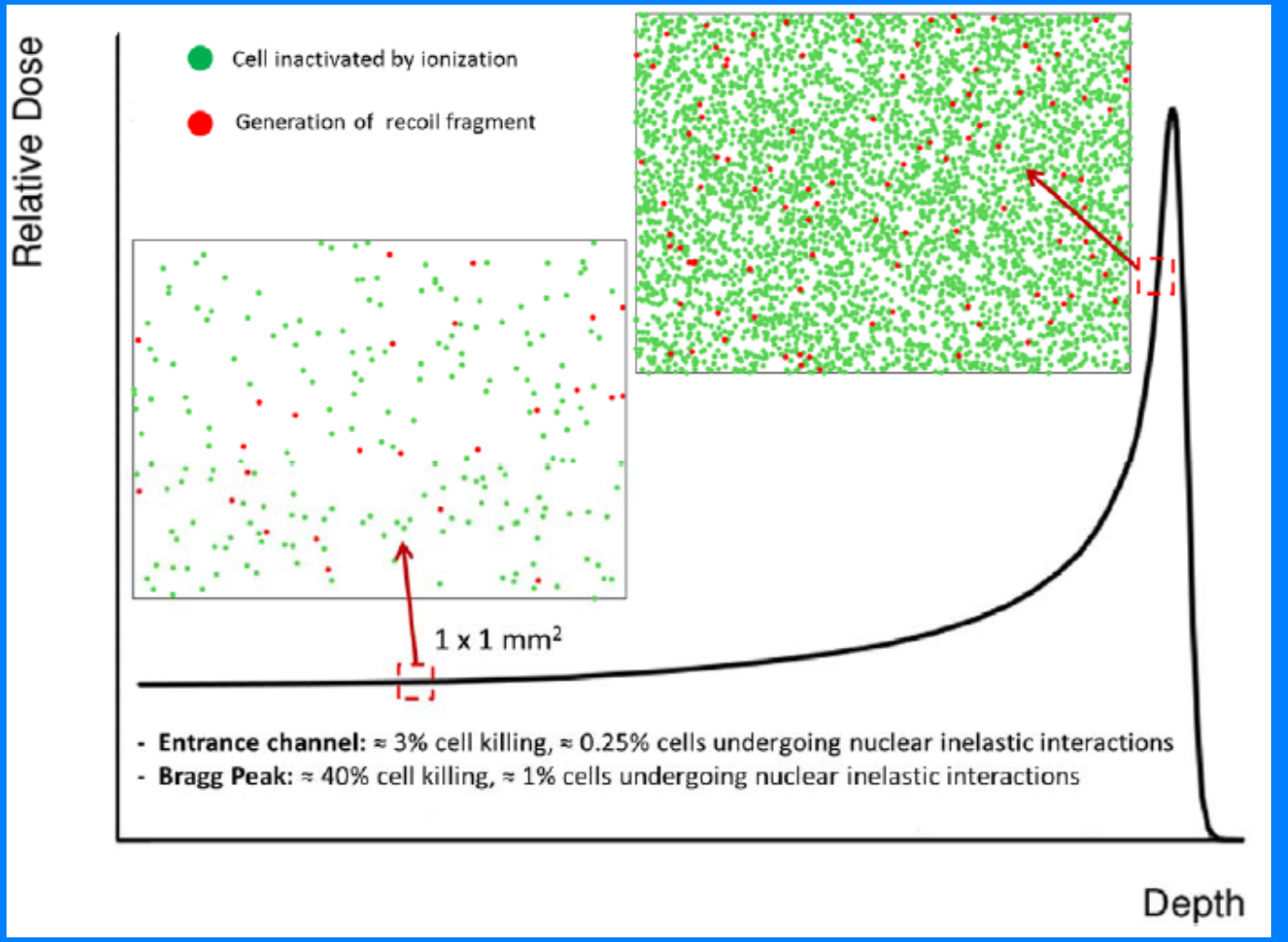


Non-elastic nuclear reactions move dose from the peak upstream.

Nuclear Reaction in Proton Therapy

about 1% cm^{-1} H_2O of the protons undergo nuclear interactions

- about 20% in a typical treatment plan
- 60% of the energy is deposited locally by charged fragments
- 40% in n and γ out of the field

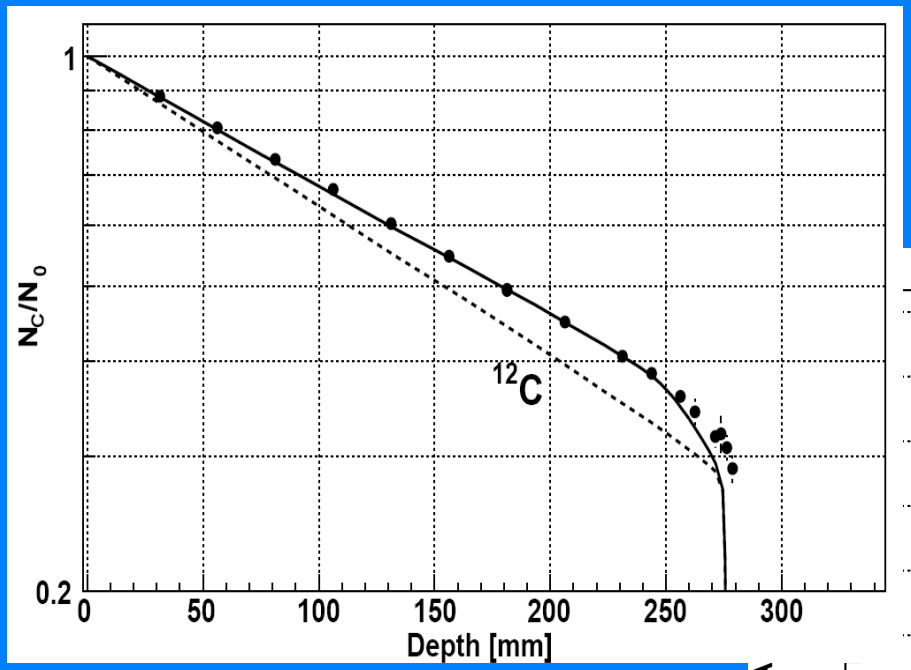


F. Tommasino & M. Durante Cancers, 2015, 6, 353-381

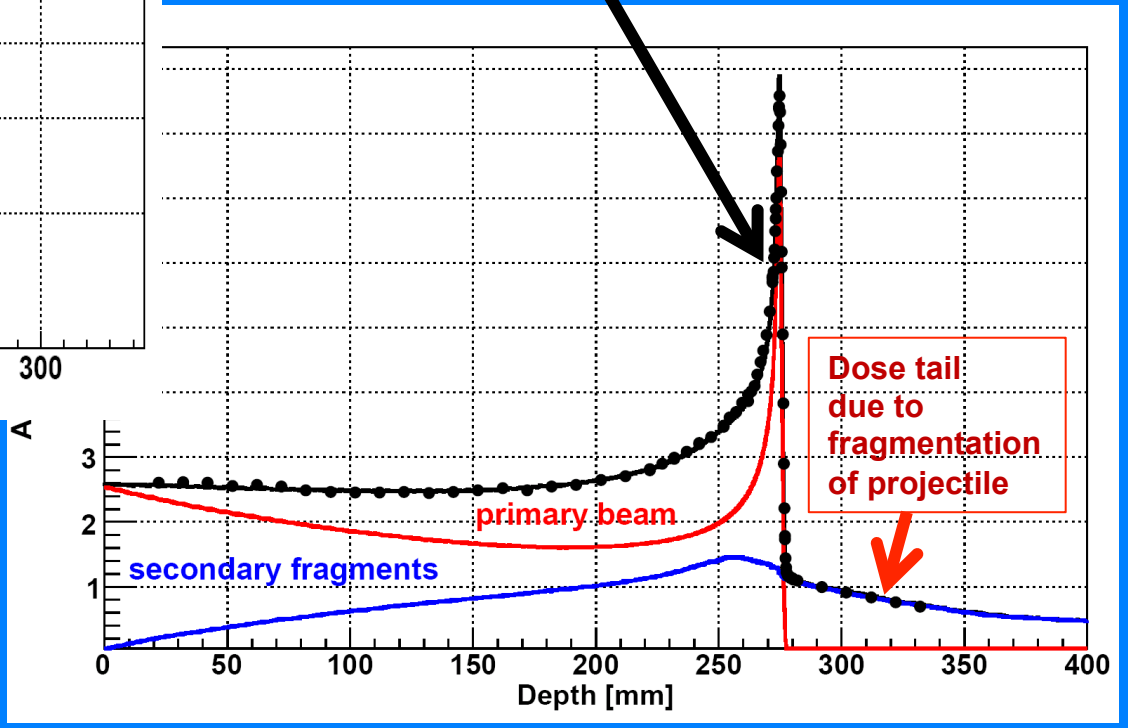
Does target fragmentation play a role which has been neglected so far?

Ion therapy: relevance of Nuclear Fragmentation

400 MeV/u C beam in a water phantom



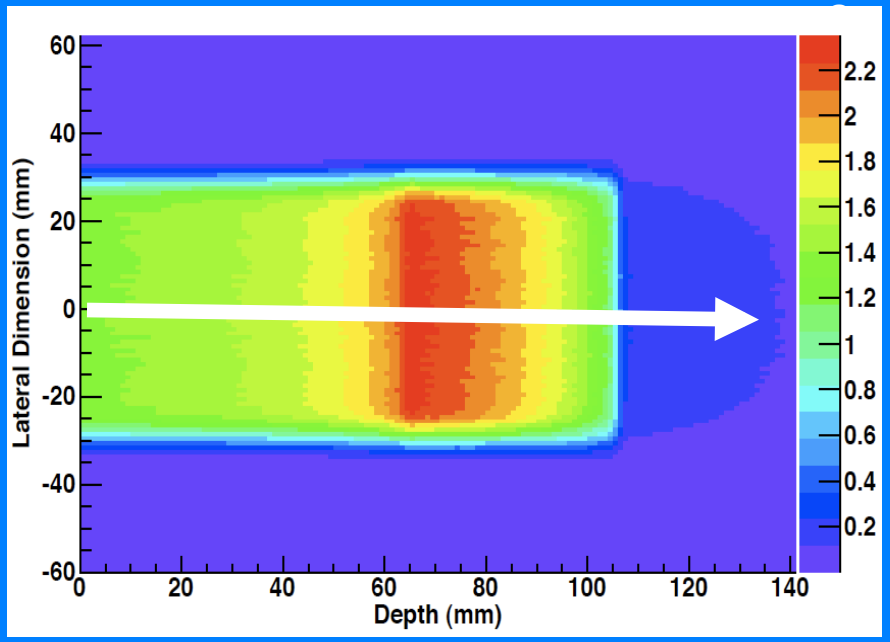
Larger mass → reduced straggling → narrower peak

