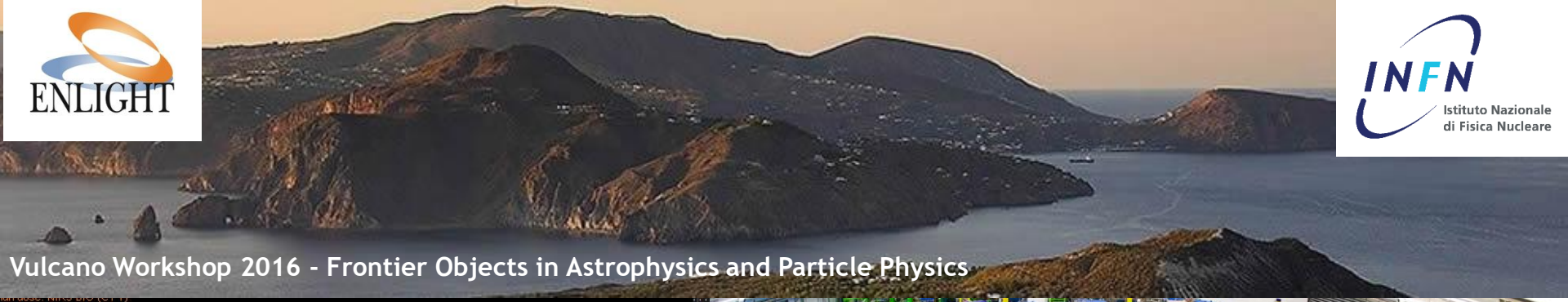
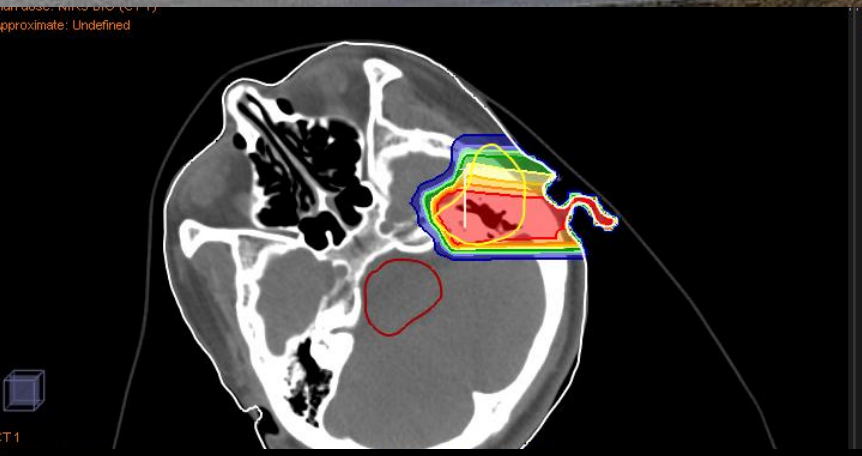
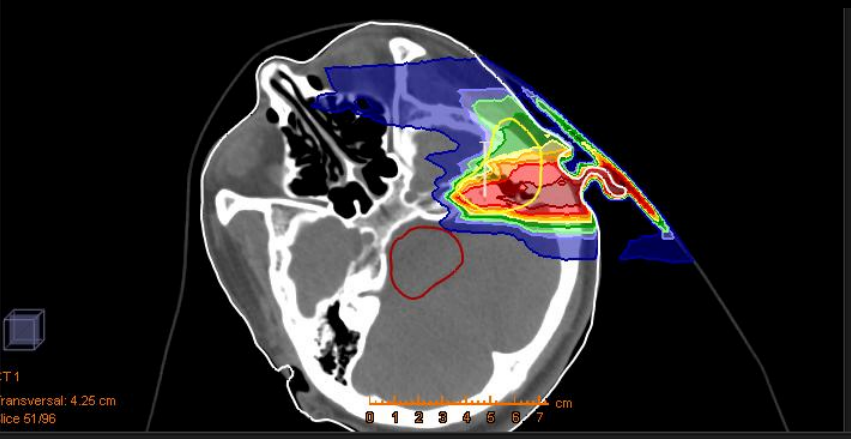


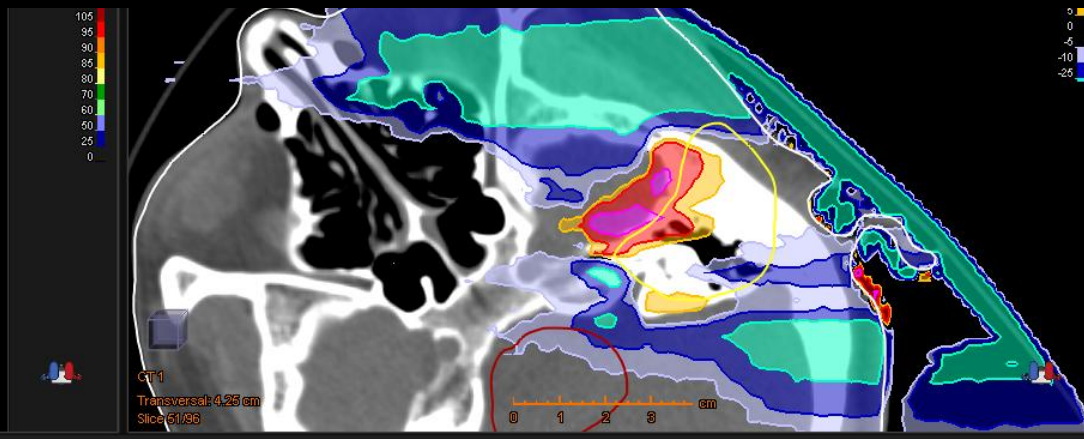
Vulcano Workshop 2016 - Frontier Objects in Astrophysics and Particle Physics



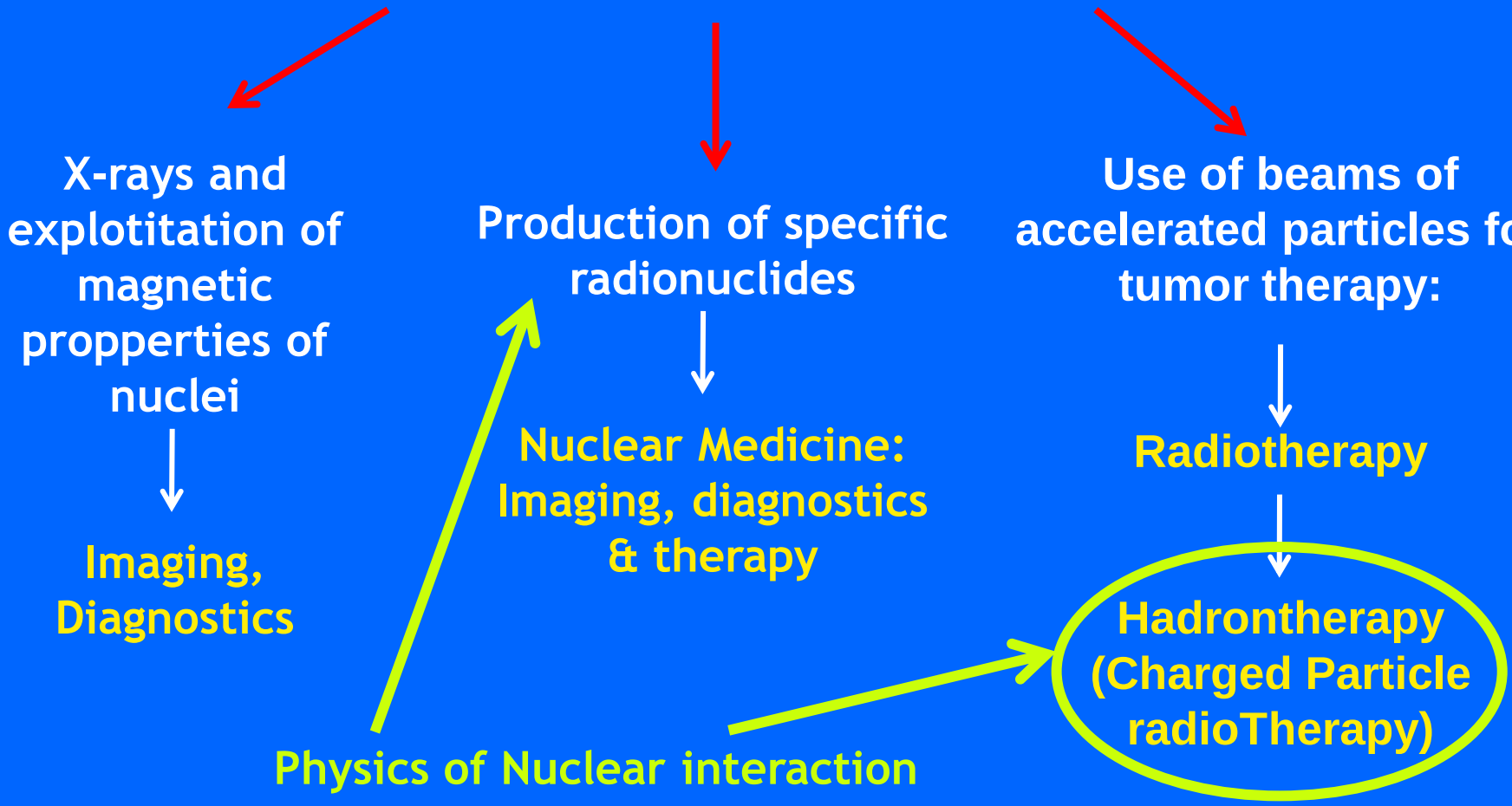
Nucleus-Nucleus interactions and their application in medicine

Giuseppe Battistoni, INFN, Milano, Italy





Application of Atomic, Nuclear and Particle Physics to Medicine



Nuclear Physics European Collaboration Committee (NuPECC)

Nuclear Physics for Medicine

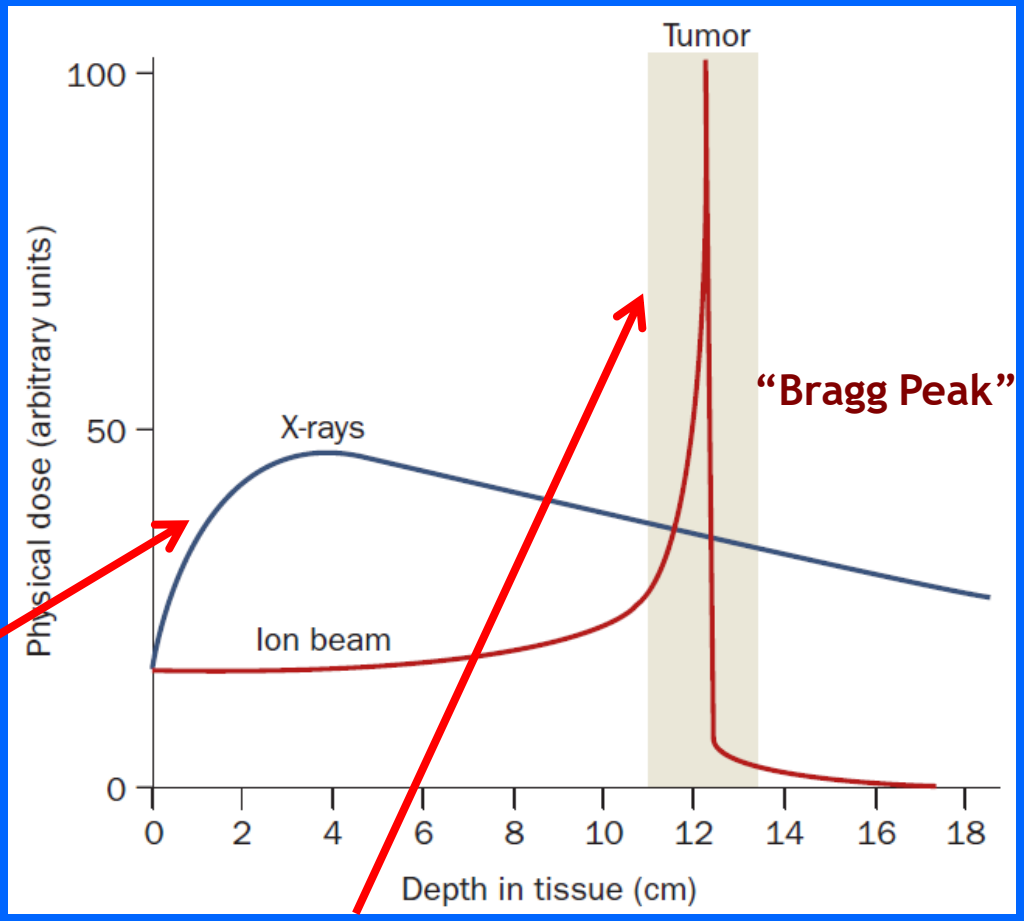
Radiotherapy & Charged Particle Therapy

GOAL

- Deliver a suffiently high Radiation Dose in a tumor region.
- At the same time try to spare as much as possible healthy tissues and Organs at Risk (OAR)

Radiation Type:

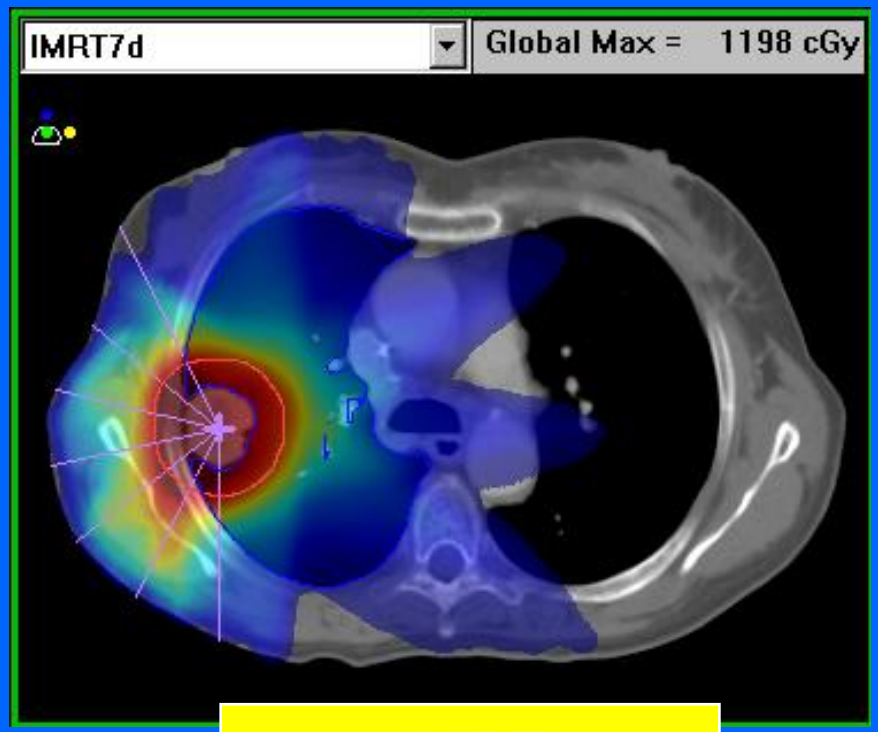
- electrons, photons (X-ray) = "Conventional Radiotherapy"
- 50% of all cancer patients, ~1.5 10^6/year
- *Now very advanced: Image guided, conformal (IMRT)*



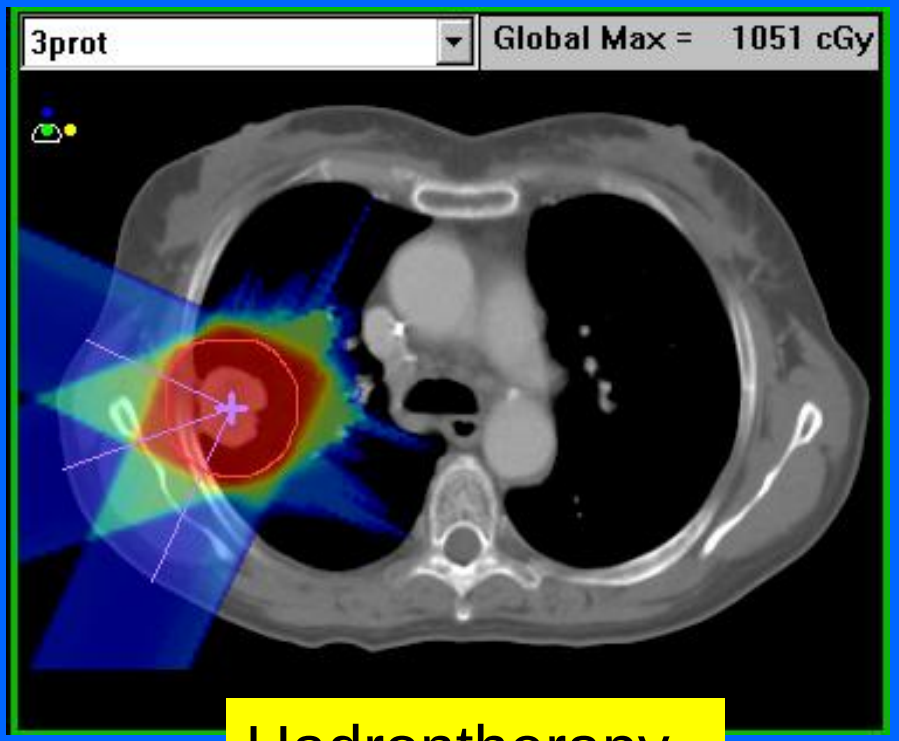
Protons, light nuclei (ions) Hadrontherapy

The highest dose is released at the end of the track range. In principle much more precise, high capability of sparing healthy tissues

The better selectivity of Charged Particle Therapy



IMRT



Hadrontherapy

Milestons of Charged Particle Therapy

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

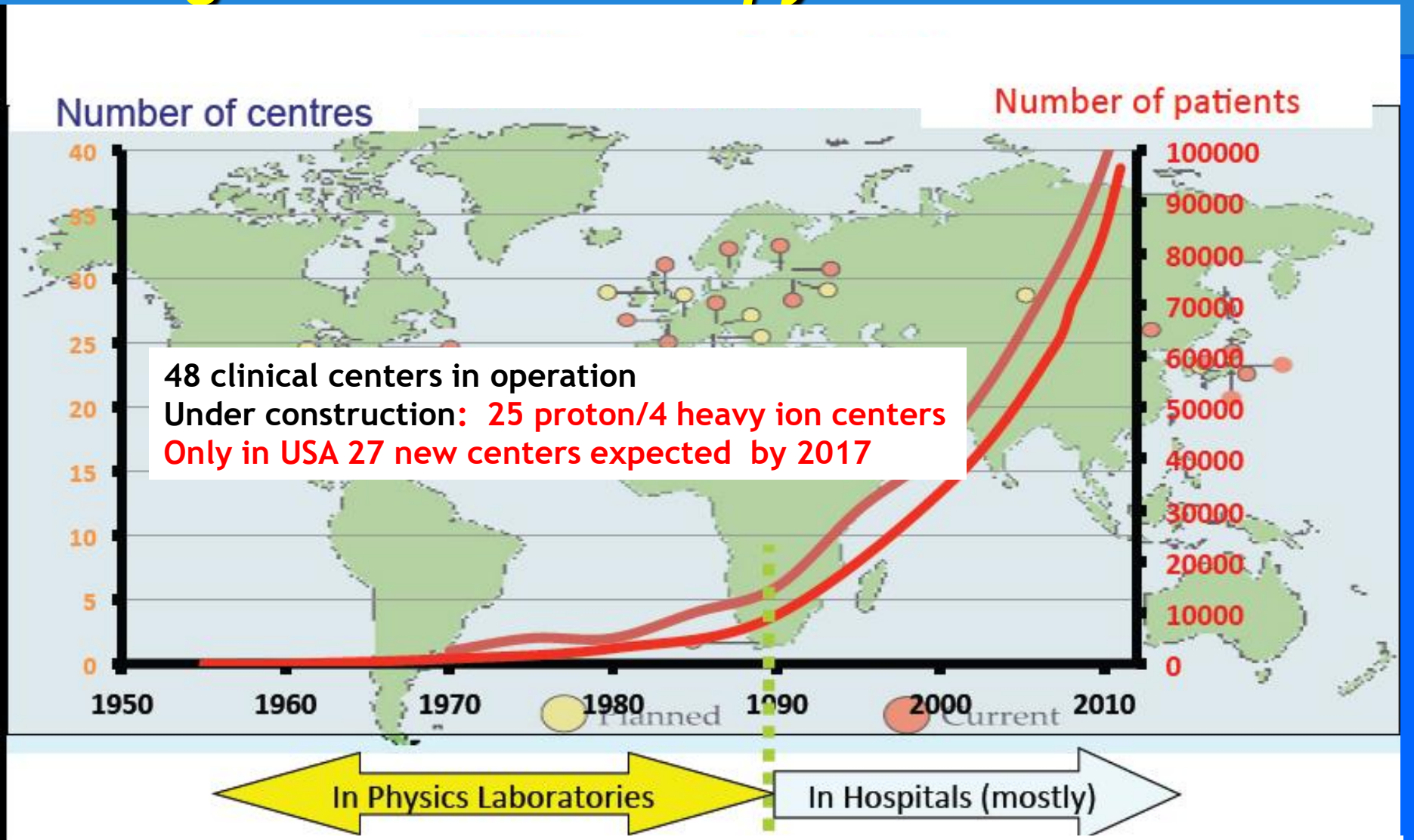
per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate intensely a strictly localized region

Radiology 47: 487-491, 1946

1954 - Berkeley treats the 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 in the world

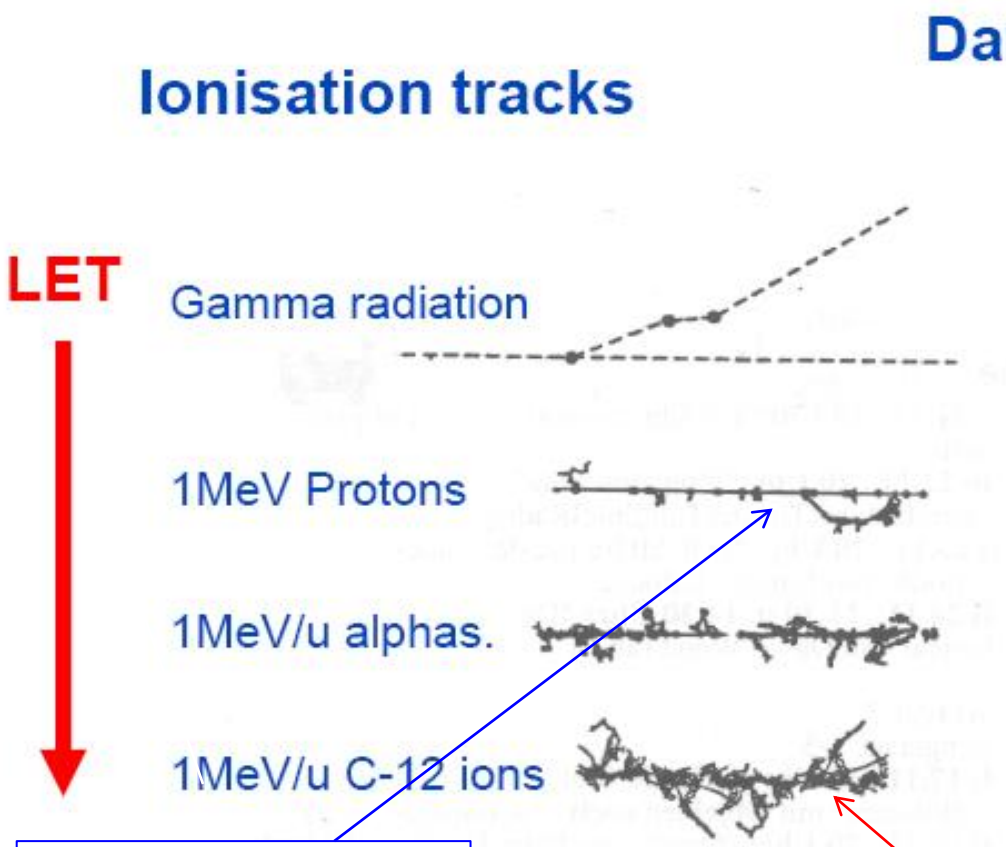


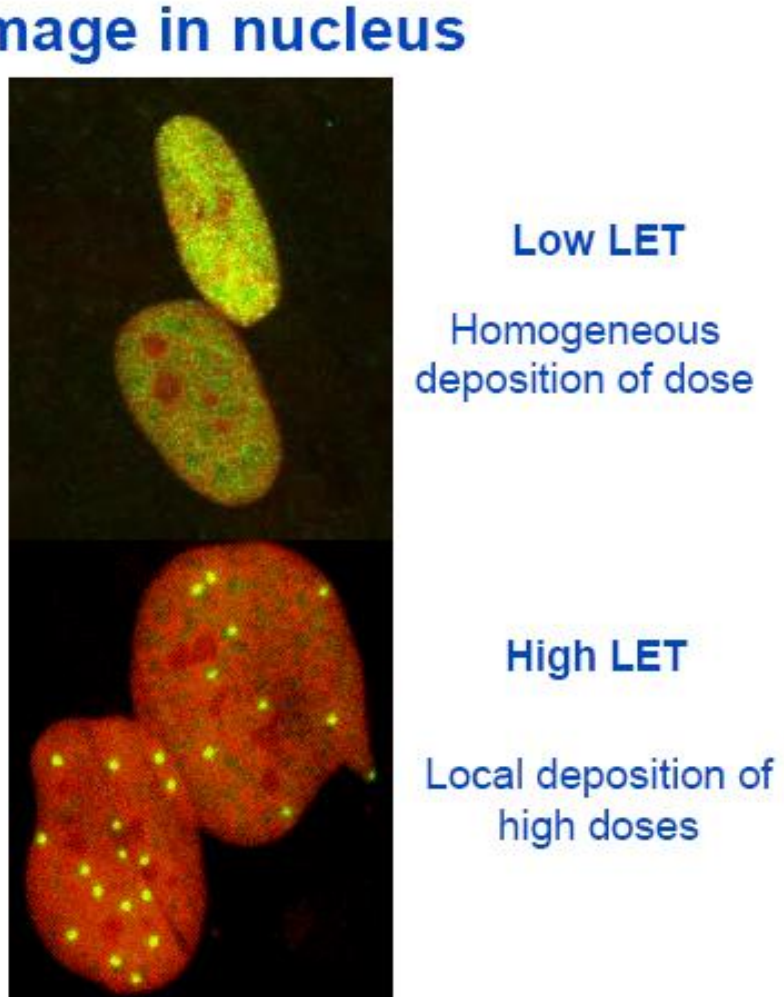
~2014: 137179 treated patients: 118195with p, mainly in USA, 53532

15736 with ^{12}C, mainly in Japan, 10993;

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

Interdisciplinary aspects: Physics and Biology





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

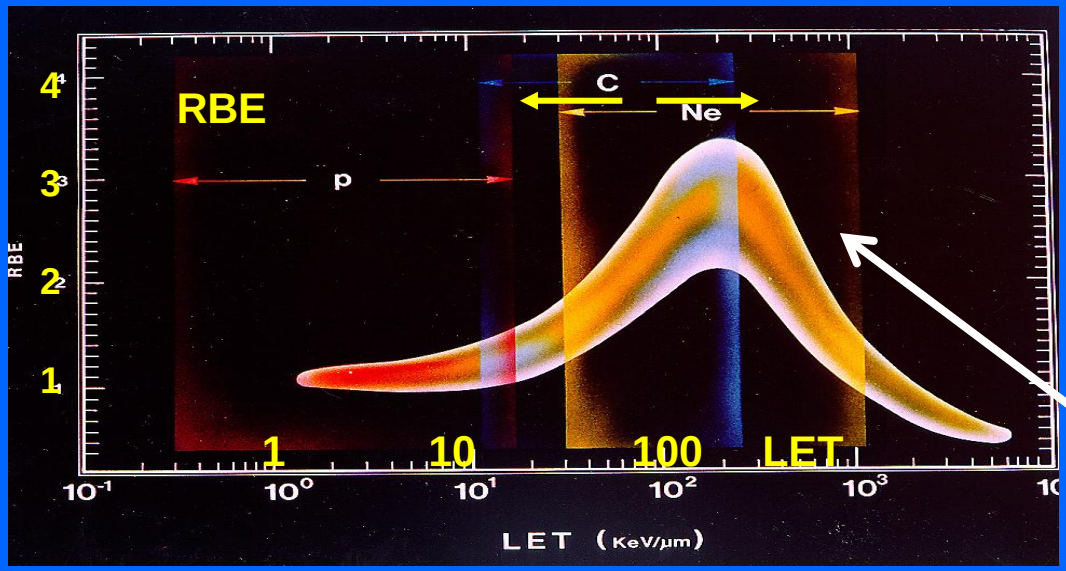
^{12}C on the Bragg peak
when R_{res} ~ 1 mm
E ~ 17 MeV/u
LET ~ 140 kev/µm
<d> ~ 0.3 nm

Radio Biological Effectiveness (RBE)

High LET nuclei can be more effective than phptons in killing a cell for the same value of delivered dose

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

RBE is defined for a given type of biological end-point and its level of expression.
For example: cell Survival Probability level of 10%

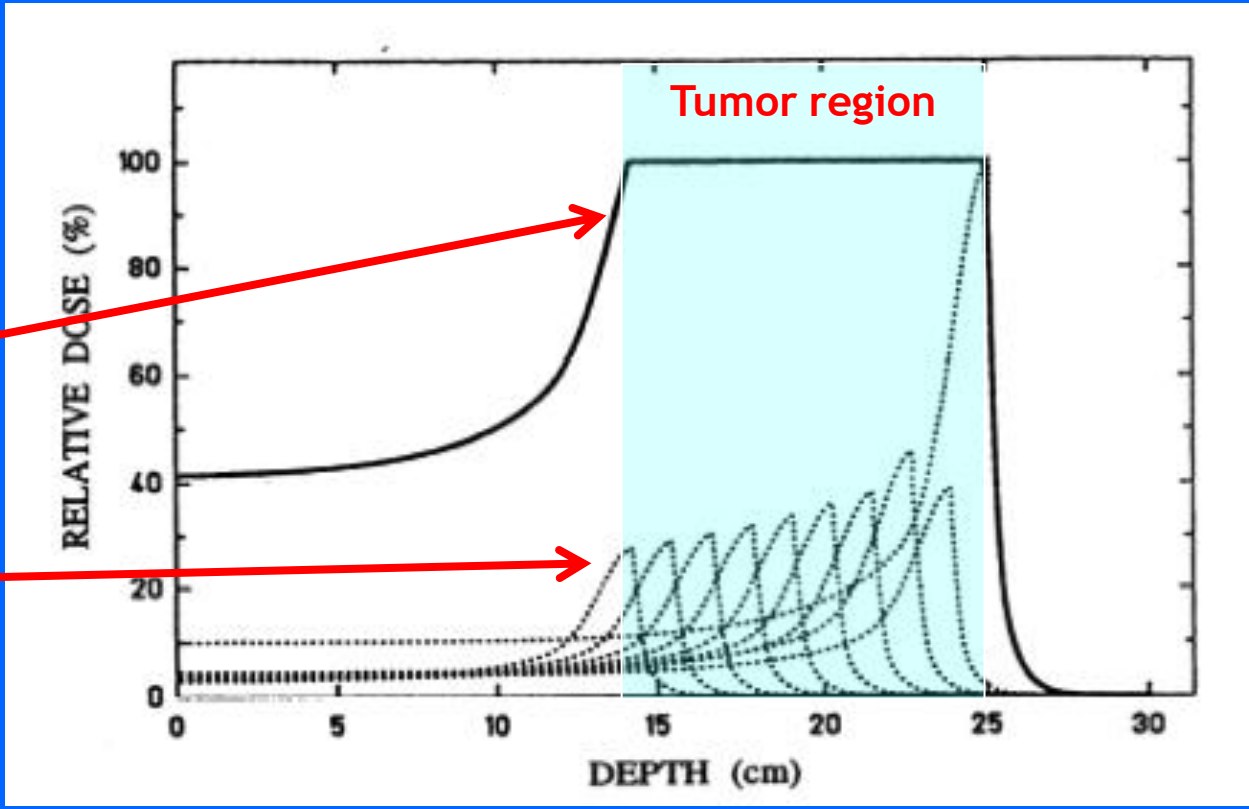


Many Factors affect RBE:
Cell line
LET
Dose
Dose rate
Fractionation
…
Large spread of measurement results, even for the same cell line!!!