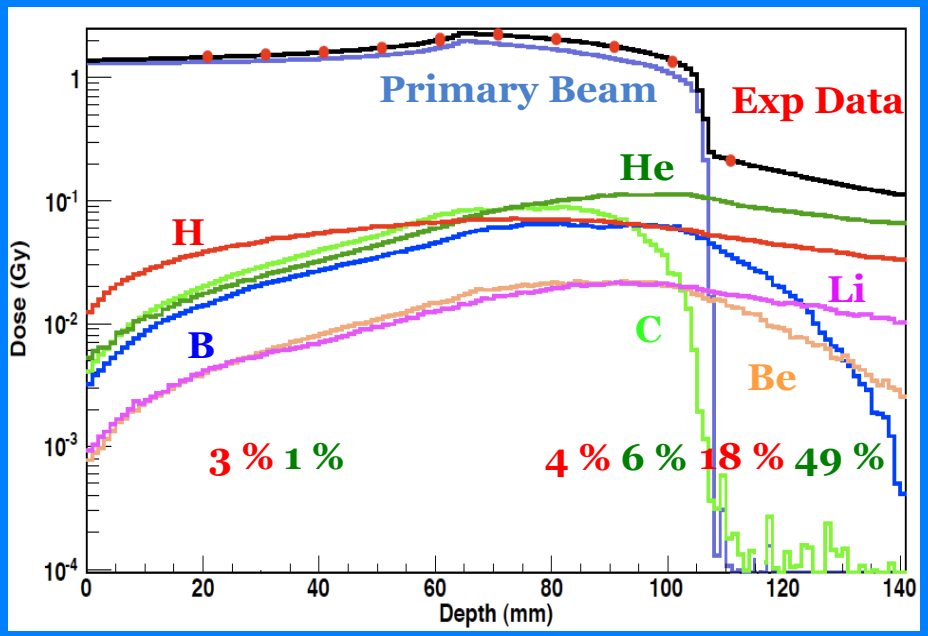


Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006
Simulation: A. Mairani PhD Thesis, 2007, Nuovo Cimento C, 31, 2008

Ion therapy: Spread Out Bragg Peak and fragmentation issues

MC calculation: FLUKA coupled with the GSI/HIT control file of raster scanning system and modeling ridge filters
(F. Sommerer , A. Mairani and K. Parodi)

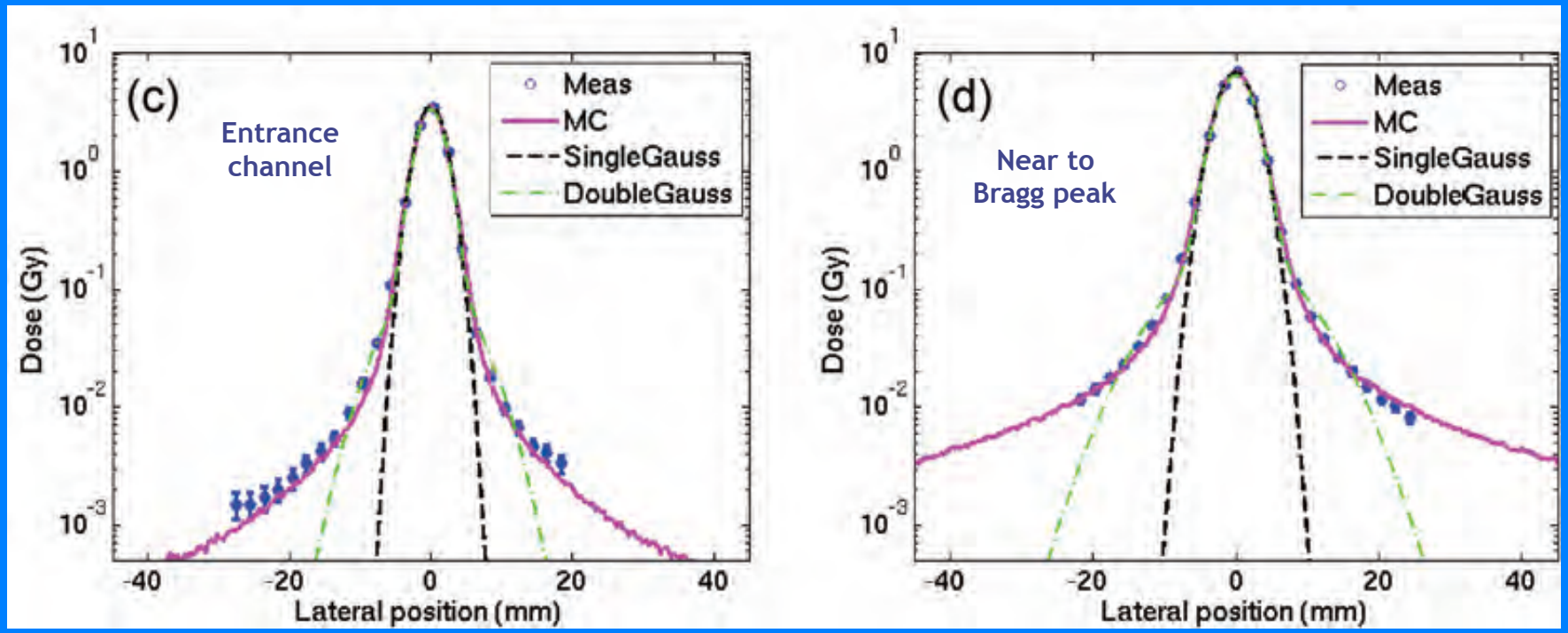




Exp. data (points) by M. Winter and S. Brons (HIT)

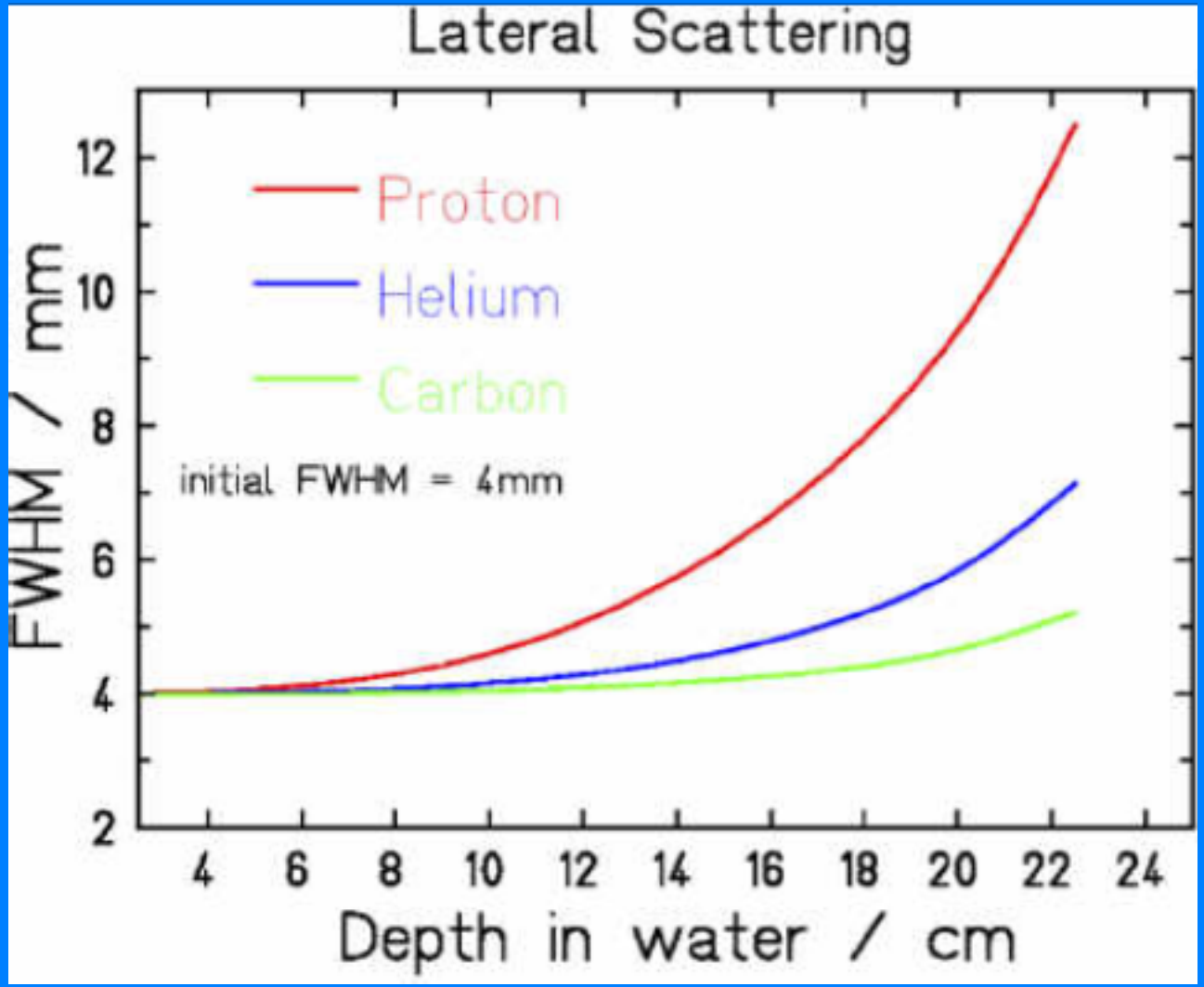
Ion Therapy: the lateral scattering

^{12}C @ 299.94 MeV/u
K. Parodi et al Journal of Radiation Research, 2013, 54, i91–i96



Measured lateral distributions with corresponding MC simulations (normalized to the data) for carbon ion 299.94 MeV/u beams in water, sampled at a depth of ~1.5 cm in the entrance channel (left, c) and of ~16.5 cm shortly before the Bragg peak (right, d). The double Gauss fit of the experimental data is also shown in comparison to the single Gauss approximation.

Lateral Scattering: the advantage of ions



Uncertainties:

Nuclear processes and monitoring of therapy

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]

A new imaging approach:

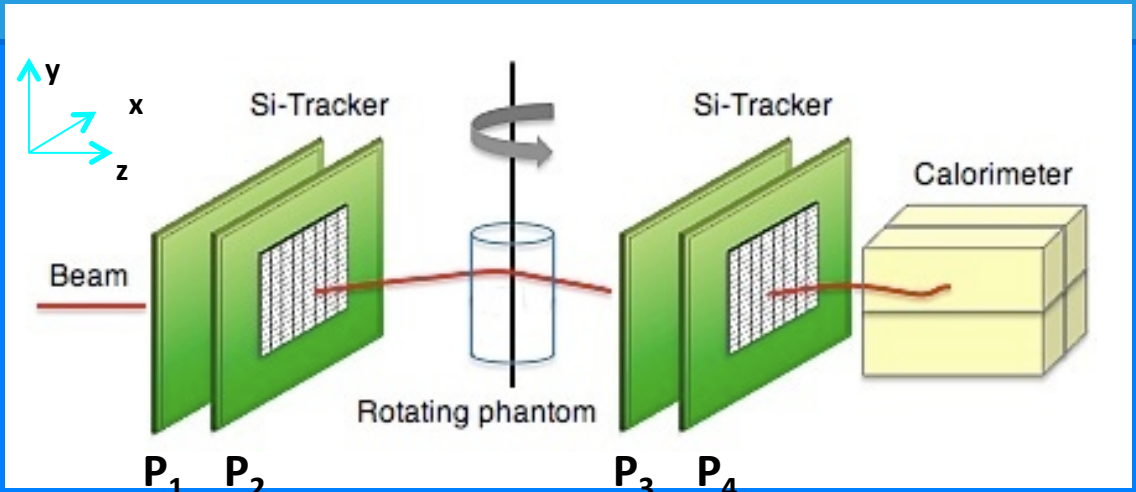
from Computed Tomography using X rays to Proton Computed Tomography (pCT)

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

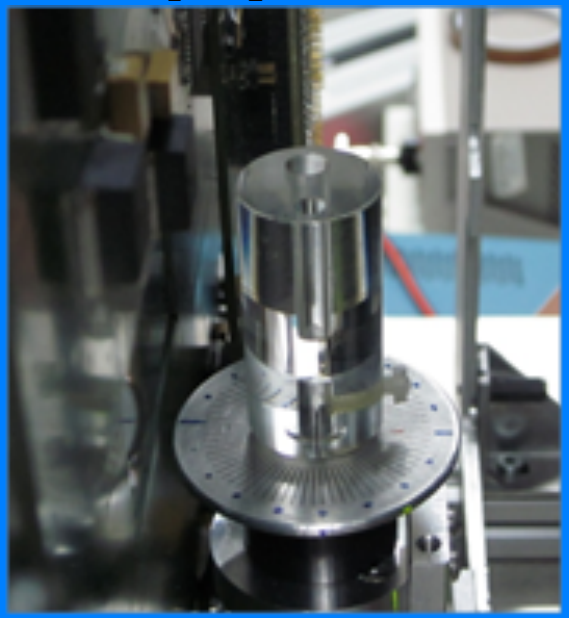
E_{in} is the incident proton energy and E_{out} is the proton energy after traversing through the object, $S(E)$ is the proton stopping power, and K is a constant.