The conformation capability: how to

longitudinal scheme in proton therapy

- Depth modulation = energy modulation
- Accurate conformal dose to tumor with **Spread Out Bragg Peak (SOBP)** achievable by optimizing the intensities of beams at different energies **(Treatment Planning)**



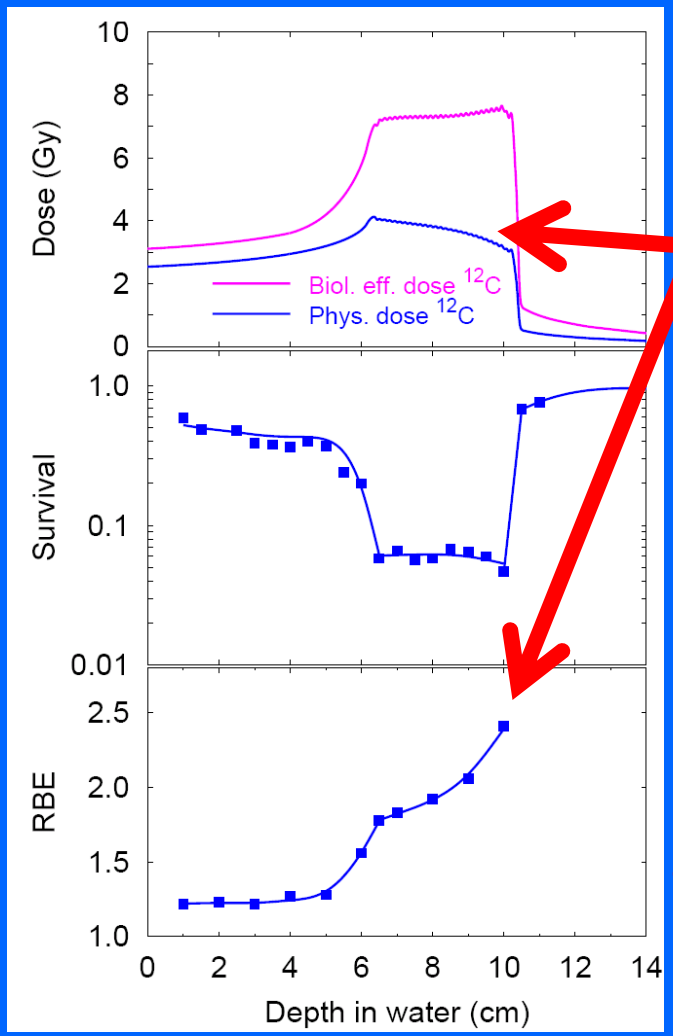
RBE of protons can be approximated as a constant: ~1.1

not really true, but considered sufficient at clinical level today (under discussion…)

Nuclear projectiles in Particle Therapy today

protons: 50-250 MeV accelerated by cyclotrons or synchrotrons

Therapy: order of magnitude ~ 70 - 80 Gy in 30-35 fractions of ~ 2Gy
2 Gy in 1 cm^3 ~4 10^8 p



^{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

Therapy:
order of magnitude ~ 70 - 80 GyE in ~15 fractions of ~ 4GyE
4 GyE in 1 cm^3 ~ 1.5 10^6 ^{12}C

However:

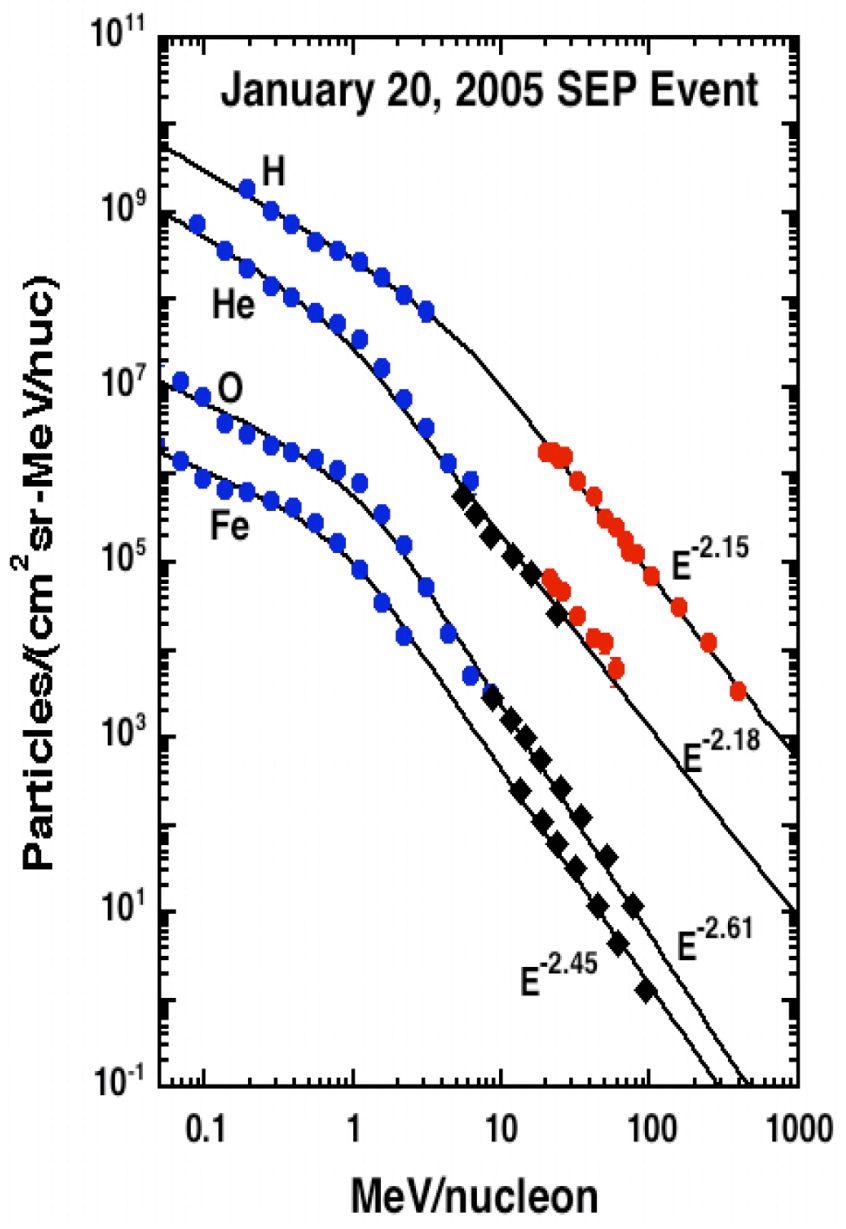
accelerated by larger machines

heavier gantries and magnets…

Nuclear Fragmentation (➜complex RBE)

variable RBE vs energy, LET, …

A comparison with the situation of radioprotection in space…



the hardest spectrum ever measured for a SEP after1956

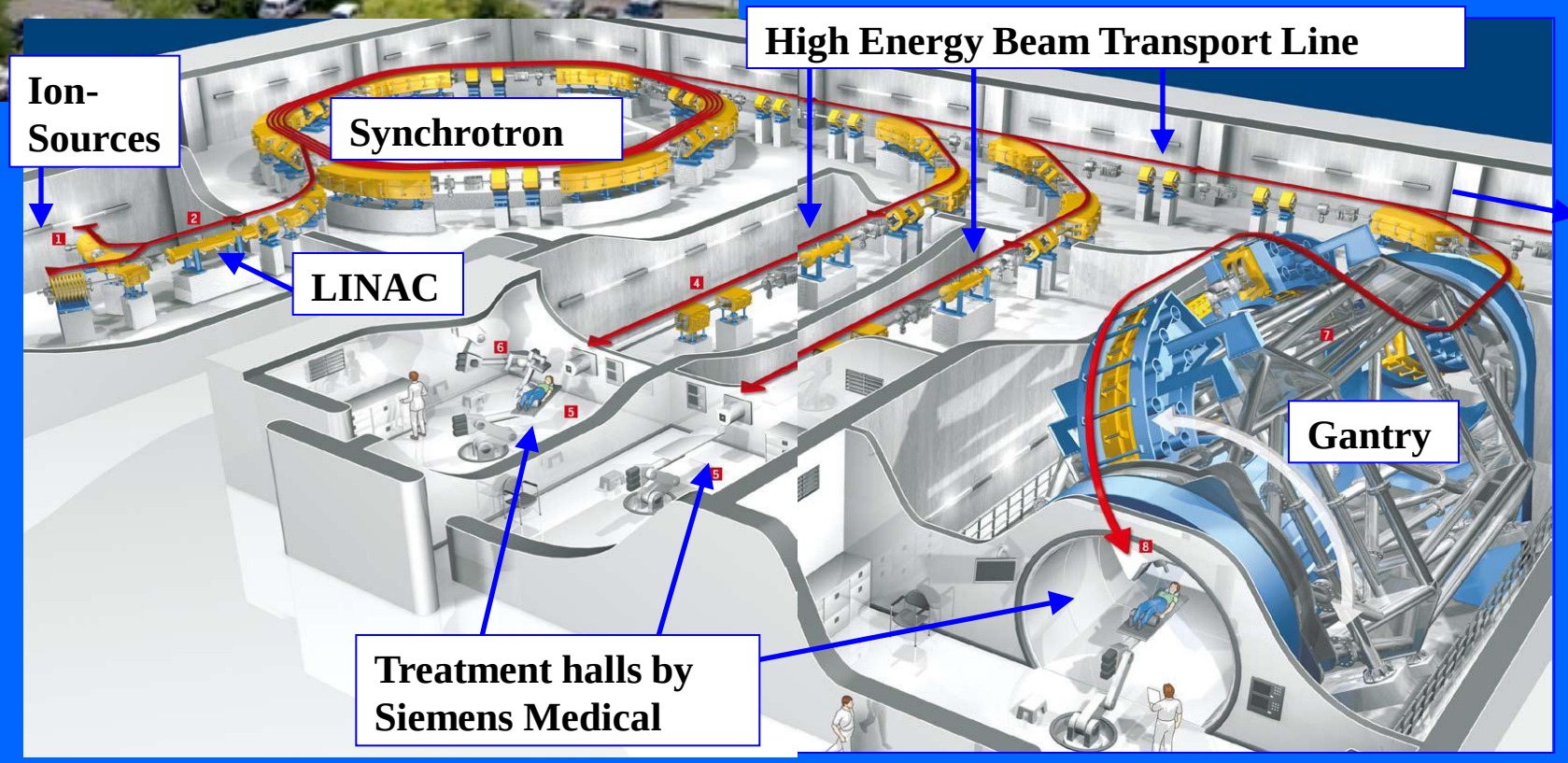
Integrated fluence:
~7 10^9 (nucleon/c m^2)
@E > 1 MeV/u

HIT - Heidelberg

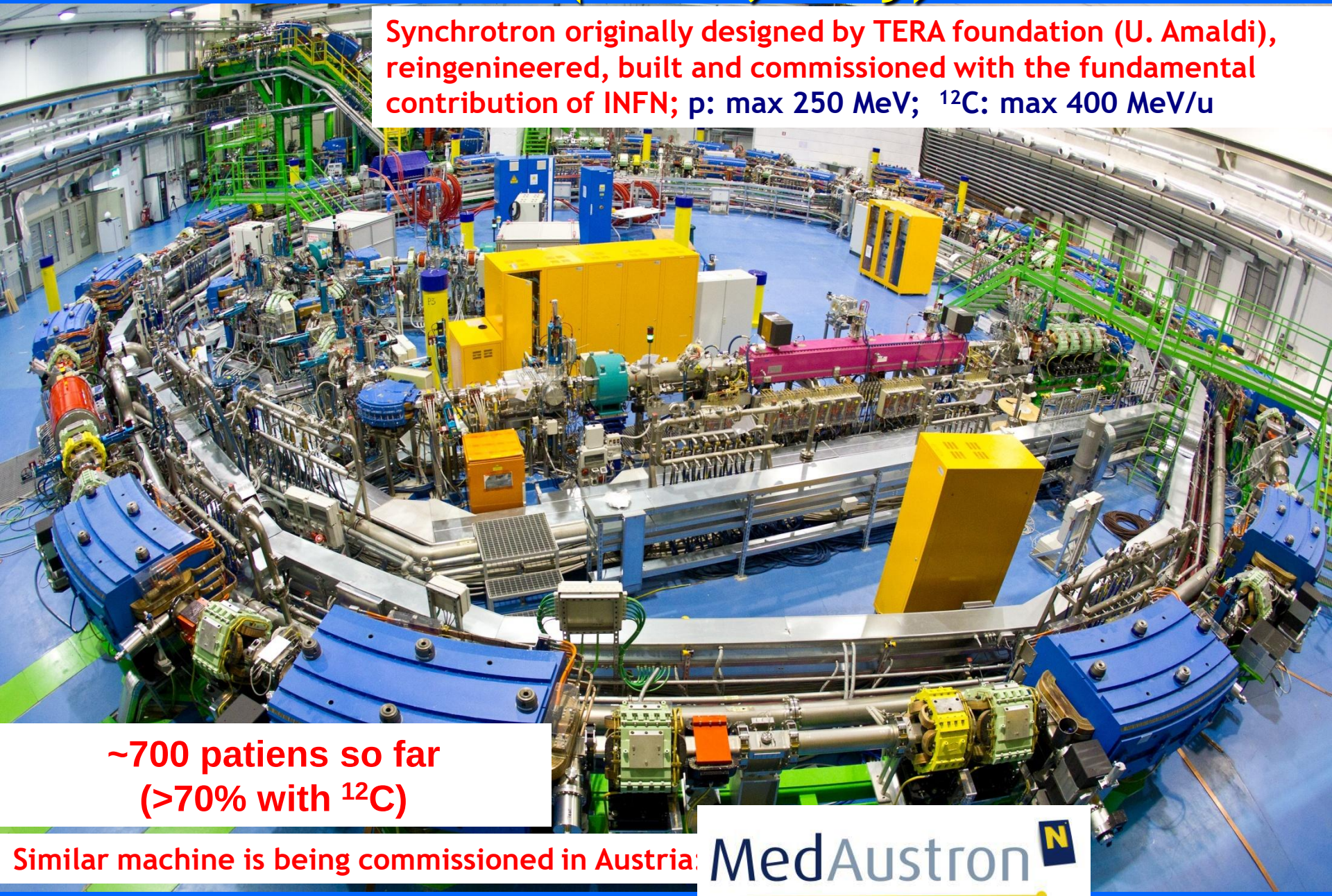
HIT
Heidelberger Ionenstrahl-Therapiezentrum

First patient: end 2009

So far >2.000 patients



CNAO (Pavia, Italy)

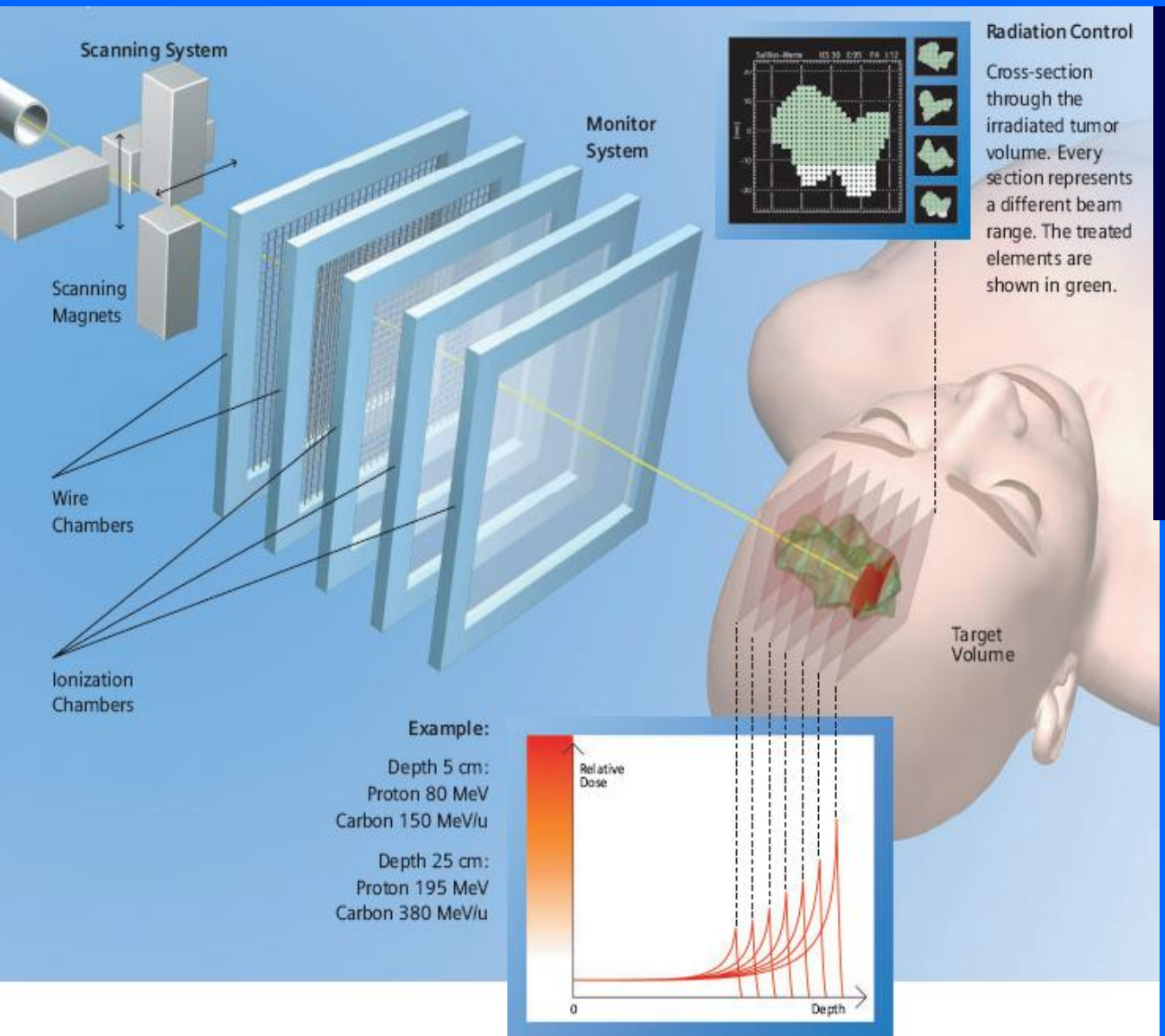


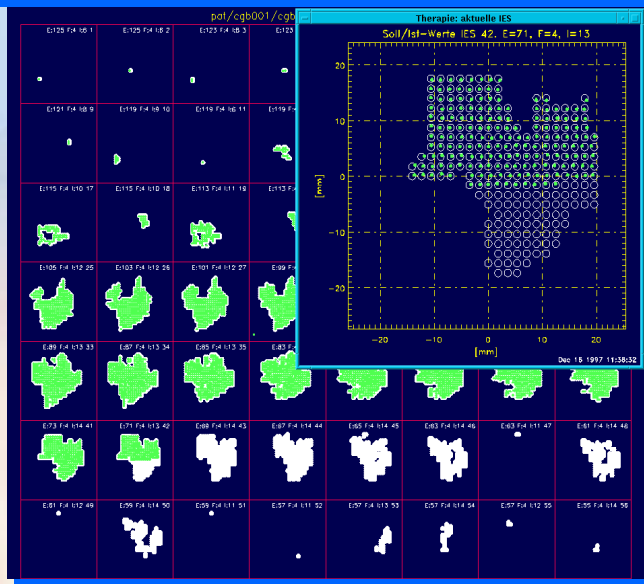
Synchrotron originally designed by TERA foundation (U. Amaldi), reingenineered, built and commissioned with the fundamental contribution of INFN; p: max 250 MeV; ^{12}C: max 400 MeV/u

~700 patiens so far
(>70% with ^{12}C)

Similar machine is being commissioned in Austria: MedAustron

The modern approach for Dose Delivery to tumor: The Raster Scan method ("Active Scanning")0





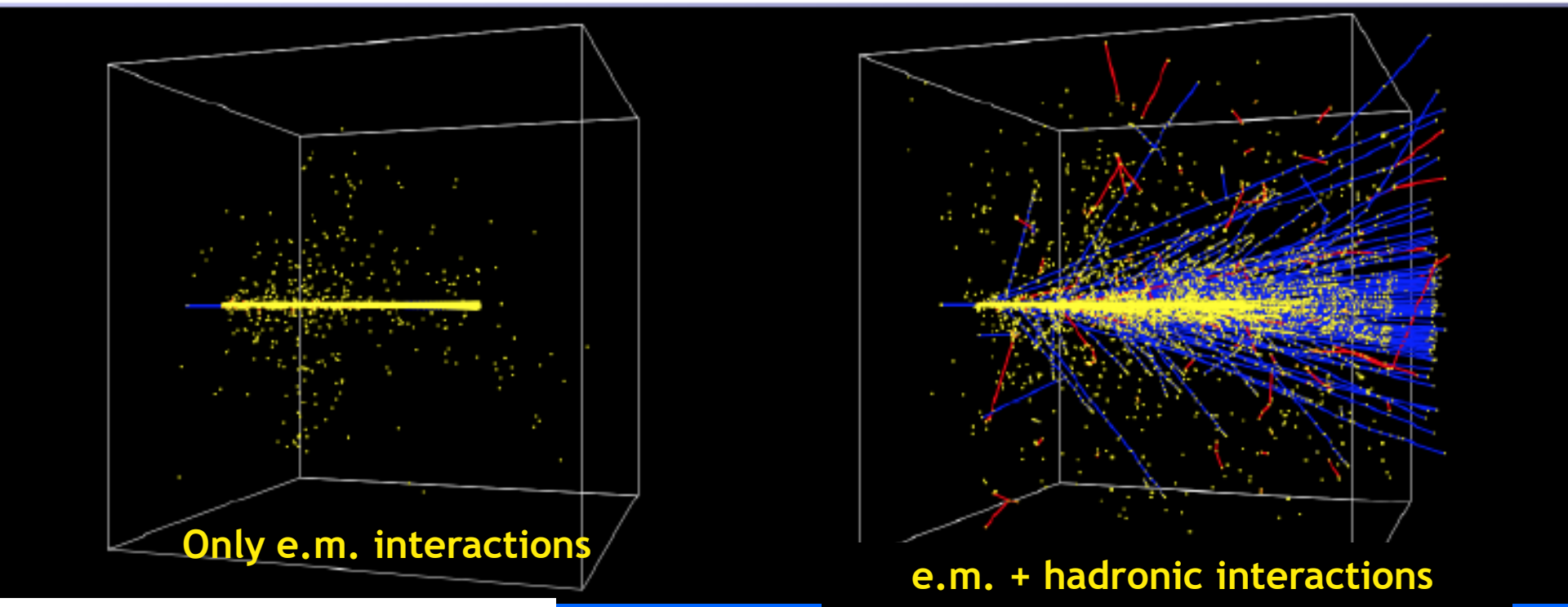
Typically:

p: ~10^9 p/s

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

The role of Nuclear Interaction

C-ions 330 MeV/n in water – simulation by MCHIT



Only e.m. interactions

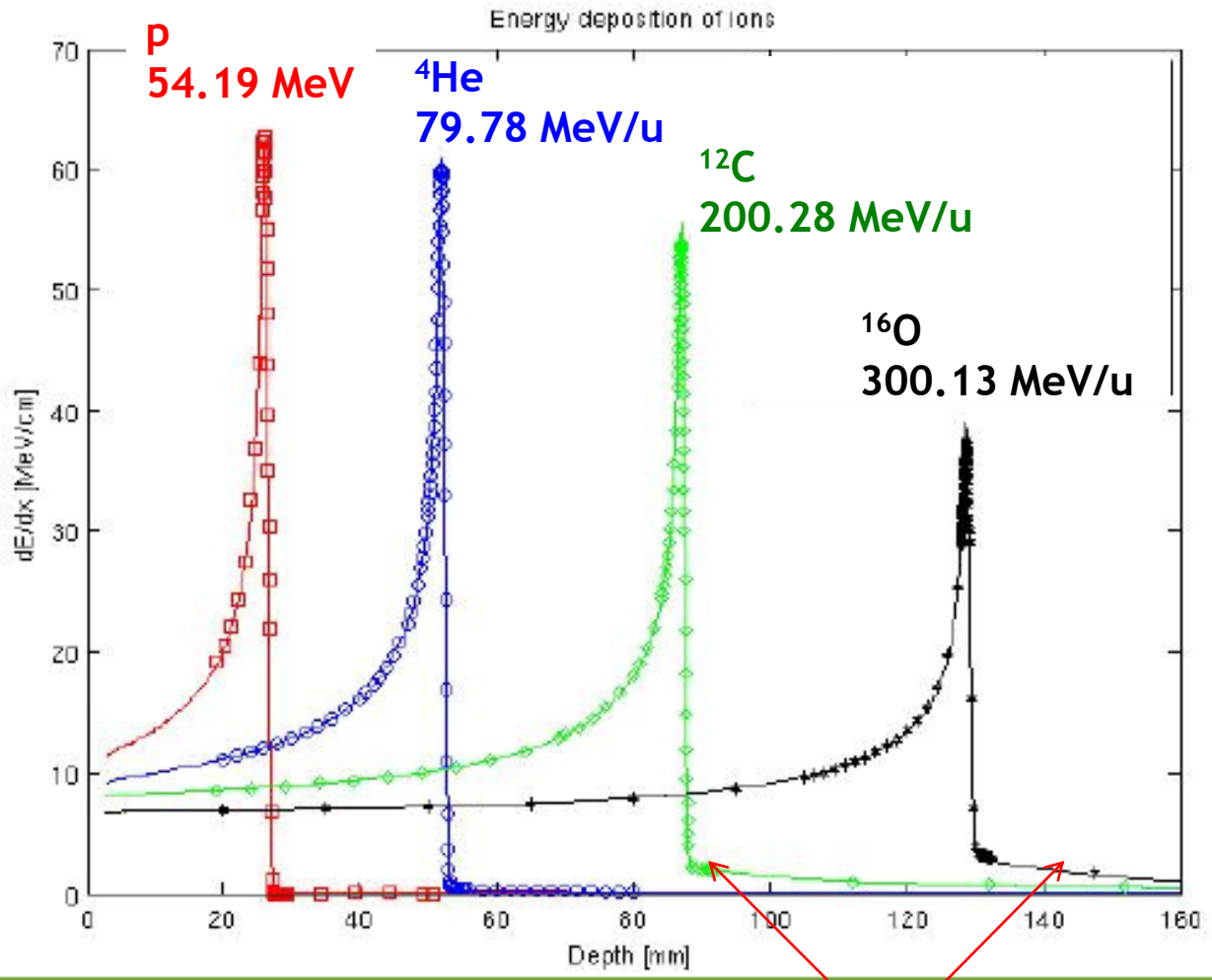
e.m. + hadronic interactions
(elastic scattering & fragmentation)

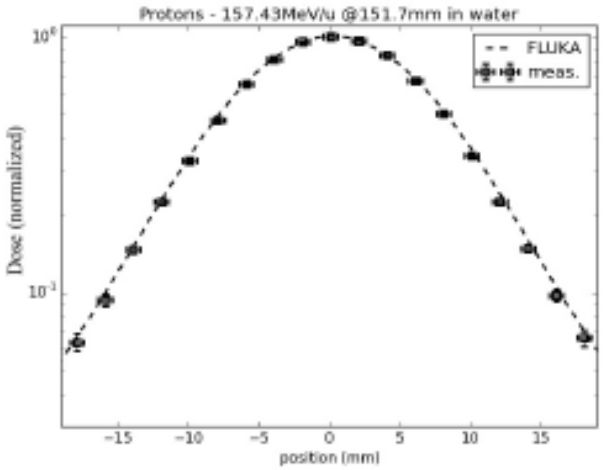
a "Mixed Field" situation:
- different particles with different properties
- different 3D structure

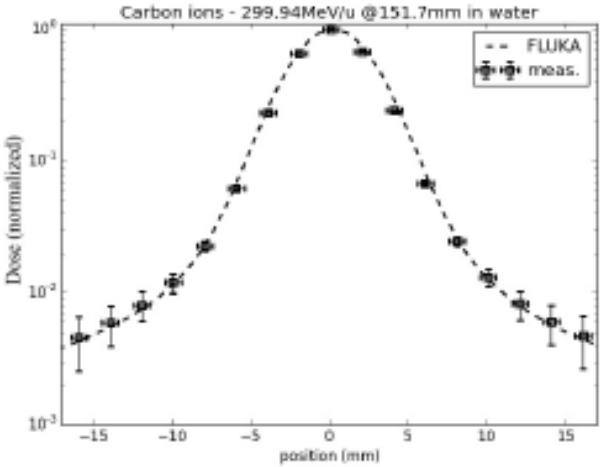
Igor Mishustin
FIAS Frankfurt Institute for Advanced Studies

1. Target fragmentation
2. Projectile fragmentation

The role of Nuclear Interaction





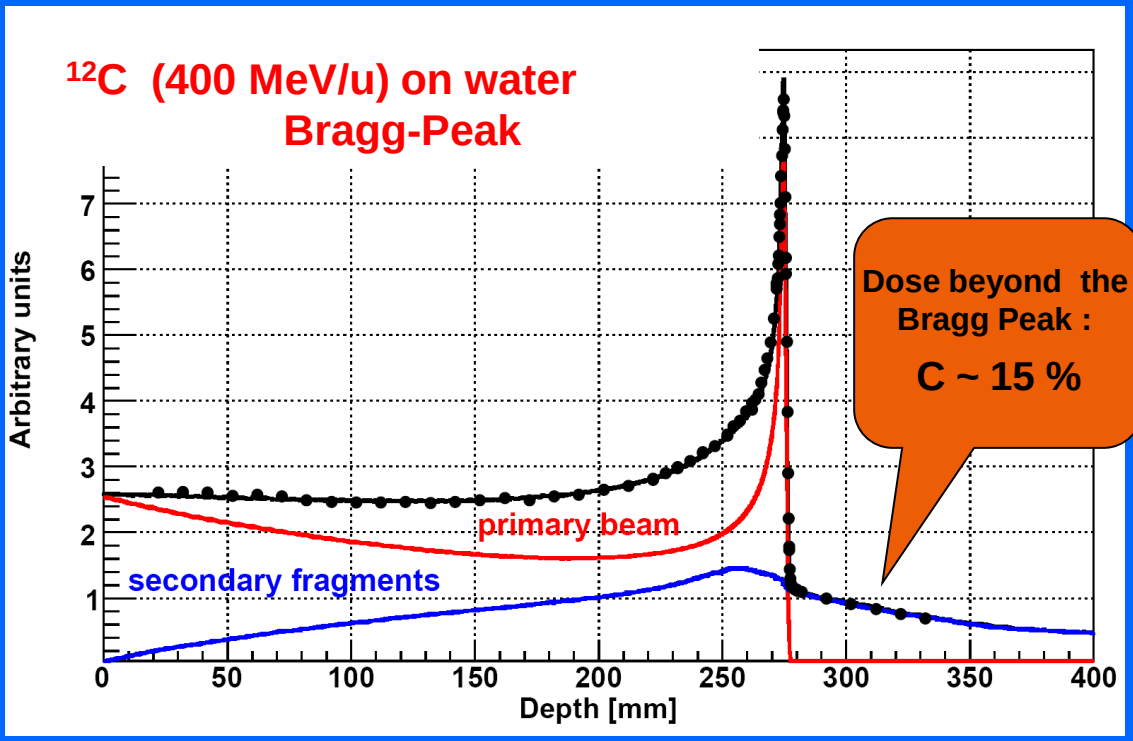


Tail beyond the Bragg Peak due to Nuclear Fragmentation of Projectile

nuclear scattering affects lateral distribution

Nuclear Fragmentation and Particle Therapy

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



1) Dose release in healthy tissues with possible long term side effects ➔must be carefully taken into account in the Treatment Planning System

2) Evaluation of RBE both in tumor and healthy tissues has to take into account all the different fragments and their energy distribution

Nuclear Fragmentation and "Treatment Planning"

The nuclear interaction description is embedded in the Treatment Planning System through a "physical" DB generated on the basis of a Interaction Model (by analytical computation or MC code) where the energy releases and the fragment produced by the beam are stored.