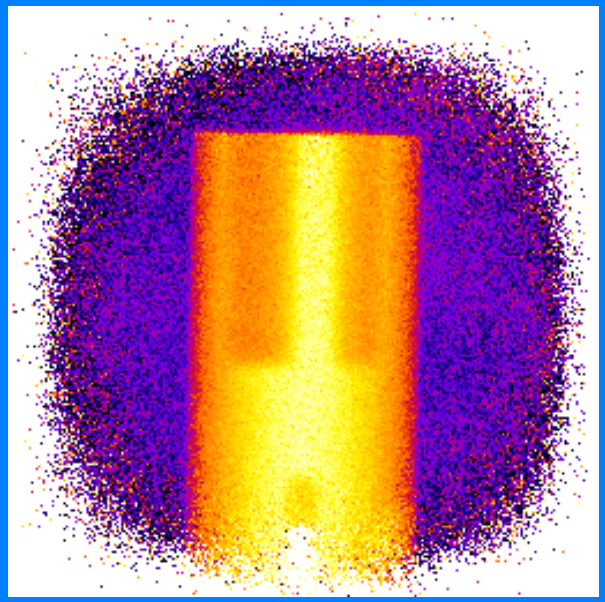
Proton CT: the INFN approach

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

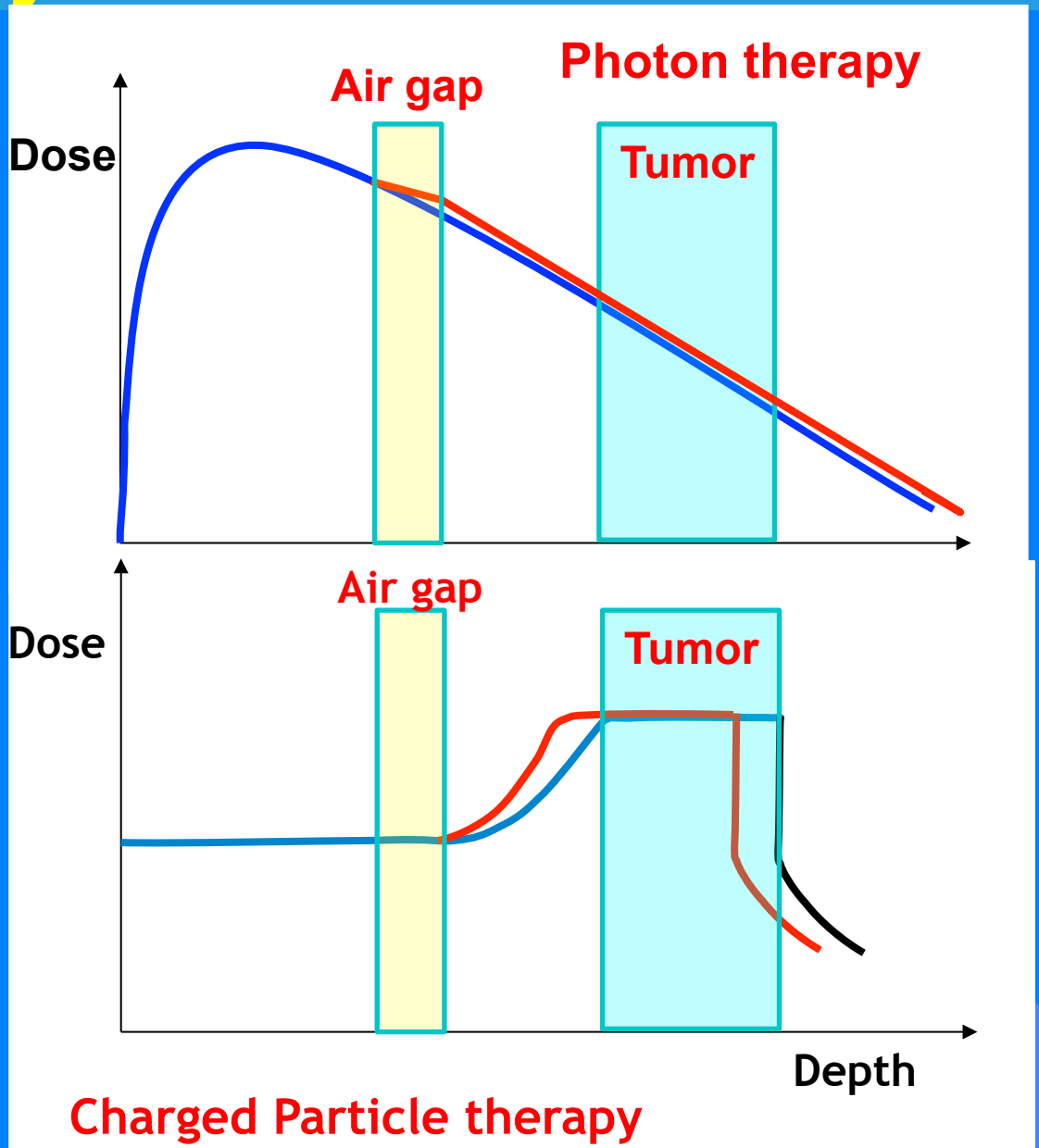




Key issues: appropriate reconstruction algorithms to produce tomographic images. More complicate that with X-Rays!

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 vatriations

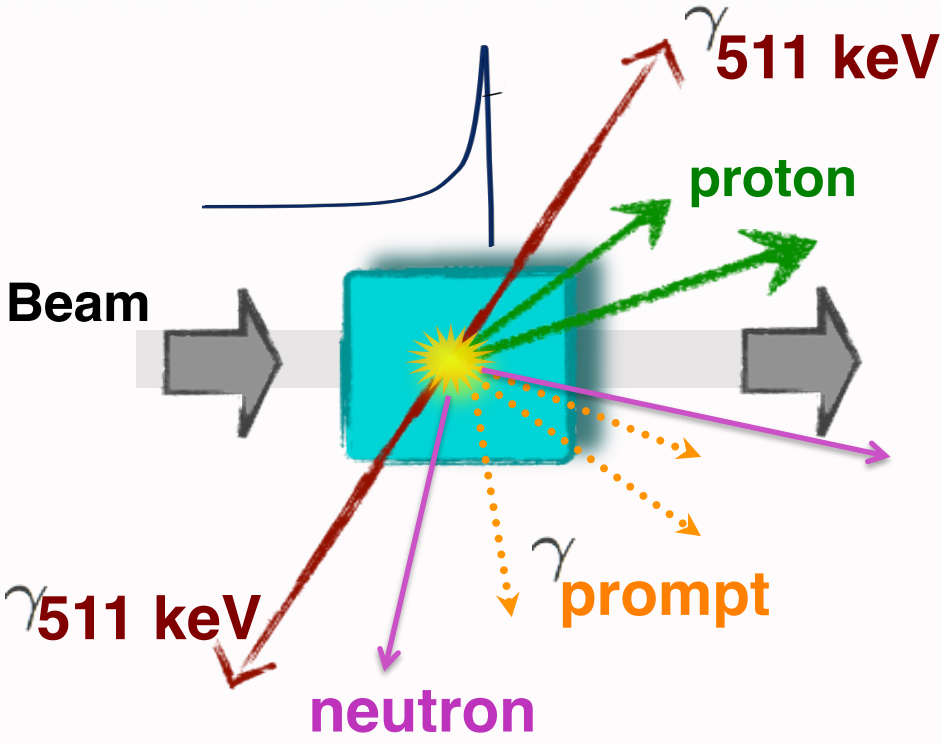


Help from Nuclear Physics: exploiting secondary products

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

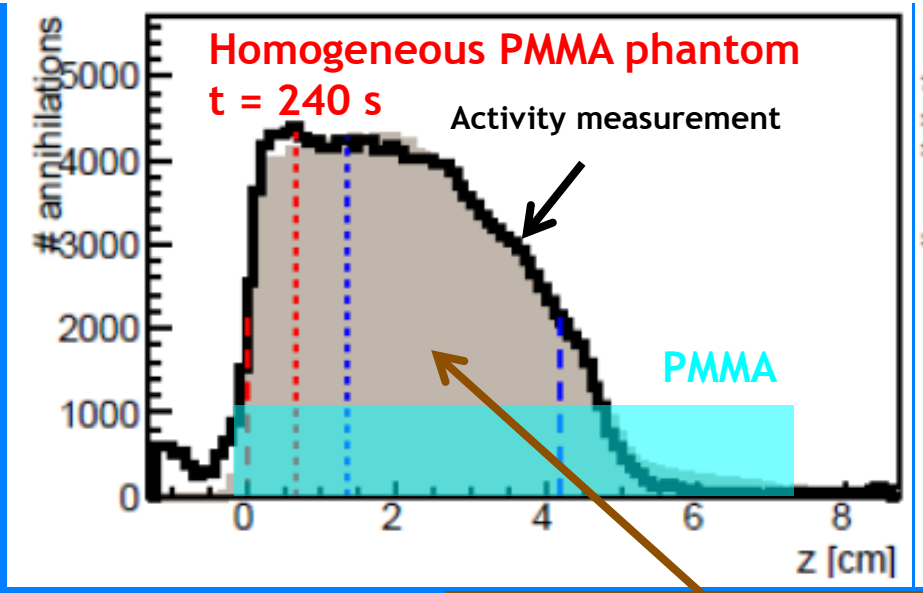
- Isotopes of short lifetime ^{11}C (20 min), ^{15}O (2 min), ^{10}C (20 s) with respect to conventional PET (hours)
- Low activity asks for quite a long acquisition time (some minutes at minimum) with difficult in-beam feedback
- Metabolic wash-out, the β^+ emitters are blurred by the patient metabolism

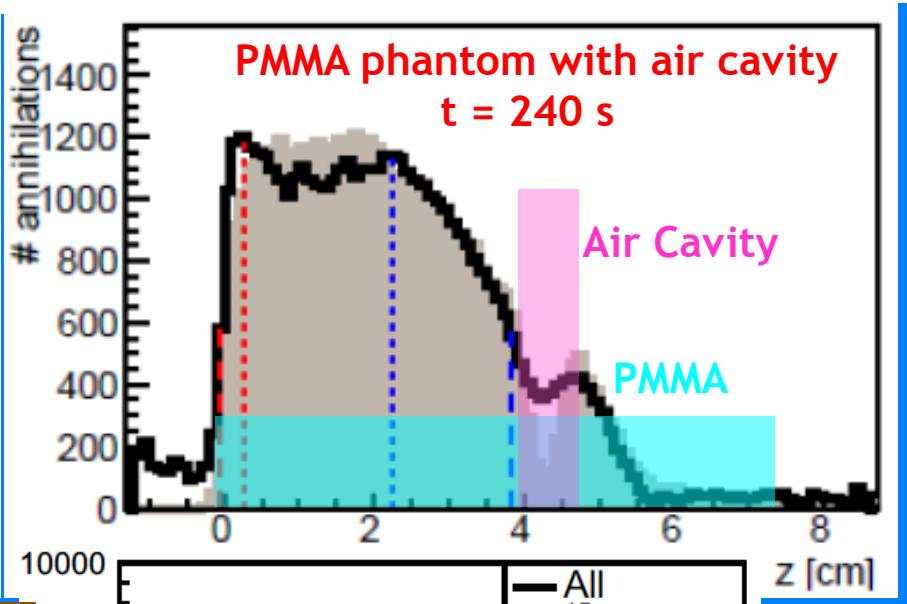


Spotting structures with β^+ activity measurement in-beam (proton beam at CNAO)

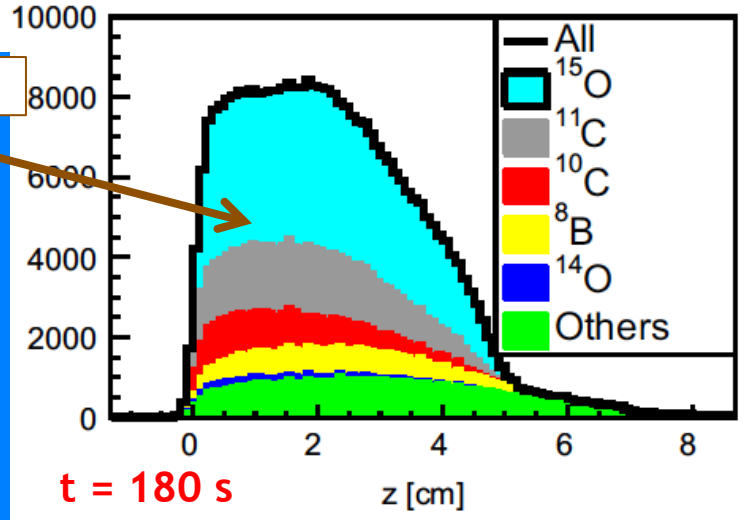
A.C. Kraan, G. Battistoni, N. Belcari, N. Camarlinghi, M. Ciocca, A. Ferrari, S. Ferretti, A. Mairani, S. Molinelli, M. Pullia, P. Sala, G. Sportelli, A. Del Guerra, V. Rosso, NIM A *786, (2015) 120-126*

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



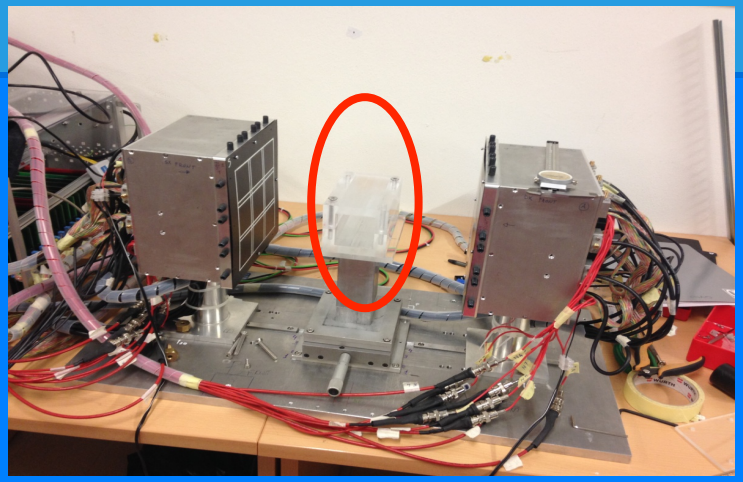


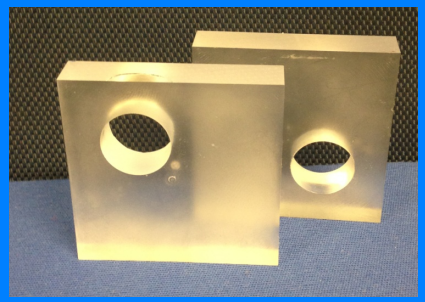
Mont Carlo prediction (FLUKA)

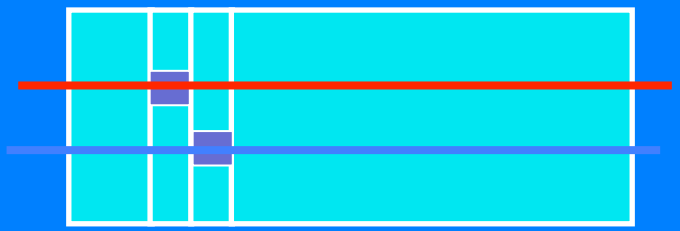


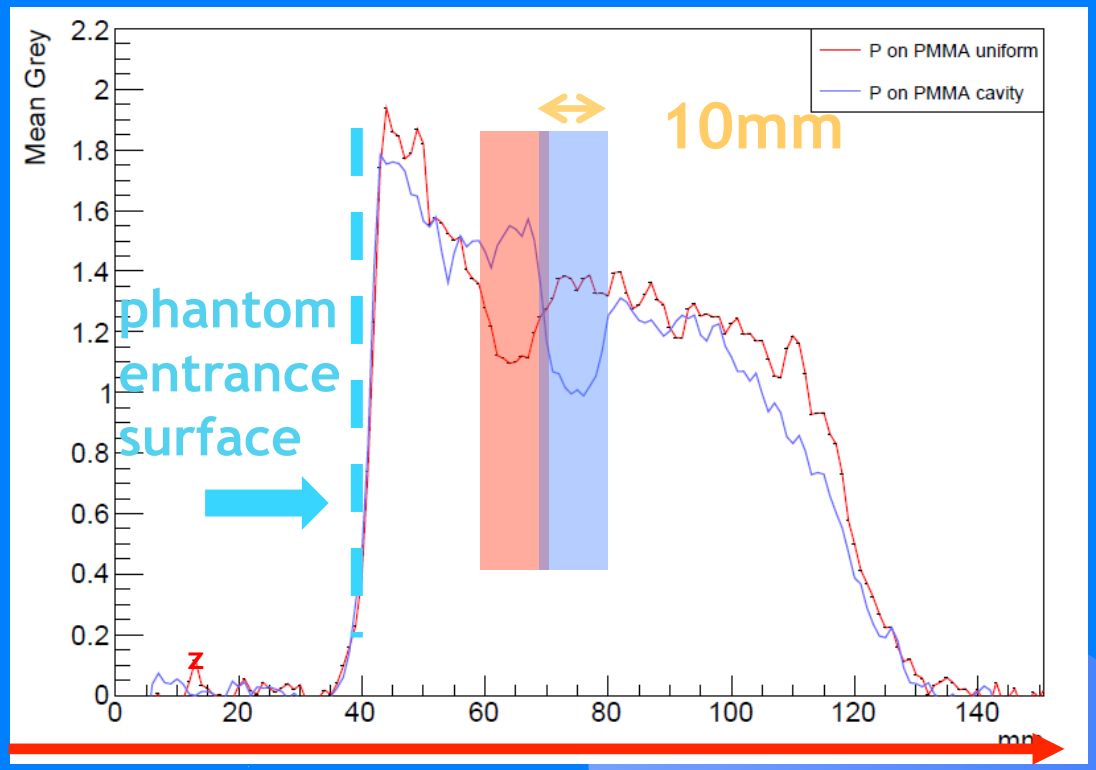
In-beam PET is a base-line solution but:
➡ Hard to go really "online" which is necessary to avoid "metabolic washout"
must sustain high rates (PET + prompt γ + n)

Test with Carbon Plan at CNAO



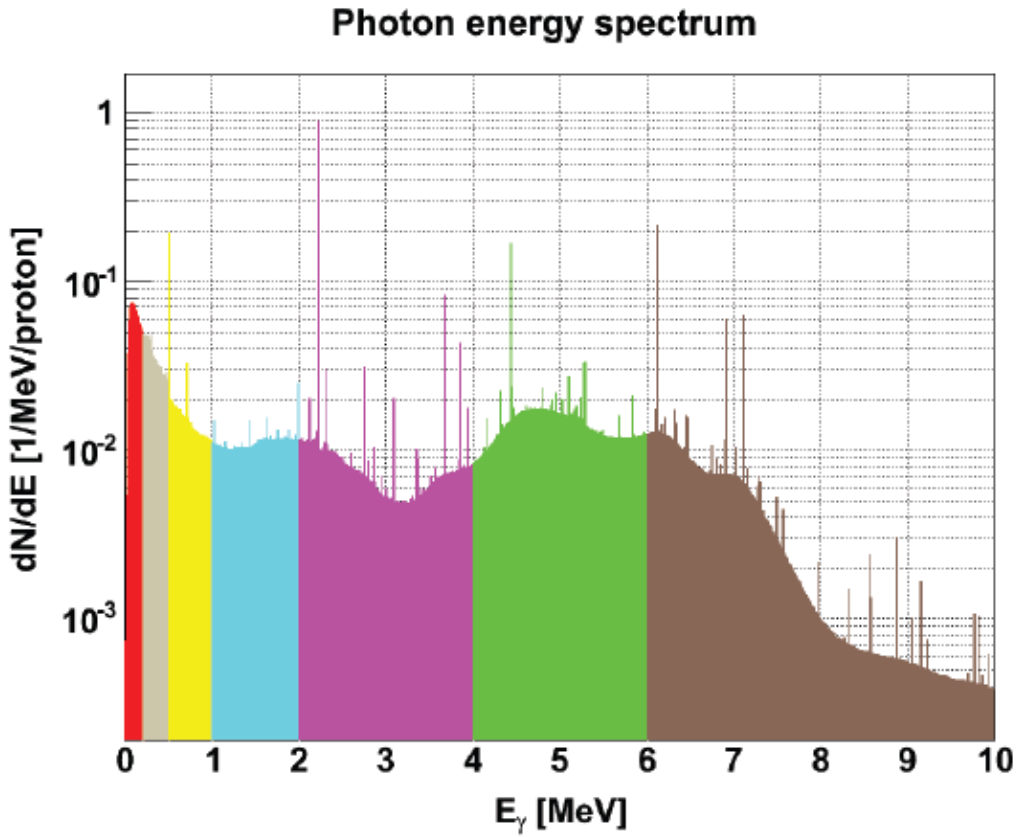






V. Rosso et al,
presented at 13° Pisa Meeting on Advanced Detectors 2015
Paper in prepariation

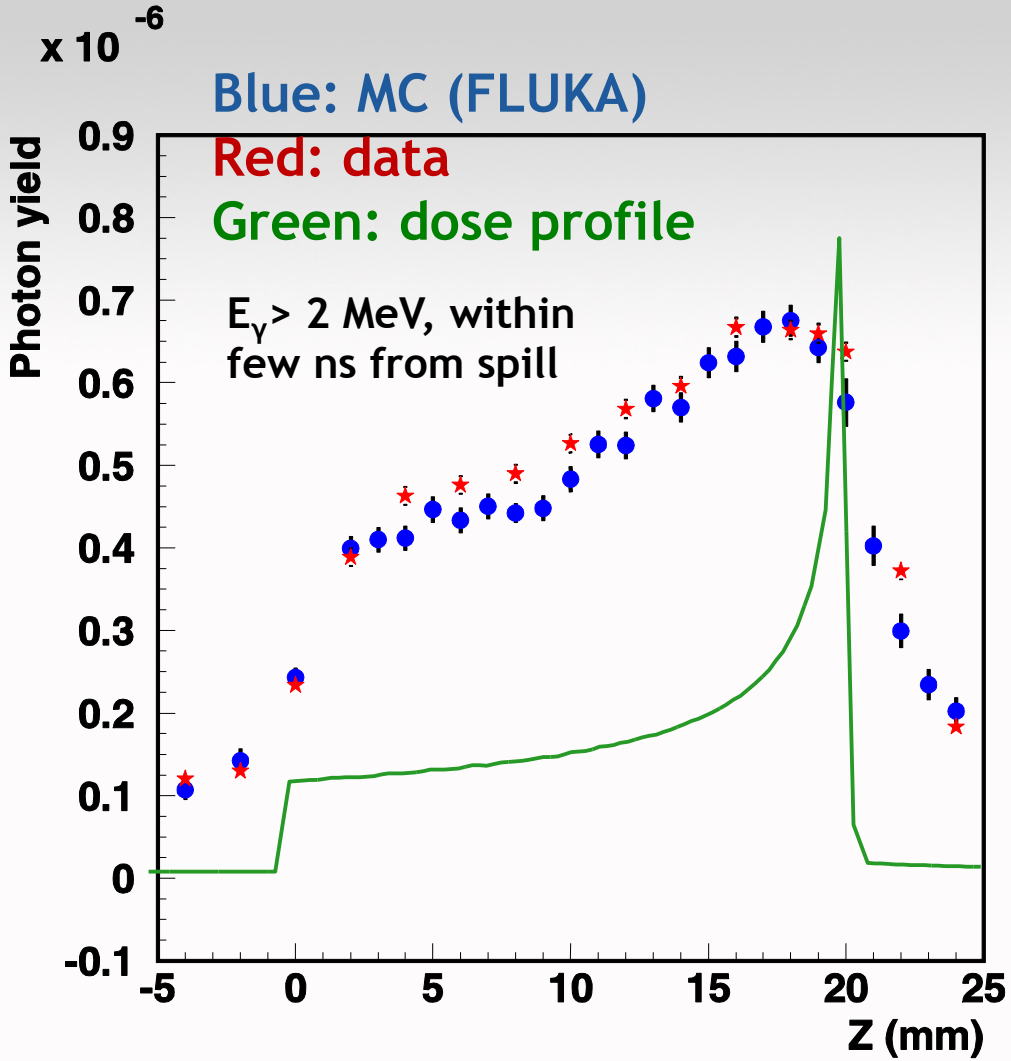
Exploiting “prompt” de-excitation photons