MC codes and their benchmarking with the measurements are becoming more and more important:

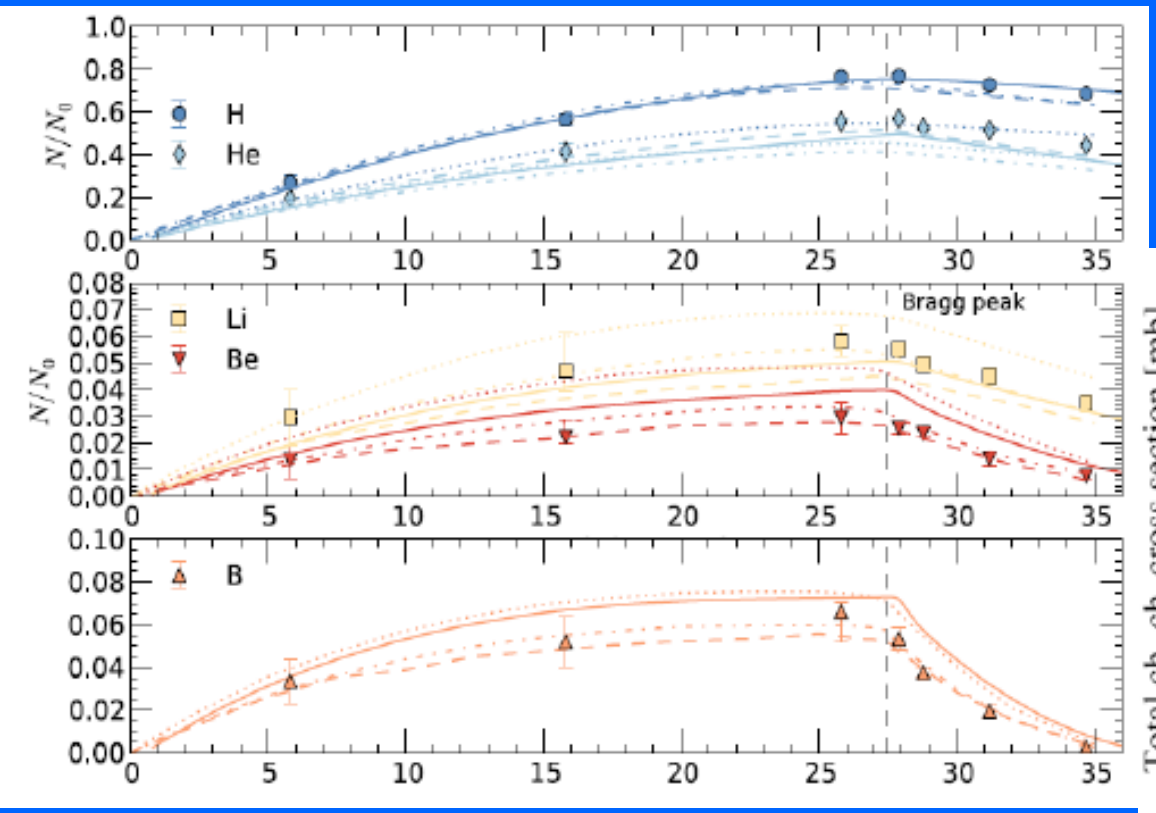
I. **Better representation of the nuclear interaction model compared to deterministic (analytical) codes**
II. **Natural and easy 3D treatment of physics processes**
III. **More accurate patient representation**
IV. **Possibility of exploiting PET online**
V. **Easily taken into account the beam features**

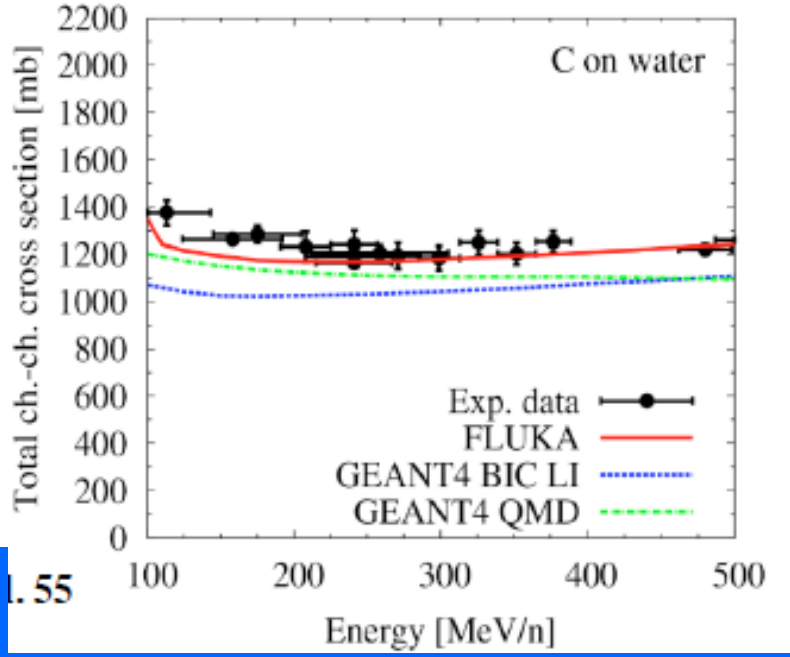
ONE OF THE KEY ISSUES:

reliability of nuclear physics models

➜ must be tuned on data

Build-.-up of charged fragments for ^{12}C 400 MeV/n in water





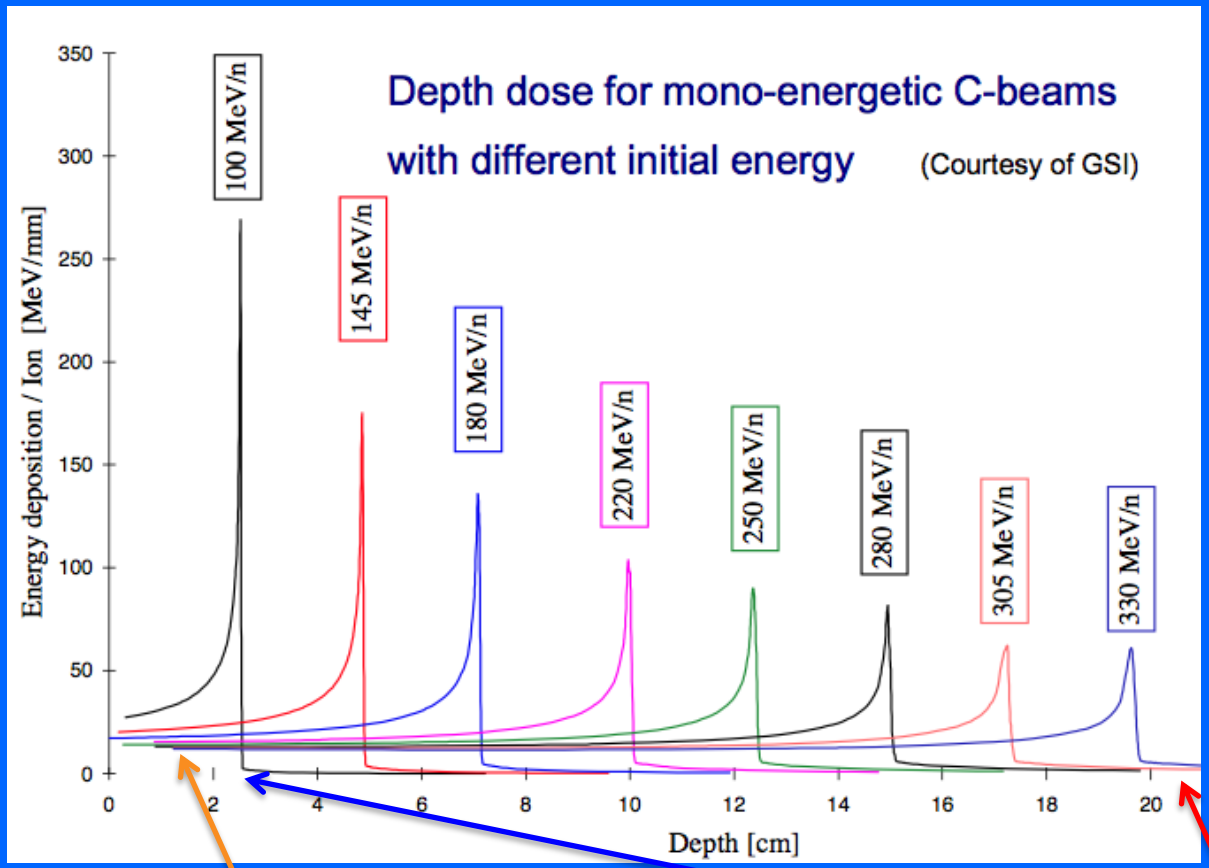
Böhlen et al. 2010, PMB

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

Integral quantities (fragment yields, charge changing cross sections) are generally within 10-20%

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

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 50AMev C beam

GANIL 95AMev C beam - E600 collaboration (2011)

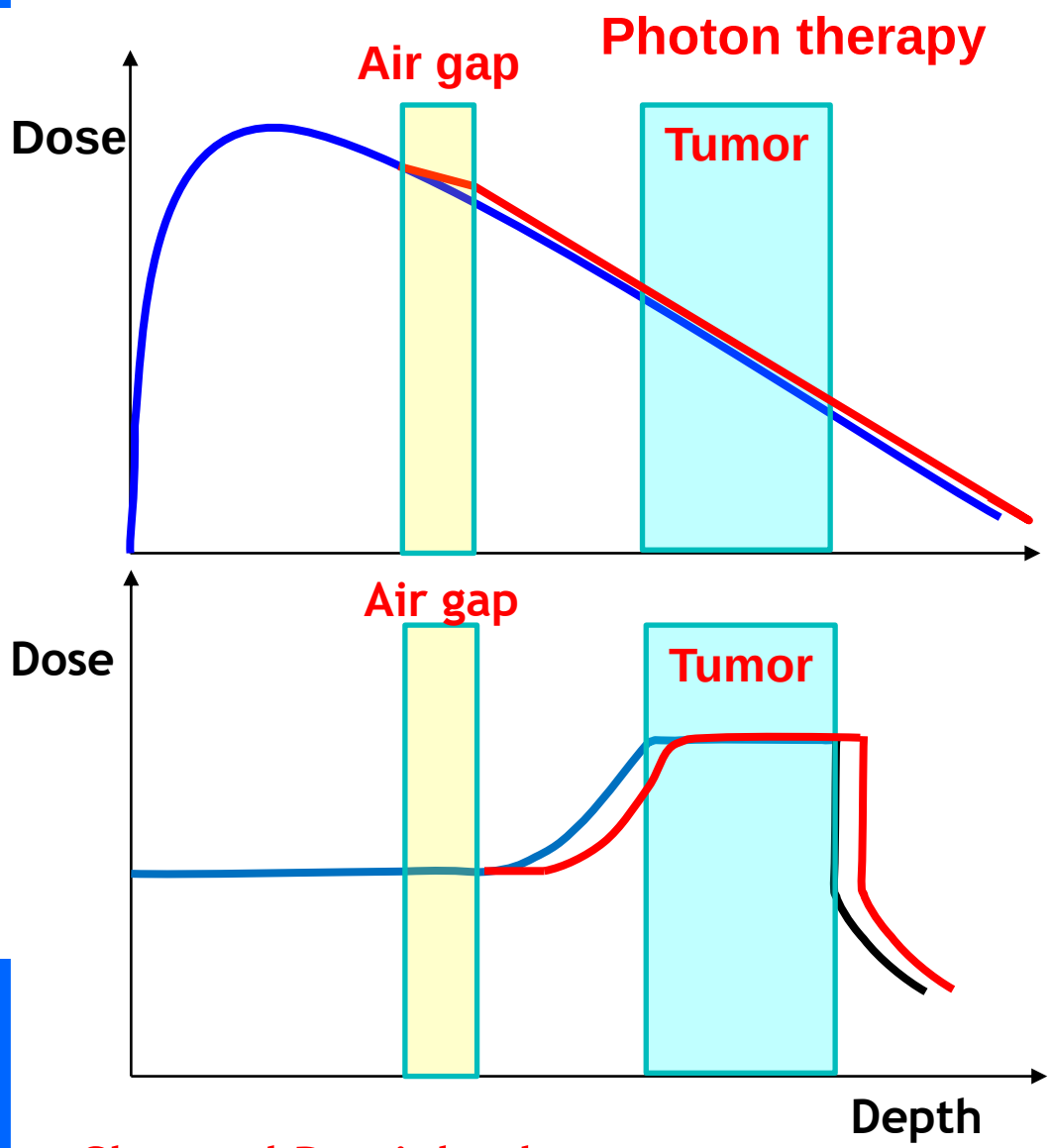
GSI 400Mev C beam FIRST experiment (2011)

The need for in-vivo monitoring of particle therapy

Again uncertainties:

- Limitations of CT data (beam hardening, noise, resolution etc)
- **Uncertainty in energy dependent RBE**
- **Calibration of CT to stopping power**
- CT artifacts
- **Variations in patient anatomy**
- **In-homogeneity along the beam path**
- Variations in ion beam energy
- Variations in patient positioning

Planning uncertainty > 5 mm (margin of 3.5% + 2 mm)



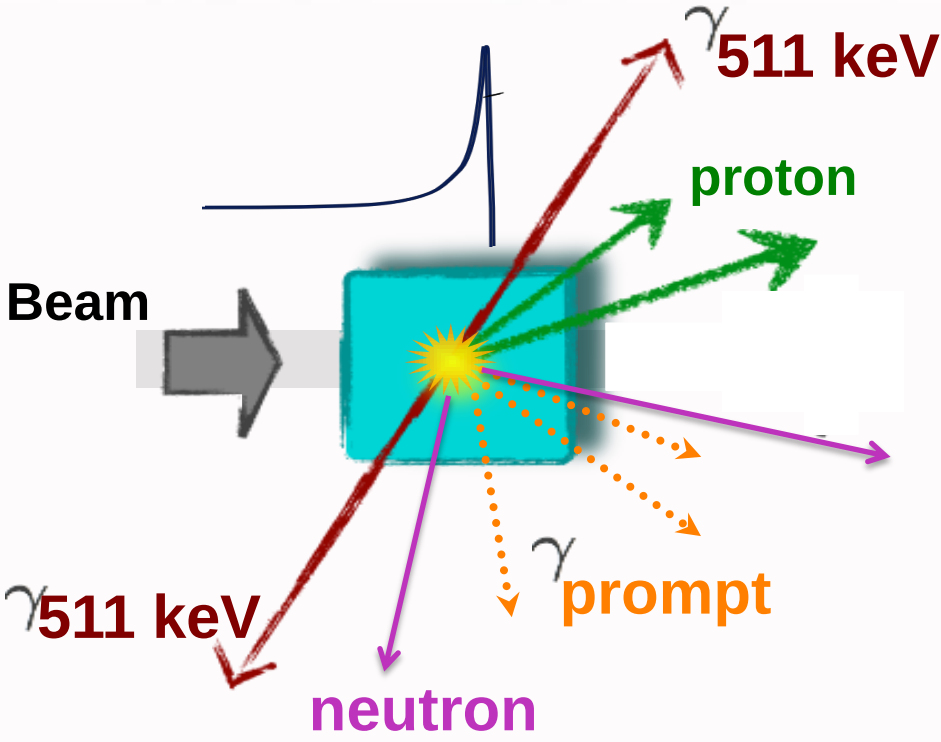
Charged Particle therapy

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 ®⁺ emitters is the baseline approach

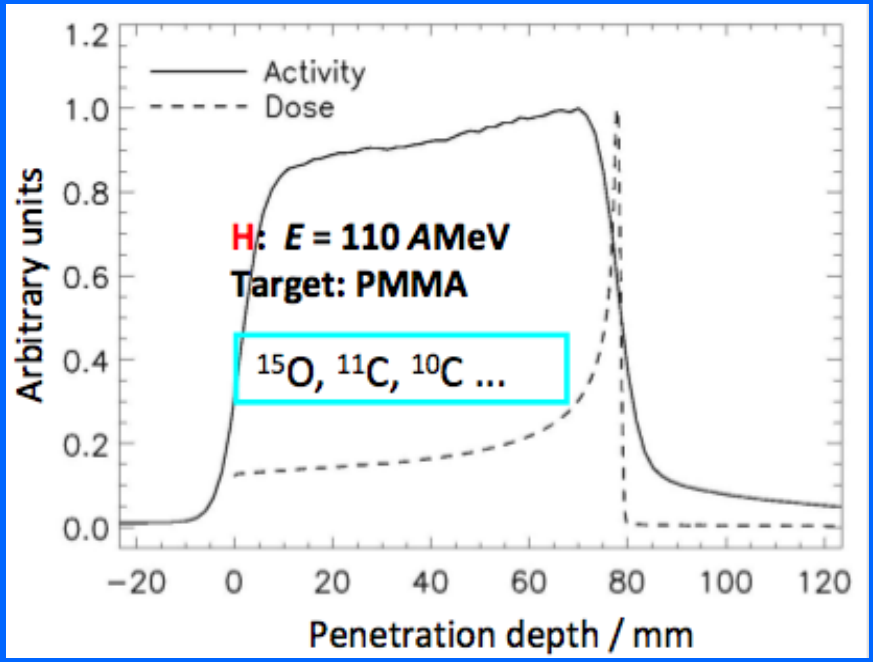
- Isotopes of short lifetime ^{11}C (20 min), ^{15}O (2 min), ^{10}C (20 s) with respect to conventional PET (hours)
- Low activity asks for quite a long acquisition time (some minutes at minimum) with difficult in-beam feedback
- Metabolic wash-out, the ®⁺ emitters are blurred by the patient metabolism