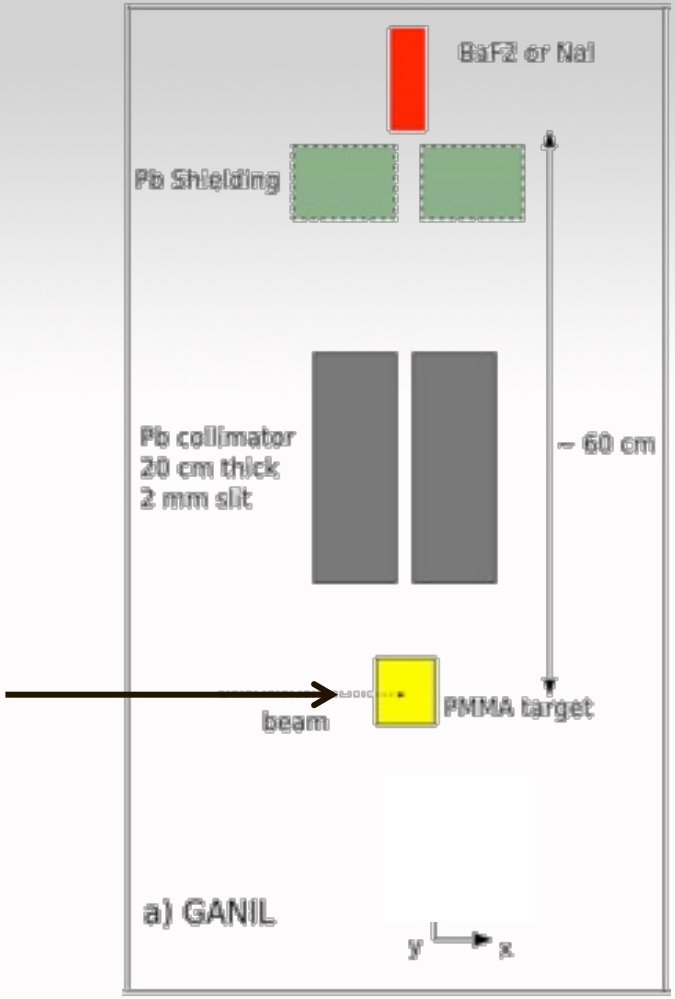


- $4 \cdot 10^9$ /fraction (2 Gy) ☺
- γ-energy: 0… ~8 MeV ☹

not suited for standard gamma-imaging devices of nuclear medicine

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

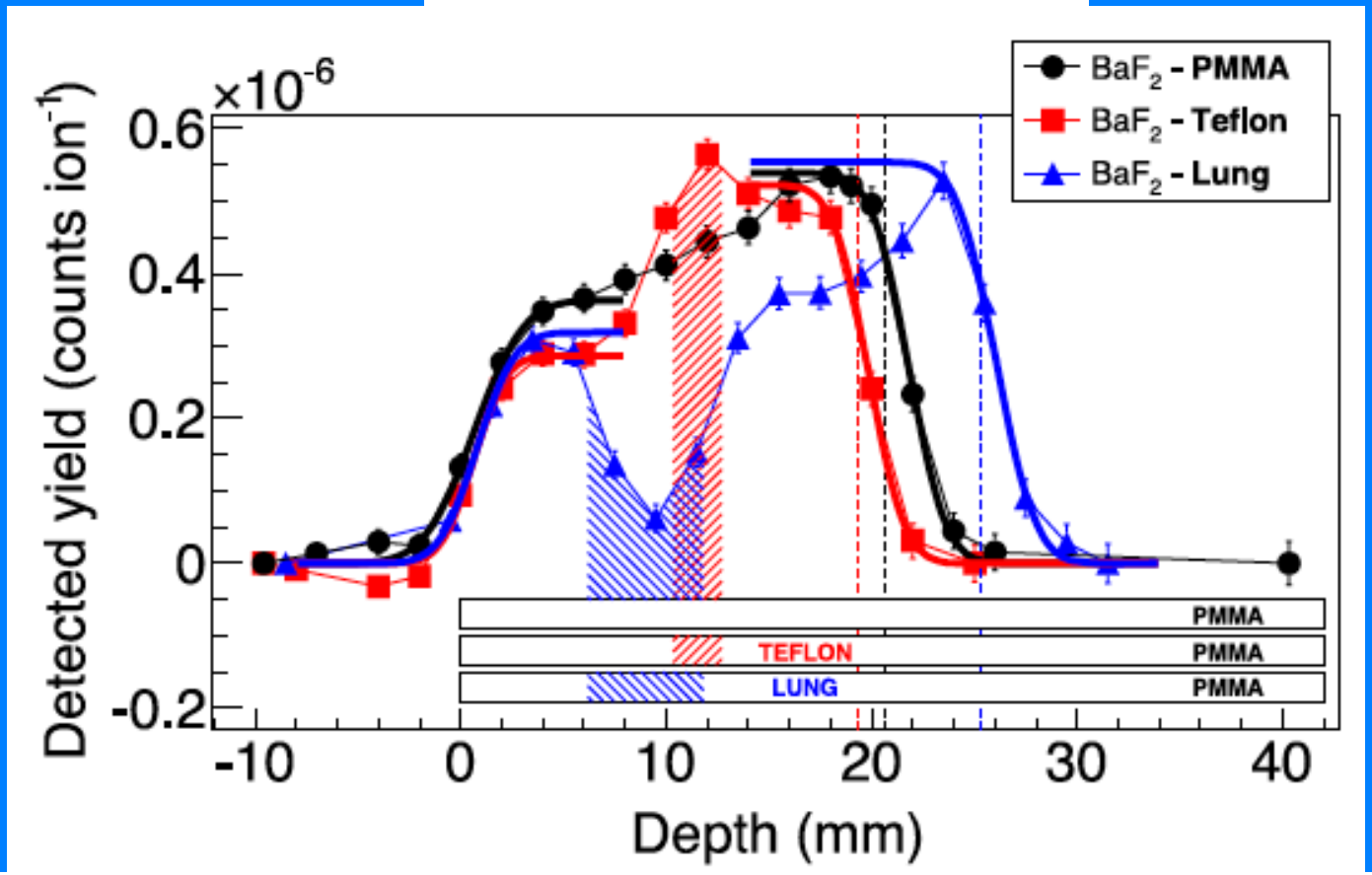




[sketch and exp. data taken from F. Le Foulher et al IEEE TNS 57 (2009), E. Testa et al, NIMB 267 (2009) 993.