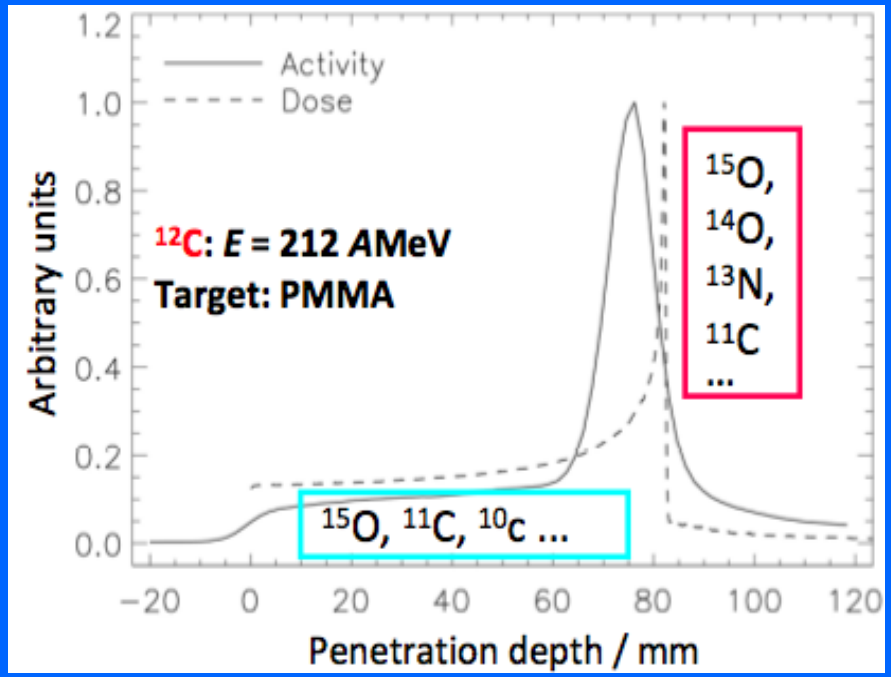
Correlation between β^+ activity and dose

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



Projectile & target fragmentation

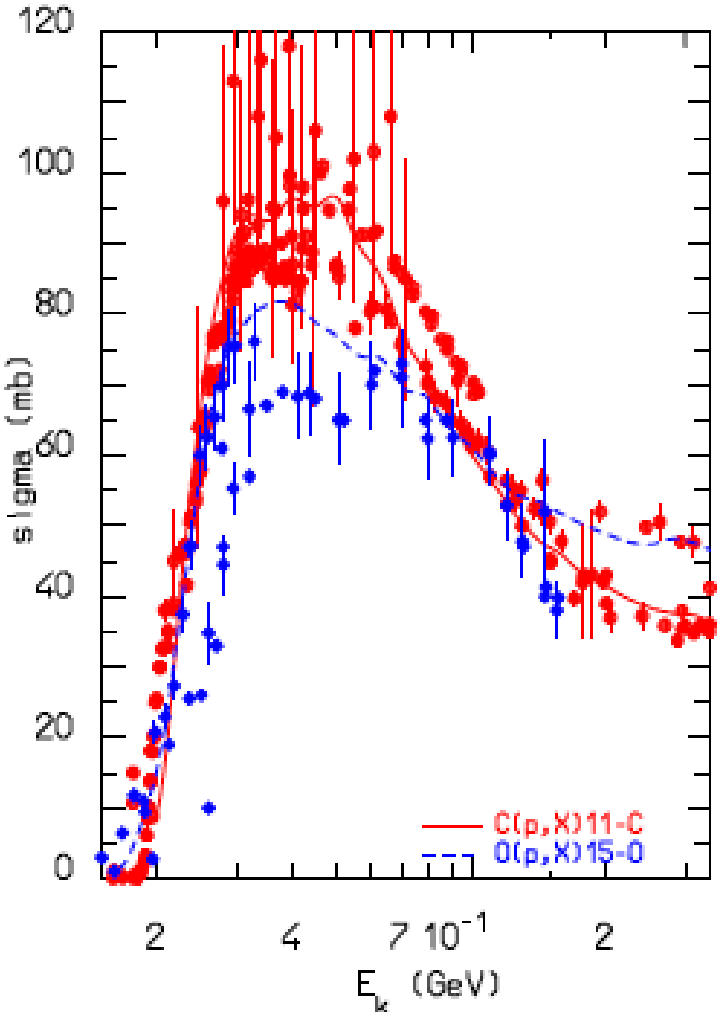


	$T_{1/2}$ (s)
^{11}C	1221.84
^{15}O	122.24
^{13}N	597.9

^{10}C (19.3 s), ^{8}B, ^{14}O + others

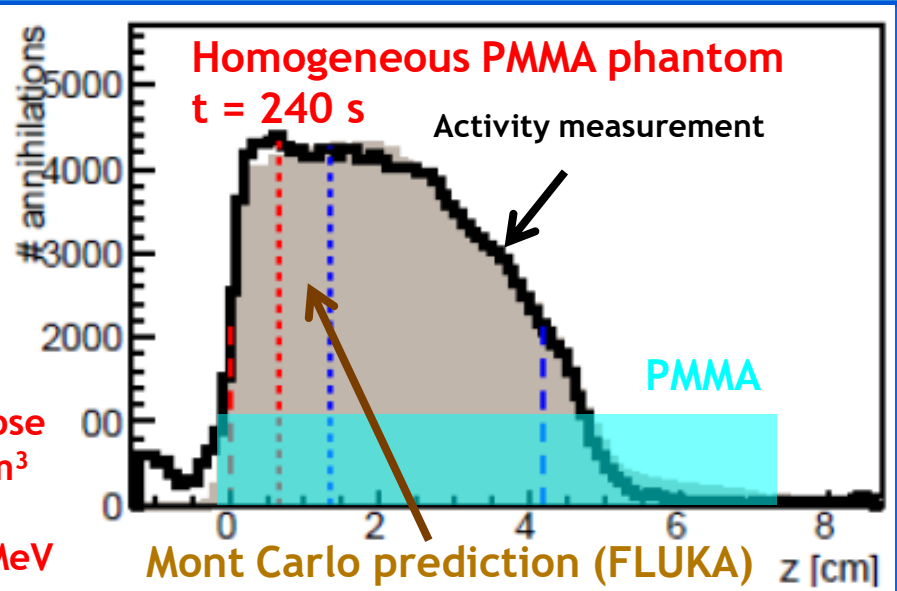
~2 mm resolution, or less, on the distal part of Bragg Peak position can be achieved

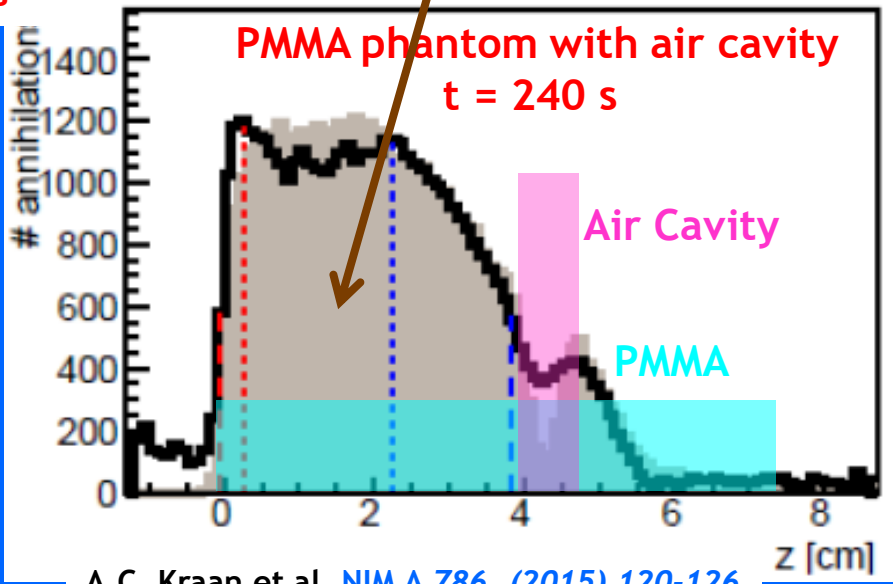
MC predictions, available data, exp. tests



$^{12}C(p,x)^{11}C$ and $^{16}O(p,x)^{15}O$ x-sect.
MC: cont. lines
Exp. Data: symbols

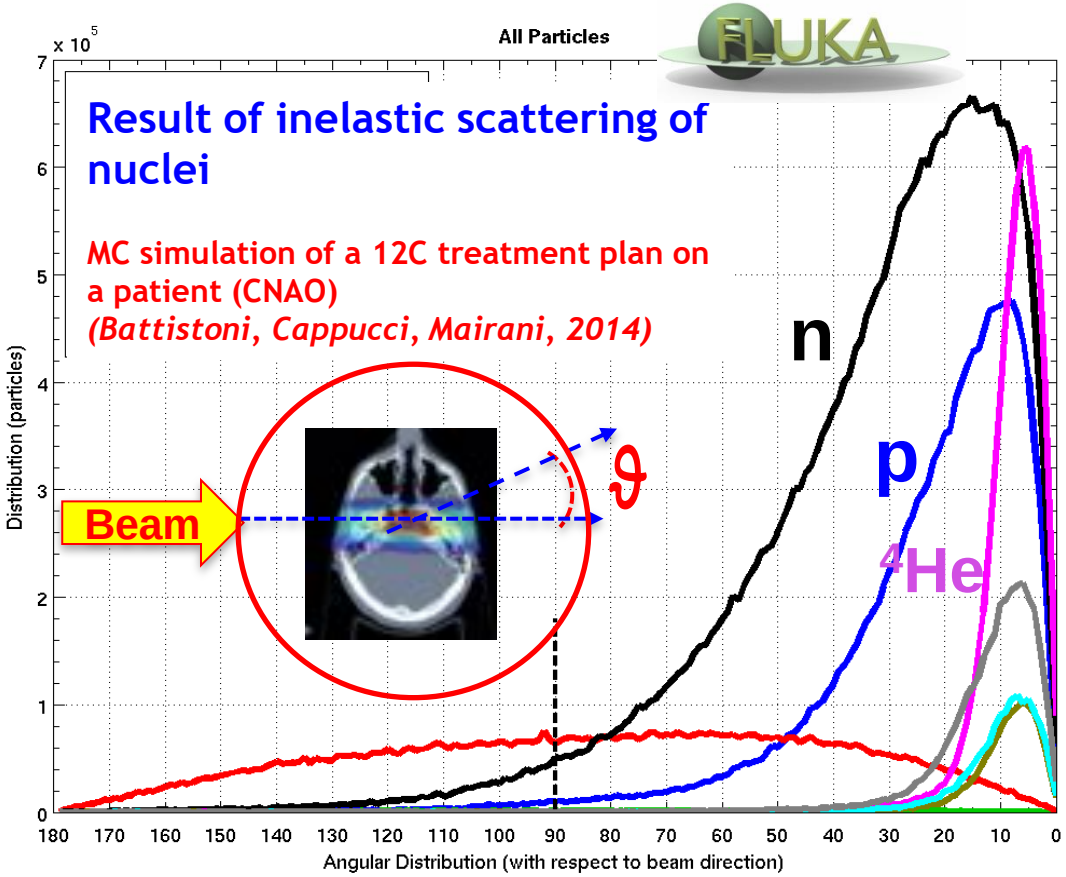
2 Gy unif. dose
in 3x3x3 cm^3
Protons:
62.3 - 90.8 MeV
T_{irr} = 146 s

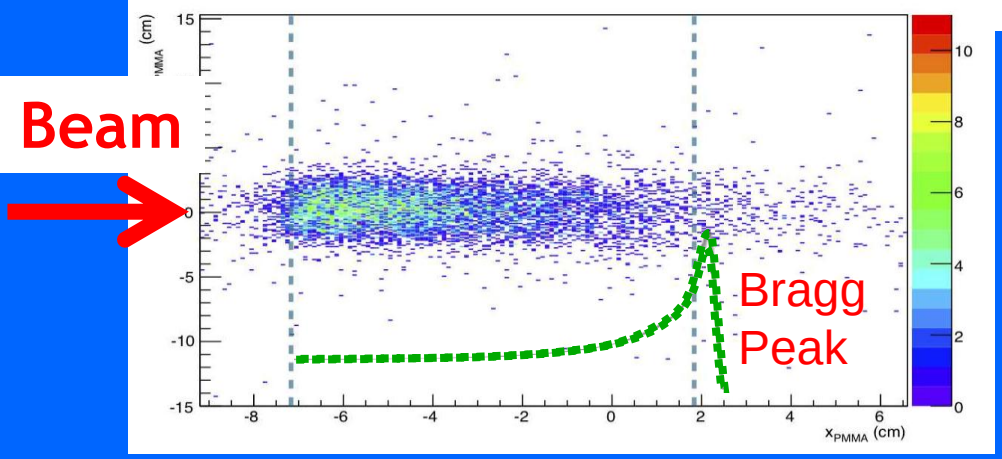




A.C. Kraan et al, NIM A *786, (2015) 120-126*

many particles/fragments out of a patient…

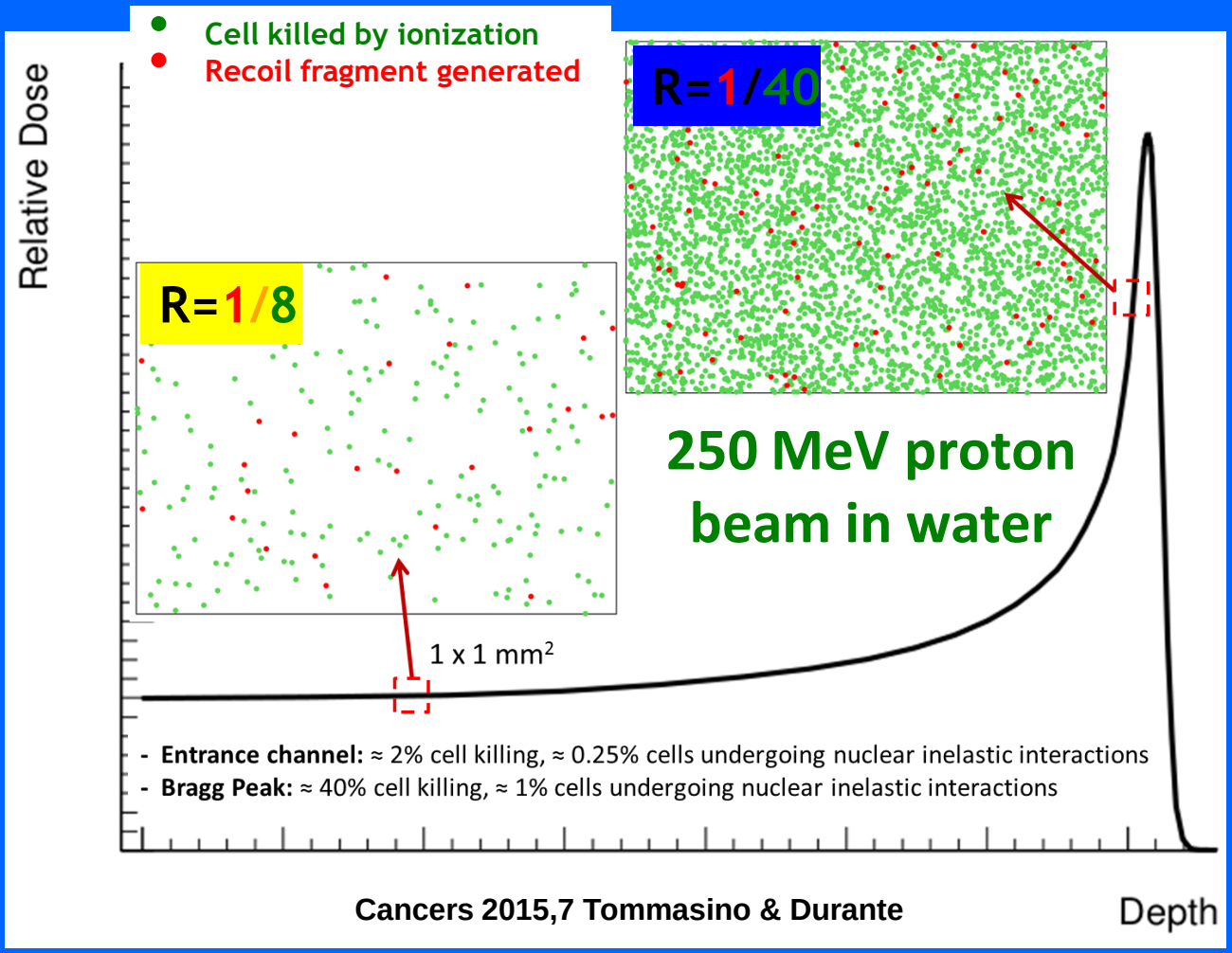




Beam XY radiography of a ^{12}C beam at 220 MeV/u obtained by protons detected at 90º on a tissue-equivalent target *(L. Piersanti et al. 2014 Phys. Med. Biol. 59 1857)*

What about Target Fragmentation?