Spotting structures with prompt photon detection

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

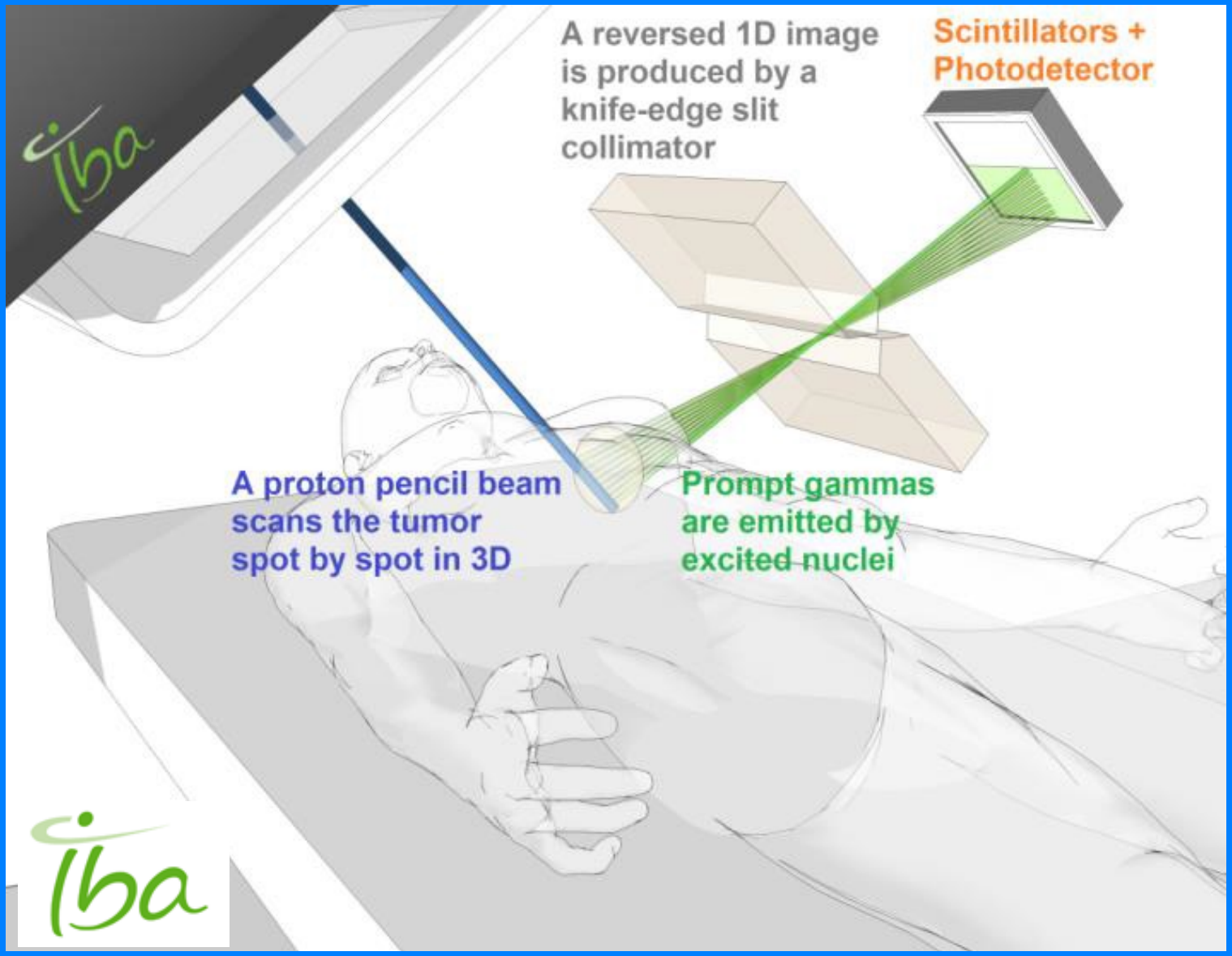


Key issue is the detection efficiency when trying to backtrack the γ

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

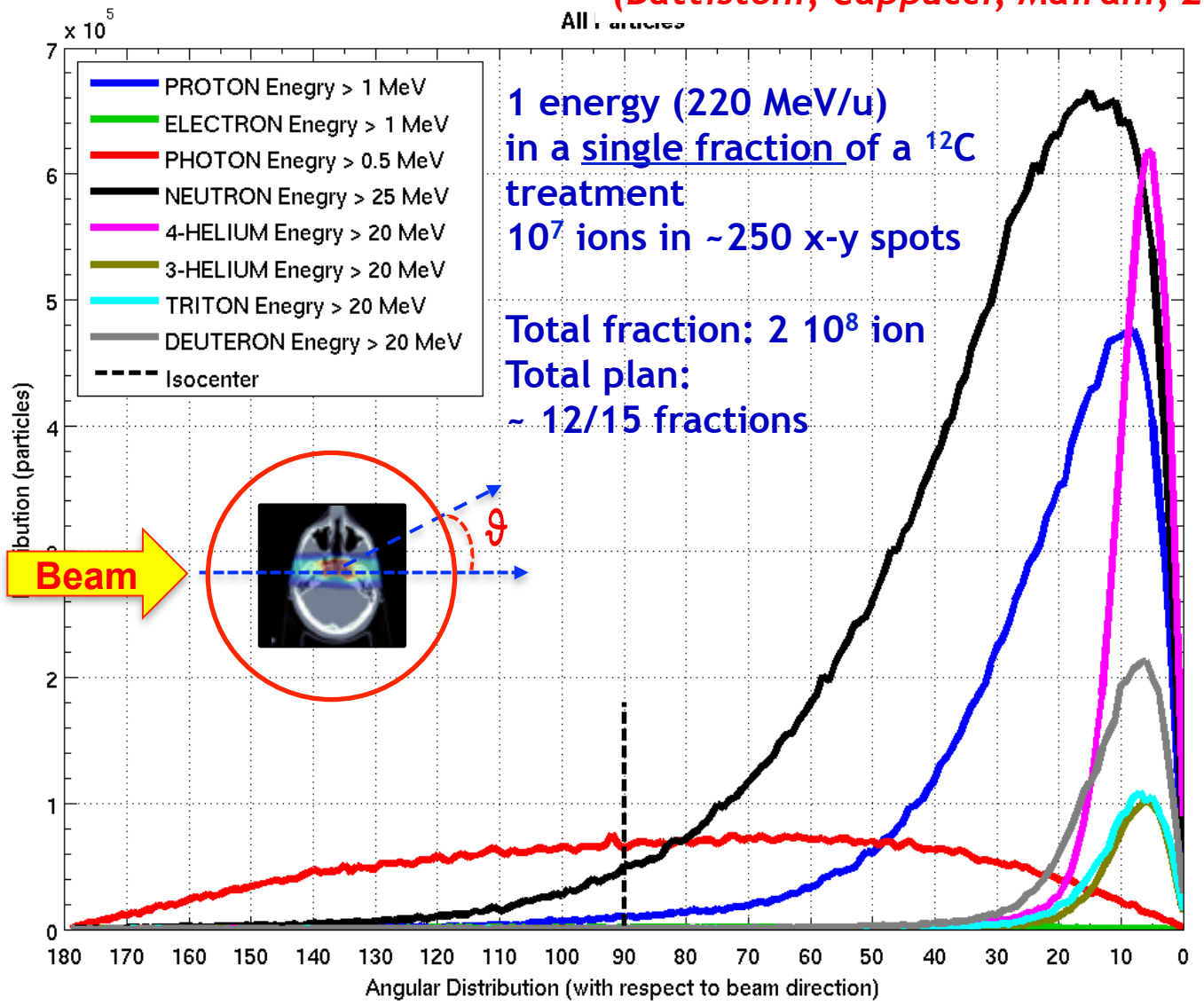
→ *New IBA system for proton therapy ready for the market*

Knife-edge-slit camera by IBA



How many particles/fragments out of a patient?

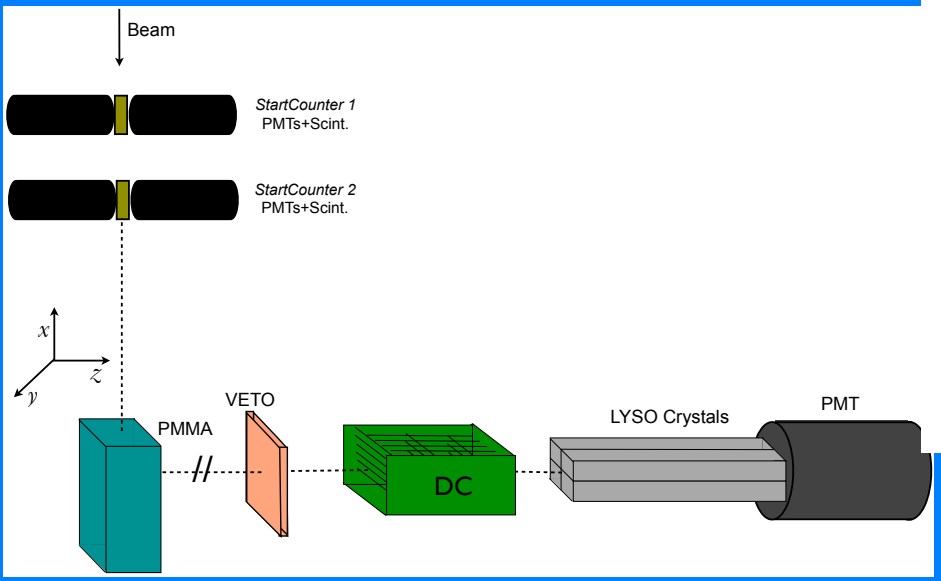
MC simulation of a 12C treatment plan on a patient (CNAO)
(Battistoni, Cappucci, Mairani, 2014)

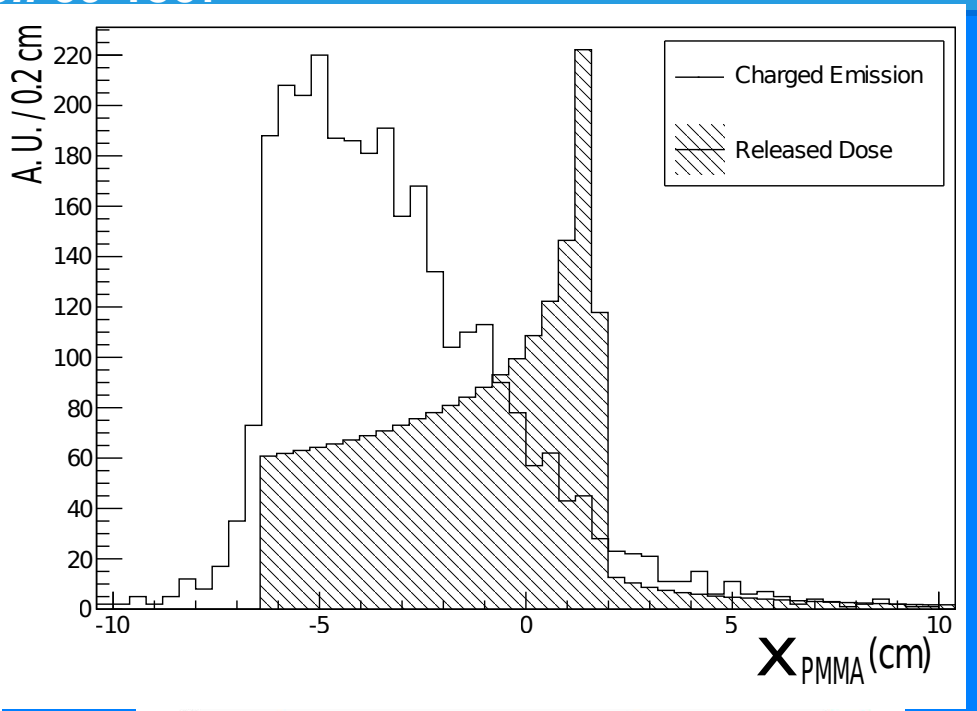


Use of charged secondary production

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

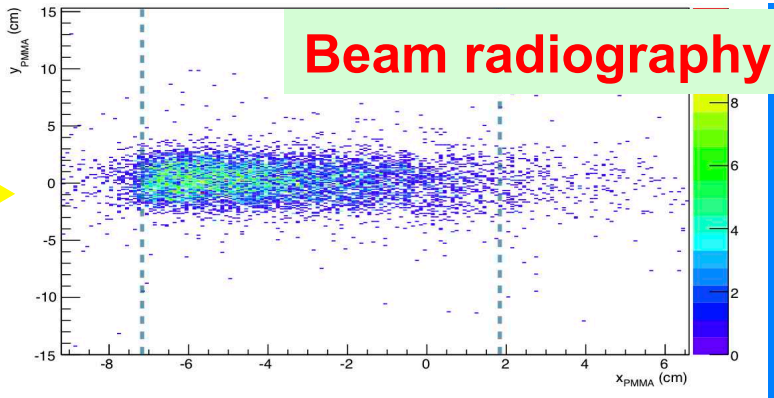
Charged secondary produced at 90⁰ by ^{12}C 220 MeV/u at GSI





Beam

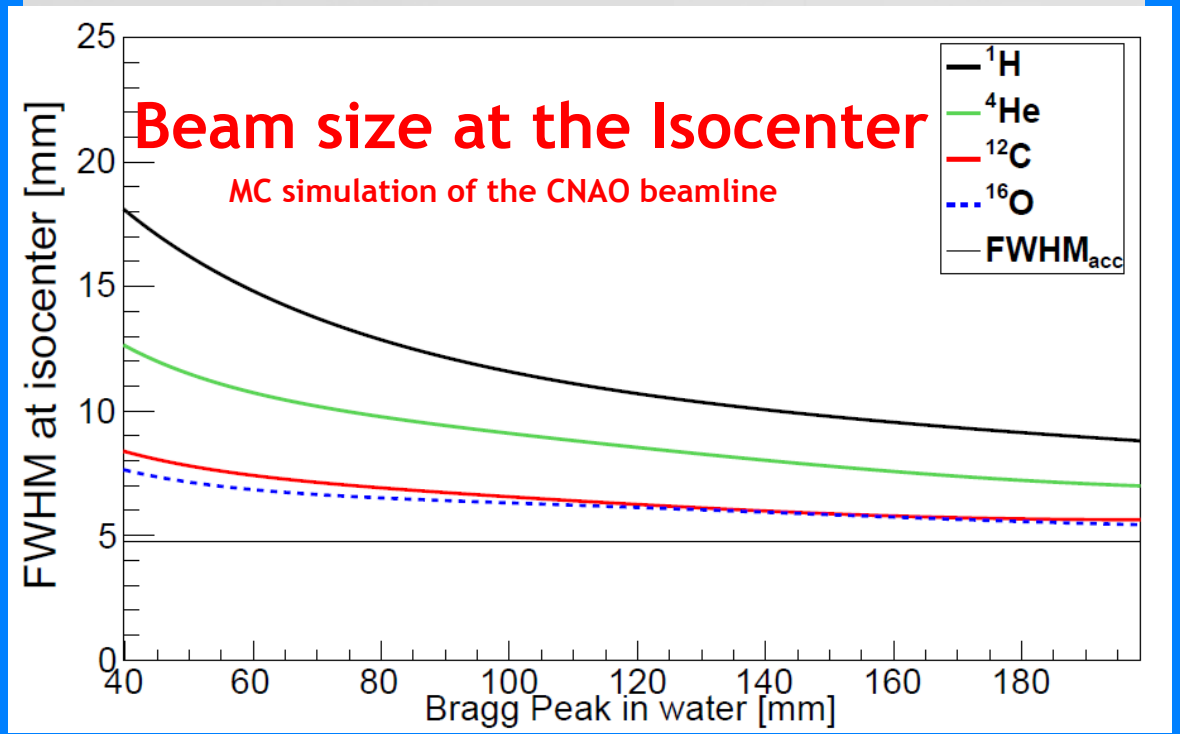
Beam



$$\frac{dN_p}{N_C d\Omega}(\theta = 90°) = (1.83 \pm 0.02_{stat} \pm 0.14_{sys}) \times 10^{-3}\ sr^{-1}$$

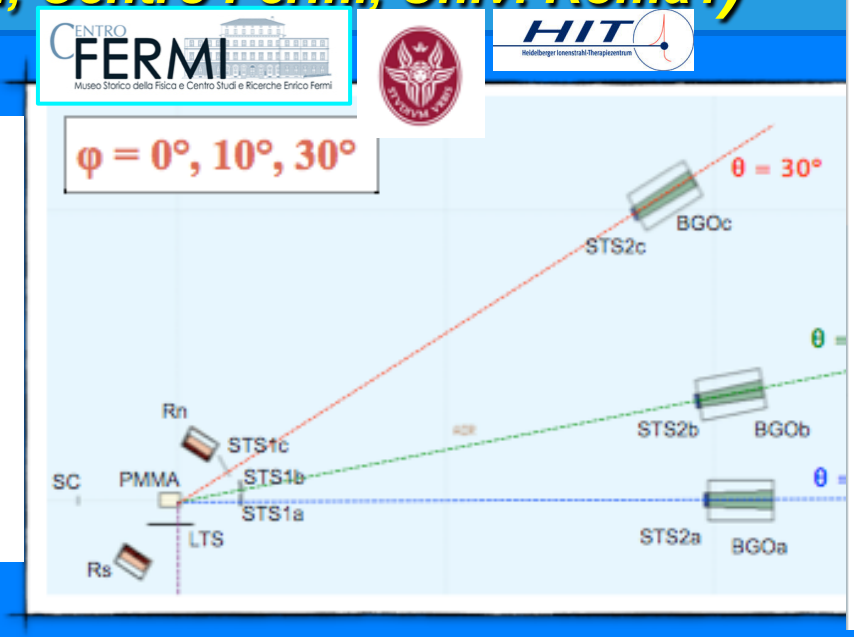
Future options

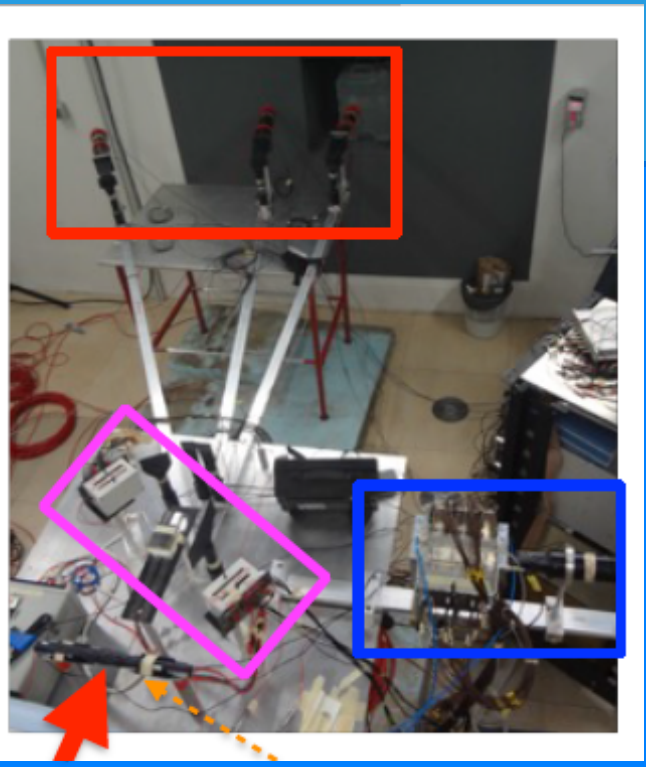
New ion beams for therapy



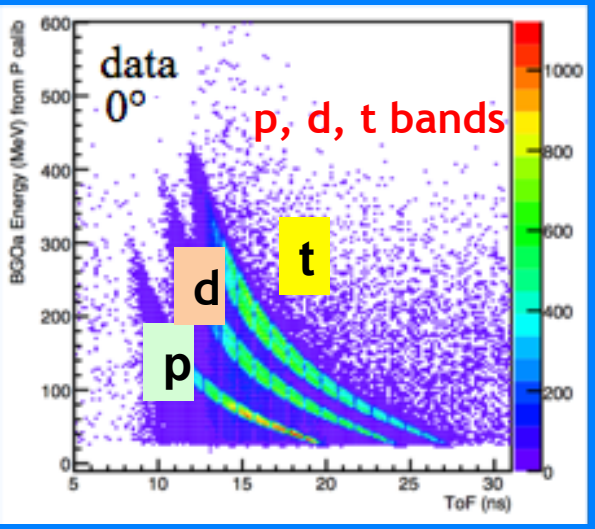
Measurement of He fragmentation at HIT (INFN, Centro Fermi, Univ. Roma1)

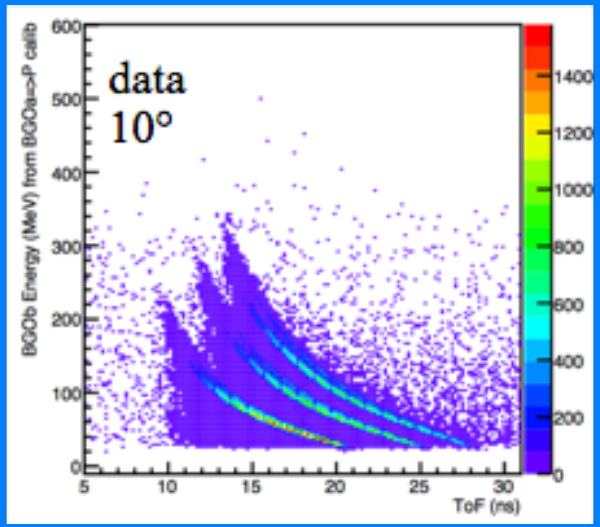
G. Battistoni, F. Bellini, F. Collamati, E. De Lucia, M. Durante, R.Faccini, M. Marafini, I. Mattei, S. Morganti, R. Paramatti, V. Patera, D. Pinci, A. Rucinski, A. Russomando, A. Sarti, A. Sciubba, M. Senzacqua, E. Solfaroli Camillocci, M. Toppi, G. Traini, C. Voena

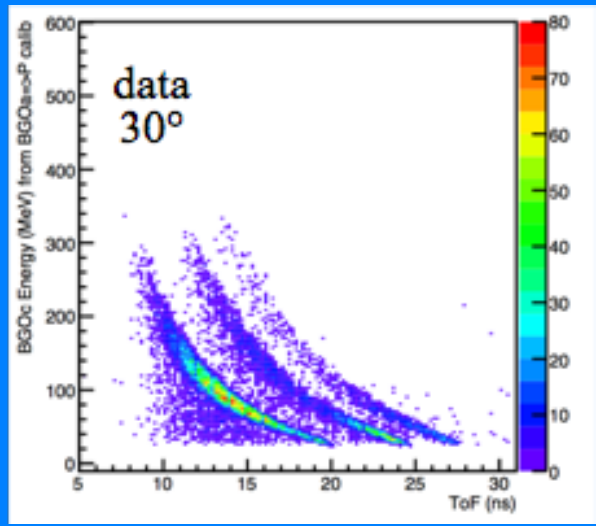




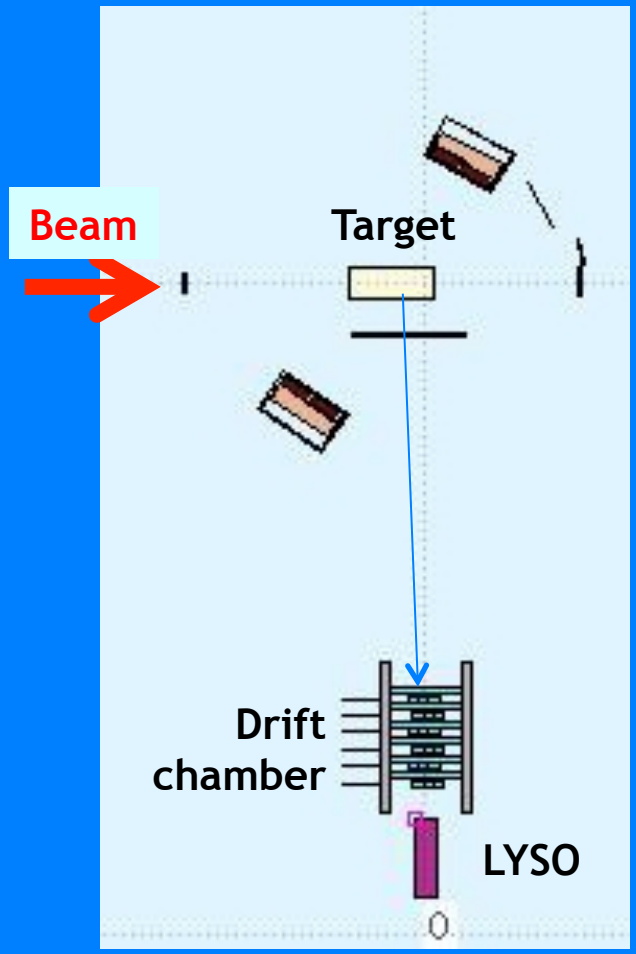
ΔE (scint) vs E (BGO) plots

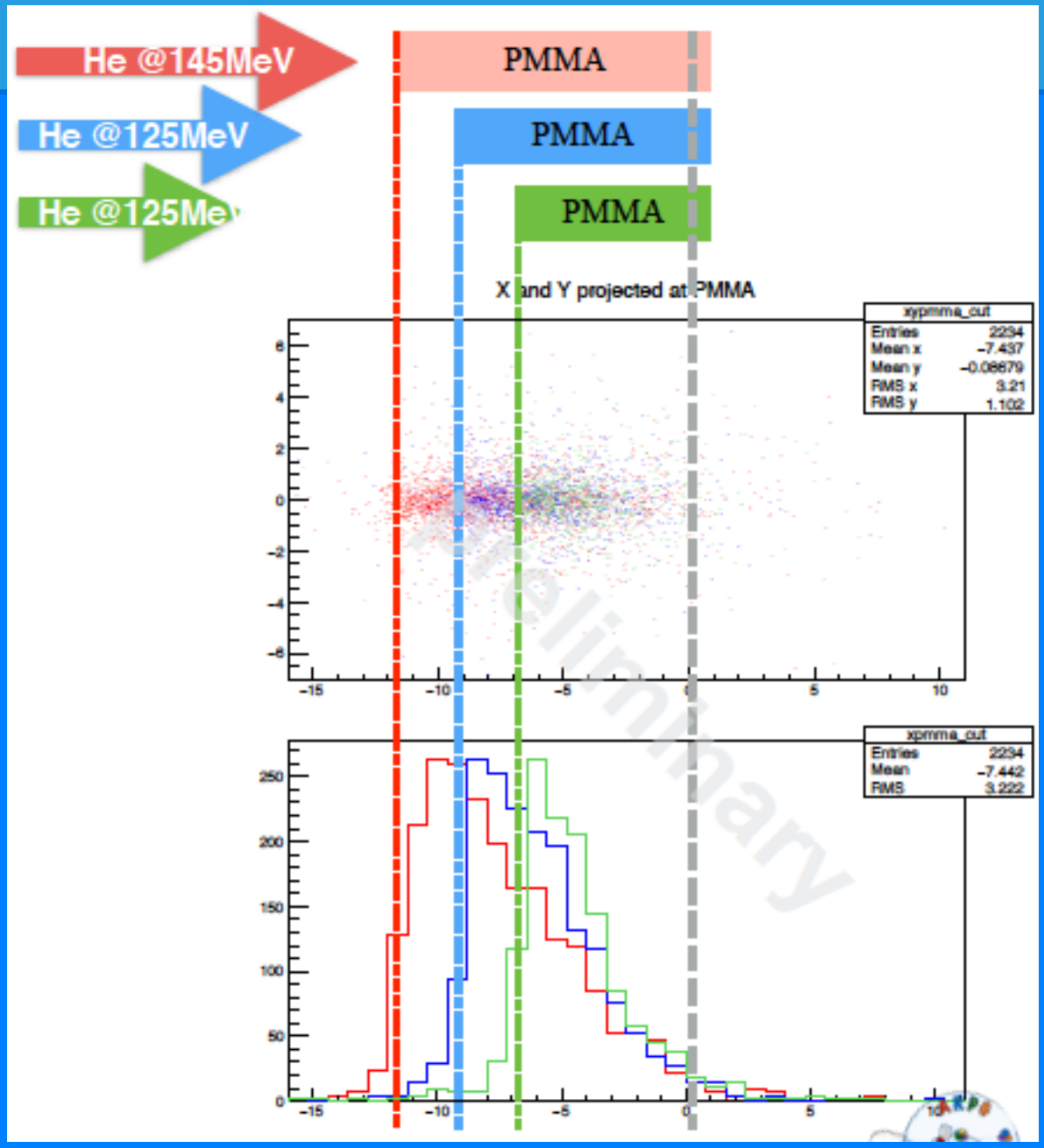






Detection of protons at ~ 90 deg from He beam





Monte Carlo codes

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)**
- **Treatment planning avoding Water Equivalent approximations**