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



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

These might be the source of an RBE>1.1

more damage than expected to healthy tissues!!

p ➜ X (C,O) scattering @200 MeV

p-N elastic interaction and the light fragment production (p,d,t) are quite well known. More uncertainty on He fragments. **Missing data on heavy fragments (A>4), largely unknown. Available nuclear models in MC code not yet reliable**

Very low energy, very short range fragments!!

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

Analitic model results on p+O

A new exp. is being proposed

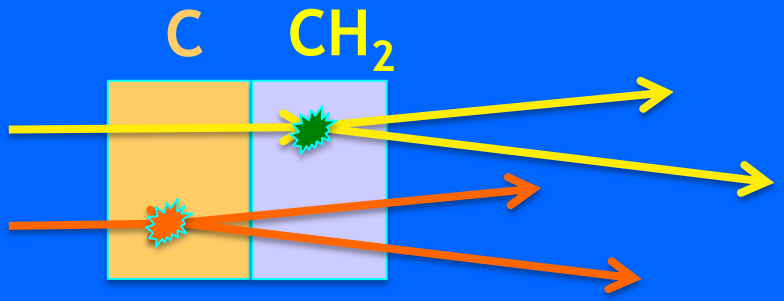
INFN Istituto Nazionale di Fisica Nucleare

FOOT:
FragmentatiOn Of Target

Rm1, Rm2, LNF, Bo, Mi, To, Pi, Na, TIFPA, LNS

To perform a fragmentation measurement in the
Inverse Kinematics Approach:

100 – 300 MeV/u C,O,N beams against a H-rich target
Detector designed for: Z-id, A-id, Energy, Angle



The fragmentation cross section on H can be obtained by subtraction.

Conclusions

- HadronTherapy is spreading out. The correct inclusions of nuclear processess in treatment planning is becoming more and more relevant.
- Fragmentation studies are still an open issue. Not only ^{12}C: the possible next use of ^{4}He and ^{16}O beams requires specific studies.
- Target fragmentation: a new game in town…
- The importance of MC in particle therapy is increasing. There are not yet enough valuable data for benchmarking
- Real Time Monitoring in Particle Therapy is important: it requires reliable nuclear physics modeling.

Space Reearch and Therapy: what ties them together?

Space: Combine the composition of the radiation field and dose to biological effects ➜ Health risk

Therapy: Treatment planning verification and optimization, online range verification, extension to other ions and diseases…

➜ Physics and biology experiments to understand basic mechanisms and characterize specific systems

➜ Improve the predictive power and accuracy of Monte Carlo codes and their nuclear models

Thank you for the attention

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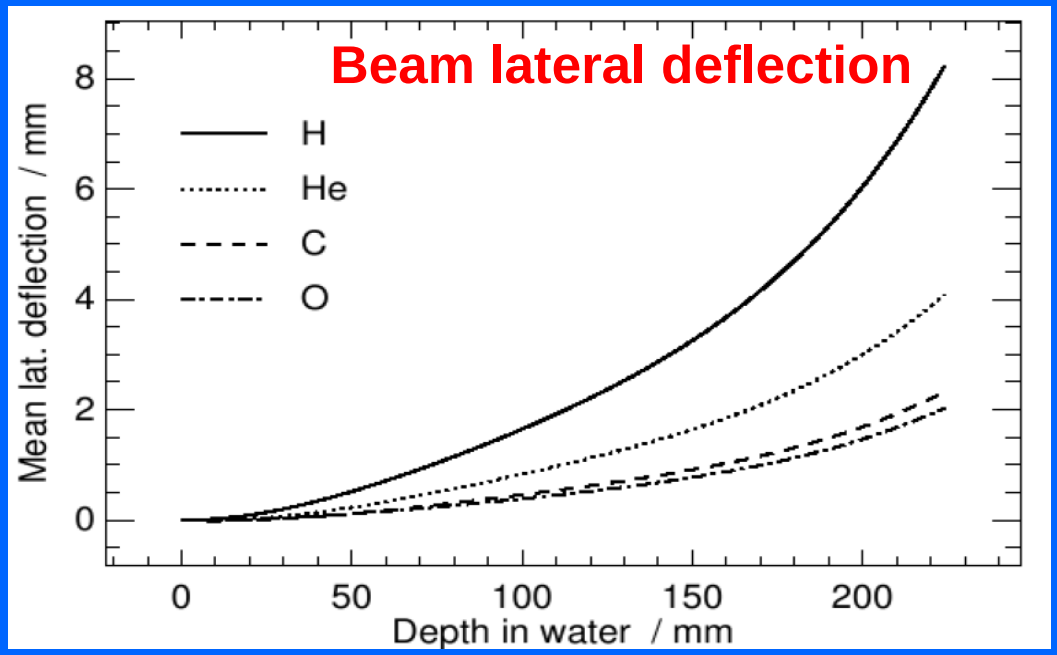
Spare Slides

New ion beams proposed for therapy

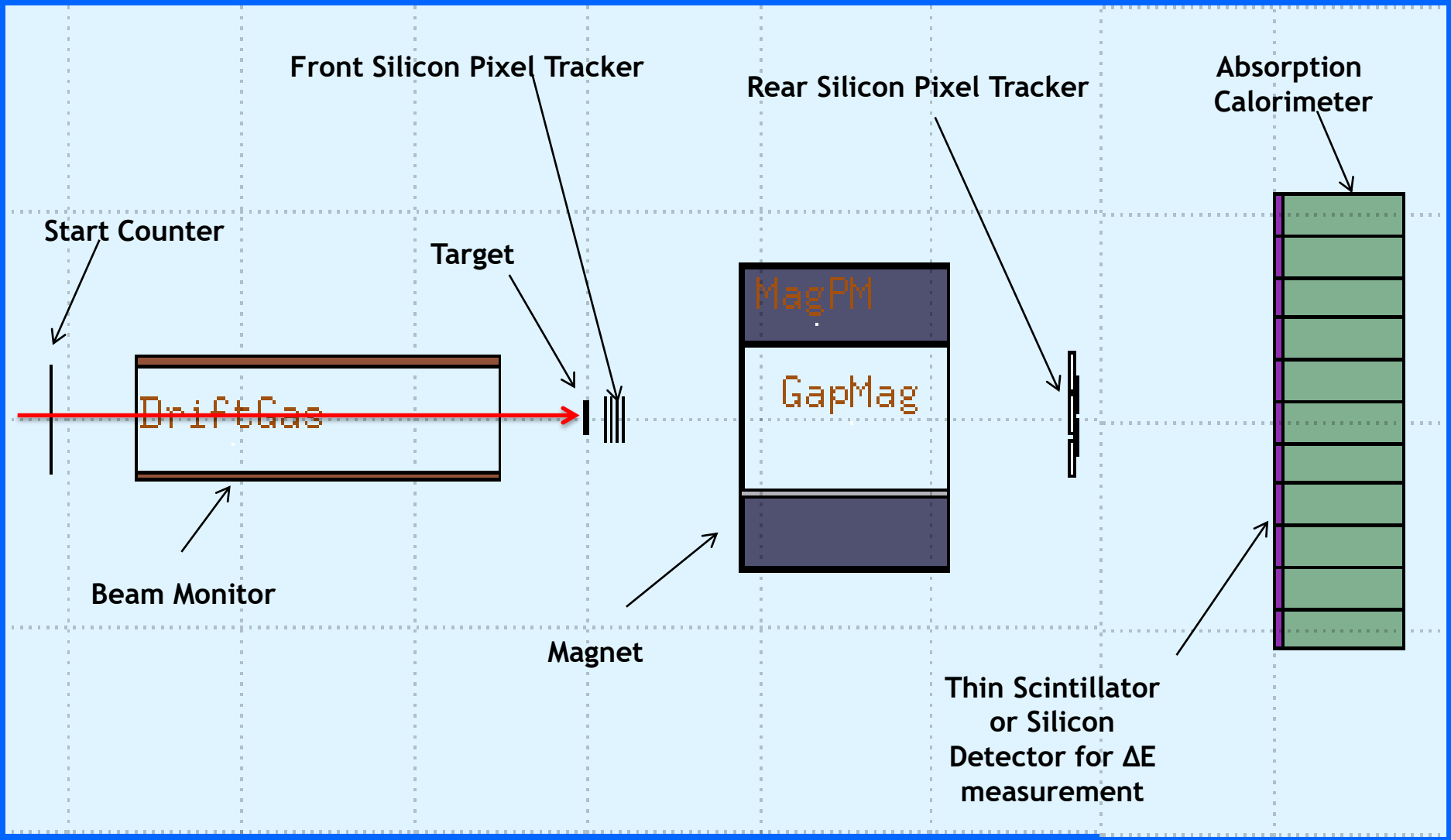
^{4}He (50-300 MeV/u):
negligible fragmentation, higher RBE than protons, but more limited lateral scattering

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

For a discussion of New Ions in therapy: F. Tommasino, E. Scifoni, and M. Durante, Int. J. Particle Ther. 2015 2:3, 428-438

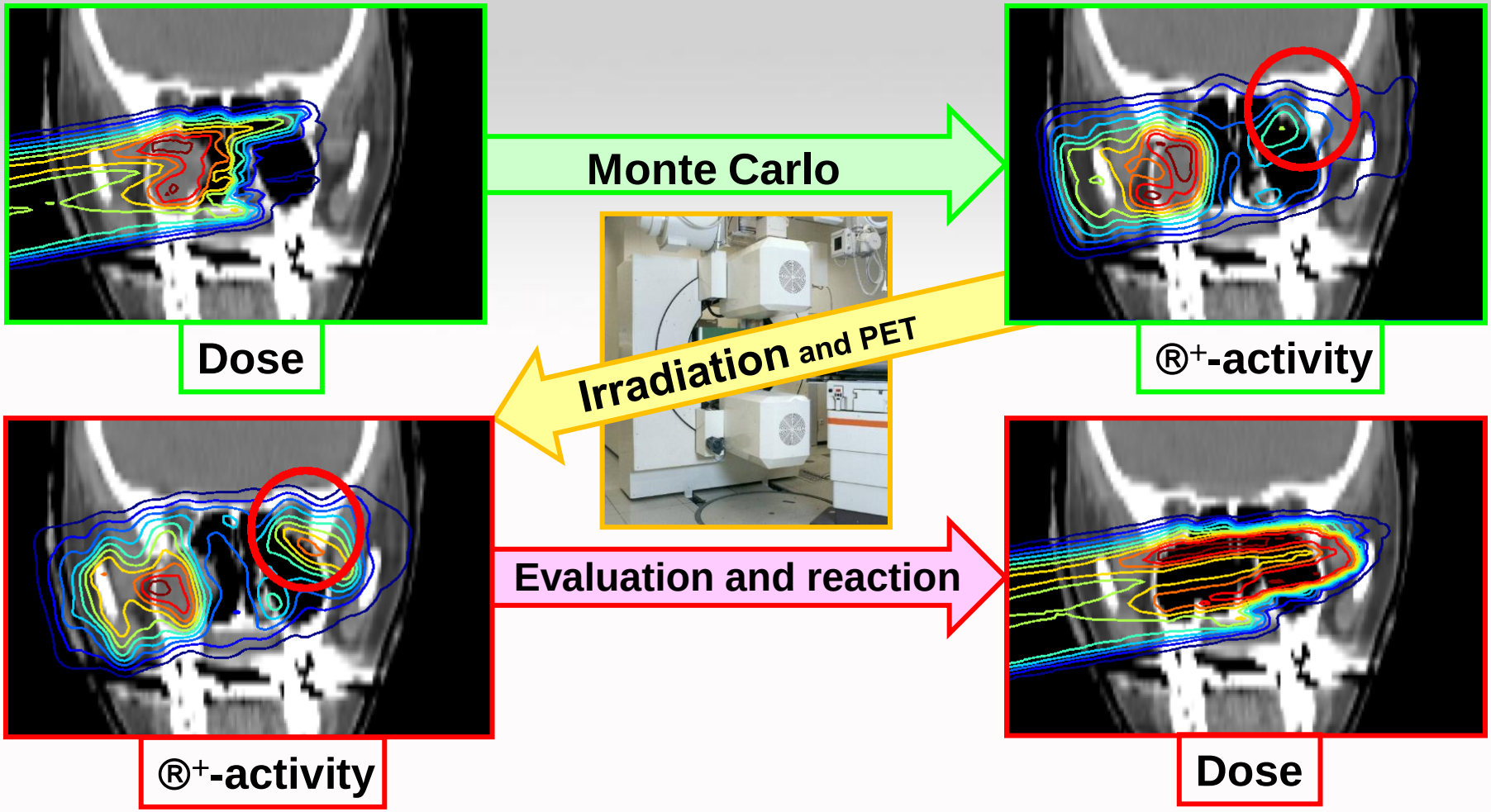


the FOOT detector

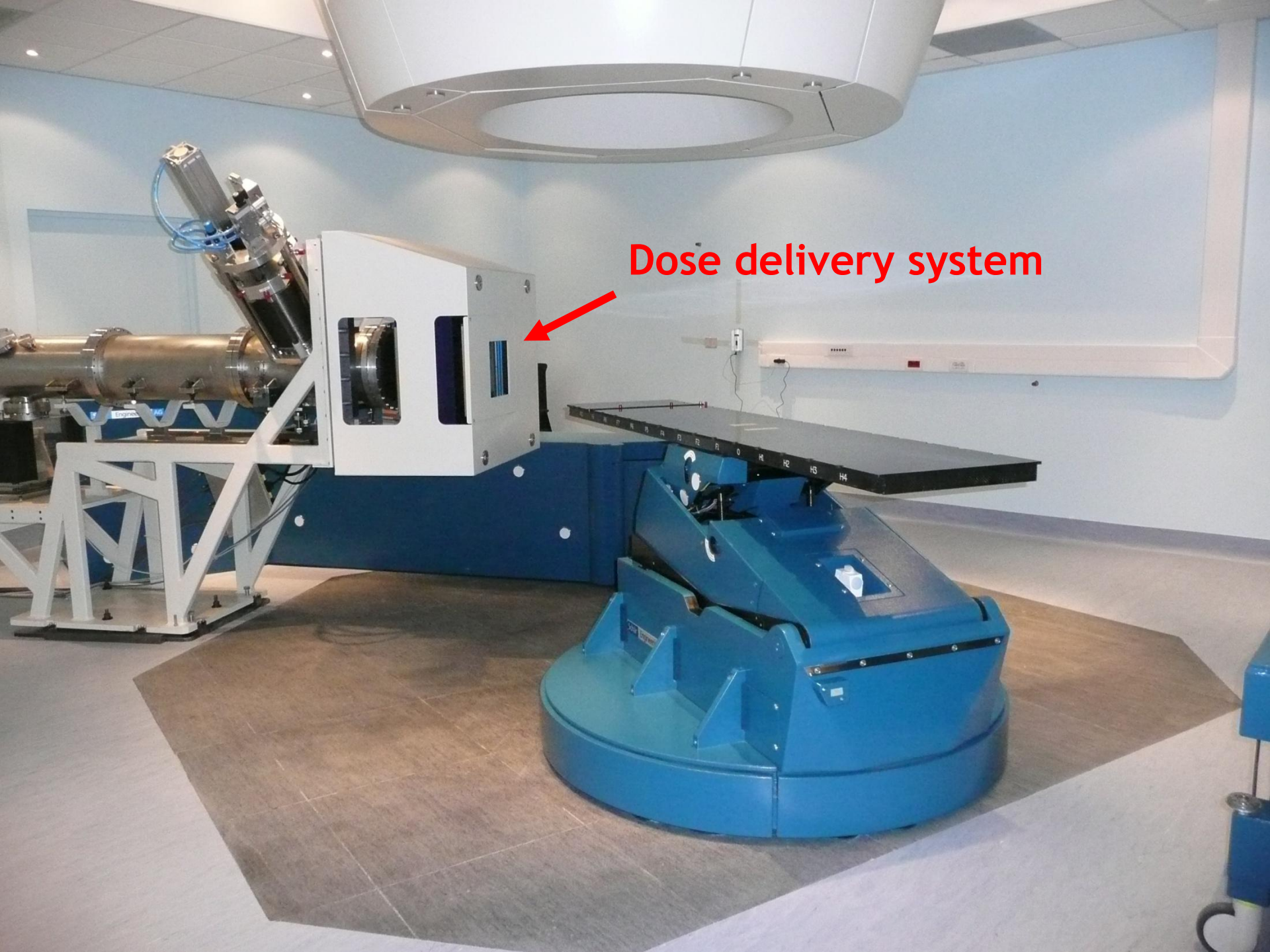


In-Vivo range measurement with PET: workflow and potential

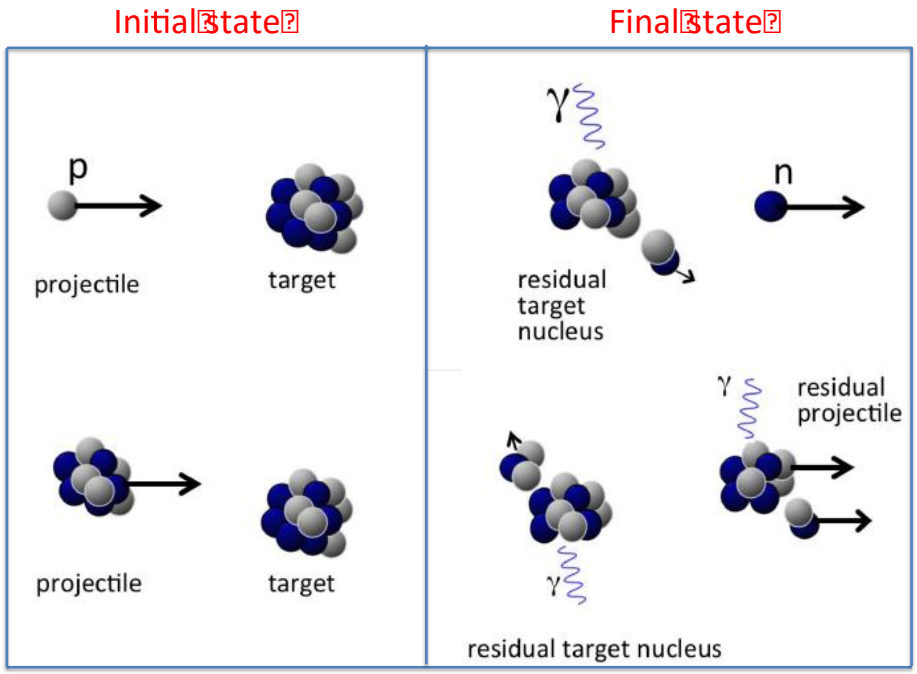
W. Enghardt et al.: Radiother. Oncol. 73 (2004) S96



Problem to solve: Metabolic Washout! In-beam measurement is really necessary, although difficult.