  Bonus:
  - **Accurate 3D tracking**
  - **Detailed description of actual patient geometry: → CT images directly read as input**
- **Prediction and analysis of secondary production by hadron beams for monitoring purposes**
- **Study of detector response**

Main Challenges:

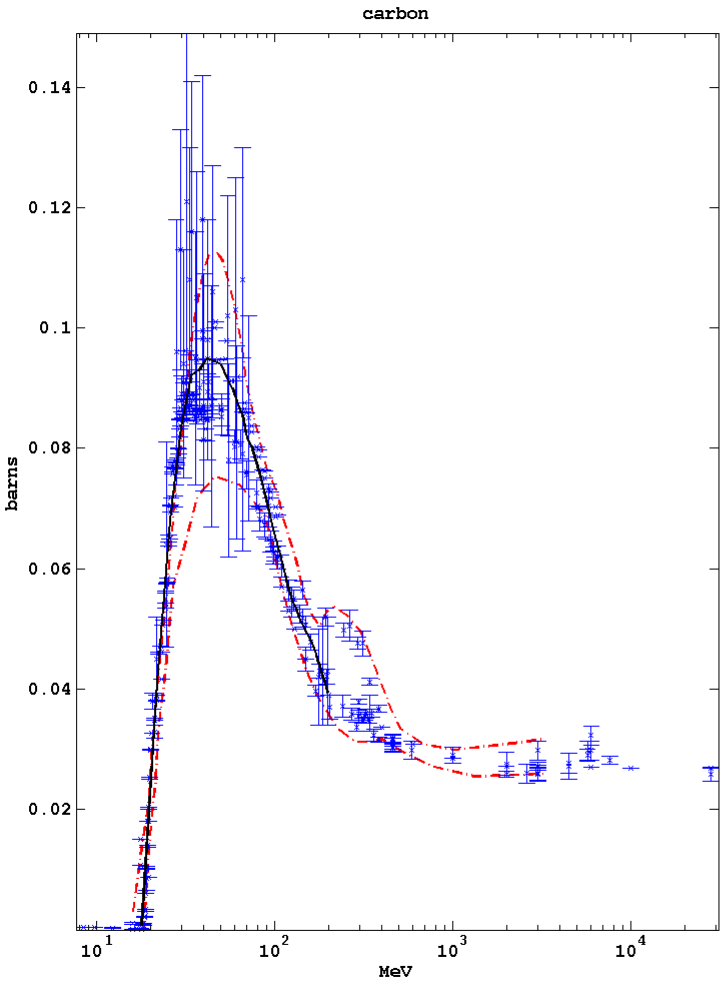
- **Nuclear physics models and exp cross sections for validation**
- **Coupling with Radiobiological models**
- **Computing time**

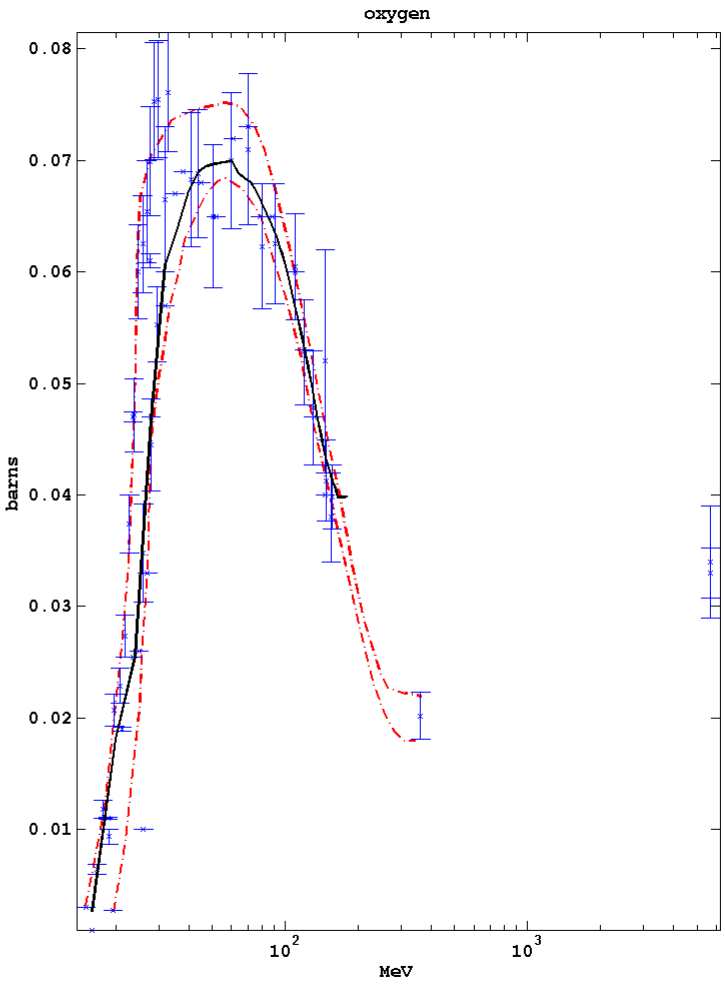
A few key issues in Monte Carlo physics

- Nuclear interaction models: phenomenological approaches to be tuned on the basis of experimental cross sections
  - Not enough data available for complete validation!
  - Fragmentation of C is still the example of open problem
- In general it is not possible to use the same model in the whole interesting energy range: great care to ensure continuity
- Interactions of very light nuclei (d, t, He, …)
- Quality of description of processes like pre-equilibrium, evaporation, break-up, de-excitation
- Extensive use of Evaluated Data bases is necessary

Huge progresses achieved in the last ~10 years.
Continous upgrade and development

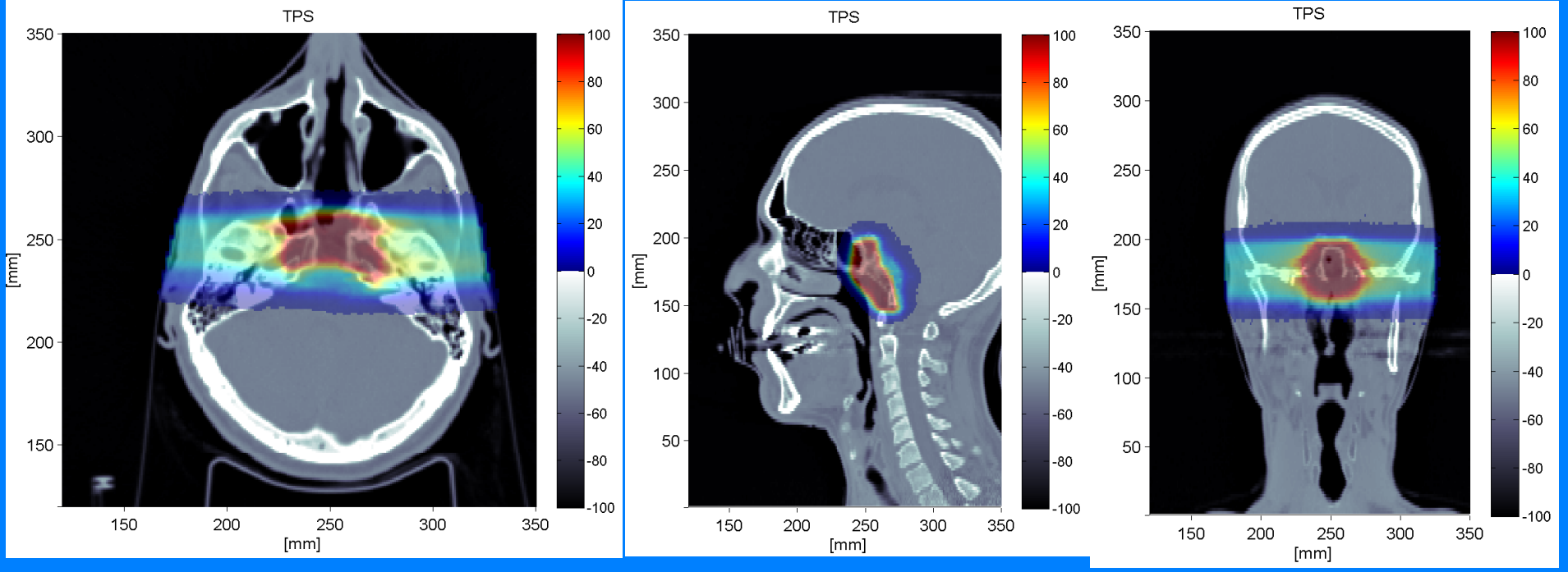
$^{12}C(p,x)^{11}C$ and $^{16}O(p,x)^{15}O$ cross sections.





Towards improved Particle Therapy with the help of nuclear physicists:

- MC treatment planning → Continuous model evolution and validation
  If possible more exp, data are needed for benchmarking
- Ultrafast treatments -> Higher intensity beams
  → Neutron dosimetry might become important
- Treatment of moving organs
- Hypofractionation, Radiosurgery (single fractions for cancer and non-cancer diseases) → Range check mandatory
- Personalized treatments:
  - LET or RBE "painting" (aiming at hypoxical/radioresistant regions) → Efficient "in-beam" imaging. Modelling, Fast computing
  - Image guided hadron-therapy
- Accelerator developments and cost reduction
  - New components (for instance: more performant ion sources)
  - Compact acceleration systems
  - Future: new acceleration techniques towards more compact structures
    → Laser driven Plasma acceleration ?



Thank you for the attention

Special thanks to:

V. Patera, (INFN & Univ. Roma 1)
M. Durante (INFN TIFPA, Trento)
V. Rosso (INFN & Univ. Pisa)
M. Bruzzi (INFN & Univ. Firenze)
C. Civinini (INFN & Univ. Firenze)
A. Mairani (CNAO & HIT)
M. Pullia (CNAO)
J. Smeets (IBA)
G. Bisogni (INFN & Univ. Pisa)
C. Fiorini (Politecnico & INFN Milano)
N. Randazzo (INFN & Univ. Ct)
G. Cuttone (INFN LNS)
M. Schwarz (APSS, Trento),
A. Ferrari (CERN)
A. Sarti (INFN-LNF & Univ. Roma 1)
M. Marafini (INFN & Univ. Roma 1)
I. Mattei (INFN Milano)
A. Rucinski (INFN Roma 1)
S. Muraro (INFN Milano)