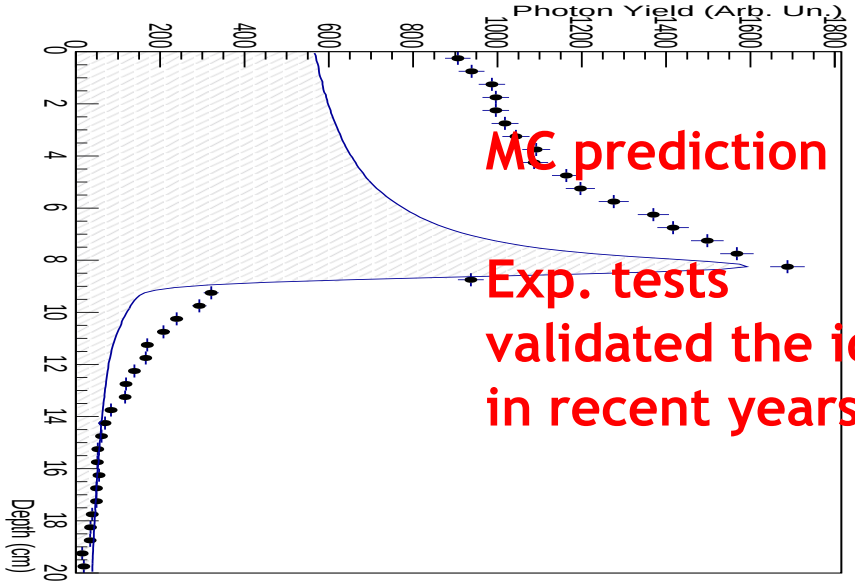

Dose delivery system

“prompt” de-excitation γ’s



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

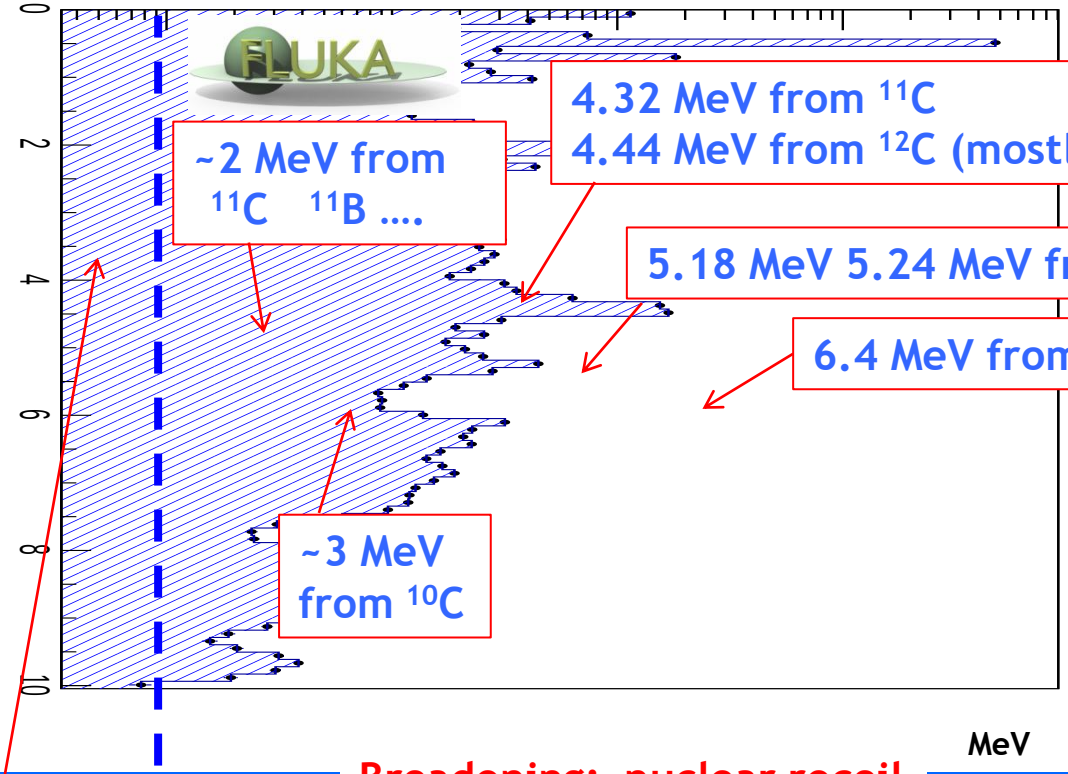
not suited for standard gamma-imaging devices of nuclear medicine



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

MC prediction of 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)

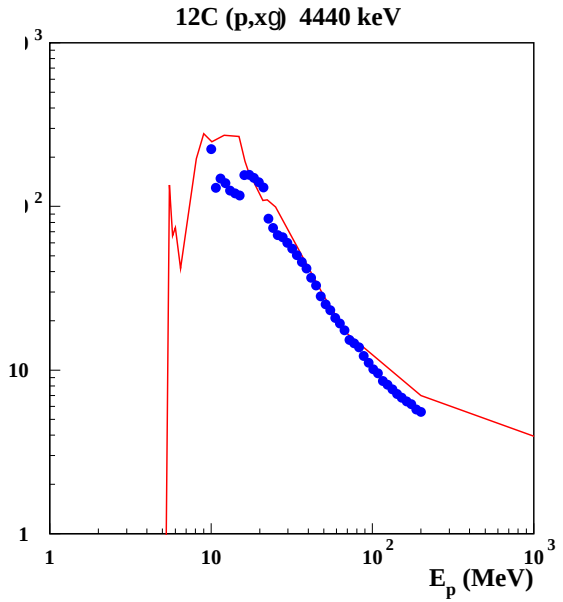
5.18 MeV 5.24 MeV from ^{15}O

6.4 MeV from ^{16}O

~3 MeV from ^{10}C

Broadening: nuclear recoil

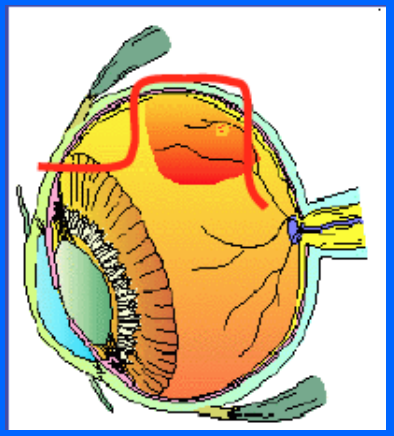
0.511 MeV from e^+ annihilation



HadronTherapy in Italy

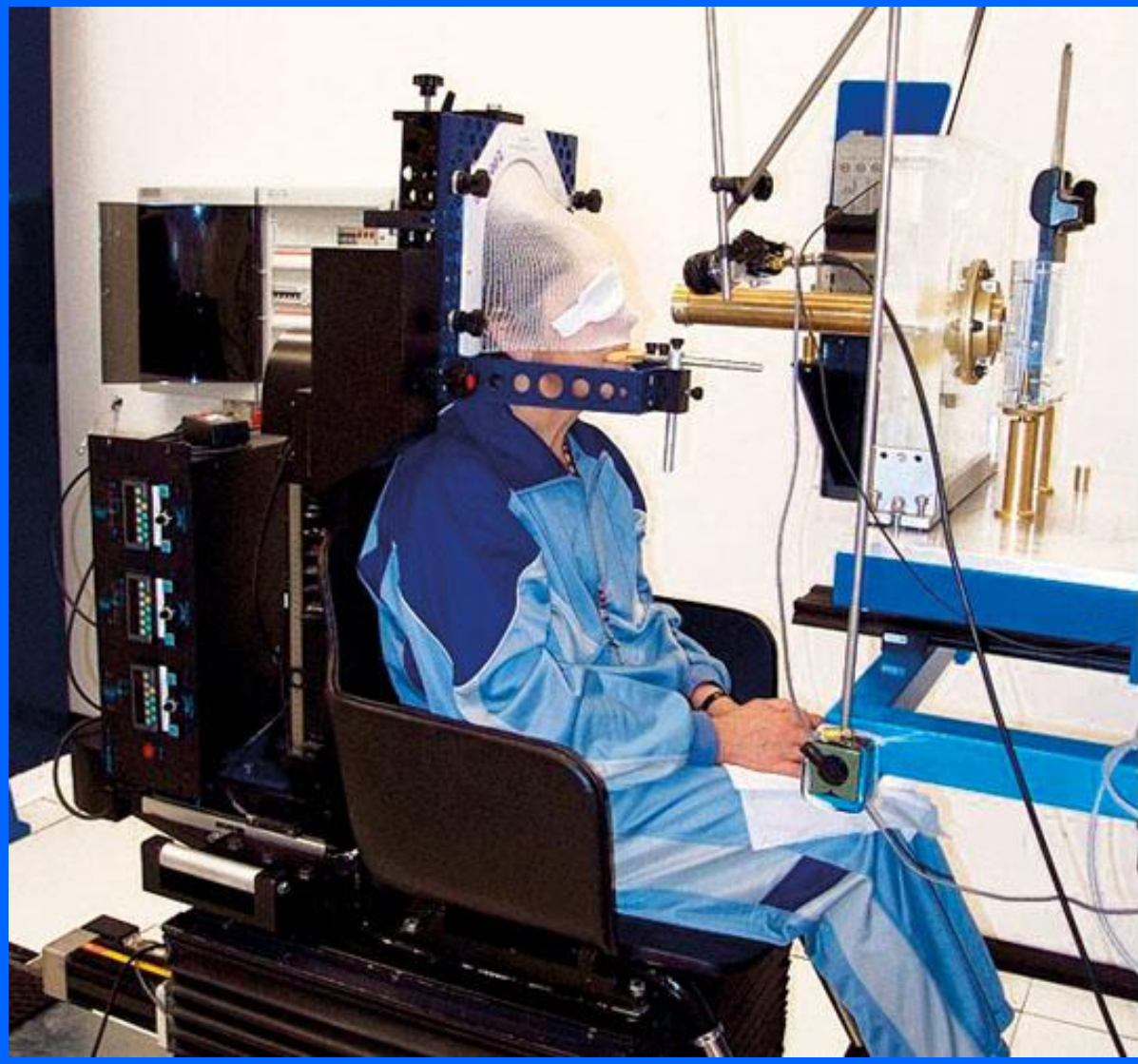
CATANA @INFN-LNS

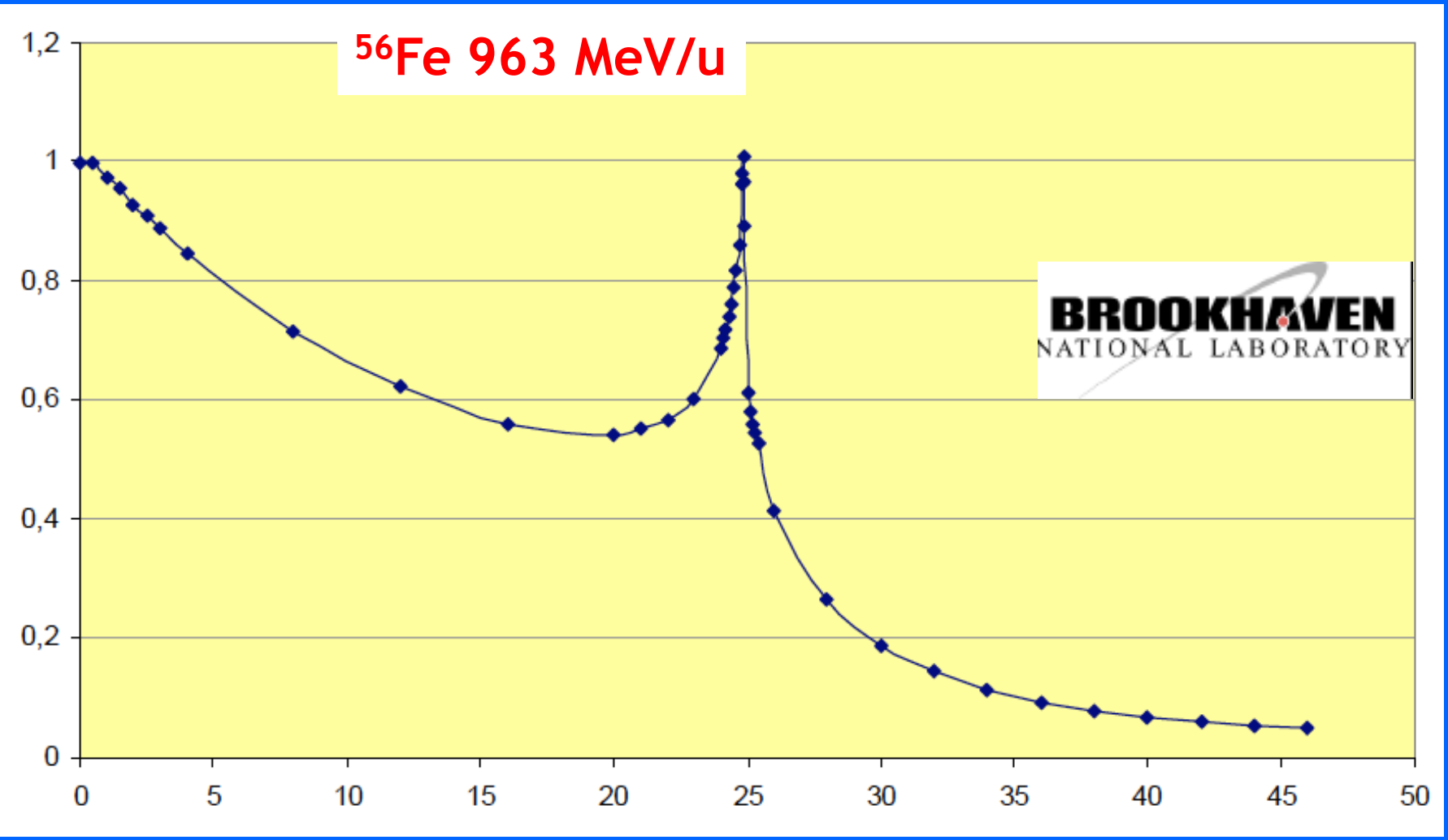
- **>350 patients since 2002**



Treatment of thechoroidal and iris melanoma (In Italy about 300 new cases for year)

Eye retention rate 95 %
Survival 98 %
Local Control 95 %




^{56}Fe 963 MeV/u
1,2
1
0,8
0,6
0,4
0,2
0
0
5
10
15
20
25
30
35
40
45
50
BROOKHAVEN
NATIONAL LABORATORY